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Anaphylaxis: a history with emphasis on food allergy

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Summary

In the century since Paul Portier and Charles Richet described their landmark findings of severe fatal reactions in dogs re-exposed to venom after vaccination with sea anemone venom, treatment for anaphylaxis continues to evolve. The incidence of anaphylaxis continues to be difficult to measure. Underreporting due to patients not seeking medical care as well as failure to identify anaphylaxis affects our understanding of the magnitude of the disease. Treatment with intramuscular epinephrine continues to be the recommended first line therapy although studies indicate that education of both the patients and the medical community is needed. Adverse food reactions continue to be the leading cause of anaphylaxis presenting for emergency care. Current therapy for food-induced anaphylaxis is built on the foundation of strict dietary avoidance, rapid access to injectable epinephrine, and education to recognize signs and symptoms of anaphylaxis. Investigation into therapy with oral and sublingual immunotherapy as well as other modalities holds hope for improved treatment of food-induced anaphylaxis.

Keywords

anaphylaxis; food allergy; immunotherapy

Anaphylaxis in history

Prior to the landmark work of Paul Portier and Charles Richet, fatal systemic reactions of normally well tolerated substances had been noted by Megendie after injection of egg albumen in rabbits. Following repeated injection of albumen the rabbits developed sudden and fatal collapse (1). Over the next several decades others recognized that laboratory animals developed severe, sudden reactions to the injection of foreign material at doses that the animal had previously tolerated. In 1902, while working with Paul Portier, Charles Richet purified the toxin from the tentacle of the genus *Physalia* or Portuguese man-of-war. After isolating the toxin from *Physalia*, Portier and Richet continued their investigations using closely related toxin from *Actinia sulcata*, a sea anemone found in great numbers along the French coast (2). Attempts to determine the lethal dose of toxin in dogs provided a number of animals which survived the initial exposure to the neurotoxin. Believing these animals would be protectively immunized, Portier and Richet were surprised when subsequent injections with small amounts of the toxin produced sudden, fatal reactions (3). Richet proposed the term *aphylaxis* indicating a lack of protection from the immunization with the toxin. He later modified this term for the sake of euphony to *anaphylaxis* (2). While

the term ‘anaphylaxis’ was coined over 100 years ago, a consistent definition of anaphylaxis has proven more difficult.

The classic presentation anaphylaxis is extreme. Symptoms typically involve the integumentary, gastrointestinal, pulmonary, and cardiac systems (4). While medical personnel easily identify such classic symptoms of anaphylaxis difficulty in diagnosis arises when few or only mild symptoms are present. The 1998 Joint Task Force of the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) defined anaphylaxis as an ‘immediate systemic reaction caused by rapid, IgE [immunoglobulin E]-mediated immune release of potent mediators from tissue mast cells and peripheral basophils’ (5). Adding further confusion is the term ‘anaphylactoid reactions’. These reactions are distinct from anaphylactic reactions in that they ‘mimic signs and symptoms of anaphylaxis but are caused by non-IgE mediated release of potent mediators from mast cells and basophils’ (5). While these definitions provide mechanistic differences, they do little to guide the physician facing reactions in the office or emergency department. Two subsequent symposia have refined the definition of anaphylaxis as ‘a serious allergic reaction that is rapid in onset and may cause death’ (6). Criteria for the clinical diagnosis of anaphylaxis recommended by the Second Symposium on the Definition and management of Anaphylaxis have been established (6) (Table 1).

Incidence of anaphylaxis

Because of varied applications of the diagnostic criteria for anaphylaxis the true incidence of the disease remains a point of debate. Studies of hospital or health maintenance organizations (HMO) place the incidence of anaphylactic events between 30 to 60 cases per 100,000 persons (7) to an estimated 2,000 events per 100,000 persons (or 0.03% to 2.0% lifetime risk) (8). Even these estimations may represent an underreporting of anaphylactic events because patients presenting with multiple organ involvement may be diagnosed as having an allergic reaction rather than the more specific diagnosis of anaphylaxis (9). Review of emergency department records found 678 patients presenting with food related symptoms which should have been classified as anaphylaxis. A second study looking at victims of insect stings found 617 patients who met the criteria for anaphylaxis but failed to receive that diagnosis (10, 11). Several factors may contribute to physician or patients failing to recognize an episode of anaphylaxis. Without a history of repeated reactions, the first episode of anaphylaxis may not be recognized as being IgE mediated. While most episodes of food induced anaphylaxis occur within minutes of ingestion, anaphylaxis triggered by mammalian meat may be delayed by several hours (12). The patient or caregiver may not recognize symptoms in the very young or in patients unable to communicate due to illness. Symptoms may be suppressed by other medications such as first generation H₁ antihistamines. Health care providers may fail to recognize symptoms of anaphylaxis without obtaining a detailed history and full physical examination. Even after a detailed history and exam, the diagnosis may be overlooked when hives or other skin manifestations are absent (9).

A review of medical records within a large HMO in the western United States found that 35% of visits diagnosed as ‘anaphylactic shock’ (ICD-9 code 995.0) and 87.3% of visits diagnosed as ‘anaphylactic shock caused by adverse food reaction’ (ICD-9 code 995.3) failed to document symptoms to meet the diagnosis of anaphylaxis (13). Anaphylaxis may be clinically misdiagnosed in patients presenting only with subjective symptoms, such as abdominal pain or itch. Many of the symptoms of anaphylaxis are not specific, thus a careful history is vital in distinguishing anaphylaxis from other diseases. Panic attack, anxiety, Munchausen syndrome/Munchausen syndrome by proxy, or scombroidosis all may be

mistaken for anaphylaxis (9). Despite the possibility of under and/or over diagnosis, the incidence of anaphylaxis can be shown to have increased significantly (14–19).

Sensitization leads to anaphylaxis

Anaphylaxis is triggered in response to allergen exposure following sensitization. Sensitization develops after the initial exposure with formation of IgE to specific portions of the allergen. Released from activated B cells, IgE binds to high affinity receptors for IgE (Fc RI receptors) located on the surface of mast cells and basophils (6, 20–23). Upon re-exposure to an antigen IgE binding brings Fc RI receptor on cell surfaces to proximity that allows cross-linking between receptors. Once receptor cross-linking occurs, several tyrosine kinases, including Lyn, Syk, and Fyn, are activated within the cell providing both positive and negative regulation of the signal cascade (21, 22). Calcium influx controlled by both positive and negative regulation is essential to mast cell degranulation (21, 25). Mast cells and basophils release preformed mediators including histamine, heparin, tryptase, chymase, and tumor necrosis factor α (TNF- α). They also release newly synthesized inflammatory mediators such as platelet activating factor, nitric oxide, TNF- α , cyclooxygenase products of arachidonic metabolism (PGD₂), and lipoxygenase products of arachidonic metabolism (leukotrienes LTC₄, LTD₄ and LTE₄). Production of interleukin-4 (IL-4), IL-5, IL-13, and granulocyte macrophage colony-stimulating factor (GM-CSF) may continue for several hours (26). Fig. 1 depicts the key cells involved in sensitization and release of preformed modifiers after subsequent exposure to antigen.

Foods, medications, and venom continue to be leading causes of anaphylaxis. Regardless of the trigger, the release of the mediators of anaphylaxis can affect several organ systems, primarily the skin, gastrointestinal and respiratory systems, and sometimes with cardiovascular involvement. Each exposure to antigen is unique, and past episodes of anaphylaxis do not predict future events. Cutaneous symptoms may include flushing or morbiliform rash, pruritis, urticaria, and angioedema. Patients with atopic dermatitis may also experience exacerbation of these lesions. Gastrointestinal symptoms may be vague or dramatic. These symptoms include nausea, crampy abdominal pain, vomiting, and diarrhea. Anaphylaxis may affect either the upper or lower respiratory system or involve both. Common oral symptoms include pruritis of the lips, tongue, and palate, edema of the lips and tongue, and a metallic taste. Symptoms affecting the upper airway include nasal congestion, rhinorrhea, pruritis, and sneezing. Itching of the ears may also be present. Anaphylaxis presenting in the lower airway may present as itching or constriction of the throat, dysphonia or stridor, dysphagia, cough, shortness of breath, and chest tightness/pain. The cardiac signs and symptoms include lightheadedness or syncope, chest pain, dysrhythmia, and hypotension. Some women may experience low back pain or uterine contractions during anaphylaxis. Because symptoms of anaphylaxis can be subtle, some patients may experience a ‘feeling of impending doom’ or dread early in the event (6).

Identifying the trigger

While anaphylaxis may result from exposure to almost any foreign substance, most episodes have an identifiable trigger. Medications may trigger anaphylaxis either via IgE interactions or by direct mast cell stimulation (4). When medications are suspected of triggering anaphylaxis, a detailed history is invaluable. The timing of the reaction with ingestion or injection of the suspected agent as well as prior exposure may help identify the offending agent. Laboratory IgE evaluations for most medications are unavailable (27). Skin testing to penicillin is once again available and its judicious use may aid diagnosis. Given lack of exposure and level of patient impairment, anaphylaxis during surgery may be identified only after cardiac symptoms arise. Anesthetic-induced anaphylaxis occurs between 1:3500 and

1:20,000 cases with mortality in up to 4% of cases (27–29). Envenomation continues to be a cause of rapid and fatal anaphylaxis. Most fatal events occur on first sting exposure, and up to 96% of fatal reactions begin within 30 minutes of the sting (30, 31). Exercise has been demonstrated to induce anaphylaxis, although the pathogenesis of exercise-induced anaphylaxis (EIA) is not known (32). At least one study suggests that up to 50% of episodes of EIA are related to food ingestion prior to the exercise (33). In children, foods are the most common trigger of anaphylaxis requiring emergency services (34). While most food-induced reactions are not fatal, the majority of fatal reactions occur in persons with a previous history of food-induced anaphylaxis (35). Idiopathic anaphylaxis remains a diagnosis of exclusion. As with other forms of anaphylaxis, the true incidence of idiopathic anaphylaxis is unknown, but some suggest that 6% to 31% of anaphylaxis cases remain without an identified trigger (36, 37).

In some cases, the clinical diagnosis of anaphylaxis may be confirmed with laboratory testing. Serum tryptase and plasma histamine levels may suggest anaphylaxis while neither test is specific to anaphylaxis. Additionally, sample collection and handling may affect the validity of the results (4, 20, 38). Comparing serial measurements of total tryptase to the patient baseline level may prove more helpful in diagnosing anaphylaxis than reliance on a single acute measurement (39, 40). As indicated above, the history of the event holds a central role in the identification of possible triggers. The history should include at minimum the suspected trigger with dose size, the timing and route of exposure, the timing, sequence, and duration of symptoms, the timing and response to interventions and associated events (e.g. exercise or co-administration of medications). If possible, medical records of the acute event should be evaluated to confirm the history. The careful history can then guide additional testing in order to confirm the presumptive trigger. Skin testing with commercial extracts to foods or venom should be performed with validated instruments and techniques. Results should be recorded so that the method of testing and source of the test sample are easily identifiable (4, 20, 38, 40–42). Skin testing may be unreliable in the 3 to 4 weeks immediately following anaphylaxis, and negative results should be repeated (43, 44). While both skin prick and intradermal testing is often required for the evaluation of venom-induced anaphylaxis, intradermal testing should be avoided in suspected food allergy because they lack specificity (high rate of false-positive tests) and the potential for inducing anaphylaxis during testing (42, 44, 45). *In vitro* evaluation of allergen-specific IgE may be utilized for confirmation of allergy. Predictive serum IgE levels for positive (failed) or negative (successful) oral food challenges for certain foods have been determined. Using the ImmunoCAP (Phadia, Uppsala, Sweden), a positive predictive value greater than 95% of a failed food challenge has been defined for cow's milk (≥ 15 kU/L), egg (≥ 7 kU/L), peanut (≥ 14 kU/L), tree nut (≥ 15 kU/L), and fish (≥ 20 kU/L) (46, 47). In children and infants less than 2 years of age, the 95% predictive value of ≥ 5 kU/L and ≥ 2 kU/L should be used for milk and egg respectively (48, 49). Lack of correlation between values generated by the several *in vitro* IgE systems may lead to inappropriate diagnosis or missed diagnosis when applying these established values using a system other than ImmunoCAP (46, 50).

Treating anaphylaxis

Management of anaphylaxis must focus on both acute events (to include possible biphasic reactions) as well as long term prevention of recurrence. While anaphylaxis accounts for a small number of ambulance dispatches and emergency department visits, prompt intervention remains important to positive outcomes (37, 51). Expert panel recommendations confirm that treatment of anaphylaxis should include early administration of epinephrine (52, 53). Regardless of the cause of anaphylaxis, the expert panel sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) within the U.S. National Institutes of Health recommends that the cornerstone of management begin with

the following concurrent steps: (i) elimination of additional allergen exposure, (ii) intramuscular injection of epinephrine, and (iii) call for help (activate the code team in the hospital or the emergency medical system in the community). This should not delay the administration of epinephrine if available. After these interventions adjuvant interventions should be considered. Table 2 outlines the NIAID expert panel recommendation (53, discussed below).

The route of administration affects the peak levels of epinephrine after administration. Studies in children and adults not experiencing anaphylaxis demonstrated higher plasma epinephrine levels after intramuscular administration in the anterior-lateral thigh when compared to either sub-cutaneous administration or intramuscular administration in the deltoid (54, 55). When intravenous (IV) access is already established such as during surgical procedures, epinephrine may be delivered by this route. Physicians must remember the potential for lethal arrhythmia following IV epinephrine administration and monitor the patient accordingly (6). Patients in anaphylaxis experiencing respiratory symptoms should receive high flow oxygen and may benefit from inhaled β_2 -agonists (52). Unless contraindicated due to vomiting or breathing difficulties, patients should be positioned in a recumbent position with the legs elevated to maximize blood return from the extremities (56). Fatalities have been reported in patients after sudden change in position (e.g. from supine to standing) caused pooling of blood volume (57). Fluid resuscitation should be tailored to the clinical situation, but physicians should be prepared for aggressive resuscitation in cases of severe hypotension (58). While epinephrine remains the recommended, first line drug studies indicate that administration is often delayed or withheld in favor of antihistamines or corticosteroids (10, 11, 51, 59). Antihistamines are useful in treatment of urticaria, angioedema, and pruritis but remain second line treatment for anaphylaxis due to slower onset of action and little effect on blood pressure. Combination use of H_1 and H_2 blocking agents has been reported more effective than H_1 agents alone in reducing cutaneous symptoms of anaphylaxis (60). Corticosteroid use in other allergic disease has led to use in anaphylaxis, although no well controlled trials exists to support this use. Recent retrospective review of emergency department treatment of anaphylaxis indicates corticosteroid use is more frequent than epinephrine for the treatment of anaphylaxis (10, 11, 61). It has been argued that corticosteroid use may prevent prolonged or biphasic anaphylaxis (6). A recent Cochrane systematic review, however, found no evidence to support the use of corticosteroids in the acute management of anaphylaxis (62). Because of the risk of prolonged or biphasic reactions, a period of observation is recommended following treatment of anaphylaxis.

Food-induced anaphylaxis

The term 'food allergy' is commonly used to describe an immunologically mediated disease triggered by dietary foods. Although anaphylaxis may be triggered by virtually any food, the most common food triggers seen in the US include milk, egg, peanut, tree nut, shellfish, fish, wheat, and soy. Food allergy to preservatives, dyes, or other additives is uncommon to rare (63). Food allergy can vary with geography. Sesame allergy is relatively uncommon in the United States, yet it continues to be a major allergen in Israel and other parts of the world. Studies to define the prevalence of food allergy have proven to be as difficult as defining the prevalence of anaphylaxis in general. Surveys that elicit self-reported food allergy indicate a prevalence of 3% to 35% of respondents have a food allergy of some type. This is in contrast to studies using oral food challenges (OFC) to identify food allergy. The prevalence of food allergy identified by OFC ranges between 1% and 10.8% (64). Food allergy prevalence also changes with age. Food allergy is the most common trigger of children presenting with anaphylaxis (34). Studies from North America as well as the United Kingdom indicate that peanut allergy has doubled, exceeding 1% of school-aged children

(65). A 2008 report from the US Centers for Disease Control and Prevention indicated an 18% increase in childhood food allergy during the decade 1997 to 2007. An estimated 3.9% of US children are affected by food allergy. Death from food allergy has primarily been reported after ingestion of peanut or tree nuts. Fatal reactions are also associated with delayed or lack of treatment with epinephrine. The victims tend to be teenagers or young adults with asthma in whom the diagnosis of food allergy had previously been made (66).

Although the morbidity of food anaphylaxis is low and mortality is exceedingly rare, current treatment significantly impacts activities of daily life and the quality of life (67, 68). Most food allergy reactions occur in early childhood. While some food allergies resolve with age others persist. An estimated 80% of children with anaphylaxis to milk or egg are able to tolerate ingestion by age 16 years (69, 70). Peanut allergy, traditionally thought life-long, may spontaneously resolve for up to 20% of children by elementary school age (65). Recurrence of peanut allergy has also been reported following successful OFC without continued exposure in the diet (65).

Current therapy for food allergy is not curative. Because the impact of food allergy on patients and their family is significant, accurate diagnosis is important. The diagnosis of food allergy does not differ from that outlined above for other forms of anaphylaxis. While skin prick testing and *in vitro* IgE measurements provide information about food sensitization, an OFC may be necessary to determine tolerance to a food. The OFC consists of gradually increasing servings of the suspected food. Close medical supervision is required, and the OFC should be performed in a location properly equipped and staffed with personnel adequately trained to recognize and treat anaphylaxis. While either an open OFC or single-blind OFC is commonly used to screen for reactions, a double-blind, placebo-control OFC (DBPCFC) remains the gold standard in the diagnosis of food allergy (71). To rule out false negative challenges, a DBPCFC should be followed by an open feeding of the suspected food, again in a controlled setting (72).

Once food-triggered anaphylaxis has been recognized, the primary therapy is avoidance of the identified food. Patients, families, and caregivers must be educated to carefully read food labels when preparing meals and evaluate the safety of foods obtained from restaurants. Education should include information about cross-contamination of food during preparation (e.g. cutting boards or mixing bowls). Recent changes in food-labeling laws in the United States now require simple English terms (e.g. 'milk' instead of 'casein') to indicate the presence of specific foods. The law applies only to milk, egg, wheat, soy, peanut, tree nut, fish, and shellfish, and other allergens may be difficult to identify in processed foods. Patients and caregivers should be encouraged to obtain medical identification jewelry. Patients and caregivers must be educated to identify symptoms of anaphylaxis and trained to respond when symptoms arise. A personalized, written action plan can aid families prepare a response to accidental ingestions (73). The contents of the written action plan may differ by provider. Table 3 provides an outline of information that should be included in a written food allergy plan.

Food allergy has significant impact on the quality of life and activities of daily living. Families report disruption of family social events, school field trips, parties, sleepovers, and play dates with friends (68). Many parents would rather minimize the anxiety by avoiding such social activities altogether, restricting their child's attendance at parties and school trips (74, 75). Children with food allergy also report anxiety with regard to possible allergen exposure. Shopping, eating out, or birthday parties can be frightening for children who may perceive such activities as life threatening (68, 76). Because past reactions cannot predict the severity future reactions, patients with food allergy and their families worry that the next exposure may result in mortality. Food allergy is already the leading cause of anaphylaxis in

the community setting and the incidence is on the rise (15). Avoidance of identified foods allergens will prevent anaphylaxis but accidental exposures continue to occur.

Investigational therapeutic interventions

Investigational treatment of food-induced anaphylaxis continues to show promise for managing the disease. Interventions have included subcutaneous immunotherapy (SCIT), oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). Additionally interventions using traditional Chinese medicine (TCM) or monoclonal antibodies offer the promise of future therapeutic interventions.

Subcutaneous immunotherapy

Subcutaneous immunotherapy for anaphylaxis has been successfully used for pollen allergy for over 100 years. Initial trials of SCIT for peanut allergy demonstrated that patients were able to achieve desensitization. During the studies, patients experienced frequent anaphylaxis after vaccine administration with one fatality following a dosing error.(77, 78) Only 3 of 6 patients were able to reach the intended maintenance dose due to adverse reactions. Systemic reactions were seen in 39% of doses.(78) Although SCIT demonstrated the ability to desensitize peanut allergic patients the risk of unpredictable, severe reactions discouraged additional investigation using this method.

Oral immunotherapy

The use of oral immunotherapy did not lag far behind subcutaneous immunotherapy. Egg was used successfully in 1908 (79). Currently oral immunotherapy represents the most active area of investigation. As with subcutaneous immunotherapy, desensitization to food has been demonstrated, but no studies have been able to demonstrate the development of tolerance. Clinical oral immunotherapy trials have been reported for peanut, milk, and egg. Patients receiving oral immunotherapy often experience symptoms of anaphylaxis during therapy (80–85). While most adverse reactions were mild, several studies reported the use of epinephrine to treat study induced symptoms (80, 81, 85). In contrast to subcutaneous immunotherapy administration in the research clinic, patients receiving oral immunotherapy self-administer multiple doses of allergen at home. The initial desensitization and dose escalation for oral immunotherapy take place in a controlled clinical setting. The allergen is administered in a vehicle food that is known to be safe for the patient. Although desensitization has been demonstrated following oral immunotherapy, some patients re-developed symptoms of anaphylaxis after discontinuing regular intake of the food (86). This finding highlights the importance of frequent exposure following desensitization, although the frequency of exposure remains unknown.

Sublingual immunotherapy

Kiwi pulp extract was the first sublingual immunotherapy reported in 2003 in a woman with kiwi-induced anaphylaxis (87). Patients have also participated in sublingual immunotherapy clinical trials to hazel nut, milk, peach, and peanut (88–91). In sublingual immunotherapy, increasing amount of allergen is placed under the tongue daily and held for a specified time. The extract is then either swallowed or expectorated. In one hazel nut study, local reactions were observed in more than 7% of doses. These were generally mild and restricted to the oral pruritis. Systemic reactions were seen in only 0.2% of doses and confined to the build up phase of the study. None of these reactions required treatment with epinephrine. After 5 months on therapy, the treatment group saw significant increase in the amount of hazel nut tolerated during OFC, while the control group did not (88, 89). An uncontrolled milk sublingual immunotherapy trial demonstrated increased tolerance to milk during OFC

following 6 months of therapy. Children escalated to 1 mL of milk daily, with 7 of 8 children completing the study. One child withdrew due to persistent oral symptoms (90). Although symptoms during sublingual immunotherapy were frequent and occasionally led to patient withdrawal from therapy, sublingual immunotherapy offers hopeful therapy with mild side effects. Additional studies will refine the dose required and length of therapy.

Epicutaneous immunotherapy

The first study of the epicutaneous delivery of antigen for milk allergy in children was recently completed in France. Eighteen children (ages 3 months to 15 years) with symptoms consistent with milk allergy and a positive OFC were treated for 90 days. Treatment consisted of 1 mg skim milk powder under an epicutaneous delivery system (EDS) applied to the back for 48 h. Placebo EDS contained 1 mg glucose. The EDS was changed 3 times each week. No severe reactions resulted, but local skin symptoms were reported in both placebo and treatment groups. After three months, epicutaneous immunotherapy-treated children demonstrated a mean increased dose tolerated on OFC compared to the placebo group (mean tolerated dose of 1.8 mL at baseline to 23.6 mL after 90 days). Although the placebo group did not change the tolerated dose (mean tolerated dose of 4.4 mL at baseline to 5.4 mL after 90 days). Neither group demonstrated a decrease in serum milk IgE after 3 months (92). Although the increased tolerance during milk OFC in the treatment group did not significantly increase over the control, the EDS was well tolerated in this small study. Additional studies of longer duration are needed to assess whether or not epicutaneous immunotherapy will induce changes seen with OIT or SLIT.

Traditional Chinese medicine

While the use of herbs in TCM dates back centuries, their use in food allergy is novel. The initial study utilized a formulation of 11 traditional Chinese herbs (FAHF-1) in a murine model of peanut anaphylaxis. FAHF-1 protected peanut-allergic mice from peanut-induced anaphylaxis (93). Subsequent trials with a simplified formulation of 9 herbs (FAHF-2) demonstrated inhibition of food-induced anaphylaxis 5 months after treatment (94). Even at the highest doses, no adverse affects were observed in the mice (93). A phase I trial in 19 subjects demonstrated that FAHF-2 was safe and well tolerated in humans (95). Future studies are anticipated to evaluate the effectiveness of TCM herbal formulations with humans.

Monoclonal antibodies

Monoclonal antibodies that bind to the constant region of the IgE molecule have been engineered. Once bound by monoclonal antibodies, IgE is unable to bind to the high affinity Fc RI receptor expressed on mast cell and basophils as well as low affinity Fc RII receptors on B cells and antigen-presenting cells. Decreasing free serum IgE also downregulates the expression of Fc RI leading to decreased activation of mast cells and basophils with decreased release of histamine and other inflammatory mediators associated with anaphylaxis (96). Peanut allergic patients treated with a humanized monoclonal anti-IgE murine IgG antibody showed a dose response with significant improvement in OFC peanut intake only in the group receiving the highest anti-IgE antibody dose (97). A study of omalizumab (Xolair®) in peanut allergic patients was halted following two severe allergic reactions during initial screening, which raised significant safety concerns. The use of anti-IgE monoclonal antibodies in combination with allergen-specific therapy has been evaluated in pollen allergy and future study may offer additional therapeutic options for food allergy (98).

Not ready for prime time players

Advances in clinical trials have spurred debate on timing of transition from research trials to the clinic. Some have suggested that OIT for food allergy move into mainstream as SCIT has for allergic rhinitis due to pollen allergy. It is argued that subcutaneous immunotherapy, with the inherent risk of anaphylaxis, is standard treatment for allergic rhinitis. Allergic rhinitis is not fatal, yet we routinely administer therapy that risks a fatal reaction (99). Others argue that subcutaneous immunotherapy for aeroallergen sensitivity and coronary artery bypass grafting became routine prior to randomized clinical trials. Subsequent trials would only refine the procedure (100). The guiding principle of medicine is to do no harm. Current therapy with oral immunotherapy or sublingual immunotherapy in the clinical setting places patients at risk of adverse reactions during the initiation of therapy as well as the risk of significant adverse reactions to doses at home without the benefit of established optimal dosing guidance or optimal length of therapy. The clinical research underway will continue to refine treatment of food-induced anaphylaxis providing realistic expectations of safety and efficacy.

Conclusion

Anaphylaxis is an immediate systemic reaction caused by rapid, IgE-mediated release of potent immune mediators from tissue mast cells and peripheral basophils which may be triggered in many ways (5). The incidence of anaphylaxis is increasing and food-induced anaphylaxis is the leading cause of anaphylaxis presenting for emergency treatment. Current treatment recommendations include avoidance of the offending food and use of intramuscular epinephrine with accidental exposure. Studies have indicated that education of patients as well as healthcare workers is needed to increase compliance with these recommendations. Current research offers the promise of therapeutic options including oral immunotherapy, sublingual immunotherapy, epicutaneous immunotherapy, and TCM, however, at currently the optimal therapeutic dose and length of treatment is undefined.

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1. .

Table 1**Criteria for anaphylaxis.**

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

- 1** Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (eg. generalized hives, pruritis, or flushing, swollen lips-tongue-uvula) **AND AT LEAST ONE OF THE FOLLOWING**
 - a.** Respiratory compromise (eg. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - b.** Reduced BP or associated symptoms of end-organ dysfunction (eg. hypotonia (collapse), syncope, incontinence)
- 2** Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a.** Involvement of the skin, mucosal tissue or both (eg. generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b.** Respiratory compromise (eg. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c.** Reduced BP or associated symptoms of end-organ dysfunction (eg. hypotonia (collapse), syncope, incontinence)
 - d.** Persistent gastrointestinal symptoms (eg. crampy abdominal pain, vomiting)
- 3** Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
 - a.** Infants and children: low systolic BP (age specific or greater than 30% decrease in systolic BP^{*})
 - b.** Adults: systolic BP less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure

^{*} Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + (2 × age)) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Taken from resource (6)

Table 2**Summary of the pharmacologic management of anaphylaxis (modified)**

Note: These treatments often occur concomitantly, and are not meant to be sequential, with the exception of epinephrine as first-line treatment.

- In the outpatient setting
 - First-line treatment:
 - ◆ Epinephrine, IM; auto-injector or 1:1,000 solution
 - Weight 10 to 25 kg: 0.15 mg epinephrine autoinjector, IM (anterior-lateral thigh)
 - Weight >25 kg: 0.3 mg epinephrine autoinjector, IM (anterior-lateral thigh)
 - Epinephrine (1:1,000 solution) (IM), 0.01 mg/kg per dose; maximum dose, 0.5 mg per dose (anterior-lateral thigh)
 - ◆ Epinephrine doses may need to be repeated every 5–15 minutes
 - Adjunctive treatment:
 - ◆ Bronchodilator (β_2 -agonist): Albuterol
 - MDI (child: 4–8 puffs; adult: 8 puffs) or
 - Nebulized solution (child: 1.5 ml; adult: 3 ml) every 20 minutes or continuously as needed
 - ◆ H₁ antihistamine: diphenhydramine
 - 1 to 2 mg/kg per dose
 - Maximum dose, 50 mg IV or oral (oral liquid is more readily absorbed than tablets)
 - Alternative dosing may be with a less-sedating second generation antihistamine
 - ◆ Supplemental oxygen therapy
 - ◆ IV fluids in large volumes if patient presents with orthostasis, hypotension, or incomplete response to IM epinephrine
 - ◆ Place the patient in recumbent position if tolerated, with the lower extremities elevated
- In the hospital-based setting
 - First-line treatment:
 - ◆ Epinephrine IM as above, consider continuous epinephrine infusion for persistent hypotension (ideally with continuous non-invasive monitoring of blood pressure and heart rate); alternatives are endotracheal or intra-osseous epinephrine
 - Adjunctive treatment:
 - ◆ Bronchodilator (β_2 -agonist): albuterol
 - MDI (child: 4–8 puffs; adult: 8 puffs) or
 - Nebulized solution (child: 1.5 ml; adult: 3 ml) every 20 minutes or continuously as needed
 - ◆ H₁ antihistamine: diphenhydramine
 - 1 to 2 mg/kg per dose
 - Maximum dose, 50 mg IV or oral (oral liquid is more readily absorbed than tablets)
 - Alternative dosing may be with a less-sedating second generation antihistamine
 - ◆ H₂ antihistamine: ranitidine
 - 1 to 2 mg/kg per dose
 - Maximum dose, 75 to 150 mg oral and IV
 - ◆ Corticosteroids

- Prednisone at 1 mg/kg with a maximum dose of 60 to 80 mg oral or
 - Methylprednisolone at 1 mg/kg with a maximum dose of 60 to 80 mg IV
 - ◆ Vasopressors (other than epinephrine) for refractory hypotension, titrate to effect
 - ◆ Glucagon for refractory hypotension, titrate to effect
 - Child: 20–30 mg/kg
 - Adult: 1–5 mg
 - Dose may be repeated or followed by infusion of 5–15 mg/min
 - ◆ Atropine for bradycardia, titrate to effect
 - ◆ Supplemental oxygen therapy
 - ◆ IV fluids in large volumes if patients present with orthostasis, hypotension, or incomplete response to IM epinephrine
 - ◆ Place the patient in recumbent position if tolerated, with the lower extremities elevated
- Therapy for the patient at discharge
- First-line treatment:
 - ◆ Epinephrine auto-injector prescription (2 doses) and written instructions
 - ◆ Education on avoidance of allergen
 - ◆ Follow-up with primary care physician
 - ◆ Consider referral to an allergist
 - ◆ Adjunctive treatment:
 - H₁ antihistamine: diphenhydramine every 6 hours for 2–3 days; alternative dosing with a non-sedating second generation antihistamine
 - H₂ antihistamine: ranitidine twice daily for 2–3 days
 - Corticosteroid: prednisone daily for 2–3 days

Abbreviations: IM, Intramuscular; IV, intravenous; MDI, metered-dose inhaler.

Presented in NIAID report(53)

Table 3

Food allergy action plan.

1	Should contain
	<ul style="list-style-type: none">a. Patient name and demographicsb. Identified triggers of anaphylaxisc. Information to identify signs and symptoms of anaphylaxisd. Dose of epinephrine and route of administration—a clear statement to administer without hesitatione. Emergency management<ul style="list-style-type: none">i. Recognition of symptomsii. Interventions to initiate—with an emphasis on epinephrine administrationf. Emergency service activation numbers
2	May contain
	<ul style="list-style-type: none">a. Location of medication storage at home, at school or in the workplaceb. Date of epinephrine auto-injector expirationc. List of personnel trained on epinephrine auto-injector use