

## Authors and Disclosures

Julie Wang<sup>a</sup> and Andrew H. Liu<sup>b</sup>

<sup>a</sup>Mount Sinai School of Medicine, New York, New York, USA and <sup>b</sup>National Jewish Health and University of Colorado Denver School of Medicine, Denver, Colorado, USA

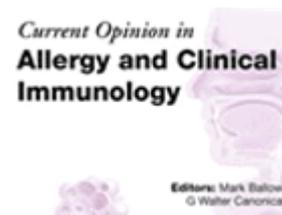
### Correspondence to

Julie Wang, MD, Department of Pediatrics, Box 1198, Mount Sinai School of Medicine, One Gustave L Levy Place, New York, NY10029, USA Tel: +1 212 241 5548; fax: +1 212 426 1902; e-mail: [Julie.wang@mssm.edu](mailto:Julie.wang@mssm.edu)

## From Current Opinion in Allergy and Clinical Immunology Food Allergies and Asthma

Julie Wang; Andrew H. Liu

Posted: 05/18/2011; Curr Opin Allergy Clin Immunol. 2011;11(3):249-254. © 2011 Lippincott Williams & Wilkins



### Abstract and Introduction

#### Abstract

**Purpose of review** To consider the possible links between food allergy and asthma.

**Recent findings** Food allergy and asthma coexist in many children, and recent studies demonstrate that having these comorbid conditions increases the risk for morbidity. Children with food allergies and asthma are more likely to have near-fatal or fatal allergic reactions to food and more likely to have severe asthma.

**Summary** Although a causal link has not been determined, increased awareness of the heightened risks of having both of these common childhood conditions and good patient/parent education and management of both conditions can lead to improved outcomes.

#### Introduction

Food allergy and asthma are two common childhood conditions that are familiar to many. Children with both food allergies and asthma are at increased risk for severe anaphylaxis, including fatal and near-fatal anaphylaxis, particularly if the asthma is uncontrolled.<sup>[1]</sup> In a study<sup>[1]</sup> of food allergy-related fatalities, 25 patients had sufficient information regarding asthma status and of these, 24 had underlying asthma. Although there is a close association between food allergy and asthma, it is unclear whether these just coexist in children predisposed to atopic conditions (i.e. atopic march) or a causal relationship exists. This review will discuss the relationship between food allergy and asthma observed in recent studies and explore the possible links between these conditions.

#### Epidemiology of Food Allergy and Asthma

Both food allergies and asthma appear to be increasing in prevalence in the past few decades. Determining the prevalence of asthma accurately is difficult due to the lack of a gold standard diagnostic tool and the variable phenotypes of asthma. On the basis of self-reports of asthma, the incidence more than doubled between 1980 and 1996,<sup>[2]</sup> and, now, nearly one in 10 children (9.4%) have asthma based on data from the 2008 National Health Interview Survey (CDC website: <http://www.cdc.gov/asthma/asthmadata.htm>; accessed 7 March 2011). The prevalence of food allergy is difficult to measure because a rigorous determination of food allergy status relies on the gold standard double-blind, placebo-controlled food challenges (DBPCFCs), which is labor-intensive, time-consuming, risky, and generally infeasible in large epidemiological population studies. Although data derived from surveys and serology (measurement of specific IgE) have various limitations, these methods have provided consistent estimates of food allergy prevalence. A US study,<sup>[3]</sup> which used several national health databases and healthcare surveys, concluded that 3.9% of US children report having food allergy, an 18% increase in prevalence between 1997 and 2007. A more recent study<sup>[4••]</sup> using serologic assessment of food allergy determined that 4.2% of children in the United States have clinical food allergy. This study also found that black race, male sex, and childhood age were risk factors for food allergy; these same demographic features are also risk factors for asthma prevalence and poor outcomes.<sup>[5]</sup> Looking at specific foods, the rates of peanut allergy in the United

States and UK have doubled in the past decade, and now affects approximately 1% of children.<sup>[6••,7]</sup>

Because food allergy and asthma are well known atopic conditions, there is a strong perception in the community that these are closely linked.<sup>[8•]</sup> This is reflected in the increasing literature investigating the relationship between food/diet and asthma.<sup>[7]</sup> In a survey of 156 patients attending an asthma and allergy clinic, 73% of people believed that foods induced their asthma symptoms.<sup>[9]</sup>

## Role of Food Allergy in Asthma

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Food allergies often affect young children, can precede the development of asthma, and are considered a risk factor for persistent, problematic asthma in young children.<sup>[10–12]</sup> Several studies have investigated whether one predisposes to the other. Sensitization to egg, one of the most common food allergens in childhood, has been shown to be a risk factor for sensitization to aeroallergens and asthma later in life.<sup>[13,14]</sup> Although, the majority of children eventually develop tolerance to egg,<sup>[15]</sup> a recent case–control study<sup>[16]</sup> investigated whether the natural history of food allergy has any impact on the risk for developing asthma. Sixty-nine young children with allergies to egg and/or fish, on the basis of a convincing history of reaction or oral food challenge, were followed until school age and then assessed with spirometry, methacholine challenge, and allergy testing. All of the children had developed tolerance to egg by school-age, and 17% of those with fish allergy developed tolerance at follow-up. The authors found not only that sensitization to egg was a marker for increased risk for later asthma, but that presence of asthma symptoms and bronchial hyperreactivity (BHR) were not associated with persistence of the food sensitization. Furthermore, there was no association between the severity of allergic reaction to foods and risk of developing asthma.

Further support for the association between food allergy and asthma stems from epidemiologic studies demonstrating a high rate of food allergies in asthmatic children. In a study<sup>[17]</sup> using serum collected from the National Cooperative Inner City Asthma Study (NCICAS) that enrolled children with asthma from the inner city, the prevalence of food sensitization was strikingly high, with 45% of the children having serologic evidence of immunoglobulin E (IgE)-mediated sensitization to at least one of the six most common food allergens (milk, egg, wheat, soy, peanut, or fish). Four percent of the group had high IgE levels that indicated very high likelihood (95% positive predictive value) of clinical reactivity. A more recent study<sup>[4••]</sup> using data from the National Health and Nutrition Examination Survey (NHANES) also demonstrates an increased prevalence of food sensitization (to milk, egg, peanut, and shrimp) and food allergy risk categories in those with asthma as compared with those without asthma. This increased prevalence is particularly evident in those reporting current asthma and having had emergency department visits for asthma in the previous year. Although 14.9% of those with no asthma had sensitization to at least one food, only 0.9% had levels that suggested likely food allergy; this is in contrast to 27.5% of those with asthma having sensitization to at least one food, of which 1.9% likely have clinical food allergy.

Several studies have found that children with asthma and concurrent food allergies tend to have worse asthma morbidity than those with asthma alone. In the NCICAS cohort above, children with sensitization to foods had increased asthma morbidity, with higher rate of asthma hospitalization, and higher requirement of steroid medications.<sup>[15]</sup> Similarly, the NHANES data demonstrated that patients with asthma and food allergy are more likely to have a severe asthma exacerbation as compared with asthmatic patients without evidence of food allergy [odds ratio (OR) = 6.9, 95% confidence interval (CI) 2.4–19.7].<sup>[4••]</sup> Although these studies defined food allergies based only on serologic testing, Roberts *et al.*<sup>[18]</sup> found that children with life-threatening asthma (as defined by exacerbation requiring ventilation) were more likely to have clinical food allergy (history of immediate reactions, positive oral food challenges or food-specific IgE levels greater than the threshold level that predicts clinical reactivity with a 95% positive predictive value) than children who had nonlife-threatening asthma exacerbations (OR 8.58; 95% CI, 1.85–39.71). Simpson *et al.*<sup>[19]</sup> specifically examined the role of clinical peanut allergy with asthma and found similar results. The authors reported that having peanut allergy (on the basis of a positive history of reactions, peanut-specific IgE >15 kU/l and positive skin test to peanut) was associated with increased rates of hospitalization and use of systemic steroids as compared with asthmatic patients without peanut allergy.

Another study<sup>[20]</sup> using clinical reactivity to define food allergies found a dose effect for the number and severity of food allergies with the likelihood of having a diagnosis of asthma. Those with severe allergic reactions to foods had higher rates of asthma, and those with milk, egg, and peanut allergies were independently associated with increased rates of asthma. This is in contrast to the aforementioned study<sup>[16]</sup> that found no correlation between the severity of egg or fish allergy with the risk of developing asthma. Another finding from Schroeder *et al.*<sup>[20]</sup> indicated that children with food allergy presented with asthma at an earlier age than those without a history of food allergy. Interestingly, there was no association between asymptomatic food sensitization and asthma prevalence or severity.<sup>[20]</sup>

Recently, several studies have examined the role of food allergy in the development of asthma by focusing on objective measurements of lung dysfunction associated with asthma (e.g. bronchial hyperresponsiveness). A prospective study<sup>[21••]</sup> of an unselected cohort of children found that having cow's milk allergy was a predictor for subsequent BHR and airway inflammation. Children with IgE-mediated milk allergy at 7 months of age diagnosed by oral food challenge had increased risk of elevated BHR (using histamine challenge) and exhaled nitric oxide at 8 years of age. A separate study<sup>[22••]</sup> also found increased BHR (using methacholine challenge) in food allergic children as compared with healthy children without food allergy; as well, these children did not have asthma or allergic rhinitis. In a classic study by James *et al.*,<sup>[23]</sup> oral food challenge-induced asthma was associated with increased BHR; rarely, increased BHR was observed in a participant with a positive food challenge but without respiratory symptoms. Even in children with asthma, respiratory symptoms were observed in only 26% of food allergic children during oral food challenge.<sup>[22••]</sup> Among those without asthma, 47% of food allergic children had increased BHR as compared with 17% of those without food allergy, demonstrating a limitation of using BHR as a surrogate marker for asthma,<sup>[22••]</sup> as other studies have shown.<sup>[24]</sup> However, it is also possible that airway inflammation as evidenced by BHR may be a precursor of later asthma as some hypothesize.<sup>[25,26]</sup>

## Role of Asthma in Food Allergy

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Although it is known that food allergic reactions can trigger lower respiratory symptoms<sup>[27]</sup> and occupational asthma,<sup>[28,29]</sup> food allergy generally does not present with chronic or isolated respiratory symptoms.<sup>[27]</sup> Bock<sup>[30]</sup> reported on 279 asthmatic patients with a history of food-induced wheezing who underwent DBPCFC; 60% had a positive challenge and, of these, 40% had wheezing as one of several symptoms, but only five participants had isolated wheezing. Similarly, James *et al.*<sup>[31]</sup> reported on DBPCFCs performed for 320 patients with food allergy and atopic dermatitis. Sixty-four percent of the challenges were positive, and of these, 27% had pulmonary symptoms as part of the allergic reaction, with only 17% of these wheezing, and fewer patients having isolated wheezing.

Although respiratory symptoms may not always accompany food allergic reactions, a concurrent diagnosis of asthma appears to worsen the general prognosis for food allergy.<sup>[32,33]</sup> For example, the presence of asthma is a predictor for persistent cow's milk allergy,<sup>[31,32]</sup> and asthma is a risk factor for fatal food anaphylaxis.<sup>[1]</sup> In a recent study<sup>[34•]</sup> of anaphylaxis prevalence in the UK, those with asthma had significantly higher rates of anaphylaxis as compared with those without asthma. Of note, the most common triggers for anaphylaxis in that population were drug and food allergies. Similar results were seen in a study<sup>[35•]</sup> from a managed care organization in northern California, which found a five times higher risk of anaphylactic shock due to food allergies in asthmatic patients as compared with those without asthma. The risk of anaphylaxis was higher in those with severe asthma (hazard ratio 8.23, 6.59–10.27) as compared with those classified as having nonsevere asthma (hazard ratio 5.05, 4.39–5.80). Recently, suboptimally controlled asthma is reported to be a risk factor for adverse reactions during oral immunotherapy to peanut.<sup>[36••]</sup>

## What is the Link Between Asthma and Food Allergy?

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It is clear that asthma and food allergies coexist for many and having both worsens the prognosis. However, there are still unanswered questions regarding the relationship between these entities. It is possible that greater atopy in general is associated with more severe, persistent, and/or earlier-onset asthma and food sensitization, with no direct causal relationship between food ingestion and asthma exacerbations.

A major limitation of current epidemiologic studies investigating rates of food sensitization based on serology alone is that clinical reactivity to potential allergens is not assessed; it is unclear how many of those patients have real clinical reactivity to foods.<sup>[4••,17]</sup> In those studies, sensitization to more foods and higher levels of sensitization correlated with the severity of asthma, but considering the possibility that positive tests were in part due to cross reactivity to environmental allergens, these tests may be indirectly measuring the level of their environmental allergies. It is well known that cross reactivity between foods and environmental allergens can lead to positive skin tests or serum IgE levels to foods that may not be clinically relevant. For example, people with birch tree pollen allergies can test positive to peanut,<sup>[37••,38••]</sup> and those with dust mite and/or cockroach allergies can test positive to shrimp.<sup>[39]</sup> Asarnoj *et al.*<sup>[38••]</sup> recently reported that children sensitized to peanut but not birch more often reported symptoms to peanut ingestion as compared with children sensitized to both peanut and birch (76 vs. 46%,  $P = 0.002$ ). Furthermore, it has been shown that sensitization to environmental allergens can be significant triggers for asthma.<sup>[40]</sup> In a study<sup>[41]</sup> in which 20% of children with reported food allergy also had asthma, the association between food allergy and asthma was stronger when participants were stratified for concurrent sensitization to aeroallergens.

It should be noted that for a subset of patients, respiratory symptoms, including wheezing, are induced by foods up to

30% of the time for food allergic individuals<sup>[22\*\*,30,31]</sup> and several reports have indicated that severe asthma is risk factor for fatal food anaphylaxis.<sup>[1]</sup> Food-induced respiratory symptoms should be managed differently from asthma exacerbations triggered by other common triggers, with injectable epinephrine as the treatment of choice as opposed to inhaled beta-agonists. Thus, the evidence supporting a causal relationship between food allergies and asthma should not be ignored.

## Management of Coexisting Asthma and Food Allergies

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Whether or not food allergies and asthma are simply associated with each other or causally related, patients with both diagnoses are at risk for poor outcomes and should be well managed to prevent potential morbidity and mortality. Accurate diagnoses of asthma and food allergies are the first step. Assessments of asthma symptoms, triggers, and response to bronchodilators are essential to establish the diagnosis.<sup>[42,43]</sup> Conventional asthma management, well detailed in national and international guidelines,<sup>[44,45]</sup> can achieve and maintain good control in the large majority of people with asthma. The recently published national guidelines by the National Institute of Allergy and Infectious Diseases provides a comprehensive review of the diagnosis and management of food allergy.<sup>[46\*\*]</sup> The history should be used as a guide to determine appropriate testing, including the use of oral food challenges.<sup>[46\*\*]</sup> As with any medical condition, alternative diagnoses should be investigated, and for the patient with possible asthma and food allergies, exercise-associated food-induced anaphylaxis, gastro-esophageal reflux, and vocal cord dysfunction are some that should be considered.<sup>[42,43]</sup>

There may be situations in which food allergy should be suspected in asthmatic patients, warranting appropriate work-up. These may include acute life-threatening asthma with no identifiable triggers or outside the typical season for viral infections, or highly atopic children with severe persistent asthma resistant to medical treatment in whom the history linking food ingestion to asthma may not be reliable due to fragmented care (e.g. children in foster care or children alternately living with divorced parents).

Once the diagnoses of both food allergy and asthma are confirmed, education regarding food allergy and asthma management is essential. Patients need to be educated about the importance of food allergen avoidance and how to read food labels as well as to the appropriate use of emergency medications in case of allergic reaction.<sup>[46\*\*]</sup> Because uncontrolled asthma is a risk factor for severe anaphylaxis, optimal management and compliance with controller asthma medication is required. Of note, patients can often be confused about whether symptoms are due to asthma or food allergy; if suspicion of food-induced anaphylaxis is high, they should not rely on short-acting bronchodilators; in this situation, injectable epinephrine is the treatment of choice.

A treatment that can potentially target both food allergies and asthma are anti-IgE antibodies. Leung *et al.*<sup>[47]</sup> performed a double-blind, randomized, dose-ranging trial of TNX-901 in 84 patients with a history of peanut allergy.<sup>[47]</sup> After 4 months of treatment, patients receiving the highest dose experienced significant decreases in symptoms with peanut challenge as compared with the placebo group. The median threshold of sensitivity to peanut increased from 178 mg peanut protein (equivalent to one peanut) to almost nine peanuts (2.8 grams). Although 25% of patients were able to tolerate over 20 peanuts posttreatment, another 25% failed to develop any change in tolerance to peanut indicating that the treatment response can be variable. A study<sup>[48]</sup> using omalizumab (Xolair; Genentech USA, Inc. and Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA), which is already approved by US Food and Drug Association for the treatment of allergic asthma, was initiated for the treatment of peanut allergy, but discontinued for safety concerns related to the pretreatment oral peanut challenge. Combination therapy of anti-IgE and allergen immunotherapy was investigated as a method to decrease adverse reactions to immunotherapy in order to allow increased safety and efficacy,<sup>[49]</sup> and there is currently an on-going trial of omalizumab in conjunction with milk oral immunotherapy.<sup>[50]</sup>

## Conclusion

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Having food allergy and asthma places people at greater risk for morbidity and mortality. With heightened awareness of the relationship between these two entities, management of food allergy and asthma and recognition of food-triggered asthma exacerbations may improve treatment and prevent severe reactions. A multifaceted approach to managing this subset of patients can lead to optimal care.

## Sidebar

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### Key Points

- Asthma and food allergy may often coexist.

- Food allergic individuals with asthma are at higher risk for severe asthma.
- Concurrent asthma places food allergic individuals at higher risk for severe allergic reactions to foods, particularly if the asthma is uncontrolled.
- Food allergy should be considered in children with acute life-threatening asthma exacerbations with no identifiable triggers, and in highly atopic children with severe persistent asthma resistant to medical management.
- In patients with coincident food allergy and asthma, educate about heightened risks, and manage both well.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 272).

#### Acknowledgements

J. W., M.D. is funded in part by a grant from the National Institutes of Health/National Institute of Allergy and Infectious Diseases; K23 AI083883.

*Curr Opin Allergy Clin Immunol.* 2011;11(3):249-254. © 2011 Lippincott Williams & Wilkins