## CME review article

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# Adverse reactions to food additives

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**Objectives:** To summarize the literature related to the classification of food additives and their reported adverse reactions and to provide a practical approach for evaluation of patients suspected of having such reactions.

**Data Sources:** Information was derived from selected reviews and original articles published in peer-reviewed journals and from authoritative textbook chapters, supplemented by the clinical experience of the authors.

**Study Selection:** Priority was given to studies that used blinded, placebo-controlled oral challenges to confirm adverse reactions to food additives. In addition, selected, appropriately evaluated case reports are included.

**Results:** A large number of food additives are widely used in the food industry. Adverse reactions to additives seem to be rare but are likely underdiagnosed in part due to a low index of suspicion. Numerous symptoms have been attributed to food additive exposure, but the cause-and-effect relationship has not been well demonstrated in all.

**Conclusions:** Reactions to food additives should be suspected in patients who report symptoms to multiple unrelated foods or to a certain food when commercially prepared but not when homemade and the allergy evaluation rules out a role for food protein. It is also prudent to investigate food additives in patients considered to have idiopathic reactions. There is a minor role for skin testing or in vitro testing. Oral challenge testing with common additives, preferably preceded by a trial of an additive-free diet, is the definitive procedure for detecting the offending agent. Once the specific additive is identified, management is basically avoidance of all its forms.

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## INTRODUCTION

The practice of using food additives goes back for thousands of years and has become essential in modern food industry. Early processes of food preserving were primarily salting, pickling, and smoking. In the past century, we have witnessed a marked increase in the number of natural and artificial substances being added to foods. Today, more than 3,000 substances are approved for use as food additives in the United States. The US Food and Drug Administration (FDA) maintains a continuously updated Web site that contains administrative and chemical information on these substances.[1] The FDA list, entitled "Everything Added to Food in the United States" or "EAFUS," can be accessed via the FDA Web site at http://vm.cfsan.fda.gov/~dms/eafus.html. Despite such an extensive list, the FDA adds the disclaimer that this is "only a partial list of all food ingredients that may in fact be lawfully added to food, because under federal law some ingredients may be added under a GRAS [generally recognized as safe] determination made independently from the FDA."

Despite the widespread use of additives, few scientific data are available on their adverse reactions, particularly immunologic hypersensitivity. Great controversy exists regarding the prevalence, manifestations, and mechanisms of reactions to food additives. A report of hypersensitivity to tartrazine dye published in 1959 generated widespread interest and debate on the subject.[2] Since then, many reports have been published, but the subject is complicated by the fact that most of the available literature is in the form of case reports or

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small series, and there is a notable shortage of large, well-controlled studies with defined criteria and appropriately conducted challenges. The pathophysiology of adverse reactions has also been difficult to elicit and has only been confirmed in a relatively few cases. The end result is the accumulation of a large body of information that is frequently inconsistent and difficult for clinicians to navigate or apply to their patient care.

The objective of this review is to summarize the topic from the allergy perspective and present the reader with a practical approach for evaluating, diagnosing, and managing food additive reactions. Information was derived from selected reviews and original articles published in peer-reviewed journals and from authoritative textbook chapters, supplemented by the clinical experience of the authors. Priority was given to studies that used blinded, placebo-controlled oral challenges to confirm adverse reactions to food additives. In addition, selected, appropriately evaluated case reports are included.

## CLASSIFICATION AND USES OF ADDITIVES

Food additives are usually classified according to their use or function (Table 1). Food dyes may be classified according to color or according to source (natural vs synthetic). Most dyes used today are synthetic, and only a few are still derived from natural sources. Therefore, classification by color would be more helpful in clinical practice (Table 2).

Modern food industry relies heavily on the use of food additives as antioxidants, colorings, emulsifiers, flavorings, taste enhancers, preservatives, and stabilizers.[3] Antioxidants such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are necessary to retard the spoilage of fats and oils. Dyes or food colorings are used to change, improve, or maintain the color of the product to which they are added. Vegetable gums are used as emulsifiers and thickening agents to enhance appearance, consistency, and palatability in many products, such as candy, certain cheeses, ice cream, and salad dressing.

Flavoring agents are probably the most commonly used additives in commercially prepared food. Many different spices are widely used worldwide, and identifying them as the offending component in a food can be difficult. Artificial sweeteners continue to increase in number and in their use. Monosodium glutamate (MSG) is a commonly used taste enhancer. Found naturally in seaweed, MSG has been used in Asia for centuries and is now used worldwide.[4] A variety of preservatives are used to prevent microbial spoilage and prolong the shelf-life of most commercial food. Stabilizers such as gums and EDTA are used to enhance the consistency of products, probably by blocking enzymatic reactions that would otherwise cause spoilage.

Table 1. Classification of Food Additives and Common Examples

| |
|---|
| Antioxidants |
| Butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate, tocopherols |
| Dyes and colorings |
| See Table 2 |
| Emulsifiers |
| Gums (eg, arabic, tragacanth, karaya) |
| Lecithin |
| Propylene glycol |
| Flavorings and taste enhancers |
| Monosodium glutamate (MSG) |
| Spices (eg, aniseed, cinnamon, coriander, cumin, fennel, flaxseed, ginger, hops, mustard, nutmeg, red pepper, white pepper) |
| Sweeteners |
| Artificial (eg, acesulfame [Sunett, Sweet One], aspartame [Equal, NutraSweet], saccharin [Sweet 'N Low], sucralose [Splenda], sorbitol) |
| Natural (eg, corn syrup, fructose, glucose, sucrose) |
| Preservatives and antimicrobials |
| Benzoates, citric acid, nitrates and nitrites, parabens, salicylates, sorbic acid, sulfiting agents |
| Stabilizers |
| EDTA, gums (eg, carrageenan, guar, others), waxes |

## ADVERSE REACTIONS

Only a few studies have investigated the prevalence of adverse reactions to additives. Most population-based studies estimate the prevalence of reactions to food additives at less than 1% in adults[5–7] and up to 2% in children.[8] The prevalence is higher in atopic children, ranging from 2% to 7%.[9] Such figures are close to those for the food allergy prevalence in general,[10] indicating that reactions to additives are underdiagnosed in clinical practice.

It is our experience that food additives are more likely to cause skin irritation in patients with underlying skin disorders, particularly atopic dermatitis or urticaria, than in those with healthy skin. A wide variety of symptoms have been described in the literature and attributed to additive exposure (Table 3). Since a comprehensive recounting of the literature on adverse reactions to food additives would be exhaustive, the following will summarize selected studies on common aspects of the subject.

Since Kwok[11] first described the "Chinese restaurant syndrome" in 1968, several studies have investigated clinical reactions to MSG. Originally, Kwok described a triad of symptoms that consisted of numbness starting in the back of the neck with radiation to the arms and back, generalized weakness, and palpitations. At that time he suspected ethanol, sodium chloride, or MSG as possible causes. Many anecdotal reports followed and described a wide variety of symptoms that were attributed to MSG ingestion.[12] On the other hand, some investigators noted no significant adverse reactions to various doses of MSG up to 3 g when given to healthy individuals and with food.[13,14] Three blinded studies evaluated doses of up to 12 g of MSG given without food to healthy individuals, and a variety of subjective symptoms were reported but without any consistent pattern.[15–17] Symptoms similar to those attributed to MSG can occur in some individuals after ingesting other foods as well, indicating that the symptoms are not specific to MSG.[18] In a multicenter

Table 2. Classification of Common Food Dyes by Color

| Color | Common name | Color index No. | European code No. | FD&C No. |
|---|---|---|---|---|
| Blue | Brilliant Blue | 42090 | E133 | Blue No. 1 |
| | Indigotin, indigo carmine | 73015 | E132 | Blue No. 2 |
| | Patent Blue V | 42051 | E131 | |
| Green | Chlorophyll | 75810 | E140 | |
| | Fast green (Patent green) | 42053 | | Green No. 3 |
| Orange | Annatto (Bixin) | 75120 | E160 b | |
| | Sunset Yellow | 15985 | E110 | Yellow No. 6 |
| Red | Allura red | 16035 | E129 | Red No. 40 |
| | Amaranth | 16185 | E123 | Red No. 2 |
| | Carmine, cochineal | 75470 | E120 | |
| | Erythrosine | 45430 | E127 | Red No. 3 |
| | Ponceau 4R (Cochineal red A) | 16255 | E124 | |
| Yellow | Quinoline yellow | 47005 | E104 | |
| | Saffron | 75100 | E164 | |
| | Tartrazine | 19140 | E102 | Yellow No. 5 |
| | Turmeric | 75300 | E100 I | |
| | Curcumin | 75300 | E100 II | |

Abbreviation: FD&C, Food, Drug, and Cosmetic [Act].

Table 3. Symptoms Reported to be Possibly Caused by Food Additives*

| |
|---|
| Dermatologic |
| Angioedema, dermatitis, eczema, flushing, itching, nonspecific rash, sweating, urticaria |
| Gastrointestinal |
| Abdominal pain, diarrhea, nausea, tongue or throat swelling, vomiting |
| Respiratory |
| Asthma exacerbations, cough, rhinitis, shortness of breath, tightness, wheezing |
| Musculoskeletal |
| Aching, arthralgias, fatigue, myalgias, tightness, weakness |
| Neurologic |
| Behavior disorder, dizziness, fasciculations, headache, migraine, neuropathy, numbness, paresthesias |
| Cardiovascular |
| Arrhythmias, palpitation, syncope, tachycardia |
| Other |
| Lacrimation, systemic anaphylaxis, trembling |

* The cause-and-effect relationship between food additives and these symptoms is not well documented in all cases.

study of 130 patients who claimed to have symptoms related to MSG, it was noted that up to 5 g of MSG given *without* food could cause symptoms in 53% vs 28% to placebo, and such symptoms were neither serious nor persistent. Furthermore, the reactions were inconsistent, not reproducible, and not observed when MSG was given *with* food.[19] MSG has also been suspected by some patients as a trigger for asthma, and such a relationship was observed by some[20,21] but not confirmed by others.[22–27] A protocol for a Cochrane meta-analysis of studies that examined the connection between MSG and asthma was published in 2002, but results are not available yet.[28]

Spices are another group of flavoring additives that have been shown to elicit a variety of adverse reactions. Recently, a comprehensive review was published on the subject, including information on their allergic potential.[29] It also induced a list of spices not known to cause IgE-mediated reactions. The latter may be especially useful to spice-sensitive patients, because it provides dietary alternatives.

Sulfites, in the form of sodium salt (sodium sulfite, sodium bisulfite, or sodium metabisulfite) or potassium salt (potassium bisulfite or potassium metabisulfite), are among the most commonly used preservatives. They reduce microbial spoilage, slow the browning of fruit, vegetables, and seafood, inhibit growth of undesirable organisms in the fermentation industry, and act as an antioxidant in some medications. Sulfites can cause bronchospasm in approximately 4% of asthmatic patients in general and in approximately 8% of steroid-dependent asthmatic patients.[30] Sulfite-sensitive asthma is more common in adults than in children.[31] Sulfites have also been implicated in several cases of systemic reactions that seem to be IgE mediated. Yang et al[32] reported 3 cases of systemic reactions confirmed by sulfite challenge; all 3 had positive skin prick test results and 2 had positive Prausnitz-Kustner test results. Sokol and Hydick[33] also reported a case of sulfite-induced anaphylaxis confirmed with multiple single-blind, placebo-controlled challenges. Two studies of a total of 37 patients have investigated the possible role of sulfites as a trigger for recurrent idiopathic anaphylaxis using challenge testing.[34,35] Only 1 of these patients consistently reacted to sulfite challenge; however, institution of a sulfite-free diet did not improve the patient's subsequent course. Sulfites as a cause of urticaria or angioedema have been reported in some patients.[36–39] However, in a study of 75

patients with chronic idiopathic urticaria or anaphylaxis, none showed a positive reaction on blind challenges with doses up to 200 mg of metabisulfite.[40]

In the past, sulfites were often added to seafood, cut fruit, and salads (especially potato salad) in restaurants and grocery stores to prevent browning. However, increased awareness of adverse reactions to sulfites led to the 1986 decision by the FDA to ban their use in fresh foods and require that any food or beverage that contain greater than 10 ppm of sulfites be declared on the label. Foods that contain less than 10 ppm of sulfites do not appear to pose a risk, even among sensitive individuals.[41] Sulfites have been used as antioxidants in many pharmaceuticals, including some asthma medications, even injectable epinephrine. Most of these have been reformulated, but in an emergency situation, the benefit of administering a sulfite-preserved epinephrine far outweighs its potential risk, even in a sulfite-sensitive individual.[42]

Nitrate or nitrite salts and benzoates are also commonly used preservatives. There have been a few case reports of chronic pruritus[43,44] and chronic urticaria[45–47] and at least 1 report of anaphylaxis[48] after ingesting nitrates. However, these are isolated cases and adverse reactions to nitrates or nitrites seem to be rare. Benzoates have been shown to be a trigger for asthma in selected patients. Weber et al[49] reported that 1 of 43 patients with moderate to severe asthma had a positive double-blind challenge result to benzoate. Tarlo and Broder[50] studied 25 patients with persistent asthma, and only 1 had a reduction in forced expiratory volume in 1 second of greater than 20% from baseline after benzoate challenge. Osterhalle et al[51] reported benzoate sensitivity in 3 of 46 cases of persistent asthma in children. Two studies investigated a link between benzoates and chronic urticaria. Ortolani et al[52] noted that 3 of 72 patients with chronic urticaria had positive double-blind, placebo-controlled challenge results to sodium benzoate (1 at 60 mg and 2 at 410 mg). Simon[53] challenged 65 patients with chronic urticaria to multiple additives, including benzoate, and reported no reactions to benzoate in any of them. Only 1 case of anaphylaxis to benzoates has been confirmed.[54] Recently, Pacor et al[55] evaluated 226 subjects (age 12 to 60 years) with persistent nonatopic rhinitis for sensitivity to 6 common food additives. Double-blind, placebo-controlled challenges revealed that 20 (8.8%) of 226 had positive oral challenge results to 100 mg of monosodium benzoate based on both subjective and objective evaluation. These patients also reported symptom improvement within 1 month of an additive-free diet.

Both BHA and BHT are widely used antioxidants that retard the spoilage of fats and oils. At least 2 studies[46,56] have identified BHA and/or BHT as a trigger for exacerbations of chronic urticaria.

Dyes or colorings are added to a wide variety of products, including foods, and many have been observed to cause adverse reactions. Carmine is a common red food coloring obtained from the dried bodies of cochineal insects. It has been shown to cause IgE-mediated anaphylaxis in some individuals.[57–60] Annatto is a yellow food coloring obtained from the seeds of the tropical tree *Bixa orellana* and has also been reported as an occasional cause of anaphylaxis[61] and urticaria or angioedema.[62] Saffron, from the flower of *Crocus sativa,* is another yellow food coloring that has been reported to cause anaphylaxis in a single patient.[63] The synthetic dye tartrazine has been reported to rarely cause urticaria[2,64] and may increase bronchial reactivity in some asthmatic children.[65] A recent Cochrane meta-analysis reviewed studies that investigated a link between tartrazine and asthma.[66] Although 90 studies were found, only 6 met inclusion criteria and none could be combined for a formal meta-analysis. None of the 6 included studies has clearly demonstrated an association between tartrazine and asthma symptoms in those patients. The authors of the Cochrane review thus concluded that the paucity of evidence did not allow firm conclusions about the effect of tartrazine on asthma. Other dyes with isolated case reports of adverse effects on pulmonary function include ponceau and erythrosine.[49]

The debate over an association between food additives and behavior disorders in children, particularly attention-deficit/hyperactivity disorder, has been ongoing and the issue is not yet definitively resolved. Feingold[67] was among the first to suggest a connection between a number of additives (eg, sweeteners, dyes, and preservatives) and a range of behavior problems in children, including attention-deficit/hyperactivity disorder and learning disabilities. Many articles followed this report, and by far, most well-conducted studies found no association between additives and behavior.[68,69] However, occasional studies seem to suggest that the behavior of at least a few patients may be influenced by diet.[70] It is hoped that, in the future, additional well-designed studies will shed more clarity on this complex and difficult area.

## MECHANISMS OF ADVERSE REACTIONS TO FOOD ADDITIVES

In general, adverse reactions to additives may be explained on a pharmacologic, irritant, toxic, immunologic, or psychologic basis. Clinically relevant specific IgE production has been demonstrated to some additives derived from natural sources, such as carmine,[57–60] annatto,[61,62] saffron,[63] and erythritol (a sweetener derived from glucose).[71] These additives contain proteins of sufficient molecular weight to evoke an immunologic response. Synthetic additives exist as simple chemicals and most likely act as haptens to induce an IgE-mediated response.[72] It is likely that multiple mechanisms are involved, but most reactions are not IgE mediated.

In sulfite reactions, some cases have been shown to be IgE mediated,[32,33] but most reactions are not, and several other mechanisms have been proposed.[31] One suggestion is that sulfites in foods and beverages are converted to sulfur dioxide by the gastric acidity, allowing the inhaled sulfur dioxide to directly induce smooth bronchial muscle constriction. Another theory is that sulfur dioxide acts indirectly by stimulating a cholinergic reflex that induces bronchoconstriction. Finally, some sulfite-sensitive individuals may lack sulfite oxidase, a mitochondrial enzyme that oxidizes sulfite to sul-

fate so that it can be excreted in the urine. Such individuals would be more sensitive to sulfites in foods and beverages they consume.

Regarding MSG, most of the proposed mechanisms of reactions have suggested some form of neurologic toxicity or excitation. Given at a dose of 500 mg/kg, MSG has been shown to cause neurotoxicity in neonatal rodents[73] but not in immature[74] or adult rodents.[75] Others have proposed that reactions to MSG may result from stimulation of peripheral nerve receptors, formation of acetylcholinosis, or esophageal irritation.[12] Fernstrom et al[76] evaluated the neurohormonal effect of 12.7 g of MSG given to 8 healthy men in a double-blind, placebo-controlled trial. No effect on the anterior pituitary was noted even with very high levels of circulating glutamate. No role for IgE has been reported in MSG reactions.

## DIAGNOSIS

A thorough, directed medical history is of utmost importance in detecting adverse reactions to food additives. One should suspect an additive hypersensitivity when a patient gives a history of reactions to several unrelated foods or reacts to a certain food when commercially prepared but not when it is prepared at home. Careful investigation into the contents of these seemingly unrelated foods may reveal a common additive, provided the labeling is complete. In most patients, the suspicion is usually initially directed to a main food; however, evaluation for food protein allergy is negative.

The next step would be to rule out a "hidden" food allergen. An example of a reaction to a hidden food allergen would be an egg-allergic child who avoids eggs but reacts to other products because they contain lecithin derived from egg. A thorough review of hidden and cross-reacting food allergens was recently published.[77] Even if the food label is complete, some food derivatives may be listed under unfamiliar names. Table 4 lists some additives derived from common allergenic foods. Ruling out a hidden food allergy will require careful checking of food labels. In some cases, contacting the source of the food (ie, restaurant or manufacturer) might be helpful. In special situations, sending the food for analysis in a specialized laboratory might identify the culprit. Errors during food manufacturing occur, and when discovered, the food industry has been diligent in disseminating information through the Food Allergy and Anaphylaxis Network (http://www.foodallergy.org/alerts.html) and in recalling the affected product. These alerts typically pertain to food proteins, and it is hoped that they encompass food additives as well.

Table 4. Examples of Common Foods That May Be Incorporated Under Unfamiliar Names Into Commercial Foods as Additives

| | |
|---|---|
| Milk | |
| | Fermented ingredients, flavor, hydrolyzed proteins, lactose |
| Soy | |
| | Hydrolyzed proteins, lecithin, fermented ingredients, oil, soy sauce |
| Wheat | |
| | Fermented ingredients, flavor, hydrolyzed proteins, soy sauce, starch |
| Peanut | |
| | Flavor, hydrolyzed protein, oil |
| Fish | |
| | Flavor, gelatin, Worcestershire sauce (from anchovies) |
| Egg | |
| | Flavor, lecithin, lysozyme |

Although food labeling is far from being ideal for allergic patients, improvement is being continuously made in both completeness and clarity. Effective January 1, 2006, a new law known as the Food Allergy Labeling and Consumer Protection Act of 2004 will go into effect.[78] This law will require food manufacturers to declare the presence of "major food allergens" contained in all food products. Major food allergens are defined as milk, egg, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans. Most importantly, this law specifies that ingredients must be listed by their "common or usual name," making it easier for consumers to recognize the presence of these allergens.

Once a hidden food protein allergen is ruled out, suspicion should be directed to food additives. Skin testing (or in vitro testing if available) might be helpful in screening for some natural additives, such as carmine,[60,79] annatto,[61] saffron,[62,80] mannitol,[81] and vegetable gums.[82] Skin testing and in vitro testing are unreliable in screening for sensitivity to synthetic additives. A trial of an additive-free diet for a few weeks can be of substantial help in supporting or ruling out suspicion of food additives. An example of such a diet is presented in Table 5. Patients need to consume only homemade meals prepared with known ingredients and to avoid all commercial and pre-prepared food during the diet period. If the patient improves on the additive-free diet, the next step is to perform a series of challenges with the available additives.

Verification of the role of a food additive requires a blinded, placebo-controlled oral challenge, which was lacking in most published reports on the subject. Details on conducting a food challenge are available elsewhere.[83] To reduce the number of challenges, mixtures of additives can be used initially (eg, dyes of similar color, gums, sweeteners, or preservatives). The components of the positive challenge mixture must be tested individually to identify the specific offending additive. The challenge doses used in the few published studies varied widely.[53,84] General guidelines on the challenge doses for a number of additives are shown in Table 6 and are based on the commonly consumed quantities of each agent and our clinical experience. Sources for obtaining challenge materials are listed below Table 6.

## MANAGEMENT

The basic management of adverse reactions to food additives is avoidance, which requires definite identification of the offending agent. To the best of our knowledge, no studies

Table 5. Example of a Diet Free of Food Additives

| |
|---|
| Meats |
| Beef, chicken, lamb, turkey, veal (fresh or frozen) |
| Fish |
| Any (fresh or frozen) |
| Vegetables |
| Carrots, lettuce, mushrooms, parsley, potatoes |
| Cereal and grain |
| Rice |
| Fruits |
| Pears (canned, fresh, or nectar) |
| Cooking oil |
| Safflower without preservatives |
| Condiments |
| Honey, pepper, salt, sugar |
| Beverages |
| Coffee, pear nectar, tea, water |
| Optional |
| Butter, cottage cheese, eggs, matzo (plain), milk, preservative free bread, spaghetti |
| Avoid |
| Apples, bananas, beer, breads not marked preservative free, breakfast cereal, cakes, cheese, chocolate, fruit juices (except pear), grapes, instant foods, jams, licorice, margarine, mayonnaise, packaged meals, pickles, prepared salad dressings, prepared sauces, rhubarb, sweets, wine |

Table 6. Suggested Challenge Dose Increments for Common Food Additives*

| Additive | Dose given every 20–30 min |
|---|---|
| Food dyes or colorants | 1, 5, 10, 15 mg each† |
| Acetyl salicylic acid | 5, 25, 50, 100, 200 mg |
| BHA and BHT | 25, 50, 100, 200 mg each† |
| Nitrites and nitrates | 25, 50, 100, 200 mg each† |
| Parabens | 25, 50, 100, 200 mg |
| Sodium benzoate | 25, 50, 100, 200 mg |
| Sorbate | 25, 50, 100, 200 mg |
| Sulfites | 25, 50, 100, 200 mg |
| Sweeteners | 100, 200, 400, 800 mg each† |
| MSG | 200, 400, 800, 1,600 mg |

Abbreviations: BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; MSG, monosodium glutamate.

* Based on the commonly consumed quantities and the authors' clinical experience. Possible sources for obtaining additives: Fisher Scientific, call or check Web site for nearest customer service location, 1-800-766-7000, www1.fishersci.com; Sigma-Aldrich, PO Box 14508, St Louis, MO 63178, 800-325-3010, www.sigma-aldrich.com.

† When using multiple additives in a mixture.

have demonstrated any role for desensitization to food additives. Once the offending additive is identified, the patient should be provided with all names that refer to that additive and the potential products that might include it. It is important also to read labels and ask questions about commercially prepared foods. It is generally recommended that patients with severe reactions should consume foods prepared at home from defined ingredients.

Since there is always a chance of unintentional exposure, an appropriate treatment plan should be developed for individual patients, particularly those with anaphylactic or severe reactions. Such patients should wear a medical identification tag (eg, MedicAlert) and have self-injectable epinephrine available at all times. Selected patients may benefit from taking an antihistamine daily or before an anticipated potential exposure. One study has also shown that patients with chronic urticaria and positive challenge results to acetylsalicylic acid and/or food additives may benefit from the addition of montelukast,[84] but these results have yet to be confirmed in larger studies.

## CONCLUSIONS

In summary, food additives are increasingly used, and many patients report a wide variety of symptoms related to their consumption. However, there is a lack of well-controlled, rigorously conducted studies of adverse reactions to food additives. Hence, knowledge of the spectrum of such reactions is far from optimal regarding manifestations, causative agents, and mechanisms. Asthma, in some patients, has been reported to have an association with sulfites and benzoates. Both MSG and tartrazine seem to be rarely if ever associated with asthma flares. Anaphylaxis is associated in isolated cases with sulfites, certain food colorings (carmine, annatto, saffron), the sweetener erythritol, and possibly nitrites and benzoates. Urticaria may be associated with BHA or BHT, sulfites, aspartame, MSG, and some dyes, but the studies had inconsistent findings.

Food additives should be suspected if patients report a history of reactions to numerous unrelated foods or to a certain food when commercially prepared but not when homemade and the evaluation rules out allergy to food protein. It is also prudent to investigate a role for food additives in patients considered to have idiopathic reactions. One study evaluated 102 patients with idiopathic anaphylaxis by skin testing using 79 foods, including some additives.[85] In 7 patients, oral challenge confirmed the clinical relevance of positive skin test results for 10 allergens, 4 of which were additives (aniseed, flaxseed, hops, and mustard). Diagnosing hypersensitivity to food additives is much more challenging than diagnosing food protein hypersensitivity, but the result can be rewarding. With more than 3,000 additives approved for use, most of the additives are unknown to health care professionals, particularly when listed under unfamiliar names. In addition, some ingredients may not be listed on the packaging at all; thus, contacting the manufacturer for a list of ingredients might be useful. Except for a relatively few natural additives, skin testing and in vitro testing are unreliable screening methods. Institution of a trial of an additive-free diet may be helpful. Appropriately conducted challenges with common additives might detect the offending agent.

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**Objectives:** After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

**Participants:** This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

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## CME Examination

1–5, Wilson BG. 2005;94:499–507.

## CME Test Questions

1. Monosodium glutamate is primarily used as a(n)
   a. antioxidant
   b. emulsifier
   c. flavor enhancer
   d. preservative
   e. stabilizer
2. All of the following food dyes are primarily yellow except
   a. carmine
   b. curcumin
   c. saffron
   d. tartrazine
   e. turmeric
3. All of the following additives are derived from natural sources except
   a. carmine
   b. annatto
   c. monosodium glutamate
   d. saffron
   e. tartrazine
4. All of the following have been proposed to play a role in the mechanisms for sulfite reactions in certain patients except:
   a. specific IgE antibodies
   b. generation of sulfur dioxide causing direct smooth muscle contraction
   c. generation of sulfur dioxide causing a cholinergic reflex
   d. neuroinhibitor effect of sulfites
   e. deficiency of sulfite oxidase
5. Hypersensitivity reactions to food additives are reliably diagnosed by which of the following?
   a. reading food labels
   b. skin prick testing
   c. ALCAT (Antigen Leukocyte Cellular Antibody Test)
   d. any of the above
   e. none of the above

**Answers found on page 570.**