

Pathophysiology of Food-Induced Anaphylaxis

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Food-induced anaphylaxis is a steadily increasing problem in westernized countries and now represents the leading cause of anaphylaxis in the outpatient setting, particularly in children. Much of our knowledge of the pathophysiology of food-induced anaphylaxis comes from animal studies. Food anaphylaxis in humans is thought to be entirely IgE mediated. Several features appear to be unique to these reactions; factors such as exercise can lower the “threshold” for anaphylaxis in certain susceptible individuals. Different methods of thermal processing can modify the allergenicity of food proteins. Alteration of stomach pH can allow for incomplete digestion of food proteins, leading to increased absorption of intact food allergens. Low serum platelet-activating factor acetylhydrolase may predispose to fatal food-induced anaphylaxis. With a greater understanding of the pathophysiology of food-induced anaphylaxis, novel approaches not only to identify those at risk, but to treat and ultimately prevent food-induced anaphylaxis, are on the horizon.

Introduction

Food allergy, the most severe form being food-induced anaphylaxis, is a steadily increasing problem in westernized countries around the world [1,2]. According to current estimates, 6% of children and 3.7% of adults have some form of food allergy [1]. Food allergens differ according to geographic location and local diet. In the United States, the major food allergens include milk, egg, wheat, soy, peanut, tree nuts, fish, shellfish, and seeds (eg, sesame) [3]. Although any food can cause anaphylaxis, peanut, tree nuts, fish, and shellfish are the most commonly implicated foods in most series of anaphylaxis

[3]. Food-induced anaphylaxis represents 15% to 57% of cases of anaphylaxis presenting to the emergency department and 81% of anaphylactic reactions in children [4,5].

Anaphylaxis

According to one definition, “Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death” [6••]. Clinical criteria for the diagnosis of anaphylaxis include acute onset of allergic symptoms involving the skin and/or mucosal tissues (urticaria, flushing, angioedema) with either respiratory compromise or hypotension [6••]. Isolated hypotension can be diagnostic of anaphylaxis in the setting of exposure to a known allergen, and persistent gastrointestinal symptoms can help make the diagnosis after exposure to a likely allergen. This broad definition encompasses both IgE-mediated and non-IgE-mediated (anaphylactoid) anaphylactic reactions.

Food-induced anaphylaxis in humans is thought to be entirely IgE dependent and is triggered by food allergens binding to allergen-specific IgE [7]. These food-specific IgE molecules are bound to mast cells and basophils, as well as several other cell types, through the high-affinity IgE receptors (FcεR1) on the cell surface. Aggregation and cross-linking of the FcεR1 leads to a signaling cascade triggering the release of preformed and newly synthesized mediators from mast cell and basophil granules (Fig. 1). These mediators exert effects on a host of different target organs, leading to the clinical manifestations of anaphylaxis.

Pathophysiology of Anaphylaxis: Murine Models

Much of our understanding of the pathophysiology of food-induced anaphylaxis comes from a large body of work generated from animal models, and in particular, murine studies. Li et al. [8] developed a murine model of cow’s milk-induced anaphylaxis by sensitizing mice via gastric gavage of cow’s milk protein and inducing anaphylaxis in the sensitized mice by the same route. Prior to this, other animal models induced food anaphylaxis by parenteral challenge, and thus were not wholly reflective of food-induced anaphylaxis where sensitization and

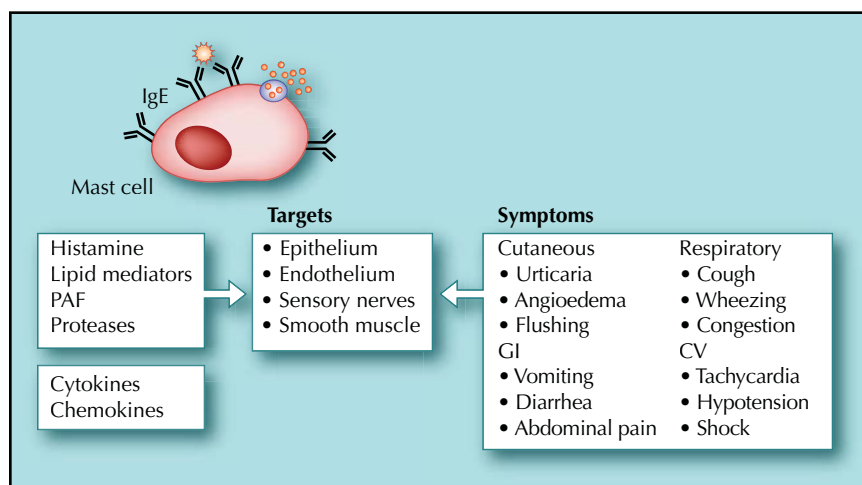


Figure 1. Anaphylaxis is triggered by allergen binding to FcεRI-bound IgE on the surface of mast cells and basophils leading to the release of inflammatory mediators, which exert specific effects on various target organs to produce the symptoms of anaphylaxis. CV—cardiovascular; GI—gastrointestinal; PAF—platelet-activating factor.

anaphylaxis are both triggered through gastrointestinal antigen exposure. The same group developed a similar model for peanut-induced anaphylaxis [9]. In both studies severity of anaphylaxis correlated with antigen-specific IgE levels. The authors also demonstrated elevations in plasma histamine levels and degranulation of tissue mast cells, suggesting that the anaphylactic reactions were due to IgE-mediated activation of mast cells.

The importance of IgE and mast cells in food-induced anaphylaxis was recently confirmed by Sun et al. [10•], who demonstrated protection against peanut-induced anaphylaxis in mast cell-deficient mice. These mice had detectable peanut-specific IgE, IgG1, and IgG2a after sensitization but had no evidence of anaphylaxis upon parenteral (intraperitoneal) peanut challenge. The authors showed that B-cell deficient and CD40L knock-out mice were unable to generate peanut-specific immunoglobulin during the sensitization protocol and were also protected from anaphylaxis upon peanut challenge. In the same study, FcεRI-deficient mice (FcεRI α-chain knock-out mice) were also protected from anaphylaxis, although only partial abrogation of anaphylactic responses occurred in these mice. Taken together, these results suggest that mast cells and antigen-specific immunoglobulin are essential for peanut-induced anaphylaxis. However, the FcεRI α-chain knock-out mice still had some symptoms of anaphylaxis, suggesting an alternate pathway for peanut-induced anaphylaxis in these animals.

In a study by Leung et al. [11] evaluating treatment with the monoclonal IgG antibody TNX-901 (anti-IgE), threshold doses for reactivity to peanut in peanut-allergic patients were increased from 178 mg (approximately half a peanut) to 2.8 g (approximately nine peanuts) in patients treated with the drug. In this study, 75% of the patients were provided some degree of protection with the drug, and likely had enough protection to prevent anaphylaxis from accidental peanut ingestion. This study supports the crucial role of peanut-specific IgE antibody in the pathophysiology of peanut-induced anaphylaxis in humans.

Previous studies have shown that mice have two distinct pathways of anaphylaxis: the IgE-mediated “classic” pathway, and the IgG-mediated “alternative” pathway [12]. (The excellent review by Finkelman [12] provides a more complete discussion of this topic.) The classic pathway results in anaphylaxis from mast cell activation by means of antigen-mediated FcεRI cross-linking. The primary mediator of anaphylaxis in this pathway is histamine, though several proteases, prostaglandins, and platelet-activating factor (PAF) also play a role [12]. The alternative pathway of anaphylaxis results from antigen-IgG complexes binding to the low-affinity FcγRIII on macrophages with resultant cell activation and degranulation [12]. The primary mediator of anaphylaxis here is PAF, with histamine playing a minor role.

The importance of the alternative pathway in food-induced anaphylaxis is unclear. The initial studies documenting the existence of anaphylaxis in IgE-deficient mice used a parenteral method of sensitization (immunization) and allergen challenge [8]. No study to date has definitively proven food-specific IgG to be capable of inducing anaphylaxis in the murine model. This is also true of food-induced anaphylaxis in humans, although food-induced anaphylaxis in the absence of detectable food-specific IgE has occasionally been reported [7].

Antigen Uptake

Several studies have demonstrated increased intestinal antigen uptake in sensitized subjects [13–15]. Normally, food proteins are taken up by two routes: transcellular transport and paracellular transport [14]. In the transcellular route, a small amount of food protein is taken up by the gut epithelium through endocytosis and is degraded in cellular lysosomes. Transport of food proteins through the paracellular route is regulated by tight junctions, and is dependent on size and charge. This normal uptake of food protein is thought to be important in the generation and regulation of oral tolerance to foods.

In the food-allergic host, food-allergen uptake via the transcellular route is enhanced by the presence of food-specific IgE [15]. CD23, the low-affinity IgE receptor, facilitates the bidirectional transcytosis of IgE. Luminal IgE-antigen complexes are bound by CD23, endocytosed, shunted away from cellular lysosomes, and transported intact across the cell to activate gut mast cells. A recent study by Li et al. [16] demonstrated increased levels of food-specific IgE and soluble CD23 in the stool of food-allergic patients after oral food challenges, suggesting that this mechanism is also important in human food allergen uptake. A second, and more intense, phase of antigen uptake occurs after local mast cell activation and is thought to be due to the disruption of epithelial cell tight junctions with resultant increased gut permeability. This increase in gut permeability allows greater paracellular transport of a large number of molecules, including food allergens [14].

Food-dependent exercise-induced anaphylaxis is thought to be due to increased gut permeability with resultant increased food allergen uptake. Several studies, in both animals and humans, have demonstrated increased intestinal uptake of food allergens after exercise [17,18•]. A similar phenomenon has been observed in patients taking nonsteroidal medications and alcohol [18•]. Patients with food-dependent exercise-induced anaphylaxis typically have low-level food-specific IgE titers and are tolerant to the implicated food unless stressed by exercise [18•,19]. In addition, in the case of wheat-dependent, exercise-induced anaphylaxis, omega-5 gliadin has been identified as an important allergen. Exercise induces the activation of tissue transglutaminase, which results in generation of high-molecular-weight complexes of omega-5 gliadin that bind IgE with increased intensity, leading to mast cell activation and anaphylaxis [19].

The relative importance of antigen uptake on the development of food-induced anaphylaxis was recently demonstrated in a series of studies from Austria [20,21]. The first study followed a cohort of adult patients taking an antacid medication for a 3-month period; 25% of treatment patients showed an increase in food-specific IgE formation and 15% showed de novo food-specific IgE formation [20]. Another study by the same group demonstrated codfish-allergic patients to be at greater risk for more severe allergic reactions when underdigested codfish was ingested during a double-blind, placebo-controlled food challenge [21]. These patients were given codfish protein pretreated with digestive enzymes at either pH 2.0 or 3.0 for varying lengths of time. The patients reacted to considerably lower doses of codfish protein when the fish was pretreated with digestive enzymes at pH 3.0 as compared with pH 2.0. Additionally, wheal diameters induced by prick skin testing (PST) were considerably larger with the fish protein extracts at pH 3.0. Taken together, these findings suggest that underdigestion of food proteins, presumably leading to greater absorption of intact food

allergens, places food-allergic patients at higher risk for more severe allergic reactions, such as anaphylaxis.

Allergenicity of food proteins can be increased in other ways, such as thermal processing. Beyer et al. [22] investigated the effects of various thermal processing methods (eg, dry roasting, boiling, and frying) on the allergenicity of the major peanut protein allergens, Ara h 1, Ara h 2, and Ara h 3. Dry roasting was associated with increased quantities of Ara h 1 and increased IgE binding to the Ara h 2 and Ara h 3 proteins as compared with frying or boiling. These results may explain the higher prevalence of peanut allergy in the United States, Canada, UK, and Australia, where dry roasting is the predominant form of thermal processing of peanuts.

Mediators of Anaphylaxis

As stated earlier, the clinical manifestations of anaphylaxis are the result of mast cell and basophil inflammatory mediators acting upon a variety of target organs. These mediators include histamine, proteases (eg, tryptase and chymase), lipid mediators (eg, leukotrienes and prostaglandins), PAF, and proteoglycans (eg, heparin and chondroitin sulfate). Additionally, several cytokines are secreted into the milieu, including interleukin (IL)-4, IL-5, IL-13, and IL-16, tumor necrosis factor (TNF)- α , and various chemokines [7]. Table 1 summarizes the physiologic actions of these mediators on their target organs and the resultant clinical symptoms. Please see the excellent reviews of this topic by Ogawa and Grant [23] and Pejler et al. [24].

Briefly, histamine appears to be the most important mediator of anaphylaxis. Kaliner et al. [25] demonstrated that infusion of histamine into human subjects rapidly reproduces symptoms of anaphylaxis. Histamine works through two receptors, H₁ and H₂, in various anatomic compartments to produce the symptoms of anaphylaxis (Table 1) [23].

Prostaglandins (PG) and leukotrienes (LT) are products of arachidonic acid metabolism and are released by mast cells within 10 minutes of Fc ϵ RI cross-linking by antigen [23]. PGD₂ has been shown to produce bronchoconstriction and vasodilation and has also been reported to be chemotactic for eosinophils and basophils. Leukotrienes also promote bronchoconstriction (LTC₄, LTD₄, and LTE₄) along with increased vascular permeability, increased mucus production, and recruitment of inflammatory cells (LTB₄) [23].

Tryptase, and several other neutral proteases including chymase and carboxypeptidase A3, are secreted by mast cells upon IgE cross-linking and activation [24]. The role of these proteases in anaphylaxis is less defined than that of histamine. However, studies in animals and in human tissues have shown proteases to enhance histamine release from mast cells, further propagating the allergic reaction [24].

Table 1. Mast cell and basophil mediators

Mediators	Targets	Physiologic actions	Clinical manifestations
Histamine and lipid mediators (prostaglandins, leukotrienes)	Vascular endothelium	Vasodilation, increased vascular permeability; vasospasm of coronary arteries	Hypotension, urticaria, angioedema, myocardial ischemia
	Bronchial SM and glands	Muscle contraction; increased mucus production and viscosity	Bronchospasm; mucus plugging
	Intestinal SM	Muscle contraction	Vomiting, diarrhea
Histamine	Myocardium	Inotropy/chronotropy	Tachycardia; increased cardiac output
	Sinoatrial node	Shortens diastole	Tachycardia
Prostaglandins and leukotrienes	Eosinophils, basophils, dendritic cells, Th2 cells	Chemoattraction	Late-phase inflammation
Proteases (tryptase, chymase, carboxypeptidase A3)	Mast cells	Activation with release of histamine	Magnification of allergic symptoms
	Neutrophils, eosinophils, monocytes	Chemoattraction	Late-phase inflammation; possibly protracted or late-phase anaphylaxis
	Angiotensin I	Conversion to angiotensin II	Hypertensive response
	Complement	Cleavage of complement components	Magnification of inflammation
Proteoglycans (heparin, chondroitin sulfate)	Mast cells	"Histamine scavenger"	Amelioration of allergic symptoms
	Antithrombin III	Inhibition of coagulation cascade	Prevention of intravascular coagulation
	Complement	Inhibition	Decreased inflammation
	Phospholipase A2	Inhibition of arachidonic acid metabolism	Decreased inflammation
Platelet-activating factor	Vascular endothelium	Vasodilation, increased vascular permeability	Hypotension, urticaria, angioedema
	Bronchial SM	Muscle contraction	Bronchospasm
	Eosinophils, neutrophils	Chemoattraction, activation	Increased inflammation
Cytokines (IL-4, IL-5, IL-13, TNF- α), chemokines (CCL1, CCL7, CCL11-eotaxin)	Neutrophils, eosinophils, monocytes	Activation, chemoattraction	Increased inflammation
	B cells	IgE production	Propagation of allergic reaction
	Mast cells	Increased Fc ϵ RI expression	Propagation of allergic reaction

IL—interleukin; SM—smooth muscle; Th2—T helper type 2; TNF- α —tumor necrosis factor- α .

Human mast cells use proteoglycans (heparin and chondroitin sulfate) to stabilize secretory proteases [23]. When these molecules are released from mast cells upon cell activation, they act as inhibitors of several inflammatory pathways (Table 1). Additionally, evidence suggests that heparin also binds to histamine in mast cell granules and may act as a "histamine scavenger" upon mast cell degranulation, thereby diminishing histamine's effects [26•]. Heflin et al. [26•] used a porcine model to demonstrate reversal of anaphylactoid hypotensive shock with heparin administration, though not as efficiently as epinephrine plus diphenhydramine.

PAF has broad proinflammatory effects and is secreted by mast cells, basophils, macrophages, and monocytes [7]. It is well known that PAF plays a major role in the alternative (IgG-mediated) pathway of murine anaphylaxis [13]. Several studies have shown that PAF is also important in human inflammatory diseases and likely plays a significant role in human anaphylaxis. Cuss et al. [27] demonstrated that inhaled PAF causes severe bronchoconstriction (1000 times more potent than histamine), and Rodriguez-Roisin et al. [28] demonstrated ventilation-perfusion mismatch and decreased systemic vascular resistance after PAF

inhalation. PAF acetylhydrolase (PAF-AH) is an enzyme that inactivates PAF. Vadas et al. [29••] showed that PAF-AH levels were markedly decreased in patients with fatal peanut-induced anaphylaxis and correlated with severity of symptoms.

Mast cells secrete a variety of cytokines and chemokines upon activation, including IL-4, IL-5, IL-13, and TNF- α [24]. TNF- α activates neutrophils and promotes monocyte chemotaxis as well as additional cytokine production by T-cells. IL-4, released by both mast cells and basophils, propagates the T-helper type 2 (Th2) cell response and induces Ig class switching to increase IgE production by B cells [24]. IL-13 is also secreted by both basophils and mast cells after Fc ϵ RI-mediated activation and leads to enhanced IgE production as well as Fc ϵ RI expression. IL-5 is predominantly an eosinophil-activating cytokine and plays a major role in several allergic diseases [24]. Anticytokine therapy is likely to have a role in the prevention and chronic treatment of allergic disease, but is unlikely to be effective in treating acute allergic reactions (eg, anaphylaxis).

Biphasic Reactions

Biphasic or late-phase reactions are characterized by a recurrence of symptoms after the complete resolution of the initial reaction. (For a more complete review of this topic, please see the excellent review article by Lieberman [30].) Late-phase reactions are not uncommon, especially in food-induced anaphylaxis, particularly in nut- and seafood-induced anaphylaxis. In fact, up to 20% of cases of fatal or near-fatal anaphylaxis are associated with a late-phase response [3]. Most late-phase reactions develop within 8 hours of resolution of the initial reaction, but may occur up to 72 hours later [30]. Risk factors for the development of a late-phase reaction include the following: food-induced (or other oral antigen-induced) allergic reaction; delayed onset of initial symptoms after antigen exposure (> 30 minutes); delayed administration or underdosing of epinephrine; prior β -blockade (patient on β -blocker); and the need for multiple doses of epinephrine to treat the initial reaction [30].

The pathogenic basis of late-phase reactions is still largely unknown. Theories to explain biphasic reactions include insufficient treatment of the initial symptoms leading to only temporary amelioration of the reaction, cytokine-mediated influx of inflammatory cells and mediators into tissues, waves of absorption of orally administered antigens, and delayed basophil degranulation [30]. Undertreatment of the initial symptoms may explain late-phase reactions that occur in the first few hours after the initial reaction, but seems unlikely to be related to late-phase reactions occurring many hours or even days after the initial anaphylactic response. However, several reports have demonstrated that patients with biphasic reactions tended to receive less (or delayed) epi-

nephine and less corticosteroid during treatment of the initial reaction [30].

Presence of inflammatory cell infiltrates in late-phase skin and respiratory responses to antigen lead to the hypothesis of cytokine/inflammatory cell-driven biphasic anaphylactic reactions. However, histologic findings in patients with fatal anaphylactic reactions do not support this theory; very often, no inflammatory cells are found in postmortem specimens from patients who had fatal biphasic anaphylactic reactions, although eosinophils and mast cells have been reported [31].

Delayed absorption of food allergens (or other oral antigens) could theoretically cause waves of mast cell degranulation leading to late-phase responses; indeed, rat gut-derived mast cells were shown to undergo degranulation at 30 minutes and 72 hours after a single oral allergen challenge [32]. However, this does not explain the majority of biphasic reactions, which typically occur within the first 8 hours. These results also contrast with findings in human late-phase respiratory responses, in which the second round of mediator release is basophil generated. Additionally, many reports exist of biphasic reactions induced by parenterally administered antigens, suggesting that alternate pathogenic mechanisms must be important [30].

Diagnosis of Food-Induced Anaphylaxis

Making a clinical diagnosis of anaphylaxis, and in particular food-induced anaphylaxis, can be difficult for a variety of reasons; this is especially true if the patient has no known history of food allergy. Of note, a large percentage of patients experiencing food-induced anaphylaxis report a positive history of food allergy [3]. However, most patients are unaware that the foods they are eating that trigger the anaphylactic reaction contain the known allergen.

The diagnosis of food-induced anaphylaxis is often overlooked because of the absence of cutaneous manifestations. Up to 20% of patients, in particular children, with food-induced anaphylaxis do not have cutaneous involvement, making the diagnosis considerably less obvious [3]. The diagnosis can also be difficult because symptoms may be transient due to endogenous production of catecholamines, or because of prehospital administration of medications (eg, antihistamines or epinephrine).

There have been immense research efforts to identify reliable laboratory markers to aid in the diagnosis of anaphylaxis; currently, total tryptase level is most commonly measured. Tryptase levels increase immediately, peak at 1 to 2 hours after the onset of anaphylaxis, and return to baseline 24 hours after complete resolution of symptoms. Levels are ideally obtained within 3 hours of onset of symptoms, and serial measurements may help establish a diagnosis of anaphylaxis [7]. However, lack of tryptase elevation does not rule out the diagnosis of anaphylaxis, especially food-induced anaphylaxis. In a study by Sampson et al. [33], the majority of patients with fatal

and near-fatal food-induced anaphylaxis did not have detectable increases in serum tryptase. Sampson and Jolie [34] also failed to demonstrate elevated tryptase levels in patients with symptoms of anaphylaxis undergoing food challenges, even though samples were obtained in the ideal time frame.

Several theories have been proposed as to why tryptase levels are often not elevated in food-induced anaphylaxis. First, food-induced anaphylactic reactions tend to be slower in onset, more protracted, and more often biphasic compared with anaphylaxis secondary to a systemic exposure [35]. This may result in a slower release of tryptase and a decreased peak. Second, Schwartz et al. [36] demonstrated that mucosal mast cells often contain less tryptase as compared with skin mast cells. Gut mucosal mast cells are expected to be major players in food-induced anaphylaxis, so this might result in less tryptase release systemically, especially if much of the tryptase is secreted into the gut lumen [37]. Finally, basophils may play a significant role in food-induced anaphylaxis [35]; because basophils do not contain tryptase, serum tryptase elevations would not be expected.

Another laboratory marker of anaphylaxis is serum histamine. Histamine levels typically peak within 10 minutes of symptom onset and decrease to baseline by 60 minutes [23]. Unfortunately, this is not a clinically useful marker because most patients with anaphylaxis, and in particular food-induced anaphylaxis, do not present to the emergency department in time to capture the histamine peak. However, urinary histamine metabolites remain elevated for up to 24 hours after anaphylaxis and may be helpful in establishing the diagnosis [38].

Research efforts are underway to find alternative clinically useful markers of anaphylaxis. Other molecules under investigation include PAF, PAF-AH, and mast cell carboxypeptidase A3. As stated earlier, PAF-AH levels have been shown to be decreased in fatal cases of peanut-induced anaphylaxis as compared with healthy controls, patients with nonfatal allergic reactions, and nonanaphylactic fatalities [29••]. Zhou et al. [39] demonstrated elevated levels of mast cell carboxypeptidase A3 in patients with suspected anaphylaxis as compared with healthy controls and asthmatic patients. These samples were drawn up to 8 hours after onset of allergic symptoms, and were found to be elevated in 83% of patients with anaphylaxis and in 70% of patients with tryptase-negative anaphylaxis. Further studies are required to determine if these enzymes could be useful markers for food-induced anaphylaxis.

Currently, the most reliable means of diagnosing food-induced anaphylaxis is double-blind, placebo-controlled food challenge to the suspected food allergen. In practice, presumptive diagnoses are more often based on a convincing clinical history of anaphylaxis within 2 hours of ingestion of a particular food allergen and detection of food allergen-specific IgE by means of PST or serum

levels of allergen-specific IgE. Unfortunately, these tests are not always sensitive or highly specific. Several studies have demonstrated that less than 40% of patients with histories of food allergy have positive PSTs or detectable food-specific IgE, and that less than 40% of patients with positive PSTs or food-specific IgE have oral food challenge-proven food allergy [40,41].

Allergen-specific IgE levels with greater than 95% predictive risk values of clinical reactivity have been determined for several of the major food allergens [7]. Unfortunately, these values are not predictive of the nature or severity of reaction to the particular allergen, and efforts are underway to better identify patients at risk of food-induced anaphylaxis.

One laboratory-based test that shows promise for identifying patients at risk for food-induced anaphylaxis is the peptide microarray immunoassay. This assay utilizes overlapping peptides of the major food allergen proteins to detect epitope (sites of antibody recognition on allergenic proteins)-specific IgE. Shreffler et al. [42] demonstrated that IgE binding to a greater number of peanut-protein (Ara h1, Ara h2, and Ara h3) epitopes correlated with reaction severity in a series of 77 peanut-allergic patients. Microarray immunoassays for the other major food allergens are under investigation at this time. Recently, Jarvinen et al. [43] demonstrated that patients with persistent egg allergy recognized a greater number of sequential (linear) egg-protein epitopes as compared with non-egg-allergic patients and patients who had developed clinical tolerance to egg ("outgrown" their egg allergy). Microarray technology is likely to be useful clinically not only to determine patients at risk for anaphylaxis, but also to identify patients who will likely develop clinical tolerance versus those with persistent allergy.

Treatment of Food-Induced Anaphylaxis

The mainstay of treatment of any anaphylactic reaction is the timely administration of epinephrine. In most series of fatal anaphylaxis, epinephrine administration was delayed for the majority of patients and may have contributed to the fatal outcome [30]. Epinephrine is the only medication available that can effectively abort an anaphylactic reaction, because stimulation of mast cell β_2 -adrenergic receptors potently suppresses IgE-dependent mediator release [44]. Epinephrine also can reverse many symptoms of anaphylaxis by stimulation of its various receptors. Specifically, epinephrine mediates vasoconstriction by stimulation of the α_1 -adrenergic receptor and mediates bronchodilation by stimulation of the β_2 -adrenergic receptor. Stimulation of the β_1 -adrenergic receptor has both inotropic and chronotropic cardiac effects, resulting in increased cardiac output [45].

For the effective treatment of anaphylaxis, peak plasma epinephrine concentrations must be reached quickly to reverse life-threatening hypotension and bronchospasm.

Simons [46] showed that intramuscular injection of epinephrine into the lateral thigh achieved faster and higher peak plasma epinephrine concentrations when compared with intramuscular or subcutaneous injection into the deltoid.

All other medications used in the treatment of anaphylaxis are considered second line. H_1 and H_2 receptor antagonists are slow in onset of action (typically 1–2 hours but as fast as 20 minutes) and only effective for cutaneous symptoms. These medications have no appreciable effect on bronchospasm or hypotension. Corticosteroids are often given to patients with anaphylaxis, although their role here has not been proven [47,48]. Certainly, corticosteroids are not effective in treating the acute reaction given their onset of action of several hours, but they are administered with the goal of preventing or ameliorating a late-phase reaction. Bronchodilators can also be given to help reverse bronchoconstriction. However, all these medications are adjunctive to treatment with epinephrine.

All patients with food allergy, and especially food-induced anaphylaxis, should be educated about the signs and symptoms of anaphylaxis and the correct use of an epinephrine autoinjector. Of the utmost importance is educating the patient regarding dietary avoidance of the food allergen(s) known to cause allergic reaction/anaphylaxis.

Future Therapies

Immense research efforts are underway to develop therapies to prevent the development of food-induced anaphylaxis. Currently the only preventative measure for food-induced anaphylaxis is strict dietary avoidance. Several therapies are under investigation at this time that show promise for the preventing food-induced anaphylaxis. These therapies are both allergen specific and nonspecific. Nonspecific therapies for food-induced anaphylaxis under investigation include anti-IgE (as outlined above) [11] and Chinese herbal medications [49•]. Allergen-specific therapies include oral immunotherapy (desensitization), recombinant proteins, with targeted mutations in the IgE-binding domains (epitopes) of food allergens, co-administered with heat-killed *Escherichia coli* to generate maximum immune response, and peptide immunotherapy [50•].

Conclusions

Food-induced anaphylaxis is an increasingly prevalent problem in westernized countries. As our understanding of the pathophysiology of food anaphylaxis increases, so does our ability to identify therapies that may aid not only in the diagnosis, but also the treatment and prevention, of food-induced anaphylaxis.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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- Of major importance

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