# A Practical Overview of Pediatric Atopic Dermatitis, Part 2: Triggers and Grading

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## PRACTICE **POINTS**

- Atopic dermatitis (AD) can be triggered by viral infections, weather, and food allergens.
- The scoring of AD is largely used experimentally and includes the eczema assessment and severity index; the SCORAD (SCORing Atopic Dermatitis); and the six area, six sign AD (SASSAD) scores.
- There is a strong genetic contribution to the development of AD.
- Children with AD may have persistent disease into adulthood in half of cases.

*In part 2 of this 3-part series on atopic dermatitis (AD) in children, triggers for the appearance and flaring of AD are reviewed. The role of AD in the atopic march is explored. Furthermore, the usage of grading systems in the development of therapeutics and in clinical care is discussed. The natural history of AD has changed from improvement to 50% persistence and therefore it is important to council guardians and patients accordingly.*

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Atopic dermatitis (AD) may be triggered by viral infections, food allergens, weather, and other causes, and it may trigger an inflammatory progression known as the atopic march. This article reviews research on triggers of pediatric AD so that dermatologists may discuss trigger avoidance with patients and guardians. Other factors affecting AD development include genetics and hygiene. Grading of AD also is discussed.

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This article is the second of a 3-part series. The third part will appear next month.

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## The Atopic March

The persistence of AD in untreated skin can trigger an inflammatory progression called the atopic march in which food and environmental allergies as well as asthma may occur progressively due to ongoing inflammatory triggering.[1] In a study of asthma and food allergy reporting and management in public schools in Chicago, Illinois, food allergies were seen in 9.3% of asthmatic students (n=18,000), and 40.1% of food allergic students (n=4000) had asthma.[2] An observational study by Flohr et al[3] in London, England, included 619 exclusively breastfed infants who were recruited at 3 months of age. The investigators determined that food sensitization was unrelated to the presence of filaggrin mutations, type of eczema (flexural vs nonflexural), and transepidermal water loss but was associated with AD severity as determined by SCORAD (SCORing Atopic Dermatitis), a composite score of AD that includes pruritus as a factor in severity. Other AD associations included 3 leading food allergens: eggs, milk, and peanuts. No association with cod, wheat, or sesame allergy was noted. The investigators concluded that AD and AD severity were the leading skin-related risk factors for food

allergies and therefore food allergy development in breastfed infants was probably mediated by cutaneous antigen-presenting cells.[3]

The skin has been documented to react to contact with known food allergens[4] and is known to be a route of allergic sensitization to allergens such as fragrance in patients with AD.[5,6] Two phenotypes of eczema that have been associated with asthma development are severe AD disease and multiple environmental allergies, supporting the theory of the atopic march.[7] There also is evidence that release of danger-associated proteins from an impaired barrier also may trigger asthma.[8] An analysis of the 2007 National Survey of Children's Health, a population-based study of 91,642 children aged 0 to 17 years, showed that children with AD had a higher prevalence of comorbid asthma (25.1% vs 12.3%), hay fever (34.4% vs 14.3%), and food allergies (15.1% vs 3.6%) compared to children without AD.[9] A recent article provided detailed information on how food and diet interplay with AD.[10]

## Triggers of Disease Flares

Triggers are the leading source of AD flare initiation, and avoidance of triggers is an important mechanism by which patients can control disease activity. Despite the best skin care and trigger avoidance, disease flares occur, sometimes due to ongoing inflammation and other times due to inability to prevent flares such as heat and humidity. A survey of patients with AD in Spain identified the following triggers: cosmetic products, clothing, mites, detergents/soaps, and temperature changes.[11] In childhood, wool also is a known trigger of AD.[12] Viral infections including respiratory syncytial virus may trigger the first onset of AD.[13] Patients with AD may become allergic to fragrance and metals causing disease exacerbation on exposure.[14,15] Food allergens contribute to approximately 40% of cases of AD in infancy but are not the cause of AD. The best evidence for improvement of AD with food allergen avoidance exists for egg white allergy.[16] Food avoidance programs should be developed in conjunction with an allergist, as it is no longer advised in many cases to completely withdraw foods; therefore, an allergist has to assess the level of allergic severity and the risk-benefit ratio of food avoidance or introduction.[17] Emotional stressors, heat, and humidity, as well as indoor heating in the winter months, can cause AD flares.[18]

A study by Silverberg et al[19] provided evidence of climate influences on the US prevalence of childhood eczema using a merged analysis of the 2007 National Survey of Children's Health and the 2006-2007 National Climate Data Center and Weather Service. Results showed that eczema prevalence was significantly lower when associated with higher annual relative humidity ($P=.01$), UV index ($P<.0001$), and highest-quartile air temperature ($P=.002$).[19] The Pediatric Eczema Elective Registry also showed that warm, humid, and high-sun-exposure climates are associated with poorly controlled eczema in affected patients.[20] The association of eczema with latitude as well as its negative association with mean annual outdoor temperature has been described by Weiland et al[21] in the ISAAC (International Study of Asthma and Allergies in Childhood) study. Long airplane flights in low humidity can trigger eczema in adults. Climate has been postulated to affect eczema through alterations in filaggrin and skin barrier function.[22] Indoor temperature and humidity regulation may be used adjunctively for daily flare prevention.

## Genetics and AD

Of 762 infants in a birth cohort with a parent with atopy in Cincinnati, Ohio, 39% developed eczema by the age of 3 years. Single nucleotide polymorphisms of IL-4Rα 175 V and CD14-159 C/T were linked to greater eczema risk at 2 to 3 years of age.[23] Monozygotic twins have a concordance rate of 0.72 to 0.86 versus 0.21 to 0.23 in dizygotic twins, demonstrating a strong genetic component in the development of AD.[24] Linkage to AD has been positively made to the epidermal differentiation complex on human chromosome 1q21, which contains the genes for filaggrin and other proteins such as loricrin. Other genes linked to AD include the serine protease inhibitor *SPINK5* (serine peptidase inhibitor, Kazal type 5) implicated in Netherton syndrome (triad of ichthyosis linearis circumflexa, bamboo hair, and atopic disorders); RANTES (regulated on activation, normal T-expressed, and secreted), which has been associated with severity of AD; IL-4; and IL-13.[5,25,26]

## The Hygiene Hypothesis

Atopic dermatitis is more common in wealthy developed countries, leading some to believe that hygiene and relative reduction in illness via vaccination have contributed to the rise of AD prevalence in developed nations.[13,27] There currently is evidence demonstrating that wild-type varicella infection confers long-standing protection against AD and mediates reduced total IgE and peripheral blood lymphocytes.[27]

## Grading of AD

Grading of AD is a subject of controversy, as there currently are no uniform grading scales.[28] A recent

outcomes group attempted to determine the best scale for disease monitoring. Schmitt et al[29] presented the Harmonizing Outcome Measures for Eczema (HOME) roadmap, which was intended to determine a core outcome set for eczema; however, because these outcome measurements have not yet been standardized, only the eczema assessment and severity index (EASI) scoring system meets criteria for standardization. In clinical practice, physicians often assign mild, moderate, or severe labeling based on their general sense of the disease extent using an investigator global assessment score.[28]

The EASI score is a well-validated composite score of AD severity based on 4 body regions: (1) head and neck, (2) trunk (including genital area), (3) upper limbs, and (4) lower limbs (including buttocks). The total area of involvement in each region is graded on a scale of 0 to 6, and AD severity is graded as a composite of 4 parameters (ranked on a scale of 0–3), including redness (erythema, inflammation), thickness (induration, papulation, swelling [acute eczema]), scratching (excoriation), and lichenification (prurigo nodules [chronic eczema]). The surface area of each region relative to body size is used as a multiplying factor, resulting in the following severity strata: 0=clear; 0.1–1.0=almost clear; 1.1–7.0=mild; 7.1–21.0=moderate; 21.1–50.0=severe; 50.1–72.0=very severe ($\kappa$=0.75).[30-32] The six area, six sign AD (SASSAD) score[32,33] is a similar score without adjustment for body surface area by region.[34]

An older, now less frequently used eczema score is the SCORAD, which addressed surface area by rule of nines and severity of 6 features—redness, swelling, oozing/crusting, scratch marks, skin thickening (lichenification), dryness (assessed in an area with no inflammation)—by region on a scale of 0 to 3. A subjective symptom parameter for itching and sleeplessness helped highlight that these comorbidities are important in gauging disease activity and impact on a child's life.[35]

## Natural History of AD

The clinical dogma has been that AD would improve with age, with reduction at grade school entry and perhaps full disappearance in adulthood; however, 3 recent surveys have suggested otherwise. The ISAAC group has found prevalence of AD in wealthy developed countries among children aged 6 to 7 years to be at a consistent increase.[36] A US-based survey from the National Health Interview Survey showed a 1-year prevalence of 10.2% of active AD in adults and 9.8% when occupational dermatitis was excluded.[37] Halvorsen et al[38] demonstrated that eczema prevalence is 9.7% in individuals aged 18 to 19 years.

A prospective trial of eighth graders followed from 1995 to 2010 demonstrated that AD persisted in 50% at school age. Persistent eczema into adulthood was associated with early-onset childhood allergic rhinitis and hand eczema.[39] In a cohort of hand eczema patients (N=368), 28% had AD and 39% had an atopic illness.[40] An association with allergic contact dermatitis and increased IgE to *Malassezia furfur* was further associated.[41]

## Conclusion

The role of triggers and allergens in disease activity in AD is an important consideration in children with AD and requires ongoing consideration with age and varied exposures. Understanding the grading of AD is important in evaluating clinical trial data. The natural history of AD has changed, which is important for the practitioner to note when counseling patients and guardians.

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