Adverse reactions to food additives

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ABSTRACT

Food additives are naturally occurring or synthetic substances that are added to food to modify the color, taste, texture, stability, or other characteristics of foods. These additives are ubiquitous in the food that we consume on a daily basis and, therefore, have been the subject of much scrutiny about possible reactions. Despite these concerns, the overall prevalence of food additive reactions is 1–2%, with a minority of the wide variety of symptoms attributed to food-additive exposure being reproduced by double-blind placebo controlled challenges. Reactions can be broadly classified into either immunoglobulin E (IgE)- and non–IgE-mediated reactions, with natural additives accounting for most IgE-mediated reactions, and both natural and synthetic additives being implicated in the non–IgE-mediated reactions. Reactions that include asthma exacerbations, urticaria and/or angioedema, or anaphylaxis with ingestion of a food additive are most deserving of further allergy evaluation. In this article, we discussed the different types of adverse reactions that have been described to various food additives. We also reviewed the specifics of how to evaluate and diagnose a food additive allergy in a clinic setting.

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Food additives are synthetic or naturally occurring substances that are intentionally added to food to modify its physical, chemical, biologic, or sensorial characteristics.[1] They have been reported as having the potential to provoke adverse effects in certain individuals.[2] The U.S. Food and Drug Administration (FDA) web site currently lists ~3000 substances on their food additive status list,[3] although it has been estimated that between 2000 and 20,000 agents are added to the foods that we consume.[4] Examples of food additives include preservatives, stabilizers, conditioners, thickening agents, sweetening agents, food coloring, flavoring agents, and antioxidants. In this article, we aimed to summarize what is currently known about adverse effects to common food additives by focusing primarily on commonly associated reactions. We also reviewed how to evaluate and diagnose a food-additive allergy in a clinic setting.

ADVERSE EFFECTS OF FOOD ADDITIVES

Food additives may cause immunoglobulin E (IgE)- or non–IgE-mediated reactions.[1] IgE-mediated reactions are quite uncommon but, if present, can be severe and life threatening. Natural additives contain molecules of sufficient molecular weight to induce an IgE-mediated response.[5] On the contrary, synthetic additives are more likely to act like haptens because of their low molecular weight. Haptens can induce an IgE-mediated response only if they are attached covalently to a large carrier molecule.[6] Both natural and synthetic additives may cause nonimmunologic, non–IgE-mediated reactions, which are classified as "food additive intolerances" or "sensitivities." Certain food additive sensitivities have been found to occur through mechanisms that include metabolic, pharmacological, toxic and direct neural stimulation, and blockade of coagulation pathways.[7,8] Although food additives may trigger adverse reactions through these mechanisms, the reactions we reviewed have unclear or unknown mechanisms except where noted.

A vast range of adverse reactions have been attributed to the consumption of food additives.[7,9] Reactions to food additives that have been reproduced by rigorous oral food challenges are typically mild and involve exacerbations of asthma, urticaria, and, rarely, anaphylaxis.[8,10] There is a wide spectrum of nonspecific symptoms that have also been associated with food additives, including myalgias, paresthesias, headaches, weakness, *etc.*[5] However, none of these have been confirmed *via* oral challenge, and the cause-and-effect relationship has not been well demonstrated.[5,11–13] Psychological factors may also play an integral role in both food and food additive reactions and should be considered on evaluation.[14,15]

Attention deficit hyperactivity disorder (ADHD) is a concern that has purportedly been associated with food additives.[16] This began in 1973 when Benjamin

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Feingold, M.D., claimed that certain food additives caused children to be hyperactive. He created a controversial diet low in salicylic acid, artificial colorings, and artificial flavors. There have since been many studies that suggest an association between food additives and hyperactive ADHD, although this association has not been substantiated with rigorous, placebo controlled, blinded challenges.[17] A 2012 meta-analysis showed that 33% of children with ADHD responded to a dietary intervention, with as many as 8% of children having symptoms to food colorants and/or dyes.[18] However, nearly all studies in this meta-analysis lacked consistency in their mixtures to allow for testing comparative effect sizes of different mixtures or individual compounds. Furthermore, the dose, exposure length, and blinding quality also varied. In fact, only a small change in parental reports of symptoms and no significant changes in teacher-reported symptoms were found.[18] This led investigators to a conclusion that renewed investigations that explore food additives and ADHD would be needed to establish a relationship.[18] The National Institutes of Health Expert Panel on Food Allergy concluded that clinicians should not recommend avoidance of food additives, including artificial colors, in patients with ADHD.[19]

Several studies[2–7, 20,21,22] investigated the prevalence of adverse reactions to food additives. Contrary to the general public perception, the prevalence of these reactions is low.[7] The prevalence in adults is estimated to be < 1% and is slightly higher in children (1–2%).[20–22] There also seems to be a discrepancy between self-perceived and clinically reproducible reactions.[2] For instance, an estimated 23–67% of individuals with asthma perceive that food additives exacerbate their asthma; however, the prevalence rate of food-additive–induced asthma exacerbations obtained by double-blind placebo controlled (DBPC) trials is < 5%.[10] It should be noted that children who are atopic may be at increased risk of reaction.[7] In a large multicenter study that involved 335 children, the incidence of intolerance of food additives was 2–7%, and children with atopic skin symptoms had a statistically increased risk of positive reaction.[23]

ADDITIVES KNOWN TO CAUSE ADVERSE REACTIONS

Although not an exhaustive list, below are some of the most frequently encountered food additives known to cause reactions, listed alphabetically.

Annatto

Annatto is a yellow-orange food coloring made from the seeds of the achiote tree (*Bixa orellana*) found in South America. An estimated 70% of natural food colors are derived from annatto.[24] Its color comes from compounds called carotenoids, which are pigments found in the seed's outer layer as well as in other fruits and vegetables. It is used to color candy, butter, margarine, mayonnaise, sauces, mustard, sausage, soup, juice, ice cream, bakery products, macaroni, and cheese, among a multitude of other products. Two studies reported adverse reactions to this additive in children, which consisted of both urticaria and angioedema.[25,26] In adults, there have been concerns for possible annatto-induced anaphylaxis.[27]

Aspartame

Aspartame is a synthetic dipeptide artificial sweetener approved by the FDA in 1981 that is frequently used in foods; medications; and beverages, notably carbonated and powdered soft drinks.[28] Given concerns that have been raised about aspartame's potential link to cancer, cardiovascular disease, and depression, the European Scientific Committee on Food conducted a review of >500 reports in 2002 and concluded from biochemical, clinical, and behavioral research that the acceptable daily intake of 40 mg/kg/day of aspartame remained entirely safe, except for people with phenylketonuria.[29,30] A multicenter, randomized, placebo controlled cross-over study challenged 21 subjects with a history of a temporal (minutes to hours) association between aspartame ingestion and the development of urticaria and/or angioedema. Only four urticarial reactions were observed, two after aspartame consumption and two after placebo ingestion.[31] Studies in adults have also shown a correlation between daily aspartame intake and chronic headache, but this was not confirmed among children.[32,33]

Butylated Hydroxyanisole and Butylated Hydroxytoluene

Butylated hydroxyanisole and butylated hydroxytoluene are closely related antioxidants that are used in a variety of foods, including breakfast cereals, cake mixes, chewing gum, drink mixes, and processed potatoes. They are also found in non–food products, such as animal feed, cosmetics, and rubber. There are paradoxical reports of both carcinogenic and anticarcinogenic properties.[34] In one report, from 1990, which involved two patients, butylated hydroxyanisole and butylated hydroxytoluene were associated with chronic spontaneous urticaria (CSU).[35] No further reports have followed.

Carmine

Cochineal carmine, or simply carmine (E120), is a red coloring that is obtained from the dried bodies of the female insect *Dactylopius coccus*.[36] It is frequently used in food, drinks, cosmetics, quasi-drugs, and medications.[37] Carmine has been implicated in urticaria and/or angioedema, recurrent intermittent bouts of

systemic dermatitis,[38] asthma,[39–41] and urticaria and/or anaphylaxis[42–44] in adults. Special consideration for carmine are the following: in a study of >3000 patients with "putative food or food additive–related cutaneous or intestinal symptoms," that examined co-reactivity among carmine, shrimp, and mite, carmine sensitization was found in 3% (94 subjects).[45] Of the subjects who were carmine sensitized, 74% also had sensitization to dust mite, and 22% had sensitization to shrimp.[45] Reactions attributed to carmine ingestion that occurred independently from dust and/or storage mite reactivity were found in 42% (39/94).[45]

Carrageenan

Carrageenan is a natural carbohydrate (polysaccharide) obtained from edible red seaweed. The name carrageenan is derived from the *Chondrus crispus* species of seaweed (Rhodophyceace) known as carrageen moss or Irish moss, and carraigin.[46] Carrageenan has gained wide applications in pharmaceutical formulations, cosmetics, and food industries, given its utility as a thickening agent and stabilizer.[46] It can be found in chocolate milk, in which it mitigates separation. It also can be used as a binder in processed deli meats and has been used as a vegan alternative to gelatin. Additional uses include its role in nonfood products such as toothpaste or air freshener gels. Reports of IgE-mediated allergy seem limited to a case report of anaphylaxis to carrageenan-containing barium enema, and a 10-month-old child who developed lip angioedema after eating icing on a cake.[47,48]

Erythritol

Erythritol is a naturally abundant sweetener that is gaining more importance within the food industry. It is widely used as sweetener in calorie-reduced food, candies, or bakery products.[49] Several isolated case reports of urticaria and anaphylaxis have been reported in response to erythritol ingestion.[50–52]

Food Dyes

Food dyes are added to different types of commodities to increase their visual attractiveness and to make food more appealing or to compensate for natural color variations. The use of these additives is strictly regulated in the European Union, the United States, and many other countries worldwide. There is a growing concern about the safety of some commonly used legal food colorants, and there is a trend to replace the synthetic forms with natural products.[53] There are many azo and non-azo dyes approved by the Federal Food, Drug, and Cosmetic Act (FD&C)[53] that are added to food, drink, and color-coded medicines. Synthetic colorants include a variety of compounds, including tartrazine, quinoline yellow, sunset yellow, azorubine, ponceau 4R, erythrosine, Allura Red, patent blue, indigo carmine, brilliant blue FCF, green S, brilliant black, and brown HT (Table 1).[54]

Tartrazine (FD&C yellow no. 5) is an approved azo dye present in many drugs and food products, including soft drinks and sports drinks. It is the best known and one of the most commonly used food additives.[55] It was also the first food additive reported to cause hypersensitivity reactions, going back as far as the 1950s.[56,57] Initial concerns were that agents used in artificial coloring (*i.e.,* tartrazine) were the cause of asthma in children; however, no objective data to support these claims was presented.[58] There have since been many attempts to link tartrazine sensitivity with bronchial reactivity, and some physicians have questioned whether patients with aspirin-exacerbated respiratory disease might be at increased risk.[59–61] However, despite these claims, to our knowledge, there have been no well-designed studies that corroborate concerns that tartrazine provokes asthma exacerbations.

In fact, in a study that evaluated 194 patients with aspirin-exacerbated respiratory disease for tartrazine sensitivity by oral challenge, no cross-reactivity between aspirin and tartrazine was demonstrated, and none of the subjects had positive reactions when DBPC challenges were performed.[62] Nevertheless, the increased attention to tartrazine[62] over the years led to new regulations that required the listing of azo dyes on package inserts of drugs and on packages of food products. In older, poorly designed studies, tartrazine was linked to other illnesses, including CSU and intermittent flares of atopic eczema; although subsequent investigations with more rigorous designs showed that the occurrence of CSU and angioedema is actually very low (perhaps 1%).[63–66] The most recent and most rigorously designed study demonstrated with 95% confidence that tartrazine was not associated with CSU.[67]

Gelatin

Gelatin is a highly purified animal protein of pig, cow, and/or fish origin, and is widely used as a coating, binding, gelling, and glazing agent in food, pharmaceuticals, and osmotic products, including confectionaries, creams, lotions, facemasks, capsule shells, and dietary supplements.[68] There are many well-documented cases of IgE-mediated anaphylactic reactions to gelatin-containing medical products, including capsules, suppositories, and plasma volume expanders.[69] There also are a number of gelatin-containing vaccines, such as intranasal influenza, measels, mumps, rubella (MMR), varicella, and rabies, with documented cases of anaphylaxis to the gelatin within these vaccines.[69] Clinical allergy to red meat and meat-derived gelatin has been observed in some reports.[70] In a prospective review of these patients, most patients allergic to red meat were

Table 1 **Food additive testing and challenge procedures**

Food Additive	Substance	Testing	OFC Vehicle	OFC Dose (every 20–30 min, unless specified)
Annatto	Annatto	SPT 1:1000 of dye or Gouda[122]; 2.33 g annatto seed powder in 5 mL saline solution SPT[26]; SPT 1:10,000, 1:1000, 1:10 with irritant at full strength annatto extract from General Mills (Minneapolis, MN) [27]; ssIgE annatto seed (*Bixa orellana*)	Capsule	ADI[117]: bixin 0–12 mg/kg BW; norbixin 0–0.6 mg/kg BW[117]
Aspartame	Aspartame	No validated skin tests; no commercially available IgE	Capsule	ADI: 0–40 mg/kg BW[117]; 100, 200, 400, 800 mg[5]; 50 mg[123]; >40 kg: dosing every 2 hr of 50 mg aspartame, 300 mg aspartame, 600 mg aspartame, and conversion products (7.5 mg β-aspartame, 15 mg aspartylphenylalanine diketopiperazine); <40 kg: half dosing[31]
Carmine	Red coloring from cochineal insect: dye provided by company that manufactures Campari[42]; commercially available carmine 0.5% (Brial Allergen GmbH, Greven Germany)[42]	10% solution carmine powder in PBS, agitate at 4° C for 2 hr and dialyze against purified water and pass through 0.22-μ filter[124]; SPT 0.1% E120, carmine 0.5%[42]; carmine 5 mg/mL[45]; vitamin capsule powder diluted 0.1 mg/mL for SPT[125]; dried insects (*Dactylopius coccus*) were purchased (http://www.cochinealdye.com/index.html), pulverized and then suspended 1:10 by weight in tap water, incubated and agitated at 80° C for 15 min in a water bath; color values were measured by absorption spectrometry and diluted to a color value of 0.1 (~0.5 μg protein/mL), 0.01, 0.001 by using PBS, and then filtered through a 0.2-μm syringe	Capsule	ADI: 0–5 mg/kg BW[117]; 1, 5, 10, 15 mg[5]

Table 1 **Continued**

Food Additive	Substance	Testing	OFC Vehicle	OFC Dose (every 20–30 min, unless specified)
		filter[37]; undiluted food grade carmine dye (≥3.5% carminic acid) obtained from Warner Jenkinson (a Sensient company, St. Louis, Missouri)[126] and Good Humor company's supplier[43]; ssIgE carmine (*Cochineal dactylopius*)		
Carob bean gum	Carob gum (raw or boiled bum, bean extract)	5, 15, 25 mg/mL[127]; ssIgE carob gum/locust bean	Capsule	ADI: not specified[117]
Carrageenan	Sodium carrageenan	0.4% w/v sodium carrageenan (Sanofi Bio-Industries, Mississauga, Ontario, Canada) may be more reliable than carrageen gum (1:50 w/v, Miles Inc., Canada) 48; ssIgE carrageenan	Capsule	ADI: not specified[117]
Dyes (see specifics for annatto above and tartrazine below)	FD&C dyes	No validated tests[128]; ssIgE amaranth/FD&C red no. 2; no ssIgE for other dyes (except carmine, see above)	Capsule	ADI[117]: not specified benzyl violet 4B, FD&C green no. 1 and 2, FD&C red no. 4 and 40/Allura, FD&C violet no. 1; FD&C blue no.1/brilliant blue: 0–6 mg/kg BW; FD&C blue no. 2/indigo: 0–5 mg/kg BW; FD&C green no. 3/fast green: 0–25 mg/kg BW; FD&C red no. 2/amaranth: 0–0.5 mg/kg BW; FD&C red no. 3/erythrosine: 0–0.1 mg/kg BW; FD&C yellow no. 6/sunset yellow: 0–4 mg/kg BW; 1, 5, 10, 15 mg[5]; 5, 20 mg each[118]
Erythritol	Erythritol	2 mg/mL, 20 mg/mL, 200 mg/mL in distilled water[129]; SPT 100 mg/mL in 50% glycerin, IDT positive between 160 and 20 mg/mL (nonirritating up to 100 mg/mL)[51]; no ssIgE	Capsule	ADI: not specified[117]; 100, 200, 400, 800 mg each[5]
Gelatin	Gelatin	1 tsp (5 g) of gelatin in 5 mL normal saline solution[130]; ssIgE gelatin	Capsule	ADI: not limited[117]

Table 1 **Continued**

Food Additive	Substance	Testing	OFC Vehicle	OFC Dose (every 20–30 min, unless specified)
Guar gum	Guar gum	1 mg of guar gum in 1 mL PBS (0.12 mg/mL), mixed for 2 hr at room temperature and centrifuged, with removal of supernatant, stored at –20° C until use[131]; ssIgE guar (bean) gum	Capsule or particles for inhalation	ADI: not specified[117]; inhalation challenge (reactions of patients with asthma): lactose control (15 min of exposure) on day 1, guar gum (progressive: one breath, 15 sec, 45 sec, 2 min) on day 2; positive, with PEV decreased by ≥ 20%; spirometry pre-exposure, and every 10 min × 60 min, then every 30 min × 60 min, then every hour × 7–8 hr[131]
Mannitol	d-Mannitol	SPT alditol-protein conjugates dialyzed against PBS at 4° C sterile filtered and used for SPT 1% w/v (10 mg/mL) 1:10 and full strength[109]; SPT 20% (Isotol, Diaco Biofarmaceutici Industry, Trieste, Italy), 1:10 ID[76]	ADI: not specified[117]; mannitol laxative 1 mg/mL, 3 mg/mL, 10 mg/mL every 1 hr[76]	ADI: not specified[117]; mannitol laxative 1, 3, 10 mg/mL every 1 hr[76]
MSG	MSG powder	100 mg/mL in NS[119]; no ssIgE available	Capsule or citrus drink	ADI: not specified[117]; 200, 400, 800, 1600 mg[5]; single dose of 5 g[132]; single dose of 2.5 g[133]; 100 mg, 500 mg, 1 g, 6 g (total 7.6 g) every 30 min[134]
Preservatives, other	Sodium benzoate, BHA, BHT, parabens (methyl-, ethyl-, butyl-), sorbate (methyl-, ethyl-, propyl-, allyl), polyoxyethylene sorbitan stearate, polysorbate (20, 40, 60, 65, 80), potassium–sodium sorbate, potassium–sodium nitrite, polyethylene glycol	Polysorbate 100% SPT, 1:10 IDT (neg pt and control), undiluted (pos pt, not tested in control)[135]; PEG 300 and 3350 1:100 and 1:10 SPT[136]; polysorbate 80 eye drop (1:10) IDT[136]; methylparaben 0.1% SPT; also methylparaben-containing local anesthetics with FS SPT, IDT 0.04 mL 1:100[137]; no ssIgE; basophil function sodium nitrite available; patch tests available – *NACDG panel (paraben mix 12% petrolatum, polysorbate 80 5% pet, BHA 2% pet); *Chemotechnique: sodium benzoate, BHT	Capsule	ADI[117]: sodium benzoate: 0–5 mg/kg BW; BHA: 0–0.5 mg/kg BW; BHT: 0–0.3 mg/kg BW; methyl-, ethylparabens: 0–10 mg/kg BW; butylparaben; methyl-/ethyl-/propyl-/allyl sorbate: no safety concern at current levels of intake when used as flavoring agent; polyoxyethylene sorbitan mono-oleate/palmitate/laurate/stearate or tristearate: 0–25 mg/kg BW; polysorbate 20/40/60/65/80: 0–25 mg/kg BW; potassium, sodium sorbate: 0–25 mg/kg; (potassium, sodium) nitrite: 0–0.7 mg/kg BW; polyethylene glycols: 1–10 mg/kg BW; all: 25, 50, 100, 200 mg[5]; BHA, BHT: 125, 250 mg each[118]; sodium benzoate: 50, 100, 250 mg[118]; parabens (anesthetic allergy): 1 mL SC NS placebo, 1 mL SC undiluted local anesthetic[137]

Table 1 **Continued**

Food Additive	Substance	Testing	OFC Vehicle	OFC Dose (every 20–30 min, unless specified)
Psyllium	Psyllium powder	SPT 2.5% w/v dissolved in 50% glycerol[138]; ssIgE psyllium (ispaghula) available	Powder or capsule	ADI not listed[117]; inhalation challenge: tipping psyllium powder from one tray to another for 5, 15, 45 sec, and 2 min × 2 with serial FEV_1 measurements immediately, 10 min after exposure and every 10 min × 1 hr, every 30 min × 1 hr for up to 8 hr; positive if FEV_1 decreases ≥ 20%; if no change, exposure increased to 30 min on a separate day[138]; oral challenge: 0.1, 0.5, 2 g every 30 min[139]
Tartrazine (FD&C yellow no. 5)	Tartrazine powder	No validated skin tests[128]; basophil function tartrazine available	Capsule	ADI: 0–10 mg/kg BW[117]; placebo, tartrazine 25 mg and 50 mg every 3 hr[140]; 1, 5, 10, 15 mg[5]; 5, 20 mg[118]; 25 mg[141]; 1 mg, 10 mg[6]; 1, 5 15, 25, 50 mg[61]
Sulfite	Potassium meta-bisulfite	1 mg/mL SPT and IDT potassium metabisulfite[103]; sodium metabisulfite 10% w/v (dissolving carmine 10% in PBS for 2 hr at 4° C with gentle agitation, dialyzed against purified water and passed through 0.22-μ Millipore filter)[124]; no ssIgE available	Capsule or solution	ADI[117]: calcium (bisulfite, hydrogen sulfite, metabisulfite), disodium, potassium (hydrogen sulfite, metabisulfite, sulfite), sodium (disulfite, hydrogen sulfite, hyposulfite, metabisulfite, sulfite, thiosulfate): 0–0.7 mg/kg BW; caramel color class II, caustic sulfite caramel: 0–160 mg/kg BW; caramel color class IV, sulfite ammonia caramel: 0–200 mg/kg; 25, 50, 100, 200 mg[5]; 1, 5, 10, 25, 50 mg[103]; capsule and neutral solution challenge: 1, 5, 25, 50, 100, 200 mg capsules and then 1, 10, 25 mg in a water-sucrose solution every 30[104]; acidic solution challenge: 0.1, 0.5, 1, 5, 10, 15, 25, 50, 75, 100, 150, 200 mg/20 mL lemonade solution every 10 min[104]
		Scripps protocol: SPT 0.001, 0.01, 0.1, 1 mg/mL every 15 min; IDT 0.02 mL of 0.001 mg/mL	Solution (sulfite-free mix or fresh lemons); capsule	Solution: 10 mL, swish in mouth for several seconds and swallow: *1, 10, 25, 50, 100 mg every 20 min; *patients with asthma: placebo, 10, 50, 100 mg,

Table 1 **Continued**

Food Additive	Substance	Testing	OFC Vehicle	OFC Dose (every 20–30 min, unless specified)
				and then placebo every 30 min; 1, 10, 25, 50, 100 mg every 30 min; for capsule and solution, spirometry before and after each dose
Sweetener (see specifics for erythritol, aspartame above)	Artificial (acesulfame, saccharin, sucralose); natural (corn syrup, fructose, glucose, sucrose)	No validated skin testing; ssIgE saccharin	Capsule	ADI[117]; acesulfame, sucralose: 0–15 mg/kg; saccharin: 0–5 mg/kg BW; sucrose acetate isobutyrate: 0–20 mg/kg BW; sucralose, trichlorogalactosucrose: 0–15 mg/kg BW; glucose, sucrose fatty acid esters: not specified; corn syrup, fructose not listed; 100, 200, 400, 800 mg each[5]; 40 mg saccharin in 120 mL water, 1 tsp sugar in 120 mL water, 80 mg saccharin in 120 mL water every 45 min[142]
Yeast	*Saccharomyces cerevisiae*	SPT: 1 mg/mL, 10 mg/mL[143]; SPT commercial extract[130]; hepatitis B, human papillomavirus vaccine if a history of a reaction[130]; may be cross-reactive with *Candida albicans*[143,144]; ssIgE baker's yeast (*S. cerevisiae*)	Capsule (regular baker's yeast), solution (beer, wine)	ADI: not listed[117]; *S. cerevisiae* may be cross-reactive with *C. albicans*,[29] with 95% of patients sensitized to *C. albicans* also being positive on skin testing with *S. cerevisiae* enolase[143]

OFC = Oral food challenge; SPT = skin-prick text; ssIgE = serum specific immunoglobulin E; ADI = acceptable daily intake; BW = Body weight; IgE = immunoglobulin E; DKP = diketopiperazine; PBS = phosphate-buffered saline; FD&C = Food, Dye, and Cosmetic Act; IDT = intradermal test; PEV = peak expiratory volume; MSG = monosodium glutamate; BHA = butylated hydroxyanisole; BHT = butylated hydroxytoluene; FS = full strength; NS = normal saline; PEG = polyethylene glycol; NACDG = North American Contact Dermatitis Group; SC = sub-cutaneous; FEV_1 = forced expiratory volume in the first second of expiration. [117] Joint FAO/WHO Expert Committee on Food Additives: not specified = listed; not listed = unable to be found.

sensitized to gelatin, and a subset was clinically allergic to both; however, the pathogenic relationship between sensitization to red meat, α-gal, and gelatin (with or without clinical reactivity) remains uncertain.[70]

Guar Gum

Guar gum is derived from the seeds of the drought-tolerant plant *Cyamopsis tetragonoloba*, a member of Leguminosae family, and is often used as an edible thickening agent.[71] It has widespread applications in the food industry due to its ability to hydrate without heating. The demand for guar gum is growing because it has been found to have potential in lowering serum cholesterol and glucose levels, and some studies have found it helpful in weight-loss programs.[72] There has been one case of severe contact urticaria to guar gum included as a gelling agent in a local anesthetic as well as a single case report of anaphylaxis to guar gum contained in a meal substitute.[73,74]

Mannitol

Mannitol is a naturally occurring polyol (sugar alcohol) that is widely used in food, pharmaceutical, medical, and chemical industries.[75] It is commercially produced for use in chocolate coatings, confections, and chewing gum. Despite its widespread use, allergic reactions to mannitol are rare, although there is a single case report in which oral mannitol used as a drug excipient induced an immediate type hypersensitivity reaction characterized by urticaria and angioedema[76]

Monosodium Glutamate

Monosodium glutamate (MSG) is a salt form of a nonessential amino acid commonly used as a food additive for its unique flavor-enhancing qualities.[77] It provides a savory and/or meaty taste to food, and is one of the most widely used food additives in commercial foods.[78] It is used in canned foods, crackers, meat, salad dressings, frozen dinners, and a myriad of other products, and can be found in local supermarkets, restaurants, and school cafeterias.[78] The cluster of symptoms that include headache, skin flushing, and sweating is now often referred to as "MSG symptom complex."[79] This was originally described as the now politically incorrect and offensive term "Chinese restaurant syndrome" in 1968.

A physician named Robert Ho Man Kwok wrote a letter to *The New England Journal of Medicine*[80] describing symptoms he allegedly developed 15–20 minutes after eating meals at several Chinese restaurants. These symptoms included posterior neck numbness that radiated to both arms and back, along with general weakness and heart palpitations that lasted up to 2 hours, with no residual effects.[80] Despite these early reports, decades of research have failed to demonstrate a clear and consistent relationship between MSG ingestion and the development of these symptoms.[34] MSG has been described as a trigger for asthma exacerbations, urticaria, and angioedema, but there are no consistent data to support this relationship.[79] Although there have been reports of a MSG-sensitive subset of the population, this has not been reproduced in placebo controlled trials.[79,81]

Nitrates and Nitrites

Nitrate is a natural constituent of the human diet and an approved food additive.[82] Nitrates and nitrites are used as preservatives, primarily for the purpose of curing meats; nitrite is recognized for its antimicrobial effects against pathogenic bacteria, even though the specific inhibitory mechanisms are not well known.[83] A single case was reported of recurrent anaphylaxis that occurred after eating takeout with nitrate- and/or nitrite-containing food; this was reproduced with DBPC capsule challenge (in which the placebo was given first and followed by a number of substances, one of which was nitrate).[84] Other than this isolated report, in which the patient also reacted to other substances during challenge (which were not, by history, problems) and neither skin-prick tests (SPT) nor serum specific IgE (ssIgE) testing was performed, we found no convincing evidence in the literature of allergic hypersensitivity to nitrates and nitrites, and there should not be concern with regard to the potential risk of anaphylactic reactions.[9]

Parabens

Parabens are derivatives of parahydroxybenzoic acid and have been widely used as preservatives in the cosmetics, food, and pharmaceutical industries for > 70 years. Their antimicrobial effects and utility as preservatives have increased their prevalence in a variety of products. In addition, they have minimal toxicity and low cost, and no perceptible odor or taste. They also do not discolor or harden, and have a neutral pH.[85] Results of some poorly designed studies have suggested the relevance of benzoates in adverse drug and food reactions, with reactions characterized by eczema, asthma, urticaria, and other cutaneous manifestations; however, to our knowledge, there are not any well-designed DBPC studies to suggest anaphylaxis with foods that contained parabens and/or benzoates.[86–89]

Psyllium

Psyllium is a natural dietary soluble viscous fiber derived from the husk of the blond psyllium seed.[90] It can slow gastric emptying and decrease the speed of absorption of fat and glucose.[91] It has gained attention as a potential cholesterol-lowering source of fiber. It is found in high-fiber cereals, ice cream, and baked

goods. Allergic reactions from handling psyllium have been reported since 1970, with health professionals and workers in laxative-manufacturing plants being at greatest risk.[92] Urticaria and anaphylaxis are the most commonly reported reactions, and tend to occur with oral ingestion after previous sensitization.[92,93]

Sulfites

Sulfites are food additives found in a large variety of food products to help reduce oxidation and browning.[94] They help to limit bacterial contamination and are generally regarded as safe for consumption by governmental regulatory agencies, at concentrations up to 5000 ppm.[95] In the 1980s and 1990s, the FDA acted to reduce the likelihood that individuals who are sulfite sensitive would unknowingly consume foods that contain sulfites by prohibiting the use of sulfites on fruits and vegetables (with the exception of potatoes) that were to be served or presented fresh to the public.[96] They also required that the presence of detectable levels of sulfites be declared on food labels, even when used as a processing aid, a component of another ingredient in the food.[96] The most commonly used sulfiting agents today include sulfur dioxide and sodium or potassium sulfite or bisulfite or metabisulfite.

Sulfiting agents have been attributed as the cause of a range of adverse effects, including anaphylaxis, urticaria, gastrointestinal symptoms, and dermatologic eruptions; however, these effects have not been largely substantiated by DBPC provocation studies.[97] The role of sulfiting agents that cause severe bronchospasm and asthma is better established.[60,98–100] It is important to note that, although epinephrine autoinjectors contain metabisulfite, there are no case reports to suggest that autoinjectors are unsafe for patients who are sulfite sensitive.[101]

Special consideration for sulfites includes the following: in individuals with asthma, reactions are often propagated by the acidification of sulfite and creation of sulfur dioxide, which is then inhaled.[102] This process occurs in the stomach, and thus solutions, rather than capsules, that contain sulfite are needed for additive challenge in these patients. Other mechanisms that underlie sulfite reactivity include IgE-mediated or abnormal metabolism (low sulfite oxidase); these individuals may respond to sulfite in capsules.[103–105] There are protocols published that include skin testing and challenge with capsules and a solution, which thus encompasses all types of reactions.[103,104] In our practice, we use an alternative protocol, with skin testing when there is a history of anaphylaxis, and then oral food challenge with either capsules or solutions when the history is consistent with nonallergic reactions (Table 1).

EVALUATION AND DIAGNOSIS

Evaluation of Patients with Suspected Food Additive Allergy

A high index of suspicion is often needed to diagnose a food additive allergy. A major problem in diagnosing reactions to additives is identification of the offending agent(s), which is based on taking a careful dietary history. Reactions to food additives should be suspected in patients who report symptoms related to multiple foods or to a specific food when commercially prepared but not when homemade.[83] In patients who are suspected to have IgE-mediated symptoms in relation to food additive consumption, further workup is warranted.[67] The goal of the evaluation is to establish if reactions are due to a particular food additive. The evaluation should use a stepwise approach, with a careful history and examination, consideration of testing for sensitization, and, often, an oral additive challenge if no contraindications exist.

The evaluation of a possible food additive allergy must always begin with a careful history and physical examination. A detailed history includes symptom onset and severity, the spectrum of clinical manifestations, interventions or treatments required, and reaction duration. Investigating preceding ingestions or exposures (including food, medications, alcohol, exercise, concurrent illness) is critical.[106] Clinicians should carefully review ingested foods and attempt to identify possible culprit additive(s) shared among all the ingestions, with special attention being paid to those that have been identified as etiologic agents in anaphylaxis (annatto, carmine, erythritol, guar gum, psyllium, carrageenan, lupine, pectin, gelatin, metabisulfite, yeast, mannitol). The physical examination should be comprehensive, exploring for other possible contributing etiologies to the patient's presentation.

Several distinct conditions must be considered on the differential diagnosis for a food additive allergy. A food additive allergy is commonly considered in the differential diagnosis of CSU. If a patient's presentation is suggestive of CSU, then food additive avoidance should not routinely be advised.[107] The clinical history may also suggest a nonimmune-mediated adverse reaction to food additive(s), in which case, further workup for an IgE-mediated food allergy would not be warranted. Multiple chemical sensitivities and/or idiopathic environmental intolerance (IEI) may also masquerade as a food additive allergy, although patients with IEI generally have a nonspecific assortment of symptoms in response to various chemicals. IEI is a highly controversial diagnosis, and there is no current consensus on the appropriate workup and/or diagnostic criteria. Other considerations in those who present with gastrointestinal symptoms include carbohydrate malabsorption

(impaired microvilli monosaccharide uptake, hypolactasia, hypoamylasemia, disaccharidase deficiency), bacterial overgrowth, or sorbitol-induced osmolar diarrhea, which are discussed in more detail elsewhere.[108]

If the history and physical examination are suggestive of an IgE-mediated food additive allergy, then identifying the culprit food additive is an imperative next step. This may pose the most challenging aspect of evaluating a possible food additive allergy.[22] Of the thousands of chemicals used in the food manufacturing process that are recognized by the FDA as food additives, only a small number have been associated with IgE-mediated food allergies, many of which are detailed in Table 1.[7] If a food additive is identified that results in consistent reactions that occur predictably and reproducibly after ingestion, further testing may be considered.[109–111]

Evaluating for Sensitization

Exploring for sensitization to food additives by using skin (SPT or intradermal test) or ssIgE values is limited in most instances.[22] The ssIgE and skin testing have not been validated for any food additives, and the sensitivity and specificity of these modalities are unknown. Despite this, ssIgE is available for several substances, *e.g.,* the natural colorants (*e.g.,* annatto, saffron, carmine, mannitol, vegetable gum) (Table 1).[7] However, the cutoffs to determine sensitization and thereby inform the risk of reactivity have not been definitively established. Data on the validity are impeded by heterogeneity between studies in the operational definition of reactions, variability between skin test reagents and concentrations, and lack of confirmation of allergy by oral food additive challenge (OFAC). The 2008 allergy diagnostic testing practice parameters recommend against SPT to food additives, given these limitations.[112]

Nonstandardized skin testing may be considered with food or purified preparations thereof, and positive and negative controls are imperative in the interpretation of these results. Ideally, positive test results should be confirmed to be nonirritating by repeating the tests by using the same concentrations on allergy control subjects, i.e someone who is not the patient, this could refer to any staff in the clinic. Similar to commercially available testing, the positive and negative predictive values for these tests are not known. Given these numerous limitations in exploring for sensitization to food additives, oral food challenges are the criterion standard for diagnosing a food additive reactivity for both IgE- and non–IgE-mediated reactions alike.

OFACs

OFACs are critical in accurately diagnosing a food additive allergy. The contraindications to OFACs are similar to other oral challenges in allergy (Table 2).[111,113,114] Determining which type of oral challenge to perform requires consideration of multiple factors. Open OFAC can be considered if the suspicion for bias is low and objective symptoms are likely.[111,113,115] Single- or double-blind food additive challenge, ideally with placebo control, should be performed if there is a suspicion for bias, anticipation of subjective symptoms, or inconclusive open OFAC.[111,113] Placebo doses can be administered in a separate session from the active food additive for a total of two sessions, either a morning and afternoon session or on two separate days.[111] Another approach is to administer placebo doses in the same session as the active food additive[111]; we favor this approach because timing (need for multiple sessions) can be problematic and medications wear off and confound interpretation of results of serial challenges, especially if placebo is administered first.[116]

For those in whom IgE-mediated reactions are considered, the initial additive dose should be 0.1–1% of the total challenge dose (serving size).[111] Dosing has not been well established, but, consistent with food challenges, should be the most that an individual would receive in a given meal. For many additives, this is not well established and the acceptable daily intake can be used as a guide.[117] Obtaining the food additive for challenge can be difficult because hospitals or compounding pharmacies, along with life sciences companies, may contain certain additives, although these are pharmaceutical- rather than food-grade reagents. Food service supply companies are an alternative. We recommend these commercial companies in preference to ordering on the Internet for safety and validity reasons, although a lack of availability may necessitate obtaining reagents online.

Demonstrating the importance of double-blind OFAC is a study in subjects with asthma, in which all who had a positive open OFAC result underwent double-blind challenge (except for one subject who had positive open challenge to non-azo dye).[118] In this study, 15.9% (7/44) were positive on tartrazine open challenge but none (0) were positive on double-blind challenge; 9.3% (4/43) were positive to azo dyes on open challenge and 2.3% (1) were positive on double-blind challenge; 7.1% (3/42) were positive to non-azo dyes on open challenge and 2.4% (1) were positive on double-blind challenge; and 4.6% (2/43) were positive to sodium benzoate on open challenge and 2.3% (1) were positive on double-blind challenge.[118] In a study of various food additives, only 32.1% of the subjects (9/28) who had positive SPT results demonstrated reactivity on open challenge.[119]

In a double-blind OFAC, placebos are important to include, given the propensity for false-positive reactions and the phenomenon of classically conditioned allergic responses.[120,121] Placebos should be unable to be differentiated from doses that contain the suspected

Table 2

Steps During Oral Additive Challenge	Additional Considerations
1. Preprocedure medication management	Inhaled bronchodilators and cromolyn: hold the morning of the procedure; anti-histamines: discontinue based on the half-life of the drug; β-blockers and ACEI: weigh risks and benefits of stopping 24 hr before challenge
2. Informed consent	Written informed consent, document in chart
3. Standard precautions	As would be undertaken for other oral challenges
4. Risk stratify the patient	History of severe reactions: intravenous access should be considered; underlying cardiopulmonary disease: intravenous access should be considered; asthma: assess control; rule out exacerbation and/or frequent SABA use; if indicated, FEV_1 should be $\geq$ 70% of patient's best results and $\geq$ 1.5 L; for the patient who is ill: reschedule challenge, patients should not be ill
5. Monitor patient closely during procedure	Baseline and recurrent vital signs; physical examination; spirometry; observe for signs or symptoms of IgE-mediated reaction; if there are only subjective symptoms, prolonging the period between doses and waiting for symptoms to resolve is reasonable before administering the next dose
6. Managing a reaction to placebo	Inform the patient that the reaction was to a placebo; reassure that this is not uncommon and discuss implications
7. Managing an allergic reaction to food additive	Stop challenge if there are signs of an allergic reaction, even if no treatment needs to be given; based on symptoms consider treatment with antihistamines, inhalers, IM epinephrine. IVF, positioning (supine or Trendelenburg), etc.; observe 2 hr after symptoms subside
8. Discharging a patient who experienced an allergic reaction to food additive during challenge	Avoidance is recommended; the patient should be instructed on how to read labels and identify the chemical and alternative names for the implicated food additive; they should also be given a prescription for injectable epinephrine and instructed on indications for use and technique

ACEI = ; SABA = ; FEV_1 = forced expiratory volume in the first second of expiration; IgE = immunoglobulin E; IM = intramuscular; IVF = Intravenous fluids.

food. When selecting a placebo, clinicians need to consider odor, texture, taste, and other unique qualities that could serve to distinguish the suspected allergen. For example, lemon juice and sugar, or sulfite-free lemonade powder can be used to mask a potassium metabisulfite solution. Patients are told that placebo will be intermixed with the additive as part of a routine procedure, but clinicians do not give further details so to minimize bias. Sucrose-containing placebos are included as the first and last steps of the challenge, and the final active dose should be greater than the likely exposure from any one meal.

There are multitudes of different materials that can be used to mask challenge foods.[111] We prefer to use capsules for food additive challenges because a full dose can be achieved with just a few capsules without adulteration, which thus limits the possible destruction or interference of absorption of relevant allergens.[114] Most of the patients who are seen for concern of food additive allergy are adults who are able to swallow capsules, although, in children or adults with dysphagia, this may not be possible. One disadvantage of capsules is that early oral symptoms are circumvented, and, also, there may be delayed absorption due to the time taken for capsule degradation; these factors necessitate longer dosing intervals (30–60 minutes, observation $\geq$2 hours).[114] However, the overall convenience and efficacy of capsules in placebo controlled challenge often justifies the few drawbacks.

At our institution, for reactions that are thought not to be IgE mediated, we perform a mixed additive challenge in the subjects who claim to have non-anaphylactic reactions to multiple different foods, primarily with the goal of ruling out food additive allergy in those with a low pretest probability for a positive reaction. Less commonly, this can be used in those who have a

Table 3 **Mixed food additive challenge**

Food Additive	Dose per Capsule, mg	Total Dose, mg (no. capsules)
Aspartame	50	50 (1)
Butylated hydroxyanisole	250	250 (1)
Butylated hydroxytoluene	250	250 (1)
Methylparaben	100	100 (1)
Monosodium glutamate	500	2500 (5)
Sodium nitrate	50	50 (1)
Sodium nitrite	50	50 (1)
Potassium metabisulfite	100	100 (1)
Sodium benzoate	100	100 (1)
Sunset yellow (FD&C yellow no. 6)	50	50 (1)

FD&C = Food, Dye, and Cosmetic Act.

history of a possible or probable reaction in which a culprit food additive cannot be identified; if the challenge result is positive, then pursuit of the causative agent should be undertaken with single additive challenges. This is not recommended for those who are "chemically sensitive" or in which IEI is suspected.[101] We give all 15 capsules at the same time with water, with the observation period to be determined by the patient's history (doubling the historically reported time between ingestion and symptom recurrence). We do not give placebo doses nor do graded challenge for this procedure (Table 3). Additional steps to consider during food additive challenge are detailed in Table 2.

MANAGEMENT ONCE DIAGNOSIS IS ESTABLISHED

If it is established that a food additive is causing adverse reactions, then avoidance of the specific additive of concern is imperative. Education plays a critical role, and the clinician should provide information about in which foods the additive is commonly found. The provider should give recommendations for patients to carefully read the ingredient lists on all food labels. It is also important that the patient learns alternative nomenclature for the relevant additive. In the rare event that an adverse reaction is found to be consistent with an IgE-mediated food additive allergy, an epinephrine autoinjector should be prescribed and instruction provided on symptoms that necessitate use as well as proper technique.

SUMMARY

- Of the thousands of food additives in use today, only a handful are associated with immunologic or nonimmunologic reactions.
- There are a variety of additional symptoms that have been attributed to food additives, although these have not been confirmed with DBPC trials.
- An allergy evaluation should be considered for patients who report asthma exacerbations, urticaria and/or angioedema, or anaphylaxis with ingestion of a food additive.
- Although IgE immunoassays are currently available for certain food additives and skin testing can be performed, the sensitivity and specificity in determining sensitization are not well defined, and, therefore, OFACs are the criterion standard for a diagnosis.
- Food additive challenges can be used to prove or disprove a food additive as the cause of a patient's reaction, and the use of placebo is important in these procedures.

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