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# The Allergic March of Childhood

## LEARNING OBJECTIVES

1. List the 4 disorders that comprise the Allergic March.
2. Identify the association between food allergies and atopic dermatitis in children and the later development of airways allergic disease.
3. Describe the basic tenets of the hygiene hypothesis.
4. List 3 categories of interventions that may reduce the risk of developing persistent asthma in children with atopy.

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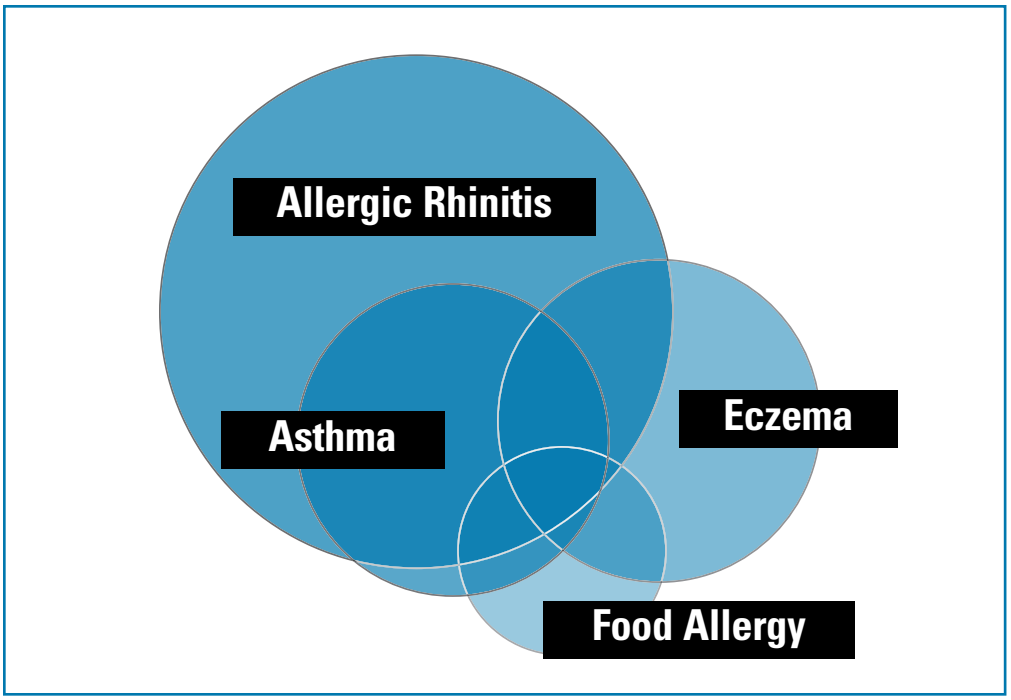
## HISTORICAL PERSPECTIVE

The "allergic march" refers to a subset of the allergic disorders that commonly begin in early childhood: atopic dermatitis or eczema, food allergies, allergic rhinitis, and allergy-associated asthma. The biological markers include skin-test sensitivities to inhaled and/or food allergens and the presence in the blood of specific immunoglobulin E molecules that recognize these allergens. This clinical and biological allergic response is called "atopy." Atopy also has a hereditary implication. In the 1920s, when this term was developed, atopy was observed to be a cluster of diseases that would tend to occur in families. Since then, we have come to understand that environments and lifestyles within families also contribute to genetic aspects to form the likelihood of developing atopic diseases.

Putting a drop of allergen on the skin of a sensitized individual and pricking the skin in that area leads to the development of the classic flush, wheal, and flare response within 10 to 15 minutes. In the 1920s, researchers first demonstrated the transfer of atopic sensitization to someone who was not previously sensitized. The serum of someone who was sensitized was injected under the skin of someone who was not sensitized. The area of the skin where the serum was injected was then pricked, and the same classic response occurred, which demonstrated that something in the serum was transferring these reactions.

**Figure 1**

**The overlap of atopic diseases in children and families.**




Atopic diseases tend to cluster in individuals and in families.

## PREVALENCE AND TRENDS

Atopic diseases are very common but vary in their peak prevalences during childhood. In 1 US study of children aged 4 to 7 years, the period prevalence of asthma was 20 to 30%; allergic rhinitis, 30 to 40%; atopic dermatitis, 5 to 10%; and food allergy, 2 to 5%.[1] By age 7 years, most children had at least 1 allergic condition. In addition, the atopic diseases cluster or overlap in some children and some families **(Figure 1)**.

The prevalence of asthma is increasing at about 50% per decade in a number of different countries.[2] Similar increases are being seen in prevalence data for other atopic diseases, including recent Centers for Disease Prevention and Control (CDC) data for skin-test sensitization.[3] These estimates in rising prevalence take into account the improvements in the diagnosis and identification of children with atopic conditions that have occurred over time.

A cross-sectional look at the prevalence of these disorders across countries reveals considerable variation for asthma, atopic dermatitis, and hay fever.[4] A wide range of reported prevalence can exist even within a single country; for example, a 10-fold variation in asthma prevalence has been demonstrated between different locales within India.[4] Children who grow up in rural areas of developing countries or in farming communities are several-fold to as much as 50-fold less likely to have allergic conditions and to manifest atopic sensitization or bronchial hyperresponsiveness when compared with children raised in nearby metropolitan areas.

## NATURAL HISTORY

Food allergy and atopic dermatitis typically appear first, not at birth, but beginning in the first 3 to 12 months of life, reaching their highest prevalence during the first 2 years of life **(Figure 2)**. Food allergy and atopic dermatitis then tend to reach a plateau or decrease in prevalence. In 1 study of children in metropolitan San Diego (Kaiser study), the most common atopic conditions in the first 2 years of life were atopic dermatitis (~10%) and food allergy (10–15%) that declined in prevalence to ~5% at ages 4 and 7 years **(Figure 2)**.[1] The earliest appearing food allergies in a German cohort were allergies to egg and cows' milk that reached a peak at about age 1 year and then stayed at similar levels through age 6, whereas allergies to wheat and soy reached peak prevalence at ages 5 to 6.[5,6] Allergies to nuts and shellfish tend to appear later and persist. Some children outgrow these disorders in the preschool years.

In contrast to food allergy and atopic dermatitis, allergic rhinitis and asthma have a somewhat delayed onset, steadily increasing in prevalence into the school years. In the Kaiser study, airways allergic diseases (allergic rhinitis and asthma) increased steadily in prevalence to age 7 years.[1] The prevalence of asthma tends to reach a plateau during school years, whereas the prevalence of allergic rhinitis continues to increase through college. Although allergies to foods peak in prevalence by ages 1 to 2 years, allergies to inhaled allergens begin to appear in children by age 3 years.[1] The incidence continues to increase throughout the school years, mimicking to some extent

**Figure 2**

**The allergic march of childhood.**

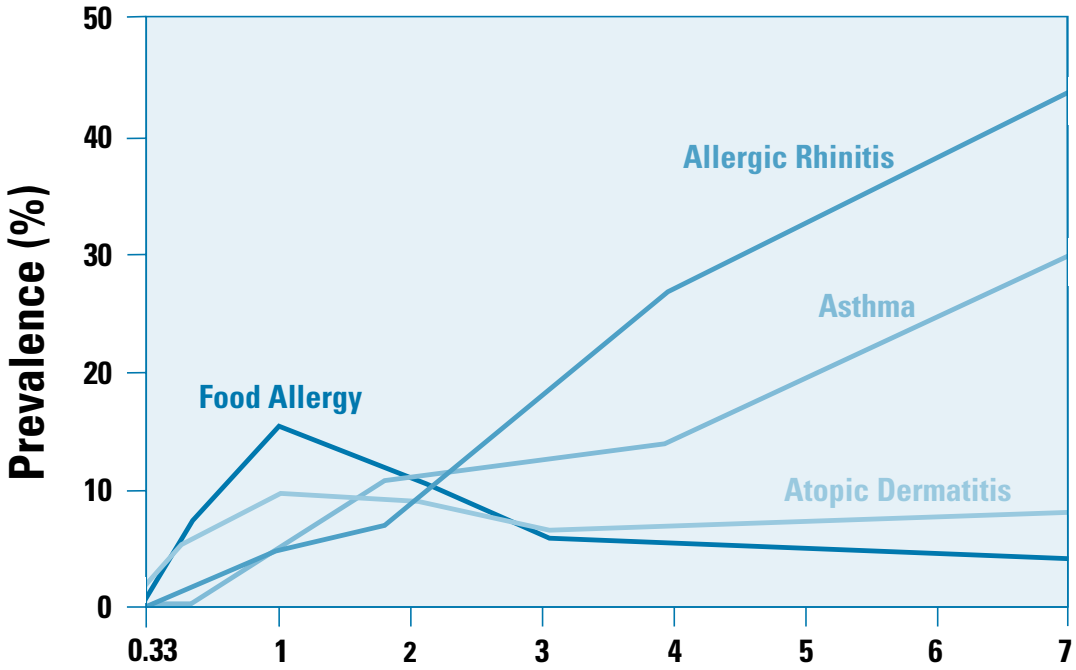



Figure legend:

There are 4 main characteristics of the Allergic March. (1) Food allergy and atopic dermatitis are typically seen first, not at birth, but beginning in the first 3 to 12 months of life. (2) These conditions can improve and be outgrown in many children during the preschool years. (3) Asthma and allergic rhinitis tend to declare themselves later, becoming increasingly common beginning at approximately 3 to 4 years and on into the school-age years. (4) The children who develop food allergy and/or atopic dermatitis often then develop allergic rhinitis and asthma; for example, atopic skin disease precedes and predicts airways allergic disease.

Zeiger RS, Heller S, Mellon MH, et al. Effect of combined maternal and infant food -allergen avoidance on development of atopy in early infancy: a randomized study. *J Allergy Clin Immunol.* 1989;84:72-89.[1]

what is seen for allergic rhinitis and asthma. Presumably, it takes a few seasons of exposure to inhaled allergens before the sharp rise in prevalence is seen. Finally, children who develop food allergies and atopic dermatitis often go on to develop airways allergic disease.

The "allergic march" is, therefore, a developmental pattern for a cluster of allergic diseases that begins in early childhood, revealing itself not only as trends in prevalence, but also as a common course of atopic manifestations in families and individual children **(Table 1)**. Food allergies and atopic dermatitis precede and predict the development of allergic rhinitis and asthma. Eczema and certain food allergies (milk, soy, and egg) tend to be outgrown or improve during the preschool years. In comparison, allergic rhinitis and other food allergies (nuts, seafood) tend to persist into adulthood, as does allergy-associated asthma. The severity of the atopic disorders is predictive of their persistence and progression.

## ROOT OF THE PROBLEM

The development of atopy early in childhood is linked with the later development of airways allergic disease. The problem of atopy begins when the nascent immune system develops aberrant immune responses to common, ubiquitous, and unavoidable exposures. Then, chronic ongoing exposures fuel inappropriate and prolonged injury and inflammation to the airways and aberrant repair of injured tissues. If these aberrant processes begin in early childhood and continue through critical periods of postnatal lung growth and differentiation, then the fully developed lung may differ from the normal lung. This may underlie the persistent asthma phenotype.

The hygiene theory states that nature may "immunize" against the development of allergic diseases and asthma through naturally occurring infections and microbial exposures of the respiratory and gastrointestinal tracts (and possibly the skin) in early life **(Figure 3)**. The classic paradigm is based on the typical, protective Th1 immune responses to microbial exposures that begin immediately after birth and after leaving the sterile environment of the mother's womb. When this process goes well, Th1-based immune development prevents pro-allergic Th2 immune development and atopy, thereby keeping environmental exposures from becoming allergens. Th1 immune responses improve host defense by inducing antiviral mechanisms that keep respiratory viruses from proliferating in respiratory epithelium and spreading down the airways. Th1 immune responses during airways injury and inflammation also inhibit aberrant repair processes that underlie pathologic

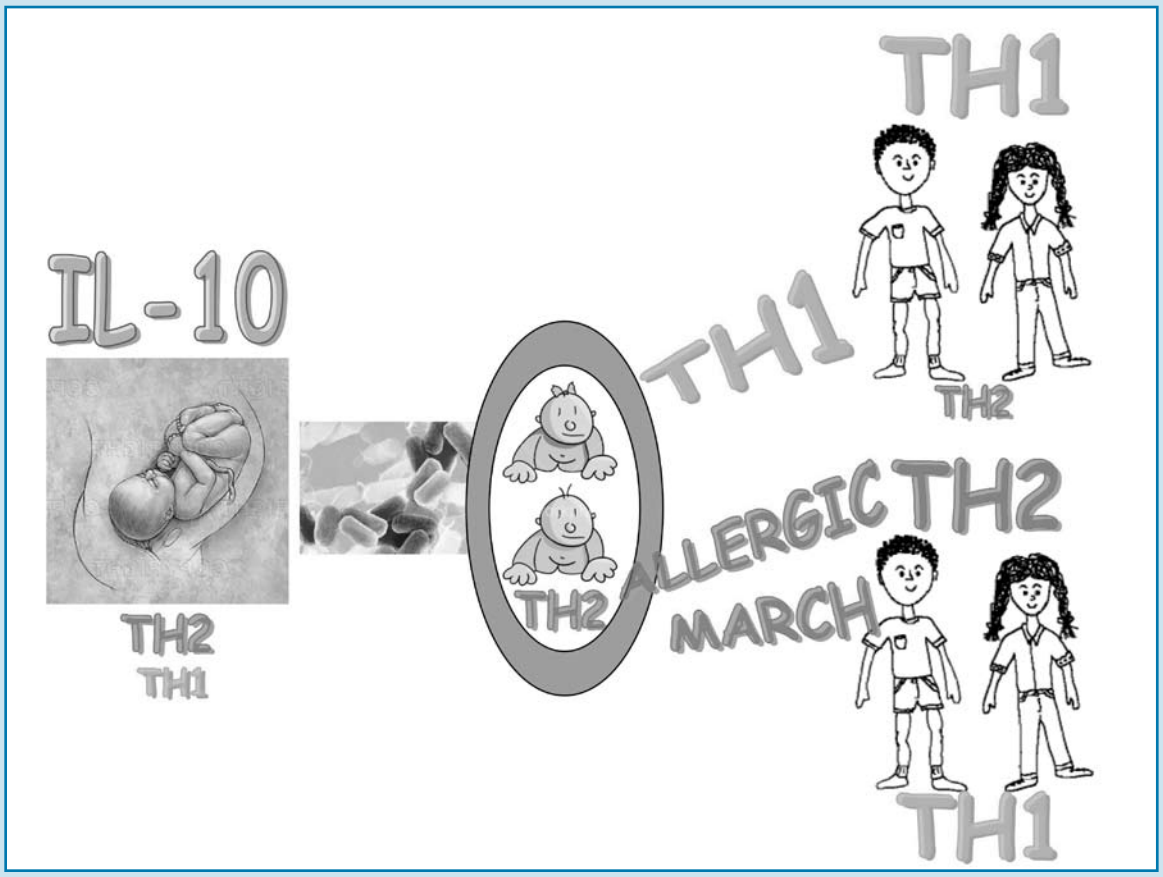
**Table 1**

### The Allergic March

1. The allergic march refers to a cluster of allergic diseases that develop in early childhood.
2. Food allergies and atopic dermatitis precede and predict asthma and allergic rhinitis.
3. Eczema and some food allergies (milk, egg, soy) tend to be outgrown or improve with age.
4. Allergic rhinitis and other food allergies (nuts, seafood) tend to persist.
5. Allergy-associated asthma persists but can improve; "asthma" without allergy tends to be outgrown or improve.
6. Disease severity predicts persistence and progression.

**Figure 3**

**The hygiene theory.**




Protective Th1 immune responses to microbial exposures begin immediately after birth. Th1-based immune development prevents pro-allergic Th2 immune development and atopy.

tissue changes in asthma. For example, interferon (IFN)-g inhibits mucous gland and smooth muscle hyperplasia, fibrotic repair processes, and mast cell activation. However, healthful immune responses also require the development of regulatory immune and cellular responses that keep allergic and autoimmune responses from developing. Microbes also induce regulatory immune responses (e.g., interleukin-10-producing regulatory T lymphocytes) to limit immune activation and inflammation when they are no longer needed, to prevent further tissue damage from "friendly fire."

## INTERVENTION AND PREVENTION

This model of atopy and asthma pathogenesis in early childhood can serve as the basis for a stratified approach to early interventions. Three categories of interventions have been described that may lead to optimal outcomes in children with atopy **(Table 2)**, that is interventions that may reduce the risk of developing persistent asthma. The first of these, "early interventions," targets disease processes early in an attempt to normalize conditions for lung growth and development. Examples of this approach include studies of the use of asthma controller therapies (e.g., inhaled corticosteroids (ICS)[7], leukotriene antagonists[8]) in young children with recurrent wheezing who are at risk for developing persistent asthma. These recent studies showed that these conventional controller therapies reduce asthma severity and exacerbations in young children, similar to their efficacy in older children and adults. However, those treated with ICS therapy for 2 years were not more likely to remain symptom-free after ICS was discontinued; such a "curative" effect has not yet been investigated or reported for leukotriene antagonists.

"Secondary preventions" are those that take place in young at-risk children prior to the establishment of chronic lung processes. Examples of some recent studies include:

- cetirizine in young children with atopic dermatitis (Early Treatment of the Atopic Child [ETAC] study)[9]
- topical calcineurin inhibitor in young children with new-onset atopic dermatitis (Study the Atopic March [SAM] study)
- pollen allergen immunotherapy in children with allergic rhinitis (PAT study)[10]

The third group, "primary preventions," aim to shape and optimize early immune development and, in doing so, override other aspects of risk. Examples of previous studies, beginning from birth or prior to birth, include supplementing the diet with lactobacillus or antioxidants (e.g., omega-3 fatty acids), reducing exposure to dust mite allergen and other major indoor allergens, and reducing exposure to allergenic foods.

**Table 2**

**Categories of Interventions and Preventions in Children with Atopy to Reduce the Risk of Developing Persistent Asthma**

1. Early interventions attempt to normalize conditions for lung growth and development.
2. Secondary preventions intervene in young at-risk children prior to the development of chronic lung processes.
3. Primary preventions try to optimize development of early immunity so children can overcome other aspects of risk.

## SUMMARY

In summary, the central developmental pattern of atopy or the allergic march is a familiar pattern in children. The development of early disorders such as food allergies and atopic dermatitis predicts the later development of the airways allergic diseases, allergic rhinitis and asthma. The severity of early disease predicts the persistence and progression of later disease. Early interventions may offer a way to shape and optimize immune development to lead to better outcomes in these children.

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1. **Which of the following allergic disorders comprise the "allergic march"?**
   A. atopic dermatitis or eczema
   B. food allergies
   C. allergic rhinitis and allergy-associated asthma
   D. All of the above

2. **The prevalence of asthma and other atopic diseases is increasing at about 50% per decade.**
   A. True
   B. False

3. **The prevalence of an atopic disease such as allergic asthma**
   A. varies among children from different countries but is typically very consistent in children from the same country.
   B. is solely related to genetic factors.
   C. is less in children raised in rural areas of developing countries compared to nearby metropolitan areas.
   D. is always greatest in school-aged children rather than younger children.

4. **Children who develop food allergies and atopic dermatitis rarely go on to develop airways allergic disease.**
   A. True
   B. False

5. **Atopy in early childhood**
   A. begins with aberrant immune responses to common and unavoidable exposures that may fuel inappropriate and prolonged injury and inflammation to the airways and aberrant repair of injured tissues, including tissues of the lung.
   B. is rarely linked to the later development of allergic rhinitis.
   C. induces immune responses during critical periods of postnatal lung growth and differentiation that protect against the development of airways allergic disease.
   D. protects against the development of the most common types of food allergies.

6. **The hygiene theory states that raising an infant in a very clean environment protects against the development of allergic diseases and asthma.**
   A. True
   B. False

7. **Which of the following does not correctly describe the hygiene hypothesis?**
   A. Protective Th1 immune responses to microbial exposures begin immediately after birth when the baby leaves the sterile environment of the mother's womb.
   B. Th1-based immune development prevents pro-allergic Th2 immune development and atopy, keeping environmental exposures from becoming allergens.
   C. Th1 immune responses induce antiviral mechanisms that keep respiratory viruses from proliferating in and spreading down the airways.
   D. T-regulatory immune responses during airways injury and inflammation promote aberrant repair processes that underlie pathologic tissue changes in asthma

8. **Healthful immune responses require the development of regulatory immune and cellular responses that keep allergic and autoimmune responses from developing.**
   A. True
   B. False

9. **Interventions designed to reduce the risk of developing persistent asthma in children**
   A. are thought to be ineffective except when employed during the prenatal period.
   B. specifically target those children who develop at least 2 other atopic disorders by the time they begin school.
   C. are based on the model linking atopy and asthma pathogenesis in early childhood.
   D. have been largely abandoned as a topic for current research.

10. **A central concept of the allergic march is that development of early disorders, such as food allergies and atopic dermatitis, predicts the later development of the airways allergic diseases, allergic rhinitis and asthma.**
    A. True
    B. False

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# The Allergic March of Childhood

## Medical Scientific Update

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