

Additives and preservatives: Role in food allergy

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ABSTRACT

Food additives are natural or synthetic substances added to foods at any stage of production to enhance flavor, texture, appearance, preservation, safety, or other qualities. Common categories include preservatives and antimicrobials, colorings and dyes, flavorings, antioxidants, stabilizers, and emulsifiers. Natural substances rather than synthetics are more likely to cause hypersensitivity. Although rare, food additive hypersensitivity should be suspected in patients with immunoglobulin E (IgE)-mediated reactions to multiple, unrelated foods, especially if the foods are prepared outside of the home or when using commercial products. A complete and thorough history is vital. Skin prick testing and/or specific IgE blood testing to food additives, if available, additive avoidance diets, and blind oral challenges can help establish the diagnosis. Once an allergy to a food additive is confirmed, management involves avoidance and, if necessary, carrying self-injectable epinephrine.

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Food additives are natural or synthetic substances added to foods at any stage of production. These substances are added to foods to enhance flavor, texture, appearance, preservation, safety, or other qualities. Classification of additives is by function, such as preservatives and antimicrobials, flavorings, colorings and dyes, antioxidants, stabilizers, and emulsifiers (Table 1). The U.S. Food and Drug Administration (FDA) manages an inventory of >3,900 substances added to foods.¹ Based on the limited literature available, the prevalence of true hypersensitivity reactions to food additives is low despite public perception.² In a study of Danish children, the prevalence of food additive reactions was 1–2% overall and 2–7% in subjects who were atopic.³ In a large British survey, the prevalence of food additive reactions was only 0.01–0.23%.⁴ Double-blind, placebo controlled oral challenges to a mixture of seven common food additives in an atopic Korean population yielded no statistically significant differences in dermatologic adverse events.⁵ This brief review focuses on hypersensitivity reactions to food additives, such as anaphylaxis and systemic allergic

reactions, exacerbations of asthma and allergic skin diseases, and immediate gastrointestinal symptoms. Delayed-type and other manifestations may suggest T cell-mediated or pharmacologic reactions rather than true allergy.

Preservatives and Antimicrobials

Sulfur dioxide and sulfites in the form of salts (sodium bisulfite, sodium sulfite, and sodium metabisulfite) are commonly used in the food industry as preservatives to prolong shelf life, prevent browning, and inhibit microbes during fermentation.⁶ Although most individuals without asthma can tolerate up to 5 parts per million (ppm) of sulfur dioxide, many individuals with asthma seem to be hypersensitive to the gas.^{7,8} An estimated 3–10% of individuals with asthma are thought to be sulfite sensitive.⁹ Hypersensitivity to sulfites can present with anaphylaxis, urticaria, abdominal pain, and bronchospasm.² The respiratory system is the most commonly affected organ system. A large series that reported adverse reactions to sulfites cited 250 cases in the United States, including 6 deaths.¹⁰ In 1986, the U.S. FDA prohibited the use of sulfites on raw fruits and vegetables. Although use is still permitted in prepared foods and drinks, levels >10 ppm are required to be listed on the label.⁶ Sulfite hypersensitivity should be considered when individuals experience asthma exacerbations after exposure to sulfite-rich foods, such as dried fruits or wines. Common foods with added sulfites > 100 ppm are listed in Table 1.

Sodium benzoate is closely related to and cross-reacts with parabens that are used as preservatives in foods and drugs. One report in 2004 described two children who experienced asthma flares after consuming beverages or liquid medications that contained sodium benzoate.¹¹ Both children developed asthma symptoms when challenged with the benzoate-

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Table 1 Selected food additives, their common food sources, and reported reactions

Function	Additive	Common Foods that Contain Additive	Reaction Reported in the Literature and References	
Preservatives and antimicrobials	Sulfites	Dried fruits, fruit juices, pickled onions, molasses, lemon and/or lime juice, wine	Bronchospasm in asthmatics, urticaria, abdominal pain ^{6,10}	
	Nitrates and nitrites	Processed meats	Anaphylaxis, urticaria, chronic pruritus ^{2,12}	
	Sodium benzoate	Alcoholic beverages, fruit juices, soft drinks, pickles	Bronchospasm in patients with asthma ^{6,11}	
Flavorings	Monosodium glutamate	Sauces, gravies, rubs, oriental dishes	Possible: urticaria, angioedema, rhinitis; unlikely: asthma exacerbations ^{2,6,13,15}	
	Natural sweeteners (xylitol, stevioside)	Chewing gum, throat lozenges, diet or low-calorie soft drinks and other sweet dishes	Anaphylaxis, contact dermatitis ^{13,16}	
	Artificial sweeteners (aspartame, saccharin, sucralose)	Diet or low-calorie soft drinks and other sweet dishes	Possible: urticaria ^{2,13,17}	
	Spices (<i>e.g.</i> , seeds, garlic, ginger, cayenne and other peppers, cinnamon)	Various foods	Urticaria, angioedema, atopic dermatitis, contact dermatitis, rhinoconjunctivitis, asthma exacerbations, anaphylaxis ^{2,6,18}	
Colorings and dyes	Natural	Carmines (red)	Foods with red coloring; juices, ice cream, yogurt, and candy	Anaphylaxis ^{2,6}
		Saffron (yellow)	Foods with yellow coloring	Anaphylaxis ²
		Annatto (orange)	Foods with orange coloring; cheddar cheese, ice cream, and beverages	Anaphylaxis, urticaria ^{2,6}
	Synthetic	Tartrazine (Yellow no. 5)	Foods with yellow coloring; soft drinks, instant puddings, cake mixes, jam, jelly, gelatins, mustard	Possible: urticaria; unlikely: asthma exacerbations ^{2,6,13}
Antioxidants	Butylated hydroxyanisole and butylated hydroxytoluene	Foods that contain fats and oils; butter, cereals, chewing gum, baked goods, snacks, dehydrated potatoes, beer	Chronic urticaria exacerbations ^{2,6}	
Emulsifiers and stabilizers	Guar gum	Processed foods; ice cream, ketchup, salad dressings, yogurt, and baked goods	Occupational asthma and rhinitis, possible anaphylaxis ^{2,6,13}	
	Arabic gum	Processed foods; candy, coating on roasted coffee beans	Occupational asthma ^{13,21,22}	
	Propylene glycol	Processed foods; salad dressings, prepared meals, mixes, fast foods	Contact dermatitis ^{6,13}	

containing formulations under observation but did not react to the same drugs in benzoate-free formulations.¹¹ Nitrate and nitrite salts are commonly used to preserve

processed meats.² There are rare case reports of hypersensitivity, including urticaria and chronic pruritus. One individual who experienced reactions after eating

takeout food developed anaphylaxis during oral challenge to nitrates and nitrites.^{2,12}

Flavorings

Monosodium glutamate (MSG) is a flavor and taste enhancer originally linked to the “Chinese restaurant syndrome.”⁶ Manifestations vary, depending on an individual’s susceptibility and dosage but are not serious nor persistent.² Symptoms that have been described are flushing, headache, diaphoresis, chest tightness, palpitations, generalized weakness, and sensory numbness in the neck, arms, or back.^{6,13} Allergic reactions to MSG have been reported, including urticaria, angioedema, rhinitis, and asthma flares.¹³ However, several double-blind, placebo controlled studies did not find MSG to be a significant trigger for urticaria or asthma flares.^{2,6,13,14} A 2012 Cochrane review found no evidence to support the avoidance of MSG in adults with asthma.¹⁵

Sugar substitutes are widely used as lower calorie options to enhance sweetness.¹³ Natural sugar substitutes include xylitol (a sugar alcohol frequently used in chewing gum and throat lozenges) and stevioside (an extract from the leaves of the *Stevia rebaudiana* plant).^{13,16} Commonly used artificial sweeteners are aspartame, saccharin, and sucralose.² Hypersensitivity reactions to natural and artificial sweeteners are rare although they are often claimed to cause adverse reactions by the public.⁶ Xylitol was reported to cause oral contact dermatitis, confirmed by patch testing.¹³ Anaphylaxis from stevioside, supported by skin prick testing, was reported in two Japanese children with atopic dermatitis.¹⁶ There are reports of skin symptoms associated with aspartame, but there was no difference between aspartame and placebo in eliciting urticarial symptoms in a well-designed study.^{13,17} Sucralose is a chlorinated sucrose with a molecular structure similar to table sugar. There are anecdotal reports of urticaria due to sucralose but no validated evidence of sucralose causing immune-mediated allergic reactions in the literature.

Spices are a diverse group of natural substances that add flavoring to foods. Various spices have been reported to cause urticaria, angioedema, contact dermatitis, atopic dermatitis, rhinoconjunctivitis, asthma exacerbations, and other reactions.¹⁸ Anaphylaxis and systemic allergic reactions to mustard, sesame, and other seed spices are of increasing concern.² Capsaicin can cause symptoms that mimic hypersensitivity reactions through non-IgE-mediated mechanisms. This makes differentiating true allergy from intolerance to hot spices difficult.^{2,6} Skin prick and/or specific IgE blood testing is available for several spices.

Colorings and Dyes

IgE-mediated hypersensitivity reactions to dyes and colorings are uncommon and largely due to natural

substances.^{2,6} Cases of anaphylaxis after ingestion of carmine (red dye derived from the cochineal insect), saffron (yellow dye derived from a flower), and annatto (orange dye derived from the seeds of a tree) have been reported.^{2,6} Annatto may also cause urticaria and angioedema.⁶ There is little evidence in the literature about hypersensitivity to synthetic dyes despite public concern. Tartrazine (Yellow no. 5) is a synthetic dye that has been reported to cause urticaria or bronchospasm in a few patients.^{2,6,19} There are mixed reports with regard to possible cross-reactivity between tartrazine and acetylsalicylic acid, especially in asthmatic subjects with aspirin sensitivity.^{2,6,13,19} However, a 2001 Cochrane review, which included studies of aspirin-sensitive asthma, concluded that asthma outcomes were not significantly modified by tartrazine challenges or dietary avoidance.²⁰

Antioxidants

Butylated hydroxyanisole and butylated hydroxytoluene are additives that slow the spoilage of fats and oils. There are rare case reports of these antioxidants possibly causing exacerbations of chronic urticaria.¹³ In a study of 100 patients with chronic urticaria, 43 of whom reported previous reactions to food or drug additives, only two patients had an urticarial response to single-blinded challenges with 11 common food additives, including butylated hydroxyanisole, butylated hydroxytoluene, MSG, sodium nitrate, sodium nitrite, tartrazine, and sodium benzoate. Neither of the two patients reacted in a subsequent double-blind, placebo controlled challenge.¹⁴

Emulsifiers and Stabilizers

Gums, used as emulsifiers and stabilizers, add bulk and thickness to foods to enhance consistency and palatability. Arabic gum is derived from an exudate of *Acacia senegal* trees in Africa, and it has been used for >4000 years as an emulsifier, thickener, and stabilizer. Case reports of occupational asthma with exposure to Arabic gum in print factory workers were reported in the 1940s and, more recently, in candy factory workers and carpet manufacturers.^{13,21} There is little evidence in the literature of IgE-mediated reactions to Arabic gum.^{13,22} Guar gum, derived from guar beans, is widely used in food and pharmaceutical products as a fixing agent for colors.⁶ Occupational rhinitis and/or asthma to guar gum has been reported.^{2,6,13} Affected individuals may also develop IgE-mediated sensitization to guar gum, as demonstrated by positive skin prick and/or specific IgE blood testing results, and clinical hypersensitivity, including anaphylaxis.^{6,13} Development of sensitization to guar gum and other vegetable gums may occur more frequently *via* inhalation rather than the

oral route.¹³ Propylene glycol, another emulsifier, may cause contact dermatitis.¹³

DIAGNOSIS

Clinicians should suspect allergy to food additives when patients report hypersensitivity reactions to a variety of foods. Reactions are more common when eating processed, restaurant-prepared, or store-bought foods rather than those cooked at home. A complete and detailed history of reactions is of utmost importance.⁶ Patients with vague symptoms not classic for IgE-mediated allergy are unlikely to be truly allergic. In addition, reactions to other food allergens are much more prevalent than to food additives and should be excluded. For those with a convincing history suggestive of food additive hypersensitivity, skin prick and/or specific IgE blood testing should be done to support the diagnosis if available, especially for natural substances.²

If testing is not available or is inconclusive, then additive avoidance diets may be helpful. Patients are instructed to eat only homemade meals without commercial products and are monitored for improvement. Examples of foods that are less likely to contain additives are fresh or frozen unprocessed fish and meats (chicken, beef, veal, lamb, turkey), eggs, milk, butter, carrots, lettuce, mushrooms, pears, rice, safflower oil, preservative-free bread, honey, pepper, salt, sugar, coffee, tea, and water.⁶ Oral challenge, preferably single or double blinded, should be performed in patients whose symptoms improve on an additive avoidance diet. Oral challenge is the criterion standard for the diagnosis of food allergy.²³ The most plausible additive should be tested first or, if the history is unclear, then mixtures of additives with the same function or color can be used. If a patient reacts to a mixture, then each additive should be challenged separately to identify the culprit(s).^{2,6} The cumulative challenge dose varies and should be at least similar to the quantity expected in a usual meal. Suggested multistep challenge protocols with quantities of each additive by type have been published.^{2,6}

TREATMENT

As with most food hypersensitivities, the standard of care is avoidance. This involves reading labels and providing the patient with a list of common foods that contain the additive to avoid. Home-prepared dishes are usually better tolerated than commercial meals. Patients with a history consistent with IgE-mediated reactions to food additives, especially those with severe or systemic reactions, should carry self-injectable epinephrine.^{2,6} Oral immunotherapy has not been extensively studied for treatment of food additive

hypersensitivity, and there are no successful desensitization protocols published in the literature.^{2,6}

CLINICAL PEARLS

- Hypersensitivity to food additives is rare overall.
- A variety of food additives can cause allergic reactions, with natural substances being the principal offenders.
- Food additive hypersensitivity should be suspected in patients with IgE-mediated reactions to multiple, unrelated foods, especially if commercially prepared.
- Diagnostic tools involve a thorough history, skin-prick and/or specific IgE blood testing to food additives, if available, additive avoidance diets, and blind oral challenges.
- Management includes avoidance and, if necessary, carrying self-injectable epinephrine.

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