Asthma and food allergy: A nuanced relationship

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ABSTRACT

Asthma is one of the most common chronic health conditions that affect children and adults. It is associated with many comorbid conditions, particularly those along the allergic spectrum, such as atopic dermatitis, allergic rhinitis, and food allergy. The relationship between asthma and food allergies involves prognosis, management, and understanding of risk for severe reactions. Both conditions are heterogeneous and can change over time, which necessitates an individualized approach toward counseling and management. Long-standing associations of an increased risk for food allergy fatality in individuals who have asthma is not as straightforward or concrete as previously believed. It is important for clinicians to have a current understanding of the evidence about the relationship between asthma and food allergy to participate in shared decision-making and counseling with patients. This review will offer background and new perspective surrounding the nuanced relationship of asthma and food allergy.

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THE HETEROGENEITY OF ASTHMA

Asthma is a chronic condition that affects the lower airways and can cause both chronic and acute symptoms, including the potential for severe exacerbations and fatalities. Asthma affects ~8–10% of all children and adults in the United States, and is a leading cause of emergency department visits and hospitalizations, and can significantly decrease quality of life.[1] Although all patients with asthma share the two underlying hallmarks of this condition, inflammation of the lower airways and recurrent episodes of reversible bronchoconstriction, not all patients have the same type of inflammation or severity of disease.[2] Asthma often changes throughout childhood in regard to frequency and severity of symptoms but can also be lifelong for many.

Given the common yet heterogeneous nature of asthma, management can vary considerably from one person to another. In the current age of biomarkers, phenotyping, and endotyping, each patient with asthma should have his or her therapy tailored toward his or her type of inflammation, triggers, and underlying level of control.[2] As highlighted in the Global Initiative for Asthma guidelines,[3] management should entail counseling of each individual patient with regard to the need to continually assess the level of control, adjust therapy periodically according to the level of impairment, and review goals for management and outcomes over time. In addition, counseling each patient surrounding the risk of future exacerbation requires an understanding of the pathophysiology of asthma and prognosis associated with various phenotypes and response to therapy. For example, a child with intermittent cough or wheeze during viral upper respiratory infections who responds well to as-needed use of bronchodilators with no history of a need for oral corticosteroids has a different risk compared with a teenager who was recently hospitalized for a fifth severe exacerbation in the past 2 years. Now more than ever, clinicians need to be comfortable discussing the variability associated with a diagnosis of asthma as well as options for management.

THE HETEROGENEITY OF FOOD ALLERGY

For the purpose of this review, food allergy refers to immediate onset immunoglobulin E (IgE) mediated hypersensitivity reactions. Food allergies also affect ~8–10% of all children and adults.[4] Food allergy reactions are acute in onset and vary in severity from cutaneous urticaria after direct contact with an allergen to life-threatening anaphylaxis after ingestion. The understanding of the heterogeneity of food allergy has expanded rapidly over the past decade. Similar to asthma, food allergy management is now individualized and can be tailored to each patient.[5] Although we

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lack reliable biomarkers or an ability to phenotype patients with food allergy as can be done with asthma, it is now understood that food allergies do not convey the same risk for each patient. It is becoming increasingly recognized that the amount of food allergen needed to cause any reaction, including anaphylaxis, varies greatly across individuals with the same food allergy.[5] Severe reactions to ingestion of trace amounts are extremely rare, and 50% of the population with peanut allergy will not elicit any reaction, let alone anaphylaxis, until they ingest ≥ 200 mg of protein. Of course, this also means that 50% of the population with peanut allergy will experience reactions to doses < 200 mg and identification of these individuals who are highly sensitive is equally an important part of understanding risk.

Although a full review of nuances surrounding risk with food allergy lies outside the scope of this review, recent publications have addressed this at length.[5–8] In addition to improved understanding surrounding risk from various eliciting doses of different food allergens, the approach toward strict avoidance of the offending food allergen has also changed in recent years. It is now widely accepted that ingestion of baked egg and baked milk is possible in the majority of children with egg and milk allergies.[9] The concept of egg and milk ladders is also being used in efforts to expand the diet with safe foods and help patients make management easier.[10] Patients with pollen fruit syndrome can often ingest the food that causes symptoms if it is cooked or processed in some manner.[11] Lastly, the implementation of oral immunotherapy (OIT) into clinical practice has fundamentally changed our understanding and approach toward management.[12]

THE ATOPIC MARCH

Atopy is strongly associated with genetic predisposition and often presents with atopic dermatitis early in infancy, followed by the development of food allergy, followed in later years by environmental allergies and asthma.[13] This relationship is complex but often reflects underlying T helper 2 inflammation. Evidence to date has identified multiple associations with early life exposures and the development of various forms of atopy but, at this time, does not support that atopic dermatitis causes food allergy to develop or that food allergy causes asthma, etc.[13] There are many children with no history of atopic dermatitis who still develop food allergy and asthma, and vice versa. New cohorts have demonstrated heterogeneity in the type of atopic dermatitis and variable risk for subsequent development of allergies or asthma.[14] Lastly, new approaches toward primary prevention of atopic dermatitis and atopy in general by focusing on daily application of emollients beginning in the first few days of life and throughout the first year have shown variable results.[15] All of this demonstrates a complex relationship between early onset atopic dermatitis and subsequent development of allergies and asthma.

FOOD ALLERGY AND ASTHMA PROGNOSIS

Although evidence does not demonstrate that food allergy causes asthma to develop, it is associated with the prognosis. The modified asthma predictive index (mAPI) is a validated tool that can be used to help predict the likelihood of persistent asthma at 6, 8, and 11 years of age for infants and toddlers who have four or more episodes of wheezing in a year.[16] The mAPI includes major and minor criteria that can be applied to assess prognosis (Table 1). IgE sensitization to milk, egg, or peanut is included as one of the minor criteria, which reflects underlying T helper 2 inflammation, which is associated with persistent asthma. Young children with a positive mAPI have a significantly higher likelihood of having persistent asthma symptoms at school age compared with those who have a negative mAPI.[16]

FOOD ALLERGY AND ASTHMA SYMPTOMS

Although many parents or patients may question the role of their diet in causing isolated acute or chronic asthma symptoms, clinicians can help reassure that this is an unlikely trigger or cause of symptoms. The clinical history is the best tool to determine if specific foods may be contributing to asthma. There is no role for random or panel food allergen testing in the evaluation of anyone with chronic asthma symptoms or without a history consistent with acute onset IgE-mediated food allergy reactions. The 2020 rhinitis practice parameter update includes a consensus-based statement recommending against food skin-prick or serum IgE testing in the routine evaluation of patients presenting with symptoms of allergic rhinitis, and this

Table 1 **Criteria for the modified asthma predictive index**

At Least 1 Major Criterion	Or at Least 2 Minor Criteria
Parental physician-diagnosed asthma	Wheezing unrelated to colds
Physician-diagnosed atopic dermatitis	>4% peripheral eosinophilia
IgE sensitization to at least one aeroallergen	IgE sensitization to milk, egg, or peanut

IgE = Immunoglobulin E.

can be extrapolated to asthma as well.[17] In addition, there are no provisions in any national or international asthma guidelines to include food allergy testing in the diagnosis or evaluation of asthma.

There are instances in which foods may be contributing to asthma symptoms that clinicians should be aware of when obtaining a detailed clinical history. Patients who have both IgE-mediated food allergies and asthma may experience acute onset respiratory symptoms as part of an allergic reaction to their food allergen. This can occur through ingestion but has also been reported through inhalation of allergen if it is aerosolized in close proximity.[18] This is almost universally associated with stove-top heating or steaming of milk or seafood, and extremely unlikely from exposures such as proximity to someone opening a fresh bag of peanuts.[19] Approximately 5% of adults with asthma experience acute-onset lower respiratory symptoms after ingestion of foods that contain high amounts of sulfites (Table 2).[20] This is not an IgE-mediated phenomenon, and the exact pathophysiology has yet to be determined; however, this has been described almost exclusively in children and adults with severe or steroid-dependent asthma. A common misconception perpetuated by medical professionals is that ingestion of milk may worsen mucus production, which then leads to unnecessary avoidance of dairy products for those with asthma or persistent cough. This myth has been properly debunked, and, although drinking milk may alter the texture or sensation of mucus already present, it will not cause increased amounts.[21]

Clinicians can serve an important role in guiding patients who have concerns about food causing their asthma by providing clarification and discussing the importance of limiting unnecessary avoidance. Steering patients toward an evidence-based approach of the diagnosis and management of these conditions can prevent delays in achieving proper control of symptoms by avoiding unhelpful approaches such as dietary avoidance of specific foods for unwarranted reasons.

ASTHMA AND RISK FOR SEVERE FOOD ALLERGY REACTIONS

Food allergy fatalities are, thankfully, extremely rare events, and the vast majority have occurred in adolescents and young adults.[22,23] In addition, peanut and tree nuts are the allergens associated with a majority of fatalities. Asthma has long been considered a risk factor given the association of comorbid asthma, with registries dating > 20 years ago.[22,23] In two separate publications, Bock *et al.*[22,23] reported on 63 fatalities from food allergy between 1994 and 2006. Among those included in the reports, only one did not have asthma as a comorbid condition and the remainder either had confirmed asthma (75%) or it was unknown (24%). A larger analysis of fatal anaphylaxis from all causes between 1999 and 2010 identified 164 deaths from food allergy reactions, among which only 16.5% had associated asthma.[24] What is missing from these and similar reports is the context of asthma severity, level of control, use of controller medications, and whether lower respiratory symptoms occurred during the fatal event.

The widespread utilization of OIT into clinical practice and through large clinical trials has advanced our understanding of how various cofactors can increase severity of food allergy reactions (Fig. 1).[7,8] A recent review on fatal food anaphylaxis by Anagnostou *et al.*[25] could not identify asthma as a risk factor and concluded that "Fatal outcomes are so rare that currently, there are no evidence-based risk factors that can be used clinically to predict who might be more at risk of fatal reactions," which was also supported by a

Table 2 **Sulfite concentrations associated with various foods**

Sulfite Concentrations	Examples
>100 ppm sulfites: very-high levels, avoidance recommended for those with sulfite sensitivity	Dried fruits, bottled lemon and lime juice, wine, molasses, sauerkraut, grape juices, pickled cocktail onions
50–99.9 ppm sulfites: moderate-to-high levels, avoidance typically advised for those with sulfite sensitivity	Dried potatoes, wine vinegar, gravies, fruit toppings, maraschino cherries
10–49.9 ppm sulfites: low-to-moderate levels, may cause symptoms for those with sulfite sensitivity	Pectin, fresh shrimp, corn syrup, pickles and/or relish, corn starch, hominy, maple syrup, imported jams and jellies, various cheeses, avocado dip and/or guacamole, ciders and cider vinegars
<10 ppm sulfites: very-low sulfite levels, generally do not pose risk for those with sulfite sensitivity	Malt vinegar, canned potatoes, beer, dry soup mix, soft drinks, frozen pizza and pie dough, gelatin, coconut, domestic jams and jellies, grapes, high fructose corn syrup

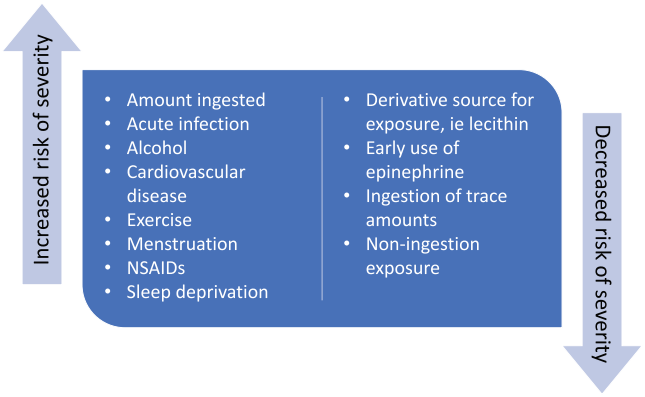

Figure 1. *Cofactors that influence the severity of food allergy reactions.*

meta-analysis from the Global Allergy, Asthma European Network.[8]

Earlier in this review, the heterogeneity of both asthma and food allergy was discussed. Given the variability and nuance involved with both of these diagnoses, it is not accurate to simply state or assume that anyone who has both asthma and food allergy is at risk for a more severe or potentially fatal reaction. Does a 5-year-old child with intermittent asthma and egg allergy that causes cutaneous urticaria but who tolerates baked egg carry the same risk for severe reaction as a 17-year-old adolescent with poorly controlled severe asthma and a history of anaphylaxis to peanut? Of course not. We now have the ability to risk stratify not only asthma and food allergy separately but, more importantly, in the context of discussing management with patients.

HOW TO DISCUSS RISK WITH PATIENTS

For clinicians to communicate risk with individual patients, they first must understand risk themselves. In an oft-quoted infographic from Shaker *et al.*,[26] the evidence demonstrates that the annual incidence of fatal food-induced anaphylaxis in an unselected population is ~1 in 10 million, which is on par with the risk of dying from a lightning strike. However, statistics such as these can be difficult for patients to comprehend. As such, once clinicians understand that the overall risk from food allergy fatality is exceedingly low and that when these tragedies do occur, the majority occur in adolescents and young adults who did not receive epinephrine in a timely manner, they can then discuss accordingly with patients. The impact of anxiety with a diagnosis of food allergy has been increasingly recognized in recent years, which has led to not only increased awareness but can and should change the dialog surrounding the risk with food allergy.[27] When patients or parents of children with food allergies are not counseled on evidence-based realistic risks associated with various exposures, they may encounter outdated fear-based messaging that lacks context and perspective.[28] Clinicians who diagnose or care for patients with food allergy must proactively engage in these conversations and help patients understand their own level of risk, particularly in relation to asthma and food allergy.

Once diagnosed with food allergies, most patients still experience accidental ingestion and reactions at some point, but these events are relatively rare, with various surveys reporting 0.3–0.5 occurrences per year, which vary by age and geographic location.[29] With proper education surrounding avoidance measures and counseling on reading labels and communication with food handlers along with reminders surrounding immediate access to epinephrine and early administration, patients can lead a confident, safe life while avoiding their allergens.

OIT changes this conversation, however. Given that OIT involves intentional daily ingestion of one's known food allergen, this changes the assessment of risk for those with asthma because they are now knowingly exposed to their allergen on a regular basis, as opposed to infrequent accidental ingestion. As such, the assessment of asthma severity and control and discussion of risk for reaction from each daily OIT dose needs to occur.[12,30] Patients undergoing OIT become engaged in active self-management and the need to appreciate the potential risk associated with increased asthma symptoms and their daily OIT dosing. Children and adolescents with severe and/or poorly controlled asthma are typically considered suboptimal candidates for OIT. In addition to focusing on gaining good asthma control before starting OIT, patients also need to be counseled on dose adjustments when they experience an increase in asthma symptoms. Education and communication with regard to the risk for patients with food allergy and asthma is a perfect scenario for shared decision-making.[31] This allows each patient to make decisions surrounding his or her individualized management based upon an understanding of risks and benefits with various options and his or her own values and preferences.

CONCLUSION

The relationship between asthma and food allergy is complex and nuanced. One does not cause the other. Foods are rarely a cause of isolated acute or chronic asthma symptoms, but lower respiratory symptoms can occur during an acute food allergy reaction. Previous recognition of the comorbidity of asthma in individuals who suffer from food allergy fatalities requires renewed perspective and context. Discussion of risk needs to occur with each patient, and this is now a highly individualized conversation that can

incorporate understanding surrounding the heterogeneity of both asthma and food allergy. Optimizing asthma control should be the goal for every patient not because of comorbid food allergies but to improve quality of life and reduce symptoms. Lastly, the perspective offered in this review will, hopefully, be obsolete in just a few years as additional evidence further accumulates and changes our understanding of these conditions. Although change can be hard, our patients benefit when we embrace shifting paradigms and follow an evidence-based path toward care.

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