

Food Intolerance and Childhood Asthma

What is the Link?

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Abstract

Food allergies and asthma are increasing worldwide. It is estimated that approximately 8% of children aged <3 years have food allergies. Foods can induce a variety of IgE-mediated, cutaneous, gastrointestinal, and respiratory reactions. The most common foods responsible for allergic reactions in children are egg, milk, peanut, soy, fish, shellfish, and tree nuts. Asthma alone as a manifestation of a food allergy is rare and atypical. Less than 5% of patients experience wheezing without cutaneous or gastrointestinal symptoms during a food challenge. In addition to acute respiratory symptoms, a food allergy may also induce airway hyper-responsiveness beyond the initial reaction. This process can occur in patients who do not demonstrate a decrease in lung function during the reaction. Inhalation of aerosolized food particles can cause respiratory symptoms in selected food-allergic individuals, particularly with fish and shellfish during cooking and aerosolization. However, this has not been demonstrated with the smelling of, or casual contact with, peanut butter. Rarely, food additives such as sulfating agents can cause respiratory reactions. This reaction occurs primarily in patients with underlying asthma, particularly in patients with more severe asthma. In contrast, there is no convincing evidence that tartrazine or monosodium glutamate can induce asthma responses. Although food-induced asthma is rare, it is common for patients and clinicians to perceive that food can trigger asthma. Avoidance of specific foods or additives has not been shown to improve asthma, even in patients who may perceive that a particular food worsens their asthma.

However, patients with underlying asthma are more likely to experience a fatal or near-fatal food reaction. Food reactions tend to be more severe or life threatening when they involve the respiratory tract. The presence of a food allergy is a risk factor for the future development of asthma, particularly for children with sensitization to egg protein.

The diagnosis of a food allergy includes skin or *in vitro* testing as an initial study when the history suggests food allergy. While negative testing generally rules out a food allergy, positive testing should be followed by a food-challenge procedure for a definitive diagnosis. The CAP-RAST FEIA (CAP-radioallergosorbent test [RAST] fluoroenzyme immunoassay system [FEIA]) is an improved *in vitro* measure that in some cases may decrease the need for food challenges. However, similar to skin testing and the RAST, there is good sensitivity but poor specificity, such that specific challenges are often warranted.

Approximately 8% of children aged <3 years experience food allergies and about 2% of adults are similarly affected.^[1,2] Both food allergies and asthma are increasing in children worldwide. Egg, milk, peanut, soy, fish, shellfish, and tree nuts are the most common food allergens confirmed in a number of well controlled, blinded food challenges.^[3,4] The most frequently observed clinical manifestations of IgE-mediated food allergies are cutaneous and gastrointestinal symptoms.^[3,5] Nevertheless, foods can also induce

a wide spectrum of respiratory symptoms that can range from rhinorrhea to life-threatening anaphylaxis with severe respiratory compromise. Other respiratory symptoms induced by food include sneezing, nasal congestion, throat swelling, coughing, shortness of breath, and wheezing. These symptoms are significantly more likely to occur in patients with underlying asthma. It is a common concern of patients and parents that a food may be triggering asthma. However, food allergy-induced lower respiratory tract

reactions most often occur as part of the broader constellation of a systemic allergic reaction and rarely as an isolated symptom.

This article discusses the various relationships between food allergy and asthma in order to help clinicians identify when patients should be further evaluated. The diagnosis of food allergy, including skin testing, *in vitro* testing, and food challenges, is also reviewed.

1. Food Allergy-Induced Asthma

Food allergy as an underlying trigger for asthma is rare. Studies of food challenges suggest an overall reaction rate between 1% and 5% for isolated food-induced wheezing or respiratory symptoms. In a study of 300 pediatric and adult asthmatic patients, 12% had a history of food allergy suggested by clinical symptoms and positive skin testing, but only 2% had a confirmed allergy using a double-blind, placebo-controlled food challenge.^[6] In a selected study of almost 600 pediatric patients from a tertiary care center at the National Jewish Medical and Research Center (Denver, CO, USA), 68% had a history of food-induced asthma^[7] upon food challenge. Sixty percent of these patients had positive challenges, 24% experienced wheezing during the challenge, but only 2% exhibited isolated wheezing. Businco et al.^[8] evaluated children with atopic dermatitis for allergy to cow's milk and egg. Nine of 70 children (13%) had asthma symptoms after the challenge. Three of nine children experienced symptoms within 2 hours following the challenge. Only one (1.4%) child presented with isolated asthma. None of the children with an egg allergy presented with asthma symptoms.^[8]

In other well controlled studies of children with food allergy only 1–2% of patients experienced wheezing as an isolated response without cutaneous or gastrointestinal symptoms.^[9,10] In our CHOP study of >1000 open food challenges in pediatric patients with food allergies at the Children's Hospital of Philadelphia (Philadelphia, PA, USA), we were able to document isolated respiratory symptoms in <5% of our patients.^[4]

It is unlikely that avoidance of specific foods in asthmatic patients without a history of food allergy will have any effect on overall asthma control. One small investigative, single-blind pilot study of 22 children with asthma evaluated the effect of milk and egg avoidance on asthma.^[11] Parents had the option to self-select their child for the avoidance group or the control group. The children in the avoidance group who were able to perform peak flow testing had improvements in their peak expiratory flow rate after milk and egg avoidance. The children in the control group did not show any improvement in peak flow readings.

In contrast, Woods et al.^[12] conducted a more formal randomized, double-blind, crossover, placebo-controlled trial investigat-

ing a population of 20 adults with asthma to assess whether milk consumption had an effect on asthma. Half of the patients perceived that their asthma became worse with ingestion of dairy products, with none having positive skin prick tests to cow's milk. Patients complied with a dairy-free diet throughout the study and were then challenged with the equivalent of 300mL of cow's milk or placebo. They found no difference in symptoms or in lung function after the milk challenge compared with placebo. In addition, patients who perceived that dairy products triggered their asthma were no more likely to react to these products than patients without this perception. Nguyen^[13] found very similar results with no objective effect of milk ingestion on forced expiratory volume in 1 second (FEV₁) and forced vital capacity 20 minutes after a milk challenge in 25 asthmatic adults without a prior history of milk allergy. The latter two studies were performed in a more rigorous scientific manner than the pilot study on milk and egg avoidance in children. The current recommendation is that general (milk) food avoidance for the treatment of asthma is not recommended.

2. Food Allergy-Induced Airway Hyper-Responsiveness

In a small subset of food-allergic asthmatic patients, ingestion of food may result in increased airway hyper-responsiveness beyond the normal challenge period. In one study, 26 patients with asthma and a previous diagnosis of food allergy were evaluated for airway reactivity changes after a food challenge.^[14] All patients had a prior history of food allergy confirmed by a double-blind placebo-controlled challenge or a convincing history confirmed with a collaborative positive skin test. Twelve of 22 positive food challenges involved lower airway symptoms including cough, chest tightness, and/or wheeze. Significant increases in airway hyper-responsiveness measured by a methacholine challenge occurred in 7 of 12 patients who experienced chest symptoms during positive food challenges. A decrease in FEV₁ was observed in only one of these seven patients during the challenge, although measurements could not be obtained at all timepoints. Foods responsible for positive challenges were egg, wheat, milk, soy, and fish.

This study indicates that specific foods may increase airway hyper-responsiveness without a demonstrable decrease in spirometry during the challenge in a selected subset of patients with food allergy and baseline moderate-to-severe persistent asthma. However, a study in eleven adults with a history of food-induced wheezing and positive skin prick tests to the suspected foods was not able to document a difference in airway hyper-responsiveness after a food challenge compared with a placebo challenge.^[12]

3. Response to Inhalation of Food Particles

Exposure to airborne food particles can cause respiratory symptoms in food-allergic individuals. These reactions are almost exclusively reported with fish and shellfish. Patients with a known fish allergy can develop wheezing or rhinitis when exposed to food particles during cooking or manipulation of the food.^[15] Similar reactions have been reported to rice,^[16] legumes,^[17,18] and milk.^[19]

Roberts et al.^[20] identified 12 children with reported reactions on inhalation of food particles. Nine children and their families agreed to a double-blind placebo-controlled challenge with the causative food by inhalation. Five children had acute asthma symptoms during the challenges. In addition, two children had late-phase reactions manifested by a decrease in lung function with fish, chickpea, and buckwheat indicated as causative food. Conversely, in a study of 30 children with peanut allergy, no reactions were noted on smelling or casual remote contact with peanut butter.^[21] These studies indicate that only if a food protein is aerosolized can a patient with known sensitivity to that food react to inhalation.

4. Food Additive-Induced Asthma

Food additives have been implicated in respiratory or other allergic reactions. Despite this common perception, there is a paucity of well controlled, double-blinded studies to support this observation and concept. Despite thousands of known food additives,^[22] relatively few have been linked to provoking bronchoconstriction in asthmatic patients.

The actual incidence of reactions to food additives is quite low but generally overestimated by the public. European studies have extrapolated the prevalence as <0.5% in the total population, and 2% in an atopic population.^[23] A large British survey of >15 000 patients reported the prevalence of adverse reactions as 0.01–0.23%.^[24] This prevalence rate of reactions to additives is much lower than the prevalence of allergic reactions to foods (2–8% in pediatric populations).^[1,2] Asthmatic responses to a variety of additives are not as prevalent as once suspected. Diets restricted in food additives have not shown to be of benefit in asthmatic patients and should not be routinely recommended.^[25,26]

The most well known of the additives for which evidence supports an association of sensitivity and asthmatic reactions is sulfating agents. These agents have long been employed in food processing and have been utilized as preservatives and antioxidants as well as being ingredients in a number of inhalation and parenteral medications.^[27] Sodium metabisulfite is the most commonly used chemical preservative and it has been estimated that 1–3mg of sulfites are consumed per person per day with an additional amount in those that consume beer and wine.^[28] In

1986, the US FDA moved to regulate the use of sulfites in fresh fruits and vegetables and the previously common practice of using these agents in salad bars is no longer in practice. In addition, the FDA regulation requires specific labeling on products that exceed 10 parts per million. Foods that are highest in sulfite content include dried fruits, wine, molasses, sauerkraut, white grape juice, dried potatoes, gravies, fresh shrimp, pectin, corn syrup, pickles, and relishes.^[29]

Reactions to sulfites have been reported primarily in patients with underlying asthma. Stevenson and Simon^[30] conducted a challenge using potassium metabisulfite in 61 adult asthmatic patients and demonstrated a 25% decrease in FEV₁ in five of these patients (8.2%). In the largest reported study, Bush et al.^[31] challenged 203 adult asthmatic patients not preselected for sulfite sensitivity with both capsules and neutral solutions of sulfite. In this study 3.9% of asthmatic patients exhibited a 20% drop in FEV₁. In the group of asthmatic patients treated with oral or inhaled corticosteroids, the positive response rate was 8.4% compared with 0.8% in the group that did not require corticosteroids for daily asthma control. This suggests that the risk of reacting to sulfites may be significantly higher in patients with more severe asthma.

Few studies have examined the prevalence of sulfite sensitivity in children. Towns and Mellis^[32] performed challenges on 29 children aged between 5 and 14 years with moderate-to-severe asthma. Although two-thirds of the children showed a fall in FEV₁ on challenge, none of the asthma symptoms improved on elimination and avoidance of sulfites. Other studies in children have only shown reaction rates of 3.5% in asthmatic children challenged to sulfite capsules or oral metabisulfite.^[25] Differences in challenge procedures and formulation of the sulfating agent may very well account for the discrepancies in reports of prevalence of reactions in specific populations.

The exact mechanism of sulfite sensitivity has not been established, but a number of hypotheses have been suggested. In some individuals, the sensitivity may be IgE mediated. Skin testing by skin prick and intradermal methods has been positive in selected individuals with positive challenges.^[33] Another potential mechanism is sulfur dioxide-induced bronchospasm. Sulfur dioxide is produced as a byproduct of metabisulfite in an acidic environment and can produce bronchospasm in patients with asthma at concentrations as low as 1 part per million. A third possible mechanism of action is deficiency of the enzyme sulfite oxidase, but evidence for this mechanism is extremely limited.^[34]

The role for other food additives as precipitating agents for asthma is much less clear, and in fact controversial. This is particularly true for tartrazine (yellow dye number 5). The cause and effect of tartrazine sensitivity in triggering asthma has not

been well established since the initial report in 1959.^[35] In an early textbook on childhood asthma, it was postulated that tartrazine precipitated asthma in some children.^[36] The interpretation of many of the studies on the role of tartrazine sensitivity and asthma is difficult due to flaws in the study designs, such as withholding of asthma medications during challenges. Stevenson et al.,^[37] in his review of tartrazine sensitivity, concluded that tartrazine does not induce asthma even among a preselected group that is aspirin sensitive. The most extensive study performed by Stevenson et al.^[37] in 240 patients, of whom 190 patients were aspirin intolerant, did not show any asthmatic response in any of the patients who were challenged with tartrazine up to doses of 50mg. There is presently no compelling evidence that tartrazine induces asthmatic responses.

Tartrazine and other food colorants including sunset yellow (yellow dye number 6), amaranth (red dye number 2), and erythrosine (red dye number 3), as well as natural colorants such as annatto, carmine, carotene, and tumeric have also occasionally been reported to trigger asthmatic responses in case reports but conclusive evidence is again lacking.^[38]

Monosodium glutamate (MSG) is a popular flavor enhancer that has been implicated in Chinese restaurant syndrome. In this syndrome, first described in 1968, patients report headache, numbness, chest discomfort, weakness, flushing, and abdominal discomfort after eating Chinese food. There are a few anecdotal reports of MSG sensitivity linked to asthma.^[39,40] In a large study of 100 asthmatic patients, including 30 with a clinical history of asthma symptoms after MSG ingestion, none of the patients had a drop in FEV₁ after challenges with MSG up to 2.5mg.^[41] Thus, even in patients with a self-reported history of MSG-induced asthma, the presence of MSG sensitivity has not been reproducible. There is a report of a delayed fall in pulmonary function beginning 6 hours after the ingestion of MSG; this was not associated with Chinese restaurant syndrome.^[39,40] In most of the anecdotal reports, the quantity of MSG required to elicit a positive response was in the range of 2.5–3mg, which is a quantity that is much higher than that usually ingested. Studies examining the Chinese restaurant syndrome suggest that MSG ingestion is not related to asthma response.^[42]

Suspected food-additive sensitivities are best studied by performing oral challenges to the suspected food additive. Challenges are best performed in a double-blinded manner. In contrast with food allergens, skin testing is not helpful. With suspected sulfite sensitivity, patients may be challenged to various forms of the additive such as capsules, neutral solutions, or acidic solutions of a sulfite preparation. Toxicity studies in healthy individuals have shown ingestion of up to 400 mg/day to be tolerated.^[43] Chal-

lenges in asthmatic patients should be conducted while patients are taking their routine medications to avoid false-positive tests.

5. Perception of Food Allergy

Although food-induced asthma is rare, the proportion of patients who perceive that food affects their asthma is relatively high. A New Zealand study found that 64% of parents had altered their asthmatic child's diet in the belief that sudden dietary manipulation would help control their child's underlying asthma.^[44] Based on several community surveys, 15–28% of people with asthma believe they have food sensitivity.^[45] In a self-administered questionnaire of asthma clinic patients, 47% reported that dietary advice had been given to improve their asthma symptoms. Fifty-four percent of those patients who had been advised to restrict their diet had received such advice from a 'doctor or specialist.' Sixty-one percent of all the asthma patients attempted to modify their diet, with 79% perceiving that this modification helped their asthma symptoms.^[46]

6. Risk of Asthma on Food Reactions

Patients experiencing respiratory symptoms are more likely to have a fatal or near-fatal reaction after accidental ingestion of food to which they are allergic.^[47,48] In a US survey of six fatal and seven near-fatal anaphylactic reactions after food ingestion, all patients experienced asthma and respiratory symptoms as manifestations of their clinical presentation.^[47] The foods responsible for these serious reactions were peanut, tree nuts, egg, and cow's milk.^[47]

Patients with asthma are at greater risk of severe and fatal food-induced anaphylaxis compared with patients without any history of asthma, allergic rhinitis, or atopic dermatitis. In a US physician-reported registry, 31 of 32 patients with food-related fatalities had a diagnosis of asthma.^[49] This finding was similar to a UK study, where eight of eight patients with fatal anaphylaxis had a history of asthma.^[50]

In summary, patients with asthma or patients who experience respiratory symptoms as part of a food reaction are at greater risk for a life-threatening allergic reaction to foods.

7. Food Allergy as a Risk Factor for Asthma

Food allergy and asthma may coexist in children, and a food allergy is a risk factor for the future development of asthma. Longitudinal studies of patients with atopic dermatitis and food allergies have found that a history of food allergy increases the risk of asthma. In a 4-year follow-up of a birth cohort of 1218 children in the Isle of Wight, UK, 2.4% developed an egg allergy.^[51] Rhinitis and asthma were associated with egg allergy with an odds

ratio of 5.0 compared with the population in general. Similarly, a study of 94 children with atopic dermatitis found that a history of egg allergy increased the risk of subsequent development of asthma.^[52] In an additional study of 80 children with wheezing within the first 2 years of life, 40% (32 patients) developed persistent asthma while of school age. Persistent asthma was significantly associated with elevated levels of IgE specific to egg and wheat, duplicating earlier observations.^[53] Finally, in another study of 100 atopic children, 63 were followed until 22 years of age. In those 63 adults, the presence of egg or milk allergy in the first year of life was a major risk for adult asthma.^[54]

Therefore, these studies confirm that food allergy, especially egg allergy in early infancy, increases the risk for developing asthma later in life. Food allergy can also be a risk factor for life-threatening asthma. In a case control study, patients with asthma and food allergy had a significantly increased risk of life-threatening asthma with an odds ratio of 8.58.^[55]

8. Diagnosis of Food Allergy

The patient history alone is unreliable in the diagnosis of food allergy. Skin prick testing to food extracts is a very useful screening method for suspected food allergy. It is the quickest, most reliable, least costly, and best-studied screening method for skin. Testing is done with the food extract as well as positive and negative controls. The extract diluent serves as the negative control since the skin test device itself may cause a non-specific reaction, particularly in patients who are dermatographic. Histamine is used as the positive control to screen for the presence of residual antihistamine or other factors that may suppress a positive response.

A positive skin prick test with appropriate controls supports the diagnosis of immediate hypersensitivity to a food in patients with a compatible clinical history. Positive skin tests are typically defined as a wheal 3mm greater than the negative control. A patient with a positive skin test but a questionable clinical history should undergo a formal food challenge to clarify the diagnosis, as the positive predictive accuracy of an isolated skin prick test is <50%.^[56] A negative skin prick test excludes an IgE-mediated food reaction with a negative predictive accuracy of >90%. False-negative skin tests can occur rarely. When a false-negative test is suspected, testing should be repeated with fresh food, particularly for fruit and vegetables.

In vitro tests, such as the radioallergosorbent test, measure levels of food-specific IgE but are less sensitive than skin prick tests. Sensitivity and specificity vary significantly by allergen. CAP-RAST FEIA¹ (CAP-radioallergosorbent test [RAST]

fluoroenzyme immunoassay system [FEIA]) tests (Pharmacia, Upsala, Sweden) provide improved *in vitro* measurement of specific IgE. However, similar to skin testing and RAST testing, there is good sensitivity but poor specificity. *In vitro* tests are most useful in circumstances when skin tests cannot be performed. These include patients who are unable to discontinue antihistamines or other medications that may interfere with testing results, patients who have significant dermatographism, and patients with severe atopic dermatitis or other skin disorders with little available surface area for appropriate skin testing. Knowledge of particular test characteristics and the illness being evaluated is required for appropriate application and interpretation of each method.

Various studies of the CAP-RAST FEIA in children have established 90% positive predictive values for four foods (milk, egg, peanut, and fish)^[57-60] similar to skin testing.^[61,62] In contrast, a 90% positive predictive value could not be established for soy or wheat. However, these values vary by the population studied and the age of the patient. Results at or above the 90th percentile indicate a high likelihood of a food allergy, and therefore a food challenge does not always need to be performed to confirm the food allergy. The specific level of IgE (CAP-RAST FEIA) does not correlate with the severity of a reaction. Therefore, although antibody titer results indicate a decreased chance of a food allergy, anaphylaxis can occur at even low levels of specific IgE.

A food challenge remains the gold standard for definitively diagnosing a food allergy after screening with either skin prick or *in vitro* RAST tests. If skin and/or *in vitro* testing is negative, and there is a minimal suspicion of allergy, the challenge can be performed at home. If skin and/or *in vitro* testing is positive, but the history is questionable, the food can be challenged by giving gradually increasing doses of the food over a prolonged observation period. The starting dose should be a dose unlikely to elicit an allergic reaction. The patient is then monitored for a reaction in the physician's office after a food challenge. With subjective symptoms, the reaction may need to be confirmed with a double-blind placebo-controlled challenge. Trained personnel and equipment should be available at all times to treat an anaphylactic reaction.

9. Treatment

The treatment of food allergies is simple: avoidance. However, the diagnosis needs to be confirmed by medically supervised food challenges since food allergies are a rare cause of asthma. For acute allergic reactions due to foods, the standard care is intramuscular epinephrine (adrenaline) with a standard dose of 0.2–0.5mL of a 1 : 1000 (weight/volume) dilution for adults and 0.01 mL/kg of 1 : 1000 (weight/volume) for children.^[63] The treatment of

1 The use of trade names is for product identification purposes only and does not imply endorsement.

asthma, whether or not food allergies are a risk factor for future development, is unchanged from the standard management of asthma.

10. Conclusion

Exposure to food allergens can cause a variety of respiratory symptoms. However, isolated asthma symptoms without concomitant cutaneous or gastrointestinal symptoms are atypical. Rarely, patients may have asthma symptoms in response to inhalation of food particles without ingestion. Reactions to food additives can infrequently involve lower respiratory symptoms, particularly in asthmatic patients. In contrast, the perception of food-induced asthma is more common. The presence of a food allergy is a risk factor for the development of asthma as well as life-threatening asthma. When food-allergy reactions affect the lower respiratory tract, the reactions tend to be more severe. In addition, patients with underlying asthma may experience more severe and potentially life-threatening allergic food reactions.

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