Anaphylaxis: Present Understanding and Future Therapies

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December 8, 2006

Biographical Sketch:

Dr. Gruchalla received a Ph.D. and a medical degree from UT Southwestern Medical Center at Dallas. After completing internal medicine training at the Hospital of the University of Pennsylvania and allergy and immunology training at UT Southwestern, she joined the UT Southwestern faculty. Currently, she is professor of internal medicine and pediatrics and director of the division of allergy and immunology in both departments. Dr. Gruchalla's initial research focus was in the area of drug allergy. However, her efforts are now directed towards pediatric asthma. Her group is involved in both clinical and mechanistic research activities in this area. Dr. Gruchalla was one of the principal investigators of the NIAID-sponsored Inner City Asthma Study and currently she is the principal investigator of the Dallas site for the NIAID-sponsored Inner City Asthma Consortium.

Dr. Gruchalla has numerous publications in the areas of drug allergy and pediatric asthma. She is active in the American Academy of Allergy, Asthma and Immunology and serves on the Board of Directors of this organization. In addition, she also serves on the Board of Directors of the American Board of Allergy and Immunology and the Editorial Board of the Journal of Allergy and Clinical Immunology.

History

In the early 1900's, Charles Richet and Paul Portier, both French physicians, participated in an oceanographic expedition led by Prince Albert I of Monaco. The purpose of the cruise was to perform studies on the actinotoxin found in the tentacles of *Physalia physalis,* the Portuguese man-of-war. The hope was that, through isolation of the toxin, a protective antiserum could be developed for vacationing bathers stung by these creatures. The experiments were based upon the premise of vaccination: exposure to a weak form of a disease leads to immunity or protection upon subsequent re-exposure to more virulent forms of the same disease.

Figure 1. Location of initial experimental studies

To the surprise of both scientists, their attempt to vaccinate dogs did not lead to protection or "prophylaxis" against the toxin. In contrast, a horrible event occurred. One of the dogs, Galathee who had received an initial injection of a "weak" dose of actinotoxin on January 14, 1902 proceeded to have a violent reaction when another dose of actinotoxin was administered on February 10th. Portier later reported, "February 10th, it [Galathee] is in perfect health…0.12 cc/kg of actinotoxin was injected. Immediately produced vomiting of mucous and blood, some bloody defecation and very marked stupor. These symptoms became worse in the following hours, and it died in the night." [1]

Richet, who coined the term anaphylaxis ("against protection") to describe the phenomenon he and Portier had witnessed, later received the Nobel Prize in 1913 for this discovery. He commented in his acceptance speech that the discovery was essentially accidental. He remarked, "[The discovery of anaphylaxis] is not at all the result of deep thinking, but of simple observation, almost accidental, so that I have no other merit than that of not refusing to see the facts which presented themselves before me, completely evident." [2]

Epidemiology of Anaphylaxis

While anaphylaxis is a severe life-threatening event, its incidence is still not clearly known. In order to gather data on the epidemiology of anaphylaxis, Yocum and colleagues [3] performed a retrospective population-based cohort study of 1255 Olmsted County residents from 1983 through 1987. Each of these individuals had had either anaphylaxis or another type of allergic reaction documented in their medical record. The goal of the study was to determine the

incidence and rate of occurrence of anaphylaxis, the prevalence of atopy in these cases, the cause of anaphylaxis and the case-fatality rate. Identification of anaphylaxis was based upon both signs and symptoms of generalized mast cell mediator release (e.g., flushing, pruritus, urticaria, angioedema, conjunctivitis/chemosis) and the involvement of one or more organ system (oral/gastrointestinal tract, respiratory system or cardiovascular system). Isolated laryngeal edema or immediate shock after the injection of a medication or radiocontrast agent also were classified as anaphylactic events.

One hundred thirty three residents experienced 154 episodes of anaphylaxis during the 5 year study period. The average incidence rate (number of Olmsted County residents with a first lifetime episode of anaphylaxis during the specific 5-year period/number of Olmsted County person-years) was 21 per 100,000 person-years (95% CI, 17-25 per 100,000 person-years). The average occurrence rate (number of episodes of anaphylaxis in Olmsted County residents during the 5-year period/number of Olmsted County person-years) was 30 per 100,000 person-years (95% CI, 25-35 per 100,000 person-years). Fifty-three percent of the cohort were atopic and in 68%, the suspect allergen was identified [food (36%), medication (17%) an insect sting (15%)]. The fatality rate for all episodes of anaphylaxis during the period studied was 0.65% (1 in 154).

More recently, Bohlke and colleagues [4] evaluated the incidence of anaphylaxis in a population of children and adolescents enrolled in a health maintenance organization. Using the most specific codes for anaphylaxis (995.0, 995.4, 995.6, 999.4), the incidence rate was found to be 10.5 per 100,000 person-years (95% CI, 8.1-13.3 per 100,000 person-years). However, upon randomly evaluating other medical records that contained related codes not specific for anaphylaxis, it was found that a large number of these events (371/559) were likely anaphylactic in nature as well. Inclusion of these codes increased the estimated incidence rate from 10.5 per 100,000 person-years (using specific codes only) to 68.4 per 100,000 person-years (95% CI, 5.1-917.6 per 100,000 person-years) (using both specific and related codes). The authors felt that the discrepancy between these two values reflected two important things, that either anaphylaxis is not being recognized by providers and/or that it is not being properly diagnosed.

Definition of Anaphylaxis

While anaphylaxis typically is not difficult to diagnose, its presentation, at times, may be enigmatic with variable symptoms and degrees of organ involvement. Thus, it often incorrectly diagnosed or miscoded as another type of clinical process. Because of these issues and because a consensus definition of this disease has not existed, a multidisciplinary Symposium on the Definition and Management of Anaphylaxis was convened so that experts in different disciplines could meet and develop a definition, treatment strategies and research objectives for this disease [5, 6].

The group that gathered included allergists/immunologists, family practitioners, pediatricians, internists, emergency physicians and anesthesiologists. Their intent was to develop a working definition of anaphylaxis that would be useful for the various types of healthcare personnel who may be faced with diagnosing and treating persons presenting with this disease. Moreover, the group wanted a definition that was clinically-, not mechanistically-, based and that was composed of readily identifiable signs and symptoms.

Some of the participants thought that the definition should be simple, aimed at high sensitivity. In contrast, others felt that a simple definition would not capture all persons with anaphylaxis and that a simple definition would come with an unacceptable number of false-positive diagnoses. A compromise was reached between these two viewpoints and a working definition comprised of three criteria was proposed. It was thought that if a patient presents with 1 of the 3 criteria outlined in Table 1, he/she is likely to have anaphylaxis.

Table 1. Clinical criteria for diagnosing anaphylaxis [6]

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to hours with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus, 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 (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 (eg, hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *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 of 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 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Pathophysiology of Anaphylactic and Anaphylactoid reactions

Anaphylaxis results from the generalized release of mediators from basophils and mast cells. Cellular activation and degranulation occurs when high-affinity IgE receptors (FcεRI) on these cells become aggregated after allergen-driven IgE cross-linking. The initial production of allergen-specific IgE antibodies is dependent upon both genetic and environmental factors. For anaphylaxis (and other allergic reactions) to occur, the allergen must cross an epithelial and/or endothelial barrier, typically after it has been breached, and then interact with cell-bound IgE

antibodies [5]. The mediators that are then released affect numerous organ systems, most frequently, the skin, the respiratory tract, the cardiovascular system and the gastrointestinal tract.

In addition to IgE-mediated mechanisms, mast cells and basophils can be stimulated to release their mediators by non-IgE mediated processes. While the clinical signs and symptoms are identical to anaphylactic reactions, these generalized non-IgE-mediated reactions are termed "anaphylactoid" reactions. These reactions can be caused by direct mediator release, disturbances in arachidonic acid metabolism and by activation of the contact and complement systems (Table 2).

Table 2. Classification of anaphylactoid reactions [7]

Direct release of mediators from mast cells and basophils • Drugs (opiates and radiocontrast media) • Idiopathic • Physical factors (cold, heat, sunlight, exercise)
Disturbances in arachidonic acid metabolism • Aspirin • Nonsteroidal anti-inflammatory drugs
Activation of contact and complement systems

A myriad of mediators are released from mast cells and basophils during anaphylactic and anaphylactoid reactions and these account for the clinical effects seen. The mediators that play the most predominant role include histamine, the prostaglandins (PG) and the leukotrienes ($LTC_4/D_4/E_4$). Typically, the effects of these mediators are seen within minutes after allergen exposure. However, it is important to note that other patterns of anaphylaxis exist as well including delayed-onset, protracted and biphasic reaction patterns. The pathophysiologic and clinical of effects of these and other relevant mediators are shown in Table 3.

Table 3. Mast cell/Basophil mediators

Mediator	Pathophysiologic activity	Clinical Effect
Histamine	Smooth muscle contraction, vascular permeability, vasodilation, increased AV node conduction, prostaglandin generation, mucus production	Flushing, urticaria, angioedema, wheezing, hypotension, headache, nasal congestion
PGD_2	Peripheral vasodilation, coronary vasoconstriction, bronchoconstriction, basophil histamine release	Flushing, bronchospasm, hypotension, myocardial ischemia
$9\alpha 11\beta\text{-}PGF_2$	Vasopressor	Hypertension
$LTC_4/D_4/E_4$	Smooth muscle contraction, vascular permeability, mucus production	Bronchospasm, hypotension
Tryptase	Inactivates fibrinogen and VIP, increased airway hyperresponsiveness	Unknown
Chymase	Inactivates bradykinin, activates angiotensin I, activates angiotensin I, inactivates neuropeptides	Unknown

Heparin	Attenuates bronchoconstriction, inhibits complement, inhibits clotting cascade	Unknown
Nitric oxide	Peripheral vasodilation, bronchodilation	Unknown

Causes of Anaphylaxis

A retrospective medical-record evaluation of 601 patients who presented with anaphylaxis to a university-affiliated allergy-immunology practice revealed most of the cases (59%) to be idiopathic in origin [8]. Of those cases that had a known etiology, the most common causes were a food or a medication (Table 4). The most frequently implicated foods were shellfish, peanuts, food additives (or spices) and tree nuts, while the most frequently implicated drugs were aspirin, other nonsteroidal anti-inflammatory drugs and β-lactam antibiotics.

Table 4. Causes of anaphylaxis [8]

Cause	No. (%) of cases (N=601)
Idiopathic	356 (59%)
Food	131 (22%)
Medication	69 (11%)
Exercise	31 (5%)
Latex	6 (1%)
Catamenial	4 (1%)
Chrysops	3 (0.5%)
Triatoma	1 (0.2%)

Anaphylaxis Evaluation: Signs and Symptoms

A summary of the signs and symptoms of anaphylaxis was reported in the recently updated Anaphylaxis Practice Parameter [9]. In the Parameter, a review of published studies totaling 1865 patients was performed, and it was found that cutaneous manifestations were, by far, the most frequent presenting symptom (Table 5). However, while an absence of cutaneous symptoms goes against anaphylaxis, this diagnosis must still be considered if the index of suspicion is high. Up to 20% of cases of anaphylaxis in children with food or insect sting allergy occur in the absence of cutaneous symptoms [10, 11].

Table 5. Frequency of occurrence of signs/symptoms of anaphylaxis (1865 patients)[9]

Cutaneous	**90%**
• Urticaria and angioedema	85-90%
• Flushing	45-55%
• Pruritus without rash	2-5%
Respiratory	**40-60%**
• Dyspnea, wheeze	45-50%
• Upper airway angioedema	50-60%
• Rhinitis	15-20%
Dizziness, syncope, hypotension	**30-35%**

Abdominal • Nausea, vomiting, diarrhea, cramping pain	**25-30%**
Miscellaneous • Headache • Substernal pain • Seizure	 5-8% 4-6% 1-2%

During any evaluation of possible anaphylaxis, objective information about the event should be gathered. If friends or family members witnessed the event, they should be questioned about any signs or symptoms that were observed. The time of the occurrence, any treatment that was given and the duration of the event all should be recorded. In addition, a comprehensive list of potential causes should be made. This list should include: foods or drugs ingested, any possible stings or bites, and whether or not the event was related to exercise, exposure to heat or cold, or sexual activity. The atopic status of the person also should be assessed since food-induced anaphylaxis and idiopathic anaphylaxis are more common in atopic compared to nonatopic individuals [9]. In addition, since asthma has been shown to be a risk factor for fatal and near-fatal anaphylaxis [11], its presence should be noted as well.

While the majority of patients who present with signs and symptoms of anaphylaxis have had a true anaphylactic event, it is important to realize that other disorders may present with similar manifestations. Other disorders to consider in the differential diagnosis of anaphylaxis are outlined in Table 6.

Table 6. Differential diagnosis of anaphylaxis

Symptoms	Disorders
Collapse	Vasovagal, panic disorder, hyperventilation, arrhythmias, seizures, myocardial infarction, pulmonary embolus
Throat swelling	Globus hystericus, vocal cord dysfunction, epiglottitis
Multi-organ symptoms	Herediatary angioedema, scromboid poisoning, cold urticaria, cholinergic urticaria, Carcinoid syndrome, mastocytosis

Fatal and Near-Fatal Food-Induced Anaphylaxis

In 1992, Samson and colleagues [11]evaluated the characteristics of 13 children and adolescents who either died (6) or who had near-fatal (7) food-induced anaphylactic reactions. The reactions occurred over a 14 month period and the subjects studied were made known to the investigators by physicians, the patients' parents or local groups interested in allergic reactions. The characteristics of the group studied are shown in Table 7.

Table 7. Fatal and near-fatal food anaphylactic reactions [11]

Parameter	Fatal	Near-Fatal
Age	2-16 years (5F; 1M)	9-17 years (5F; 2M)
Asthma	6/6	7/7
Location	1/6 home (4/6 school)	7/7 home
Food	Peanut – 3, Egg – 1, Nut – 2	Nut – 4, Milk – 2, Peanut -1

Five of the six children who experienced a fatal reaction and six of the seven children who experienced a near-fatal reaction had experienced definite previous allergic reactions to the implicated food. In none of the fatal and near-fatal cases was the food knowingly ingested. All of the children had asthma and in the majority of them (12/13), it was considered to be well-controlled. The majority (4/6) of the fatal reactions occurred at school while all of the near-fatal reactions occurred at home. Peanut was implicated in 4 of the reactions; nut in 6, milk in 2 and egg in 1.

In all cases, the symptoms developed within 1-30 minutes after ingestion. All the children had respiratory symptoms and the majority had skin and gastrointestinal manifestations as well. In 6 of 13 children the reactions were either biphasic or protracted. While 6 of the 7 children who experienced near-fatal anaphylaxis received epinephrine within an hour after ingestion, only 2 of the 6 children who died received epinephrine within this time frame.

The results of this study led to the development, by the American Academy of Allergy, Asthma and Immunology (AAAAI) and the Food Allergy and Anaphylaxis Network (FAAN), of a food allergy registry. The purpose of the registry is to track the occurrence of food-induced anaphylactic reactions and to use this information to educate patients, parents, physicians, lawmakers and physicians about the prevention of these reactions.

Laboratory Evaluation of Anaphylaxis

In evaluating anaphylaxis (Table 8), the most helpful tests in establishing the diagnosis are serum tryptase and 24-hour urinary histamine metabolites. Plasma histamine levels are typically not very useful since they are elevated for only a short time. In contrast, urinary histamine and tryptase levels may be elevated for hours after the anaphylactic event.

Tryptase is a neutral protease that is present in mast cells but not basophils. There are two forms, α-tryptase, that is secreted constitutively, and β-tryptase, that is released only during mast cell degranulation. It is the β-tryptase form that rises during anaphylaxis and, since it peaks about 1 to 1 ½ hours after anaphylaxis, it is best to perform this test within two hours after the initiation of symptoms [12].

In addition to anaphylaxis, tryptase levels may be elevated in patients with systemic mastocytosis. However, in patients with this disorder, it is the α-tryptase form that is elevated. Since the elevation is caused by an increased mast cell burden, tryptase levels are consistently abnormal in these patients.

Tryptase determinations are available through commercial laboratories. However, because the antibody used in the assay (mAb B12) measures both α- and β-tryptase, only total tryptase levels are reported (normal < 15 ng/ml). Beta-tryptase-specific levels are available through the Medical College of Virginia and normal levels are < 1 ng/ml [13].

Table 8. Laboratory evaluation of anaphylaxis [9]

To be measured	Comment
Serum tryptase	Peaks 60-90 minutes after the onset of anaphylaxis; may persist for hours; may be negative in food-induced anaphylaxis
Plasma histamine	Increases within 5-10 minutes but remains increased for a short time only (30-60 minutes)
24-hour urinary histamine	Increased for up to 24 hours
Plasma-free metanephrine	To rule out a paradoxical response to a pheochromocytoma
Urinary vanillylmandelic acid	To rule out a paradoxical response to a pheochromocytoma
Serum serotonin	To rule out carcinoid
Urinary 5-hydroxyindoleacetic acid	To rule out carcinoid
Serum vasointestinal hormonal polypeptide panel (pacreastatin, pancreatic hormone VIP, substance P)	To rule out the presence of a vasoactive polypeptide-secreting gastrointestinal or a medullary carcinoma of the thyroid

Patients who have experienced anaphylaxis should be referred to an allergy/immunology specialist for further evaluation. Specific IgE antibodies should be assessed through prick skin testing or *in vitro* laboratory methods and management strategies should be derived. For insect venoms and certain foods and foreign proteins, valid skin test reagents are available. However, for most medications, including all of the antibiotics, no valid skin test reagents exist. In the case of food allergy, Sampson [14] has established diagnostic decision points for foods often implicated in food-induced anaphylaxis. The decision points are food-specific IgE levels that identify food-allergic patients who have a greater than 95% probability of reacting to a food challenge (Table 9). Thus, a milk-allergic patient with an IgE level above 15 kU_A/L would not need to undergo a milk challenge since it is greater than 95% likely that the child would have a positive reaction. If the level is less than 0.35 kU_A/L, and there is no compelling history of milk allergy, milk can be reintroduced at home. For levels between 0.35 kU_A/L and 15 kU_A/L, the allergy/immunology specialist should perform some type of milk challenge in the office to determine if the patient is truly allergic.

Table 9. Recommended interpretation of food-allergen-specific IgE levels (kU_A/L) in the diagnosis of food allergy [14]

	Egg	Milk	Peanut	Fish	Soy	Wheat
Reactive if ≥ (no challenge necessary)	7	15	14	20	65	80
Possibly reactive (MD challenge)					30	26
Unlikely reactive if < (home challenge*)	0.35	0.35	0.35	0.35	0.35	0.35

* In patients with a strongly suggestive history of an IgE-mediated food allergic reaction, food challenges should be performed with physician supervision, regardless of food-specific IgE value. If the food-specific IgE level is less than 0.35 kU_A/L and the skin prick test response is negative, the food challenge can be performed at home unless there is a compelling history of reactivity.

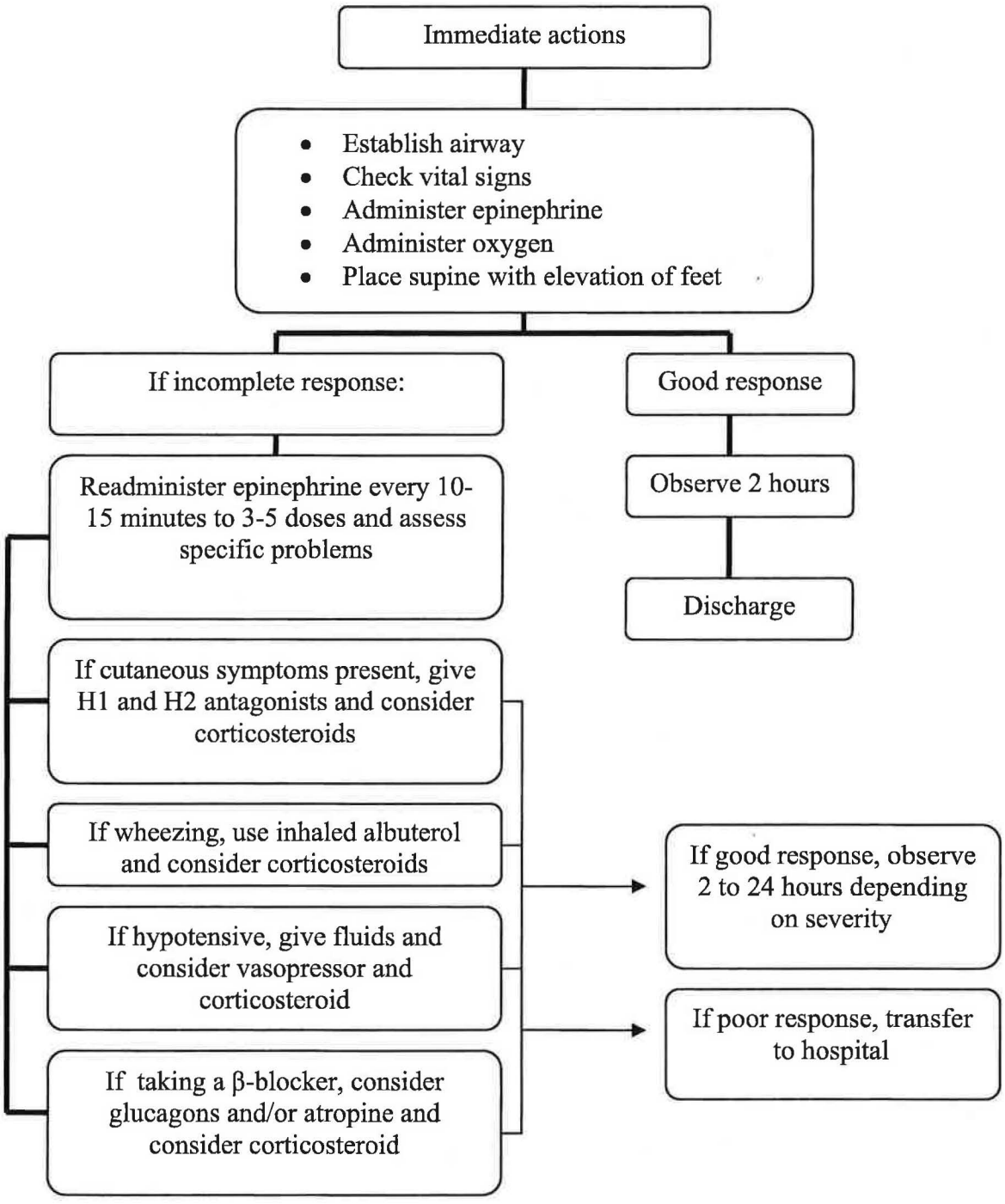
Management of Anaphylaxis

Initially, a person experiencing an anaphylactic event should be rapidly assessed for the adequacy of oxygenation, cardiac output and tissue perfusion and therapy should be directed at maintaining the airway and the circulatory system. Intramuscular epinephrine is the drug of choice [15]. Dosages for this drug and others used to treat anaphylaxis are outlined in Table 10 and an algorithm for acute treatment is presented in Figure 2.

Table 10. Drugs and other agents used to treat anaphylaxis [7]

Drug/agent	Dose and route of administration
Epinephrine	1:1000, 0.3-0.5 mL IM (adult); 1:1000, 0.01 mg/kg or 0.1-0.3 mL IM (child) 0.1-1.0 mL of 1:1000 aqueous epinephrine diluted in 10 mL normal saline IV (if no response to IM epinephrine and the patient is in shock)
Antihistamines	Diphenhydramine: 25-50 mg IM or IV (adult); 12.5-25 mg PO, IM, or IV (child) Ranitidine: 1 mg/kg IV or Cimetidine: 4 mg/kg IV
Corticosteroids	Hydrocortisone: 100 mg-1 g IV or IM (adult); 10-100 mg IV (child); for milder episodes, prednisone 30-60 mg may be given
Drugs for resistant bronchospasm	Aerosolized β-agonist (albuterol, metaproterenol): 0.25-0.5 mL in 1.5-2 mL saline every 4 hours as needed
Volume expanders	Crystalloids (normal saline or Ringer's lactate): 1000-2000 mL rapidly (adults); 30 mL/kg in first hour (child) Colloids (hydroxyethyl starch): 500 mL rapidly followed by slow infusion (adult)
Vasopressors	Dopamine: 400 mg in 500 mL; dextrose 5% in water as IV infusion; 2-20 mcg/kg/min
Drugs used in patients who are β-blocked	Atropine sulfate: 0.3-0.5 mg IV; may repeat every 10 min to a maximum of 2 mg (adult) Glucagon: Initial dose of 1-5 mg IV followed by infusion of 5-15 mcg/min titrated against blood pressure

Figure 2. Algorithm for management of anaphylaxis [7]

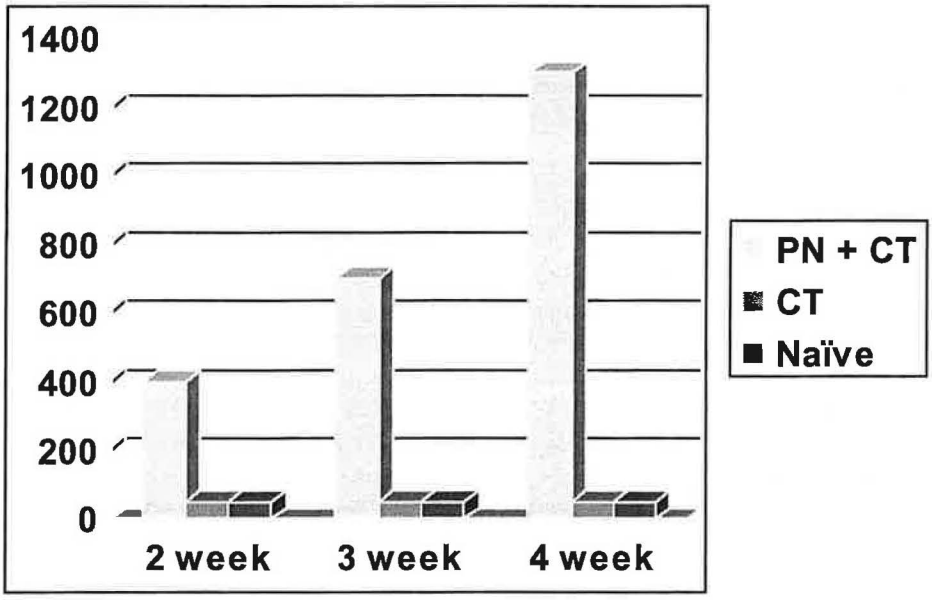


Murine Model of Anaphylaxis

In order to better understand the pathophysiology of peanut anaphylaxis and to devise and study new therapeutic strategies, Li and colleagues [16] developed a murine model of peanut anaphylaxis. Since animals tend to demonstrate immunologic tolerance to ingested antigens, cholera toxin, a known activator of Th2 cells and promoter of IL-4 and IgE antibody production [17, 18], was incorporated into the sensitization protocol. C3H/HeJ mice were sensitized via intragastric gavage with 5 mg of ground whole peanut (PN) along with 10 μg/mouse of cholera toxin (CT) on day 0 and again on day 7. Three weeks later the mice were challenged with 10 mg of crude peanut extract (CPE).

As shown in Figure 3, PN-specific IgE antibodies increased over time in mice that were sensitized to PN in the presence of CT.

Figure 3. Levels of peanut-specific IgE levels at various times after sensitization [16]



Anaphylactic symptoms that occurred after challenge were evaluated using a scoring system that is presented in Table 11 (score of 0: no symptoms; score of 5: death). Initial symptoms consisted of puffiness around the eyes and mouth and diarrhea. These were then followed by more severe symptoms such as labored breathing and cyanosis. The mean anaphylaxis score, in the 16 mice that were initially sensitized with 5 mg of PN + CT, was 3.43 with 12.5% of the animals dying.

Table 11. Murine model of anaphylaxis: Scoring system [16]

0: No sign of a reaction
1: Scratching and rubbing around the nose and head
2: Decreased activity with an increasing respiratory rate
3: Labored respiration and cyanosis around the mouth and tail
4: Slight or no activity after prodding, or tremors and convulsion
5: Death

In addition to establishing an animal model for peanut anaphylaxis, this study demonstrated numerous similarities between mouse and human anaphylaxis. The investigators showed that T cell proliferative responses could be generated in the mouse, not only to crude peanut allergen, but also to Ara h1 and Ara h2, the major peanut allergens in humans. In addition, mice were found to produce Ara h1 and Ara h2-specific IgE antibodies that recognized similar Ara h epitopes as human-derived IgE antibodies [16].

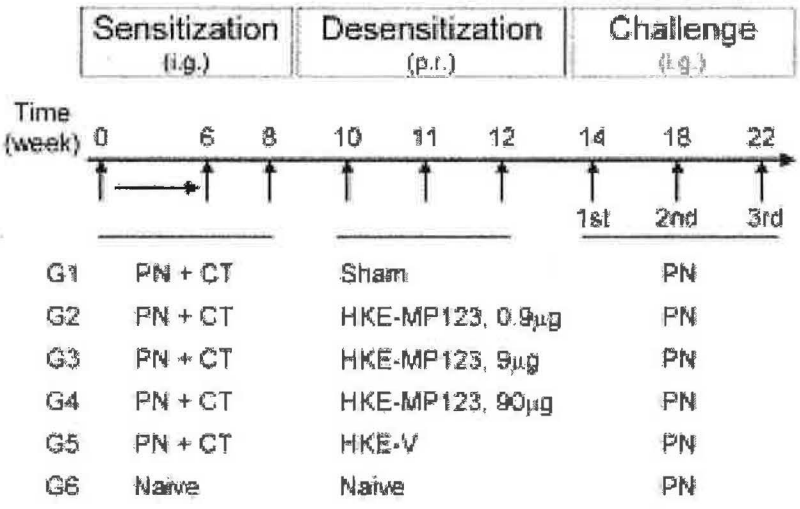
Future Therapies

While antigen-specific immunotherapy is routinely used for the treatment of allergic rhinitis and bee sting allergy, an unacceptable reaction rate was observed in a trial of rush immunotherapy in patients with peanut allergy [19]. Thus, alternatives forms of immunotherapy were sought for patients with food allergy and anaphylaxis.

In 2003, Li and colleagues [20] developed and studied engineered or mutated peanut proteins in their murine model. Ara h1, Ara h2 and Ara h3 were modified in such a way that IgE binding, and thus allergic reactions, were reduced. The investigators showed that subcutaneous administration of these modified proteins, (mAra-h123) along with a bacterial adjuvant known to enhance Th1 responses (heat-killed *Listeria monocytogenes* [HKLM]), led to reduced histamine levels and anaphylactic symptom scores in PN-sensitized mice (compared to sham-treated mice) after PN challenge.

Since the engineered proteins were produced in *E coli*, an adjuvant thought to promote Th1 responses, the group then decided to examine the long-term protective effect of per rectally administered heat-killed-*E coli*-(HKE)-producing mAra h1, 2, and 3 (HKE-MP123) in the treatment of peanut allergic mice [21]. The protocol that was used is presented in Figure 4.

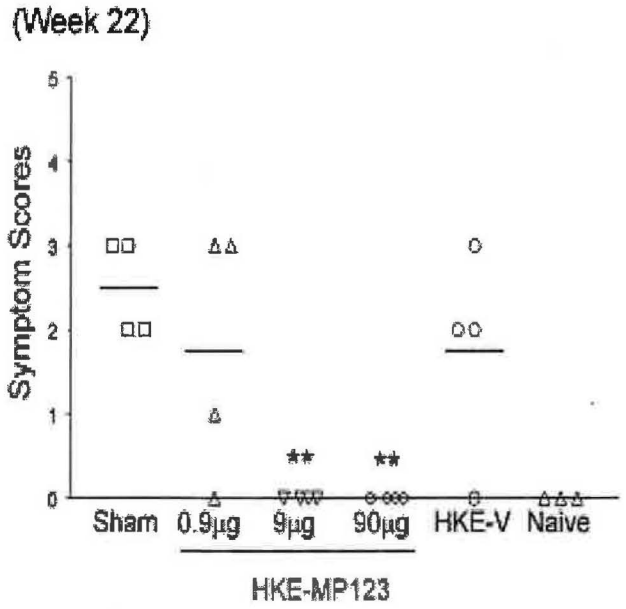
Figure 4. Experimental protocol [21]



Mice were first sensitized intragastrically, over an 8-week period, with grounded whole PN together with cholera toxin. On week 10, treatment was initiated. There were six different groups of 12 mice each: group 1 – received sham treatment only; group 2 – received 0.9 μg HKE-MP123 (low dose) PR; group 3 - received 9 μg HKE-MP123 (medium dose) PR; group 4 - received 90 μg HKE-MP123 (high dose) PR; group 5 – received HKE vector only and group 6 were neither sensitized nor treated. All mice were challenged 2, 6 and 10 weeks after therapy had been terminated (weeks 14, 18 and 22, respectively). Four mice were killed after each challenge and blood and tissue samples evaluated.

After the first challenge (week 14), all 3 HKE-MP123-treated groups demonstrated significantly lower anaphylactic symptoms scores compared to the sham-treated group. No dose response difference was noted among the three groups after the first challenge. However, after the second and third challenges, only those animals that received the medium and high doses of HKE-MP123 were protected from anaphylaxis (Figure 5). Thus, using this strategy, these investigators showed that prolonged protection against peanut anaphylaxis can be achieved in an animal model of anaphylaxis. More recently, this group has demonstrated that a certain Chinese herbal medicine (food allergy herbal formula [FAHF]-2) also prevents anaphylaxis in previously sensitized mice and that the protection persists weeks after the discontinuation of therapy [22, 23].

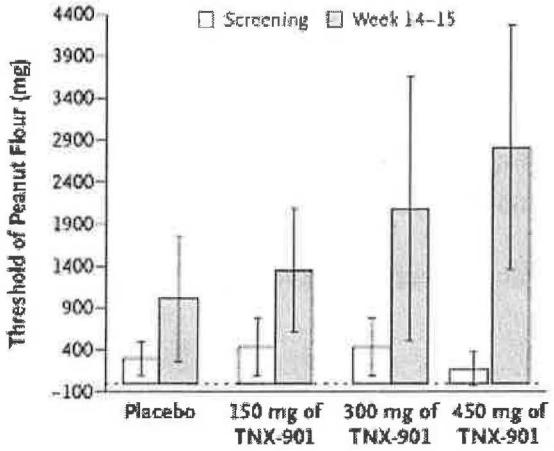
Figure 5. Persistent protection against peanut-induced anaphylactic reactions by HKE-MP123 [20]



Studies of treatment of anaphylaxis in humans are few in number. However, in 2003, a very promising study was reported by Leung and colleagues [24]. These investigators studied the effects of a humanized IgG1 monoclonal antibody (TNX-901) against IgE in patients with known peanut allergy. The antibody not only inhibits binding of IgE to mast cells and basophils, but also, it down regulates the expression of the high affinity IgE receptor (FcεRI) on these cells. A double-blind, randomized, dose-ranging trial was conducted in 84 patients who had known peanut allergy. Immediate hypersensitivity was confirmed by challenge and the threshold dose

of peanut that elicited the reaction was determined. Patients then were randomized to receive one of four treatments at weekly intervals for four doses: TNX-901 150 mg, TNX-901 300 mg, TNX-901 450 mg or placebo. A final oral challenge was performed within two weeks after the last dose. As shown in Figure 6, greater amounts of peanut flour were required to elicit symptoms in all groups after treatment. However, the mean increase in sensitivity threshold (as compared to that in the placebo group) reached significance only in the 450 mg group ($p < 0.001$).

Figure 6. Mean threshold dose of peanut flour eliciting symptoms in patients receiving TNX-901 or placebo [24]



Thus, TNX-901, at the 450 mg dose, markedly increased the threshold of sensitivity to peanut from a level equal to about half a peanut (178 mg) to one equal to about nine peanuts (2805 mg). The drug was well-tolerated and the degree of decreased sensitivity achieved was thought to be sufficient to protect against most accidental ingestion of peanuts. While these results are encouraging, this drug remains experimental.

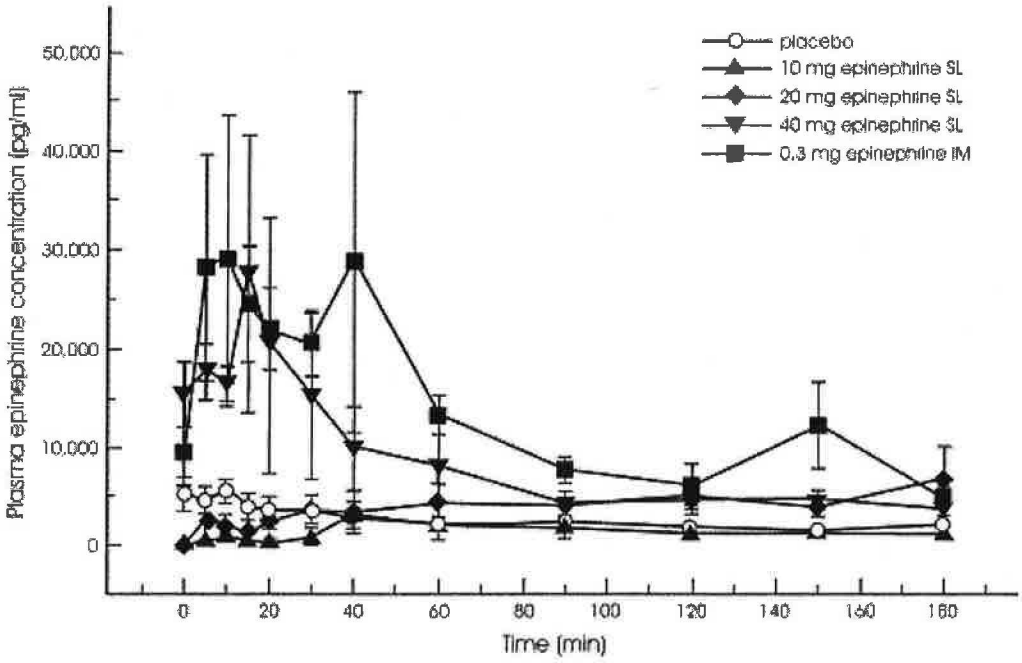
Another anti-IgE monoclonal antibody, omalizumab, is FDA approved for use in allergic asthma but not for anaphylaxis. Clinical trials of this drug for peanut allergy were halted early in 2006 after two children experienced anaphylactic reactions. The children had not yet received the drug but had reacted to peanut challenges that were done at baseline to determine their reactivity threshold. While anaphylaxis studies with this drug have been suspended for now, there is hope that they may be resumed at some point in the future.

There is universal agreement that epinephrine is the drug of choice for anaphylaxis [5-7, 9, 25, 26]. Since most anaphylactic reactions occur unexpectedly in a non-clinic setting, it is recommended that patients with a known history of anaphylaxis carry an epinephrine autoinjector such as an EpiPen (Dey LP, Napa California), EpiPen Jr., Twinject 0.3 mg or Twinject 0.15 mg (Verus Pharmaceuticals Inc., San Diego , California) [5, 9, 27, 28]. However, despite the emphasis on the importance of using self-injectable epinephrine in treating anaphylaxis, it remains underutilized

by patients [29, 30]. One reason for this underutilization is the fear associated with the use of needles.

Recently, Rawas-Qalaji and colleagues [31] sought to determine if an alternative route of epinephrine administration would be effective in treating anaphylaxis. They evaluated epinephrine absorption from a sublingual tablet using a rabbit model. Rabbits received one of the following treatments on 5 different study days at 4 week intervals: epinephrine 10 mg (sublingual tablet); epinephrine 20 mg (sublingual tablet), epinephrine 40 mg (sublingual tablet), a placebo sublingual tablet as a negative control, and epinephrine 0.3 mg by IM injection in the thigh as a positive control. A plot of the mean epinephrine concentrations versus time is depicted in Figure 7. As shown, the maximum plasma epinephrine concentration and the time of maximum plasma epinephrine concentration did not differ significantly between the 40 mg sublingual dose and the 0.3 mg IM dose. Thus, these encouraging findings suggest that, at some point in the future, sublingual epinephrine may prove to be effective in the treatment of human anaphylaxis.

Figure 7. Plasma epinephrine concentration versus time plots after administration or placebo sublingually (SL) and after epinephrine intramuscular (IM) [31]



Therapeutic strategies for the management of anaphylaxis are currently based on clinical experience [5, 6, 9]. Thus, there is a critical need for further research into this area. More information about the dosing, timing, route and frequency of epinephrine administration is needed as is information regarding the effectiveness of H_1 and H_2 antihistamines and corticosteroids. In addition, new treatment modalities need to be further explored in animal models and ultimately in humans. Universal acceptance of the proposed criteria for identifying

anaphylaxis, developed in the recent NIAID/FAAN symposium, hopefully will facilitate the necessary research so that important progress can be made in treating this life-threatening disease [6].

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