Respiratory Manifestations of Food Allergy

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ABSTRACT. Food allergy may present with a variety of respiratory tract symptoms that generally involve immunoglobulin E antibody-mediated responses. Exposure is typically through ingestion, but in some cases, inhalation of airborne food particles may trigger these reactions. Upper and lower respiratory tract reactions are often a significant component of multisystem, anaphylactic reactions. However, chronic or isolated asthma or rhinitis induced by food is unusual. It is important to recognize that food allergy in early childhood is a marker indicating an increased risk to develop respiratory allergy. The role of food allergy in otitis media is controversial and probably is extremely rare. Likewise, asthmatic responses to food additives can occur but are uncommon. Studies using blinded oral food challenges have demonstrated that foods can elicit airway hyperreactivity and asthmatic responses. Therefore, an evaluation for food allergy should be considered in patients who are at risk, including those with recalcitrant or otherwise unexplained acute, severe asthma exacerbations, asthma triggered after ingestion of particular foods, and asthma that is accompanied by other manifestations of food allergy (e.g., anaphylaxis, moderate to severe atopic dermatitis). Pediatrics 2003;111:1625–1630; food allergy, asthma, anaphylaxis, bronchial hyperresponsiveness.

ABBREVIATIONS. FEV₁, forced expiratory volume in 1 second; IgE, immunoglobulin E; MSG, monosodium glutamate.

Cutaneous and gastrointestinal symptoms constitute the most commonly observed acute and chronic clinical manifestations of food allergy. Although food-induced respiratory symptoms are less frequent, their presence, usually in conjunction with symptoms in other organ systems, generally indicates a more severe disease manifestation. In fact, asthmatic reactions triggered by food allergy constitute a more worrisome symptom complex because they are usually observed in fatal and near-fatal reactions after food ingestion. More challenging than acute respiratory responses to foods, chronic respiratory complaints such as rhinitis and asthma, which may be attributed to food allergy, are particularly difficult to evaluate. Although the vast majority of these symptoms will not be related to food allergy, the notion that food allergy may play a role should be acknowledged and investigated.

In the overall evaluation of patients with specific respiratory symptoms that are thought to be the result of an adverse food reaction, numerous allergic, as well as nonallergic, causes must be considered in the differential diagnosis (Table 1). The main objective of this review is to summarize the scientific literature concerning the role of food allergy in respiratory tract symptoms. Specific circumstances in which food allergy should be considered as a cause for respiratory tract symptoms are highlighted. This information should provide a practical foundation on which the pediatrician and related health care professional may evaluate patients with respiratory tract manifestations that could be attributed to food allergy.

EPIDEMIOLOGY

The true prevalence of respiratory tract symptoms induced by food allergy has been difficult to ascertain. In general, there is an erroneously inflated public perception of food allergy-induced asthma; therefore, it is understandable that many associations have been made between the ingestion of certain foods and food additives and respiratory tract symptoms. Individual perceptions of allergy are often not substantiated when food challenges are used to confirm patient histories. The incidence of confirmed food-induced respiratory reactions induced by food is estimated to be between 2% and 8% in children.

| TABLE 1. Selected Disorders in the Differential Diagnosis of Food-Induced Respiratory Disease |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Nasal symptoms                  | Allergic rhinitis (environmental allergens) | Food allergy                   | Nonallergic rhinitis (rhinorrhea from spicy food/heat) | Infection (viral, bacterial) | Inflammatory response (nonallergic rhinitis with eosinophilia) | Vasomotor rhinitis               | Rhinitis medicamentosa            | Foreign body                    | Lower airway symptoms           | Allergic extrinsic asthma       | Food allergy                    | Anaphylaxis                     | Heiner’s syndrome               | Nonallergic intrinsic asthma   | Infection                      | Irritant foreign body           |
and adults with asthma. The epidemiology of food-induced respiratory allergy is best considered among 3 types: respiratory reactions during 1) food-induced anaphylaxis, 2) food-induced rhinitis, and 3) food-induced asthma.

**Food-Induced Respiratory Reactions as a Component of Anaphylaxis**

Egg, milk, peanut, soy, fish, shellfish, and tree nuts are the most common food allergens that are implicated in respiratory reactions and confirmed in well-controlled, blinded food challenges. A recent investigation summarized data from a voluntary registry of 5149 individuals, mostly children, with peanut and/or tree nut allergy. Respiratory reactions, including trouble breathing, wheezing, throat tightness, and nasal congestion, were reported in 42% and 56% of respondents as part of their initial reactions to peanuts and tree nuts, respectively. One half of the reactions involved >1 organ system, and registrants with asthma were significantly more likely than those without asthma to have severe reactions (33% vs 21%; P < .0001).

As mentioned above, respiratory symptoms, especially asthmatic reactions, induced by food allergens are a very worrisome and dramatic group of clinical symptoms because they have been frequently observed in fatal and near-fatal reactions after food ingestion. These symptoms typically include pruritus in the oropharynx, angioedema (eg, laryngeal edema), stridor, cough, dyspnea, wheezing, and dysphonia. In a survey of 6 fatal and 7 near-fatal anaphylactic reactions after food ingestion, all patients had asthma and respiratory symptoms as part of their clinical presentation. The foods responsible for these serious reactions were peanut, tree nuts, egg, and cow milk. Another report summarized acute allergic reactions to peanut and/or tree nuts in 122 atopic children. Overall, 52% had lower respiratory tract symptoms as part of their overall reactions.

The causal foods may differ by geographical region and local cuisine. A recent investigation from Italy summarized the clinical characteristics and treatment of 113 episodes of acute anaphylaxis triggered by different agents including food allergens (8%). The most frequent symptoms involved the respiratory tract (90%). Specific foods identified as triggers included mustard, mussels, shrimp, soy, peanut, and fish. In summary, the presence of asthma is a risk factor for severe, food-induced anaphylaxis; respiratory symptoms are a common and important indicator of severe food-induced anaphylaxis; and a short list of common foods are often implicated.

**Rhinitis-Induced Food Allergy**

Adverse nasal symptoms, especially rhinitis, are sometimes attributed to food ingestion. Nasal symptoms, especially rhinitis, accounted for 70% of the respiratory symptoms observed in children who underwent double-blind, placebo-controlled food challenges. Rhinitis typically occurs in association with other clinical manifestations (ie, cutaneous and/or gastrointestinal symptoms) during acute allergic reactions to foods and rarely occurs in isolation. In addition, rhinitis induced by oral food challenges is more frequently observed in infants and young children than in adults. Overall, isolated rhinitis is rarely a symptom of food allergy.

Many patients associate the ingestion of cow milk and other dairy products with an increase in the production and thickness of nasal secretions. This association often cannot be attributed to a specific allergic reaction. Pinnock et al investigated the relationship between milk intake and mucus production in adult volunteers challenged with rhinovirus-2. Milk and dairy product intake was not associated with an increase in upper or lower respiratory tract symptoms of congestion or nasal secretions. Overall, no statistically significant association was detected between milk and dairy product intake and symptoms of mucus production in healthy adults, whether asymptomatic or symptomatic with rhinovirus infection. Taking this a step further, another investigation used a randomized, crossover, double-blind, placebo-controlled trial to examine the effects of dairy products in patients who perceived that their asthma worsened with the ingestion of these products. For both forced expiratory volume in 1 second (FEV₁) and peak expiratory flow rate, there was no statistically significant differences in the group means between active challenges and placebo challenges. Taken together, these data suggest that it is unlikely that dairy products have a specific effect in patients with isolated rhinitis or a bronchoconstrictor effect in patients with asthma.

**Asthma Induced by Food Allergy**

Like rhinitis, asthma is rarely an isolated manifestation of food allergy, but food-induced asthma is observed during systemic allergic reactions to food. In one investigation, 300 consecutive patients with asthma (age range: 7 months–80 years) were evaluated in a pulmonary clinic. Twenty-five (12%) patients had a history of food allergy suggested by clinical symptoms and/or positive tests of food-specific immunoglobulin E (IgE) antibodies. Food-induced wheezing was documented in 6 (2%) of the cases; all of the cases were children aged 4 to 17 years. In another investigation, 140 children who were aged 2 to 9 years and had asthma were screened by clinical history and testing for food-specific IgE antibodies. Of these children, 32 underwent blinded food challenges: 13 (9.2%) had food-induced respiratory symptoms, and 8 (5.7%) had specific asthmatic reactions documented during food challenges. Only 1 patient had asthma as the sole symptom during a positive food challenge. It is interesting that the patients with food allergy and asthma were generally younger and had a medical history of atopic dermatitis. Oehling et al reported that food-induced bronchospasm was present in 8.5% of 284 children with asthma. The majority of the allergic sensitization occurred in the first year of life and was caused by a single food, especially egg. Finally, Businco et al evaluated 42 children (age range: 10–76 months) with atopic dermatitis and...
milk allergy. Eleven (27%) of these patients developed asthmatic symptoms during a positive food challenge; in 6 children, these asthma exacerbations were the only adverse symptom observed.

The prevalence of food-related wheezing seems to be highest in the youngest patients with atopic disease. Hill et al23 in Australia studied 100 children (mean age: 16 months) who had clinical histories of adverse reactions to cow milk. The children were separated into 3 distinct groups based on symptoms. The first group consisted of 27 infants who reacted acutely to cow milk ingestion (29% had lower airway responses on oral challenges) and had cow milk–specific IgE antibodies. A second group consisted of 53 infants with primarily non–IgE-mediated gastrointestinal reactions to cow milk challenges. Only 4% in this group experienced lower airway symptoms. The third group included 20 patients characterized with late-onset reactions to oral challenges with cow milk. The majority of these patients had chronic asthma or atopic dermatitis, and 50% had wheezing after the milk challenges. Likewise, an investigation from Turkey confirmed that food allergy can elicit asthma in children younger than 6 years, but the incidence is low (4%), even for major food allergens such as egg and cow milk.24

Over 2 consecutive decades, 598 children with pulmonary disease were evaluated at the National Jewish Center for Immunology and Respiratory Medicine.25 Of the 410 (69%) children with a history of asthma, 279 (68%) had a history of food-induced asthma. There were positive food challenges in 168 (60%) of the 279 patients. This investigation documented that 67 (24%) of the 279 children with a history of food-induced asthma had a positive blinded food challenge that included wheezing. The most common foods responsible for these reactions were peanut (19), cow milk (18), egg (13), and tree nuts (10). It is interesting that only 5 (2%) of these patients had isolated wheezing.

A total of 320 children who had atopic dermatitis and underwent blinded food challenges at Johns Hopkins Hospital were monitored for respiratory reactions.17 The patients, ages 6 months to 30 years, were highly atopic and had multiple allergic sensitivities to foods, and more than one half had a previous diagnosis of asthma. Food allergy was confirmed by blinded challenges in 205 (64%) of these patients; almost two thirds of these patients experienced respiratory reactions during their positive food challenges (nasal, 70%; laryngeal, 48%; pulmonary, 27%). Overall, 34 (17%) of 205 children with positive food challenges developed wheezing as part of their reaction. Furthermore, 88 of these patients were monitored with pulmonary function testing during positive and negative food challenges. Thirteen (15%) developed lower respiratory symptoms, including wheezing; however, only 6 patients had a >20% decrease in FEV1. As documented in the investigations cited earlier, wheezing as the only manifestation of the respiratory reaction was rare.

In summary, these results suggest that respiratory symptoms may be provoked in a subset of patients with asthma. Table 2 provides a comparison of the prevalence of food allergy-induced asthmatic reactions in different patient populations.

### Increased Risk of Respiratory Allergy Among Patients With Food Allergy

Allergic sensitization to egg in infancy has been identified as a predictor for respiratory tract allergic disease later in life. For example, investigators from the Isle of Wight recently reported on a 4-year follow-up of a birth cohort of 1218 children in whom 29 (2.4%) developed egg allergy.26 Increased respiratory allergy (eg, rhinitis, asthma) was associated with egg allergy (odds ratio: 5.0; 95% confidence interval: 1.1-22.3; P < .05) with a positive predictive value of 55%. Furthermore, the diagnosis of concomitant eczema increased the positive predictive value to 80%. The investigators concluded that egg allergy in infancy, especially when associated with eczema, increases the risk of respiratory allergy in early childhood. In addition, Rhodes et al27 conducted a prospective birth cohort study in England of subjects at risk for asthma and atopy. Of the 100 infants of atopic parents who were recruited, 73 were followed up at 5 years, 67 were followed up to 11 years, and 63 were followed up to 22 years. Skin sensitivity to hen’s egg, cow milk, or both in the first 5 years of life was predictive of asthma (odds ratio: 10.7; 95% confidence interval: 2.1-55.1; P = .001; sensitivity: 57%; specificity: 89%). Food and respiratory allergy are also closely associated because sensitization to pollen proteins can result in food-allergic reactions to fruits and vegetables with homologous proteins (pollen-food syndrome).28

### PATHOGENESIS

Immune responses mediated by specific IgE antibodies to food allergens are the most widely recognized mechanism for food-induced respiratory tract symptoms.29 These antibodies bind to high-affinity IgE receptors on basophils and tissue mast cells throughout the body, including the upper and lower respiratory tract. The establishment of IgE-bearing cells in the nasal or bronchial mucosa during the allergic sensitization process sets the stage for their activation during subsequent allergen exposure.30 When antigen binds to multiple IgE antibodies on a mast cell or basophil, these cells become activated, which leads to degranulation and release of proinflammatory mediators such as histamine, tryptase, leukotrienes, and prostaglandins. These mediators are responsible for the immediate allergic reaction characterized by vasodilatation, smooth muscle contraction, and mucus secretion, which in turn leads to

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<td>Clinical Population</td>
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the different clinical symptoms observed in the respiratory tract.

These specific mediators can also contribute to late-phase allergic reactions that occur 4 to 8 hours after an immediate allergic response. Mast cell-derived mediators can cause endothelial cells to up-regulate their expression of adhesion molecules for eosinophils, basophils, and lymphocytes. In addition, tryptase may activate endothelial cells, increasing vascular permeability. Leukocytes are then drawn to the airways during a relatively symptom-free recruitment phase, where they release cytokines and tissue-damaging proteases that contribute to the late-phase response, including congestion in allergic rhinitis and bronchoconstriction in asthma. Chronic inflammation eventually produces airway hyperresponsiveness. Specific T cells also generate a memory response, which may contribute to the exacerbation of asthma symptoms on reexposure to certain stimuli.

Although the primary route of exposure to food that can cause or exacerbate respiratory symptoms (eg, asthma) is oral ingestion, asthmatic responses may also occur from direct inhalation of aerosolized particles that contain allergenic food. For example, highly allergic people may react when exposed to clinically relevant levels of allergenic food in a seafood restaurant or when fish, shellfish, or eggs are cooked in a confined area. Moreover, patients with peanut allergy may experience similar reactions when they are exposed to peanut dust on airline flights that serve peanut snacks.

Airway Hyperresponsiveness Induced by Food Allergy

In a subset of food-allergic children, the chronic ingestion of a food to which one is allergic may result in increased airway hyperresponsiveness despite the absence of acute symptoms on ingestion. In one specific investigation, 26 children with asthma and food allergy were evaluated for changes in their airway hyperresponsiveness before and after blinded food challenges. Airway hyperresponsiveness was measured with standardized methacholine inhalation challenges both at baseline (ie, before blinded food challenges) and 4 hours after the food challenge. Of the 22 positive blinded food challenges, 12 involved chest symptoms (cough, laryngeal reactions, and/or wheezing). Another 10 positive food challenges included laryngeal, gastrointestinal, and/or skin symptoms without any chest symptoms. Significant increases in airway hyperresponsiveness occurred in 7 of the 12 patients who experienced chest symptoms during positive food challenges. Decreases in FEV₁ were not generally observed in these 7 patients during the food challenges; however, significant changes in airway hyperresponsiveness could be detected in the majority of patients who experienced chest symptoms during a positive challenge. These data indicate that food-induced allergic reactions may increase airway hyperresponsiveness in a subset of patients with moderate to severe persistent asthma despite the absence of symptoms immediately after ingestion.

In contrast, an investigation of adults with asthma concluded that food allergy is an unlikely cause of increased airway hyperresponsiveness. Eleven adults with asthma, a history of food-induced wheezing, and positive prick skin tests to the suspected foods were evaluated. An equal number of patients had increased airway hyperresponsiveness, which was determined by methacholine inhalation challenges, after blinded food challenges to either food allergen or placebo. Unfortunately, the small number of patients investigated and the lack of environmental controls before the repeat methacholine challenges limited the certainty of their conclusions.

OTHER FOOD-INDUCED RESPIRATORY SYNDROMES

Serous Otitis Media Induced by Food Allergy

Serous otitis media has multiple causes, the most prominent of which is viral upper respiratory tract infection. Allergic inflammation in the nasal mucosa may cause eustachian tube dysfunction and subsequent otitis media with effusion. A role for food allergy in recurrent serous otitis media has been proposed; however, this association has been overestimated and is controversial. Respiratory atopy (eg, allergic rhinitis, allergic asthma) may be the more important predisposing factor than food allergy alone. In contrast, another report cautiously suggests that in a subset of infants with recurrent otitis media, IgG complexes with food antigens, particularly cow milk proteins, may contribute to the middle ear inflammation in this disorder. Obvously, more data obtained from well-controlled investigations are needed before general recommendations can be made regarding this association. Until better data are available, the routine testing for food allergy in patients with otitis media is not recommended.

Food-Induced Pulmonary Hemosiderosis (Heiner’s Syndrome)

In 1960, Heiner and Sears reported in infants a syndrome that consisted of recurrent episodes of pneumonia associated with pulmonary infiltrates, hemosiderosis, gastrointestinal blood loss, iron-deficiency anemia, and failure to thrive. This rare syndrome is most often associated with a non-IgE-mediated hypersensitivity to cow milk proteins. Although peripheral blood eosinophilia and serum precipitins to cow milk are commonly observed, the specific immunologic mechanisms responsible for this disorder are not known. The diagnosis is suggested when milk precipitins are demonstrated and elimination of the milk leads to subsequent resolution of symptoms.

Respiratory Symptoms Induced by the Inhalation of Food Allergens

Occupational exposures to airborne food allergens can result in chronic asthma. For example, baker’s asthma is caused by an occupational exposure to airborne cereal grain dust. Patients with this disorder experience cough and shortness of breath after the inhalation of wheat proteins while baking. Affected
patients usually have positive skin tests to extracted wheat proteins. Inhalation of lupine flour may also be an important cause of allergic sensitization in exposed workers and may actually give rise to occupational asthma and food allergy. Three patients reported work-related symptoms immediately after being exposed to lupine. Prick skin test results with an extract of lupine seed flour were positive in all patients; lupine-specific IgE antibodies were detected in 2 subjects. It is interesting that 1 patient underwent a bronchial provocation with lupine seed flour extract and experienced an immediate fall (up to 25%) in FEV1.

In children as well as adults, nonoccupational exposures to airborne food particles can also elicit respiratory reactions, usually during cooking or manipulation of the food. Allergic reactions associated with airborne fish particles have been reported in patients with fish allergy. This report highlighted children who reported allergic reactions on incidental inhalation of fish odors or fumes. Of the 21 patients evaluated, 9 had wheezing or rhinitis alone and 3 had respiratory and cutaneous symptoms together. Methods of exposure included boiling or frying fish and simple exposure to fish. Sichener et al reported a series of peanut-allergic patients who experience adverse respiratory reactions when they are exposed to peanut dust on airline flights that serve peanut snacks. Another report focused on 3 patients who developed asthma and rhinitis provoked by exposure to raw but not cooked green beans and chards in a nonoccupational environment. The investigators observed very minor differences of IgE reactivity between nitrocellulose-blotted raw and boiled green bean extracts.

Food Additives and Respiratory Symptoms

A high percentage of patients with asthma perceive that food additives contribute to worsening of their respiratory symptoms; however, well-controlled investigations in this area have reported a prevalence rate well below 5%. For example, there is conflicting evidence that patients with asthma are more likely to have adverse effects from monosodium glutamate (MSG) compared with the general population. Woods et al designed a randomized, double-blind, placebo-controlled, MSG challenge protocol for identifying early and late asthmatic reactions. They were unable to demonstrate MSG-induced immediate or late asthmatic reactions in a group of 12 adults who had asthma and perceived that this food additive negatively affected their overall asthma control. In addition, these investigators observed no significant changes in bronchial hyperresponsiveness or soluble inflammatory markers (eg, eosinophil cationic protein, tryptase) during this challenge protocol. Another investigation used double-blind, placebo controlled oral challenges with MSG in subjects with histories of adverse reactions to this food additive. This study failed to demonstrate upper or lower respiratory symptoms. However, 22 (36.1%) of the 61 subjects had confirmed adverse reactions to MSG, including headache, muscle tightness, numbness, generalized weakness, and flushing.

### Table 3. Role of Food Allergy in Respiratory Disease: Key Points

| 1. Acute food-induced respiratory tract symptoms are typically accompanied by either cutaneous or gastrointestinal symptoms. |
| 2. Chronic, isolated food-induced respiratory tract symptoms are uncommon. |
| 3. Egg, milk, peanut, soy, fish, shellfish, and tree nuts are the most common food allergens confirmed to elicit respiratory reactions. |
| 4. Allergic sensitization (positive tests) or clinical reactions to foods in infancy predict the later development of respiratory allergies and asthma. |
| 5. Food-induced asthma is more common in young pediatric patients than in older children and adults. |
| 6. Children with atopic dermatitis, especially those with food reactions confirmed during blinded food challenges, are at increased risk for food-induced asthma. |
| 7. Food-induced allergic reactions may increase airway hyperresponsiveness in patients with moderate to severe asthma and may do so without inducing acute asthma symptoms. |
| 8. The role of food allergy in otitis media, particularly in patients without other manifestations of atopy (eg, atopic dermatitis, allergic rhinitis) is controversial and probably is extremely rare. |
| 9. Asthmatic reactions to food additives can occur but are very uncommon. |
| 10. Respiratory symptoms, especially asthmatic reactions, induced by food allergens are considered risk factors for fatal and near-fatal reactions. |

Sulfite-containing foods (eg, dried fruits, wines) have been shown to cause bronchospasm and severe asthmatic attacks in patients with sensitive asthma.

### Table 4. Features That May Indicate the Need for Evaluation of Food Allergy in Patients With Asthma

| 1. Recalcitrant or otherwise unexplained acute, severe asthma exacerbations |
| 2. Asthma triggered after ingestion of particular foods |
| 3. Patients with asthma that is accompanied by other manifestations of food allergy (eg, anaphylaxis, moderate to severe atopic dermatitis) |

CONCLUSION

In summary, studies have established a pathogenic role for food allergy in the development of respiratory tract symptoms. Acute food-induced respiratory reactions are typically accompanied by cutaneous and gastrointestinal symptoms as a component of systemic anaphylaxis. There are also circumstances when isolated rhinitis or asthma is induced by foods, but these are uncommon. An overview of the role of food allergy in respiratory tract disease is summarized in Table 3. Allergic sensitization to foods in infancy is a risk factor for respiratory tract allergic disease, including asthma, later in life. Table 4 highlights key clinical features that may indicate that an evaluation for food allergy should be considered. Finally, asthma is a significant risk factor for life-threatening food-allergic reactions. Among patients who experienced life-threatening food hypersensitivity reactions, the vast majority had a history of asthma. With this in mind, practice parameters for the diagnosis and treatment of asthma have recently highlighted the potential role of food allergy in asthma in some patients.
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