ANAPHYLAXIS: FACTS, FALLACIES, AND THE FANTASTIC

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DE L'ACTION ANAPHYLACTIQUE DE CERTAINS VENINS,

par MM. PORTIER et CH. RICHET.

Nous appelons *anaphylactique* (contraire de la phylaxie) la propriété dont est doué un venin de diminuer au lieu de renforcer l'immunité, lorsque il est injecté à doses non mortelles.

Il est probable que beaucoup de venins (ou toxines) sont dans ce cas; mais, comme on s'est attaché surtout à leur action prophylactique ou vaccinante, on a fort peu cherché encore à les étudier méthodiquement à ce point de vue (1).

Le poison extrait des tentacules des Actinies donne un éclatant exemple d'effet anaphylactique.

Nous ne décrirons pas ici la marche de l'empoisonnement par cette actinotoxine. Dans l'ensemble, les effets sont à peu près les mêmes que ceux de la toxine extraite des tentacules des Physalies, toxine que

(1) Quelques faits de sensibilité croissante d'un animal à des injections répétées ont été signalés pour la toxine antitétanique par Brieger et Knorr; et pour la toxine antidiphtérique par Behring et Kitashima. (Voy. Metchnikoff. *Immunité*, p. 387-389). — Quant au venin des Physalies m. d., Guérin a publié récemment (*Ann. d'Hyg. coloniale*. 1901, p. 268) des observations intéressantes desquelles il résulterait que les corps des Physalies, desséchés et ingérés par la voie stomacale, amènent assez rapidement la mort. Nous avons vu, au contraire, qu'en ingestion stomacale, même à dose assez forte, l'actinotoxine est inoffensive; mais le poison dissous n'est pas tout à fait comparable aux tentacules desséchés.

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HISTORY OF ANAPHYLAXIS

The phenomenon of anaphylaxis was first recognized in 1902 by two French scientists Charles Richet and Paul Portier. The story of how these two scientists became collaborators, and the unique setting of their initial set of experiments is a fascinating tale of discovery, worth recanting in some detail.[1]

Albert I, Prince of Monaco (1889-1922) was interested in the natural sciences and oceanography. In 1873 he acquired the first of several yachts equipped for oceanographic studies. In 1898 he launched the third of these yachts, the *Princesse Alice II*, a 1400 ton vessel which maintained a scientific staff on board under director Jules Richard. Prince Albert and Richard developed a curiosity regarding the way *Physalia*, Portugese man-of-war, captured their prey. Fish appeared to be stunned by brushing against their long tentacles, allowing the man-of-war to easily grasp and digest the fish. Sailors at the time were well aware of stings and occasional fainting when touched by the tentacles. Prince Albert and Richard were actually responsible for providing the topic for Richet & Portier's historic discovery. The Prince and Richard suggested that Richet and Portier attempt to isolate and study the poison from the Portugese man-of-war.

Charles Richet (1850-1935) was Professor of Physiology at the University of Paris when Prince Albert invited him to join the scientific staff for the 1901 cruise of the *Princesse Alice II*. Prior to obtaining his medical degree in 1877, he had already made some important discoveries on the role of conditioned reflexes in gastric secretion by observations made on a boy with a gastric fistula.[2]

Paul Portier was a regular member of the scientific staff of the Princesse Alice II from 1901 to 1904. He was an assistant in the Laboratory of Physiology at the Sorbonne and had become acquainted with the Prince through an associate in his lab. In 1898, he had accompanied Prince Albert on a previous scientific cruise.

On July 5, 1901, the Princesse Alice II departed from Toulon, France, carrying an assortment of pigeons, ducks, guinea pigs, and frogs for use in the aforementioned experiments. In August, they encountered an abundance of *Physalia*, and Portier and Richet prepared extracts from the tentacles. Various concentrations of the extract were developed and injected into the different species on board. They discovered that the extract caused marked effects on the central nervous system and designated the toxin as "hypnotoxin".[3] By the time the cruise ended on September 19, 1901, they had completed these experiments.

Portier and Richet decided to continue their collaboration on their return to Paris. Unable to obtain a supply of *Physalia*, they used an extract from another coelenterate, *Actinia sulcata*, a sea anemone abundant along the French coasts. Using anenome toxin extracts designated "actinotoxin" they did further experiments with dogs. After determining lethal doses of the actinotoxin, the investigators then attempted to desensitize animals against the toxin. Although Richet reported that the idea to attempt immunizations was accidental,[4] Portier in a joint report published after the death of Richet indicated that these experiments were intentional:[5]

> "We considered our work as almost finished when I proposed to Richet to proceed to some trials of immunization. My proposition did not arouse much enthusiasm in him and I considered it more or less as a routine completion of our work. Was it not, in effect, evident that we would repeat the classic phenomenon, commonplace, since the work of Pasteur and his school?
>
> Then we injected a series of dogs and pigeons, either with the toxin attenuated by heat or with nonlethal doses of the toxin. After a certain period of incubation, another injection [was administered] of a stronger dose which ought to be tolerated if the animal was immunized.
>
> It was then that we noticed with surprise that the results were not those we expected. No, the animals were not immunized. Certain ones seemed "sensitized".
>
> The fast appeared so unfore-seen and paradoxical that Dr. Richet asked me if I had not mixed the animals in the two series: those vaccinated and the controls. I was almost sure not, but finally we began a new series to confirm the first result."

They continued to pursue this new phenomenon with other animals. After further studies they noted: "A new impression penetrated us... the dogs which exhibited "sensitivity" are the animals which have received the first injection at a remote date." [6] The following excerpt is a translation directly from the pages of Richet and Portier's laboratory notebook:

14 Jan 1902.	Dog Neptune received an injection of 0.05cc of toxin per kg. One hour after injection, the dog walked cheerfully about the laboratory.
17 Jan.	In order to see if the dog is sensitized, it was injected with 0.1cc of the toxin per kg.
18 Jan.	The dog did not appear ill, very cheerful.
10 Feb.	(26 days after first injection) the dog was in perfect health, cheerful, active, the coat was shiny. On this day at 2 PM .it was injected with 0.12cc toxin per kg. Immediately produced vomiting, defecation, trembling of front legs. The dog fell on the side, lost consciousness, and in one hour was dead.

From their joint report of 1936[6]:

> This dog offered us a very striking spectacle which brushed away all doubts that possessed us before; we were obliged to yield to the evidence: not only our animals injected several times with weak doses of toxin, and after a sufficient time, were not immunized, but they were certainly "sensitive" compared to "untreated" animals.

The derivation of the word "anaphylaxis" also deserves mention and is best described in Portier's own recollection many years later:[5]

> "When the phenomenon had been solidly established from the experimental standpoint, M. Richet decided to baptize it. I tried to persuade him of the inutility of creating a neologism, since there

were already so many in the scientific literature, and especially as we have forgotten our Greek--- You might be right, answered Richet, if the phenomenon we have discovered is a rarity, but if it presents a certain general interest, we have to have a name for it--- At the moment he approached a small blackboard hidden under the stairs and asked me if I knew the Greek word for 'immunity', 'protection'--- No, I said, I might have known it but I have forgotten--- It is" phylaxis", and so let us affix a privative" a" --- The resulting word aphylaxie not being very euphonic, we decided to adopt the word anaphylaxie (anaphylaxis). At the moment we could not dream of the great value attached to this expression."

The definitive experiments with the dogs Galathée and Neptune were performed on Feb. 10, 1902. Five days later, Portier and Richet presented their discovery of anaphylaxis before the Societe de Biologie under the title, "De l'action anaphylactique de certains venins," with Portier being listed as principled author.[7] For his work on anaphylaxis, Charles Richet was awarded the Nobel Prize in Medicine and Physiology in 1913. In Richet's Nobel acceptance speech, Paul Portier received only a passing mention.

The earliest record of anaphylaxis dates back more than 4000 years ago and was recorded on an ebony tablet discovered in the tomb of King Menes of Egypt (26 century BC).[8] According to the hieroglyphic translation, King Menes, founder of the first Dynasty and ancient city of Memphis, died after being stung by a wasp while on a sea exploration in 2641 BC. Ironically, the image of a bee was used to depict his domain of Lower Egypt! Other historians dispute this translation, stating that King Menes was killed by a hippopotamus.[9] The Egyptian word for hippo was the same value as a word for wasp. To further complicate matters, the word for hippo has a similar sound to an Egyptian town which had a determinative sign of a wasp or bee.

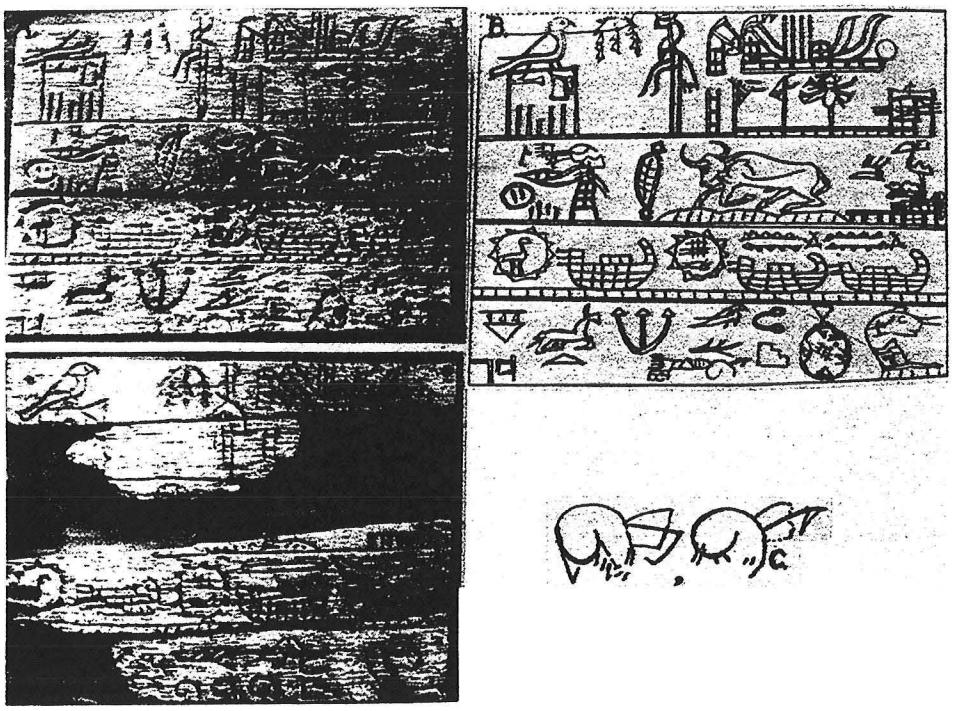


FIG. 1. Great Ebony label from King Menes' tomb at Abydos. Drawing on right from same by L.A. Waddell. Lower right figures are depictions of the "fatal fly". From: Levine[99]

DEFINITIONS: ANAPHYLAXIS vs. ANAPHYLACTOID

Anaphylaxis is a clinical syndrome, explosive in nature, due to an immunological reaction caused by a variety of inciting agents. The constellation of symptoms in anaphylaxis includes cutaneous, respiratory, cardiovascular and gastrointestinal manifestations often occurring in combination. The term "anaphylaxis" historically has been used to describe those reactions caused by prior sensitization with production of antigen-specific IgE, followed by antigen exposure resulting in mediator release from mast cells and basophils. "Anaphylactoid" reactions are clinically indistinguishable from anaphylaxis, however the mechanism is not mediated by IgE antibody and does not require prior sensitization. Despite these distinctions, the term"anaphylaxis" is often used to describe both of these clinical syndromes, especially when the mechanism is unknown.

EPIDEMIOLOGY

There is a paucity of data regarding the actual prevalence and incidence of anaphylaxis and deaths attributed to anaphylaxis. A thirteen year retrospective review of anaphylactic shock including various discharge diagnosis from a hospital in Denmark found an incidence of 3.2 cases per 100,000 inhabitants per year.[10] The mortality rate in this study of 20 cases was 5%. Klein painstakingly, individually reviewed all 19,122 emergency room records during a 4 month period from the major tertiary care emergency center serving Olmsted County, Minnesota.[11] The incidence of anaphylaxis found in this community was 17 per 19,122 emergency visits or 0.09%. Only 4/17 had ICD-9 codes for anaphylaxis, most were simply classified as having an "allergic reaction".

Somewhat more information is available on the incidence of anaphylaxis for specific agents. The most common cause of anaphylaxis or anaphylactoid reactions are due to drugs and radiocontrast dyes. A review of reports to the Committee on Adverse Drug Reactions in the Danish National Health System identified 30 fatal cases of drug induced anaphylaxis, only 20% were listed in the Central Death Register as anaphylaxis.[22] This yielded an estimated incidence for fatal drug induced anaphylaxis of 0.3 per million inhabitants per year. The most frequent causes were radiocontrast media, antibiotics, and allergen extracts (the latter all under a general practitioner's care).

Based on multiple surveys and investigations from several developed countries in the 1950's and 1960's, the frequency for all types of allergic reactions to penicillin falls within a wide range of 0.7-10%, but most figures are < 1%.[12] However anaphylaxis occurs worldwide in 0.015%-0.04% of patients treated with penicillin and fatal anaphylaxis is estimated to occur in 0.0015%-0.002%. Data from the CDC's Venereal Disease Branch is in agreement with that of other countries with an incidence of penicillin induced anaphylaxis of 0.04%.[13] Moderate-severe anaphylaxis occurred with a frequency of 25 per 100,000 penicillin treated patients. Crude data based on surveys of a

small number of fatalities from the 1950's provide for the frequently quoted US penicillin anaphylaxis fatality rate of 100-300 per year.[23],[24]

Table 1. EPIDEMIOLOGY OF ANAPHYLAXIS	
Etiology of Anaphylaxis	**Incidence of anaphylaxis**
Penicillin	0.015%-0.04%[12],[13] 0.0015%-0.002% fatal anaphylaxis[12]
Radiocontrast Media	0.02%-0.04%[14]
Insect Stings	0.15% to 1.8%[15] 0.33 deaths per million in Texas[16]
Idiopathic	20-47,000 cases in US[17]
Hemodialysis	3.3 reactions/yr/1000 patients (hollow fiber)[18] 0.3 reactions/yr/1000 patients (flat-plate) 5 deaths/yr in US dialysis population
Allergy Injections	1 death per 2 million injections[19]
Protamine	0.06%-0.12%* non-insulin patients[20] 0.6%-2.1%* NPH diabetics *(catheterization-surgery)
Dextran	22 per 100,000 units of dextran[21] 3.6 deaths per 100,000 units

Severe anaphylactoid reactions that require treatment occur in 0.04% and 0.02% of patients receiving ionic and nonionic contrast media respectively.[14] After medications and radiocontrast media, reactions to stinging insects of the order Hymenoptera are the next most common cause of anaphylaxis. The largest US study was a questionnaire based study of 4,992 Boy Scouts which showed the incidence of history validated systemic Hymenoptera allergy was 0.3**%**.[25] Anaphylaxis occurred in 4 (0.08%) of these Boy Scouts. Other studies utilizing medical examinations, venom skin tests or RAST have shown a prevalence of systemic reactions from 0.15% to 1.8%.[15] Twenty-five to forty deaths occur per year in the US due to Hymenoptera stings.[16],[26] Texas has the notoriety of having one of the highest death rates per 1 million population (0.33).[16] The vast majority of these deaths are due to anaphylaxis. Interestingly, most of these fatal reactions are caused by stings to the head or neck regions.[26],[27] Almost twice as many people die from anaphylaxis to Hymenoptera stings than bites from venomous snakes in the US.

Idiopathic anaphylaxis is another well described type of anaphylaxis, with almost 400 well defined cases reported in the literature.[17] Based on a questionnaire administered to graduates of Northwestern University's Allergy-Immunology fellowship program, Patterson estimated that there are 20,000 - 47,000 patients with a history of idiopathic anaphylaxis in the US.

The estimates of incidence of anaphylaxis are most likely underestimates. Lack of notification and improper coding certainly contribute to this underestimation. Furthermore, unrecognized anaphylaxis may be another cause for under reporting of cases. In a recent study of 68 cases of sudden unexpected death, 13% had elevated post-mortem serum tryptase levels, indicating substantial mast cell activation, most likely due to unrecognized fatal anaphylaxis.[28]

An important aspect of anaphylaxis is the fact that re-exposure to the inciting agent does not always result in anaphylaxis. In individuals with a prior history of systemic reactions, approximately 25% to 60% have a systemic reaction to subsequent Hymenoptera stings in prospective studies.[29],[30] A repeat reaction rate of 16%-35% has been reported for radiocontrast media anaphylactoid reactions[31],[32] and 30-100% for penicillins.[33],[34] Several factors may influence anaphylaxis reaction rates. The route of administration may effect the incidence of anaphylaxis with the oral route being the least likely to cause anaphylaxis, as exemplified by the extremely rare cases of fatal anaphylaxis due to oral penicillin.[12] Despite long intervals between exposures, anaphylaxis may still occur. For example, patients with a remote history of a systemic reaction to Hymenoptera who were stung > 10 years later had a reaction rate higher than patients with shorter re-sting intervals.[35] There is a dose response for IgE mediated reactions and this may be another variable in the incidence of anaphylaxis. It is important to note that extremely minute quantities of antigen can cause anaphylaxis as indicated by reports of anaphylaxis from inhaled penicillin in hospital rooms, and fatal anaphylaxis to an intravenous test dose of only 0.01 IU of penicillin![12]

Other factors that may predispose individuals to anaphylaxis include age, gender, and atopy. Race and geographic location do not appear to be important. Anaphylaxis appears to occur more frequently in adults than children. This may reflect differences in exposure. Idiopathic anaphylaxis is primarily an adult condition. Females are at higher risk to develop allergy to latex[36] and muscle relaxants [37] while men have a higher incidence of Hymenoptera anaphylaxis.[38] These gender differences in latex and Hymenoptera allergy are probably due to differences in exposure. Atopy is considered to be a predisposing risk in anaphylaxis. Kemp et al. found 37% of 266 anaphylaxis subjects to be atopic while Yocum and Khan found an atopic history in 49% of 179 anaphylaxis cases.[39],[40] Other studies have found atopy to be increased in specific types of anaphylaxis due to exercise,[41] insect sting,[38] latex,[42], radiocontrast dye[43], and idiopathic anaphylaxis.[44],[45],[39]

PATHOPHYSIOLOGY

The mechanism by which an agent causes anaphylaxis is dependent on the type of immune pathway activated. Three well established mechanisms of anaphylaxis have been identified. First, foreign proteins or protein-hapten conjugates can elicit an IgE mediated Gell & Coombs type I reaction. Second, complement activation from immune complexes or other agents may generate anaphylatoxins C3a and C5a which can directly trigger mediator release from mast cells and basophils. Third, various agents can directly stimulate mast cells, basophils, or both causing mediator release through non-IgE dependent pathways. Finally, a number of different syndromes of anaphylaxis have been identified that occur through yet undefined mechanisms.

Table 2. MEDIATORS OF ANAPHYLAXIS

MEDIATOR	PHYSIOLOGIC EFFECT	CLINICAL EFFECT
Histamine	Smooth muscle contraction ? Vascular permeability Vasodilatation ?AV node conduction Prostaglandin generation Activates airway vagal afferent Mucus production	Flush Urticaria/angioedema Wheezing Hypotension Headache Nasal congestion
PGD_2	Peripheral Vasodilation Coronary vasoconstriction Bronchoconstriction ?Basophil histamine release	Flushing Bronchospasm Hypotension ?Myocardial ischemia
$9\alpha,11ß\text{-}PGF_2$	Vasopressor	Hypertension
$LTC_4/D_4/E_4$	Smooth muscle contraction ?Vascular permeability ?Mucus production	Bronchospasm ?Hypotension
Tryptase	Inactivates fibrinogen Degrades CGRP Inactivates VIP ??Airway hyperresponsiveness	Unknown
Chymase	Inactivates bradykinin Activates Angiotensin I Inactivates neuropeptides	Unknown
PAF	?Vascular permeability Bronchoconstriction	Unknown in humans
Heparin	Attenuates bronchoconstriction Inhibits complement activation Inhibits clotting cascade	Unknown
Nitric oxide	Peripheral vasodilatation Bronchodilation	Unknown

Exposure to foreign proteins in susceptible individuals can result in sensitization with generation of IgE antibody. The production of IgE *in vitro* requires IL-4 along with a variety of other second signals including cognate and noncognate T/B cell interactions.[46] Secreted IgE antibody may then associate with the high affinity IgE receptor FcεRI on the surface of mast cells and basophils. Antigen reexposure results in cross-linking of these receptors and the release of a variety of pre-formed and newly generated mediators. The physiologic effects of these mediators results in the clinical picture of anaphylaxis. It is still unclear why certain sensitized individuals react with anaphylaxis on reexposure while others who also have specific IgE against the putative antigen do not.

In the past, only mast cells and basophils were known to have FcεRI on their cell surface. Recently, FcεRI has been identified on other cell types including Langerhan cells[47],[48], monocytes from atopic individuals,[49] and eosinophils from hypereosinophilic patients.[50] The role of these cells in anaphylaxis remains to be defined.

Histamine (β-imidazolethylamine) has been identified in a number of different types of anaphylaxis and is stored in cytoplasmic granules of mast cells and basophils as a pre-formed mediator. Histamine mediated activities occur through binding to different subclasses of histamine receptors: H_1, H_2, and H_3. H_1-mediated effects include smooth muscle contraction, increased vascular permeability, vasodilitation, pruritus, prostaglandin generation, decreased A-V node conduction, and activation of airway vagal afferent nerves.[51] With the exception of increased airway mucus secretion, other H_2-mediated effects alone are probably less important in anaphylaxis. However, combined H_1- and H_2-receptor mediated effects are important in anaphylaxis including vasodilatation-related symptoms such as hypotension, flushing, and headache. Intravenous infusions of histamine result in a dose related increase in pulse rate, a widening of the pulse pressure, cutaneous flushing, nasal stuffiness and a pulsatile headache.[52] Studies of the effects of histamine on isolated human hearts have demonstrated that histamine can increase sinoatrial rate, contractile force, automaticity and cause vasoconstriction of coronary arteries.[53] In view of the above data, histamine seems to be an important mediator in many of the important physiologic events in anaphylaxis.

In addition to its numerous physiologic effects, histamine also may be a mediator of immune and inflammatory reactions. Histamine can down modulate mitogen- and antigen-induced lymphocyte proliferation, T-cell colony formation, and cytotoxicity, inhibit immunoglobulin production, and cause marked enhancement of natural killer (NK) cell activity.[54] Histamine can also modulate production of many cytokines including inhibiting synthesis of TNF-α,[55] IL-2 and IFN-γ[56] primarily through H_2 receptors. The role of histamine's immunomodulatory actions in anaphylaxis is unknown.

Products of the cyclooxygenase pathway are also important in allergic reactions. Prostaglandin D_2 (PGD_2) is the major prostaglandin generated by mast cells. PGD_2 has several

biologic functions in humans including peripheral vasodilatation, coronary vasoconstriction, bronchoconstriction, and platelet aggregation.[57] In vitro effects of PGD_2 include neutrophil chemotaxis and augmentation of basophil histamine release. The latter may be important in anaphylaxis. PGD_2 is rapidly metabolized to multiple PGF-ring structures,[58] including the major metabolite $9\alpha,11\beta$-PGF_2.[59] This metabolite differs from PGD_2 in that it is a pressor substance. Recently, $9\alpha,11\beta$-PGF_2 has been detected in the blood of a patient with anaphylaxis.[60] Thromboxane A2, another cycloxygenase product, has similar activity to $9\alpha,11\beta$-PGF_2, however there is little evidence for its role in human anaphylaxis.

Leukotrienes are newly generated mediators of the lipoxygenase pathway of arachidonic acid metabolism. Leukotriene C_4 is the predominant leukotriene released from mast cells by IgE stimulation and belongs to the group of sulfidopeptide leukotrienes LTC_4, LTD_4, and LTE_4. The sulfidopeptide leukotrienes are potent at inducing smooth muscle contraction, approximately 1000 times that of histamine. Other biological activities include increased vascular permeability, enhanced mucus production, and immunomodulatory activities.[61] In contrast to mast cells, IgE sensitized basophils predominately release LTB_4, a potent neutrophil chemoattractant. Recently, evidence for production of sulfidopeptide leukotrienes in human anaphylaxis was published.[62] Urinary LTE4 levels were found to be increased 1.9-52 fold above control levels in anaphylaxis due to a variety of IgE and non-IgE dependent mechanisms.

Tryptase is a tetrameric neutral protease released from the secretory granules of mast cells during mast cell degranulation. Tryptase is considered a specific marker for mast cells since it has not been detected in other cells except for relatively small amounts in basophils (0.04 pg per basophil).[63] Schwartz et al. have developed a sandwich enzyme-linked immunoassay for tryptase[64] and have shown elevated serum tryptase levels in anaphylaxis due to penicillin, wasp sting, exercise, food, anti-lymphocyte globulin, and aspirin.[65] The biological function of human tryptase is still unclear. Human tryptase inactivates fibrinogen and degrades calcitonin gene related peptide while dog tryptase inactivates VIP, stimulates fibroblast proliferation and renders canine airway smooth muscle hyperresponsive to histamine.[66] The pathophysiologic significance of these actions of tryptase in anaphylaxis is uncertain.

Other neutral proteases in human mast cells include two chymotryptic enzymes (chymase and cathepsin G-like protease) and carboxypeptidase. These enzymes are found along with tryptase in MC_{TC} type mast cells as opposed to M_T cells which contain tryptase as the sole neutral protease. Human chymase inactivates bradykinin, activates angiotensin I, and can hydrolyze Leu^5-enkephalin and kinetensin while carboxypeptidase can hydrolyze neurotensin in addition to the latter neuropeptides.[66],[67] Like tryptase, the functional role of these other proteases in anaphylaxis is currently unknown.

Platelet activating factor (PAF) is a putative mediator in immediate hypersensitivity reactions. However, its role in human allergic reactions is unclear since conflicting evidence exists for whether mast cells release PAF.[68] PAF can induce hypotension, bronchoconstriction, and increase vascular permeability. In mice, PAF may be a lethal mediator of anaphylaxis and PAF

antagonists can protect mice from death due to anaphylaxis.[69] The role of PAF in human anaphylaxis, if any, remains to be defined.

Nitric oxide (NO) is a recently identified autacoid that is synthesized by numerous cell types including mast cells and has a wide range of biological function. Data on the role of NO in anaphylaxis is limited to animal studies. The enhanced formation of NO in anaphylaxis is primarily through endothelial cell nitric oxide synthase (eNOS) and not inducible macrophage-type NOS (iNOS).[70] Several mast cell mediators including histamine and leukotrienes can activate eNOS. NO may be both beneficial and detrimental in anaphylaxis. A NOS inhibitor attenuates hypotension from peripheral vasodilation induced by anaphylaxis in mice, guinea pigs and dogs.[71], [72], [70] NO may be beneficial in other aspects of anaphylaxis since NOS inhibition promotes bronchospasm and is detrimental to cardiac function in rabbit anaphylaxis.[70] The role of NO in human anaphylaxis is unknown.

Proteoglycans form the backbone of mast cell and basophil granules to which other preformed mediators are bound and account for the metachromasia seen when these cells are stained with basic dyes.[73] Heparin proteoglycan due to its strong negative charge, is crucial in binding and stabilizing positively charged molecules like histamine and neutral proteases. The anticoagulant effects of heparin are well known, however heparin may also have anti-inflammatory effects. In fact, studies in the 1920's showed that heparin could prevent guinea pig anaphylaxis.[74] In animal models, heparin attenuates antigen-induced bronchoconstriction, possibly due to modulating mast-cell mediator release.[75] Heparin can also mitigate toxicity of one of the eosinophil cationic proteins.[76] Eosinophils have been shown to be increased in some tissues in fatal anaphylaxis, and one may speculate that heparin may have a protective role in potential tissue damage from eosinophil proteins. Chondroitin sulfate E is another glycosaminoglycan which can inhibit activation of the alternate complement pathway and activate the Hageman factor contact system. Whether proteoglycans play any role in human anaphylaxis remains to be determined.

Acid hydolases, superoxide dismutase, peroxidase, and neutrophil and eosinophil chemotactic factors of anaphylaxis (NCF-A, ECF-A) are other mast cell products that potentially could be involved in anaphylaxis. Recently, human mast cells have been found to be sources of cytokine production. Cytokines identified in human mast cells include TNF-α,[77] IL-4,[78] IL-5 and IL-6.[79] Little is known regarding the role of cytokines in anaphylaxis. In a study of insect sting-challenge induced anaphylaxis, IL-6 and IL-8 levels were not elevated in those with anaphylactic shock.[80]

Other mediators that may be important in non-IgE mediated anaphylaxis include anaphylatoxins C3a and C5a which may be generated due to immune complex activation. Recently, elevations in C3a and C5a were shown in 2 patients with severe post-transfusion anaphylaxis associated with vWF complexes and complement activation.[81] Neuropeptides such as substance P,VIP, somatostatin, and neuropeptide Y can activate mast cells through IgE independent mechanisms. Interestingly, these neuropeptides cause less eicosanoid release from mast cells than anti-IgE and calcium ionophore stimulation.[82], [83] Finally, elevated bradykinin levels have been

detected in a patient with an anaphylactoid reaction undergoing hemodialysis with an AN69 membrane.[84]

Although several animal species can exhibit systemic anaphylaxis, none have the same degree of multi-organ invovement as humans. In guinea pigs, the respiratory tract is the prime shock organ when challenged intravenously, the rabbit responds with circulatory collapse and the liver appears to be the primary shock organ in the dog.[85] Therefore each animal model may represent a certain component of anaphylaxis, but none serve asan encompassing model of the spectrum of multi-organ involvement in human anaphylaxis.

Recently, van der Linden et al. have provided some fresh insights into the pathophysiology of anaphylaxis by studying patients with anaphylaxis after intentional Hymenoptera sting challenge. They performed in-hospital insect sting challenges on 138 patients with a history of a prior anaphylactic reaction to yellow jacket or honeybee.[29] Systemic reactions occurred in 39 challenged patients, 21 which would be considered anaphylactic. Reactions occurred within 1-40 minutes of being stung with a median time of 10 minutes. Various mast cell mediators were measured over 60 minutes after symptoms began in the 17 patients with anaphylactic shock and compared to normal volunteers, a sample of non-reacting patients, and patients with mild cutaneous reactions only. As seen in Figure 2, all but one patient with anaphylactic shock had elevated histamine and tryptase levels compared to controls. Plasma PGD_2 levels were not significantly elevated in patients with anaphylaxis. The changes in histamine and tryptase levels inversely correlated with changes in mean arterial pressure as shown in Figure 3. The single patient who did not have an elevation in histamine and tryptase levels had a different clinical presentation in that she had no symptoms of pruritus, urticaria, or dyspnea but instead had angina, hypotension, bradycardia, and signs of ischemia on an

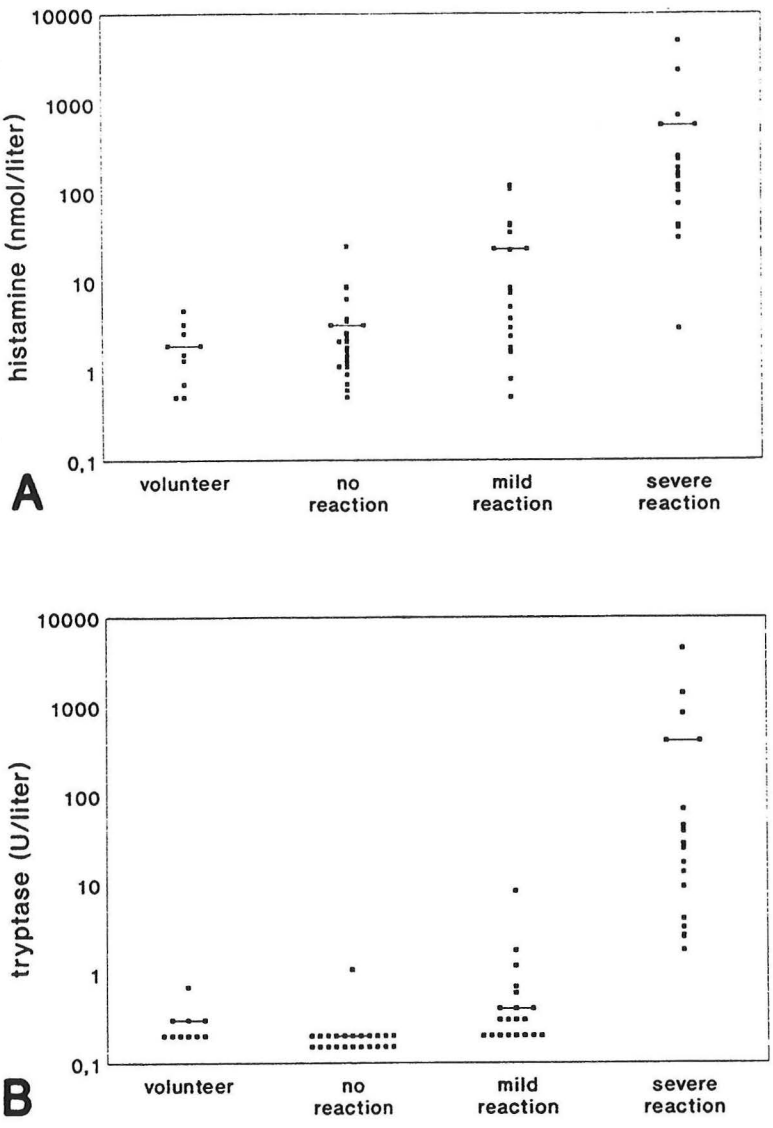


FIG. 2. Histamine and tryptase levels in individual patients after intentional sting challenge grouped according to clinical reaction. From: van der Linden et al.[29]

electrocardiogram. Coronary angiography the day after the sting reaction was normal and the authors suspected she suffered from myocardial mast cell activation with localized histamine release and coronary artery spasm.

In another report, these authors reported on cardiovascular mediators in this same group of patients.[86] Of the 17 patients with anaphylactic shock, 10/17 had tachycardia (>25% increase in initial heart rate) preceding their hypotension, while 5/17 had bradycardia (>25% decrease in initial heart rate). Remarkably, the authors only treated 3/17 hypotensive patients with epinephrine and used parenteral antihistamines and fluid resuscitation in all the others! The three patients requiring epinephrine therapy were excluded from analysis of the catecholamine studies. Values of epinephrine and norepinephrine were significantly greater in patients with anaphylactic shock than patients with mild or no reactions and the controls. Angiotensin II levels were also significantly higher in those with anaphylactic shock but angiotensin I levels did not change significantly. There was an inverse correlation between changes in mean arterial pressure and changes in epinephrine, norepinephrine, and angiotensin II.

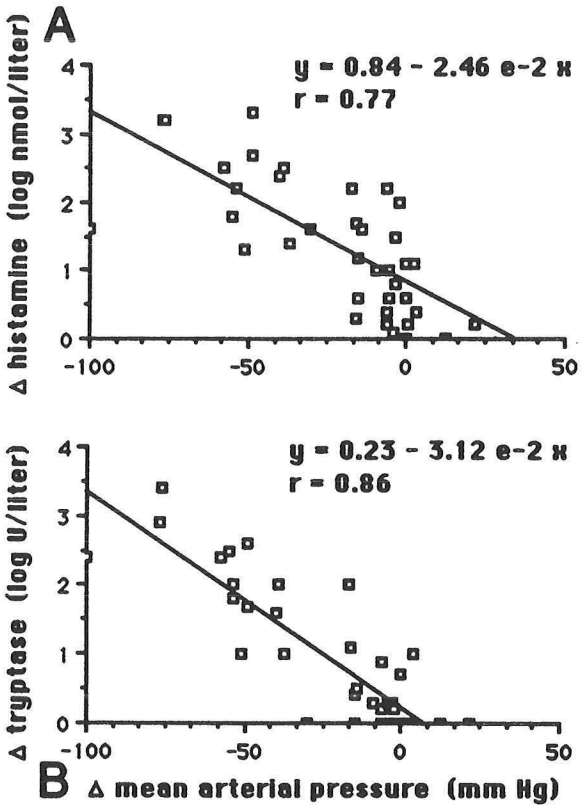


FIG. 3. Relationship between changes in plasma histamine and tryptase and changes in MAP after sting-challenge. From: van der Linden[29]

Van der Linden and colleagues also studied a subgroup of 20 patients with systemic reactions after sting challenge to evaluate activation of the fibrinolytic and coagulation system.[80] In seven of these patients with anaphylactic shock, they found significant elevations in levels of von Willebrand factor (vWF), tissue-type plasminogen-activator (tPA), and plasminogen-α2-antiplasmin complex (PAP-c). Levels of tryptase and histamine correlated with the levels of vWF, tPA, and PAP-c. The degree of activation of plasminogen seen in the patients with anaphylactic shock has only been described after thrombolytic therapy. The clinical significance of this plasminogen activation in anaphylaxis is unknown. Although mild elevations in D-dimer levels were seen in anaphylactic shock, platelets did not decrease and overall their observations did not suggest a strong activation of the coagulation system. However, others have reported depletion of Factor V, Factor VIII, and fibrinogen in anaphylaxis after sting-challenge, consistent with intravascular coagulation.[87]

Finally, van der Linden and colleagues reported on yet another subset of sting challenge patients, this time to investigate the activation of the contact system in anaphylaxis.[88] The main findings of this study were that patients with systemic reactions with angioedema as one of their

findings of this study were that patients with systemic reactions with angioedema as one of their symptoms, had evidence of activation of the contact system as determined by decreases in (pre)kallikrein and high molecular weight kininogen levels and sustained increases in C1-inhibitor complexes. Patients with hereditary angioedema during acute attacks have also been shown to have similar contact system changes.[89] Since heparin and chondroitin sulfate E can activate the contact system in vitro,[90] mast cell activation could provide the stimulus for contact system activation.

CLINICAL PRESENTATION

The clinical signs and symptoms of anaphylaxis are quite variable between patients. However anaphylaxis affects primarily only four "shock" organs, the skin, respiratory tract, cardiovascular system and the gastrointestinal tract. The majority of information on the presentation of anaphylaxis derives from retrospective studies with medical chart reviews as the primary source of data and therefore is limited by recall accuracy and inadequate documentation.

Initial signs and symptoms of anaphylaxis are typically cutaneous in nature often beginning with a feeling of warmth, flushing, pruritus and erythema. Pruritus characteristically involves the palms, soles, groin, and axilla initially and can become diffuse later in the course. Urticaria and angioedema is the most common finding in anaphylaxis and usually resolves within 24 hours but more severe angioedema may persist for a few days. Respiratory symptoms include both lower respiratory symptoms of dyspnea, wheezing, and chest tightness and upper respiratory symptoms of nasal congestion, sneezing, rhinorrhea, and laryngeal edema. Laryngeal symptoms often begin with a sensation of a "lump in the throat" and may then progress to dysphonia, hoarseness, drooling due to inability to swallow secretions, stridor, and finally asphyxia. Gastrointestinal symptoms often manifest early as abdominal cramping and then progress to nausea, vomiting, and diarrhea which can be bloody. In addition to airway obstruction, cardiovascular symptoms are the other serious and potentially fatal symptoms of anaphylaxis. Cardiovascular symptoms and signs include lightheadedness, tachycardia, bradycardia, hypotension, vascular collapse and arrhythmias. Multiple types of arrhythmias have been reported to occur in anaphylaxis, most prior to the administration of epinephrine and include premature atrial contractions,[91] atrial fibrillation[92], bundle branch block,[93] peaked P waves and right axis deviation,[93] ventricular premature contractions,[94] ventricular fibrillation,[95] and asystole.[96] Non-specific ST-T wave changes[97] and even myocardial infarction have been rarely reported to occur with anaphylaxis.[98],[99] Other signs and symptoms of anaphylaxis include a metallic taste in the mouth, a sense of "impending doom", headache, diaphoresis, fecal and urinary incontinence, and seizures.

The frequency of these various signs and symptoms of anaphylaxis varies between studies but general trends can be observed in Table 3. Kemp et al. recently reported on a large series of anaphylaxis cases retrospectively identified from a university affiliated private clinic in Memphis between 1978-1992.[39] Urticaria and angioedema occurred in 90% of patients and was the most common symptom followed by symptoms of bronchospasm in 60%. Gastrointestinal symptoms

occurred in 26%, upper airway edema in 24%, and hypotension in 20%. Ditto et al. reported on updated data from Northwestern University's experience with idiopathic anaphylaxis(IA).[44] In comparison to anaphylaxis of all types reported by Kemp et al., the Northwestern IA patients all had urticaria and angioedema, more frequent upper airway obstruction (63%), less frequent bronchospasm (39%), and similar rates of hypotension and gastrointestinal symptoms.

Table 3. FREQUENCY OF ANAPHYLACTIC SYMPTOMS

Signs & Symptoms	Kemp et al. 266 cases of anaphylaxis	Ditto et al. 335 cases of IA
Urticaria, Angioedema	**90%**	**100%**
Dyspnea, Wheezing	**60%**	**39%**
Dizziness, Pre-syncope, Syncope	**29%**	**23%**
Gastrointestinal	**26%**	**22%**
Upper airway edema	**24%**	**63%**
Hypotension	**20%**	**23%**
Rhinitis	**16%**	**ND**
Conjunctivitis, Periorbital edema	**12%**	**ND**

In the majority of cases, anaphylactic symptoms begin within seconds to minutes of exposure to the causative agent. In 151 cases of fatal anaphylaxis to penicillin, symptoms occurred within 15 minutes of penicillin administration in 85%, half of these "immediately".[12] More than half of the deaths occurred within 15 minutes. One group provided this befitting description: "The drama lasted 3 minutes maximum".[100] Van der Linden et al. noted the development of anaphylactic symptoms within 1-40 minutes (median 10 minutes) after insect-sting challenge.[29]

Stark and Sullivan performed a prospective study of 25 patients seen at Parkland Memorial Hospital who had experienced anaphylaxis.[101] Of these, 5 (20%) had "biphasic anaphylaxis" in which there was a recurrence of anaphylactic symptoms 1-8 hrs later and 6 had "protracted anaphylaxis" with persistent symptoms lasting from 5 hrs to 8 days. Anaphylaxis provoked by an oral agent and anaphylaxis that began > 30 minutes after exposure to the stimulus were associated with recurrent or prolonged anaphylaxis. Interestingly, glucocorticoid therapy started during the initial phase of anaphylaxis did not prevent either recurrent or prolonged anaphylaxis. In contrast to the findings of Stark and Sullivan, Douglas et al. found an incidence of biphasic anaphylaxis in

only 5% of 44 inpatients with anaphylaxis.[102] All patients with biphasic anaphylaxis had been initially treated with glucocorticoids. Both of these studies showed that in the absence of hypotension or laryngeal edema, no patient had a recurrence of anaphylaxis. In a study of fatal and near-fatal anaphylaxis to foods, 3/6 fatal reactions had a biphasic pattern (1-2 hour symptom free interval) and 3/7 near-fatal reactions had a protracted pattern.[103]

PATHOLOGIC FINDINGS

The anatomic and microscopic changes seen in cases of anaphylaxis are nonspecific and may occur in a number of other conditions. Therefore, a diagnosis of anaphylaxis cannot be made on a morphologic basis alone. The predominant pathologic feature of anaphylaxis involves the respiratory tract.[85][104][26] In 1972 Delage and Irey reported on 43 autopsy cases of anaphylaxis from the Armed Forces Institute of Pathology, the largest reported detailed series to date.[104] Findings in the pulmonary system included pulmonary congestion and edema, intra-alveolar hemorrhage, increased tracheobronchial secretions, laryngeal edema, and acute pulmonary hyperinflation. Of these, nonspecific pulmonary congestion, pulmonary edema, and intra-alveolar hemorrhage were the most frequent findings, even in those cases where death occurred within 10 minutes. Laryngeal edema occurred in 15/43 cases but was thought to be the cause of death in only 4. In contrast, James and Austen found laryngeal edema to be the primary cause of death in 3/6 cases of fatal anaphylaxis.[85] This discrepancy may due to the brief interval from death to autopsy in the cases reported by James and Austen since this edema can disappear in a few hours.

Splenic tissue eosinophilia was a notable finding in both aforementioned series, while James and Austen noted additionally some degree of tissue eosinophilia in pulmonary vessels and vessels and lamina propria of the upper airway. Other cases have demonstrated visceral congestion or even no anatomic findings at all.[85],[30] Travis et al. reported a case of acute colorectal ischemia occurring after anaphylaxis with biopsy findings of necrotic mucosal glands and occlusion of some capillaries with proteinaceous material.[105] Finally, various arrhythmias and myocardial infarction have occurred in anaphylaxis as mentioned previously.

DIFFERENTIAL DIAGNOSIS

When anaphylaxis occurs with typical cutaneous, respiratory, cardiovascular, and gastrointestinal symptoms, the proper diagnosis is readily made. However, not all patients may present so dramatically and therefore confusion may arise. Although the vast majority of patients with anaphylaxis will have cutaneous symptoms of urticaria, angioedema, flushing or pruritus, others may simply present with sudden collapse. A common cause of sudden collapse is vasovagal syncope. Vasovagal attacks can often be differentiated by their lack of pruritus, respiratory symptoms and a typical inciting trigger of a painful injection or anxious situation. Bradycardia and diaphoresis are common in vasovagal episodes but can also occur with anaphylaxis. However, hypotension from anaphylaxis is usually more longstanding and does not respond as quickly to lying recumbent as do patients with vasovagal episodes. Panic disorder and hyperventilation can also present with dyspnea and collapse. Features such as perioral and extremity paresthesias and

maintenance of blood pressure are typical of hyperventilation episodes. Other organic causes of collapse such as arrhythmia, seizures, pulmonary embolus and myocardial infarction may also be considered and evaluated appropriately.

Patients with symptoms of "throat swelling" due to nonorganic disorders are often difficult to differentiate from true laryngeal edema from anaphylaxis. The presence of orofacial swelling that is visible to others (not perceptions of swelling) in addition to "throat swelling" favors laryngeal edema as a cause. True laryngeal edema typically lasts several hours while perceived throat swelling may be fleeting. Direct visualization of the larynx with fibreoptic endoscopy during an attack can easily diagnose laryngeal edema, however this is usually not readily available. Globus hystericus, the sensation of a lump in the throat, tends to be more chronic and non-progressive. Vocal cord dysfunction is a functional disorder characterized by attacks of stridor, wheezing, and breathlessness, due to paradoxical inspiratory adduction of the vocal cords during attacks.[106] Patients with vocal cord dysfunction due not have any other accompanying systemic symptoms and therefore present typically as status asthmaticus.

Table 4. 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	Hereditary angioedema, Scromboid poisoning, Cold urticaria, Cholinergic urticaria, Carcinoid syndrome, Systemic Mast Cell Disease

Only a few uncommon disorders have several of the objective clinical features of anaphylaxis and need to be considered in the differential diagnosis. C_1-esterase inhibitor deficiencies, both hereditary and acquired, may present with angioedema accompanied by gastrointestinal symptoms of nausea, vomiting, bloating, and cramping. These disorders typically lack urticaria, are slower in onset, the angioedema is often precipitated by trauma, and are refractory to conventional anaphylaxis treatment including epinephrine. C_1-esterase inhibitor deficiencies can be diagnosed by obtaining a C_1-esterase inhibitor functional level which will be abnormal in all cases. Scromboid poisoning presents with symptoms of flushing, pruritus, nausea, vomiting, diarrhea, headache, palpitations, dizziness, and occasionally swelling of the face and tongue within an hour of ingestion of spoiled fish of the families Scromboidae and Scomberesocidae including tuna, mackerel, skipjack, and bonito and some nonscromboid fish such as mahi-mahi, sardines, anchovies, bluefish, herring, and amberjack, as well as cheese. Scromboid fish contain substantial amounts of free histidine that can be decarboxylated by enteric bacteria in spoiled fish to form "scromotoxin", which has been determined to be histamine.[107] The symptoms of scromboid poisoning are due to the

pharmacologic effects of histamine, and all who eat the fish become ill. Two physical urticarias can present with systemic symptoms in addition to urticaria, cold urticaria and cholinergic urticaria. Patients with cold urticaria can occasionally develop systemic symptoms including hypotension, most often when swimming in cool water. These patients develop urticaria on exposed surfaces during cold weather and will develop a localized urticarial lesion at the site of an ice cube when placed for 5 minutes on the skin, the "ice cube test". Cholinergic urticaria should be considered in the differential diagnosis of exercise-induced anaphylaxis and will be discussed under that section. Most of the flushing syndromes do not present with other symptoms that may mimic anaphylaxis other than carcinoid syndrome and systemic mast cell disease (SMCD). Most patients with carcinoid syndrome tend to have more chronic gastrointestinal symptoms, especially diarrhea, and have non-pruritic flushing without urticaria. In the extemely rare patient where carcinoid syndrome is a consideration, a 24 hour urine for 5-hydroxyindoleacetic acid (5-HIAA) if > 30 mg/day is considered diagnostic.[108] Patients with SMCD (mastocytosis) may have identical symptoms to anaphylaxis including pruritus, flushing, dyspnea, gastrointestinal symptoms, hypotension, and syncope. True urticaria (not urticaria pigmentosa) and angioedema are not a feature of SMCD. Similarly, wheezing is usually not present in SMCD. The physical findings of urticaria pigmentosa, lymphadenopathy, and splenomegaly favor a diagnosis of SMCD. Although a bone marrow biopsy demonstrating increased mast cells is diagnostic, many cases can be diagnosed through measurement of mast cell mediators. In SMCD these mast cell mediators may be elevated during asymptomatic periods, as opposed to anaphylaxis in which mast cell mediators are only elevated during acute attacks.

EVALUATION OF PATIENTS WITH ANAPHYLAXIS

The key to evaluating patients with suspected anaphylaxis is a thorough history. The first critical step is to determine whether the patient has had anaphylaxis. A working definition of anaphylaxis is often helpful in this regard. In their retrospective study of anaphylaxis cases at the Mayo Clinic, Yocum and Khan determined subjects to have a valid diagnosis of anaphylaxis if they manifested symptoms of either: 1) airway obstruction such as laryngeal, pharyngeal, or glossal edema or severe bronchospasm; or 2) documented hypotension or syncope.[40] In addition, all patients were required to have had symptoms of generalized mediator release such as urticaria, angioedema, pruritus, or flushing. In addition to the patient's verbal history, many times it may be necessary to review emergency department records for objective physical findings of anaphylaxis, especially in patients with suspect histories.

Determining the etiology of anaphylaxis requires a detailed history. The apparent cause of anaphylaxis is often not readily apparent with the exception of anaphylaxis to therapeutics agents, stinging insects, and sometimes food. Patients should be questioned about events preceding the anaphylactic episode(s) including time of day, relationship to exercise, meals, and medications. In addition to a list of prescribed medications, intake of other non-prescribed ingestants including vitamins, health food supplements, laxatives, and suppositories should be obtained. Patients should be questioned regarding different formulations or lots of medications, since changes in additives to medications has been reported to cause anaphylaxis.[109] Information regarding specific ingredients of meals should be obtained in those with suspected food related anaphylaxis. When possible, a detailed list of all ingredients should be obtained as spices may be an overlooked cause

of food induced anaphylaxis. It is important only to document what has been eaten within the last 4 hours since this is the longest time interval between ingestion and anaphylactic symptoms as shown in double blind placebo controlled food challenges.[110] In women, information regarding a relationship between menses or intercourse and anaphylaxis should also be obtained.

In cases of IgE mediated anaphylaxis, determination of IgE through skin testing or radioallergosorbent tests (RAST) is often helpful in establishing an etiology of the anaphylactic event. Skin testing is more sensitive and specific than RAST testing and is therefore the preferred diagnostic modality. Skin testing should be performed by trained personnel with resuscitative equipment available, due to the risk of potentially fatal and fatal reactions to skin testing in anaphylaxis.[111],[112] Prick puncture testing should be performed prior to intradermal testing due to the lower risk of prick testing. Skin testing is helpful in assessing sensitivity to medications, anesthetics, venoms, foods, heterologous sera, insulin, chymopapain, latex, vaccines, and other foreign proteins. With the exception of food skin tests, the specificity of most of these other skin tests is fairly high. However, the sensitivity of many of these tests is unknown so a negative skin test cannot always exclude the possibility of that substance causing anaphylaxis. Skin testing is further complicated by drugs which can cause direct histamine release (opiates, radiocontrast media, some muscle relaxants), others which are skin irritants, and those that are unreactive. RAST testing while without risk, has limited applicability due to its lower accuracy and since it is only readily available for venoms, foods, latex, and the major determinant of penicillin.

In patients with anaphylaxis who do not have a readily apparent etiology, skin testing to a panel of foods known to cause anaphylaxis may be helpful. Stricker et al. used a panel of 79 food antigens in skin testing 102 patients with idiopathic anaphylaxis and identified 7 patients with food-induced anaphylaxis.[113] Frequently, patients are unaware of the foods that caused their reactions. In a study of food allergic patients in which the culprit food was confirmed through double blind placebo controlled food challenge, the patients failed to identify the causative food 67% of the time.[114] In Sampson et al.'s study of fatal food anaphylaxis, many of the patients were unaware that the fatal food had been eaten.[103] Furthermore, since commercial food extracts may lack some antigenic epitopes, food testing with fresh foods has been advocated by some, not only for fruits and vegetables but other foods as well.[115]

Results of Various Investigations in Mayo Patients Who Underwent Assessment for Anaphylaxis

Assessment	Overall group of patients	Subgroup No.	Subgroup %
Positive skin tests	104	71	68
Positive to anaphylactic series	81	50	62
Positive to other allergens	23	21	91
Increased allergen-specific IgE	44	23	52
Tested only by allergen-specific IgE	179	19	11
Tested by skin test or allergen-specific IgE	179	123	69
Challenged with dyes, preservatives, metabisulfites, or aspirin	179	29	16*
Other studies performed	179	49	27†

*No positive results.
†No abnormal results.

FIG. 4. Results of investigations in Mayo patients with anaphylaxis. From: Yocum and Khan[40]

Other than specific skin tests to suspect items and screening food skin tests, other laboratory investigations are often not helpful.(Table 4) In the study by Yocum and Khan, measurement of C_1-

esterase inhibitor, complement, 5-HIAA, and cryoglobulin levels as well as metabisulfite, dye and preservative, and aspirin challenges were not helpful in determining a cause of anaphylaxis. It is important to mention that mast cell mediators were also normal but these measurements were taken when patients were asymptomatic.

MEASUREMENT OF MAST CELL MEDIATORS IN ANAPHYLAXIS

In those patients who still have a tentative diagnosis of anaphylaxis, measurement of mast cell mediators may be helpful. Although several mast cell mediators can be measured, including histamine and its metabolites, tryptase, and PGD_2 metabolites, many obstacles hinder our ability to use these tests for diagnosis of systemic mast cell activation.

Table 5. MEASUREMENT OF MAST CELL MEDIATORS IN ANAPHYLAXIS

MAST CELL MEDIATOR	BODY FLUID	COMMENTS
Histamine	Plasma, Urine	• In circulation breifly • False positives in urine
Histamine metabolites (MIAA)	24 hr Urine	• Cumbersome • More specific and sensitive than histamine measurements
Tryptase (G5 & B12)	Serum	G5-measured tryptase commercially available but less sensitive and may not be detectable in first hour
9α,11ß-PGF_2	24 hr Urine	May be available soon from Mayo Labs

Histamine is rapidly removed from the circulation and therefore measurement of plasma histamine levels is not clinically useful.[52] Urinary histamine levels are elevated in patients with anaphylaxis, however, urinary histamine levels may not reflect endogenous histamine production, especially in females, because commensal urogenital bacteria may have histidine decarboxylase activity and produce histamine locally in the lower urinary tract.[116] Measurement of urinary histamine metabolites, such as N^{τ}-methylhistamine and N^{τ}-methylimidazole acetic acid (MIAA), using mass fragmentographic and gas chromatographic methods, respectively, has been shown to be more specific and sensitive than measuring urinary histamine for diagnosing SMCD and can be therefore be used to assess histamine production in anaphylaxis.[117] Thin-layer chromatography and more recently HPLC methods, which are less labor intensive, have also been used to measure MIAA.[118],[119],[120] Unfortunately, 24 hour urine collections are required for measurement of

MIAA, making this somewhat cumbersome and it is certainly not available from stored routine labs performed in the emergency department.

Two forms of **tryptase** have been identified in humans and are encoded by separate genes. α-Tryptase appears to be the predominant form of tryptase in the circulation in both normal subjects and in patients with SMCD.[121] In contrast, ß-tryptase is the predominant form released in systemic anaphylaxis. Schwartz and colleagues have developed an ELISA for mast cell tryptase using a mAb termed G5, which detects primarily ß-tryptase, and has been used as a specific marker for mast cell activation in anaphylactic shock and SMCD.[64],[122][65] Recently this group developed a newer tryptase immunoassay termed B12 that measures both α- and ß-tryptase. Normal values for G5-measured tryptase is < 1ng/ml while B12-measured tryptase is <20 ng/ml. The kinetics of tryptase release is clinically relevant, since elevated levels of tryptase cannot be detected until 30 minutes after antigen challenge and usually reach a maximum by 1-2 hours.[123] However, B12-measured tryptase may rise quicker and is more sensitive than G5-measured tryptase in anaphylaxis.[124] Tryptase immunoreactivity is also quite stable. When serum is stored at room temperature, tryptase levels decline by 55% after 2 days. Serum frozen at -20°C, immunoreactivity is preserved for at least one year,[123] and elevated tryptase levels have been detected in post-mortem sera frozen for over 10 years![28] Patients with SMCD may be differentiated from those with anaphylaxis by elevations primarily in B12-measured tryptase during asymptomatic periods. The finding of an elevated tryptase level is specific for mast cell activation usually due to anaphylaxis or SMCD and rarely is elevated in other allergic diseases. Schwartz et al. found only 1/13 patients with chronic urticaria to have a mildly elevated tryptase level.[121] The true sensitivity of elevated tryptase levels are not known. Sampson et al. reported on 5 cases of food-induced anaphylaxis whom were all hypotensive, and one of which was fatal and found only one patient with a tryptase > 2.5 ng/ml and 2 patients with normal tryptases.[103] Therefore, given the <100% sensitivity of tryptase levels, repeated measurements as well as measurement of other mediators may be required in some cases to confirm mast cell activation.

PGD_2 is metabolized predominantly to PGF ring metabolites in humans.[59] **9α,11ß-PGF_2** is a major urinary PGD_2 metabolite whose measurement may be useful in documenting mast cell activation, as has been shown recently in the plasma of a patient with anaphylaxis.[60] The measurement of these PGF ring urinary metabolites is typically performed in very few laboratories by a combination of gas chromatography and mass spectrometry techniques [125][58] and is indeed so cumbersome that they are not used routinely in those institutions having the capability to perform these assays.[126] A more clinically useful immunoassay is in development at the Mayo Clinic which measures 9α,11ß-PGF_2 levels in 24 hour urine collections[127] and may be available for clinical use shortly (G.G. Klee, personal communication).

Various other nonspecific laboratory abnormalities can occur in anaphylaxis including hemoconcentration with shock, creatinine phosphokinase elevation due to myocardial injury, and decreased C3 and C4 levels.[87] Since none of these abnormalities are diagnostic for anaphylaxis, they should not be obtained.

CAUSES OF ANAPHYLAXIS

There are hundreds of potential causes of anaphylaxis, therefore only some of the more frequently encountered or commonly used agents will be discussed. Specific interesting causes of anaphylaxis will be discussed in detail later including exercise-induced anaphylaxis, human seminal plasma anaphylaxis, "Texas insect" anaphylaxis, idiopathic anaphylaxis and radiocontrast media anaphylactoid reactions.

Anaphylaxis to penicillin is probably the most common cause of anaphylaxis. Penicillin and its metabolites, the major and minor determinants are haptens that bind covalently to carrier proteins which can then induce IgE mediated reactions in susceptible individuals. Although the parenteral route is most likely to cause anaphylaxis, oral, topical and even inhaled particles can cause anaphylaxis. Multiple other antibiotics have been also been implicated in anaphylaxis. The degree of cross-reactivity between cephalosporins and penicillin is quite variable but it has been estimated that 8% of penicillin allergic patients will have a reaction to a cephalosporin [128] and that the risk is lower for second and third generation cephalosporins .[129] However, in a recent review on the subject, Anne and Reisman concluded that the administration of cephalosporins to penicillin allergic patients is no greater than the rest of the population.[130] The only antibiotic for which skin testing with known predictive values is available is for penicillin. A negative penicillin skin test to both the major and minor detreminants of penicillin has an excellent negative predictive value and one can safely administer penicillin without concern for anaphylaxis.

Multiple foreign proteins have been implicated as causes of IgE-mediated anaphylaxis. The most common of these is insect venoms. Nationwide, yellow jackets are responsible for most venom anaphylaxis,[38] but imported fire ants are the most common cause in Texas. Patients with anaphylaxis to insect venoms, should undergo skin testing to Hymenoptera venoms, and if positive should undergo venom immunotherapy for 3-5 years. In some European countries, patients are selected for immunotherapy based on deliberate insect-sting challenge,[29] but this is controversial and not done in the US other than for research purposes only.[131] Other stings and bites can rarely cause anaphylaxis including mosquitoes[132], deer flies, Triatoma, and Gila Monsters.[133]

Heterologous sera, especially horse serum, is used in the treatment of snake bites, botulism, and in organ transplantation and can cause IgE-mediated anaphylaxis. Skin testing is typically performed prior to administering these agents. Hormonal preparations including ACTH, insulin, parathyroid hormone, and recently gonadotropin-releasing hormone [134]. Although allergic reactions to insulin are less common with recombinant human insulin, IgE-mediated reactions can occur due to tertiary structure differences between endogenous and recombinant insulin.[135] Skin testing can exclude insulin allergy and desensitization protocols have been successfully used in cases of insulin allergy.[136] Enzymes used for therapeutic purposes are another cause of anaphylaxis. Chymopapain was once widely used for treatment of herniated lumbar discs. By injecting chymopapain into the intervertebral disc space, chemonucleolysis can be used as an alternative to laminectomy. The first report of anaphylaxis to chymopapain was reported in 1974,[137] and

subsequently the incidence of anaphylaxis has been estimated at 0.2-0.5% for the first injection and 17% for the second injection.[138] Fatal anaphylaxis occurs in 0.015-0.0052% of chymopapain chemonucleolysis cases.[139] Skin testing with chymopapain has been shown to have an excellent negative predictive value with no reports of anaphylaxis occurring in skin test negative patients.[140],[138] Skin testing to chymopapain can itself cause anaphylaxis.[141]

Table 6. CAUSES OF ANAPHYLAXIS

Mechanism	Allergens	Examples
IgE mediated	Antibiotics	Penicillin, Cephalosporins, Sulfamethoxazole
	Proteins	Venoms Heterologous sera Latex Seminal fluid Hormones: ACTH, Insulin, PTH, GnRH Enzymes: Chymopapain, Streptokinase
	Therapeutics	Allergen extracts Vaccines - including fillers (gelatin) Intraoperative agents: Thiopental, Muscle relaxants ?Protamine, Fentanyl Chemotherapeutics Seminal plasma Ethylene oxide gas Psyllium Local anesthetics ?Corticosteroids ?NSAID's
	Foods	Peanut, Tree nuts, Crustaceans, Fish, Seeds, Spices Milk, Egg, Soy, Many others
Immune Complex/ Complement Activation	?RCM Blood/Blood products Hemodialysis membranes IVIG	plasma, serum, FVIII, cryoprecipitate
Direct Histamine Release	Hypertonic Solutions	RCM, Mannitol
	Plasma Expanders	Dextran, Hydroxyethyl starch
	Drugs	Opiates, Vancomycin, Curare, Fluoroscein
Unknown	Exercise	
	Preservatives	
	Progesterone	
	Idiopathic	

Latex allergy is another important cause of anaphylaxis to foreign proteins and has been recently reviewed as a Medicine Grand Rounds by Dr. Gruchalla. However, two recent case reports are worth mentioning. Schwartz, reported one case of anaphylaxis and another with urticaria after eating food prepared by food handlers wearing latex gloves.[142] The patient with anaphylaxis was not known to be latex sensitive prior to this event. Another case report described a woman with anaphylaxis after a barium enema initially attributed to latex allergy, but the enema tip did not contain latex and instead the episode was induced by allergy to an emulsifier in the barium solution, carrageenan.[143]

A number of other therapeutic agents can cause IgE-mediated anaphylaxis. Allergen extracts used in immunotherapy cause systemic reactions in approximately 1-4% of individuals, but anaphylaxis is much less common. The risk of fatal anaphylaxis from allergen immunotherapy is estimated at 1 in 2 million doses.[19] Anaphylaxis to aeroallergens is extremely uncommon but has been reported,[40] including anaphylaxis to ingesting food contaminated with parasites [144] or dust mites![145] Vaccines can also cause anaphylaxis and the measles vaccine has caused a great deal of consternation in its administration to egg allergic individuals since it is prepared from chick-embryo fibroblasts. Sampson and colleagues recently demonstrated that the MMR vaccine can be given safely to children with anaphylaxis to eggs,[146] however anaphylaxis may occur due to IgE mediated reactions to gelatin in the MMR vaccine.[147] Corticosteroid preparations can also rarely cause anaphylaxis. It is controversial whether these reactions are IgE-mediated or pseudoallergic reactions.[148],[149] Anaphylaxis to carboxymethylcellulose as an additive to parenteral triamcinolone has also been reported to cause anaphylaxis.[150] Ethylene oxide-altered human serum albumin can cause anaphylaxis in hemodialysis patients in which ethylene oxide gas is used to sterilize dialyzers.[151] Anaphylaxis has been reported to psyllium in laxatives.[152] Although a commonly reported allergy, true local anesthetic allergy is quite rare and anaphylaxis extremely uncommon. Reactions to parabens, preservatives in local anesthetics, has been reported but is also rare. Potential non-cross-reacting local anesthetic groups have been defined but this is based on patch testing for contact dermatitis, and it is unclear if there is any relevance to using this classification scheme in immediate allergic reactions. A superior approach is to use skin testing followed by incremental challenge which can be performed in patients with a history of reactions who require local anesthesia.[153]

Intraoperative anaphylaxis to intravenous agents used in general anesthesia occurs in 1 in 5,000 to 1 in 15,00 operations.[154] Substances which may cause intraoperative anaphylaxis include thiopental, muscle relaxants, latex, antibiotics, blood products, protamine, and plasma expanders. IgE-mediated mechanisms are thought to be involved in reactions to thiopental,[155] muscle relaxants,[37, 156] latex, and antibiotics. In patients with a history of intraoperative anaphylaxis, intradermal skin testing to both suspect agents as well as alternatives has been shown to be helpful in reducing subsequent general anesthesia reactions.[154] Radioimmunoassays may also be helpful in screening for IgE to muscle relaxants as has been shown by French investigators.[157] Anaphylaxis to protamine used in reversal of heparin anticoagulation is another cause of intraoperative anaphylaxis. Diabetics on insulin containing protamine are at a 40-50 fold higher risk.[158] The mechanism of protamine anaphylaxis is probably humorally mediated but the role

of IgE is still not clear but appears to be more important in diabetics on insulin containing protamine. Other anesthetic agents reported to cause anaphylaxis, possibly via IgE, include fentanyl[159],[160] and propofol [161][162]. Reactions to plasma expanders such as dextran [163] and hydroxyethyl starch are thought to be anaphylactoid reactions.[21][164][165]

Food-induced anaphylaxis is another common cause of anaphylaxis, especially in children. Although numerous foods have been implicated in anaphylaxis, only a few foods such as peanut, tree nuts, fish, crustaceans, milk, egg, and soy are responsible for the majority of food-induced anaphylaxis.[166] Seeds and spices are potent antigens capable of producing anaphylaxis and are often identified as the culprit based on skin testing to a battery of antigens followed by elimination or blinded food challenge.[113],[167],[168],[169],[170] In 1988, Yunginger et al. published the first series of 7 case reports of fatal food-induced anaphylaxis.[171] All but one case (an alcoholic) unknowingly ingested foods (peanut in 4/6 cases) they were known to be allergic to away from home, and only one patient self-administered epinephrine. One cod allergic patient died after eating french fries that may have been fried in oil used for deep frying fish. Of the 4 patients with a known atopic history, all had asthma. Sampson et al. later reported on 6 children and adolescents with fatal food-induced anaphylaxis (Figure 5) and compared them to 7 non-fatal cases.[103] Similar to the previous study, all unknowingly ingested the fatal food (peanuts in 3/6), all cases were asthmatics, and 5/6 fatal reactions occurred away from home. Patients with near-fatal anaphylaxis received epinephrine sooner than their fatal counterparts.

Patient No.	Setting	Initial Onset of Symptoms	Time of Epinephrine Dose	Onset of Severe Symptoms	Type of Symptoms	Time of Death
		min after ingestion				*min after ingestion*
1	School	10	125	125	Gastrointestinal, respiratory	180
2	School*	20	80	65	Gastrointestinal, respiratory	95
3	School	20	180	150	Gastrointestinal, respiratory	300
4	Fair	30	60	35	Skin, respiratory	105
5	School	30	90	35 and 100†	Gastrointestinal, respiratory	240
6	Home	3	25	20	Gastrointestinal, respiratory	120

*The symptoms began at home.

†The severe symptoms subsided after treatment with supplemental oxygen and then recurred.

FIG. 5. Timing of fatal food-induced anaphylaxis. From: Sampson et al.[103]

Avoidance of the food allergen is the only successful treatment measure in food-induced anaphylaxis. This is clearly difficult to do given the aforementioned fatal cases. Food avoidance requires compulsive food label reading and a knowledge of the many ways that certain foods may be labeled. These hidden food allergens are a common problem in food-induced anaphylaxis.[172] For example peanuts may be found in chili, plain M & M's, egg rolls, pastry, biscuits, and milk formula. Even genetically engineered foods, such as transgenic soybeans, have been found to contain Brazil nut protein.[173] Children may taunt classmates with food allergy and hide allergenic foods in the child's lunch![174] Individuals with food allergies to peanut, tree nuts, shellfish, and fish do not spontaneously lose their sensitivity in contrast to milk, egg, and wheat allergy which are common food allergens in children and are usually "out grown".

Anaphylactoid reactions can occur with administration of blood, plasma, serum and fractionated serum products, and immunoglobulin. These reactions are thought to occur due to

immune complex formation with subsequent complement activation. One fascinating case report exists of a patient who had eaten fish prior to a tranfusion of blood products and developed anaphylaxis due to passive transfusion of IgE to fish from a fish allergic blood donor![175] Anaphylactoid reactions occur in 0.02% to 21% of plasmapheresis when fresh frozen plasma is used as the replacement, which is much more common than when albumin is used as a replacement.[176] Parenteral iron preparations are in the form of iron-dextran complexes and can cause anaphylactoid reactions in 0.1% of injections.[177] Patients with IgA deficiency are at increased risk of reactions to IgA containing products. Approximately 20-30% of IgA deficient patients have anti-IgA antibodies[178] which can then bind to donor IgA forming immune complexes which can then activate complement. Rarely, IgE anti-IgA antibodies have been detected in patients with common variable immunodeficiency and thought to cause an IgE mediated anaphylaxis due to intravenous immunoglobulin.[179] These true anaphylactic reactions to IVIG are much less common than the nonanaphylactic variety thought to be due to aggregates with anticomplementary activity.[180] Factor VIII may cause IgE mediated anaphylaxis as was determined in a hemophiliac.[181]

Anaphylactoid reactions can also occur on the basis of agents that can cause the release of histamine from basophils or cutaneous mast cells. Opiates, curare, mannitol, vancomycin, plasma expanders, ethanol, fluorescein and radiocontrast media may all cause anaphylactoid reactions. Although the "red man syndrome" is a well recognized phenomenon due to direct histamine release caused by vancomycin, true anaphylactoid reactions accompanied by urticaria and hypotension have been reported with vancomycin due to a non-IgE mediated mechanism.[182]

There are several types of anaphylaxis in which the pathogenesis is unknown including exercise-induced anaphylaxis, idiopathic anaphylaxis, progesterone anaphylaxis, ethanol anaphylactoid reactions[183] and reactions to preservatives. Progesterone sensitive anaphylaxis was first reported by Meggs et al. in 1984.[184] They described a 36 year-old woman with chronic urticaria who went on to have recurrent anaphylaxis that worsened with pregnancy, resolved during lactation, and was controlled with lutenizing hormone-releasing hormone (LHRH) and ultimately cured by oopherectomy. A few years later, Slater et al. also described 2 other women with a similar course and response to LHRH.[185] These three women shared several features: 1) age > 36, 2) evidence of previous ovarian dysfunction, 3) systemic reactions to intradermal injections of medoxyprogesterone without local immediate wheal and flare response, and 4) systemic reactions after LHRH infusions with ultimate control of symptoms. Progesterone failed to increase basophil histamine release in several patients [186] and the mechanism of this progesterone sensitive anaphylaxis remains unknown.

Nonsteroidal anti-inflammatory drugs are well known triggers of severe bronchospasm in aspirin sensitive asthmatics and can exacerbate urticaria in 40% of patients with chronic urticaria. True anaphylactic reactions to NSAID's were thought to be rare, however, Kemp et al. reported that NSAID's were the most common cause of medication induced anaphylaxis in their study of 266 anaphylaxis cases. It is not clear from this report whether the authors distinguished NSAID anaphylaxis from the more common aspirin idiosyncratic reaction seen in aspirin sensitive asthmatics. Idiosyncratic reactions to aspirin are related to cycloxygenase inhibition and are not drug

specific, therefore aspirin-sensitive asthmatics must also avoid most all NSAID's. In contrast, true anaphylactic reactions to NSAID's typically occur in healthy individuals and are drug specific as shown by challenge studies.[187] The pathogenesis of NSAID anaphylaxis may be IgE mediated but limited data is available.

ACUTE TREATMENT OF ANAPHYLAXIS

The clinical syndrome of anaphylaxis is caused by different mechanisms and its effects on different organ systems is variable, therefore no simple algorithm is sufficient. Due to the unpredictable onset of anaphylaxis and its potential for fatality within minutes, no randomized controlled studies have been performed, and probably never will. Therefore, treatment strategies developed for anaphylaxis have been based on known immunologic mechanisms, pharmacologic properties of drugs, animal studies (despite the fact that there is no animal model that truly resembles human anaphylaxis), and primarily clinical observations and anecdotes.

Successful treatment of anaphylaxis is aided by timely recognition of anaphylaxis and early treatment. Studies have demonstrated that delays in therapy are associated with fatalities.[26],[103] Once anaphylaxis is suspected other general measures are indicated including assessing the nature (laryngeal edema vs. hypotension vs. bronchospasm) and severity of the reaction, and obtaining a brief history, including medications (especially β-blockers) to determine a possible cause so that other specific steps can be taken to reduce further absorption of the antigen. All patients should have supplemental oxygen, intravenous fluids and close monitoring of vital signs including cardiac monitoring. The goals of therapy in anaphylaxis are similar to those in cardiopulmonary resuscitation, maintaining an effective airway and circulatory system.

Epinephrine continues to be the first-line drug of choice in anaphylaxis. It has potent α, β_1, and β_2-adrenergic properties that are essential in countering the effects of the multiple mediators released in anaphylaxis. The α-agonist effects of epinephrine help to increase blood pressure by peripheral vasoconstriction, reversing the vasodilation seen in anaphylaxis. The β-agonist effects help reverse bronchoconstriction, cause positive inotropic and chronotropic cardiac activity, and cause increased cyclic AMP levels which can inhibit further mediator release from mast cells and basophils.[188] The generally preferred method of administering epinephrine is subcutaneously in a dose of 0.3 to 0.5 mg of a 1:1,000 dilution, and can be repeated as needed every 10-15 minutes. For patients initially seen in cardiovascular collapse, IV epinephrine is indicated. There is a wide range of dosages recommended by different authors however Barach et al. make some compelling arguments for their dosage of 0.1 mg (0.1 ml) of a 1:1,000 dilution of aqueous epinephrine mixed in 10 ml of normal saline infused over 5-10 minutes(100 mg bolus) followed by an infusion of epinephrine using the standard ACLS protocol.[188] Epinephrine may also have detrimental effects including severe hypertension, arrhythmias,[189] and myocardial ischemia and infarction.[190]

Table 7. THERAPY FOR ACUTE ANAPHYLAXIS			
AGENTS	**INDICATIONS**	**DOSE**	**COMMENT**
Epinephrine	All symptoms	0.3-0.5 ml of 1:1,000 SC (0.3-0.5 mg) q 10-20 min	1st line therapy for all anaphylaxis Administer immediately
	Hypotension	0.1 ml of 1:1000 in 10 ml NS IV over 5-10 min Maintenance drip: 1 ml of 1:1,000 in 500 ml D5W IV @0.25-2.5 ml/min (0.5-5μg)	Increased side effects Cardiac monitoring mandatory
Antihistamines	Urticaria	Hydroxyzine 25-50 mg IM or po every 4-6 hr	Not a substitute for epinephrine Second line therapy Reduces pruritus Hydroxyzine more potent H_1-antagonist than diphenhydramine
	Hypotension	Ranitidine 300 mg IV	Antagonize H_2-receptors on vasculature
Corticosteroids	Bronchospasm	Methylprednisolone 125 mg IV then 40 mg IV q 6 hr prn	May not prevent biphasic response
Bronchodilators	Bronchospasm	Albuterol 0.5 ml in 2.5 ml via nebulizer	May help bronchospasm refractory to epinephrine
		Aminophylline 6 mg/kg IV loading dose followed by IV drip 0.3-0.9 mg/kg/hr	Only indicated if bronchospasm refractory to β–agonist
Oxygen	All patients	Dosage to maintain O_2 Sat >90%	
Intravenous fluids	Hypotension	1 liter q 20-30 min prn of crystalloid or colloid	
Vasopressors	Hypotension	Dopamine 400 mg in 500 cc D5W IV @ 2-20 mg/kg/min	Dopamine drug of choice but norepinephrine can also be used
Misc. Agents	Refractory Hypotension or β-blockade complicated	Glucagon 1 mg in 1 liter D5W IV @ 5-15 ml/min (5-15 μg)	Nausea and vomiting common
		MAST trousers	
	Bradycardia	Atropine sulfate 0.3-0.5 mg IV	
	Bronchospasm	Isoproterenol	

There are several misconceptions regarding the use of epinephrine. Patients often think they will have plenty of time either to seek medical attention or to "wait and see" if things get worse. This type of erroneous decision making can lead to death. Even when used in a timely fashion, anaphylaxis will not always respond to epinephrine and fatalities may still occur.[87],[103],[191],[16],[26] Finally it is critical to realize that the benefits of epinephrine far outweigh the risks in anaphylaxis. It is more important to administer epinephrine to a patient in anaphylactic shock with a history of cardiac disease than to withhold this therapy since the physiologic effects of improperly treated anaphylaxis would be more detrimental to the patient.

Patients with a history of anaphylaxis should carry epinephrine with them at all times. The two most common forms of epinephrine prescribed for patient self-use are the Ana-Kit® and the Epi-Pen®. The Ana-Kit contains 1:1,000 epinephrine in a syringe, capable of administering two 0.3 mg doses , along with four 2mg chlorpheniramine tablets and a tourniquet. The Epi-Pen contains a single 0.3 mg dosage of 1:1,000 epinephrine in a spring-loaded auto-injector. The Epi-Pen is preferred by most since it is much simpler and quicker to use and since the needle is not visible and, less anxiety provoking. The Ana-Kit requires holding the syringe upright and expelling the air and excess epinephrine, followed by rotating the plunger 1/4 turn to the right prior to injecting the needle. Its advantages are that it is less expensive, and can deliver 2 doses of epinephrine.

Epinephrine can also be delivered by inhalation through a metered dose inhaler. Two studies have compared inhaled epinephrine using a Medihaler® MDI in normal subjects.[192],[193] Both studies demonstrated rapid rises in plasma epinephrine levels after inhalation of epinephrine in dosages ranging from 10-30 puffs (1.5-4.5 mg). The studies differed in that Heilborn et al. found that a 0.5 mg subcutaneous injection of epinephrine in the thigh produced variable absorption that was very slow to peak in some, while Warren et al. found no variation or delay in peak levels using the same dosage administered subcutaneously in the deltoid. Both studies showed that elevations in plasma epinephrine were of shorter duration when given by the inhaled route. Müller has stated that inhaled epinephrine acts more rapidly on respiratory symptoms in anaphylaxis to venom immunotherapy and that it can rapidly reduce uvulopharyngeal edema due to its topical effects.[194] He also states that his patients use inhaled epinephrine more readily than injectable epinephrine due to fear of injections. Plomley and Czarny described a patient with anaphylactic shock who failed to respond to 30 inhalations of epinephrine (0.4 mg) but did respond to a 0.5 mg subcutaneous injection.[195] In contrast, Peltz et al . described a patient with uvular angioedema unresponsive to subcutaneous epinephrine who responded to topical epinephrine squirted through a needle at her uvula within 10 minutes.[196] The American Academy of Allergy and Immunology in a 1994 position statement did not recommend inhaled epinephrine for first-line treatment of anaphylaxis.[197] However, for patients with stereotypical attacks of anaphylaxis with mild throat swelling, especially if idiopathic or in those whom true laryngeal edema is uncertain, inhaled epinephrine is a reasonable first-line therapy but subcutaneous epinephrine should always be available.

Several other medications are useful adjuncts to epinephrine in the therapy of anaphylaxis. Antihistamines, especially H_1-antagonists are thought to be useful, especially for the cutaneous

symptoms of anaphylaxis. The role of H_2-antagonists is somewhat controversial but overall the evidence favors the addition of H_2-antagonists [198],[199], especially in the presence of hypotension.[200] A combination of H_1 and H_2 antagonists was required for optimal prevention of hypotension in studies of histamine infusions.[52] Other medications used in anaphylaxis are listed in Table 7. The opiate antagonist naloxone [201],[202] and MAST trousers[203],[204] have also been reported to be helpful anecdotally. Tranexamic acid was also reported to be helpful in a patient with suspected anaphylactoid shock due to a transfusion reaction.[205] The proposed mechanism of action was due to tranexamic acid's ability to inhibit the complement and plasmin and kallikrein systems. Any patient suffering from life-threatening anaphylaxis should be admitted for 23 hour observation, or at a minimum be held in observation for 8-12 hours.

Patients who are taking β-blockers and develop anaphylaxis may be especially refractory to therapy. Beta blockade can increase release of mediators, and enhance the responsiveness of the pulmonary, cardiovascular, and cutaneous systems to these mediators.[206] β-blockers can also cause paradoxical responses to epinephrine due to unopposed α-adrenergic and reflex vagotonic effects leading to bronchoconstriction and bradycardia. Persisting anaphylaxis complicated by β-blockers can be treated with high doses of isoproterenol or dopamine, atropine, MAST trousers, and glucagon. Glucagon has been used to treat propranolol toxicity[207] and was reported to be helpful in reversing hypotension due to an RCM anaphylactoid reaction.[208] Glucagon may exert its beneficial effect through increasing cyclic AMP independent of the β–adrenergic receptor[209],[207] however nausea and vomiting are common and may increase the risk of aspiration.

PREVENTION OF ANAPHYLAXIS

Almost all patients with anaphylaxis should be referred to a BC/BE allergist for follow-up evaluation. The role of the allergist is to help determine an etiology for the anaphylaxis, educate the patient on avoidance measures, and develop a management plan to prevent and reduce further anaphylactic episodes. If an IgE-mediated mechanism is suspected, further evaluation may include skin testing, challenges, or desensitization when appropriate. Patients need to be instructed on the proper use and indications of injectable epinephrine, when to seek medical attention, and to obtain a Medic-Alert® bracelet (Medic-Alert Foundation, 2323 Colorado Ave, Turlock, CA 95382, 1-800-432-5378) or at the very least carry information on their person regarding their anaphylactic condition. If a patient is on β-blockers, an alternative drug should be selected.

Ideally, alternative agents should be selected for therapy in patients known to be sensitive to particular agents. However, if there is an absolute indication for the anaphylactic agent, desensitization is required. The technique of acute desensitization involves administering gradually escalating doses of the antigen over a brief period. Typically, the initial amount of antigen is diluted to $1:10^5$-10^6 and in a stepwise fashion, the dose is doubled every 15-30 minutes. The oral route of desensitization is preferred when possible (penicillin, aspirin) since it is safer but parenteral administration may be the only alternative (e.g. insulin). Desensitization procedures are dangerous and often can produce systemic reactions and therefore should not be entered into without exploring all other options. The mechanism of desensitization is unknown but the desensitized state is antigen

specific and not due to tachyphylaxis to mediators, mast cell depletion, or unresponsiveness to any IgE signal.[210] One theory suggests that during desensitization, free drug or univalent drug-carrier conjugates might out-compete multivalent conjugates for IgE binding.

EXERCISE-INDUCED ANAPHYLAXIS

Exercise-induced anaphylaxis (EIA) is a newly recognized form of anaphylaxis. In 1979, Maulitz et al. described a 31 year old long distance runner with recurrent episodes of facial flushing, pruritus, urticaria, and angioedema occurring immediately after exercise, but not every time he exercised.[211] Further evaluation revealed he had positive skin tests to clams, oysters, shrimp, and crab, yet he had no reactions from ingesting these shellfish. However, eating shellfish several hours prior to exercising would result in anaphylaxis with exercise.

Since this case report , numerous other cases have been reported and EIA has been classified into 3 subtypes. EIA may occur independent of ingesting food or it may only occur after food ingestion prior to exercise. Food dependent EIA can be further subdivided into specific food dependent EIA in which individuals will have EIA only if they exercise after eating a specific food or foods, and non-specific food dependent EIA which can occur if exercising after eating any food. Specific food dependent EIA has been reported to occur with a limited but growing number of foods including shellfish,[211] wheat [212],[213], celery[214],[215] tomato,[216],[217] apple,[218] grapes,[219] litchi,[220] hazlenut,[221] chestnut,[216] peanut[222],[223], milk,[223] rice[216],[223] and potato.[222] One case of celery-dependent EIA would occur only if the patient ingested celery after exercising![215]

EIA has been studied using exercise challenges with various exercise stimuli. Similar to historical data, exercise does not always elicit anaphylaxis in patients with EIA. In a study of 11 Japanese patients with EIA, only 3/11 had both anaphylactic symptoms and a rise in plasma histamine.[219] Other groups have reported similar findings with reaction rates of 4/7 and 3/8 EIA subjects.[224],[217] Evidence of mast cell activation has been demonstrated in

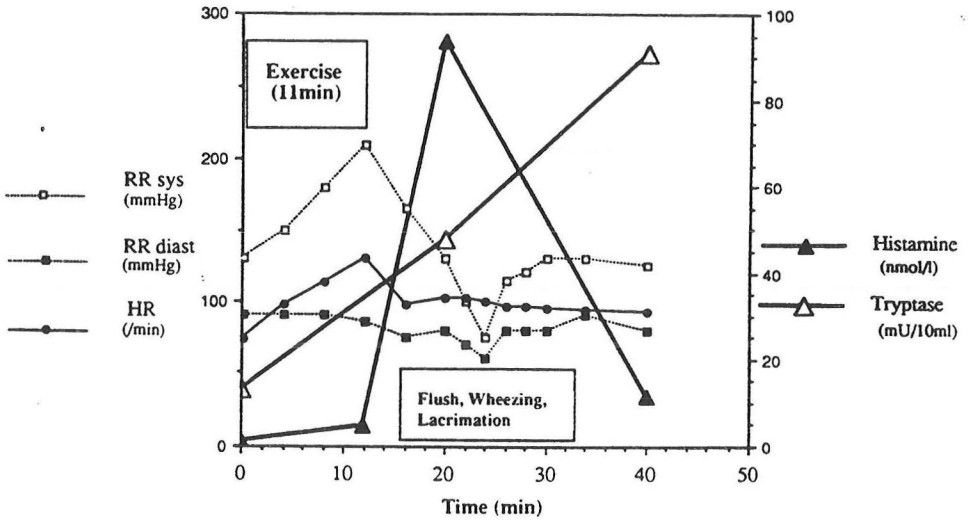


FIG. 6. Bicycle exercise test in patient with EIA demonstrating rise in histamine and tryptase levels. From: Attenhofer et al.[95]

these exercise challenge studies of EIA including elevations in serum histamine[224],[219] and tryptase as shown in Figure 6.[95],[225] Skin biopsy specimens comparing mast cell morphology by both light and electron microscopy before and after exercise challenge of EIA subjects has revealed variable but reproducible alterations in mast cell granule morphology.[226](Figure 7) These changes include a relative loss of electron density and internal structures of granules, fusion of granule membranes with adjacent granules, and an apparent decrease in the number of granules per cell. These changes are similar to IgE dependent mast cell degranulation *in vivo*.

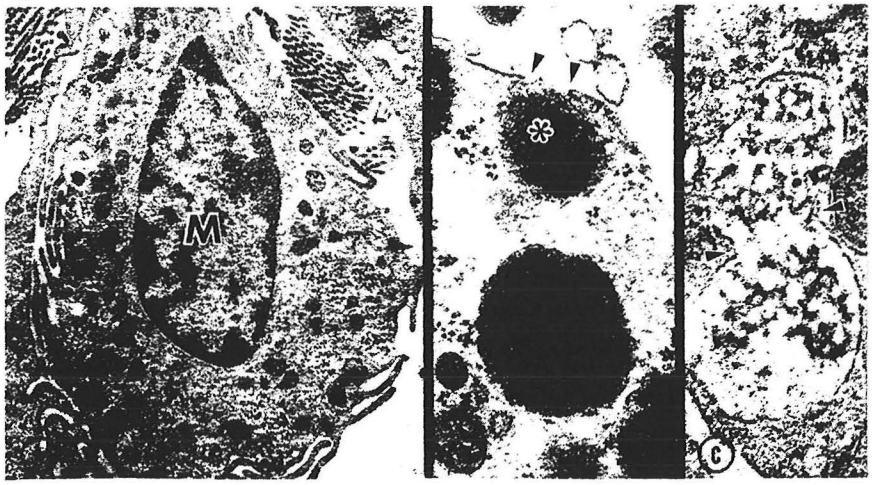


FIG. 7. (A) Mast cell (M) in a patient with EIA post-challenge showing depletion of dense granules, (B*) loss of electron density , and (C)fusion of adjacent membranes (arrowheads). From: Sheffer et al.[226]

The mechanisms responsible for mast cell degranulation in EIA are not known. Increases in codeine skin test reactivity after exercise was shown in a single patient with food specific EIA and not controls.[227] The authors postulated that ingestion of a specific food may cause a subthreshold amount of mast cell associated IgE cross-linking and that exercise can then provide an endogenous opioid stimulus that can then trigger the primed mast cells to degranulate. Skin testing with compound 48/80 (a histamine releasing substance) was shown to have an increased wheal response in individuals with food-dependent EIA, but only after challenges with a combination of specific foods and exercise.[228] This data adds further support of the concept of subthreshold mast cell activation occurring in food-dependent EIA. Another postulated mechanism for food dependent EIA is that gastrin secretion may be linked to triggering EIA. Tharp et al. demonstrated that gastrin can stimulate mediator release from human cutaneous mast cells in vitro and in vivo and hypothesized that subclinical antigen-IgE stimulation may be potentiated by postprandial gastrin release.[229] Finally, Fukotomi et al. found abnormal responses of the autonomic nervous system in 4 subjects with EIA who underwent autonomic testing before and after exercise challenge which did not provoke anaphylactic symptoms.[230] Increases in parasympathetic responses, as measured by the Aschner test, and decreases in sympathetic activity, as determined by postural and cold pressor tests, were found in these EIA subjects. The clinical significance of these findings however is unclear.

The prevalence and natural history of EIA are unknown. In a review of 179 cases of anaphylaxis identified over a 3.5 year period at the Mayo Clinic, Yocum and Khan identified

exercise as an etiology in only 12 subjects or 7% of cases, which is in agreement with Kemp et al.who determined exercise to be the etiology of anaphylaxis in 7% of their 266 subjects.[40],[39] The symptoms and signs of EIA are similar to other forms of anaphylaxis and range from mild cutaneous symptoms to wheezing, hypotension and even ventricular fibrillation.[95] Typically, premonitory symptoms include generalized warmth and pruritus, usually followed by urticaria. In EIA, urticarial lesions are usually 10-15 mm in diameter, but smaller 2 mm urticaria may occur and then coalesce to larger lesions. Urticaria is often followed by angioedema most often involving the face, palms, and soles. Other anaphylactic symptoms are variable. Although Sheffer et al. were unable to document airway obstruction after exercise challenge in 7 EIA subjects,[224] Caffarelli et al. demonstrated2 patients with decreases in FEV_1 and peak flows after food-exercise challenge.[222]

The types of exercise that may trigger EIA are quite variable ranging from mild tennis warmups to strenuous exercise including dancing, soccer, basketball, and running.[231] One case of EIA was even reported to be triggered by vaginal delivery.[232] The vast majority of EIA reactions occur while exercising or shortly thereafter and last 30 minutes to 4 hours, however one case of isolated late EIA was reported to manifest 4 hours after a grain flour-exercise challenge.[213]

Several other factors may predispose susceptible patients to EIA. Most patients reported have a personal or family history of atopy. Familial EIA has been reported in 2 male siblings with EIA and a paternal cousin with exercise induced urticaria and was thought to be linked with the HLA haplotype A3-B8-DR3.[233] Sheffer et al. reported that aspirin ingestion prior to exercise may have been a trigger in almost 1/3 of EIA subjects, while other subjects noted exercising in warm or humid weather to be an aggravating factor.[41] Some women with EIA report increased attacks in relation to their menses.[219],[234]

The main other diagnostic consideration in patients with anaphylactic symptoms after exercise is cholinergic urticaria. Cholinergic urticaria is another form of "physical allergy" that can be precipitated by not only exercise but also passive heating and emotional stress.[235] Cholinergic urticaria usually produces a distinctive skin lesion of tiny 1-3 mm pruritic wheals as opposed to most cases of EIA in which subjects have urticaria of >10 mm in diameter. As mentioned previously, rare EIA patients can have urticaria more typical of cholinergic urticaria. Patients with cholinergic urticaria may also have systemic symptoms other than urticaria including wheezing, gastrointestinal symptoms[236] and syncope.[237] Plasma histamine levels have been found to be elevated in cholinergic urticaria but serum tryptase may not be[238] One method of distinguishing between EIA and cholinergic urticaria is through passive heat challenge. Elevating the core body temperature through passive heating will reproduce anaphylactic symptoms in patients with cholinergic urticaria but not in EIA patients.[239]

The acute treatment of EIA is no different than any other type of anaphylaxis and epinephrine remains the drug of choice. All patients should have self-injectable epinephrine available while exercising and should exercise with a partner who has been instructed on administering epinephrine. Preventing EIA can usually be achieved by limiting exercise and discontinuing exercise at the first sign of prodromal symptoms. Patients should avoid nonsteroidal antiinflammatories and exercising in certain types of weather if these factors have been previously suspected. For patients with food

dependent EIA, either the specific food(s) or meals in general should be avoided prior to exercise. Although some authors recommend avoiding specific foods for 12 hours (for specific food dependent EIA) and all foods for up to 8 hours prior to exercise,[234] other authors recommend avoiding foods for 4-5 hours prior to exercise and have demonstrated success in long term follow-up.[217],[223] Prevention of EIA has been attempted with different antihistamines with variable success. Although often helpful, antihistamines usually are unable to totally prevent attacks. Beta agonists and phosphodiesterase-inhibiting agents have provided no prophylactic benefit.[41] One case report described successful prevention of wheat dependent EIA in a single patient with oral disodium cromoglycate.[240] This study was limited to an open challenge with a single exercise challenge. Two independent groups reported successful prevention of EIA in 2 patients by ingesting 3 g of sodium bicarbonate prior to exercise,[241],[242] while in another patient it was unsuccessful.[243] Finally, Kaplan reported a patient with EIA vs. cholinergic urticaria who had a progressive reduction in symptoms with daily exercise for 15 min/day, however this was only continued for 5 days and no long term follow-up was reported for this "exercise desensitization".[237]

RADIOGRAPHIC CONTRAST MEDIA ANAPHYLACTOID REACTIONS

Radiographic contrast media (RCM) is used in > 10 million diagnostic procedures per year in the U.S.[244] Severe anaphylactoid reactions that require treatment occur in 0.04%-0.02% of patients receiving ionic and nonionic contrast media respectively.[14] Fatal reactions occur in approximately 1:10,000[31] to 1;40,000 [245] intravenous procedures and it is estimated that over 500 deaths per year occur in the U.S. due to RCM reactions.[246] Anaphylactoid reactions to RCM occur in the setting of intravenous or intrarterial administration, with the latter procedures having an even higher rate of fatal reactions.[31]

Traditional RCM are derivatives of tri-iodinated benzoic acid.[247] RCM must contain sufficient iodine for adequate opacification. Ionic RCM tend to have a higher osmolarity. By forming dimers of benzoic acid, newer nonionic RCM have been developed which have a lower osmolarity due to increases in the ratio of iodine atoms to dissolved particles. These low-osmolar nonionic RCM are 20-30 times more expensive than traditional ionic RCM.

The pathogenesis of anaphylactoid reactions to RCM is not known however several mechanisms have been postulated. First, RCM infusions have been shown to cause elevations in plasma histamine, but this occurred in the absence of signs or symptoms of anaphylaxis. Plasma histamine can be normal during an RCM anaphylactoid reaction. Secondly, complement activation has also been shown to occur with RCM infusions. Severe reactions may be associated with complement activation and patients with a history of RCM reactions have lower C1 esterase inhibitor and CH50 levels than nonreactors.[247] However, falls in complement do not consistently correlate with the anaphylactoid event.[248] Third, RCM produces numerous other biologic effects including inhibition of platelet aggregation, inactivation of several enzymes, hypocalcemia, and disruption of vascular endothelium with the potential to activate Factor XII initiating the clotting, clot lysis, and kinin formation.[248] Patients with RCM reactions also have an increased ability to convert prekallikrein to kallikrein,[247] suggesting bradykinin may mediate some of the symptoms.

Although it has been postulated that RCM reactions may be due to the high osmolarity alone, no increases in plasma osmolarity were seen after administration of hyperosmolar media.[247] Finally, the majority of evidence does not support an IgE-mediated or other antigen-antibody mechanism in RCM reactions.

Despite the common belief that individuals with seafood allergy have a higher risk of RCM reactions, there is no data to support this and it has no theoretical basis. Individuals with seafood allergy have specific IgE directed against specific proteins, not iodide. As mentioned previously, the mechanism for anaphylactoid reactions to RCM is not due to the iodide per se, but physiochemical properties of the RCM complex itself. In fact, low-ionic RCM, have a lower incidence of reactions despite containing more iodide per dissolved particle.

Table 8. HIGH RISK PATIENTS FOR RCM ANAPHYLACTOID REACTIONS

High Risk Patients	Estimated Risk
History of prior anaphylactoid reaction	35-60%
Asthma	4-5 times greater risk
Use of β-blockers	2.7 times greater risk
Cardiovascular disorder	7.7 times greater risk for severe reaction

There are several risk factors for anaphylactoid reactions to RCM. Patients with a history of "allergy" have been shown in several large studies to be at increased risk for RCM reactions.[31],[245],[32],[14]. These studies were further validated by a study by Enright et al. who showed that RCM reactors were twice as likely to have positive skin tests to a panel of inhalants and foods as nonreactors.[43] However, there was no difference in frequency of seafood allergy. Asthmatics are 4-5 times more likely to have an anaphylactoid reaction, especially severe anaphylactoid reactions.[249][245] Bronchospasm occurred in almost 15% of asthmatics compared to 4% of nonasthmatic patients in a group of 4,120 patients receiving intravascular contrast.[31] Patients on ß-blockers also have a 2.7 fold increased risk and are 9 times more likely to be hospitalized after an anaphylactoid reaction.[249] A history of cardiac disease increases the prevalence of severe RCM reactions.[14],[249] While some authors feel patients older than 50-60 have a higher risk,[247][250] the largest study of 337,647 cases did not find a significant difference in RCM reactions in various age distributions.[14]

Patients with a history of prior reactions to RCM are also at higher risk of a recurrent reaction. Anaphylactoid reactions may recur in 35-60% of repeated RCM exposures.[32],[31] Shehadi provided the most detailed report on recurrence of specific symptoms after another RCM procedure.[31] Of 268 patients with a prior reaction of urticaria, 60% had recurrence of hives; 68%

of 134 patients had recurrence of facial; edema; 59% of 39 patients had recurrence of dyspnea; and hypotension recurred in 2/19 patients.

There is no type of testing procedure that can identify patients who will develop a reaction to RCM. Initially, skin testing was performed but this was abandoned due to low accuracy. Intravenous test doses had been used in the past and have not been shown to be reliable predictor of future reactions.[251],[32],[252] Furthermore, fatal reactions have occurred form test doses as small as 0.5 cc![253],[251]

Due to the failure of predicting reactors, prophylactic pharmacotherapy evolved as a method of reducing recurrent reactions. Greenberger et al. reported the largest study of patients with a history of an anaphylactoid reaction to RCM and the results of 3 pretreatment strategies.[254] Pretreatment with prednisone (50 mg orally 13, 7, and 1 hour before) and diphenhydramine (50 mg orally or intramuscularly one hour before) in 415 high-risk patients demonstrated a 10.8% reaction rate. However, most were minimal reactions with hives in 1% and transient hypotension in 0.6%. The addition of 25 mg of ephedrine orally 1 hour before in 180 patients resulted in a further reduction of reaction rate to 5%, none of which were serious. Interestingly, addition of cimetidine 300 mg orally to the prednisone-diphenhydramine-ephedrine combination resulted in a statistically significant increased reaction rate of 14% in 100 studied patients. Marshall and Liberman compared these same three regimens in a smaller group of 149 patients with a prior reaction to RCM and found similar reaction rates in all three groups (6-8% reaction rates).[255] Ring et al. found that a combination of cimetidine and an antihistamine clemastine, reduced reaction rates compared to intravenous prednisolone or clemastine or saline alone.[256] However, patients enrolled in this study did not have to have a history of prior RCM reaction and those with severe reactions were excluded. Taken together the data suggest that addition of an H_2-antagonist is not helpful and may actually increase reaction rates in high-risk patients.

The use of nonionic contrast media in high-risk groups has also been evaluated. Katayama et al. studied 25,750 patients with a history of any reaction to RCM and found 22% of 11,751 patients reacted with ionic contrast while 6% of 13,999 reacted to nonionic contrast without premedication.[14] Severe reactions occurred in 0.56% of ionic RCM cases and 0.1% of nonionic RCM cases. Premedication reduced the rate of severe reactions in ionic RCM cases from 0.56% to 0.28% but there was an even lower severe reaction rate in both ionic and nonionic RCM cases of 0.1% whether they received pretreatment or not. These authors concluded that nonionic contrast renders premedication unnecessary. In a smaller series of 291 repeat reactors, Siegle et al. found a repeat reaction rate of 5.5% for all reactions and 1.7% for severe reactions using a nonionic contrast material.[257] Although the repeat reaction rate was not statistically different between those premedicated and those who were not, the authors felt this relationship was of questionable significance, since patients with more severe reactions tended to be premedicated. Greenberger and Patterson combined pretreatment with nonionic contrast in 181 high-risk patients, and found only one reaction of mild urticaria or a reaction rate of 0.1%.[258] In coronary angiography, use of low-osmolality contrast agents reduced "moderate adverse reactions" by three-fold and was deemed to be cost effective in high risk patients.[250]

In summary, patients at high risk for severe anaphylactoid reactions include: 1) patients with prior history of anaphylactoid reaction to RCM, 2) asthmatics, 3) patients on β-blockers, and 4) patients with cardiovascular disorders. If use of an RCM is essential, β-blockers should be discontinued and a nonionic contrast agent selected. These patients should also be pretreated with prednisone 50 mg 13, 7, and 1 hour before and diphenhydramine 50mg 1 hour before. Emergency equipment should always be readily available to treat severe reactions.

INSECT STING ANAPHYLAXIS IN TEXAS

Anaphylaxis to stinging insects is quite common occurring in 0.3-3% of the population.[15],[259],[25] Stinging insects are of the order Hymenoptera and are from two major subgroups: vespids include the yellow jacket, hornet and wasp, and apids include the honeybee and bumblebee. Imported fire ants are from the same Vespoidae superfamily as vespids. Almost all physicians recognize that stings from apids and vespids can cause anaphylaxis and that specific testing and immunotherapy is available and effective. Furthermore, several recent review articles from experts in the field have been published on this subject.[38],[260],[261] Therefore, I will focus on insects in Texas that ,may cause anaphylaxis, including imported fire ants, Triatoma, and "killer bees".

Imported Fire Ants

Imported fire ants (IFA) are probably the most common cause of anaphylaxis to stinging insects in this area. The imported fire ant species, Solenopsis invicta and Solenopsis richteri, were native to South America. S. Richteri was introduced from either Uruguay or Argentina accidentally into the USA through the port of Mobile, Alabama on agricultural products in 1918 and is currently localized an area of northeastern Mississippi and northwestern Alabama.[262] The Brazilian species, S. Invicta was introduced later between 1933 and 1941 and has spread throughout the Southeast as far north as Richmond, VA and westward into Texas. IFA mounds in the US can reach far greater sizes and numbers of ants than those in South America.[263] IFA are endemic to the Southeast inhabiting more than 250 million acres and cause widespread damage with an estimated $125 million loss of soybean crops in 1981.[264]

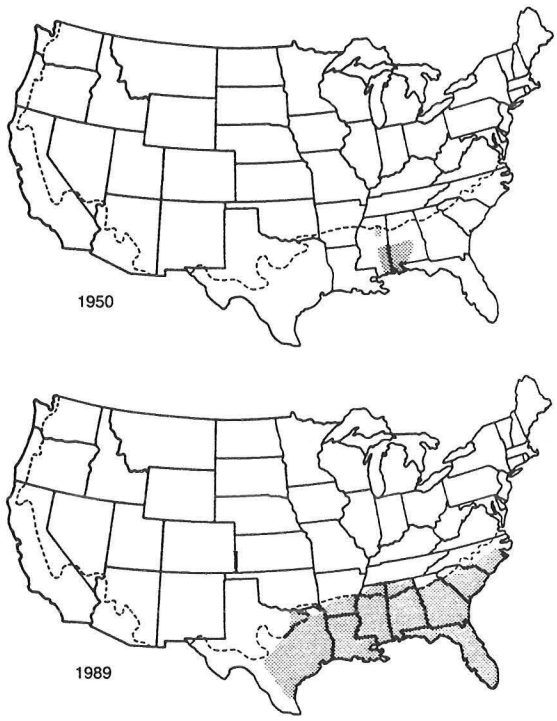


FIG.8. Areas infested by IFA in 1950 and 1989. Dotted line is 10° isotherm. DeShazo et al.[267]

IFA are quite aggressive as demonstrated by their high attack rates. A recent study of medical students enrolled in a military training program with limited outdoor activity revealed an attack rate of 51% during 3 weeks in the summer.[265] In another study of a military base at Ft. Stewart, Georgia, IFA reactions were responsible for 49% of outpatient and 71% of hospitalizations for all insect bites and stings during a 6 month period.[266] The vast majority of anaphylactic reactions were due to IFA.

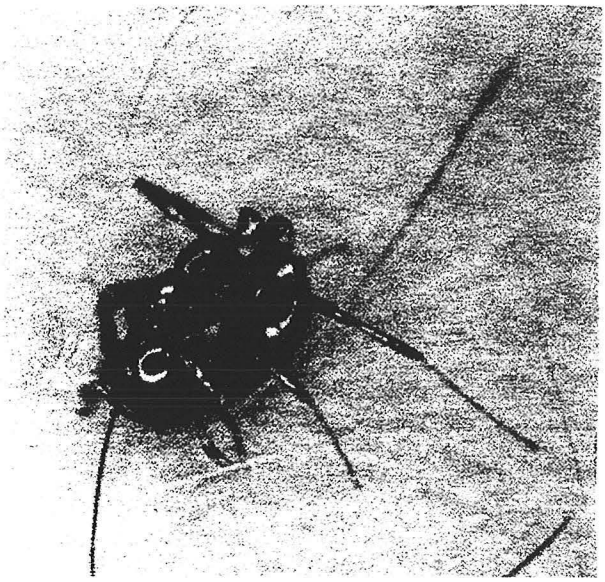


FIG. 9. Imported fire ant in the process of stinging. De Shazo et al.[267]

Fire ants grasp their victim with their mandibles and sting using a modified ova-positer (all workers are female) which slowly injects venom.(Figure 9) A fire ant pivots upon its head and reinserts the stinger to inject venom again. Each sting contains 10-100 ng of protein. The name "fire ant" comes from the burning, pruritic sensation shortly after the sting. Within 12-24 hours, the majority of individuals will develop a pathognomonic "sterile pustule". These pustules are actually necrotic tissue due to alkaloid components of the venom. If left alone, the pustule will spontaneously heal over several days, however a great deal of morbidity to IFA stings is from people scratching the pustules which become infected and can develop cellulitis. Large local reactions which are erythematous, edematous, indurated, and pruritic occur in 17-56% of patients and can be confused with cellulitis.[267] Treatment with antihistamines, topical or systemic steroids may be useful for large local reactions.

Anaphylaxis to IFA occurs in 0.6% to 2% of patients requiring medical treatment for stings.[268][269] Fatal anaphylactic reactions to IFA have been reported. A survey of 2,506 physicians reported 84 fatal anaphylactic reactions, with Texas having the second highest number of fatalities.[270] As opposed to other Hymenoptera, there are no reported deaths due to toxic doses of IFA venom with some victims suffering from thousands of stings with no adverse consequences other than pustules.[271] However, a 5 day old infant developed shock, coma, hemolytic anemia, and a coagulopathy after being home one day and being stung by an estimated 2,000 ants, some of which were found in his posterior pharynx at intubation![272] Given his age, negative RAST to IFA and normal serum histamine, it is unlikely that his reaction was due to anaphylaxis.

The diagnosis of anaphylaxis to IFA is based on a history compatible with anaphylaxis temporally related to a sting with development of the characteristic pustule over the next 12-24 hours. Most individuals who are stung by IFA recognize the sting due to pain. Further confirmation is made through demonstration of fire ant-specific IgE as determined by skin testing or RAST. However, about 25% of nonallergic individuals in endemic areas will have IFA specific IgE.[273] IFA whole body extract is the only commercially available extract for diagnostic and therapeutic use. Unlike honey bee and vespid whole body extracts, IFA whole body extracts contain significant

amounts of immunoreactive allergens. IFA venom obtained originally by hand-milking fire-ants and more recently by electrostimulation[262] has been compared to IFA whole body extracts in diagnosis of IFA allergy.[274] Although venom was more potent, both preparations were equally sensitive. RAST testing was more sensitive with venom than whole body extract, but was not as sensitive as skin testing with either preparation. Large delayed local reactions occurred in 53% of nonallergic controls with whole body extract and was attributed to extraneous, immunogenic body proteins that are not felt to be important in clinically significant allergic sting reactions.

For patients with systemic reactions, especially anaphylaxis, to IFA stings, immunotherapy with IFA whole body extracts is recommended. A retrospective study found that 47 patients on immunotherapy had 112 field restings resulting in one anaphylactic reaction (2.1%).[275] Six patients who declined immunotherapy had 11 field restings resulting in 6 systemic reactions including 4 anaphylaxis reactions. All 6 untreated patients who were restung had systemic reactions. Furthermore, 30 patients on immunotherapy had an intentional sting challenge resulting in no systemic symptoms. Although this study was retrospective and not controlled, it supports the use of immunotherapy in IFA anaphylaxis. The duration of immunotherapy for IFA is unknown. Preliminary data suggest that 2 years of immunotherapy is adequate to protect 94% of patients from intentional sting challenge.[276]

Although IFA are currently a medical hazard only in the Southeast, they may soon become a national hazard. It is expected that S. Invicta will spread west to California and as far north as the Canadian border over the next decade.[273] The 10°F isotherm was thought to be the thermal boundary for IFA, but S. invicta-richteri hybrids appear to be adapting to cooler climates, able to travel north beneath paved roads acting as heat sumps. Furthermore, Northerners have had anaphylaxis to their first IFA sting due to cross reactivity between vespid venom proteins (such as in yellow jacket) and the proteins Sol I 1 and Sol I 3 in S. invicta venom. Finally, since fire ants have been responsible for indoor sting fatalities,[277] and travelers can be stung in the airport (personal observation), there may be no safe refuge from fire ants, which have earned the name "The ants from hell".[264]

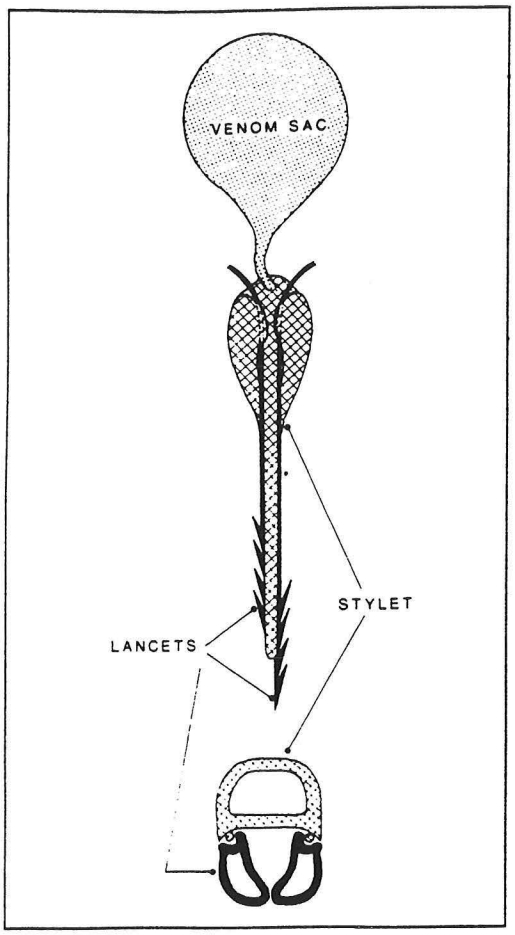
"Killer Bees"

Africanized honeybees, popularly known as "killer bees", entered Texas in 1990. African honeybees were initially reported to produce more honey than European honeybees which were brought to the New World by European settlers. In 1957, during studies of the African honeybee in Brazil, the queens and workers of 26 hives escaped establishing wild, or feral, African colonies.[278] These bees bred with European honeybees to form hybrid "Africanized honeybees". This Africanization process has spread north 200 miles/year and Africanized honeybees have now been identified in California and Arizona in addition to Texas.

Africanized honeybees retained several African traits including excitability, aggressive defense, and frequent swarming. Because of these traits, individuals stung by Africanized honeybees often involve multiple stings. Several hundred fatal bee-sting incidents have been reported over the past few decades in South and Central America.[279] These fatal sting incidents typically involve

hundreds of individual stings. The clinical manifestations of these multiple sting reactions have not been well characterized but have included hypotension or hypertension, pulmonary edema, acute or delayed renal failure, rhabdomyolysis, anemia, thrombocytopenia,andneurologic complications.[280][281] The most likely etiology for these reactions is due to toxic effects from the venom and not hypersensitivity reactions.[38] The median lethal dose of honeybee venom has been estimated at 19 stings/kg or 500-1400 stings.[278] Older age, cardiopulmonary disease, and the number of stings are important factors in these toxic reactions.[280]

Africanized honeybees often build their hives in old tires, hollowed trees, holes in walls and fences and other exposed areas. If a hive is encountered and bees recruit to swarm, the first response should be to escape, as most children and adults can outrun a swarm even though a swarm may pursue a victim as far as 1 km. Others should not try and rescue a victim as they will usually succumb to a similar attack by an already aggressive swarm. In south Texas, firefighters have been trained to use heavy smoke screens and use a high-pressure spray containing surfactant to rescue victims. Stingers should be removed as quickly as possible as well as attached sacs with a blunt item such as a credit card. Victims should receive immediate medical attention and observation for delayed reactions. The number of stings should be estimated to determine the potential severity of attack. The role of immunotherapy is controversial since most sting reactions are toxic reactions to venom constituents including phospholipase A_2 and mellitin. Africanized honeybees contain less venom but more phospholipase A_2 than European honeybees.[282] However, since European and African honeybee venoms are similar in their physiochemical and allergic properties, commercial honeybee venoms can be used for skin testing and immunotherapy.[283]



The schematic drawing shows the honeybee-sting mechanism. The ventral view shows the alternating motion of lancets. The lower portion of the drawing shows a cross-section (based on Snodgrass[41] and Mulfinger et al[42]).

FIG. 10. Honeybee stinging mechanism. Sherman[278]

It has been estimated that with the spread of Africanized honeybees, the number of fatal reactions due to insect stings will increase from 40 to 100 per year.[283] However, it may be reassuring to remember that African societies have lived peacefully with Africanized honeybees for centuries managing their hives and harvesting honey.

"Kissing Bugs"

Allergic reactions to the bite of the insect genus Triatoma have been known since the late 1800's.[284] Many Triatoma harbor Trypanosoma cruzi but are thought to be rarely involved in the transmission of Chagas' disease.[285] Six species of Triatoma may be encountered in the continental US, primarily in the Southwest. Triatoma bugs have several names including kissing bugs, cone-nose bugs, assassin bugs and Mexican or Texas bedbugs.[286] Adult Triatoma are 2-3 cm long, dark brown to black, winged insects with a proboscis and long antennae. Their primary hosts are wood rats, opossums, armadillos, and other rodent nests. Triatoma have seasonal dispersal coinciding with peak egg laying, usually in the spring and summer. They fly at night and may be attracted to the light of houses. Triatoma are exclusive blood feeders. Since they usually feed at night, and have a painless bite which may take 10 to 25 min for a feeding, the host is usually not awakened. Furthermore, Triatoma are quite stealthy, emerging only at night and can remain undetected in well-kept rooms.

Most bites occur on uncovered areas of the body, are multiple and typically appear as 2-3 cm pruritic urticarial nodules with a central punctum, but may be vesicular or hemorrhagic.[287],[286] The prevalence of specific IgE to Triatoma saliva was found to be 6.7% in a study of a rural southern California population.[288] The incidence of anaphylaxis is unknown and limited to numerous case reports.[289],[285],[290] Shields and Walsh allowed Triatoma to intentionally bite themselves and found increasing reactions with successive bites.[287] Most cases of anaphylaxis awaken the individual from sleep due to the nocturnal bites. Another unusual feature of Triatoma allergy is its association with altered menstrual cycles and metorrhagia.[291] Patients from endemic areas, with nocturnal anaphylaxis, and typical bite lesions can be diagnosed by skin testing with Triatoma whole body extracts or salivary gland extracts. The salivary gland extracts are preferred due to higher potency and less extraneous compounds in the extract.[291] Immunotherapy has been shown to be successful with whole body extracts as judged by later field stings[285] and salivary gland extracts which prevented anaphylaxis after intentional Triatoma bite challenges.[291], [284] These latter studies used Triatoma protracta and it has been shown that there is no cross reactivity to a few other Triatoma species.[288]

IDIOPATHIC ANAPHYLAXIS

The term idiopathic anaphylaxis (IA) was first used in 1978 to identify a group of patients in whom anaphylactic symptoms occurred without an apparent etiology.[292] Since that time, IA has become a well described entity with a classification system and management plan.[293],[294],[295], [296],[297], [298]. Most data on IA is derived from Patterson and colleagues at Northwestern University who have followed over 335 cases since the 1970's.[44]

Ditto et al. recently updated Northwestern's experience with IA consisting of 335 patients. Few other groups have reported their experience with idiopathic anaphylaxis, usually with much smaller numbers of patients and limited characterization of clinical features.[299],[300],[39] The second largest group of IA patients comprehensively reported was from Khan and Yocum at the Mayo Clinic.[45] The characteristics of this group of 35 patients is similar in many respects to the

335 IA patients reported by Ditto et al. Both patient groups were of a similar age distribution, mostly female, and had a higher prevalence of atopy and drug allergy than the general population. Manifestations of anaphylaxis were also similar in that virtually all patients had either urticaria or angioedema and the majority had upper airway obstruction. However, the Mayo IA patients had more frequent hypotension (69% versus 23%) and gastrointestinal symptoms (57% versus 22%) than Northwestern IA patients. Of interest, 37% of Mayo IA patients experienced nocturnal symptoms which was not commented on in the Northwestern experience. Given the very similar clinical features of IA patients from 2 different referral centers, IA appears to be a fairly homogeneous entity.

The etiology for IA is unknown. Patterson et al. have provided several theories to explain the features of IA including: 1) uncontrolled activation of different types of mediator releasing cells, 2) dysregulation of histamine-releasing factors, 3) autoimmune activation of mast cells via anti-IgE antibodies, and 4) uncontrolled release of bioactive mediators.[295] Unfortunately, all of these theories are purely speculative and other than clinical characterization and therapeutic trials, there has been no published studies addressing the etiology of IA using immunologic or molecular biologic techniques.

Table 9. CLINICAL FEATURES OF IA	**Northwestern** (Ditto et al.) 335 IA patients	**Mayo** (Khan and Yocum) 35 IA patients
Atopy	48%	43%
Age	Median age: 30-39	Mean age: 48
Female Gender	65%	72%
Drug Allergy	40%	34%
SYMPTOMATOLOGY		
Urticaria/Angioedema	100%	97%
Upper Airway Obstruction	63%	63%
Bronchospasm/Dyspnea	39%	51%
Hypotension/Syncope	23%	69%
Gastrointestinal Symptoms	22%	57%
Nocturnal Symptoms	NR	37%

The diagnosis of IA is by definition one of exclusion. Appropriate work up of anaphylaxis patients has been discussed earlier. Patterson et al. have suggested that a trial of prednisone 40 mg daily for two weeks can be used as a diagnostic and therapeutic trial in patients with frequent episodes.[294] Failure to respond to this treatment is not compatible with a diagnosis of IA. Like other forms of anaphylaxis, serum tryptase can be elevated during acute attacks of IA.[301]

Patterson and colleagues have classified IA into 11 separate classifications.(Figure 11) The first classification was based on whether patients had generalized symptoms (IA-G) or symptoms isolated to upper airway angioedema (IA-A), however this may not be a useful classification since both groups responded to treatment similarly and had similar outcomes.[293] The next type of classification was based on frequency of attacks.[302] IA-Infrequent (IA-I) have attacks < 6/year while IA-Frequent (IA-F) have attacks ≥ 6/year. Later IA-Single episode (IA-SE) was added.[294] This frequency based classification is important in terms of treatment and prognosis as will be discussed later. In 1992, Orfan et al. Reported on 4 patients who lacked objective evidence of IA during symptomatic episodes and did not respond to systemic steroids and were considered to have IA-Questionable (IA-Q).[303] Another similar classification is IA-Variant (IA-V) in which patients have a history that does not completely fit with known presentations.[294] Along the same lines, Undifferentiated somatoform disorder-IA (US-IA) is used to designate patients lacking objective findings and meeting DSM criteria for somatoform disorder.[298] Lastly, corticosteroid dependent-IA designates patients with IA unable to be taken off prednisone[297] and malignant-IA patients cannot taper below a prednisone dose of 60 mg q.o.d. or 20 mg daily.[304] Overall, I think this classification scheme is fairly burdensome and not particularly useful with the exception of designating the frequency of episodes.

Type of IA	Description
Idiopathic anaphylaxis-generalized-infrequent; (IA-G-I; n=100)	Urticaria or angioedema with bronchospasm, hypotension, syncope, or gastrointestinal symptoms with or without upper airway compromise with infrequent episodes (<6/y)
Idiopathic anaphylaxis-generalized-frequent; (IA-G-F; n=101)	As above, with frequent episodes (≥6/y)
Idiopathic anaphylaxis-angioedema-infrequent; (IA-A-I; n=64)	Urticaria or angioedema with upper airway compromise such as laryngeal edema, severe pharyngeal edema, or massive tongue edema without other systemic manifestations with infrequent episodes (<6/y)
Idiopathic anaphylaxis-angioedema-frequent; (IA-A-F; n=56)	As above, with frequent episodes (≥6/y)
Idiopathic anaphylaxis-questionable; (IA-Q; n=9)	Applied to a patient whose history of episodes of idiopathic anaphylaxis are inconsistent with idiopathic anaphylaxis-generalized or idiopathic anaphylaxis-angioedema, and whose diagnosis is questionable until further documentation can be achieved.
Idiopathic anaphylaxis-variant; (IA-V; n=2)	Applied when symptoms and physical findings of idiopathic anaphylaxis are variable from classic findings of idiopathic anaphylaxis. Idiopathic anaphylaxis-variant may subsequently be classified as idiopathic anaphylaxis-questionable, idiopathic anaphylaxis-angioedema, idiopathic anaphylaxis-generalized or idiopathic anaphylaxis may be excluded.
Undifferentiated somatoform-idiopathic anaphylaxis; (US-IA; n=3—initially diagnosed as IA-G-F, IA-G-I and IA-Q)	Applied for a patient whose history mimics idiopathic anaphylaxis but lacks correlating objective physical findings, shows no response to the therapeutic regimen for idiopathic anaphylaxis and meets the criteria for undifferentiated somatoform disorders as defined in the Diagnostic and Statistical Manual for Mental Disorders.

FIG. 11. Classification of Idiopathic Anaphylaxis. Ditto et al.[44]

The clinical course of IA has been determined to be quite variable.[299], [45],[39],[303],[44] Lieberman et al. reported on their experience with 18 patients with IA and noted that 50% of their patients who were available underwent remission, but attacks continued in the other 50% .[299] However, the duration of follow-up was not stated and 8 of 18 patients had no follow-up. Of interest, only one patient from this group had frequent idiopathic anaphylaxis by the current classification system. The largest group of IA patients with follow-up data were reported by Orfan et al. Out of 225 patients, 147 had follow-up data reported and 64% underwent remission (no episodes for more than one year in the absence of glucocorticoid therapy) and 14% still had frequent episodes. Remission occurred in 77% with infrequent episodes and 48% with frequent episodes of IA. In the study by Khan and Yocum, 35 of 37 patients were available for follow-up and 86% of patients had either resolution or improvement in their disease, while only 6% had a worsening of their disease.[45] Similar to Northwestern's experience, remission occurred more often in those with infrequent IA than those with frequent IA. Kemp et al. reported that 94% of 34 IA patients had a gradual reduction in attack frequency. Overall there is appears to be a favorable clinical course with IA, however 3 fatalities have recently been reported.[305],[306]

Patients with infrequent episodes of IA do not require chronic therapy. However, all patients should have self-injectable epinephrine available. Interestingly, 91% of the IA patients in Kemp et al.'s study carried epinephrine, while only 53% of those with other types of anaphylaxis did. It has been recommended that patients with frequent episodes of idiopathic anaphylaxis be treated with prednisone and antihistamines based on the results of several clinical studies which suggested that prophylactic medications controlled attacks of idiopathic anaphylaxis.[293],[302],[307],[308] These reports were followed by an open protocol involving 53 patients who were treated with antihistamines, sympathomimetics, and prednisone depending on the frequency and severity of idiopathic anaphylaxis.[309] This study showed that prophylactic treatment improved clinical outcome, however, a control group was not used for ethical reasons. In the study by Khan and Yocum, of 11 frequent IA patients, 6 had no glucocorticoid treatment and all of them improved or underwent remission. This raises the question of whether glucocorticoids actually induce remission or whether remission is part of the natural history of idiopathic anaphylaxis. Although certain patients with idiopathic anaphylaxis have anecdotally been noted to have increased episodes when their steroids were tapered,[297] controlled trials have not been published. Since so little is known regarding the pathogenesis of idiopathic anaphylaxis, it is not clear what effect glucocorticoids have on this disease from a pathophysiologic standpoint. Furthermore, how glucocorticoids control or lessen episodes of anaphylaxis is currently unknown. Ketotifen has been shown to be efficacious in the majority of corticosteroid dependent idiopathic anaphylaxis patients in which it was tried.[310],[311] Ketotifen as well as newer antihistamines and other non-glucocorticoid agents such as leukotriene receptor antagonists and lipoxygenase inhibitors should be further studied.

HUMAN SEMINAL PLASMA ANAPHYLAXIS

Immediate hypersensitivity reactions to human seminal plasma (HSP) in women have been increasingly recognized over the last few decades. In 1958, Specken reported the first case of HSP anaphylaxis in a 65 year-old women who suffered from urticaria and bronchospasm after

intercourse.[312] Since then at least 40 cases of HSP allergy have been reported.

The first insight into the pathogenesis of HSP reactions was provided by Halpern et al. in 1967.[313] They evaluated a woman who developed symptoms of urticaria, angioedema, dyspnea, nasal congestion, uterine contractions, and syncope occurring 15-30 minutes after coitus. Scratch tests were positive to both whole sperm and seminal fluid devoid of spermatozoa from her husband as well as other human donors but was negative to her husband's serum, and semen from rabbit, guinea-pig, horse and bull. Passive transfer (Prausnitz-Küstner reaction) was positive in 5 female controls as well as in monkeys. Employing chromatography and electrophoresis, they were able to identify in seminal fluid, basic protein fractions that were the most antigenic. Further evidence that this was an IgE mediated mechanism was provided by Levine and colleagues who were able to prevent PK reactivity by anti-IgE.[314],[315] Leukocyte histamine release (LHR) assays have mostly been positive but RAST testing has yielded mixed results.[314-23] Only one case has been reported of a women reactive to spermatozoa and she was also reactive to HSP.[320] Another case report described a women with HSP allergy who also had positive skin tests to sweat from her husband and 2 sons.[324] Canine sperm can also induce anaphylaxis as reported in a very bizarre case of a pregnant woman with anaphylaxis due to bestiality with her German Shepherd.[325]

Since then several other investigators have attempted to isolate the antigenic fraction of seminal fluid and have found peak allergenic activity in fractions with a MW of predominately 20,000 to 30,000 daltons (range 12-75 kd).[314],[317],[316],[326] The antigen has been shown to be heat stable and of prostatic origin.[315] Seminal plasma has numerous potentially immunogenic substances, some specific to semen and others common to other body fluids.[327] The immunogenicity of semen was demonstrated in the early 1970's during studies on infertility where 50% of women given injections of diluted semen had anaphylactic reactions during the course of attempted immunization.[328] Yunginger has provided preliminary data using RAST inhibition that prostate specific antigen (PSA) may be a major allergen in HSP.[329]

Several cases of HSP allergy are temporally related to events involving the female reproductive tract including pregnancy, hysterectomy, insertion of an IUD, or tubal ligation.[330],[318],[331] It has been postulated that immunoregulatory mechanisms may be dampened after these events, predisposing women to a HSP allergic reaction. Some cases have involved vasectomized men[314],[318] and experimental evidence suggests that the immunosuppressive activity of seminal plasma may be diminished after vasectomy.[318] Bernstein et al. reported on 3/4 women with HSP allergy who had HLA sharing with their partners and speculated that this may be involved in the pathogenesis of HSP allergy.[320] These finding have yet to be confirmed.

The clinical manifestations of HSP allergy are quite variable. Symptoms can be purely local vulvovaginitis with pruritus, burning, pain and localized swelling or manifest as potentially life-threatening anaphylaxis.[331] The onset of symptoms is typical for an IgE mediated reaction occurring within 30 minutes of intercourse and often sooner. HSP allergy usually occurs in younger women who are atopic.[323] It often presents after first intercourse or after the first intercourse following pregnancy.[320] Since the HSP antigen(s) are thought to be from prostate tissue, most women who have had more than one partner react to each partners ejaculate. Only one case of familial HSP allergy has been reported but this was confined to local vulvovaginitis only.[332]

Age of onset		**Predisposing conditions**	
<20	1	First intercourse	13
20–30	18	History of pregnancy	8
31–40	5	Gyn surgery	1
41–50	1	Urological surgery	1
>50	1	Unknown	10
Unknown	6		33†
	32		
Reactions		**Onset, min**	
Dermatitis/Urticaria/Pruritus	27	<5	12
Edema	15	5–30	2
Dyspnea	7	31–60	1
Local pain	18	>60	7
Anaphylaxis	7	Unknown	10
	32		32
History of atopy		**Family history of atopy**	
Yes	19	Yes	12
No	10	No	4
Unknown	3	Unknown	16
	32		32
Multiple partners		**Prevented by condom**	
Yes	7	Yes	20
No	8	No	0
Unknown	17	Unknown	12
	32		32

FIG. 12 Clinical presentation of 32 women with HSP allergy. Presti and Druce[323]

Allergic symptoms occurring after intercourse are not always attributable to HSP allergy. There are a few case reports of exogenous allergens ingested by the male partner and excreted in seminal fluid causing allergic reactions after intercourse in women sensitized to these allergens. These seminal fluid reactions have been reported with walnuts,[333] vinblastine,[334] penicillin,[335] and thioridazine.[336] In the case of the walnut induced reaction, walnut protein was detected in the man's seminal fluid. Anaphylaxis after intercourse due to latex in a condom has also been reported.[337]

A comprehensive history is essential to the evaluation of suspect HSP anaphylaxis. Skin testing with dilutions of the partner's semen or seminal plasma can be performed and is always positive in patients with anaphylaxis. In patients with local symptoms, a validated questionnaire may be more reliable.[330] Due to the other bioactive properties in HSP, the partner should also be tested since at higher concentrations non-specific irritant reactions can occur. Finally, skin testing to HSP can cause systemic reactions[322] and anaphylaxis[324] and should therefore be performed by trained personnel with appropriate resucitative equipment available.

The use of a condom prevents contact of HSP allergens and is universally successful in preventing allergic symptoms and may even induce remission if used for prolonged periods. Kroon reported 4 women with symptoms of urticaria and angioedema who used condoms for 6-12 months.[338] All four women's skin tests to seminal fluid converted from positive to negative after this time. Furthermore, 3/4 women had unprotected intercourse with no symptoms following the 6-12 months of condom usage. None of these women had anaphylaxis. Intravaginal cromolyn has been reported to be helpful in local HSP reactions,[339] however others have noted it no different than placebo.(JW Yunginger, personal communication) Prophylactic antihistamines are sometimes successful at controlling local HSP reactions

but are thought to be ineffective for systemic reactions.[327] Finally, Shapiro et al. reported a case of a women with HSP anaphylaxis who was successfully impregnated using artificial insemination with isolated spermatozoa.[340]

The first trial of immunotherapy was by Halpern et al. using whole seminal plasma and was completely unsuccessful.[313] Mathias et al. next reported on a woman with HSP anaphylaxis who requested immunotherapy due to the presence of a well-publicized rapist in her neighborhood.[319] Treatment with dilutions of her husbands seminal plasma resulted in a reduction of LHR and RAST binding. Six months into the immunotherapy a condom broke during intercourse and she had only mild urticaria instead of anaphylaxis. Bernstein and colleagues reported the first completely successful trial of immunotherapy using the fraction of HSP causing the greatest LHR.[318] Two weeks after the final dose of immunotherapy, unprotected intercourse was performed in a medical facility and "under the supervision of a physician" without any symptoms. The patient remained symptom free until a 2 week period of abstinence occurred and she had mild respiratory symptoms. By maintaining sexual activity 2-3 times per week she remained asymptomatic. Several other reports of successful immunotherapy have followed including rapid desensitization protocols[341],[321] and long term success up to 8 years after immunotherapy.[322] Immunologic changes occurring with HSP immunotherapy have been variable, but one report revealed a decrease in IgE to an unmeasurable level with a progressive rise in IgG,[326] a pattern typical of other forms of immunotherapy. Finally, rapid intravaginal immunotherapy has been reported to be successful in HSP allergy and allowed one woman to become pregnant through unprotected intercourse.[342],[343] Therefore it appears that by using the antigenic fraction of HSP, desensitization may be a successful long term approach for women desiring not to use condoms regularly.

CONCLUSION

Anaphylaxis is the most dramatic and potentially fatal manifestation of immediate hypersensitivity. The majority of reactions are due to medications, insect stings, radiocontrast media and food, however a large percentage are idiopathic in nature. Most anaphylactic reactions respond to aggressive therapy, but fatalities still occur, especially if treatment is delayed. Epinephrine is still underutilized in many patients, despite being the drug of choice in anaphylaxis, . Given the complexities involved with diagnosis, education, and proper management of this life-threatening syndrome, almost all cases of anaphylaxis should be referred to an allergist. Hopefully with further research into the pathogenesis of anaphylaxis and the development of newer immunomodulatory agents, further fatalities from anaphylaxis may be prevented.

FIG. 13 Postage stamp issued in 1952 by the Principality of Monaco to commemorate the 50th anniversary of the discovery of anaphylaxis. From: May[1]

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