

## REVIEW

## Food allergy and asthma

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**Abstract**

Food allergy and asthma commonly co-exist in the same patient with approximately one-third of children with food allergy having asthma. When both atopic conditions are present a food allergic patient is placed at greater risk of having a fatal reaction from food allergen exposure. For this reason asthma should be diligently managed in a food allergic patient and these patients should be carefully instructed on allergen avoidance and the proper use of self-injectable epinephrine. This review summarises the available literature regarding patients with both food allergy and asthma specifically looking at disease prevalence, IgE-mediated effects on the lower respiratory tract secondary to foods, the interplay of food additives and asthma, and food allergy as a risk factor for asthma morbidity with practical applications for clinicians.

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**Introduction**

Food allergy is defined as an adverse immune response to food proteins. Reactions may be either IgE-mediated or non-IgE-mediated. IgE-mediated reactions typically involve the skin, gastrointestinal and respiratory tracts, and include symptoms such as urticaria, angioedema, vomiting, diarrhoea, asthma or stridor.<sup>1</sup> Wheezing is a common manifestation of food allergy in association with other systemic symptoms, but it is seldom the only symptom. While dietary manipulation rarely results in improved asthma control, children with asthma and food allergy are more likely

to have fatal allergic reactions to food;<sup>2</sup> therefore, aggressive asthma control must be achieved in this patient population. This review explores the relationship between food allergy and asthma and gives practical applications for the clinician.

**Prevalence of asthma and food allergy**

Western countries have noticed an increase in the prevalence of asthma and allergies since about 1960. Devenny *et al.* showed an increase in the prevalence of children with asthma – as reported by parental-completed questionnaires – in Aberdeen, UK, from less than 5% in 1964 to approximately

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25% in 1999.<sup>3</sup> Between 1980 and 1996 the incidence of self-reported asthma in the United States increased from 2.5 per 1000 to 6.0 per 1000.<sup>4</sup> However, it is important to note that recent surveys have shown asthma prevalence to be plateauing in developed countries such as Belgium,<sup>5</sup> Great Britain,<sup>6</sup> Singapore,<sup>7</sup> Hong Kong,<sup>8</sup> and Switzerland.<sup>9</sup> According to the National Health Interview Survey in the USA it was estimated that an annual average of 20 million people had a diagnosis of asthma between 2001 and 2003. Of these, 6.2 million were children less than 18 years-old.<sup>10</sup>

There is also evidence that the prevalence of food allergy has increased in the past 10 to 15 years. Reports from the USA and the UK have shown approximately a two-fold increase in the number of children with peanut allergy with more than 1% of children affected.<sup>11-13</sup> The prevalence of IgE-mediated food allergy in the USA varies between 2–5%.<sup>14</sup> It is greater in the pediatric population than in adults, with estimates of 6–8% in children under 5 years old and 3–4% in adults.<sup>15</sup> Reports in Europe suggest the prevalence of food allergy to be between 0.3 and 7.5% in children and 2–4% in adults.<sup>16,17</sup> It is also seen more often in individuals with atopic dermatitis.

Various factors in a Westernised lifestyle have been proposed as possible links to an increase in atopy, though none have been proven. These factors include:

1. Increased exposure to house dust mite due to people spending more time indoors as well as changes in modern housing being more favourable for house dust mite growth.<sup>18</sup>
2. The “hygiene hypothesis” suggests that “declining family size, improved household amenities and higher standards of personal cleanliness have reduced opportunities for cross-infection in young families.”<sup>19</sup> In turn, the decreased exposure to microorganisms has been theorised to increase susceptibility to allergic diseases by altering immune system development.
3. Epidemiologic studies have linked obesity with the development and severity of asthma.<sup>20</sup>
4. Decreased antioxidant intake and increased fat consumption in the Western diet have been implicated, though results have been inconclusive in proving the link between allergy, asthma and diet.<sup>21</sup>
5. Children raised on a farm have been shown to have reduced prevalence of allergic disease. One study suggests that consumption of unpasteurised milk by children raised on farms may contribute to decreased allergic sensitisation.<sup>22</sup>

## Food allergy and asthma: public perception

The public perception of the role of food allergy in asthma control is different from what has been proven in medical

studies. Dawson *et al.* reported that 64% of parents with asthmatic children in New Zealand had made dietary changes believing this would help control their child's asthma.<sup>23</sup> In another study looking at questionnaires given to asthma clinic patients, 61% reported that they had made dietary changes to improve their asthma control, and of those patients 79% believed that it helped.<sup>24</sup>

## Food allergy as a predictor of asthma

Considering both food allergy and asthma together, approximately one third of children with food allergy have asthma and 4–8% of children with asthma have food allergies.<sup>25,26</sup> Developing asthma has been linked to certain food sensitivities. Tariq *et al.* looked at the Isle of Wight cohort and found that children with egg allergy as an infant were more likely to develop asthma or allergic rhinitis with an odds ratio of 5.0.<sup>27</sup> Similarly, Rhodes *et al.*<sup>28</sup> examined a cohort of 100 babies from atopic parents in Poole, England. In this cohort respiratory events were reported annually, skin prick tests were done, and total serum IgE measurements were made during the first five years of life. They found that a positive skin prick test response to hen's egg, cow's milk, or both, in the first year of life was independently predictive of adult asthma with an odds ratio of 10.7. Studies performed by Gustafsson<sup>29</sup> and Kotaniemi-Syrjanen<sup>30</sup> found similar results in smaller cohorts followed over shorter periods of time. Kotaniemi-Syrjanen also reported sensitivity to wheat as being predictive of the development of childhood asthma.

## Lower respiratory tract reactions to foods

A few foods cause the majority of reactions. In young children in the USA the most common causal foods are cow's milk (2.5%), egg (1.3%), peanut (0.8%), wheat (approximately 0.4%), soy (approximately 0.4%), tree nuts (0.2%), fish (0.1%) and shellfish (0.1%).<sup>1</sup> It is believed that allergies to soy and wheat will resolve by school age in the majority of young children, though rigorous studies have not been performed.<sup>31</sup> Recent studies have shown that cow's milk allergy is resolved in 19% of children by the age of 4 years, 42% by age 8 years, 64% by age 12 years, and 79% by the age of 16 years.<sup>32</sup> Egg allergy typically resolves in 4% of children by the age 4 years, 12% by 6 years, 37% by 10 years, and 68% by 16 years.<sup>33</sup> Peanut, tree nut, and seafood allergies are more likely to be persistent. In adults in the USA the most common allergens are shellfish (2%), peanut (0.6%), tree nuts (0.5%), and fish (0.4%).<sup>1</sup> In addition to these foods, the European Union requires sesame, mustard, celery, sulphites, and lupin to be declared on food labels.<sup>34</sup> Allergic reactions to fruits and vegetables are more often reported in Europe with *Rosaceae* fruits and vegetables topping the list of reported allergens in France.<sup>17</sup>

The most common pulmonary manifestation of IgE-mediated food allergy is wheezing. This may occur after ingestion of the food allergen or after exposure to aerosolised particles of the allergen. Wheezing may develop when food such as fish, egg or shellfish is cooked in a confined space.<sup>35</sup> Fish allergen has even been detected from air samples in a fish market by using a competitive IgE immunoassay.<sup>36</sup> Peanuts and tree nuts have been implicated as causing allergic reactions when aerosolised in an airplane.<sup>37</sup> The most widespread epidemic of airborne food-induced asthma has been reported in Barcelona.<sup>38</sup> Unloading soybean and the resulting soybean dust at a local port was linked to episodic epidemics of sudden, severe and sometimes fatal asthma attacks which decreased after filtering methods were instituted to decrease the amount of aerosolised soybean.

Several studies have looked at reactions to foods after double-blind placebo-controlled food challenges (DBPCFC), the gold standard for diagnosing food allergy. Rarely is wheezing alone described as the presenting symptom. In 1992 Bock published a report of 279 asthmatic children with a history of food-induced wheezing who underwent DBPCFCs.<sup>39</sup> One hundred and sixty-eight (60%) of these children had at least one organ system affected upon challenge with the suspected food. Sixty-seven of the 168 children (40%) had wheezing. Only five patients had wheezing as the only symptom. The same group reported that out of 188 patients with food allergy but without a history of wheezing after ingestion, only 10 (5%) had wheezing along with reactions in other organ systems and none had wheezing alone.

James *et al.* reported DBPCFCs in 320 patients (aged 6 months to 30 years) with atopic dermatitis and food hypersensitivity.<sup>40</sup> More than half of these patients had a prior diagnosis of asthma and all had sensitivities to multiple foods. Blinded challenges confirmed the presence of food allergy in 205 (64%) of these patients with reactions in at least one organ system. Respiratory reactions were experienced in almost two-thirds of the patients (nasal, 70%; laryngeal, 48%; pulmonary, 27%). Overall 17% (34 patients) developed wheezing as part of their reaction. Spirometry was performed in a subset of patients undergoing challenges. Thirteen of those experienced lower airway symptoms but only six had a decrease of more than 20% in the first second of exhalation. Wheezing as the sole manifestation was rare.

In another study 300 asthmatic patients (aged 7 months to 80 years) were screened in a respiratory clinic.<sup>41</sup> DBPCFCs were performed in 25 of these patients suspected of having food-related asthma based on history and/or positive tests of food-specific IgE antibodies. Only six (2%) of these patients had food-induced wheezing. All six patients were children from 4 to 17 years of age.

In addition to those studies, reports from Novembre,<sup>42</sup> Oheling,<sup>25</sup> Businco,<sup>43</sup> Hill,<sup>44</sup> Spergel,<sup>45</sup> and Yazigoclu<sup>46</sup> support these findings. Blinded challenges have confirmed that respiratory reactions are most often caused by peanut, tree nuts, egg, milk, soy, fish, and shellfish.<sup>47-50</sup> Peanuts and tree nuts seem to play a very prominent role, with Sampson *et al.* reporting 25 episodes of wheezing in 101 atopic children with acute reactions to peanut.<sup>48</sup>

## Dietary effects on asthma control

Investigators have looked at the role of diet in the aetiology of asthma. A single-blind prospective study performed by Yusoff *et al.*<sup>51</sup> looked at the effect of egg and milk avoidance in 22 asthmatic children between the ages of 3 and 14. Assignment to either the avoidance group or the control group was determined by parental choice. Children in the experimental group that were able to perform peak flow testing had a significant change in peak expiratory flow (PEF) rate as compared to the control group – leading the investigators to conclude that an egg- and milk-free diet can reduce atopic symptoms and improve lung function in asthmatic children.

Similar results have not been replicated in adults. A double-blind, crossover, placebo-controlled trial was conducted looking at 20 adults to see if the consumption of dairy products worsened their asthma control.<sup>52</sup> Ten of the patients perceived that dairy products worsened their asthma. None of the patients had positive skin prick tests to milk. Subjects complied with a dairy-free diet throughout the study. The active challenge was a single-dose drink equivalent to 300 ml of cow's milk. For both forced expiratory volume in one second (FEV<sub>1</sub>) and PEF there were no statistically significant differences in group means between active challenge and placebo challenge, between sequence of administration, or between perceptions. The authors concluded that it is unlikely that dairy products have a specific bronchoconstrictor effect in most patients with asthma, regardless of their perception. In a similar study conducted by Nguyen,<sup>53</sup> 25 adult asthmatic patients without evidence of cow's milk sensitisation showed no evidence of bronchoconstriction following a 14-day period without cow's milk and then a challenge. A more rigorous scientific approach used in the Woods<sup>52</sup> and Nguyen<sup>53</sup> studies may explain differences between their outcomes and those reported by Yusoff.<sup>51</sup> There are currently no published studies in children apart from the Yusoff report showing a benefit to milk and egg exclusion in asthma control. General food avoidance for the treatment of asthma is not currently recommended.<sup>54</sup>

The effect of sodium, potassium, magnesium, antioxidants (vitamin C and E), and fatty acids on asthma have all been investigated.<sup>55-58</sup> Despite various reports of improvement in

bronchial reactivity there is no conclusive evidence of improvement in asthma with dietary control.<sup>26</sup> Therefore, apart from allergen avoidance in patients with documented IgE-mediated food allergies currently there are no recommendations to avoid any foods in the treatment of asthma.<sup>54</sup>

## Food additives and asthma

Food additives as a trigger of asthma have been a controversial area with little data to support a cause and effect. Patients may perceive that food additives have a role in worsening their asthma,<sup>59</sup> but studies have shown the prevalence to be much less than 1% of the total population.<sup>60</sup> In fact, one survey in Britain of more than 15,000 patients who self-reported challenges found the prevalence of adverse reactions to additives to be from 0.01%–0.23%.<sup>61</sup> There are more than 2500 food additives with few linked as triggers of asthma. Sulfites and monosodium glutamate (MSG) are the most often implicated and the most studied.

Sulfites are used as a preservative and found in many foods. Foods with the highest sulfite content include dried fruits, wine, molasses, sauerkraut, white grape juice, dried potatoes, gravies, fresh shrimp, pectin, corn syrup, pickles, and relishes.<sup>54</sup> The largest study performed looking at the role of sulfites in asthmatics showed that out of 203 asthmatics tested, five non-steroid-dependent and 16 steroid-dependent asthmatic patients experienced a >20% reduction in their FEV<sub>1</sub> within 30 minutes following oral challenge.<sup>62</sup> Twelve of these sulfite reactors were re-challenged with metabisulfite capsules in a double-blind protocol. Only three of seven steroid-dependent patients had a positive response on re-challenge, and only one of five non-steroid-dependent patients had a response to double-blind challenge. The authors estimated the prevalence of sulfite-induced asthma responses to be less than 3.9% and more prevalent in those with steroid-dependent asthma.

Monosodium glutamate (MSG) is the flavour enhancer that has been held responsible for the “Chinese restaurant syndrome” – which consists of headache, numbness, chest discomfort, weakness, flushing and abdominal discomfort after eating Chinese food.<sup>54</sup> A large study performed at Scripps Research Institute in La Jolla, California challenged 100 asthmatic subjects with 2.5 grams of MSG, 30 of whom reported a history of asthma attacks after eating Chinese food.<sup>63</sup> The mean change in FEV<sub>1</sub> with MSG challenge was no different from that of placebo challenge for any of the patients tested. A randomised, double-blind placebo-controlled MSG challenge conducted by Woods *et al.* was unable to demonstrate MSG-induced immediate or late asthmatic reactions in a group of 12 adults who had asthma and believed MSG was detrimental to their asthma control.<sup>64</sup>

Of note, there were also no changes in soluble inflammatory markers such as eosinophil cationic protein or tryptase. Reports of a fall in FEV<sub>1</sub> six hours after MSG ingestion have been published, though it was concluded that this was not associated with Chinese restaurant syndrome.<sup>65,66</sup>

There are a few case reports but no conclusive evidence that other food additives such as carmine,<sup>67</sup> sunset yellow (yellow dye number 6), amaranth (red dye number 2), erythrosine (red dye number 3), annatto, ponceau,<sup>68</sup> or tartrazine (yellow dye number 5)<sup>69</sup> will trigger an asthmatic response.

## Occupational asthma

In adults, it has been shown that aerosolised food particles may lead to the development of asthma. Baker's asthma is an example of exposure to aerosolised cereal grain leading to the development of asthma.<sup>70</sup> Symptoms include coughing and wheezing after exposure to wheat proteins. Skin prick tests to wheat or serum IgE detection to wheat proteins are positive. The risk to a baker of developing baker's asthma is estimated at 0.3% per year.<sup>71</sup> Other implicated foods reported to cause occupational asthma include egg,<sup>72</sup> enzymes used in the cheese industry,<sup>73</sup> shellfish,<sup>74</sup> milk,<sup>75</sup> and carob bean flour.<sup>76</sup> Pathologically, occupational asthma looks similar to allergic asthma. Oedema, airway smooth muscle hypertrophy and an eosinophilic infiltrate may be observed in both forms.<sup>77</sup>

## Food-induced anaphylaxis and asthma

Food allergy has been identified as an independent risk factor for asthma morbidity. A higher fatality rate of children with asthma was seen in a peanut allergic cohort over a 2- to 14-year follow-up.<sup>78</sup> Out of the 46 subjects in the cohort, four died of an asthma exacerbation. Similarly a diagnosis of asthma was confirmed in 31 of 32 patients with food-related fatalities in a USA physician reported registry.<sup>79</sup> Peanuts and tree nuts were the most commonly implicated foods, followed by egg and milk. In the UK, eight from eight patients with fatal food-induced anaphylaxis had asthma.<sup>80</sup>

The relationship between asthma and concomitant food allergy has been examined in both adults and children. Ernst *et al.* investigated a group of asthmatic adults looking specifically to see if frequent inhaled beta-agonist use was associated with life-threatening asthma.<sup>81</sup> They found that the second most significant risk factor associated with life-threatening asthma was a history of an asthma attack being precipitated by food. Berns *et al.* also found an increase in asthma morbidity in adult patients with concomitant food allergies.<sup>82</sup> Specifically they found that patients with allergies to more than one food had increased asthma hospitalisations, emergency department visits, and use of oral steroids.

Roberts *et al.* looked at a group of children in England being ventilated for a life-threatening exacerbation of



asthma.<sup>83</sup> Out of 19 cases, half had persisting food allergy compared with only 10% of the controls. Similarly Vogel *et al.* found in the USA that children admitted to the intensive care unit for an asthma exacerbation were 3.3 times more likely to report at least one food allergy compared with children admitted to a regular nursing floor and 7.4 times more likely to report at least one food allergy compared with children seen in the ambulatory setting.<sup>84</sup> Recently it has been reported that elevated food-specific IgE levels and allergies to peanut and milk have been associated with increased rates of hospitalisation for asthma in children.<sup>85,86</sup>

Though a clear link between the pathophysiology of food allergy and asthma has not been established, it is suggested that worsening of asthma in patients with an associated food allergy might occur due to four different factors:

1. Immune cells such as T lymphocytes from the intestinal mucosa are activated in food allergic patients.<sup>87-89</sup> These lymphocytes then stimulate bronchial mucosa leading to bronchial hyperresponsiveness.
2. Food allergy may only be a presenting sign of a patient whose immune response is skewed towards a pro-inflammatory allergic reaction.<sup>82</sup>
3. Repeated oral exposure of the food allergen or chronic inhalation of food particles may result in chronic cellular activation with pro-inflammatory cytokines released that worsen asthma.<sup>26</sup>
4. Finally, it is suggested that reactions to food ingestion may have been misdiagnosed as asthma exacerbations since food-induced bronchospasm is often seen in anaphylaxis and there is a delay between allergen exposure and the development of respiratory symptoms.<sup>90</sup>

It should be emphasised that patients with food allergy and asthma are at a greater risk of having a fatal or near-fatal outcome than asthmatics without food allergy.<sup>91</sup> Aggressive treatment of the patient's asthma and education regarding the use of an injectable epinephrine device should always be performed in this patient group.

## Managing food allergy and asthma

Aggressive management of asthma in a patient with underlying food allergy is of the utmost importance since these patients are at increased risk of having fatal or near-fatal anaphylaxis.<sup>90</sup> Diagnosing food allergy begins with a careful history, taking particular note of the timing of the onset of symptoms in relation to food ingestion. IgE-mediated reactions occur within seconds to minutes of ingestion and rarely beyond two hours.<sup>92</sup>

Diagnostic testing by skin prick or *in vitro* testing to measure levels of food-specific IgE should be tailored based on the history. An oral food challenge is performed when history and specific testing do not confirm or refute a food

allergy convincingly. Oral food challenges are structured protocols in which the patient ingests a suspect food under clinician supervision<sup>93</sup> – as mentioned above, double-blind placebo controlled food challenges (DBPCFCs) are the gold standard for diagnosing food allergy. All food challenges should be done in settings equipped with the necessary medications, equipment, and staff to treat anaphylaxis, and should only be performed by allergy specialists familiar with food-allergic reactions.

In the case of unexplained asthma exacerbations a food may be investigated as the underlying trigger with careful detail regarding the patient's diet history in relation to exacerbations. Identification of the allergen and elimination along with the assistance of a dietician is often very helpful in preventing inadvertent allergen exposure. Gastroesophageal reflux, vocal cord dysfunction, and exercise-induced anaphylaxis should be included in the differential diagnosis.<sup>26</sup> Given the higher likelihood of a fatal or near-fatal incident in patients with asthma and food allergy, many allergists will prescribe a self-injectable epinephrine/adrenaline device (e.g. EpiPen, EpiPen, Jr., TwinJect) to any patient with both asthma and food allergy.<sup>91</sup>

Avoidance of the causal food is the mainstay of food allergy treatment. Those affected should receive dietary education as well as education on the proper treatment of anaphylaxis in case of accidental exposure. Comprehensive educational materials are available through the Food Allergy and Anaphylaxis Network ([www.foodallergy.org](http://www.foodallergy.org)).

## Conclusions

Food allergy and asthma may often coexist, though the incidence of a food contributing to a person's asthma control is extremely uncommon. Particular attention should be given to patients with both food allergy and asthma as these patients have been found to have a higher incidence of fatal or near-fatal anaphylaxis. Dietary management is important for avoiding the causal allergen as well as insuring adequate nutrition. Practitioners should be comfortable in educating patients on the symptoms associated with an allergic reaction, prescribing self-injectable epinephrine devices, and instructing patients in the proper use of such a device.

## Conflict of interest declarations

JA Bird has no conflicts of interest.

AW Burks has received remuneration from the following companies for consultant and advisory board services: ActoGeniX NV, Dannon Co Probiotics, Intelliject, McNeil Nutritionals, Novartis, and Nutricia. He is a minority stockholder in Allertein and MastCell Inc. Over the last year, he has received funding for research projects for which he has served as an investigator or co-investigator from: the National Institutes of Health; the Food Allergy and Anaphylaxis Network; and the Wallace Research Foundation.

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