

Urticaria, Angioedema, and Anaphylaxis Provoked by Food and Drug Additives

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KEY CONCEPTS

- Only a small fraction of the thousands of agents added to our foods have been associated with cutaneous and/or anaphylactic hypersensitivity responses.
- Early (pre-1990) literature overestimated the prevalence of such reactions due to poorly controlled studies.
- Additive-induced urticaria, angioedema, and anaphylaxis is relatively rare.
- Hypersensitivity responses to “natural” additives appear to be primarily IgE based, while the basis of most reactions to synthetic additives is unclear.
- Chronic idiopathic urticaria/angioedema is rarely associated with food-additive hypersensitivity.
- Recommendations for food-additive challenge protocols for patients with urticaria, angioedema, and/or anaphylaxis are reviewed in the text.

Many agents are added to foods that we consume [1], the number ranges from 2000 to 20,000. These substances include preservatives, stabilizers, conditioners, thickeners, colorings, flavorings, sweeteners, and antioxidants. Despite the multitude of additives known, only a surprisingly small number have been associated with hypersensitivity reactions.

Urticaria, angioedema, and anaphylaxis from food additives should be suspected when adverse reactions after food or beverage consumption occur; some, but not all the time, suggesting that the reaction occurs only when an additive is present.

A number of investigators have suggested that urticaria, angioedema, and anaphylaxis related to the ingestion of food additives are relatively common. This apparent misconception is based on several poorly controlled studies, mostly reported before 1990. Emerging evidence appears to contradict this notion, suggesting that the incidence of such reactions is relatively low.

Table 28.1 lists the food and drug additives that may be associated with adverse reactions. In this chapter, these additives are discussed in detail as they relate to urticaria and angioedema, as well as to anaphylaxis or anaphylactoid reactions.

General considerations and description of some additives

A brief overview of selected additives follows [2]. For additional information, the reader is referred to Chapters 27, 29–34 in this book.

Food dyes

Dyes approved under the Food, Drug and Cosmetic (FD & C) Act are coal tar derivatives, the best known of which is tartrazine (FD & C Yellow No. 5). In addition to tartrazine, the group of azo dyes include ponceau (FD & C Red No. 4) and sunset yellow (FD & C Yellow No. 6). Amaranth (FD & C Red No. 2) was banned from use in the United States in 1975 because of claims related to carcinogenicity. Non-azo dyes include brilliant blue (FD & C Blue No. 1), erythrosine (FD & C Red No. 3), and indigotine (FD & C Blue No. 2).

Sulfites

Sulfites and the burning of sulfur-containing coal have been used for centuries to preserve food. In addition, sulfiting agents (including sulfur dioxide and sodium or potassium sulfite, bisulfite, and metabisulfite) are used by the fermentation industry to sanitize containers and to inhibit the growth of undesirable microorganisms. Sulfites act as potent antioxidants, which explains their widespread use in foods as preventatives against oxidative discoloration (browning)

Table 28.1 Additives associated with adverse reactions

Synthetic additives

FD & C dyes

Azo dyes

- Tartrazine (FD & C Yellow No. 5)
- Sunset yellow (FD & C Yellow No. 6)
- Ponceau (FD & C Red No. 4)
- Amaranth (FD & C Red No. 2)

Non-azo dyes

- Brilliant blue (FD & C Blue No. 1)
- Erythrosine (FD & C Red No. 3)
- Indigotine (FD & C Blue No. 2)

Parabens

p-hydroxybenzoic acid

Methyl-, ethyl-, butyl-, and propyl-paraben

Sodium benzoate

Butylated hydroxyanisole (BHA)

Butylated hydroxytoluene (BHT)

Nitrates/nitrites

Monosodium glutamate (MSG)

Sulfites

- Sulfur dioxide
- Sodium sulfite
- Sodium/potassium bisulfite
- Sodium/potassium metabisulfite

Aspartame

Isosulfan blue (medical diagnostic agent)

Natural additives (Plant/animal sources)

Annatto

Carmine

Saffron

Mannitol

and as fresheners. Many packaged foods, including fresh and frozen cellophane-wrapped fruits and vegetables, processed grain foods (crackers and cookies), and citrus-flavored beverages, may contain sulfites.

The highest levels, however, occur in potatoes (any peeled variety), dried fruits (apricots and white raisins), and possibly shrimp and other seafood, which may be sprayed with sulfiting agents after unloading on the dock. Sulfites are listed as ingredients in prepared and packaged foods or drink that contain at least 10ppm SO₂ equivalents. In 1986, the US Food and Drug Administration (FDA) banned the use of sulfites on foods marketed as “fresh.”

Parabens

Parabens are aliphatic esters of *p*-hydroxybenzoic acid. They include methyl-, ethyl-, propyl-, and butyl-parabens. Sodium benzoate is a closely related substance, usually reported to cross-react with these compounds. These agents are widely used as preservatives in both foods and drugs, and are well recognized as causes of severe contact dermatitis.

Monosodium glutamate

Glutamic acid is a non-essential dicarboxylic amino acid that constitutes 20% of dietary protein. Glutamate occurs naturally in some foods in significant amounts: 100g of Camembert cheese, for example, contains as much as 1g of monosodium glutamate (MSG). The greatest exposure to MSG, however, occurs through its role as a flavor enhancer. Manufacturers and restaurateurs add MSG to a wide variety of foods. About 85 years ago a Japanese chemist established that MSG produced the flavor-enhancing properties of seaweed, a traditional component of Japanese cooking. Large amounts of MSG are sometimes added to Chinese, Japanese, and other Southeast Asian cooking. As much as 6g of MSG may be ingested in a highly seasoned oriental meal, and a single bowl of wonton soup may contain 2.5g of MSG. MSG may also be found in manufactured meat and chicken products.

MSG has been reported to provoke, within minutes to hours of eating, a syndrome characterized by headache, a burning sensation along the back of the neck, chest tightness, nausea, and sweating. Recently, a trend toward reducing MSG use in Asian cooking has emerged, likely in response to consumer dissatisfaction related to the occurrence of the syndrome.

Aspartame

Aspartame is a dipeptide composed of aspartic acid and the methyl ester of phenylalanine. This popular low-calorie artificial sweetener is 180 times sweeter than sucrose.

Butylated hydroxyanisole and butylated hydroxytoluene

Butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are antioxidants used in cereal and other grain products.

Nitrates/nitrites

Nitrates and nitrites are widely used preservatives. Their popularity stems from both flavoring and coloring attributes. These agents are found mostly in processed meats such as frankfurters and salami [3].

Isosulfan blue

Isosulfan blue (ISB; Lymphazurin 1%, US Surgical Corporation) is an isomer of the triphenylmethane dye patent blue. It is a contrast agent for the delineation of lymphatic vessels. Following subcutaneous administration, this dye binds to interstitial proteins in lymphatic vessels, imparting a bright blue appearance that makes the lymphatics more readily discernable from surrounding tissue. ISB is indicated as an adjunct to lymphangiography, assessing lymph node response to therapeutic modalities and for visualization of the lymphatic system draining the region of injection [4].

Annatto

Annatto dye is an orange-yellow food coloring extracted from the seeds of the tree *Bixa orellana*, a large fast-growing shrub cultivated in the tropics. It is frequently used in cereals, beverages, cheese, and snack foods.

Carmine

Carmine (or cochineal extract) is a biologically derived red colorant derived from the dried bodies of female cochineal insects (*Nopalea coccinellifera*). It is commonly used in cosmetics, textiles, and foods. It is responsible for giving the liqueur Campari its characteristic color. It is often designated E 120.

Saffron

Saffron color, a dark yellow-orange, derives from the crocus plant. The saffron spice consists of the dried stigmas and style of the crocus bulb, while the saffron colorant, crocin, also comes from the dried stigmas and style. It is used to color soups, bouillabaisse, sauces, rice dishes (paella, "risotto Milanese"), cakes, cheese, and liqueurs [5].

Mannitol

Mannitol is a sugar alcohol widely distributed in plants. It is a white, crystalline sweetener added to processed foods for

the purpose of thickening, stabilizing, and sweetening. It is also widely used as a drug excipient. In addition, it is widely used as a therapeutic agent for glaucoma, increased intracranial pressure, drug intoxication, and oliguric renal failure [6].

Mechanisms of additive-induced urticaria, angioedema, and anaphylaxis

As of now, the mechanisms underlying additive-induced urticaria, angioedema, and anaphylaxis remain largely unknown. It seems reasonable to postulate, however, that multiple mechanisms are responsible for these adverse reactions, given the heterogeneity of chemical structures found among these additives (Fig. 28.1). Natural food colorants (e.g. annatto and carmine) are derived from proteins with molecular weights consistent with common food allergens.

Immediate (IgE-mediated) hypersensitivity

Naturally derived food colorings, such as annatto and carmine, contain proteins recognized in sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE), appearing as gel bands that appear in the 10–100 kDa range. Therefore, these colorants can be expected to potentially elicit IgE-mediated responses in some atopic individuals. Synthetic

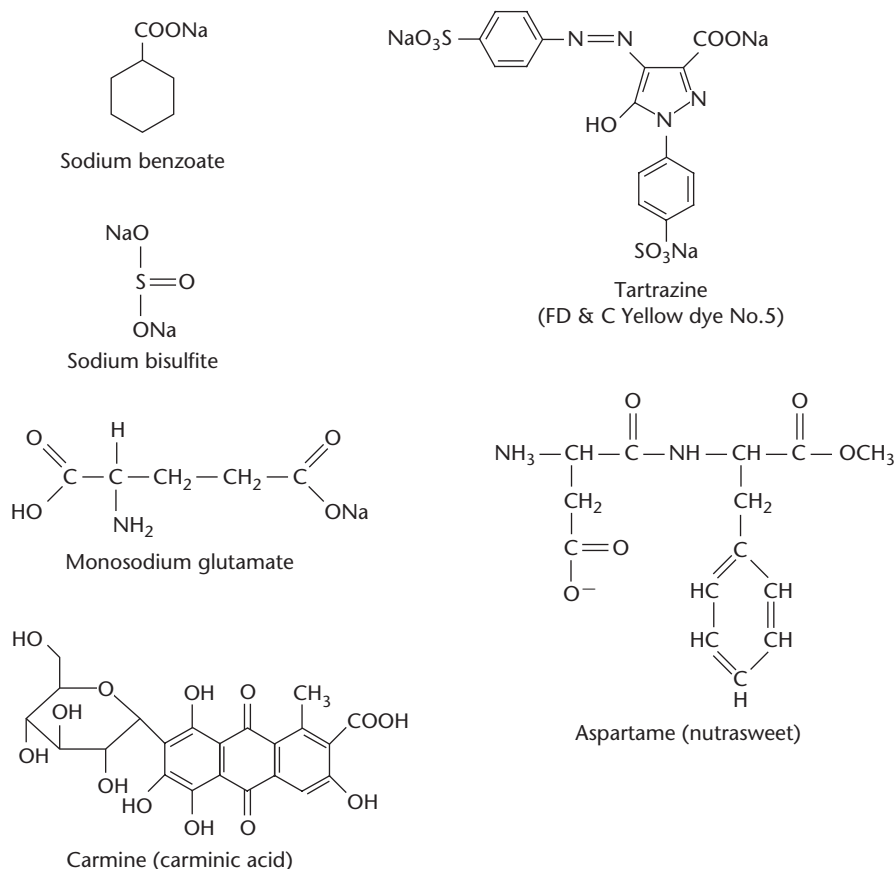


Figure 28.1 Chemical structure of common food additives.

additives would appear to have to act as haptens to create a response mediated by IgE. Only a few reports have suggested IgE-mediated reactions to synthetic additives, notably to sulfites and parabens. Instead, the overwhelming majority of these reactions are not of the immediate hypersensitivity type. In fact, many cases of additive-provoked urticaria are said to occur as late as 24 hour after challenge, arguing against an IgE-mediated mechanism.

Evidence for an IgE-mediated mechanism as the cause for identified anaphylactic episodes associated with carmine-colored foods derives from studies that have demonstrated associated positive skin prick test (SPTs), a positive Prausnitz-Küstner (PK) test, a positive basophile histamine release assay, positive IgE RAST (radioallergosorbent test) studies, and positive SDS-PAGE with IgE immunoblot [7–11]. Chung *et al.* [12] identified (in minced cochineal insect extracts) several protein SDS-PAGE bands of 23–88 kDa. The sera from three patients with episodic urticaria/angioedema/anaphylaxis occurring 3–5 hours after ingestion of foods containing carmine recognized these bands on immunoblot. This reactivity was inhibited by carmine. Patient reactivity to specific bands varied. Commercial carmine appears to retain proteinaceous material from the source insects. These insect-derived proteins, possibly complexed with carminic acid, are responsible for IgE-mediated carmine allergy.

Nish *et al.* [13] reported on a case of annatto dye-induced anaphylaxis. SPTs to annatto were strongly positive with negative control results. SDS-PAGE demonstrated two bands in the range of 50 kDa. Immunoblotting showed patient IgE specific for one of these bands and controls showed no binding. Residual or contaminating seed protein was the likely responsible antigen in this rare cast. Revan *et al.* [14] reported their experience with annatto at the University of Michigan allergy clinic. They found 9 (12%) of 77 atopic patients were SPT positive to liquid undiluted annatto. However, only 2 of these 9 subjects had symptomatic annatto allergy: 1 patient with a 4+ SPT had a history of annatto-induced anaphylaxis, and another with a 3+ SPT had angioedema. Only one SPT-positive reactor was challenged (2+) and was negative. The negative predictive value (NPV) of SPT in this cohort was 100%; however, the positive predictive value (PPV) was low (22%). Perhaps the undiluted extract was too potent to differentiate between true reactors and an irritant response. Double-blind, placebo-controlled (DBPC) challenges are needed to confirm these results.

In 1976, Prenner and Stevens reported an anaphylactic reaction occurring after the ingestion of food sprayed with sodium bisulfite [15]. Minutes after eating a restaurant lunch, this 50-year-old male experienced generalized urticaria, pruritus, swelling of the tongue, difficulty swallowing, and tightness in the chest. He responded promptly to treatment with subcutaneous epinephrine. Subsequently, the patient's SPT and an intradermal test gave positive results (with negative controls). The authors were able to demonstrate

PK transfer to a non-atopic subject. Yang and associates [16] also described one patient with a history of sulfite-provoked anaphylaxis. A borderline result was obtained via intradermal skin test, followed by a positive response to a single-blind oral provocation challenge with 5 mg of potassium metabisulfite. This patient's cutaneous reactivity was also passively transferred via the PK reaction. However, this group was unable to elicit positive responses from challenges in nine patients with histories of hives related to eating restaurant food. In addition, Sokol and Hydock [17] reported a case of sulfite-induced anaphylaxis that provided evidence for specific IgE-mediated mechanism. Despite these isolated reports, IgE-mediated immediate hypersensitivity reactions to sulfites (possibly via a hapten mechanism) appear to occur only rarely.

Studies measuring serum levels of neutrophil chemotactic factor of anaphylaxis (NCF-A) did not find an increase in this mast cell (MC) mediator post-challenge in subjects with negative metabisulfite skin tests, suggesting that MC degranulation is not associated with non-IgE-mediated sulfite reactions [18]. Cromolyn pre-treatment did not ablate an urticarial reaction in an individual sensitive to potassium metabisulfite [19]. In the overwhelming majority of cases, the mechanisms behind sulfite-provoked urticaria, angioedema, and anaphylaxis (or anaphylactoid reactions) remain unknown.

At least three cases of apparent IgE-mediated, paraben-induced urticaria and angioedema have been reported [20,21]. All of these cases concerned reactions to benzoates used as pharmaceutical preservatives. The three patients had positive skin test responses to parabens, but negative results when exposed to the drugs themselves minus the paraben preservatives. These subjects, however, could tolerate oral benzoates in their diets without reactions. Macy *et al.* [22] recently reported a series of 287 patients who underwent immediate hypersensitivity skin test to methylparaben-preserved local anesthetics. Only three patients had positive skin tests. These three individuals underwent skin testing as well as provocative dose testing to 0.1% methylparaben, in addition to local anesthetic without preservative. All three reacted definitely to the methylparaben, suggesting that methylparaben is a potential cause for local immediate hypersensitivity reactions previously attributed to the local anesthetics themselves.

Delayed (type IV) hypersensitivity

Another suggested mechanism focuses on delayed hypersensitivity. Studies in this area have been few in number and often of questionable design. Warrington and co-workers [23] measured the release of a T-lymphocyte-derived leukocyte-migration inhibition factor in response to incubation with tartrazine, sodium benzoate, and aspirin (acetylsalicylic acid) *in vitro* using peripheral blood mononuclear cells from patients with chronic urticaria, with or without associated additive or

aspirin sensitivity. Significant production of the inhibitory factor occurred in response to tartrazine and sodium benzoate in individuals with chronic additive-induced urticaria. The groups of patients studied (four patients per group) reportedly exhibited sensitivity to tartrazine, sodium benzoate, and aspirin as determined either by response to elimination diet alone or by challenge-proved sensitivity. In this study, the potential for false-positive reactions on the basis of response to diet alone presented a problem. Essentially no details of the challenge procedures were given.

Valverde and associates [24] studied *in vitro* lymphocyte stimulation in 258 patients with chronic urticaria, angioedema, or both, using a series of food extracts and additives that included tartrazine, benzoic acid, and aspirin. They found positive stimulation (using the lymphocyte transformation test) to additives in 18% of subjects. After the patients were placed on a diet that excluded the offending additives, 62% had total remission of symptoms and 22% had partial remission. The investigators concluded that this response to diet lent credence to the lymphocyte transformation test as an *in vitro* diagnostic test for chronic urticaria and angioedema related to food additives. However, no provocation challenges were performed in this study. No definitive conclusions regarding the presence or absence of a delayed-type hypersensitivity mechanism in additive-provoked urticaria can be made from the studies described above. It does seem reasonable to conclude that a reaction with an onset between 30 minutes and 6 hours after exposure to the material in question (most reactions began within the first 6 hours) is not typical of a type IV mechanism.

Cyclooxygenase, aspirin, and tartrazine

The possibility of tartrazine sensitivity remains controversial. Many claims of cross-reactivity between aspirin and tartrazine have been made; estimates of its incidence based on earlier studies ranged from 21% to 100% [25–29]. In a DBPC study (with objective reaction criteria and withholding of antihistamines for 72 hours prior to challenge), only 1 (4.2%) of 24 patients experienced urticaria after challenge with 50 mg of tartrazine [30]. When challenged with 975 mg of aspirin, this patient did not react, suggesting that cross-reactivity between aspirin and tartrazine may not occur. An earlier DBPC crossover challenge with 0.22 mg of tartrazine found sensitivity in 3 (8%) of 38 patients with chronic urticaria and 2 (20%) of 10 patients with aspirin intolerance [28]. This dose of tartrazine is similar to that used to color medication tablets, but remains far less than that typically encountered in the diet. The report did not mention, however, whether antihistamines were withheld during the challenges. No convincing evidence has been found to prove that tartrazine inhibits the enzyme cyclooxygenase (in the arachidonic acid cascade), an often-suggested mechanism for aspirin sensitivity.

Neurologically mediated hypersensitivity

Considerable evidence exists that MSG has both neuroexcitatory and neurotoxic effects in animals [31] and humans [32]. Neurologically mediated urticarias have been described [33]. Several factors, including heat, exercise, and stress, may induce cholinergic urticaria. This mechanism represents only a theoretical basis for MSG-induced urticaria, possibly via release of cutaneous neuropeptides.

Anticoagulation

In 1986, Zimmerman and Czarnetzki [34] sought to disprove claims by earlier investigators that changes in bleeding time play an important role in diagnosing anaphylactoid reactions to aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), and food additives. They measured bleeding time, prothrombin time, and partial thromboplastin times in 10 patients with histories of anaphylactoid reactions to these drugs and various food additives. Challenges were not placebo-controlled, nor were they blinded. Nevertheless, the investigators found no correlation between patient's reactions and the aforementioned coagulation parameters.

Conclusion

Thus, aside from several case reports describing IgE-mediated reactions to sulfites and parabens, the majority of synthetic additive-induced urticaria, angioedema, and anaphylactic reactions involve mechanisms that have not been elucidated. This stands in contrast to the natural food additives carmine and annatto, which show definite IgE binding to residual source protein antigens.

Food additive challenge studies in patients with urticaria/angioedema

Patient selection

Selection of patients for study of urticaria/angioedema has included three types of subjects: (1) all available patients with chronic urticaria (or only those with chronic idiopathic urticaria); (2) patients with histories suggestive of food additive-provoked urticaria; or (3) patients who have responded to a diet free of commonly implicated additives. The percentage of positive reactors will depend on the group selected. This variability adds more confusion to the already difficult task of comparing results from differing studies.

Activity of urticaria at the time of study

The relative degree of activity or inactivity of urticaria or angioedema at the time of challenge appears to affect the ability to obtain cutaneous responses to food additives. Challenges performed on patients with active urticaria are more likely to yield false-positive results. Challenges performed on patients whose urticaria is in remission, on the other hand, are more likely to yield false-negative results. In a study by Mathison and colleagues [35], only 1 of 15 patients whose urticaria

was in remission experienced a reaction to aspirin, whereas 7 of 10 patients with active urticaria reacted to aspirin. These challenges were performed using objective reaction criteria, and the reactions observed were then compared with baseline observations.

Medications

Several studies made no reference to whether medications – particularly antihistamines – were continued or withheld during challenge. The following caveats must be considered when interpreting such challenge studies: (1) Discontinuation of antihistamines immediately before or within 24 hours of challenge often facilitates more false-positive results. (2) Continuation of antihistamines during challenges may block milder additive-induced cutaneous responses and, therefore, give more false-negative results. (3) Subjects become increasingly likely to experience breakthrough urticaria as the interval from the last antihistamine dose to the “positive challenge” increases. Such results would be even more confusing if placebo-controlled challenges preceded additive challenges.

Reaction criteria

Often no period of baseline observation is made by the investigators for comparison with reaction data. Most challenge studies performed have employed a loosely defined and rather subjective means to define urticarial responses. The reaction criteria might simply consist of “clear signs of urticaria developing within 24 hours.” The studies by Stevenson *et al.* [30] and Mathison *et al.* [35], in contrast, utilized an objective system of scoring urticarial responses.

Placebo controls

The use of placebo-controlled studies in additive challenge protocols is desirable because studies without these controls are difficult to interpret when assessing positive urticarial challenge responses. Nevertheless, a number of reported additive challenge studies do not employ placebo controls. Even in many placebo-controlled studies, the placebo is always the first challenge, followed by aspirin, and finally by an additive. Thus, a spontaneous flare of urticaria would be least likely to coincide with the first placebo challenge. We also question the validity of having only a single placebo in challenge studies that test large numbers of additives. A need exists for multiple placebos and randomization of placebo usage in the order of challenges.

Blinding

Among the most important features of any protocol for food additive challenge is a double-blind challenge, because urticaria may be exacerbated by emotional stress. In addition, it is necessary to eliminate observer bias given the subjective nature of positive responses. Open challenges are useful tools for ruling out additive-associated reactions. Positive challenge

responses, in contrast, need double-blinded confirmation before they can be accepted as “true positives.”

Multiple additive challenges in patients with chronic urticaria

Examples of studies with less stringent design criteria

One of the earliest additive challenge studies in patients with chronic urticaria was reported by Doeglas [36]. Seven (30.4%) subjects reacted to tartrazine and “four or five” (17.4% or 22.7%) reacted to sodium benzoate. Placebo-controlled challenges were not performed. Thune and Granholt [37] reported that 20 (21%) of 96 patients reacted to tartrazine, 13 (15%) of 86 reacted to sunset yellow, 5 (71%) of 7 reacted to parabens, and 6 (13%) of 47 reacted to BHA and BHT. Furthermore, in the group of patients with chronic idiopathic urticaria, 62 (62%) of the 100 patients challenged reacted to at least 1 of the 22 different agents used. The challenges were not placebo-controlled, however, so any conclusions about the incidence of reactions to a particular agent derived from this study would be difficult to support.

In a study of 330 patients with recurrent urticaria, Juhlin [38] performed single-blind challenges using multiple additives and a single placebo, which always preceded the additive challenge. He found that one or more positive reactions occurred in 102 (31%) of patients tested. Reaction criteria were relatively subjective in this study. In fact, 109 (33%) of patients had reactions judged to be “uncertain” because, as the author stated, “Judging whether a reaction is positive or negative is not always easy.” Furthermore, if patients reacted to the lactose placebo, retesting involved a wheat starch placebo. Questionable reactors were retested. If the repeat test gave a positive result, the first test was assumed to be positive as well; the same logic applied for negative retesting.

Supramaniam and Warner [39] described 24 of 43 children as reacting to one or more additives used in their double-blind challenge study. No baseline observation period was established, however, and only one placebo was interspersed among the nine additives used for challenge. Furthermore, no mention was made about whether antihistamines were withheld prior to or during challenges.

In 1985, Genton and co-workers [40] performed single-blind additive challenges on 17 patients with chronic urticaria or angioedema. The patients were placed on a 14-day elimination diet (free of food additives) before challenge and medications were discontinued at the beginning of the diet. Of the 17 patients in the study, 15 reacted to at least one of the six additives used for challenge.

Examples of studies with more stringent design criteria

In 1988, Ortolani and associates [41] reported 396 patients with recurrent chronic urticaria and angioedema; this report

was a follow-up to a study performed in 1984 [42]. DBPC oral food provocations were performed on patients that had experienced significant remissions while following an elimination diet. The diet was maintained, but medications were discontinued during challenges. The report did not describe the timing of discontinuation of medications. On the basis of history alone, 179 patients were considered for an elimination diet for suspected food or food additive intolerance; only 135 patients ultimately participated in the study. Eight (9.2%) of 87 patients who had significantly improved on the diet after 2 weeks gave positive responses to food challenges. Of the 79 patients with negative responses to food challenges, 72 underwent DBPC, oral food additive provocations. Twelve (17%) of these patients experienced positive responses to challenges with one or more additives. Many of these patients reacted to two or three additives. Five (31%) of the 16 patients with positive responses to aspirin challenges gave positive responses to additive challenges; four of these subjects tested positive to sodium salicylate.

The similarity in chemical structure observed between aspirin and sodium salicylate supports the possibility of cross-reactivity between these agents. They differ in that sodium salicylate is a “non-acetylated” salicylate. The doses used (>400 mg) in the sodium salicylate challenge, however, far exceed the levels encountered in most conventional diets. Furthermore, although it is important in assessing food sensitivity, a patient’s history is usually a poor indicator of a possible additive hypersensitivity, because patients are usually unaware of all additives that they consume daily.

Hannuksela and Lahti [43] challenged 44 chronic urticaria patients with several food additives, including sodium metabisulfite, BHA or BHT, β -carotene, and benzoic acid in a prospective, DBPC study. Only 1 (2.2%) of the 44 patients had a positive response to challenge, reacting positively to benzoic acid. Another patient also reacted to the placebo challenge. All medications were discontinued 72 hours before the first challenge and during the study. Patients were not placed on an additive-free diet prior to the challenge. The challenge dose of metabisulfite was low, only 9 mg. Similarly, Kellet and associates noted that approximately 10% of 44 chronic idiopathic urticaria patients reacted to benzoates, tartrazine, or both, but 10% of the subjects reacted to placebo challenges [44].

Elimination diet studies

An alternative strategy for investigating additive-induced urticaria involves the elimination of all additives from the diet and the observation of its effects on hives. Unfortunately, there are no reported blinded or placebo-controlled studies of this nature. In uncontrolled studies, Ros and co-workers [45] reported an additive-free diet to be “completely helpful” in 24% of patients with chronic urticaria; 57% of patients were deemed “much improved,” and 19% were “slightly better” or experienced no change in their urticaria. Rudzki and associates [46] reported that 50 (32%) of 158 patients

responded to a diet that eliminated salicylates, benzoates, and azo dyes. These studies did not address the question of which, if any, additives constituted the cause of the problem.

Gibson and Clancy [47] found that 54 (71%) of 76 patients who underwent a 2-week, additive-free diet “responded.” They then challenged the responders with individual additives. Although the challenges were controlled, the patients always received the placebo first. No mention was made of whether the challenges were blinded. A diet that eliminated the offending additive was then continued for 6–18 months, followed by repeat challenge. All three patients who initially responded positively to tartrazine challenge had negative results upon re-challenge, as did one of the four patients with initially positive responses to benzoate challenges. Thus, despite this approach, the incidence of additive sensitivity in urticaria remains unknown.

Reports of single additive challenge studies

Sulfites

The reports by Prenner and Stevens [15] and Yang *et al.* [16] discussed earlier presented single cases of sulfite-provoked anaphylaxis and gave skin test and PK-transfer evidence to suggest that an IgE-mediated mechanism played a role in these reactions. In addition, Yang *et al.* [16] performed a single-blind oral challenge. Their patient responded positively to a challenge with 5 mg of potassium metabisulfite.

In 1980, Clayton and Busse [48] described a non-atopic female who developed generalized urticaria that progressed to life-threatening anaphylaxis within 15 minutes of drinking wine. Her symptoms were not reproduced by ingestion of other alcoholic beverages. This case may have involved sulfite-provoked urticaria and anaphylaxis.

Habenicht and co-workers [49] described two patients who experienced several episodes of urticaria and angioedema after consuming restaurant meals. Only one of these individuals underwent a single-blind oral challenge with potassium metabisulfite. Generalized urticarial lesions developed in this patient within 15 minutes of receiving a 25-mg challenge dose. No placebo challenge was performed. Avoidance of potential sulfite sources apparently resolved this patient’s recurrent symptoms.

Schwartz reported two patients with restaurant-related symptoms who underwent oral challenges with metabisulfite [50]. Both subjects had symptoms temporally related to ingestion of salads: weakness, a feeling of dissociation from the body, dizziness, borderline hypotension, and bradycardia. These signs and symptoms are more consistent with vasovagal reactions than with anaphylaxis. One report has described a patient who received less than 2 ml of procaine (Novocaine) with epinephrine administered subcutaneously by her dentist [51]. Within several minutes, she developed

flushing, a sense of warmth, and pruritus, followed by scattered urticaria, dyspnea, and anxiety. Skin tests of various local anesthetics and sulfite proved negative. Thirty minutes after receiving a single-blind, oral dose of 10 mg of sodium bisulfite, she developed “a sense of fullness in her head, nasal congestion, and a pruritic erythematous blotchy eruption.” No respiratory symptoms developed and the investigators did not observe any pulmonary function test abnormalities. This patient was able to tolerate local anesthetics without epinephrine. Importantly, this patient did not describe a history of food-related symptoms. Furthermore, the usual dose of aqueous epinephrine (adrenalin) contains only 0.3 mg of sulfite and local anesthetics contain only as much as 2 mg/ml of sulfite. Thus, the usual doses, even in the most sensitive persons, would not provoke reactions. The mechanism of this patient’s reaction cannot be definitively linked to sulfite and likely was a vasomotor response to the effects of epinephrine.

A DBPC challenge that reproduced urticaria after challenge with 25 mg of potassium metabisulfite was reported by Belchi-Hernandez *et al.* [19]. Skin tests were negative in this subject.

Two reports have demonstrated the inability to provoke reactions to sulfites in patients with idiopathic anaphylaxis, some of whom had histories of restaurant-associated symptoms [52,53]. In a study describing food-related skin testing in 102 patients with idiopathic anaphylaxis, only one patient was found to have metabisulfite sensitivity [54]. In addition, the authors performed sulfite-ingestion challenges in 25 patients with chronic idiopathic urticaria and angioedema without a reaction (unpublished observations). At present, sulfite-induced urticaria, angioedema, or anaphylaxis appears to be a rare phenomenon.

Acute urticaria associated with leukocytoclastic vasculitis and eosinophilia was induced by a single placebo-controlled challenge with 50-mg sodium bisulfite in a subject suffering from recurrent urticaria and angioedema of unclear etiology. Blinded challenges were performed during a symptom-free period, followed by biopsy confirmation of the leukocytoclasia. Conscious avoidance of sulfites reduced the frequency of subsequent reactions dramatically [55].

Tartrazine/azo dyes

Murdoch *et al.* [56] found at least 2 (8.3%) of 24 patients who developed hives after ingesting a panel of four azo dyes, including tartrazine. As previously indicated, Stevenson *et al.* [30] found that only 1 (4.2%) of 24 aspirin-sensitive subjects undergoing double-blind challenge with 50-mg tartrazine developed urticaria. It appears, therefore, that tartrazine and other azo dyes rarely induce urticaria. The tartrazine-sensitive individual identified in Stevenson’s study did not react to a blinded challenge with doses of aspirin of as much as 975 mg, suggesting a lack of cross-reactivity between tartrazine and aspirin.

Aspartame

Two cases of aspartame-provoked urticaria and angioedema have been reported. In these individuals, hives emerged only after aspartame’s 1983 approval as a sweetener in carbonated beverages. Both patients reported the onset of urticaria within 1 hour of ingesting aspartame-sweetened soft drinks. DBPC challenges induced urticaria with doses of aspartame (25–75 mg) that fell below the amount contained in typical 12-oz cans (100–150 mg) [57].

In a multi-center, randomized, placebo-controlled crossover study, Geha *et al.* [58] challenged 21 subjects with histories of a temporal (minutes to hours) association between aspartame ingestion and urticaria/angioedema. These subjects were identified after an extensive recruiting process spanning 4 years. Only four urticarial reactions were observed: two following aspartame consumption and two following placebo ingestion. Doses ranged as high as 600 mg of aspartame.

Butylated hydroxyanisole and butylated hydroxytoluene

In a DBPC study, Goodman *et al.* [59] challenged two patients with chronic idiopathic urticaria who experienced remissions following dye- and preservative-elimination diets. Both patients noted significant exacerbations of their urticaria after challenge with BHA and BHT. Subsequent avoidance of foods containing these antioxidants resulted in marked abatement of the frequency, severity, and duration of urticaria episodes. Long-term follow-up revealed urticarial flares after dietary indiscretion, but an otherwise quiescent disease.

Monosodium glutamate

Squire described a 50-year-old man with recurrent angioedema of the face and extremities that was related to a history involving ingestion of soup-containing MSG [60]. A single-blind, placebo-controlled challenge with the soup base resulted in “a sensation of imminent swelling” within a few hours, with visible angioedema emerging 24 hours after the challenge. In a graded challenge with only MSG, angioedema occurred 16 hours after challenge with a dose of 250 mg. Avoidance of MSG led to an extended remission. Details of the challenge were not reported, nor did the author mention whether medications were withheld during challenges.

Nitrates/nitrites

Hawkins and Katelaris [61] reported a single case of recurrent anaphylaxis occurring after eating take-out food. DBPC capsule challenge with 25 mg each of sodium nitrates and sodium nitrite resulted in an acute anaphylactic reaction, with hypotension within 15 minutes of the active challenge.

Sodium benzoate

Nettis *et al.* [62] performed DBPC challenges on 47 patients suspected to have acute urticaria/angioedema induced by

sodium-benzoate-containing foods. Only one subject (2%) had a reaction after the ingestion of 75 mg of sodium benzoate without an adverse reaction to placebo, suggesting that even when confronted with suspected historical data on potential reactions to sodium benzoate, true sensitivity rates are quite low.

Food additive sensitivity in chronic idiopathic urticaria/angioedema

Malamin and Kalimo [9] performed prick and scratch skin tests on 91 individuals with chronic idiopathic urticaria/angioedema (CIUA), utilizing a panel of 18 food additives and preservatives. A positive response was defined as a wheal greater than or equal to the size of the histamine control. Sixty-four (26%) subjects had at least one positive skin test as compared with 25 (10%) of 247 non-urticaria control subjects. Ten of the 24 CIUA patients with positive skin tests underwent oral provocation with the additives that gave the positive skin test results. Details of the challenge procedure were not provided. Only one patient reacted, experiencing an urticarial reaction to benzoic acid. The activity level of the patient’s prechallenge urticaria was not noted.

At Scripps Clinic and Research Foundation, patients with CIUA are undergoing single-blinded challenges with a panel of additives. Amounts of each additive are listed in Table 28.2. Positive reactors are confirmed with DBPC challenges. To date, no true positive reactors have been identified among more than 100 patients [63 and unpublished data]. From these data, we can conclude with a 95% confidence limit that sensitivity to any of the 11 food and drug additives in patients with CIUA is less than 1%.

Volonakis and colleagues [64] performed an extensive analysis of etiologic factors in 226 children with chronic urticaria. Elimination of food additives and DBPC challenges performed with a panel of four additives (tartrazine, sodium benzoate, nitrates, and sorbic acid) plus aspirin resulted in an overall incidence of 6 (2.6%) of the 226 cases attributable to these additives. Half of these patients (3 of 226, or 1.3%) reacted to aspirin (a known exacerbator of chronic urticaria), and the remaining 3 subjects (1.3%) reacted to tartrazine. No benzoate, nitrate, or sorbic acid reactions occurred among these subjects.

Table 28.2 Suggested maximum doses for additives used in challenge protocols

Yellow dyes No.5 and No.6:	50 mg
Sulfites:	100 mg
MSG:	2.5 g
Aspartame:	150 mg
Parabens/benzoates:	100 mg
BHA/BHT:	250 mg
Nitrates/nitrites:	50 mg

Di Lorenzo and colleagues [65] studied a large series of 838 patients with recurrent chronic idiopathic urticaria for sensitivity to a panel of common food additives. After undergoing historical screenings, all patients had negative food allergen SPTs. After a 4-week food-additive-free diet (FAFD), patients were then screened with a DBPC mixed additive challenge, consisting of tartrazine, erythrosin, sodium benzoate, *p*-hydroxybenzoate, sodium metabisulfite, and MSG. Positive reactors underwent DBPC single challenges with individual additives with 1-week intervals between challenges. An additional control used included patients with negative DBPC mixed challenges. The incidence of patients having positive histories, clinical response to FAFD, positive DBPC mixed, and DBPC single challenges was only 16 of the 838 patients studied (1.9%; 95% CI 1–3%). Twenty-four total reactions occurred in these 16 patients, due to some individuals reacting to multiple agents.

Food and drug additive skin test and case report studies

Carmine

Several cases of carmine-induced urticaria, angioedema, and anaphylaxis have been described [7,10–12]. These have followed the initial case reports of carmine-induced anaphylaxis by Kagi *et al.* [66] and Beaudouin *et al.* [67]. The food products reported implicated in the past include campari-orange liqueur, Yoplait brand custard style strawberry–banana yogurt, imitation crab meat, Good Humor SnoFruit Popsicle, and ruby red grapefruit juice. SPTs were positive with undiluted carmine in the history positive patients and negative in control subjects. Contact urticaria associated with carmine-colored cosmetics has also been reported [12]. Specific challenges have not been performed with carmine in any of the above reports, with the exception of Baldwin *et al.* [10], whose patient showed negative oral challenges to each of the other components of the Good Humor SnoFruit Popsicle. As noted above, these collaborators at the University of Michigan have demonstrated that an IgE-mediated mechanism is responsible for these reactions.

Annatto

Case reports of anaphylactic reactions to annatto dye have been documented. Revan *et al.* [14] describe one patient with anaphylaxis (4+ SPT with undiluted extract) and one with angioedema (3+ SPT with undiluted extract) after ingesting annatto-containing foods. Neither patient was challenged.

Saffron

Saffron-induced near-fatal anaphylaxis was reported by Wuthrich [5]. The subject, a 21-year-old atopic farmer, developed violent abdominal cramps, laryngeal edema, and generalized urticaria a few minutes after a meal of saffron rice and mushrooms. This progressed to pulse-less collapse

which responded to advanced cardiac life support. SPTs to ingredients of the meal were negative except for a strong reaction to saffron. RAST testing to two saffron preparations were both positive. SDS-PAGE and immunoblotting showed five IgE-binding bands with molecular weights between 40 and 90 kDa.

Mannitol

One report of mannitol-induced anaphylaxis has been well described by Hegde and Venkatesh. An individual who demonstrated anaphylactic reactions to mannitol found in pomegranate and cultivated mushroom also experienced severe allergic reactions to mannitol as an excipient in the chewable pharmaceutical cisapride. The authors utilized SPTs, serum mannitol-specific IgE by enzyme-linked immunosorbent assay (ELISA), and multiple chemical purification techniques for mannitol separation to demonstrate an immediate hypersensitivity mechanism to mannitol as the explanation for the reactions [6].

Parabens/benzoate

One local anesthetic analysis noted above strongly suggested that methylparaben is a cause of local immediate hypersensitivity reactions previously attributed to the local anesthetics themselves [22]. One isolated case report of sodium-benzoate-induced anaphylaxis was reported by Michils [8].

Isosulfan blue

Askenazi *et al.* [68] reported three cases of anaphylactic shock to ISB dye used as a lymphatic contrast agent. All three patients reacted within 30 minutes of subcutaneous injection of ISB and all three have positive ISB skin tests. All of the 10 control subjects had negative skin tests to ISB. Two patients had elevated tryptase levels, indicating MC degranulation. All three patients were re-exposed to latex and the other perioperative concomitant medications after their reactions to ISB and demonstrated tolerance to them. Previous retrospective analyses demonstrate an acute allergic reaction rate of 1.1–2.0% [69,70].

Nitrates

Asero [71] reported a case of chronic generalized pruritis without skin eruption that disappeared on an additive-free diet. DBPC challenge with multiple additives resulted in symptom reproducibility within 60 minutes of the 10-mg sodium nitrate challenge. The patient did not react to seven other additives and multiple placebos.

Recommendations for food additive challenge protocols in patients with urticaria, angioedema, and/or anaphylaxis

A review of the literature on food and drug additive challenges in patients with urticaria suggests that more rigorously

conducted studies are needed. With the use of more objective criteria and stringent design, more meaningful conclusions may be drawn regarding the true incidence of food additive-induced urticaria, angioedema, and anaphylaxis. Our recommendations for future additive challenge protocols in patients with chronic or acute urticaria/angioedema are presented in the following sections.

Patient selection

In view of the ubiquitous and frequent dietary exposure to food and drug additives, the study population should be selected from patients with chronic “idiopathic” urticaria or angioedema, unless the study is intended to examine another defined subgroup of patients with acute or intermittent urticaria, angioedema, and/or anaphylaxis (e.g. patients with a convincingly positive acute history or patients responsive to an elimination diet). The diagnosis of chronic idiopathic urticaria or angioedema should be made in subjects with recurrent urticaria of at least 6 weeks duration without identifiable cause. In addition, appropriate challenges should be conducted to ascertain any physical urticarias. After a negative workup, a patient’s urticaria may then be considered idiopathic [72].

Activity of urticaria

Chronic urticaria should preferably be in an active phase (e.g. some lesions should have appeared within 1 month prior to challenge), as additives may not only provoke urticaria *de novo*, but also exacerbate ongoing urticaria, as is true with aspirin [35]. For patients with an intermittent and/or acute anaphylactic history associated with an additive, challenges should not be conducted for at least 2 weeks time after the acute reaction.

Medications

Antihistamines should be withheld for 3–5 days prior to the challenges, if possible. For patients with intractable chronic symptoms, antihistamines should be tapered to the minimal effective dose. Although corticosteroids are not first-line treatment for chronic urticaria/angioedema, when necessary their use should also be tapered to the minimal effective dose.

Food-additive-free diet

Patients should be placed on a diet free of all additives included in the challenge protocol at least 1 week prior to challenge.

Reaction criteria

Reaction criteria should be as objective as possible. The “rule of nines” used for assessing thermal burns provides a useful method for estimating skin surface area. On each of the 11 divided areas of the body, the investigator assigns a score of 0–4, then derives a total scored (0–44 points). A positive urticarial response may be defined as either an absolute

increase in the total score of 9 points or an increase of more than 300% from the baseline score determined immediately before challenge. A positive angioedema response may be defined as a relative increase in size of more than 50% in the body part affected.

Baseline observation

Prior to any challenges, skin scores should be recorded at the same intervals during a baseline period of observation as during challenges. The appropriate length of the baseline observation period depends on factors such as the activity of the patient's urticaria, the interval of time between discontinuation of antihistamines and the challenges, and the length of the challenge protocol.

In general, 1 day of pure observation with skin scoring should be followed by 1 day of single-blind placebo challenge with skin scoring, except perhaps in patients who are completely free of hives at challenge (in this instance, 1 day of placebo challenge should be sufficient). Skin scores on those 2 days should not vary by more than 3 points or 30% (whichever is greater) before proceeding to additive and further placebo challenges.

Placebo controls

Placebo challenge should be conducted in a randomized fashion. Ideally, at least an equal number of placebo and active challenges should be undertaken. Screening open challenges may be performed without placebo. Here, a negative result does not require further confirmation, but positive reactors must undergo a placebo-controlled protocol, preferably double-blinded (DBPC).

Blinding

Confirmatory challenges should preferably be conducted in a double-blind manner. Coded opaque capsules will serve for this purpose. The code should not be broken until the completion of all challenges. Screening challenges may be performed open or single-blinded. Any "positive challenges" should be confirmed with a double-blind protocol.

Additive doses

The additive doses used in challenge protocols should reflect natural exposure to each agent. Suggested limits for some common additives are listed in Table 28.2. Starting doses should be individualized on the basis of the patient's history, but usually consist of 1/100 of the maximum dose. Challenges must be performed with informed consent and in a setting where severe reactions may be appropriately treated.

Conclusion

Only a small number of well-designed clinical studies have been conducted in the area of additive-provoked urticaria, angioedema, and anaphylaxis. The true incidence of such

reactions remains unknown, although it appears to be relatively rare, despite claims in earlier (pre-1990) additive literature.

Most natural additives (carmine, annatto, and saffron) contain source proteins capable of inducing direct IgE-mediated immediate hypersensitivity reactions. Perhaps the route of sensitization for a subset of the carmine-sensitive patients derives from exposure to topically applied carmine-containing cosmetics, as contact urticaria to this natural additive has been described.

The case for similar immediate hypersensitivity mechanisms is less compelling when the synthetic additive group is analyzed. A relatively small number of case reports describing IgE-mediated reactions to sulfites and parabens exist, compared with the overall number of positive challenges reported.

It is now well accepted that many cases of CIUA have an autoimmune basis, as demonstrated by the presence of autoantibodies directed against the IgE receptor and/or IgE itself [72]. CIUA is frequently associated with other autoimmune syndromes, most notably thyroid autoimmunity [72]. Most studies attempting to link causation and/or exacerbation of this condition by food or drug additives have been poorly designed. Emerging evidence appears to refute the earlier notion that these additives are frequently associated with chronic urticaria. Guidelines for conducting additive challenges in CIUA as well as in episodic urticaria/angioedema patients are reviewed in the text.

Although rare, IgE-mediated paraben reactions can confound the diagnostic evaluation of local anesthetic allergy, given the use of this preservative in multi-dose vials of these medications.

Finally, given the anticipated widespread usage of ISB as a lymphangiography contrast agent, the incidence of reported hypersensitivity reactions to this agent may escalate in the future.

Further well-designed trials addressing additive-provoked urticaria, angioedema, and anaphylaxis are needed before more complete practice parameters can evolve.

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