

Food allergy and asthma

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ABSTRACT

Food allergies (FA) and asthma commonly coexist in patients, with asthma affecting 14% of school-age children and with FA affecting up to 8% of children in the United States. Compared with children without FA, children with FA are two to four times more likely to have asthma. The timings of food sensitization and FA seem to be strong predictors of asthma onset in childhood; results of studies show that food sensitization in the first few years of life is associated with increased odds of developing early wheeze. Having multiple FAs as opposed to a single FA further compounds the risk of asthma. Reciprocally, there is a strong association between the presence of food sensitization and/or FA and poor asthma control, including increased asthma-related health-care utilization and emergency medication use. Asthma is a risk factor in ~75% of fatal food-related anaphylaxis cases. Therefore, besides FA education and management, patients with FA and with asthma should optimize medical therapy of their asthma and receive asthma education, including identifying possible asthma triggers. Furthermore, allergists should ensure that asthma must be well controlled before conducting oral food challenges. Timely administration of epinephrine is lifesaving and remains the first-line treatment during food-induced anaphylaxis, especially in patients with asthma. Among those biologic therapies that have been highly effective in treating asthma, omalizumab and dupilumab are now also being studied as treatments for FA.

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Food allergies (FA) and asthma are increasingly prevalent, with asthma affecting 14% of school-age children,¹ and FA affecting up to 8% of children in the United States.² The atopic march, which classically begins with atopic dermatitis, followed by immunoglobulin E (IgE)-mediated FA, asthma, and allergic rhinitis, is considered a progression of allergic conditions with shared genetic and environmental predisposing factors and allergen-specific T-helper 2 (Th2) responses.³ Therefore, it is not surprising that many patients who are food sensitized and/or have FA also have asthma. Although it is not well understood whether or how one condition leads to the other or if they simply coexist, the presence of both conditions has important implications for clinical management and potential outcomes.

FOOD SENSITIZATION AND FA AND RISK FOR CHILDHOOD ASTHMA

Compared with children without an FA, children with an FA are two to four times more likely to have

asthma.⁴ A large retrospective birth cohort study of ~30,000 children estimated that the presence of an FA was associated with more than twice the risk of developing asthma.³ Similarly, Vermeulen *et al.*⁵ showed an increased risk of developing asthma in children with an FA at age 1 year. Subsequent development of asthma was significantly associated with peanut (odds ratio [OR] 1.74), milk (OR 1.38), and egg (OR 1.60) allergy.³ Food sensitization and FA, particularly to egg, have been associated with the development of asthma, irrespective of eczema history.⁶ Interestingly, children with an egg allergy had an increased risk of developing asthma, regardless of whether the child did (relative risk [RR] 1.92) or did not (RR 2.6) outgrow the allergy at 4 years compared with children without any history of egg allergy.⁵

Timing of food sensitization and FA seem to be strong predictors of asthma onset in childhood, particularly in the first few years of life. A meta-analysis by Hill *et al.*³ demonstrated that food sensitization in the first 2 years of life was associated with an increased odds of childhood asthma (OR 2.8 [95% confidence interval {CI}, 2.1–3.9]). A study in a high-risk birth cohort of 620 infants with a positive atopic family history, showed that food sensitization at 1 year of age, defined as skin-prick testing results of at least 3 mm wheal to a specific food, was associated with an adjusted RR of 1.63 for development of wheeze at 18 months.⁷

Children with multiple FAs also have a higher risk of asthma than children with one FA. Vermeulen *et al.*⁵ specifically showed 1.69 and 2.76 increased odds of developing asthma in children with one FA at one year of age and in children with more than one FA at one year of age, respectively. The odds of developing

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asthma also seem to be cumulative with each additional FA (OR 1.43, 2.75, 3.94, and 5.44, for one, two, three, and four FA, respectively).⁸ It seems that children with asthma and multiple FAs, as opposed to children with asthma and one FA and children with asthma and no FA, also have greater small airway obstruction, indicated by significantly decreased predicted forced expiratory flow at 25% to 75%, which suggests that having multiple FAs may be a marker for increased asthma severity.⁹

The modified asthma predictive index (mAPI), which is referenced in the Global Initiative for Asthma (GINA) and the National Asthma Education and Prevention Program (NAEPP) guidelines, incorporates food sensitization in its assessment of children at 1, 2, and 3 years of age to predict asthma risk at 6, 8, and 11 years of age.¹⁰ A positive mAPI score is based on a history of four or more wheezing episodes, with at least one physician diagnosis, and one of three major criteria (parental asthma, physician-diagnosed atopic dermatitis, sensitization to at least one aeroallergen) or two of three minor criteria (wheezing unrelated to colds; peripheral eosinophilia at least 4%; and allergic sensitization to milk, eggs, or peanuts) and is significantly associated with an increased probability of future asthma.¹⁰ Although the mAPI is often used in asthma clinical trials, results of studies indicate that it can be a useful clinical tool for determining asthma development and therapeutic management, such as using inhaled corticosteroids, in children with atopy and at high risk.¹⁰

ASTHMA AND THE PROBABILITY OF FOOD SENSITIZATION AND FA

Compared with children without asthma, children with asthma were more than twice as likely to have food sensitization.¹¹ In a study of 504 pediatric patients with asthma, 45% had serum IgE-mediated sensitization to at least one of the six common allergenic food groups (egg, milk soy, peanut, wheat, fish).¹¹ Specifically, children with asthma were found with increased odds of sensitization to egg, peanut, milk, and shrimp.¹²

In children with asthma, there also seems to be a strong association between the presence of food sensitization and FA and poor asthma control, defined as increased daytime symptoms, asthma-related health-care utilization, corticosteroid use, and lower functional status scores.¹² This was further illustrated in a study by Wang *et al.*,¹¹ in which the prevalence of food sensitization was increased incrementally with asthma severity, reported as 14.9% in those without asthma, 20.6% in those with asthma without recent emergency department visits, and 35.0% in those with asthma with recent emergency department visits.

ASTHMA IN FOOD-INDUCED ANAPHYLAXIS

According to the European Academy of Allergy and Clinical Immunology Taskforce on Anaphylaxis,¹³ the Joint Task Force on Practice Parameters,¹⁴ and the National Institute of Allergy and Infectious Diseases,⁴ a history of asthma is a significant risk factor in ~75% of patients with fatal food-related anaphylaxis.^{11,16} Large studies done on individuals with peanut and tree nut allergy showed that patients with asthma were more likely than those without asthma to have severe reactions, characterized by increased odds of severe lower airway obstruction (bronchospasm) during acute FA reactions.¹⁵⁻¹⁶ Even a history of mild asthma has been associated with increased odds (OR 2.7) of bronchospasm during FA reactions.¹⁶

Asthma, regardless of severity, is one of several factors listed as a safety consideration when planning for and conducting oral food challenges (OFC) in addition to administering food oral immunotherapy (OIT). In a study of OFCs at a pediatric tertiary care center, the rate of asthma was significantly higher among those for whom oral challenge failed (47% versus 72%; $p = 0.001$).¹⁷ According to the 2020 American Academy of Allergy, Asthma, and Immunology (AAAAI) Work group report¹⁸ on conducting OFCs, asthma should be well controlled when beginning OFC because asthma itself can theoretically increase the pretest probability of OFC failure.

MANAGEMENT AND PREVENTION

Given that suboptimal asthma control increases the risk for severe and fatal food-related anaphylaxis, it is imperative to identify early comorbid asthma in patients with FA and to enforce compliance with any controller therapies needed. Asthma may be assessed by specific symptoms on clinical history, fractional exhaled nitric oxide value, and office spirometry or pulmonary function tests with appropriate bronchodilator response. Medical management includes rescue β -agonists and asthma controller therapies, such as daily inhaled corticosteroids, long-acting β -agonist combinations, long-acting muscarinic antagonists, and/or leukotriene modifiers, based on asthma severity, as put forth in the GINA and the NAEPP guidelines.¹⁰

Comorbid conditions, such as obesity and gastroesophageal reflux disease, can often complicate asthma control. Therefore, it is particularly important to consider the diagnosis and management of reflux in patients who have persistent or recurrent asthma symptoms. Patients in the community often have the misperception that food is a trigger for chronic asthma when the food may be exacerbating underlying reflux symptoms, thereby contributing to poor asthma control. Furthermore, reactions to food additives by patients

with asthma are rare (Pepper and Glaum, Additives and preservatives: Role in food allergy). Although the causal link between FA and asthma has yet to be determined, dietary modification has been shown, by a few studies, to be essential to asthma control.¹⁹ Conducting trials with H₂-receptor blockers or proton-pump inhibitors to assess the efficacy of these inhibitors on asthma symptoms may also be considered.

Another cornerstone in asthma control is trigger avoidance and management. Although upper respiratory tract infections are a common asthma trigger in children, environmental history and allergy testing to aeroallergens are helpful in identifying possible environmental factors and in reducing risks for asthma-related complications. Asthma is one of several risk factors for fatal food-induced anaphylaxis, so symptom recognition and preparedness are essential when encountering severe food reactions and asthma exacerbations. All children with FA and with asthma should receive both asthma and FA education. In fact, written emergency action plans specifically highlight asthma as a risk for more severe reactions.¹ Asthma exacerbations and food-induced allergic reactions with predominantly respiratory symptoms can present similarly. Families and caregivers should understand that, even if the patient has predominantly asthma symptoms as part of an allergic reaction, the first-line treatment is epinephrine, whereas albuterol or other rescue inhalers may be adjunct treatment.

Patients with an FA who are undergoing OFC should be advised to continue all their asthma controller therapies before challenge. The 2020 AAAAI Work group¹⁸ on OFCs recommends that an OFC should be rescheduled or delayed if the patient has active respiratory symptoms, including coughing or wheezing, and/or having used a short-acting β -agonist in the preceding 48 hours. For patients who are undergoing food OIT, treatment may need to be deferred or withheld until the asthma is well controlled (Scurlock and Jones, Food allergy OIT).

CURRENT AND EMERGING BIOLOGIC IMMUNOMODULATOR THERAPIES

In the past 2 decades, highly effective biologic therapies have been developed to target specific immunologic mediators in asthma, especially in patients with mainly Th2 driven inflammation. Omalizumab, a humanized IgG1 monoclonal anti-IgE antibody that binds IgE, is approved for the treatment of individuals ages ≥ 6 years with poorly controlled moderate-to-severe persistent allergic asthma and perennial aeroallergen sensitization.²⁰ Dupilumab, a monoclonal antibody that targets the α -subunit of the interleukin (IL) 4 receptor (IL-4R) that blocks IL-4 and IL-13 signaling pathways,²⁰ is approved

for individuals ages ≥ 12 years with moderate-to-severe eosinophilic asthma and steroid-dependent asthma.

It has been shown that the addition of dupilumab to maintenance asthma regimens demonstrates efficacy in reducing the oral glucocorticoid dose and is associated with fewer exacerbations and improvements in lung function.²⁰ Other biologics also approved for the treatment of severe asthma in the past 5 years include mepolizumab and reslizumab, which are monoclonal antibodies directed against IL-5 and result in decreased numbers of peripheral blood and tissue eosinophils, and benralizumab, which binds the IL-5 receptor α (IL-5R α), which results in the cell death of eosinophils and basophils via antibody-dependent cell-mediated cytotoxicity.

These aforementioned biologics, in particular, omalizumab and dupilumab, are now being studied as treatments for FA (Nadeau and Chen, Biologic therapy for food allergy). Omalizumab has been evaluated as an adjunct therapy to OIT, which allows for potentially faster and effective desensitization in patients who are very sensitive.²⁰ Dupilumab is currently undergoing clinical studies to evaluate its safety and efficacy as an adjunct therapy to peanut OIT, as monotherapy for peanut allergy, and in comparison with omalizumab and placebo in multifood OIT.²⁰

SUMMARY

Asthma and FA are frequent comorbid atopic conditions. Although the exact relationship between FA and asthma is not clearly understood, asthma seems to impact the development and natural history of FA and vice versa. Concurrent management of both FA and asthma is paramount to decreasing risks and morbidity. The biologic therapies that have already been approved for asthma are now being studied as therapeutic modalities for FA. Their potential contribution to improved outcomes for these patients remains to be seen.

CLINICAL PEARLS

- Children with FAs are at least twice as likely than those without FAs to have asthma.
- Children with two or more FAs have increased odds of developing asthma as compared with children with one FA.
- Food sensitization and/or FA in children with asthma is associated with worse asthma control, including increased daytime symptoms, corticosteroid use, and asthma-related health-care utilization.
- OFCs are contraindicated if the patient has suboptimally or poorly controlled asthma.
- Asthma history is a risk factor in $\sim 75\%$ of fatal food-related anaphylaxis cases; timely administration of

epinephrine is lifesaving and remains a first-line treatment during food-induced anaphylaxis, especially in patients with FA and with asthma.

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