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Aeroallergens in eosinophilic esophagitis: Significant triggers or noise in the system?

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Since initial description in the early 1990s, eosinophilic esophagitis (EoE) has morphed from obscurity to a commonly identified condition in children with feeding issues and adolescents and adults presenting with dysphagia or food impaction.^{1, 2} In 2011, the updated eosinophilic esophagitis (EoE) consensus recommendation defined EoE as a chronic, antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.³ Thus, by definition, antigen exposure is the driving force of the observed eosinophilic inflammation leading to the symptoms suffered by EoE patients. Identification, followed by removal of exposure to the triggering antigen(s) is the cornerstone of one preferred treatment approach. Unfortunately, accurately identifying or adequately avoiding the offending antigen(s) can be challenging for some patients. In these situations, the alternative approach is treatment with swallowed topical steroids, which is usually successful.³

Recognition of the central role of antigen exposure in the pathogenesis of EoE underscores the importance of accurately identifying all potential triggers in any given patient. As the major function of the esophagus is carrying food from the oropharynx to the stomach, the esophageal mucosa is regularly bathed in large amounts of numerous food antigens. Thus, it is not surprising that food proteins have been implicated as the most common antigens triggering EoE by studies examining the efficacy of elemental diets, empiric diets eliminating the six most common food allergens (SFEDs) and targeted elimination diets (TEDs) based on the identification of food antigen triggers through the use of skin prick testing (SPT) and atopy patch testing (APT).^{4–9} Since many EoE patients form IgE specific to food allergens, it is somewhat surprising that empiric SFEDs outperform TEDs. This most likely occurs because although there may be an IgE-mediated contribution to EoE pathogenesis in selected patients, the yet to be clarified central immune mechanisms at play in EoE appear to be primarily non-IgE-mediated. The inability to confidently predict the food antigens involved based on the results of SPT and APT dictates monitoring the individual patient response to elimination diets and food reintroductions through symptom reports and repeated endoscopies until the optimal diet is determined.

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The lack of an adequate response to elimination diets in some EoE patients implies that antigens other than food allergens play a role. Several lines of evidence suggest that aeroallergens are capable of triggering EoE. Murine models of EoE have been induced by initial sensitization followed by challenging mice with the corresponding aeroallergen.¹⁰ Many patients with EoE also have asthma and/or allergic rhinitis and are sensitized to environmental inhalant allergens as evidenced by positive SPT and increased ocular, nasal and/or chest symptoms during their corresponding pollen seasons.³ Clinical experiences also suggest that EoE symptoms worsen in some patients during the spring and/or fall pollen seasons and the correlation between EoE disease activity and seasonal aeroallergen exposure has been documented in isolated case reports and studies implying a seasonal pattern of EoE diagnosis.^{11 – 12} Although esophageal aeroallergen exposure is miniscule in comparison to food allergen exposure, the ubiquitous nature of aeroallergens makes complete avoidance difficult. Suggested mechanisms for worsening of EoE during pollen seasons include exposure of the esophageal mucosa of the sensitized patient to the minute amounts of pollen inhaled into the nose or mouth and subsequently swallowed. In some patients ingestion of foods containing antigens that cross react with allergens in the pollens to which they are sensitized is suspected of playing a role.¹³ Often overlooked is the fact that allergic nasal mucous contains not only pollens, but sheets of eosinophils and the mediators that recruited them to the allergic reaction occurring in the nasal mucosa. Thus, it seems reasonable that repeatedly swallowing eosinophil rich nasal secretions might contribute to worsening of EoE, suggesting that aggressive treatment of allergic rhinitis in affected patients is warranted.

To further explore the potential role of aeroallergens in pediatric EoE, Kahey and colleagues elsewhere in this issue report their results from a retrospective chart review of pediatric patients diagnosed with EoE over a 10 year period extending through 2012 at New York Presbyterian Weill Cornell Medical Center.¹⁴ They compared both the dates of initial symptoms and dates of diagnosis with pollen counts from two local certified NYC pollen-counting stations. They found that the highest number of pediatric EoE patients in this area reported symptoms onset in July – September, correlating with higher grass pollen counts at one station and higher ragweed pollen counts at the other. The highest number of pediatric patients was diagnosed with EoE from October – December.

The results of the study by Kahey and colleagues are enticing and raise important questions while supporting the need for well-designed prospective studies examining the role of inhalant aeroallergens in triggering EoE in patients of all ages. For example, are multiple pollen-sensitized EoE patients more difficult to treat than those who are mono-sensitized? Is the EoE in patients regularly eating foods containing allergens that cross-react with the allergens in the pollens to which they are sensitized harder to control? Types of pollens and levels of pollen exposure vary geographically, affecting patterns of pollen sensitization as well as the timing of symptoms from pollen exposure. Thus, it seems reasonable to expect that the predominant pollen triggers of EoE might vary regionally. If pollens are capable of triggering EoE, it is likely that perennial allergens such as animal dander, dust mite, cockroach and molds also impact the ability to control EoE in selected patients sensitized and regularly exposed to these allergens. For example, the perennial cat dander exposure encountered by a cat allergic EoE patient with a cat in their home might increase the

difficulty of EoE management. However, the perennial nature of exposure might make it difficult to prove an association, unless strict avoidance measures resulted in significant timely improvement. Whether allergen immunotherapy has a positive or negative impact on the natural history of EoE in sensitized patients remains to be determined. To begin to address these and a multitude of other questions and to gain further insight into the immune pathogenesis of EoE, well-designed prospective studies of thoroughly characterized EoE patients in regard to not only food allergies, but perennial allergen sensitizations (animal dander, dust mites, molds) in addition to seasonal allergen sensitizations (tree, grass and weed pollens and certain molds) and documentation of differences in the timing and levels of exposures to these allergens is necessary. Additionally, the accurate monitoring of symptoms along with strategically timed endoscopies with biopsies will be required. Until the impact on EoE of perennial and seasonal aeroallergen exposure of sensitized patients is better defined, attempting to identify each patient's allergen sensitivities and exposures and working to minimize these exposures while aggressively treating co-morbid allergic disease such as allergic rhinitis, asthma and atopic dermatitis is required.

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