

# Therapeutic Intervention for Atopic Dermatitis to Prevent Atopic March

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Atopic march is defined as the sequential progression from atopic dermatitis (AD) to other atopic diseases, including food allergy (FA), allergic rhinitis (AR), asthma, and allergic rhinoconjunctivitis. It is well-known that eczema or AD is the first clinical manifestation, followed by asthma, allergic rhinitis, or both. Several endotypes that increase the risk of having other allergic diseases after AD onset have been identified: early AD onset, greater severity, disease persistence, having a FLG mutation, polysensitization, and parental atopy.

## Mechanisms underlying the atopic march

The pathogenesis of the development of AD and subsequent progression to other allergic diseases are not completely understood. The atopic march can occur because of sensitization through the disrupted skin barrier of AD, because similar genetic and environmental factors contribute to the development of atopic disorders. Impaired skin barrier helps penetration of variable antigens and activation of innate immune cells. Pathogen-associated molecular patterns and damage-associated molecular patterns are secreted secondary to tissue damage and antigen stimulation leads to release of cytokines (TSLP, IL-33, and IL-25) and Th2 responses. Recently, investigators showed neonates with top-quartile TEWL had an 18.7-fold increased risk (vs bottom quartile) of FA by 2 years of age if they had AD and a 3.5-fold increased risk of FA without AD. It supports that skin barrier dysfunction can promote systemic sensitization, and cutaneous sensitization may result in later development of allergic airway disease.

## Treatment approaches for primary prevention of allergic diseases

Many of the primary prevention options have been targeted in order to reduce the risk of AD development through skin barrier protection very early in life in high-risk babies. In this regard, two study results were published to journals in 2014. An emulsion-type moisturizer was applied daily during the first 32 weeks of life to 59 of 118 neonates at high risk for AD. The authors reported 32% reduction in AD diagnosis at age 32 weeks in 118 high-risk infants who received daily moisturizer since birth. However, they could not show the significant effect of emollient on the prevention of allergic sensitization based on the level of IgE antibody against egg white, although a higher proportion of infants with AD had allergic sensitization compared with infants without AD. However, it remains unclear whether regular application of emollients to the skin of neonates might decrease the risk of sensitization to food allergens. In a recent study, which used topical applications of a ceramide-dominant emollient in high-risk infants from birth to 6 months, showed decreased food sensitization at age 6 and 12 months when emollient therapy was introduced during the first 3 weeks of life. However, it was not powered to detect important differences or measure true food allergy or respiratory allergy outcomes.

## Treatment approaches for secondary prevention of the atopic march

A previous study examined the benefits of pimecrolimus therapy in 3- to 18-month-old patients with recent-onset AD. In this study, patients were randomized to pimecrolimus or vehicle and then open-label pimecrolimus for a planned further 3 years. As a result, no significant differences in the percentage of patients who developed FA, AR, or asthma were detected between the treatment and control groups. Other efforts have attempted to modify the atopic march using prophylactic antihistamines. A previous study evaluated whether the use of cetirizine compared with placebo for 18 months in infants with AD suppressed the onset of asthma. Asthma was defined when children had had any episodes of wheezing beyond the age of 6 months or more than 1 episode of persistent nocturnal coughing. No significant difference was observed between treatment with high-dose cetirizine or placebo with regard to development of asthma. In a subgroup of sensitized children, however, cetirizine delayed the occurrence of asthma compared with placebo.

There is growing evidence that *Staphylococcus aureus* is closely related to the pathogenesis of AD, disease flares, more severe skin barrier dysfunction, and AD phenotype. Therefore, it is postulated that cutaneous infection with *S. aureus* contributes to the development of atopic march by enhancing chronic skin inflammation and allergen sensitization. Interestingly, a recent study showed a novel role of *S. aureus* superantigen in augmenting allergen

ovalbumin induced atopic march in mouse model. However, there is no data regarding the preventive effect of *S. aureus* eradication such as bleach bath or antibiotics on the development of atopic march in children with AD.

Recently, biologic agents have been introduced and tried for the treatment of AD. Dupilumab, an IL-4 receptor mAb, has shown efficacy in the treatment of asthma and AD. Skin improvement in patients with AD was shown with tissue reversal of the immune and barrier abnormalities. Early blockade of the Th2 skewing with dupilumab in patients with severe AD might be effective for secondary prevention of the atopic march; however, longitudinal studies are needed to prove the efficacy of this approach. Larger studies are underway to evaluate whether comprehensive therapeutic strategies are effective for the prevention of the atopic march in children with AD.

## Conclusions

There is a strong link between early-life AD and allergic disease through an impaired skin barrier and upregulated inflammatory responses. Emerging evidence suggests that interventions to improve skin barrier function in neonates could reduce the occurrence of AD. Although the available data are not sufficient to make recommendations at this time, future researches will help determine whether therapeutic interventions for AD might lead to decreased allergic airway diseases.

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