

Correspondence

A march by any other name



The allergic (or atopic) march refers to the natural history of allergic diseases as they develop during infancy and childhood. The march conventionally begins with atopic dermatitis (AD) and progresses to IgE-mediated food allergy (IgE-FA), asthma, and allergic rhinitis (AR).¹ The observation that allergic manifestations tend to develop in this stereotyped progression stems from decades of observational research, including birth cohort studies. It has also been the basis for large, longitudinal studies of individual disease associations. Together, the allergic march model and the studies on which it has been built have improved our understanding of allergic pathophysiology and our care of patients with allergy.

Nevertheless, as with any long-standing tenet of medicine, the concept of the allergic march has been the subject of healthy debate.² Several potential concerns about the allergic march model have been raised, a few of which we hope to address here. First, the original studies that described the characteristic acquisition of allergic manifestations during childhood were cross-sectional and, as such, described population-level patterns in disease prevalence. However, the individual disease associations that make up the allergic march have subsequently been confirmed in multiple longitudinal birth cohort studies^{1,3–6} and as such are now not in doubt. Nevertheless, we agree that future studies of the allergic march should continue to include longitudinal assessment of disease associations in individuals to ensure the highest level of rigor.²

A second concern that has been raised relates to the lack of association between childhood AD and adult-onset asthma. For example, in a longitudinal study of 1,246 healthy newborns, Stern et al³ found that the presence of AD by 2 years of age was associated with childhood-onset asthma (both inactive and persistent) but not adult-onset asthma. We agree that childhood AD and adult-onset asthma are unlikely to be related. However, we do not view this disconnect as a weakness in the allergic march model. Rather, we think that this reflects the nonallergic pathophysiologic mechanism for adult-onset asthma, possibly incited by age-related changes to the lungs and immune system.⁷ It is therefore not surprising that this particular asthma endotype is not associated with childhood

AD, as may be the case for other asthma endotypes that are nonallergic in nature. As we develop better ways to differentiate allergic vs nonallergic asthma and cease using umbrella terms to describe disease entities, as others have suggested,² we anticipate improved understanding about the diverse associations.

Third, others have suggested that the associations observed among allergic manifestations could occur by chance or be the result of confounding genetic or environmental risk factors, as opposed to representing causal relationships. This topic was the focus of a well-designed prospective study of 12 European birth cohorts, which concluded that the coexistence of AD, rhinitis, and asthma in the same child is more common than expected by chance alone.⁴ Although this coexistence could be solely the result of a shared set of polymorphisms that predispose patients to multiple allergic manifestations,⁸ studies suggest otherwise. For example, mutations in *FLG*, encoding filaggrin, confer susceptibility to AD but not to IgE-FA, asthma or AR in the absence of concurrent AD.^{9,10} Flohr et al¹¹ conversely found that AD was highly associated with development of IgE-FA, independent of *FLG* mutation status. Together, these and other observations suggest that although common genetic and environmental factors almost certainly contribute to disease development,⁸ additional immunologic mechanisms influence the risk of developing subsequent allergic manifestations.¹

Fourth, the fact that relatively few individuals progress through all the allergic manifestations has been noted as a potential weakness in the allergic march model. For example, Belgrave et al¹² used 2 prospective cohorts to identify 8 classes of allergic disease progression. The authors concluded that 3.1% of children followed a trajectory profile similar to that of the allergic march (AD first, followed by asthma, and then AR). We find this definition to be overly restrictive and suggest that AD followed by any of the other allergic manifestation is consistent with the allergic march. If one considers such individuals in the data from Belgrave et al,¹² the prevalence of the allergic march increases to 16.2%—a number that is more than half the total number of patients with AD in that cohort and more consistent with prior figures.

Together, we are learning that we must recognize the existence of nonallergic endotypes within our classic allergic disease entities and that it may be more appropriate to consider the existence of multiple routes on the allergic march (Fig 1). As we refine our understanding of this important model, new questions are becoming apparent. Why do certain individuals progress on the march, whereas others seem to skip allergic manifestations or halt such manifestations altogether? We may also find that certain routes on the march are more common than others. Addressing these fascinating and fundamental questions through the identification of additional genetic and environmental modifiers will facilitate patient risk stratification and the development of new interventional strategies to arrest this pathophysiologic cascade.

Disclosures: Authors have nothing to disclose.

Funding Sources: Dr Hill is supported by Institutional Training in Pediatric Research Grant T32 HD043021 from the Children's Hospital of Philadelphia National Research Service Award program and a Senior Fellow K-readiness grant. Dr Camargo is supported by grants R01 AI-114552, R01 AI-127507, and UG3 OD-023253 from the National Institutes of Health. Dr Paller is supported in part by the Walter J. Hamlin Professorship in Dermatology. Dr Spergel is supported by the Stuart Starr Endowed Chair of Pediatrics, The Children's Hospital of Philadelphia Eosinophilic Esophagitis Fund, a Food Allergy Research & Education Inc Clinical Network grant, grant U54 AI117804 from the Consortium of Eosinophilic Gastrointestinal Disease Researchers, and grant R01 AI-127507 from the National Institutes of Health.

Disclaimer: The contents of this article are solely the responsibility of the authors and do not represent the official view of the National Institutes of Health.

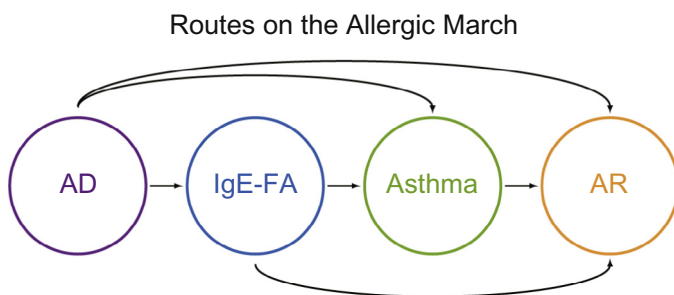


Figure 1. Routes on the allergic march. Although some individuals progress from atopic dermatitis (AD) through all 3 subsequent allergic manifestations (IgE-mediated food allergy [IgE-FA], asthma, and allergic rhinitis [AR]), it is also common to skip a manifestation or initiate the march later in the progression.

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