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Food Allergy: Diagnosis and Management

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A rise in food allergy, accompanied by heightened public awareness, guarantees that clinicians will increasingly be consulted to accurately distinguish adverse reactions to foods from other disorders. The potential impact of inaccurately labeling a food as a cause of symptoms includes delaying appropriate treatment for another disorder or needlessly removing a food from the diet, with potential adverse nutritional and social consequences. When symptoms are triggered by food ingestion, determining the type of adverse reaction to the food responsible is important because of the implications regarding the mechanism involved, reproducibility, and the prognosis.

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A rise in food allergy, exemplified by the doubling of self-reported peanut allergy among children in the United States from 1997 to 2002, accompanied by heightened public awareness, guarantees that clinicians will increasingly be consulted to accurately distinguish adverse reactions to foods from other disorders [1]. The potential impact of inaccurately labeling a food as a cause of symptoms includes delaying appropriate treatment for another disorder or needlessly removing a food from the diet, with potential adverse nutritional and social consequences. When symptoms are triggered by food ingestion, determining the type of adverse reaction to food responsible is important because of the implications regarding the mechanism involved, reproducibility, and the prognosis.

Definitions

In a logical scheme developed as a framework for the categorization of food-induced reactions by mechanism, an adverse reaction to a food is the general term used to refer to any unpleasant reaction occurring as a result of food ingestion [2]. An adverse reaction to a food is further categorized into either a toxic or a nontoxic reaction [3]. In toxic reactions, the symptoms are caused by a toxin synthesized by the food or by an organism or substance contaminating the food. For example, individuals ingesting predatory reef fish, such as snapper, grouper, barracuda, or sea bass, contaminated with ciguatoxin, produced by the marine dinoflagellate *Gambierdiscus toxicus*, develop nausea, vomiting, and diarrhea within minutes to hours later, followed by sensory disturbances, muscle aches, and fatigue that can last for months [4]. Although there is individual variability regarding sensitivity to different toxins, one characteristic of toxic reactions is that they occur in virtually every person ingesting enough of the food containing the toxin [2].

Nontoxic reactions are further categorized into food intolerance or food allergy, depending upon whether the immune system is the primary cause of the reaction [3]. Reactions in which the immune system is not involved are categorized as examples of food intolerance. Categories of food intolerance include metabolic, pharmacologic, or idiosyncratic reactions. Individuals who are malnourished, ill, taking certain medications, or have acquired or inborn errors of metabolism are more likely to experience metabolic reactions to foods. One of the most commonly encountered examples of a metabolic reaction to a food is lactose intolerance, where a lactase-deficient host, because of the inability to metabolize lactose, develops nausea, abdominal cramping, and diarrhea following the ingestion of lactose-rich dairy products [5]. Pharmacologic food reactions occur following the ingestion of foods containing pharmacologically active ingredients. For example, the ingestion of foods or beverages containing methylxanthines, such as caffeine or theobromine, may cause central nervous system stimulation, headache, and abdominal pain when ingested in large amounts or by sensitive individuals [6]. Idiosyncratic reactions resemble allergic reactions to foods but are not mediated by the immune system and result from a quantitatively abnormal response to a food or food additive that is not caused by a pharmacologic or physiologic effect of the food.

“Food allergy” is the term used to refer to those nontoxic reactions to foods primarily mediated by the immune system [3]. Allergic reactions to foods are further divided into IgE-mediated reactions, nonIgE-mediated reactions, or combined reactions where both IgE- and nonIgE-mediated mechanisms are implicated [7]. Disorders caused by IgE-mediated reactions to foods typically involve the gastrointestinal tract, the skin, and the respiratory tract. For example, IgE-mediated gastrointestinal disorders include pollen-food allergy syndrome and gastrointestinal anaphylaxis.

Pollen-food allergy syndrome is encountered in patients sensitized to pollens containing allergens that cross react with those found in fresh fruits and vegetables [8] and [9]. Although the list of described pollen-food syndromes continues to grow, the more common clinically encountered examples include ragweed pollen sensitive patients, who experience symptoms with the ingestion of melons or banana; birch pollen sensitive patients, who experience symptoms when eating apple, hazelnut, celery, carrots, or raw potato; and mugwort pollen sensitive patients, who react upon ingesting fresh apples, celery, peanuts, or kiwi [10]. The syndrome was initially called “the oral allergy syndrome,” in reference to the typical pattern of rapid onset pruritus and mild edema localized to oropharyngeal tissues. Because some patients experience significant laryngeal edema or symptoms extending beyond the oropharynx, including anaphylaxis, this name has been considered misleading and the pollen-food allergy syndrome has been proposed as a suitable alternative [11].

Gastrointestinal anaphylaxis presents with cramping abdominal pain, nausea, and vomiting occurring within minutes to hours after ingestion of the offending food, and is often accompanied by cutaneous or respiratory symptoms. IgE-mediated cutaneous symptoms include acute urticaria, angioedema, generalized pruritus, and flushing, whereas respiratory disorders mediated by IgE-mediated reactions to foods include acute rhinoconjunctivitis and acute onset bronchospasm. The most severe form of an IgE-mediated allergic reaction to a food is anaphylactic shock, in which multiple organ systems are involved, along with the presence of hypotension [6].

Examples of nonIgE-mediated allergic reactions to foods, considered to be cell mediated, that involve the gastrointestinal tract, include food protein-induced syndromes such as food protein-induced enterocolitis, food protein-induced proctocolitis, and food protein-induced enteropathy syndromes [12] and [13]. These disorders are seen primarily in infants or young children presenting with abdominal complaints, such as vomiting, cramping abdominal pain, diarrhea, and occasionally blood in the stool. Celiac disease, resulting from sensitivity to gliadin found in grains such as wheat, rye, and barley, is another example of a nonIgE-mediated gastrointestinal reaction to a food considered to be cell mediated [14] and [15]. Dermatitis herpetiformis and contact dermatitis are examples of cutaneous nonIgE-mediated reactions to food. Mixed IgE and cell mediated allergic reactions to foods are exemplified by eosinophilic gut disorders, such as eosinophilic esophagitis and allergic eosinophilic gastroenteritis, or potentially other entities, such as atopic dermatitis or asthma [16].

As might be expected, most patients are unacquainted with the terms used in medical discussions of adverse reactions to foods and are unaware of the different types of these reactions. This is one of the reasons the public perceived prevalence of food allergy is significantly higher than the true prevalence, as illustrated by a telephone poll revealing that as many as 25% of American households alter their diet because of a suspected food allergy in at least one family member [17]. Defining terms and reviewing the different types of adverse reactions to foods with patients early in the evaluation reduces the potential for misunderstanding and lays the framework for discussions about whether the diagnosis is food allergy, another type of adverse reaction to a food, or some other entity not related to food ingestion.

Risk factors and prevalence

Genetic and environmental factors have been proposed as capable of increasing the risk for the development of food allergy. The concordance rate of peanut allergy in 64% of monozygotic twins, versus 6.8% of dizygotic twins, in one study suggests a role for genetic influences in the development of food allergy [18]. Environmental factors, other than dietary factors that have been suggested as potential but not proven risk factors, include C-section delivery [19] and [20], early multivitamin supplementation [21], antacid use, [22] and exposure to tobacco smoke early in life [23].

The foods most commonly implicated in allergic reactions include milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish [16]. The documented prevalence of food allergy is highest in infants and young children, where it approaches 6% to 8% in children less than 3 years of age and decreases in older children, adolescents, and adults, so that overall approximately 4% of Americans are estimated to be food allergic [24] and [25]. This age-associated decrease in prevalence is attributed to the development of tolerance with age in most children allergic to cow's milk, egg, wheat, and soy. Thus, the estimated prevalence of food allergy to milk and egg is higher in young children than adults, whereas the estimated prevalence of allergy to tree nuts, fish, and shellfish is higher in adults than in young children [25]. For example, epidemiologic studies suggest that of the approximately 2.5% of infants allergic to cow's milk, 80% will develop tolerance by 5 years of age [16]. Whereas it was previously considered that peanut allergy was rarely outgrown [26], more recent studies reveal that as many as 20% of peanut allergic infants and young children lose their clinical sensitivity over time [27] and [28].

Most children and adults with food allergy have a personal history of other allergic disease. Studies of children with moderate to severe atopic dermatitis reveal that approximately 35% are food allergic [29]. It has been estimated that from 2% to 8% of asthmatic children and adults experience respiratory symptoms triggered by allergic reactions to foods [30] and [31]. Although adult asthmatics often report that food additive ingestion triggers respiratory symptoms, a prevalence of less than 5% has been documented in well-controlled studies [30].

The severity of allergic reactions to foods varies from mild to life threatening. Of the cases of anaphylaxis treated in hospital emergency rooms, allergic reactions to foods are the most common cause encountered, accounting for from one third to one half of the cases seen [25]. It is estimated that approximately 200 deaths each year are attributable to food-induced anaphylaxis, with peanuts and tree nuts the most common cause of these fatal reactions [25] and [32]. An analysis of 32 cases of fatal allergic reactions to foods in the United States revealed that most of the victims were adolescents or young adults who knew they were allergic to the food that caused the reaction. Delays in the administration of epinephrine and concomitant asthma were other identified risk factors for fatal food-induced anaphylaxis in this group [32].

Diagnosis of food allergy

History

Accurately diagnosing patients complaining of adverse reactions to foods requires a certain amount of detective work that begins by obtaining a complete history. The initial step involves identifying the food or foods suspected of causing symptoms. Obtaining a list of all foods ingested within a few hours before the onset of the reaction is suggested when patients present with an acute reaction after a meal but are uncertain of the causative food. Foods eaten since the reaction in similar amounts without symptoms are removed from the list, whereas those foods not subsequently ingested remain suspect. Complaints of chronic symptoms not temporally associated with food ingestion, or symptoms reported to be significantly delayed in onset after ingestion of the suspected food, often pose a diagnostic challenge.

Determining the source, ingredients, and manner of preparation of the suspected food occasionally provides an explanation for a lack of reproducible symptoms with each exposure, or implicates a previously unsuspected food, food ingredient, or contaminant as the cause of reactions. All ingredients in suspected foods should be identified, and ingredient labels for processed foods should be examined for the presence of substances capable of causing reactions. Cooking denatures heat labile food allergens while others are heat stable. For example, patients who experience isolated oropharyngeal symptoms after ingesting raw fruits or vegetables, often report tolerating these foods when cooked [16] and [33]. Patients allergic to raw egg who tolerate cooked egg have been reported [34], as have patients who react to rare beef, but tolerate thoroughly cooked beef [35]. Occasionally, contamination of the suspected food with other food allergens, either intentionally as exemplified by the addition of spices [36], [37] and [38], or accidentally during meal preparation, is the cause of the reaction. The ability of nonfood allergens contaminating foodstuffs to cause reactions is exemplified by reports of reactions in dust mite allergic individuals after the ingestion of dust mite contaminated pancakes, waffles or beignets [39], or latex as a contaminant in foods [40].

Obtaining a list of foods eliminated from the patient's diet and documenting whether the elimination of these foods led to a reduction in symptoms provides useful information. The patient's current diet should be thoroughly reviewed, not only for nutritional adequacy, but to determine whether the suspected food is being inadvertently ingested in significant amounts (as a hidden ingredient in other foods), or whether a food with significant immunologic cross reactivity to the suspected food remains in the diet. In some instances, patients thought to be on elimination diets continue to have symptoms because of the unrecognized continued ingestion of the culprit food as an ingredient in other foods. Alternatively, the ability to tolerate hidden sources of suspected foods in the diet raises suspicion as to whether these foods are truly causing symptoms. For example, a patient suspected of being milk allergic who tolerates goat's milk should raise suspicion, given the documented extensive cross reactivity between homologous proteins in goat's and cow's milk [41]. Similarly, the patient considered to be wheat allergic, who tolerates spelt, may not be wheat allergic, given that spelt is an ancient variety of wheat [42].

After the foods suspected of causing symptoms are identified, a precise description of each previous reaction should be obtained, including the suspected route of exposure, the estimated dose, the symptoms experienced, the timing of symptom onset in relation to food exposure, and the severity of symptoms. In addition, the duration of the reaction, the treatment, the response to treatment, the reproducibility of reactions, and the date of the most recent reaction should be ascertained. While the majority of reactions to foods are caused by ingestion or topical contact, symptoms resulting from the inhalation or injection of food allergens have been documented [43]. Fortunately, unless a large surface area is exposed or the patient is exquisitely sensitive, contact reactions are generally localized to areas of contact and self-limited, rarely progressing to systemic reactions. For reactions triggered by ingestion, determining the amount of food ingested before each reaction provides one means of gaining insight about the patient's level of sensitivity. In regards to reactions triggered by the ingestion of miniscule amounts of the offending food, these place the patient at higher risk for more frequent reactions, and suggest the potential for more severe reactions if a larger dose of the food is ingested.

Increasingly severe reactions following the ingestion of a similar amount, or symptoms caused by the ingestion of significantly smaller portions, suggests an increasing level of sensitization. Alternatively, tolerating exposure to amounts of the food that previously caused reactions could be an indication that sensitivity to the food is waning. A dose response relationship in regard to the amount of food ingested and the severity of symptoms encountered is commonly observed in patients with allergic reactions to foods. For example, some children tolerate milligram amounts of egg as an ingredient in baked goods, but have significant reactions when foods containing larger amounts of egg are ingested. Threshold doses and target organ involvement for specific foods vary considerably from patient to patient and among different foods in the patient with multiple food allergies. Studies attempting to determine the lowest threshold doses for allergic reactions to common foods allergens have documented patients with reactions after the ingestion of milligram amounts of these foods during blinded, placebo-controlled food challenges [44] and [45].

Allergic reactions to foods affect different target organs, either individually or in combination. The most often-involved target organs are the gastrointestinal tract, the skin, and the upper and lower respiratory tract. Although urticaria is frequently encountered in allergic reactions to foods, the lack of urticaria does not rule out an allergic reaction, as fatal allergic reactions to foods have been observed in the absence of urticaria. Fatalities from allergic reactions to foods are usually caused by extensive laryngeal edema, severe bronchospasm, or refractory hypotension. Most allergic reactions to foods begin within minutes to hours of ingestion of the offending food, and last from approximately one to several hours, although cases of biphasic and protracted anaphylaxis to foods have been observed [46]. Often patients describe reactions that are similar in onset and progression when a comparable dose of allergen is ingested. Inconsistencies in the timing and severity of allergic reactions to the same food may result from a difference in the amount consumed, the manner of food preparation, the presence of other foods, or factors such as vomiting, which impact digestion or absorption, changes in the patient's level of sensitivity, and the ingestion of medications such as antihistamines, that can mask symptoms. The time elapsed since the last reaction is of interest, as some patients develop tolerance after prolonged successful elimination of the food from their diet, whereas recent reactions document continued sensitivity.

In rare instances, the ingestion of a food must be accompanied by another stimulus in order for a reaction to occur. For example, food-dependent exercise-induced anaphylaxis is an interesting form of anaphylaxis that occurs when the ingestion of a specific food is followed within several hours by exercise [47], [48] and [49]. Ingestion of the specific food in the absence of exercise does not cause symptoms, even though the patient usually has a positive skin test to the food. Alternatively, exercise not preceded by ingestion of the specific offending food is well tolerated, except in rare cases where the ingestion of any meal before exercise triggers symptoms. A wide variety of foods have been implicated in causing these reactions, such as fish, shellfish, wheat, celery, mushrooms, and fruit [50] and [51]. The typical age of patients with food-dependent exercise-induced anaphylaxis extends from adolescence through the late thirties, with women outnumbering men. The mechanism responsible for these reactions remains to be defined. This entity should be considered when reactions occur only following exercise preceded by food ingestion. Skin testing the patient to foods ingested shortly before the exercise preceding the reaction may aid in identification of the offending food [52] and [53].

Other factors that could cause confounding symptoms or impact the course of an allergic reaction, such as an acute illness, drug ingestion, alcohol ingestion, vigorous exercise, or psychologic distress, should be considered. A history of illness in others ingesting the same food raises concern about food poisoning rather than food allergy. Because most patients with food allergy have other family members with allergic disease and a personal history of other allergic disease, questioning to obtain this information is indicated. Studies examining fatal allergic reactions to foods suggest that food allergic patients with asthma are at higher risk for fatal or near-fatal reactions [32] and [46]. These same studies reveal that the majority of patients suffering from fatal allergic reactions to foods were aware of their food allergy and ingested the offending food unknowingly.

Physical examination

The focus of the physical examination varies, depending upon the patient's presenting symptoms, their acuity, chronicity, and the mechanism suspected, based upon the history. In those patients presenting in the midst of an acute allergic reaction to a food, attention is directed to the upper and lower airway to determine whether significant airway obstruction caused by laryngeal edema or bronchospasm is present or evolving, as severe laryngeal edema and bronchospasm refractory to treatment are common causes of death in food-induced anaphylaxis [32] and [46]. Continuous monitoring of the oxygen saturation during these reactions is required. Other airway findings, such as marked nasal congestion, repetitive sneezing, profuse clear rhinorrhea, hoarseness, stridor, coughing, accessory muscle use, nasal flaring, and wheezing should be noted. Close monitoring of the vital signs and physical examination for changes suggestive of impending shock, such as delayed capillary refill or changes in mental status, is indicated, as refractory shock is the other major cause of death in these reactions [54]. Cutaneous changes, including flushing, generalized pruritus, angioedema, urticaria, and flaring of eczema are often encountered, along with gastrointestinal findings of oropharyngeal edema, increased or decreased bowel sounds, abdominal tenderness, vomiting, or diarrhea.

Physical findings, such as allergic shiners, conjunctival injection, clear rhinorrhea, nasal congestion with a pale, edematous nasal mucosa, a transverse nasal crease, wheezing, and xerosis or patches of eczema observed in a less acute setting, suggest the presence of other allergic disease and increase the likelihood of coexistent IgE-mediated sensitivity to foods. Occasionally, an associated physical finding may suggest a specific diagnosis or raise concern about more serious disease. For example, the presence of a rash consistent with dermatitis herpetiformis suggests a diagnosis of celiac disease. The diagnosis of dermatitis herpetiformis should be considered in the patient with "eczema" not responding to standard therapy, as mistaking dermatitis herpetiformis for eczema has been reported [55].

Careful monitoring of weight and growth parameters at each visit and over time is required for food allergic patients. Weight loss, or failure to

thrive, is rarely encountered in patients with IgE-mediated reactions to few foods or those less pervasive in the diet. Alternatively, patients with nonIgE-mediated or mixed gastrointestinal allergy, young children with food refusal, or patients on severely restricted diets because of suspected or documented multiple food allergy may fail to maintain their weight. Although specific or multiple food refusal in young children with limited verbal ability is often attributed to behavioral issues, further questioning and a careful physical examination is indicated to rule out other potential causes. Infants and toddlers often shun foods to which they are allergic, as the ingestion of these foods causes oropharyngeal tingling and burning, a metallic taste, abdominal pain, or nausea. Children with active esophagitis or dysphagia may avoid solid foods swallowed as a firm bolus, because the resultant esophageal distention or spasm is painful. Other potential causes of food refusal in these children include chronic or intermittent aspiration resulting from swallowing disorders, or oral tactile defensiveness in which certain food textures are not tolerated. Continued weight loss, or failure to thrive and not responding to dietary intervention to provide adequate caloric intake, should prompt further evaluation to rule out other disease.

Evaluation of the food allergic patient

Prick skin testing

Skin testing to foods is essentially a bioassay that involves introducing miniscule amounts of food allergens into the patient's epidermis and monitoring the result. If mast cells in the patient's skin have IgE on their surface specific for the food being tested, binding of the food allergen by these IgE antibodies triggers mast cell degranulation, resulting in histamine release and mediator generation. The localized mediator release results in the rapid formation of a cutaneous wheal surrounded by an erythematous flare. In the absence of IgE specific for the introduced food allergen, no reaction occurs.

Glycerinated commercial food extracts are widely available for skin testing to many common food allergens. Fresh food extracts, prepared by crushing the fresh food in an aliquot of saline, are also occasionally used [56]. These fresh extracts can be further diluted if there is concern regarding exquisite sensitivity. Alternatively, the "prick to prick" technique can be employed, which involves first pricking the food with the skin test device, immediately followed by pricking the patient's skin [57]. These methods are useful when testing for sensitivity to fruits or vegetables containing labile allergens susceptible to degradation during the extraction process used in the preparation of commercial extracts, or when no commercial extract of the suspected food is available. Fresh extracts can also be prepared to verify the results obtained using a commercial extract when the history is highly suggestive, but the skin test to the commercial extract is negative. In addition, skin testing with freshly prepared extracts can provide a direction for further evaluation. Skin testing with fresh extracts prepared from foods or sauces from a restaurant meal thought to have caused a reaction can suggest which foods or ingredients are worthy of further investigation. The potential for irritant reactions exists, but can be ruled out by skin testing others not sensitive to the food with the same extract.

After pricking the skin with a lancet or bifurcated needle through which a small drop of food allergen extract is applied to the back or forearm, any resultant wheal and erythema observed at the site after approximately 15 minutes is measured and recorded. A histamine skin test is applied as a positive control, with a saline skin test serving as the negative control. Based on initial studies performed in children by Bock and colleagues [58] in the late 1970s, a food skin test is defined as positive if a wheal 3 mm in diameter larger than the negative saline control, is observed. Systemic symptoms resulting from prick or puncture skin testing are exceedingly rare. The use of intradermal skin testing to foods is discouraged, as it has been shown to be less specific and carries a higher risk of systemic reactions [59]. Rather than routinely skin testing to a broad panel of food allergens, skin tests are selected based on foods suggested by the history or limited to the foods considered to be common food allergens.

In general, the positive predictive accuracy of a properly performed food skin test is considered less than 40% when the 3-mm cutoff for defining a positive skin test is used, indicating that many individuals who have a positive skin test to a food can eat that food without ill effects [58]. However, Sporik and colleagues [60], evaluating a large cohort of children with a median age of 3 years with skin testing followed by food challenges, were able to calculate skin test diameters to peanut (greater than 8 mm), cow's milk (greater than 8 mm) and egg (greater than 7 mm) with positive predictive accuracies approaching 95%. Although their findings cannot be extrapolated to other populations because of potential differences in age, extracts, and technique used, they demonstrate that using a larger wheal diameter to define a positive skin test results in a decrease in sensitivity but an increase in specificity. As with other investigators, they found no correlation between skin test size and the severity of a reaction.

Removing a previously tolerated food from the diet based on skin testing alone is rarely recommended. However, a positive skin test is useful for identifying foods worthy of further investigation and is highly suggestive of a diagnosis in situations when a patient experienced a significant reaction following the ingestion of an isolated food. Alternatively, the negative predictive accuracy of a properly performed skin

test is greater than 95% [61]. Thus, skin testing is a rapid, sensitive, efficient method of ruling out IgE-mediated reactivity to a food when quality extracts are applied using proper technique, and the patient has not taken medications known to interfere with testing.

Atopy patch testing

Although prick skin testing and the measurement of serum food-specific IgE antibodies are indispensable in the evaluation of patients with IgE-mediated food allergy, these tests are not useful in identifying the responsible food in patients with nonIgE-mediated reactions where cell mediated immune mechanisms are involved. In an effort to identify a test that might be predictive in these situations, the use of the atopy patch test (APT) has been explored in recent years in the evaluation of patients with atopic dermatitis [62], eosinophilic esophagitis [63], food protein-induced enterocolitis syndrome (FPIES) [64], and others with gastrointestinal symptoms suspected of being food-related, but not IgE-mediated [65]. The foods most commonly evaluated with the APT are milk, egg, soy, and wheat. The APT is performed by applying the intact food allergen to noninflamed skin on the back under occlusion in a small aluminium cup. After 48 hours the patch test is removed and the resulting reaction is assessed and recorded, initially at 20 minutes and again 24 hours after patch test removal. The reactions are graded based on the degree of erythema and the presence of papules or vesicles. Thus, the APT has been referred to as an epicutaneous patch test using allergens capable of causing IgE-mediated reactions, where the test sites are evaluated for an eczematous response after 24 to 72 hours. Although side effects are uncommon, irritant reactions and contact urticaria have been reported [66].

The utility of the APT in the evaluation of food allergic patients remains a topic of debate [67], [68], [69] and [70]. At this point, the interest lies in the potential utility of this test as an aid in identifying the responsible foods in patients with nonIgE-mediated gastrointestinal disorders, such as FPIES, or mixed reactions involving both IgE and lymphocyte mediated mechanisms, as seen in eosinophilic esophagitis and atopic dermatitis. Aspects that hinder wider use of the APT include the lack of standardization of the procedure, including the lack of standardized reagents or how best to prepare them, in addition to the time and expertise required for the accurate performance of the test [66].

Laboratory testing

While prick skin testing to foods determines the presence of food allergen-specific IgE bound to specific receptors on the surface of mast cells in a patient's skin, laboratory assays have been developed that determine the presence and amount of food allergen-specific IgE circulating unbound in the serum. These assays are particularly useful when medications that impact skin testing cannot be discontinued, widespread skin disease is present, or some other circumstance, such as unavailability of an extract, precludes skin testing. In addition, these assays are used to further investigate situations involving a suggestive history but a negative skin test, or to determine the level of circulating food-specific IgE in the patient with a positive skin test, to aid in deciding whether a food challenge to document tolerance of the food is indicated. Although the sensitivity of skin testing and selected immunoassays is comparable [71], in the patient with a highly suggestive history and a negative immunoassay, if not already obtained, the performance of a skin test is advised before ingestion of the food is encouraged. Following the levels of food allergen-specific IgE in an individual patient over time can be used to evaluate whether sensitization to the food is increasing, stable, or waning. Food allergen-specific IgE levels aid in predicting the likelihood of a reaction, but do not predict reaction severity.

One of the most widely used and evaluated immunoassays is the ImmunoCap radioallergosorbent test (CAP RAST) system, which measures the amount of circulating allergen-specific IgE in the serum in kilounits of allergen-specific IgE per liter ($\text{kU}_\text{A}/\text{L}$). In 1997, in a retrospective study analyzing the sera of food allergic children in light of highly suggestive histories or the results of food challenges, Sampson and Ho [72] reported predictive threshold levels for several of the commonly allergenic foods, including milk, egg, peanut, and fish. Patients with values higher than the calculated threshold values had a 95% likelihood of reacting upon ingestion of the food. In a subsequent prospective study, Sampson [73] evaluated 100 children by history, oral food challenges, and measure of allergen-specific IgE levels to egg, milk, peanut, soy, wheat, and fish. This study was undertaken to determine if the 95% predictive decision points for egg, milk, peanut, and fish determined in the previous study were accurate. Using the previously defined predictive decision points, more than 95% of the food allergies to these foods in this population of patients were correctly identified. These diagnostic decision points have been further investigated and refined, and their use in clinical settings has significantly reduced the need for food challenges [25]. CAP RAST levels, above which 95% or more of children would be expected to react, have been reported for several of the major food allergens. Children less than 2 years of age with a CAP RAST to egg of greater $2 \text{ kU}_\text{A}/\text{L}$ or a CAP RAST to milk of greater than $5 \text{ kU}_\text{A}/\text{L}$, have a greater than 95% chance of reacting on food challenges. For older children the decision points for foods commonly causing allergic reactions are as follows: egg $7 \text{ kU}_\text{A}/\text{L}$, milk $15 \text{ kU}_\text{A}/\text{L}$, peanut $14 \text{ kU}_\text{A}/\text{L}$, tree nuts approximately $15 \text{ kU}_\text{A}/\text{L}$, and fish $20 \text{ kU}_\text{A}/\text{L}$. However, individual patient CAP RAST results often fall in an indeterminate zone below the diagnostic threshold but above the value predicting tolerance. In addition, because these decision points have been determined for a relatively small number of foods, threshold values for the suspected food may not have

been established. As a result of these and other nuances, food challenges remain an important tool for documenting the association between the ingestion of a suspected food and the onset of symptoms.

Elimination diets

Elimination diets are used in both the diagnosis and treatment of patients suffering from adverse reactions to foods, regardless of the mechanism involved. During the diagnostic phase suspected foods are eliminated from the diet while the patient's clinical course is carefully monitored for a reduction in or resolution of symptoms. A lack of significant improvement prompts a search for additional offending foods or potential causes other than foods. During the treatment phase, an elimination diet is constructed that removes all offending foods from the diet while meeting the patient's nutritional requirements and taste preferences. Elimination diets should be carefully constructed, as the overzealous elimination of foods unnecessarily from the diet has been associated with adverse physical and psychologic consequences [74] and [75].

Different versions of elimination diets, which vary in regard to the number of foods removed, are used. Limited elimination diets involve the removal of only those foods for which there is a high level of suspicion, based either upon the history or the results of testing. These are the simplest to prepare and use when a single food not widely found in the diet is suspected, and become more difficult to design as more foods or those pervasive in the diet come under suspicion. Oligoantigenic diets are constructed using only a few foods classically considered to rarely be allergenic. Elemental diets consist of an elemental formula, with or without the addition of a few foods considered to be safe. Oligoantigenic and elemental diets are used when there is uncertainty about which foods cause symptoms or when a large number of foods are suspected. Elemental diets are useful in young infants not yet on solids, but adherence to these diets is often difficult to maintain beyond infancy. One food-associated disorder in which the use of elemental diets has been shown to be of particular benefit is eosinophilic esophagitis, where improvement in 98% of patients placed on elemental diets has been reported [76]. When oligoantigenic and elemental diets are used, foods are added back to the diet individually at selected intervals, accompanied by symptom monitoring. Tolerated foods are left in the diet, while those associated with a return of symptoms are removed.

When elimination diets are instituted for extended periods, care must be taken to ensure that the patient's nutritional requirements are met. Children on dairy-free diets have been shown to have difficulty meeting their requirements for calcium, vitamin D, and phosphorous [75]. Consultation with a registered dietitian to provide a nutritional assessment and patient education regarding label reading, food preparation, hidden sources of food allergens, and alternative nutrient sources is encouraged.

Food challenges

The goal of performing an oral food challenge is to document the presence or lack of clinical reactivity to a food. Oral food challenges are categorized into open, single-blind, placebo-controlled, or double-blind, placebo-controlled, depending upon who is aware of the contents of each dose given during the challenge. The type of oral food challenge selected for use depends upon the expected need to control for patient or observer bias. In a double-blind, placebo-controlled food challenge (DBPCFC) neither the patient nor the medical team involved in administering the challenge is aware of the contents of the challenge. The DBPCFC remains the gold standard for diagnosing food allergy, as it best controls for both patient and observer bias. Thus, the DBPCFC is the challenge of choice in the research setting. In a single-blind, placebo-controlled food challenge (SBPCFC) the medical staff knows the contents of challenge doses, but the patient does not. SBPCFCs are performed to eliminate bias on the part of the patient and the patient's family. In an open food challenge (OFC), because the food is provided in its usual edible form, both the patient and medical staff knows which and how much food is being eaten. A benefit of the OFC is the relative ease of performance, as masking the challenge food is unnecessary, thereby significantly reducing preparation time. In most clinical situations an OFC suffices when objective symptoms are used to determine if the challenge is positive.

Oral food challenges are performed to address a variety of clinical questions. When the food responsible for a reaction remains unclear, even after a thorough history and attempts to document sensitization, or when more than one food is implicated based on the history and test results, food challenges are indicated to determine which, if any, of the suspected foods cause symptoms. Accurately identifying the causative food prevents future reactions and avoids the needless elimination of foods from the diet. Food challenges are also performed to prove that a food is not or is no longer the cause of symptoms. An example is the patient who has been inaccurately labeled as food allergic, despite an unconvincing history or suspicious skin test or immunoassay results. A food challenge is indicated for reassurance that the food can be safely returned to the diet. The majority of children, who as infants and toddlers were allergic to milk, egg, soy, or wheat, develop tolerance to these foods as they age. More recent studies have shown that 20% of children with allergic reactions to peanut in the first years of life outgrow their sensitivity [28]. Children determined to be allergic to a specific food at an early age, and during the course of their initial evaluation have evidence of sensitization to other foods they have yet to eat, are often kept on diets eliminating these foods until they are

older. A thorough exposure history, combined with information obtained from skin testing and immunoassay for the level of food allergen-specific IgE, is used to determine if and when to challenge children to these foods. Carefully performed food challenges safely determine when these foods can be added to the diet. When immune mechanisms other than IgE-mediated sensitivity are suspected, as exemplified with FPIES, a food challenge may be the only accurate means of verifying the diagnosis [13].

Contraindications to the performance of food challenges are relatively few. The performance of a food challenge is not advised in a patient with a history of a previous life threatening reaction and no evidence to suggest a significant decrease in the patient's level of sensitivity to the food. Challenging a patient with unstable asthma is ill advised. Patients with severe eczema should have their eczema under control before being challenged. When a previous reaction was severe and the obvious causative food is rarely encountered in the diet, or if the patient dislikes the food and, if given the opportunity, would chose to avoid it, the potential benefit is unlikely to outweigh the risks of challenge. Patients frightened by the consideration of a food challenge often benefit from working with a psychosocial clinician before a food challenge is performed. Decisions about who should be challenged are finalized only after a thorough discussion with the patient or the patient's family regarding the reasons for challenge, in addition to a review of the potential benefits and risks. Although significant risk can be associated with the performance of oral food challenges, a retrospective analysis of 253 failed food challenges to the common food allergens (milk, egg, peanut, soy, or wheat), performed in a tertiary care center, along with the experience of other centers that routinely perform these challenges, provide evidence that controlled oral food challenges are safe when performed in a medical setting, with the necessary medications and equipment, in addition to personnel experienced in the treatment of anaphylaxis [77].

Before beginning a challenge, the history of previous suspected reactions to the food is reviewed and an interim history is taken to verify that the patient is medically stable. The basic structure of a food challenge involves feeding gradually increasing doses of the suspected food at predetermined time intervals, until objective symptoms occur or a normal portion of the food ingested openly is tolerated. In blinded studies the challenge food is disguised in another food that the patient will ingest. Typical total doses are the normal age adjusted single serving amounts, or 8 g to 10 g when freeze-dried or powdered foods are used. When freeze-dried or concentrated foods are used, the potential for alteration of labile allergens must be taken into consideration. Standardized recipes for DBPCFC to milk, soy, cooked egg, raw whole egg, peanut, hazelnut, and wheat in their usual edible form, and validated by professional panelists in a food laboratory, have been published [78]. Although the dosing and interval between doses can be established based upon the patient's history, different schemes have been successfully used in different centers [79] and [80]. If subjective symptoms are encountered after a dose, options include waiting longer before administering the next dose, repeating the previous dose, or stopping the challenge.

A food challenge is completed when the patient has an obvious reaction or a normal portion of the food has been ingested openly without symptoms. The observation period following completion of the challenge depends upon several factors, including the immune mechanism involved, timing, severity and duration of previous reactions, whether the patient reacted and the severity of that reaction, in addition to the level of concern about biphasic anaphylaxis. Usually patients are observed until they have been asymptomatic for a couple of hours after a reaction, or for about two hours after the last dose if the food was tolerated. Patients with nonIgE-mediated reactions, such as the food-protein induced enterocolitis syndrome or other delayed reactions, are observed longer. The implications of the challenge results should be thoroughly reviewed with the patient and the patient's family, and all questions thoroughly addressed. If the challenge is negative, including the challenged food regularly in the diet is encouraged.

Management of the food allergic patient

Current management of food-allergic patients consists of the dietary avoidance of causal foods and optimizing the prompt treatment of symptoms resulting from accidental exposure. An individualized approach, taking into consideration the immunologic mechanism involved, the age of the patient, the suspected degree of sensitivity, the number of implicated foods, and the severity of previous reactions, is required. Dietary avoidance of implicated foods is accomplished through the design of a palatable, nutritionally adequate elimination diet, education regarding label reading, and a review of potential sources of accidental exposure. The ease of designing a single food elimination diet depends upon the pervasiveness of the offending food in the diet. Diets eliminating commonly encountered foods or multiple foods are best developed with the aid of a skilled dietician experienced in working with patients with food allergies. Reliable resources for obtaining further information, such as the Food Allergy and Anaphylaxis Network (http://www.sciencedirect.com/science?_ob=RedirectURL&_method=externObjLink&_locator=url&_cdi=13157&_plusSign=%2B&_targetURL=http%253A%252F%252Fwww.foodallergy.org), should be provided.

Wearing a medical information bracelet or necklace or carrying a card listing the patient's allergies and other important medical information can save time, particularly when the patient is found unconscious or cannot communicate as a result of a reaction. A food allergy action plan should be developed that lists the steps to take in case of a reaction, including the order and doses of all medications to be administered, as

well as contact information for family members and health care providers. This plan should be thoroughly reviewed with patients, their family members, and all other caretakers.

Fatal allergic reactions to foods have been associated with the delayed administration of epinephrine [32] and [46]. As a result, an epinephrine autoinjector, along with instruction about when and how to use it, should be provided to those patients considered to be at risk for food-induced anaphylaxis. Features of the history that should prompt providing an epinephrine autoinjector include: a previous severe reaction or one involving the respiratory or cardiovascular system; generalized urticaria or angioedema during previous reactions; coexistent asthma; allergy to peanuts, nuts, fish, or shellfish; or a history of other family members with severe allergic reactions to foods [81]. Injection of the epinephrine dose intramuscularly into the lateral thigh is recommended, based upon studies demonstrating improved absorption by this route over subcutaneous administration [82]. Currently, epinephrine autoinjectors are available in doses of 0.15 mg and 0.30 mg, with the 0.15-mg dose suggested by the manufacturer for patients weighing 15 kg to 30 kg, and 0.30-mg dose recommended for those over 30 kg, with the caveat that physician discretion regarding dosing is suggested based upon the history. Autoinjector use is preferred over the use of an epinephrine ampule and syringe, to avoid delay in administering the dose and reduce the potential for significant errors in dosing [83]. Providing more than one autoinjector is generally recommended, particularly in situations where access to medical care is limited or could be delayed. Once an epinephrine autoinjector is used, emergency medical services should be notified for transport of the patient to the appropriate medical facility.

Other medications commonly available to patients, for use in the immediate treatment of allergic reactions to foods, include oral antihistamines and inhaled bronchodilators. Antihistamines carried for the first-aid treatment of allergic reactions should be chewable or liquid preparations, to reduce the time required for absorption. Appropriate doses of these medications and when to use them should be reviewed. The first-aid treatment of food-induced anaphylaxis, including the rationale for epinephrine administration, has been reviewed by Simons [54]. Although epinephrine is the drug of choice for the treatment of anaphylactic reactions to foods, it does not reverse the symptoms of nonIgE-mediated reactions, such as food protein-induced enterocolitis, where the mainstay of therapy is fluid replacement.

Upon arrival at a medical facility for treatment of an allergic reaction to a food, the patient should be rapidly assessed and supportive care provided as indicated. Oxygen should be rapidly provided for any evidence of respiratory distress. If 10 to 15 minutes have elapsed since the initial dose, and the reaction persists or is progressing, another dose of epinephrine should be given. Patients presenting with hypotension should receive intravenous fluids with consideration for instituting vasopressor therapy. If antihistamines have not been given or symptoms persist, an additional dose of antihistamine should be administered and use of an H₂ blocker considered. Other supportive care, such as bronchodilator therapy for patients with bronchospasm, should be provided as indicated. Looking for factors that inhibit response to therapy, such as beta-blocker use, is encouraged in patients unresponsive to standard treatment. Intravenous glucagon may effectively treat hypotension in patients on beta blocker therapy who are not responding to the vasopressor effects of epinephrine [54]. Before the patient with food-induced anaphylaxis is released from medical care, the means for obtaining an epinephrine autoinjector should be provided, along with appropriate teaching and arrangement for follow-up with an allergist.

Long term management of the food allergic patient involves monitoring for evidence of the development of tolerance, or for the acquisition of new food allergies, by obtaining interim histories regarding reactions to foods, and evaluating the results of immunoassays for food-specific IgE or skin testing as indicated. Other important aspects of long-term follow-up include analyzing the diet for nutritional adequacy, reviewing the first-aid treatment of allergic reactions to foods, discussing patient concerns, and providing psychologic support. The psychologic impact on patients and their families is a frequently ignored aspect of food allergy, often successfully managed with appropriate psychosocial intervention, resulting in a significant improvement in quality of life.

Future directions

Promising results observed in recent studies suggest that improved diagnostic methods and treatments other than merely avoiding the offending food are forthcoming. For example, examination of specific epitopes, or the number of epitopes on specific food allergens recognized by a patient's food-specific IgE, may improve the ability to predict the likelihood of the eventual development of tolerance or the potential for severe reactions [84], [85], [86] and [87]. In addition, a variety of immunotherapeutic approaches, including oral immunotherapy [88], [89] and [90], sublingual immunotherapy [91], and immunotherapy using altered allergens administered with specific adjuvants [92] are under investigation, as are novel therapies, including treatment with humanized monoclonal anti-IgE antibodies [93] and a modified Chinese herbal therapy [94]. The findings of these, and other studies underway to better define the immune mechanisms involved in the development of oral tolerance as well as food allergy, suggest that viable therapies will become available within the next decade.

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