Help me doctor! I can barely eat any foods anymore!” “I am down to eating just 10 foods!” “I can’t go out to eat anymore.”

Such complaints about adverse reactions to foods are all too common. Yet for many patients, help can be elusive. Clinicians worry that exploring food reactivity will be time-consuming and that their actions won’t be effective. Thus, they may not always consider it as a cause of common symptoms. Yet, adverse food reactivity needs to be considered in the differential diagnosis for many common medical concerns including headaches, asthma, atopic dermatitis, GERD, IBS, fatigue, brain fog and urticaria.

Evaluating patients for food reactivity is essentially a three-step process that involves 1) taking the history, 2) having the patient keep a food and symptom diary and 3) making the differential diagnosis. This article describes that process and offers further guidance for assessing whether a patient’s problems may be related to foods they are eating.

1. Take the History
To begin, patients are very adept at recognizing connections between foods eaten and symptoms experienced. “I will never eat that again!” is a common statement. But are they too adept? Your task is to figure out whether experiencing a certain symptom after eating is a coincidence or if food is a causal factor. The absence of IgE-specific reactivity does not rule out food as a causal factor (consider, for example, the connection between foods rich in vasoactive amines such as aged wines or cheeses and headaches). Likewise, reactivity identified through allergen-specific IgE antibody testing does not confirm food as a causal factor, nor does IgE sensitivity for a given allergen mean clinical responsiveness. For those reasons, all evaluations for adverse food reactivity need to be done in the context of the clinical history.

To take a good history, you will need to ask questions related to onset, timing, severity and frequency of symptoms. To understand cross-reactivity or contributing co-factors, you also will need to ask about:
- Known environmental allergies (birch, grasses, ragweed, for example)
- Season of environmental allergies (spring, summer or fall)
- Latex reactivity
- Costume jewelry or nickel reactivity
- Presence of co-factors such as use of non-steroidal anti-inflammatory drugs (NSAIDs), alcohol, angiotensin-converting inhibitors, antacids, beta-blockers, lipid-lowering drugs and probiotics; exercise; mold exposure; pancreatic exocrine insufficiency; and gastric atrophy.

2. Have the Patient Keep a Food and Symptom Diary
The second step is to ask the patient to keep a diary for two weeks. Have them list all foods eaten, the amount consumed and the timing of meals. Ask them to include details about how the foods were prepared, as knowing whether foods eaten were cooked or raw can be helpful. The diary also should include information about symptoms such as the time of onset, their severity and the length of time before resolution.

This exercise engages the patient, saves time and strengthens the physician-patient partnership, as you are essentially saying to the patient: “Please teach me about your experience.” The result provides significant data physicians and/or dieticians can use to generate testable hypotheses.

Downloadable forms for tracking this information are readily available online. Many people have found the MySymptom Tracker app helpful.

3. Generate a Differential Diagnosis
Equipped with information from the history and the patient’s diary, you then can begin considering possible causes. Each of the following should be explored:
Classic IgE-mediated allergies including cross-reactivity

Classic allergies, typically defined as IgE-mediated mast cell/basophil degranulation, are associated with acute onset of signs and symptoms after food ingestion. Circulatory and airway compromise are the greatest concerns. But there are many less-dramatic manifestations. One is oral allergy syndrome, a condition involving itching, tingling and possibly edema of the lips, tongue, palate and pharynx. IgE-related food reactivity may be a causal factor for unexplained hoarseness and coughing; skin conditions such as atopic dermatitis and contact dermatitis; and gastrointestinal problems including diarrhea, nausea, vomiting, abdominal pain, bloating, gastroenteritis and colitis. Laboratory tests that can be helpful include total IgE and IgE-specific food testing. Guidelines for diagnosis and management of food allergy were recently published.

The potential role of cross-reactivity of common environmental allergens and foods also should be considered. For example, birch allergy, which is common in the spring, is linked to reactivity with several other species: Apiaceae (carrot, celery, fennel, parsley), Betulaceae (hazelnut), Fabaceae (peanut, soybean, mungbean) and Rosaceae (apples, cherries, peaches). Grass allergies, common in the summer, are linked to reactivity to foods such as tomatoes and melons. Allergies to plants such as mugwort and ragweed, which bloom in the fall, are linked to reactivity to raw apples, bananas, broccoli, carrots, celery, chamomile, honey, melons, mustard, peaches and peppers, along with chestnuts, hazelnuts, peanuts and sunflower seeds. Spices noted for mugwort cross-reactivity include parsley, caraway, fennel, coriander, anise seed, garlic, onion, leek, paprika and pepper.

Patients with latex allergies can have severe cross-reactivity to avocado, banana, kiwi and chestnut. Other foods that may evoke allergic symptoms in individuals with latex allergy include apricots, celery, grapes, pineapple, spinach, tomato, melon, mango and peach.

Finally, persons with dust mite allergies may have reactions if they eat crustaceans (shrimp, mussels, oysters and scallops) and gastropods, cephalopods and octopods.

The biologic basis for this unexpected cross-reactivity is the presence of similar marker allergenic molecules, “homologues,” in different species (such as the Bet v 1 in birch pollen and the Mal d 1 in apples) or a protein family well-preserved throughout many different species that can trigger IgE antibody binding. Albumins or prolamins are examples of such protein families. Glutens are the prolamins (termed “gliadins” and “glutenins”) in wheat. Prolamins are found in many other grains as well (eg, secalins in rye and hordeins in barley), which is why a completely gluten-free diet contains no wheat, rye, barley, triticale, kamut or spelt.

On a practical note, many allergens can be degraded by acidic pH (gastric acid), temperature (cooking) or proteinases (gastric or pancreatic function). These are termed “labile allergens.” Three important nuances must be considered. First, not all allergens are labile. For example, the ns lipid transfer proteins found in wheat and corn are very stable, but the birch pollen-related Bet v 1 homologues are considered labile. Yet, even with cooking, the Bet v 1 homologues found in hazelnuts, celery, peanuts and soybeans can result in systemic reactions when ingested. Second, hypochlorhydria, either functional or iatrogenic, has been correlated with enhanced sensitization to food allergens. This can be significant in the elderly. Third, concomitant use of non-steroidalas or concomitant exercise may worsen a known allergic reactivity.

Predominantly non-IgE–mediated immune reactivity

Food-specific T-cell–mediated reactivity can occur from several hours to more than 24 hours after exposure. Manifestations include atopic dermatitis, protein contact dermatitis, rhinoconjunctivitis, bronchial asthma, gastroenteritis, and brain fog or confusion.

People of all ages can have T-cell–specific reactions—beginning in infancy with food protein-induced enterocolitis. Signs of such reactions include delayed reactivity, vomiting, diarrhea and dehydration. Cow’s milk and soy proteins are the most common culprits; but grains, vegetables and poultry have been identified as causes as well. Milk-specific, skin-homing cutaneous lymphocyte antigen (CLA+) T-cells (Th2) have been found in atopic dermatitis lesions in older people. Likewise, wheat glutens elicit a Th1-mediated immune response in persons with variants in the HLA-DQ2 or HLA-DQ-8 genes.

In patients with other forms of predominantly non-IgE–mediated reactivity, such as eosinophilic esophagitis and non-celiac gluten sensitivity, resolution of signs and symptoms can occur with elimination or elemental diets. For example, in both celiac and non-celiac wheat reactivity, the pest-resistant molecules α-amylase/trypsin inhibitors (ATIs) CM3 and 0.19 engage the TLR4-MD2-CD14 complex to activate monocytes, macrophages and dendritic cells. This results in the release of proinflammatory cytokines with subsequent consequences to intestinal wall integrity.

These observations may explain why, even with negative IgE and gluten reactivity markers (IgA and IgG forms of TTG, anti-gliadin antibodies), the adoption of dairy-free, wheat-free or grain-free diets correlates with improvements in systemic inflammatory conditions including autoimmune disease.

At this time, there are no validated, standardized testing protocols. Clinicians can try guided elimination diets followed by guided reintroductions and oral food challenges. Many have found specialized lymphocyte proliferation assays and IgG food reactivity panels to be helpful for generating hypotheses to guide elimination diets beyond wheat, dairy and corn.
Non-immune–mediated (pharmacologic) reactivity

Tyramine, tryptamine, putrescine, cadaverine and beta-phenylethylamine are considered dietary biogenic or vasoactive amines and are linked to headaches/migraine headaches, angioedema and urticaria. Excessive amounts of the most well-known of these amines, histamine, is associated with an incredible array of symptoms ranging from classic signs of allergy to arrhythmias, asthma, brain fog, cold flashes, flushing, hypotension, profound fatigue and diarrhea. In general, people suffering from histamine-associated disorders, including mast cell activation syndrome, have extremely thick medical records because of extensive evaluation of multisystem disabling symptoms. Some patients have been misdiagnosed with bipolar or personality disorders.

Foods can be rich sources of histamine. Examples include leftovers, especially meat, poultry or fish, as well as alcohol, pickled or fermented foods including vinegar, aged cheeses, shellfish, pulses (beans, chickpeas, lentils), nuts and chocolate. Some foods, including citrus fruits, tomatoes, wheat germ, black or green tea, and sulfite preservatives, also can release histamine.

Histamine is metabolized in the gastrointestinal tract by diamine oxidase in the cytosol of cells by histamine-N-methyltransferase. Significant genomic variability exists for these two genes in the population. Epigenetic challenges to optimal functioning appear to follow from episodes of infectious gastroenteritis.

Maldigestion

The differential diagnosis needs to extend to the patient’s capacity to digest foods, especially carbohydrates. Dietary carbohydrates must be digested by pancreatic amylase and the three intestinal epithelial enzymes (lactase, sucrase and maltase) into absorbable monosaccharides. Lactose intolerance caused by lactase enzyme deficiency is the most widely recognized form of maldigestion. However, in adults, one needs to consider fructose and sorbitol malabsorption, as well as intolerance of FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols).

Carbohydrates that are not absorbed in the intestinal tract are fermented by the intestinal microbiota, causing production of gas. These nonabsorbed carbohydrates also exert an osmotic force that draws fluids into the lumen resulting in osmotic diarrhea. Clinically, patients will complain of abdominal distension and pain, nausea, diarrhea and flatulence. They also may note extra-intestinal symptoms including headache, vertigo, brain fog, muscle/joint pain and fatigue. These symptoms are likely caused by the production of toxic metabolites (signaling-mechanism disruptors) by the anaerobic digestion (fermentation) of nondigested carbohydrates by intestinal bacteria.

Lactose is found in all dairy products unless they are specifically labeled as lactose-free (such as kefir and processed milks). Lactose malabsorption can be demonstrated primarily through genetic testing. Risk for lactase deficiency is reported as part of the 23andme direct-to-consumer genetic testing results.

Fructose is found in all fruits as well as beans, broccoli, carrots, cauliflower, corn, green peppers, honey, peas, sweet potatoes and tomatoes. Of course, it is in all foods sweetened with high-fructose corn syrup.

FODMAPs are short-chain carbohydrates that are poorly absorbed at the intestinal level. Foods containing FODMAPs include those with lactose and fructose plus fructans, galactans and polyols. Fructans are found in wheat, persimmon and watermelon as well as asparagus, chicory, beets, broccoli, Brussel sprouts, cabbage, eggplant, fennel, onions, garlic and leeks. Galactans are found in legumes, predominantly beans. Polyols are in the artificial sweeteners erythritol, mannitol, sorbitol and xylitol plus apples, apricots, cherries, peaches, pears, plums, cauliflower, corn and mushrooms.

Recent clinical trials of a diet low in FODMAPs for persons with IBS have demonstrated that the diet clearly reduced functional gastrointestinal symptoms. Because of the very restrictive nature of a low FODMAP diet, patients who try it will do best with the help of a nutritionist or dietician.

Other considerations

Clinicians need to be aware of a number of other factors. The first is the presence of classic allergic contact dermatitis from allergens such as nickel sulfate or flavorings such as vanillin. For example, reactions people may have to nickel-containing jewelry can extend to the nickel found in many (healthy) foods. In sensitized patients, dietary nickel can cause both a relapse of contact eczema as well as widespread chronic dermatopathies quite similar to those triggered by IgE-mediated food allergies including atopc dermatitis and chronic urticaria with angioedema.

The nickel content of foods can vary. Those with consistently high nickel content include whole wheat, whole grain, rye, oat, millet, buckwheat, cocoa, chocolate, tea, gelatin, baking powder, soy products, red kidney beans, legumes including lentils, peanuts, soy beans and chickpeas, dried fruits, canned foods and strong lico-rice. Foods with variable nickel content include mackerel, tuna, herring and shell-fish; sunflower seeds, hazel-nuts, marzipan and walnuts; and tomatoes, onions and carrots. Cooking acidic foods in stainless steel cookware may increase their nickel content.

The second is salicylate-rich foods—a category of foods that have been linked to imbalanced release of pro-inflammatory eicosanoids from arachidonic acid. Salicylate intolerance has been defined as “a nonspecific antigen-induced pseudo-allergic hypersensitivity reaction to salicylic acid, its derivatives or other related organic or inorganic acids of similar chemical structure.” Dietary salicylates are COX-2 inhibitors. Persons who are NSAID-intolerant, including those with NSAID hypersensitivity or aspirin-exacerbated respiratory disease, may also be intolerant of salicylates in foods.

Foods rich in salicylates include fruits and vegetables such as apples, cherries,
lemons, nectarines, oranges, peaches, strawberries, raspberries, raisins, kiwi, asparagus, corn and tomatoes. Spices that are a rich source of salicylates include cardamom, cinnamon, cumin, fenugreek, ginger, licorice, mint, nutmeg, oregano, paprika, pepper, peppermint, rosemary, thyme and turmeric. Liqueurs, wines and rum as well as citrus fruit juices and tomato juices/sauces are also high in salicylates.14,15

The third is sulfites added to foods as preservatives or the consumption of sulfur-rich foods. In 1984, the U.S. Food and Drug Administration noted that it had received more than 250 reports of significant suspected sulfite reactions including six deaths.16 Reactivity is believed to primarily affect the lungs and is especially prominent in persons with steroid-dependent asthma. Anaphylaxis, urticaria, skin reactions and rhinitis have also been well-described.17

In my experience, both genomic and nongenomic impairment of the sulfite oxidase enzyme appear to increase sensitivity to dietary sulfites and/or thiols. This enzyme catalyzes the oxidation of sulfite to sulfate, the final reaction in the oxidative degradation of the sulfur amino acids cysteine and methionine. Although frank deficiency is fatal at an early age, sulfite oxidase insufficiency can result in neurological abnormalities including seizures. Molybdenum and vitamin B2 (riboflavin) are necessary co-factors.18 Key upstream enzymes are vitamin B6-dependent. The sulfite oxidase enzyme is believed to be inhibited by mercury.

Sulfites can be added to lettuce, shrimp, crab sticks, squid, dried fruits, dried mushrooms, dehydrated potatoes including cakes, fries and croquettes, cider, wine, beer, fruit drinks, white grape juice, horseradish sauce and caramel coloring including that found in cola. Sulfur-rich foods include cruciferous vegetables, eggs, cheese, beans including soybeans, garlic and onions, mustard, horseradish, quinoa, whey and turmeric.

The fourth is monosodium glutamate (MSG). Ingestion of this additive has been linked to asthma, headaches, urticaria, angioedema, rhinitis, mental health concerns and seizures. Glutamate decarboxylase (GAD1) is the enzyme that converts glutamate, an excitatory neurotransmitter, into GABA, an inhibitory neurotransmitter. This enzyme has great variability in function among people because of both genomic and nongenomic factors. Vitamin B6 as pyridoxal-5-phosphate is a co-factor. Impairment or overwhelming of this enzyme would be expected to result in an imbalance between excitatory and inhibitory neurotransmitters. Deficiency of this enzyme can result in pyridoxine dependence with seizures.19

MSG is a common ingredient in Asian foods (“Chinese restaurant syndrome”) and is the secret in the Colonel’s secret recipe for Kentucky Fried Chicken; it is also added to Parmesan cheese, soups, gravies, rubs, sauces, instant rice and noodle dishes. A complete list of foods containing MSG can be found at: www.truthinlabeling.org/hiddensources.html.

Summary
The differential diagnosis for many common conditions seen in clinical practice should include adverse food reactivity. The three steps described in this article allow clinicians to assess the likelihood of an adverse food reaction underlying an illness. You will note that many of the lists of foods for each consideration overlap. This may help explain why people without markers of gluten immune reactivity, for example, feel better after eliminating wheat from their diets. Because of this, a patient often can judge for himself what works using an elimination/reintroduction diet. Finally, this approach implicitly identifies the very important role nutritionists and dieticians can play in helping identify and address adverse food reactivity. MM

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