

Anaphylaxis

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Anaphylaxis, the most severe type of allergic reaction, occurs when a large number of mast cells and basophils are stimulated to release mediators such as histamine, prostaglandins, and leukotrienes. This paper reviews the various causes of anaphylaxis and focuses primarily on recent reports in the area of insect sting allergy. The role of challenge stings in determining the use of venom immunotherapy, the proper interval between venom injections, the kinetics of venom delivery, and the spread of killer bees are examined. Latex sensitivity, a new cause of anaphylaxis, is also discussed.

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Anaphylaxis is a clinical syndrome that is rapid in development, often catastrophic, and sometimes fatal. The usual target tissues include the airways (laryngeal edema, bronchospasm), skin (urticaria, angioedema), cardiovascular (hypotension), and gastrointestinal systems (diarrhea, abdominal cramping). Yocum and Khan [1] and Schwartz [2] reviewed 3.5 years of experience with anaphylaxis at the Mayo Clinic. Of 179 patients with anaphylaxis (mean age 36 years), 66% were female and 49% had atopy. In this study, those patients who had only urticaria were omitted from consideration. Although urticaria can occur in anaphylaxis, many clinicians believe that urticaria must be associated with airway or cardiovascular symptoms in true anaphylaxis. Causes of anaphylaxis were as follows: foods including predominantly nuts, legumes, vegetables, spices, and shellfish (59 patients); idiopathic (34 patients); Hymenoptera stings (25 patients); medications (23 patients); exercise (12 patients); and false-positive diagnosis of anaphylaxis (18 patients). Allergy consultation was obtained in 79% of cases. Allergen skin testing and serum allergen-specific IgE measurements were often helpful. Normal test results included C1 esterase inhibitor in 33 patients, metabisulfite challenge in 15, and dye or preservative challenge in 10. The authors called for a national incidence study of anaphylaxis. Many cases, they believe, go unidentified because there is no International Classification of Diseases code for food anaphylaxis.

Douglas *et al.* [3**] conducted a study of biphasic anaphylaxis. The first part examined 44 episodes of anaphylaxis that occurred during the prescribed 30-minute waiting period after about 81,000 allergy immunotherapy injections. Two of these had a biphasic pattern, which was defined as a recurrent episode of systemic anaphylaxis not secondary to repeat antigen

exposure. Reactions consisted of the following symptoms: 57% cutaneous manifestations, *eg*, urticaria or angioedema; 7% laryngeal swelling; 18% bronchospasm; 7% rhinoconjunctivitis; and 11% involved multiple systems.

Douglas *et al.* [3**] also examined a group of 59 patients who were admitted to the hospital for anaphylaxis. Of these 59 patients, four had a biphasic pattern. Two of the patients with biphasic anaphylaxis had hypotension and generalized urticaria when first seen. The cases of biphasic anaphylaxis were triggered by antibiotics in two cases and food (shrimp) in two cases. The causes of anaphylaxis that required hospitalization were as follows: drugs (22 patients), idiopathic reactions (12 patients), foods (13 patients), exercise (five patients), Hymenoptera stings (three patients), allergy skin tests (one patient), allergy immunotherapy injection (one patient), contrast dye (one patient), and horse serum (one patient). In all, there were six episodes of biphasic anaphylaxis in 103 episodes of anaphylaxis, a considerably lower number than found in previously published reports, some as high as 20% of the total cases of anaphylaxis [4]. Surveys of anaphylaxis such as these provide important information to the clinician.

Challenge stings to select patients for venom immunotherapy

The treatment of insect sting allergy was revolutionized in the late 1970s with the development of honeybee, yellow jacket, hornet, and wasp venoms for skin testing and immunotherapy [5]. The new therapy had a success rate of about 97% in preventing recurrent sting-induced anaphylaxis, and patient selec-

Abbreviations

RAST—radioallergosorbent test; VIT—venom immunotherapy.

tion for venom immunotherapy (VIT) has continued to evolve (eg, children with mild reactions limited to the skin do not require VIT [6]). Recently, van der Linden *et al.* [7] reported their study from the Netherlands of the use of an intentional sting challenge as a diagnostic test to determine the need for VIT. They found that only 39 (28%) of 138 patients who had experienced systemic reactions after a previous insect sting developed generalized symptoms after the in-hospital sting. In the subgroup of 73 patients who had a history of sting-induced hypotension, 29 patients had a recurrent systemic reaction; of these, 17 patients suffered hypotension again (mean arterial pressure decreased from 97 ± 11 mm Hg to 65 ± 19 mm Hg). In the accompanying editorial, Valentine [8] states that the policy at Johns Hopkins has been to avoid deliberate stings in unimmunized patients since several challenge stings resulted in near-catastrophic consequences even when conditions for urgent treatment seemed ideal [9].

A short time later, another paper from the Netherlands reported on a similar, but extended, protocol. Sixty-one patients who had had a history of anaphylaxis to an in-field yellow jacket sting showed no clinical response when first challenged. Franken *et al.* [10**] rechallenged this group of patients and found 13 (21%) had anaphylactic reactions after the second challenge (performed 1 to 12 years later). Six of these patients had severe reactions, including symptomatic hypotension. The initial group had consisted of 228 patients; 90 (39%) had reacted to the first challenge; an additional 13 of 61 patients who agreed to a second challenge reacted to it. Extrapolating from this data, if all of the patients who had a negative first challenge had submitted to a second challenge, the total reaction rate to either of the two possible challenge stings would be 52% in this group of patients. This intermittent reaction pattern in patients with known sensitization and exposure to insect stings shows parallels to food and drug reactions. A single negative response must, therefore, be interpreted with caution. These authors believe that because sting challenges in untreated patients may result in serious reactions and for most patients provide no useful information, they need not be used routinely to exclude patients from VIT.

Two papers by van der Linden *et al.* [11,12] investigated the activation of the contact system and plasminogen in the pathogenesis of anaphylaxis induced by insect venom. Of 16 patients with a history of insect-sting anaphylaxis who underwent sting challenge, seven of 12 patients who developed anaphylaxis had significant changes in factor XIIa-C1-inhibitor complexes, kallikrein-C1-inhibitor complexes, or cleaved high-molecular weight kininogen. No changes were seen in the four patients who did not develop anaphylaxis or the five normal volunteers who also underwent challenge stings [11].

In the second study, 55 patients with a history of insect-sting anaphylaxis and eight volunteers were as-

sayed for activation of fibrinolytic and coagulation systems [12]. Of 20 patients who developed anaphylactic symptoms, seven developed hypotension. In these seven patients, but not in the other challenged subjects, plasma levels of von Willebrand's factor doubled, circulating tissue-type plasminogen-activator rose 10-fold, and plasminogen- α 2-antiplasmin complex increased 50-fold 5 minutes after the onset of clinical symptoms. The authors concluded that both the contact and plasminogen systems may be involved in the pathogenesis of severe allergic reactions.

Finally, van der Linden *et al.* [13**] reported their entire experience in 324 patients with a history of insect-sting reaction seen from 1982 to 1990. Of 272 patients with yellow jacket sensitivity, 75% failed to react to a challenge sting; for honeybee sensitivity, 48% did not react. Plasma levels of venom-specific IgE and IgG4, venom skin tests, severity of previous reaction, sex, age, atopic constitution, histamine skin test results, location and number of previous stings, and time interval between sting challenge and onset of anaphylaxis were studied in relation to the clinical severity of a reaction after sting challenge. Only age and the time interval between sting challenge and the onset of anaphylaxis correlated with the severity of the challenge-induced anaphylaxis. The authors concluded that the current criteria to assess insect-sting hypersensitivity such as skin test or radioallergosorbent test (RAST) do not correlate with the occurrence or severity of anaphylaxis after an insect-sting challenge. Lichtenstein [14*] called for a study in the United States to investigate the use of sting challenge-induced anaphylaxis as the criterion for initiating VIT.

Interval between venom injections

The usual schedule for VIT achieves an interval between maintenance injections of 100 μ g per venom after about 6 months. Many clinicians extend the interval of VIT to 6 weeks and to 8 weeks after 1 and 2 years, respectively. Goldberg *et al.* [15*] showed that extending the interval between venom injections to 3 months was well tolerated, and the authors monitored the efficacy with intentional sting challenges. In 19 honeybee-venom patients who had received monthly venom injections for a mean duration of 17 months (range 4 to 45 months), the challenge sting resulted in a mild urticarial reaction in only one patient. If the majority of VIT patients could have the interval between their injections lengthened to 3 months, the cost savings would be substantial.

Kinetics of venom delivery following honeybee sting

Schumacher *et al.* [16*] induced honeybees to sting rabbits, removed the stings from the skin at various

time intervals, and then measured the residual venom in the venom sacs. The authors also had honeybees sting preweighed filter-paper disks, which were then weighed again after removing the sting at different time intervals. They determined that 90% of the venom sac contents was delivered within 20 seconds. Such information may lead to changes in the often suggested strategy of carefully flicking off the stinger. It appears that speed may be more important than care, and that one should endeavor to flick the stinger off immediately after being stung. Furthermore, the authors found a wide range in the amount of venom delivered for each time point, suggesting that this may explain inconsistencies in relationships among reactions to field stings, sting challenge testing, venom skin tests, and RAST.

Africanized ("killer") bees

Tunget and Clark [17] reviewed the subject of killer bees. Africanized honeybees were the result of interbreeding between escaped African queens and existing Brazilian honeybee colonies. These colonies, which have spread rapidly northward through South and Central America, reached Texas in 1991. The venom composition and antigenicity in these bees are essentially the same as the European honeybee, which populates the United States. However, the label "killer bees" was applied by the media in response to their aggressive nature. Disturbing a hive results in eight to 10 times more stings from Africanized versus European honeybees, and deaths have resulted from greater than 1,000 stings in an individual.

Ariue [18] discussed the case of a 6-year-old Costa Rican boy who had received numerous honeybee stings. On admission he was obtunded and received epinephrine, chlorpheniramine, and dexamethasone. He returned to normal mental state approximately 3.5 hours later and was discharged just 7 hours after admission. Whereas reactions to single bee stings are due to an allergic hypersensitivity, multiple bee stings may have a toxic effect.

McKenna [19•] discussed reports of multiple Africanized honeybee stings. Six victims received 20 to 99 stings and six victims received 100 to 1000 stings. Operating machinery, specifically lawn mowing, was the most common type of activity leading to the attack. The head and neck area was the most common site of stings. Examinations revealed hypotension in three cases, hypertension in two cases, pulmonary edema in two cases, and loss of consciousness in three cases. Renal insufficiency was noted in two patients, with 800 and 1000 stings, respectively. One person, an 82-year-old with a history of emphysema and a "heart condition," died after receiving only 50 stings.

Latex

Allergic reactions to natural rubber latex have become an important health problem. Over 1100 allergic reactions and 15 deaths have been reported to the US Food and Drug Administration. In a review article, Hamann [20] describes the types of symptoms that may occur (urticaria, angioedema, abdominal cramps, laryngeal swelling, bronchospasm, hypotension), the populations at risk (patients with spina bifida or urogenital abnormalities, health care and rubber industry workers), diagnostic tests, and treatment.

Kelly *et al.* [21•] reported 12 anaphylactic reactions (fall of ≥ 30 mm Hg in systolic blood pressure and either rash or bronchospasm) in 7386 procedures for the period of January 1990 to January 1991 as compared with no reactions in 5925 procedures in the preceding 12 months. The only new product was an intravenous butretol and tubing system, containing two internal latex valves. The 12 anaphylactic reactions occurred in 10 patients with spina bifida and one patient with a congenital urinary tract abnormality. One of the patients with spina bifida had two reactions. All reactions occurred within 5 to 30 minutes after the start of anesthesia and before any surgical incision. Other patients with spina bifida who were undergoing surgery were selected as control subjects. The patients who experienced anaphylaxis were more likely to have a history of asthma, rubber contact allergy, food allergy, nine or more prior surgical procedures, and latex-specific IgE (as measured by skin prick test or RAST). The patients who experienced anaphylaxis also were skin tested to anesthetics and muscle relaxants; all these yielded negative test results.

Charous *et al.* [22] obtained serum samples and medical histories from 47 symptomatic workers with occupational latex exposure. Of 24 workers with a history of systemic reactions related to latex, all but three had initially experienced either latex-induced contact dermatitis (characterized by redness, pruritus, cracking, and exudation) or latex-induced contact urticaria (noted by erythema and pruritus) within 30 minutes of contact. Sera were analyzed in a blinded fashion at Johns Hopkins or Mayo Clinic using a variety of antigen sources, including ammoniated and nonammoniated raw latex preparations and three finished glove preparations. Positive test results were noted in 15 of 24 workers (62%) with systemic reactions, but only four of 15 workers (27%) with contact urticaria.

Yunginger *et al.* [23••] showed that a 3000-fold difference in latex allergen levels existed among gloves from 71 lots from different manufacturers. Powdered gloves had higher latex levels than nonpowdered gloves. Examination gloves tended to contain higher levels of extractable latex than surgical or chemotherapy gloves. Allergen levels in toy balloons were as high as those found in powdered gloves. Condoms and anesthesia rebreathing bags had lower levels.

The institution of universal precautions, necessitated by the AIDS crisis, has led to a great increase in the use of latex gloves. It has been estimated that 5.6 million American health care and other workers use over 7 billion pairs of gloves a year. It is probable that the use of lower allergen latex gloves would reduce the risk of sensitization and anaphylaxis. Many medical institutions have begun to purchase only gloves with lower latex allergen content.

References and recommended reading

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