

The Respiratory Tract and Food Hypersensitivity

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KEY CONCEPTS

- The medical history supplemented with appropriate laboratory testing and well-designed food challenges can provide useful information in the workup of patients with respiratory symptoms that may be induced by food allergy. A diagnosis based solely on history, skin testing, or *in vitro* measurements of specific IgE to a given food allergen(s) is not acceptable.
- There continues to be an elevated public perception of food allergy, including an elevated public perception of food allergy-induced asthma and other respiratory disorders. The true prevalence established by standardized challenges is much lower.
- Skin sensitivity to certain food allergens (e.g. hen's egg, cow's milk, or both) in the first several years of life may be predictive of later respiratory allergic disease, including allergic rhinitis and asthma.
- Several recent investigations have highlighted cases of respiratory allergic disease that have been precipitated by the inhalation exposure to airborne food allergens, as opposed to the ingestion of the implicated food allergen.
- If no specific foods are implicated in the history and if skin tests to foods are negative, further workup for IgE-mediated allergy is not generally indicated. If respiratory symptoms persist after food elimination diets are implemented, food is not likely to be the problem, except in some cases of atopic dermatitis or chronic asthma. Respiratory symptoms recurring after a regular diet is resumed should be evaluated with a properly designed food challenge.
- The vital prognosis of food-induced anaphylaxis is determined by respiratory symptoms. Epinephrine can be life-saving and should be made available to patients with asthma and food allergy, and to patients at risk for food-induced respiratory reactions.

Introduction

The skin, with urticaria and atopic dermatitis, is the organ which classically harbors IgE-mediated manifestations of food allergy. However, more recently, food-induced anaphylaxis has received major public and scientific attention. It also has been well established that respiratory manifestations of food-induced anaphylaxis often determine the outcome of the reaction, since the severity of the reaction is mainly determined by upper or lower airway obstruction. Recognizing the severity of a food-induced allergic reaction by assessing the importance of airway involvement has become a major task not only to allergists, but also to primary care physicians. In addition, food-induced allergic reactions are frequently suspected in patients with recurrent

episodic or chronic asthma, or in patients with recurrent upper airway infections. Although few patients with these conditions benefit from a food-exclusion diet, it is a major challenge to properly identify and diagnose the few patients who might suffer from chronic respiratory manifestations. This chapter will review various aspects of respiratory manifestations of food allergy, including the less commonly suspected reactions by inhalation of the offended food.

Epidemiology/etiology

Overview of adverse food reactions

Understanding the terminology and basic classification of adverse food reactions will aid in the interpretation of the scientific studies implicating food hypersensitivity and respiratory tract symptoms [1]. The two broad groups of immune reactions are IgE mediated and non-IgE mediated. The IgE-mediated reactions are usually divided into immediate-onset reactions and immediate plus late-phase reactions (i.e. in

which the immediate-onset symptoms are followed by prolonged, in time, or ongoing symptoms). The former have been well characterized in many studies, whereas the latter are under more intense scrutiny to determine their mechanisms and to unravel the role of the immune system. Non-IgE-mediated reactions are typically delayed in onset (i.e. 4–48 hours) and most frequently involve the gastrointestinal tract (Fig 12.1).

Prevalence

While there has been an increase in the prevalence of food allergy and its clinical expression in westernized societies over the past two decades [2], there continues to be an elevated public perception of food allergy, including an elevated public perception of food allergy-induced asthma [3]. These public perceptions, however, have not always been substantiated when careful objective investigations, including food challenges, have been undertaken to confirm patient histories [4,5]. It is generally assumed that questionnaire-based studies vastly overestimate the prevalence of food hypersensitivity. For example, the reported, perceived prevalence of food hypersensitivity varied from 3.24% to 34.9%, which may be explained partly by the difference in reporting lifetime prevalence compared with point prevalence. The high prevalence of pollen-related food allergy in younger adults in the population suggests that the increase in pollen allergy is also being accompanied by an increase in pollen-related food allergy [6]. Adult food allergy has been estimated at approximately 3.2% worldwide. Factors favoring the acquisition of allergy could be sensitization to pollens and occupational sensitization by inhalation [7].

A group of investigators in Denmark evaluated a cohort of 898 patients by questionnaire, skin prick test, histamine release test, and specific IgE followed by oral challenge to the most common allergenic foods. The prevalence of food hypersensitivity confirmed by oral challenge was 2.3% in children 3 years of age, 1% in children older than 3 years of age, and 3.2% in adults. The prevalence of clinical reactions to pollen-related foods in pollen-sensitized adults was estimated to be 32% [8]. Likewise, an investigation in the United Kingdom measured the prevalence of allergic sensitization in a large birth cohort ($n = 13,638$) and examined the associations between sensitization to different allergens. Seven-year-old children were primarily sensitized to aeroallergens (e.g. grass pollen, dust mites, animal dander), but also to peanut and tree nuts. A relationship was observed between aeroallergen and food-allergen sensitization in these children [9]. Finally, a total of 94 (11.8%) 6-year olds in the Isle of Wight, UK, reported a problem with a food or food ingredient. The rate of sensitization to the predefined panel of food allergens was 25/700 (3.6%). Based on open food challenge and/or suggestive histories and skin tests, the prevalence of food allergy was 2.5% (95% CI: 1.5–3.8). Based on double-blind challenges, a clinical diagnosis or

suggestive history and positive skin tests, the prevalence was 1.6% (95% CI: 0.9–2.7). Milk, egg, and peanut were the key food allergens among those with positive challenges [10].

A few population-based studies have investigated the incidence of food hypersensitivity in the first year of life. One birth cohort ($n = 969$) was recruited and the investigators examined feeding practices and reported symptoms of allergy at 3, 6, 9, and 12 months. At 1 year, infants underwent a medical examination and skin prick testing to a battery of allergens. Symptomatic infants underwent food challenges. Of these infants, 1% was sensitized to aeroallergens and 2.2% to food allergens. The cumulative incidence of food hypersensitivity by 12 months was 4% on the basis of open food challenges and 3.2% on the basis of double-blind, placebo-controlled food challenges (DBPCFCs). Using this data, the investigators were able to conclude that the rate of parental perception of food hypersensitivity was higher than the prevalence of atopic sensitization to major food allergens or objectively assessed food allergy [11]. In another investigation by the same group, it was determined that 2.3% of both 11- and 15-year-old children had food hypersensitivity as determined by objective assessment including food challenges [12].

When the specific focus has been on the role of food allergy and respiratory tract manifestations, the incidence has been estimated to be between 2% and 8% in children and adults with asthma [13,14]. Children with a family history of atopy and sensitization to food proteins in early infancy are at high risk of subsequent respiratory allergic disease and they may require specific prevention measures [15].

A French population study of food allergy determined the prevalence, clinical features, specific allergens, and risk factors of food allergy [16]. The overall prevalence of food allergy was estimated to be 3.24%. Of the respiratory reactions reported, rhinitis and asthma were documented in 6.5% and 5.7% of cases, respectively. In addition, the clinical expression of food allergy was dependent on the existence of sensitization to pollens and was typically expressed in the form of rhinitis, asthma, and angioedema. A different survey found that 17% of 669 adult respondents in Australia reported food-induced respiratory symptoms [17].

Investigators from the Isle of Wight have reported that egg allergy in infancy predicts respiratory allergic disease by 4 years of age [18]. A cohort of 1218 consecutive births was recruited and followed until 4 years of age. Of these, 29 (2.4%) developed egg allergy by 4 years of age. Increased respiratory allergy (e.g. rhinitis, asthma) was associated with egg allergy (OR: 5.0; 95% CI: 1.1–22.3; $p < 0.05$) with a positive predictive value of 55%. Furthermore, the addition of the diagnosis of eczema to egg allergy increased the positive predictive value to 80%. The investigators concluded that egg allergy in infancy, especially when associated with eczema, increases respiratory allergic symptoms in

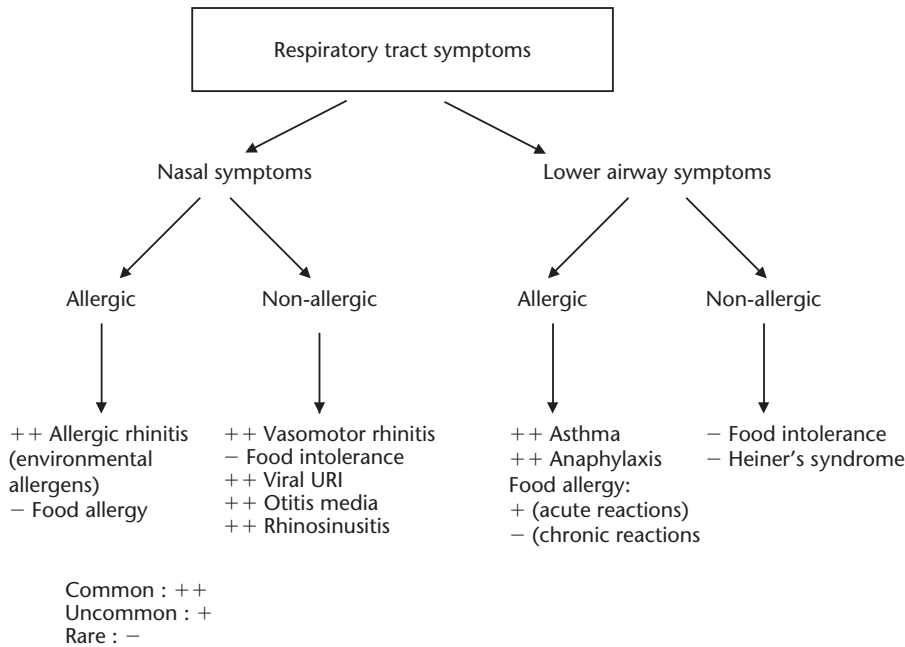


Figure 12.1 Respiratory tract symptoms and food allergy: differential diagnosis.

early childhood. In addition, Rhodes *et al.* conducted a prospective cohort study of subjects at risk of asthma and atopy in England [19]. Of the 100 babies of atopic parents who were recruited at birth, 73 were followed up at 5 years, 67 at 11 years, and 63 at 22 years. Skin sensitivity to hen's egg, cow's milk, or both in the first 5 years of life was predictive of asthma (OR: 10.7; 95% CI: 2.1–55.1; $p = 0.001$; sensitivity 57%; specificity 89%).

Recently, investigators examined the degree of food-allergen sensitization in inner-city patients with asthma included in the National Cooperative Inner City Asthma Study in the United States [20]. The children ranged in age from 4 to 9 years (median age 6 years) and 504 random serum samples were evaluated for specific IgE to six common food allergens (e.g. egg, milk, soy, peanut, wheat, and fish). There was a significant correlation between sensitization to foods and sensitization to aeroallergens, with sensitization to the highest number of aeroallergens correlating with sensitization to soy, wheat, and peanut. Children sensitized to foods had higher rates of asthma hospitalization ($p < 0.01$) and required more steroid medications ($p = 0.25$). In addition, sensitization to foods was correlated with sensitization to more indoor and outdoor aeroallergens ($p < 0.001$). The association of increased asthma morbidity with at least one food sensitization, and findings that patients with sensitization to multiple foods had significantly more asthma morbidity than those with single-food sensitization, suggests that food-allergen sensitivity may be a marker for increased asthma severity.

An investigation by Sicherer and colleagues summarized data from a voluntary registry of 5149 individuals (median age: 5 years) with peanut and/or tree nut allergy [21].

Respiratory reactions, including 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 more than one system and more than 75% of those surveyed required some form of medical treatment. Interestingly, registrants with asthma were significantly more likely than those without asthma to have severe reactions (33% versus 21%; $p < 0.0001$). A more recent, yet related investigation by the same group of investigators estimated the prevalence of seafood allergy in the United States using a nationwide, cross-sectional, random telephone survey and standardized questionnaire. A total of 5529 households completed the survey, representing a census of 14,948 individuals. Fish or shellfish allergy defined by established criteria was reported in 5.9% of households. Recurrent reactions were common. Shortness of breath and throat tightness were reported by more than 50% of those surveyed and 16% were treated with epinephrine. The investigators concluded that physician-diagnosed and/or convincing seafood allergy is reported by 2.3% of the general population, or approximately 6.6 million Americans [22].

Pathogenesis

It has become evident in recent years that the gut, which is the classic site of sensitization to foods, is only responsible for primary sensitization in a subset of the patients. These patients are mainly young children who exhibit the first symptoms shortly after initial feedings with the food. The newly recognized route of sensitization in food allergy is by initial exposure to allergens through inhalation, mostly

pollens, with secondary clinical reaction upon ingestion of specific cross-reactive foods. In these patients, many years may elapse before the first respiratory symptoms appear. Pathogenic mechanisms in relation to food allergy due to cross-reacting respiratory allergens will be developed in the corresponding sections.

In food allergy with initial sensitization to foods in the gut, the site of antigen-specific activation for the immune system is believed to be mostly the Peyer's patches [23,24]. The risk that a specific antigen may act as the sensitizing protein is very low. Physical "barriers" such as acidic and proteolytic digestion, the gastrointestinal peristalsis, mucous coating of the epithelium, secretory IgA antibodies, and the epithelial barrier prevent most potentially pathogenic proteins from entering the sub-mucosa of the gut [25,26]. Potential allergens will be taken over by antigen-presenting cells such as dendritic cells of the sub-mucosa, and presented to naive T-cells via their T-cell receptors generating the initial priming of the immune system. In IgE-mediated food allergy, the immune mechanism mostly involved in respiratory reactions to foods, primed allergen-specific CD4+ cells, will facilitate antigen-specific IgE antibodies by plasmacytes. Circulating antigen-specific IgE antibodies will be distributed in the various organs and attached to organ-resident mast cells. Further ingestion of the offending allergen will then directly, by bridging IgE on the Fcε receptor on mast cells, trigger mast cell degranulation and liberation of vasoactive substances such as histamine or tryptase [27].

Unlike in respiratory allergy, most patients with food allergy will experience mostly symptoms in organs distal to the site of primary sensitization, suggesting that a specific tropism of inflammatory cells might favor organ-specific reactions. It has been shown that patients with atopic dermatitis as a symptom of food allergy exhibit a much larger number of circulating antigen-specific cutaneous lymphocyte antigen (CLA)-expressing T-cells than patients with gastrointestinal symptoms [28]. Likewise, patients with immediate-type IgE-mediated food allergy have a high number of the mucosal homing integrin, α4β7 expressing lymphocytes [29]. These observations suggest that memory T-cells could play a role in the preferential localization of allergic reactions. However, it is not clear if homing receptor expressing T-cells favor local IgE production and secondarily mast cells degranulation, or if they may help to prime the allergic reaction. A specific feature of the food-induced respiratory reaction, similarly to atopic dermatitis, is the possibility of the occurrence of a late-phase reaction mostly related to the inflammatory response [30].

Allergens

A short list of specific foods has been implicated in allergic reactions, including cutaneous, gastrointestinal, and respiratory symptoms that have been subsequently confirmed in

well-controlled, blinded food challenges [4,31–33]. Anaphylactic reactions to foods including significant respiratory symptoms, and in some cases, fatal and near-fatal anaphylactic reactions have been reported [34–36]. Some food allergens seem to be more prone to present with respiratory tract symptoms. Respiratory reactions, including 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 [21]. The presence of asthma was a risk factor for these patients to have more severe reactions (33% versus 21%; $p < 0.0001$). Fish or shellfish allergy defined by established criteria was reported in 5.9% of households using a nationwide, cross-sectional, random telephone survey and standardized questionnaire [22]. Respiratory symptoms included shortness of breath and throat tightness and they were reported by more than 50% of those surveyed. Moreover, sesame allergy is a significant, serious, and growing problem. Immediate hypersensitivity, including respiratory symptoms and systemic anaphylaxis, has been observed [37].

Other food allergens have been implicated by the inhalation route as opposed to the ingestion route as a cause for respiratory tract symptoms secondary to food hypersensitivity. Investigations confirming this have included foods including poppy seed [38], carrot [39], sunflower seeds [40], lupine [41,42], asparagus [43], and soybean [44]. For example, asthma attacks and mortality due to inhalation of soybean antigens in Barcelona, Spain, have been well documented. Strict protective measures in the unloading process were established in 1998 to avoid the release of soybean dust into the atmosphere. These measures have reduced the concentration of soybean dust in the atmosphere and have demonstrated the effectiveness of these measures [44].

A high percentage of patients with asthma perceive that food additives contribute to a worsening of their respiratory symptoms [45]. Several different food additives, including monosodium glutamate (MSG), sulfites, and aspartame, have been implicated in adverse respiratory reactions [46]. Well-controlled investigations in this area, however, have reported a prevalence rate of less than 5% [14,31].

There is conflicting evidence that some people with asthma are more likely to have adverse effects from MSG compared to the general population. Woods and co-workers [47] 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 adult asthmatic subjects who perceived that MSG adversely affected their overall asthma control. In addition, these investigators observed no significant changes in bronchial hyperresponsiveness or soluble inflammatory markers (e.g. eosinophil cationic protein, tryptase) during this investigation. In addition, another recent investigation performed double-blind, placebo-controlled oral challenges with MSG

in subjects who had histories of adverse reactions [48]. While the participants experienced no specific upper or lower respiratory complaints, 22 (36.1%) of the 61 enrolled subjects had confirmed adverse reactions to MSG including headache, muscle tightness, numbness, general weakness, and flushing.

Routes of exposure and subsequent respiratory symptoms

Oral ingestion of food allergens

Oral ingestion is the primary route of exposure to food that can cause or exacerbate respiratory symptoms (e.g. asthma). The vast majority of published reports, which are highlighted in this chapter, focus on respiratory tract symptoms following the ingestion of food allergens. These reactions will be discussed in more detail throughout this chapter and in other chapters.

Common food allergens implicated in respiratory reactions

All respiratory reactions	Near-fatal and fatal anaphylaxis
Hen's egg	Peanuts
Cow's milk	Tree nuts
Peanut	Shellfish
Fish	
Shellfish	
Tree nuts	

Inhalation of food allergens

As opposed to the oral ingestion of food allergens, several investigations have highlighted cases of respiratory allergic disease that have been precipitated by the inhalation exposure to airborne food allergens. Highly allergic persons 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 [49]. Seafood allergens aerosolized during food preparation are a source of potential respiratory and contact allergens. Shrimp and scallops demonstrate significant cross-reactivity. The primary cross-reactive allergen of these two foods is the 35–39kDa heat-stable allergen, previously demonstrated to be muscle tropomyosin [50]. Another report highlighted allergic reactions associated with airborne fish particles in patients with fish allergy [51]. These investigators evaluated children who reported allergic reactions upon incidental inhalation of fish odors or fumes. By using air sampling and an immunochemical analytic technique, fish allergen was detectable in the air of an open-air fish market. Avoidance of a food allergen, such as fish, should include the prevention of the exposure to aerosolized particles through inhalation in relevant environments [52]. An Internet-based survey of

51 anaphylactic reactions to foods revealed that most reactions (40 (78%)) occurred after ingestion, while eight (16%) reactions occurred after exclusive skin contact and three (6%) after inhalation [53]. Of interest, anaphylaxis after inhalation was graded as severe in three of eight subjects (38%).

Roberts *et al.* recently reported that a group of children with food allergies also developed asthma when exposed to the aerosolized form of the food [54]. Children with IgE-mediated food allergy developed asthma on inhalational exposure to the relevant food allergen while it was being cooked. Subjects were exposed for 20 minutes to the aerosolized form of the allergen and adverse clinical symptoms and lung functions were monitored. Twelve children with food allergy developed asthma on inhalational exposure to relevant food allergens. The implicated foods were fish, chickpea, milk, egg, or buckwheat. Nine of the 12 children consented to undergo a bronchial food challenge. Five challenges were positive with objective clinical features of asthma. In addition, two children developed late-phase symptoms with a decrease in lung function. Positive reactions were seen with fish, chickpea, and buckwheat. There were no reactions to the seven placebo challenges. These data demonstrate that, as in the case of other aeroallergens, inhaled food allergens can produce both early- and late-phase asthmatic responses. The investigators highlighted the importance of considering foods as aeroallergens in children with co-existent food allergy and allergic asthma. For these children, dietary avoidance alone may not be sufficient and further environmental measures may be required to limit exposure to aerosolized food.

Occupational as well as non-occupational exposures to food allergens by the inhalation route have been investigated. For example, a recent investigation from Greece examined the prevalence, work-related symptoms and possible risk factors for IgE-mediated sensitization in seafood-processing workers [55]. Sixty-four fish and seafood-processing workers were compared with 60 controls regarding sensitization to seafood allergens. Twenty-three of 64 workers (35.9%) were sensitive to at least one of the seafood allergens tested, as opposed to 10% of the controls. Presence of atopy ($p = 0.02$) and the intensity ($p = 0.03$) and duration of exposure ($p = 0.03$) were found to be the potential risk factors for sensitization. Four of 64 (6.25%) workers reported work-related symptoms. Therefore, occupational exposure to fish and seafood may increase the likelihood of sensitization to these important allergens, and atopy and the duration and intensity of exposure are the associated risk factors. Moreover, another report focused on three patients who developed asthma and rhinitis caused by exposure to raw, but not cooked, green beans and chards in a non-occupational environment [56]. Minor differences were observed in IgE reactivity between nitrocellulose-blotted raw and boiled green bean extracts. Rhinitis symptoms among bell pepper greenhouse employees can be caused by an allergy to occupational

allergens, such as green pepper pollen. Sensitization to bell pepper pollen had a significant negative effect on all the domain and mean quality of life scores tested. Bell pepper greenhouse employees have impaired overall quality of life assessments because of their sensitization to bell pepper pollen [57]. One case report highlighted a 40-year-old female cook who experienced sneezing, rhinorrhea, contact urticaria, and wheezing within a few minutes of handling or cutting raw carrots. IgE sensitization to carrot and an inhalation provocation test while handling carrots were both positive [58]. Finally, another case report implicated lupine inhalation as a provocative trigger for asthma in a child [42].

Allergic sensitizations to other foods have been reported through the inhalation route. A case of oral syndrome after eating sunflower seeds has been reported. Allergic sensitization most likely occurred through inhalant route when these seeds were used to feed birds [40]. In addition, airborne carrot allergens have been implicated in patients with carrot-induced asthma. Airborne carrot allergens were able to sensitize these patients without the implication of a previous birch pollen allergy [39]. Finally, Sicherer and colleagues have reported that patients with peanut allergy might experience adverse respiratory reactions when they are exposed to peanut dust on airline flights serving peanut snacks [59].

Occupational exposures to airborne food allergens can also result in chronic asthma. For example, Baker's asthma is caused by occupational exposure to airborne cereal grain dust [60]. Published data suggest that a significant percentage of bakers develop occupational asthma and chronic obstructive bronchitis. Interestingly, the frequency of a positive methacholine test was 33% in bakers with atopic status, compared to 6.1% ($p < 0.01$) in those without atopic status. In another investigation involving bakers who displayed a positive skin test to wheat flour, a specific bronchial challenge test with flour was positive in two (13.3%) bakers versus none in the bakers with a negative skin test to wheat [61]. Inhalation of dust from different enzymes can be the cause of occupational asthma in exposed workers. One study characterized exposure to inhalation dust, wheat flour, and α -amylase allergens in industrial and traditional bakeries [62]. Furthermore, occupational allergens including wheat and fungal α -amylase can be found in house dust from the homes of bakers and levels are associated with hygienic behavior and distance to the bakery [63].

Bakery workers have been reported to develop IgE-mediated occupational asthma to soybean flour. The allergens involved are predominantly high-molecular-weight proteins that are present in both soybean hull and flour, and they are different from the allergens causing asthma outbreaks, which are mainly low-molecular-weight proteins concentrated in the hull [64]. Sensitization to soybean hull allergens has been reported in subjects from Argentina, a soybean producing

country. Specific IgE and IgG4 to an identified soybean hull allergen are common in serum samples from allergic individuals living in rural areas in this country. Sensitization to this allergen is common in subjects who are repeatedly exposed to soybean dust inhalation [64,65]. Furthermore, bakery workers may develop IgE-mediated allergy to liquid and aerosolized hen's egg proteins that are commonly used in the baking and confectionery industries. Four bakery workers were studied who had work-related allergic respiratory symptoms upon exposure to egg aerosols. Specific IgE determinations to egg white were positive in all patients, to lysozyme in two, to ovalbumin in three, to ovomucoid in two, and to egg yolk in two of them. Methacholine inhalation challenges revealed bronchial hyperresponsiveness in all workers. Specific inhalation challenges elicited early asthmatic reactions in all subjects, and DBPCFCs with raw egg white were positive in three subjects. Therefore, these bakery workers had developed IgE-mediated occupational asthma to hen's egg white proteins [66].

Another report highlighted an observation that inhalation of lupine flour may be an important cause of allergic sensitization in exposed workers and may actually give rise to occupational asthma and food allergy [41]. Therefore, lupine seed flour may be a potential sensitizing agent by inhalation in exposed workers and may give rise to occupational asthma and food allergy. Finally, asparagus is a relevant source of occupational allergy. Severe disease (e.g. anaphylaxis or asthma) has been reported [43].

Differential diagnosis of food-induced respiratory syndromes

Many open questions remain when evaluating respiratory manifestations possibly related to foods. Unlike common skin symptoms such as urticaria, respiratory manifestations are typically chronic or may be delayed mostly due to the pattern of inflammatory manifestations of the respiratory tract. This section will review potential manifestations of food allergy in the respiratory tract according to questions most frequently raised by the clinician.

Which respiratory symptoms could be due to food allergy?

Recurrent or chronic rhinitis induced by food allergy

Acute symptoms of rhinitis accounted for 70% of the overall respiratory symptoms observed in a large group of children undergoing DBPCFCs [67]. These symptoms typically occur in association with other clinical manifestations (i.e. cutaneous and/or gastrointestinal symptoms) during allergic reactions to foods, and rarely occur in isolation [31,67]. Chronic or recurrent rhinitis, mostly in pre-school children, is sometimes associated to allergic reactions mostly to milk. While some patients claim of a significant decrease of the symptoms

on an avoidance diet, a clear relation has not been reproduced by validated studies. Some patients also link consumption of milk-protein-containing products to increased amounts of secretion of the nose and the upper respiratory tract. Again there is no evidence of an allergy-related mechanism.

Recurrent or chronic otitis media induced by food allergy

Serous otitis media has multiple etiologies, of which the most common is viral upper respiratory tract infections. Allergic inflammation in the nasal mucosa may cause Eustachian tube dysfunction and subsequent otitis media with effusion. The few studies that have investigated an allergic mechanism for the role of food allergy in recurrent serous otitis media are controversial both by the study design and by interpretation of the results [68,69].

Dyspnea associated to anemia in infants

In 1960, Heiner reported a syndrome in infants consisting of recurrent episodes of pneumonia associated with pulmonary infiltrates, hemosiderosis, gastrointestinal blood loss, iron-deficiency anemia, and failure to thrive [70]. This syndrome is most often associated with a non-IgE-mediated hypersensitivity to cow's milk proteins. While increased peripheral blood eosinophils and multiple serum precipitins to cow's milk are commonly observed, the specific immunologic mechanisms responsible for this disorder are not known [71]. The diagnosis is suggested by infiltrates on the chest X-ray, anemia, hemosiderosis evidenced by bronchio-alveolar lavages and elimination of the precipitating allergen leading to subsequent resolution of symptoms. The presence of characteristic laboratory data including precipitating antibodies to cow's milk is also considered necessary to make the diagnosis. This food-induced syndrome with respiratory manifestations has not led to any recent publications and is only very rarely observed even in referral clinics for childhood food allergy.

Acute asthma induced by food allergy

The wide use of standardized food challenges has provided a better view of the type and the frequency of respiratory reactions in food allergy. Hill and colleagues challenged 100 milk-allergic patients with a mean age of 16.2 months and elicited cough and/or wheeze in 20 patients, rhinitis in 12 patients, and stridor in 2 patients. Cough and wheezing were more frequent in the groups of patients who initially presented with chronic eczema and recurrent bronchitis, and with urticaria and eczema. Lower respiratory symptoms were only observed in 2 of the 53 patients (4%) with mostly gastrointestinal symptoms [72]. Respiratory reactions induced by food challenges in children with pulmonary disease at National Jewish Center for Immunology and Respiratory Medicine have been reported by Bock [73]. Of

the 410 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 that were responsible for these reactions included: peanut 19, cow's milk 18, egg 13, and tree nuts 10. Interestingly, only 5 (2%) of these patients had wheezing as their only objective adverse symptom. In addition, 10 of the group of 188 children without a history of asthma had wheezing elicited by the food challenge, showing a tendency for a bronchial response in the absence of a concomitant asthma.

A total of 320 children predominantly presenting with atopic dermatitis undergoing blinded food challenges at Johns Hopkins Hospital were monitored for respiratory reactions [67]. The patients, aged 6 months to 30 years, were highly atopic, had multiple allergic sensitivities to foods, and over one-half had a prior diagnosis of asthma. In the 205 (64%) patients with food allergy confirmed by blinded challenges, almost two-thirds experienced respiratory reactions during their positive food challenges (e.g. 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 in 10 patients, however, only six patients had a >20% decrease in forced expiratory volume in 1 second (FEV1). As documented in the investigations cited earlier, wheezing as the only manifestation of the respiratory reaction was a rare observation.

In 2002, Rancé and Duteau reported a series of 163 children in which 385 DBPCFCs were performed [74]. Overall, 250 (65%) tests were positive to mostly peanuts (31%), hen's egg (23%), and cow's milk (9%). Cutaneous symptoms were observed in most positive challenges (59%), but respiratory reactions were also frequent (24%). Among the respiratory reactions, oral symptoms (5%), rhinitis and conjunctivitis (6%), and asthma (10%) were observed. Again, isolated asthma was rare, as it was documented as the sole manifestation in only 2.8% of the challenges.

If lower respiratory reactions are present in patients without asthma, does food allergy predispose to bronchial hyperreactivity?

It has been observed in patients with atopic dermatitis and food allergy that the food avoidance diet significantly improved their asthma, despite absence of respiratory symptoms during food challenges. This prompted a series of investigation on bronchial hyperreactivity (BHR) in food-allergic patients without overt respiratory symptoms. In one investigation, 26 adolescents and young adults with asthma and food allergy were evaluated using methacholine inhalation challenges

for changes in their BHR before and after blinded food challenges [75]. Of the 22 positive blinded food challenges, 12 (55%) involved chest symptoms (cough, laryngeal reactions, and/or wheezing). Another 10 (45%) positive food challenges included laryngeal, gastrointestinal, and/or skin symptoms without any chest symptoms. Significant increases in BHR were documented several hours after positive food challenges in 7 of the 12 (58%) patients who experienced chest symptoms during these challenges. During the actual food challenges decreases in FEV1 were not observed in these seven patients suggesting that significant changes in BHR can occur without demonstrable pulmonary function changes in a preceding food challenge. These data confirmed that food-induced allergic reactions may increase airway reactivity in a subset of patients with moderate to severe asthma, and may do so without inducing acute asthma symptoms.

In contrast, another investigation concluded that food allergy is an unlikely cause of increased airway reactivity [76]. 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 BHR, as determined by methacholine inhalation challenges, 24 hours after blinded food challenges to either food allergen or placebo. Unfortunately, the small number of patients investigated and the lack of environmental controls prior to the repeat methacholine challenges limit their conclusions. Overall these studies suggest induction of BHR for a limited time (<24 hours) after a single exposure to a food.

Two more recent studies indicate that patients with food allergy in the absence of asthma might have increased BHR. Thaminy *et al.* studied 35 non-asthmatic patients with food allergy, and found BHR by methacholine inhalation challenges in 10 of 19 patients (53%) [77]. Similarly, Kivity *et al.* investigated patients with food allergy with or without asthma and/or allergic rhinitis by spirometry, methacholine challenges, and sputum-induced cell analysis [78]. BHR by methacholine challenge was observed in all patients with asthma, and in 40% of patients with food allergy alone. They also found mainly eosinophils in the sputum of patients with asthma, and neutrophils in the patients with food allergy but no asthma. This observation has been confirmed by other investigators, who in addition to an increased proportion of neutrophils in non-asthmatic food-allergic patients found also increased levels of IL-8 [79].

An animal study came to a similar conclusion, as mice sensitized by intraperitoneal injection of ovalbumin in the presence of alum and then exposed to intratracheal ovalbumin had a significant airway inflammation for up to 12 days after a single intranasal challenge to ovalbumin [80]. Interestingly, an unrelated antigen, house dust mite, induced a similar inflammatory response. Taken together, these observations suggest that food sensitization with non-respiratory manifestations of food allergy might also enhance inflammation

in other mucosal tissues. Hence, non-asthmatic patients diagnosed with food allergy should be carefully evaluated for bronchial inflammation in order not to delay appropriate anti-inflammatory treatment if necessary.

Do respiratory symptoms contribute to the severity of acute allergic reactions to foods?

Until two decades ago, fatal food-induced anaphylaxis had mainly consisted of anecdotal reports of isolated cases. In 1988, Yuninger *et al.* reported a series of seven cases identified over a 16-month period [35]. Five patients reacted to a nut or to peanuts. The authors highlighted the fact that “the majority were highly atopic individuals with histories of asthma, eczema, and/or rhinitis.” Only 4 years later, Sampson *et al.* reported on the circumstances of 13 fatal and near-fatal anaphylactic reactions in children and adolescents [34]. Again, most patients reacted to a nut or to peanuts, and all patients had a history of asthma. This report provided additional information on current asthma medication in these patients. Inhaled β -adrenergic drugs were taken by all but one, and most were either on inhaled beclomethasone or cromolyn and/or theophylline. Taken together these reports revealed that chronic bronchial inflammation may have contributed to the acute reaction to the food. Moreover, respiratory symptoms were prominent in all patients, and most probably determined the outcome of the reaction. More recently Bock *et al.* analyzed the circumstances of 32 fatal cases after food-induced anaphylaxis reported to a national registry [81]. Similar results to the two publications described above were reported, as allergies to peanuts and tree nuts elicited most fatalities. In addition, all patients with adequate information but one were known to have asthma. These reports highlight an increased risk for severe food-induced anaphylaxis in patients with asthma, in particular those needing chronic medications. Follow-up visits in these patients should emphasize the importance of a good asthma control plan, and should assure availability and proper instruction of the use of self-injectable epinephrine.

Should patients with recurrent or chronic asthma be routinely tested for food allergy?

Food allergy is often suspected in the quest for allergic triggers of recurrent or chronic asthma. However, a clear link between ingestion of a specific food and worsening of asthma is only exceptionally reported. In one investigation, 300 consecutive patients with asthma (age range: 7 months to 80 years) were evaluated in a pulmonary clinic [14]. Twenty-five (12%) patients had a history of food allergy suggested by clinical symptoms, and/or positive tests of food-specific IgE antibodies. Food-induced wheezing was documented in 6 (2%) of the cases; all were children aged 4–17 years. In another investigation, 140 children, aged

2–9 years, with asthma were screened by clinical history, and testing for food-specific IgE antibodies [82]. Of these children, 32 patients were able to undergo blinded food challenges: 13 (9.2%) had food-induced respiratory symptoms and 8 (5.7%) had specific asthmatic reactions documented during food challenges. Only one patient had asthma as the sole symptom during a positive food challenge. Interestingly, the patients with food allergy and asthma were generally younger and had a past medical history of atopic dermatitis.

Estimated prevalence of food allergy-induced asthmatic reactions	
Clinical population	Estimated prevalence (%)
Infants with cow's milk allergy	29
Food-induced wheezing	2–24
Food additive-induced wheezing	<5
Patients with atopic dermatitis	17–27

In a similar investigation, Oehling and co-workers reported that food-induced bronchospasm was present in 8.5% of 284 asthmatic children evaluated [83]. The majority of the allergic sensitization occurred in the first year of life and was caused by a single food, especially egg. In addition, Businco and colleagues evaluated 42 children (age range: 10–76 months) with atopic dermatitis and milk allergy [84]. Eleven (27%) of these patients developed asthmatic symptoms during a positive food challenge. Finally, an investigation from Turkey confirmed that food allergy can elicit asthma in children less than 6 years; the incidence was 4%. The most common food allergens implicated were egg and cow's milk [85].

In order to evaluate food allergy as a risk factor for severe asthma, Roberts and colleagues investigated 19 children with exacerbations of asthma requiring ICU ventilation [86]. When compared to controls, these patients had an increased risk of food allergy (OR: 8.58; 95% CI: 1.85–39.71), multiple allergic diagnoses (OR: 4.42; 95% CI: 1.17–16.71), and frequent asthma admissions (OR: 14.2; 95% CI: 1.77–113.59). The authors concluded that food allergy and frequent asthma admissions appear to be significant, independent risk factors for life-threatening asthmatic events.

A different population, mostly young women with brittle asthma, was investigated for food allergy triggers by Baker *et al.* [87]. They randomized patients into groups with open or blinded food challenges. Challenges were performed with specific foods or a mix of potentially allergenic foods (egg, milk, wheat, fish, orange, peanut, soy) over a 5–9 day period. Peak expiratory flow and FEV1 measures were performed at regular intervals during and after the challenges. More than half of the patients (52–62% according to the groups) had positive tests with significant respiratory reactions. All foods tested elicited reactions: most frequently

oranges (20–58%), wheat (33–62%), egg (17–77%), and milk (42–62%).

In summary, these results suggest that respiratory symptoms may be provoked in a subset of patients with asthma. However, the patient group most frequently tested for food allergy, namely pre-school children with BHR, and mostly virus-triggered asthma, is the one least likely to have food allergy as a trigger of asthma.

Evaluation/management

Medical history

A comprehensive medical history should be obtained in patients suspected of having food allergy-induced respiratory tract symptoms or anaphylaxis [49]. The history should include questions about the timing of the reaction in relation to food ingestion, the minimum quantity of food required to cause symptoms, specific upper and lower respiratory signs and symptoms, the reproducibility of the symptoms, and a current or past clinical history of allergy to specific food allergens (e.g. egg). A family history positive for allergy and/or asthma can be a useful historical point. When there is a history of an unexplained sudden asthma exacerbation, details about preceding food ingestion should be elicited. A history of a severe or anaphylactic reaction following the ingestion of a food may be sufficient to indicate a causal relationship. Finally, documentation of the specific treatment received and its response should be compiled.

Physical examination

In evaluating patients with respiratory system complaints that may be induced by food allergy, the physical examination can be useful. Findings here are helpful in assessing overall nutritional status, growth parameters, and any signs of allergic disease, especially atopic dermatitis. Moreover, this examination will help rule out other conditions that may mimic food allergy.

Skin testing for food allergy

When used in conjunction with standard criterion of interpretation, skin testing (e.g. percutaneous) can give reliable clinical information in a short period of time (i.e. 15–20 minutes), and should provide reliable clinical information in the overall workup of a patient with suspected food allergy-induced respiratory tract reactions. The routine use of skin testing to foods in patients presenting with asthma, however, is not practical. Of children evaluated in a tertiary care hospital emergency room, 97 patients with asthma or bronchiolitis were skin tested to common foods and aeroallergens and compared to similar testing in 60 control patients without any respiratory disease [88]. Most specific IgE antibody responses among wheezing children were to aeroallergens; the prevalence of specific IgE antibodies to food allergens was low.

Other testing

Laboratory assessment of food allergy may include the measurement of food-specific IgE in the serum (e.g. IgE RAST, radioallergosorbent testing or quantitative IgE (UniCap; Phadia, Uppsala, Sweden)). When highly sensitive assays are used, the sensitivity is similar to that of skin tests [89–92]. In contrast, basophil histamine release assays, which are mainly limited to research settings, have not been shown conclusively to be a reproducible, diagnostic test for food allergy [93]. The diagnostic values of the following tests are not currently supported by objective scientific evidence: food-specific IgG or IgG subclass antibody concentrations, food antigen–antibody complexes, cytotoxic food tests, and subcutaneous provocation and neutralization [94,95].

Food challenges

When there is a clinical suspicion of a food-induced respiratory tract reaction and the test for specific IgE antibody to the food is positive, an elimination diet may be implemented to see if there is a resolution of clinical symptoms. Confirming this association, however, can be very difficult. Food challenges can be very useful and reliable in the diagnostic evaluation of a patient with food-induced respiratory symptoms. An excellent publication has reviewed the combined clinical experience of six centers conducting food challenges [96]. Of these procedures, the DBPCFC is the best method to diagnose and confirm food allergy and other adverse food reactions. These challenges should be conducted in a clinic or hospital setting with available personnel and equipment for treating systemic anaphylaxis. If the clinical history does not suggest a high risk of a severe reaction, an oral food challenge can be performed in the office setting.

Treatment

Once a food allergy has been confirmed as a cause for respiratory tract symptoms, strict avoidance of the offending food is necessary [31,90,93]. A properly managed elimination diet can lead to resolution of clinical symptoms, such as chronic asthma. Appropriate nutritional counseling is important to ensure that an elimination diet is well balanced, to provide appropriate substitutes for foods that are eliminated from the diet, and to avoid any anticipated nutritional deficiencies, such as calcium deficiency [97–99]. Growth parameters should be closely monitored, especially in infants and children on elimination diets. Woods and co-workers were unable to prove that the ingestion of dairy products induced bronchoconstriction in a group of adults with asthma. They recommended that patients with asthma should not be unnecessarily restricting their dairy product intake, which could lead to the development of nutritional deficiencies [47]. Therefore, restriction diets should exclude only those foods proven to provoke food allergy [31,90].

An emergency plan should be written to help patients manage their clinical symptoms caused by accidental ingestion of a relevant food allergen [34,90,100]. For children, the written plan should be given to the appropriate school personnel. Self-injectable epinephrine and antihistamines must be immediately available to treat allergic reactions after accidental ingestions. Epinephrine is the drug of choice to treat acute, severe reactions and to allow time to seek immediate medical attention.

Summary and conclusions

Previous investigations have clearly established the pathogenic role of food allergy in respiratory tract symptoms in a subset of patients. These symptoms are typically accompanied by skin and gastrointestinal manifestations and rarely occur in isolation. Specific foods have been implicated in these reactions. Allergic sensitization to foods in infancy predicts the later development of respiratory allergies and asthma. The role of food allergy in otitis media is controversial and probably is very rare. Likewise, asthmatic reactions to food additives can occur but are very uncommon. Food-induced asthma is more common in young pediatric patients, especially those with atopic dermatitis, than in adolescents and adults and can be triggered by inhalation of a relevant food allergen. Respiratory symptoms, especially asthma, induced by food allergens are considered risk factors for fatal and near-fatal anaphylactic reactions.

Studies have demonstrated that foods can elicit airway hyperreactivity and asthmatic responses; therefore, evaluation for food allergy should be considered among patients with recalcitrant or otherwise unexplained acute severe asthma exacerbations, asthma triggered following ingestion or inhalation of particular foods, and in patients with asthma and other manifestations of food allergy (e.g. anaphylaxis, moderate to severe atopic dermatitis). Practice parameters for the diagnosis and treatment of asthma have recently highlighted the potential role of food allergy in asthma in some patients [101].

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