Anaphylactic Shock: Pathophysiology, Recognition, and Treatment

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ABSTRACT

Anaphylaxis is a systemic, type I hypersensitivity reaction that often has fatal consequences. Anaphylaxis has a variety of causes including foods, latex, drugs, and hymenoptera venom. Epinephrine given early is the most important intervention. Adjunctive treatments include fluid therapy, H_1 and H_2 histamine receptor antagonists, corticosteroids, and bronchodilators; however these do not substitute for epinephrine. Patients with a history of anaphylaxis should be educated about their condition, especially with respect to trigger avoidance and in the correct use of epinephrine autoinjector kits. Such kits should be available to the sensitized patient at all times.

KEYWORDS: Anaphylaxis, epinephrine, shock, allergy

Objectives: After reading this article, the reader should be able to: (1) discuss the pathophysiology of anaphylactic shock; (2) recognize anaphylactic reactions; and (3) summarize the essential steps in treatment of anaphylactic shock.
Accreditation: The University of Michigan is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.
Credits: The University of Michigan designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award.

Anaphylaxis is a systemic, type I hypersensitivity reaction that occurs in sensitized individuals resulting in mucocutaneous, cardiovascular, and respiratory manifestations and can often be life threatening. Anaphylaxis was first described in 1902 by Portier and Richet when they were attempting to produce tolerance in dogs to sea anemone venom. Richet coined the term *aphylaxis* (from the Greek *a,* against, –phylaxis protection) to differentiate it from the expected "prophylaxis" they hoped to achieve. The term *aphylaxis* was replaced with the term *anaphylaxis* shortly thereafter. Richet won the Nobel Prize in medicine or physiology in 1913 for his pioneering work.[1]

Anaphylaxis occurs in persons of all ages and has many diverse causes, the most common of which are foods, drugs, latex, hymenoptera stings, and reactions to immunotherapy. Of note, a cause cannot be determined in up to one third of cases.[2–4] Anaphylactoid reactions are identical to anaphylaxis in every way except the former are not mediated by immunoglobulin E (IgE). Common causes of anaphylactoid reactions include radiocontrast media, narcotic analgesics, and nonsteroidal antiinflammatory drugs.

Signs and symptoms can be divided into four categories: mucocutaneous, respiratory, cardiovascular, and gastrointestinal. Reactions that surpass

Management of Shock; Editor in Chief, Joseph P. Lynch, III, M.D.; Guest Editors, Arthur P. Wheeler, M.D., Gordon R. Bernard, M.D. *Seminars in Respiratory and Critical Care Medicine*, volume 25, number 6, 2004. Address for correspondence and reprint requests: Roger F. Johnson, M.D., Center for Lung Research, T-1217 MCN, Vanderbilt University Medical Center, 1161 21st Ave. South, Nashville, TN 37232-2650. E-mail: roger.johnson@vanderbilt.edu. [1]Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee. 1069-3424,p;2004,25,06,695,703,ftx,en;srm00340x.

mucocutaneous signs and symptoms are considered to be severe, and, unfortunately, mucocutaneous manifestations do not always occur prior to more serious manifestations. Mucocutaneous symptoms commonly consist of urticaria, angioedema, pruritis, and flushing. Common respiratory manifestations are dyspnea, throat tightness, stridor, wheezing, rhinorrhea, hoarseness, and cough. Cardiovascular signs and symptoms include hypotension, tachycardia, and syncope. Gastrointestinal manifestations include nausea, vomiting, abdominal cramps, and diarrhea.[2,3,5,6]

First-line treatment of anaphylactic shock is epinephrine. Other adjuvant treatments are often also used; however, there is no substitute for prompt administration of epinephrine.

A century has passed since the discovery of anaphylaxis, and much knowledge has been added to our understanding of this syndrome. This article reviews the pathophysiology, recognition, and treatment of anaphylactic shock.

SCOPE OF THE PROBLEM

For several reasons the incidence and prevalence of anaphylaxis are unknown. Notably, because anaphylaxis is not a reportable event, no national registry exists to maintain statistics concerning anaphylactic reactions. In addition, the lack of a standard definition and misdiagnosis by health care personnel hampers efforts to describe the frequency and severity of anaphylaxis. Furthermore, many people that suffer mild reactions never seek medical treatment. Finally, attempting to extrapolate data from small, nonstandard patient populations to a national scale is fraught with problems.[2,3]

The Rochester Epidemiology Study provides the best characterization of anaphylaxis in the United States.[3] This computerized, indexed database contains medical records from residents of Olmsted County, Minnesota. Because of this registry, the residents of Olmsted County have been the subjects of multiple epidemiological studies that are believed to most accurately depict the situation nationally. Important points to note, however, are that Olmsted County is 95% white and has a higher representation of health care workers than the general population. The Rochester Epidemiologic study yielded 154 separate anaphylactic reactions in 133 residents between 1983 and 1987. This translated into a 30/100,000 person-year occurrence rate and a 21/100,000 person-year incidence rate of anaphylaxis. The most common symptoms and signs were cutaneous (100%), respiratory (69%), oral and gastrointestinal (24%), and cardiovascular (41%). Anaphylaxis was more common in the summer months (July–September) and episodes were equal among males and females. Episodes were temporally related to suspected triggers between a few minutes to 2 hours. Atopy was present in 53% of those experiencing anaphylaxis and an allergy consultation was obtained in 52%. The hospitalization rate was 7% and the case fatality rate was 0.91% (one patient out of 133 expired).[3] When projected to the entire U.S. population on an annual basis these numbers are significant.

Neugut et al sought to improve understanding of the epidemiology of anaphylaxis by surveying the medical literature.[2] They estimated that between 3.3 and 43 million people in the United States (based in 1999 population estimates of 272 million) are at risk for anaphylaxis. In addition, they estimated that between 1453 and 1503 people die each year from anaphylactic or anaphylactoid reactions (due to food 100, penicillin 400, radiocontrast media 900, latex 3, stings 40–100). Limitations of this study include underreporting, misdiagnosis, and failure to recognize cases of anaphylaxis by health care providers.[2] Regardless, these numbers show that anaphylaxis is a serious health problem in the United States.

PATHOPHYSIOLOGY

Anaphylactic and anaphylactoid reactions result from systemic release of mediators from mast cells and basophils. Again, anaphylactoid reactions are chemically and clinically indistinguishable from anaphylactic reactions except that they are not IgE mediated. These mediators consist of preformed substances stored in the granules of mast cells and basophils (e.g., histamine, tryptase, heparin, chymase, and cytokines), as well as newly synthesized molecules that are principally derived from the metabolism of arachadonic acid (e.g., prostaglandins and leukotrienes).[4]

Anaphylaxis occurs in an individual after reexposure to an antigen to which that person has produced a specific IgE antibody. The antigen to which one produces an IgE antibody response that leads to an allergic reaction is called an allergen. The IgE antibodies produced may recognize various epitopes of the allergen. These IgE antibodies then bind to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Upon reexposure to the sensitized allergen, the allergen may cross-link the mast cell or basophil surface-bound allergen-specific IgE resulting in cellular degranulation as well as de novo synthesis of mediators.[7] Histamine is thought to be the primary mediator of anaphylactic shock. Many of the signs and symptoms of anaphylaxis are attributable to binding of histamine to its receptors; binding to H_1 receptors mediates pruritis, rhinorrhea, tachycardia, and bronchospasm. On the other hand, both H_1 and H_2 receptors participate in producing headache, flushing, and hypotension.[4]

In addition to histamine release, other important mediators and pathways play a role in the pathophysiology of anaphylaxis. Metabolites of arachadonic acid,

including prostaglandins, principally prostaglandin D_2 (PGD_2) and leukotrienes, principally leukotriene C_4 (LTC_4), are elaborated by mast cells and to a lesser extent basophils during anaphylaxis and, in addition to histamine, are also thought to be pathophysiologically important.[8,9] PGD_2 mediates bronchospasm and vascular dilatation, principle manifestations of anaphylaxis. LTC_4 is converted into LTD_4 and LTE_4, mediators of hypotension, bronchospasm, and mucous secretion during anaphylaxis in addition to acting as chemotactic signals for eosinophils and neutrophils.[8,9] Other pathways active during anaphylaxis are the complement system, the kallikrein–kinin system, the clotting cascade, and the fibrinolytic system.[8]

Specific lymphocyte subtypes (CD4+ Th2 T-cells) are central in the induction of the IgE response. CD4+ T-cells are segregated into either T-helper 1 (Th1) or Th2 types, defined by the cytokine profile produced by the individual T cell. Th1 cells are important in cellular immunity and make interferon gamma. Th2 responses are important in humoral immunity and critical for the allergic response. Cytokines produced be Th2 cells include interleukin (IL)-4, IL-5, IL-9, and IL-13.[10] Of great importance, IL-4 is the isotype switch factor for B cells to begin producing IgE.[10] The IgE response is thought to be an overly robust immune response in certain predisposed (atopic) individuals.[10] Multiple factors influence whether one produces a Th2 versus a Th1 response including genetic variables, environmental factors, and triggers. The hygiene hypothesis suggests that exposure to microbes in infancy leads to "immune deviation" from a Th2 response, which predominates in utero, to a predominantly Th1 response. Lack of this "immune deviation" leads to further perpetuation of the Th2 response to allergens. Stimuli (microbes) that lead to a Th1 response cause IL-12 to be produced by antigen-presenting cells. IL-12 not only perpetuates the Th1 response but inhibits IgE production. Furthermore, cytokines such as interferon gamma (produced by Th1 cells) and IL-18 (produced by macrophages) suppress production of IgE. Thus the Th1 response is considered to be inhibitory to allergy.[10]

The incidence of allergic diseases is on the rise in the United States.[2,10] There are several potential reasons for this observation. Diet may play a role because new allergens are increasingly being introduced into the American diet. For example, the United States is the third largest consumer of peanuts in the world, 40% of consumption is accounted for by peanut butter.[11] Furthermore, the dramatic increase in the use of latex products, particularly gloves, in the past 20 years has also been implicated. Finally, some invoke the "hygiene" hypothesis for the increase in the prevalence of allergic disease.[10] The basis of this hypothesis is that inhabitants of Westernized countries are exposed to fewer (or different) immunologic challenges during immune system development, which leads to less stimulation of the Th1 pathway.

DIAGNOSIS

Diagnosis of anaphylaxis in the acute setting is a clinical one and starts with a brief, directed history because treatment must be rendered quickly. This history should include questions regarding a previous history of atopy or anaphylaxis, and exposure to new foods, medications, and insect bites or stings. Due to the varied presentation of anaphylaxis, it is often not recognized or misdiagnosed. Other conditions that mimic anaphylaxis include vasovagal events, mastocytosis, pheochromocytoma, cardiac arrhythmias, scromboid poisoning, panic attacks, and seizures.[5,12,13] Evaluation should focus on manifestations that are likely to be life threatening. This includes evaluation of the respiratory and cardiovascular systems with particular attention to signs and symptoms of airway compromise and impending cardiovascular collapse.[5] See Table 1 for common manifestations and their frequency.

After or while the patient is being stabilized, a complete history should be obtained. Exposure history prior to the reaction is paramount and must include foods, drugs, stings, or other agents. The time course of events is also important because anaphylactic episodes usually occur shortly after exposure to a trigger; however, manifestations may be delayed by minutes to hours.[3,5] In anaphylaxis induced by foods, this delay is presumably attributable to the time between ingestion and absorption of the offending allergen.[8] In general, it has been observed that the faster the onset of manifestations, the more severe the reaction.[2,5] Although history is essential, it is important to note, however, that anaphylaxis may be the presenting manifestation of hypersensitivity; therefore, lack of previous history of allergy does not rule out anaphylaxis. Atopic persons, as one might imagine, are predisposed to develop anaphylaxis. Asthma, although a predictor for more severe reactions, is not recognized to be a predisposing factor.[2,6] Two laboratory studies, serum tryptase and urinary N-methylhistamine, are useful in confirming anaphylaxis. These tests must be obtained in fairly close proximity to the reaction to be useful. For example, tryptase levels peak 1 hour after anaphylaxis to bee stings and have a half-life in the serum of 2 hours.[14] Similarly, urinary N-methylhistamine peaks 1 hour after IV infusion of histamine and returns to baseline levels after 2 hours.[14] Tryptase level does seem to correlate with severity of the reaction.[4] Furthermore, in cases of suspected fatal anaphylaxis, massively elevated ($>$ 50U/L) postmortem serum tryptase has been shown to be a specific indicator of anaphylaxis.[15]

Causes of anaphylaxis are varied and are listed in Table 2. The discussion of each and every cause of anaphylaxis is beyond the scope of this report; however,

Table 1 Symptoms and Signs, the Number Out of 133 Patients with Anaphylaxis Who Experienced Them

	Patients (N = 133)	
Symptom or Sign	**N**	**%**
Cutaneous		
Urticaria	73	55
Angioedema	74	56
Pruritus	73	55
Flushing	48	36
Conjunctivitis or chemosis	30	23
Respiratory		
Dyspnea	57	43
Throat tightness	37	28
Wheezing	34	26
Rhinitis	22	17
Laryngeal edema	9	7
Hoarseness	9	7
Oral and gastrointestinal		
Intraoral angioedema	20	15
Emesis	12	9
Nausea	12	9
Abdominal cramps	11	8
Dysphagia	7	5
Oral pruritus	5	4
Diarrhea	1	1
Cardiovascular		
Tachycardia	36	27
Presyncope	20	15
Hypotension	15	11
Syncope	4	3
Shock	7	5
Chest pain	4	3
Bradycardia	2	2
Orthostasis	2	2

Reproduced with permission from Yocum et al.[3]

Table 2 Some Causes of Anaphylactic and Anaphylactoid Reactions

MEDICATIONS
Nonsteroidal antiinflammatory drugs, aspirin, antibiotics, opioid analgesics, insulin, protamine, general anesthetics, streptokinase, blood products, progesterone, radiocontrast media, biologic agents, immunotherapy
FOODS
Peanuts, tree nuts, fish, shellfish, milk, eggs, bisulfites
HYMENOPTERA VENOM
Yellow jackets, hornets, wasps, honeybees, fire ants
MISCELLANEOUS
Latex, exercise, gelatin, menstruation, seminal fluid, dialysis membranes

Adapted from Rusznak and Peebles.[41]

new information regarding a new method to prophylax against peanut allergy and recognition that gelatin is a significant cause of anaphylaxis are summarized in the next sections. Also, latex allergy has been recognized as an important cause of anaphylaxis in the past 20 years, and we will review some aspects of latex allergy as well.

PEANUT ALLERGY

It is estimated that 1.5 million people in the United States suffer from peanut and other nut allergies. Nut allergies account for a majority of life-threatening and fatal anaphylactic reactions involving food in the United States.[2,11,16] Peanut allergic patients typically live a life of careful avoidance. Avoidance, however, is not always enough because inadvertent exposure still occurs in sensitized patients every 3 to 5 years.[17]

Currently, management options for patients who suffer from peanut allergy are limited. Prevention by exposure avoidance is the first line of management, and treatment of reactions caused by accidental exposures constitutes the next tier. Desensitization has an unfavorable risk:benefit ratio and is therefore rarely performed.[16] Recently Leung et al reported the effect of anti-IgE therapy in patients with a history of peanut allergy.[16] In this randomized, double-blind trial, patients were randomized to four monthly subcutaneous doses of placebo or three dosage levels (150 mg, 300 mg, 450 mg) of a humanized monoclonal antibody to IgE. Tolerance to peanuts increased significantly in the higher-dose group (450 mg), and there was a trend toward increased tolerance in the other two groups. The mechanism of protection afforded by this treatment is to block binding of IgE to the FcεRI receptors but also leads to down-regulation of the FcεRI receptors on basophils. The increase in tolerance in patients treated with the 450 mg dose translates into an increase in tolerence from 1 to ~9 peanuts. Obviously patients so treated will not have a normal tolerance to peanuts, but this treatment should afford protection against unintended ingestions, which typically are no more than one or two peanuts.[16]

Anti-IgE therapy has also been used effectively to treat allergic asthma.[18] Final approval for anti-IgE therapy to treat patients 12 and over with moderate to severe allergic asthma is anticipated to occur in June 2003.

GELATIN

In 1993, Kelso et al described an anaphylactic reaction to the measles, mumps, rubella (MMR) vaccine in a child, which they ultimately proved was caused by gelatin, included as a stabilizer.[19] The measles and mumps components of the vaccine are produced in cultures of chick fibroblasts and contain minute amounts of egg proteins.[20] Allergic reactions to vaccines, particularly MMR or components thereof, were previously attributed to

hypersensitivity to eggs. In the minds of Dr. Kelso and his colleagues, this made little sense because many children with egg hypersensitivities were uneventfully administered MMR vaccines whereas only two of 28 reports of anaphylactic reactions to vaccines occurred in egg-allergic children.[21] The astute observations of these investigators, coupled with serendipity (their patient reported that the reaction to the vaccine was "kind of like what happens when I eat Jell-O")[21] led these investigators to a paradigm-shifting discovery.

Following the lead of Kelso et al, investigators in Japan characterized anaphylactic reactions to vaccines as also mediated by anti-gelatin IgE.[22] In addition, they uncovered a link to hypersensitivity reactions to orally ingested gelatin, which, interestingly, developed after the vaccine-related reaction in five of seven children. The same investigators also traced gelatin as the cause of anaphylaxis in erythropoietin administered intravenously to hemodialysis patients.[23]

Gelatin is not only a food product but a component of both enteral and parenteral medications. Sensitization to gelatin appears to occur via oral intake or previous vaccination.[21] It is also interesting to note that despite the use of gelatin in the formulations of many oral drugs, particularly capsule forms, there are scant reports in the literature of hypersensitivity to gelatin administered enterally.[21] Therefore, parenterally administered gelatin is more likely to produce hypersensitivity than enterally administered gelatin.[21]

The story for vaccines procured from chick embryos (influenza and yellow fever), which contain significantly more egg protein than MMR, is still unclear. There is a paucity of evidence concerning administration of influenza vaccine in egg allergic individuals, although James et al uneventfully administered influenza vaccine to egg allergic children using a two-dose regimen in which one tenth of the recommended dose was given followed by nine tenths of the recommended dose 30 minutes later.[24] The formulation of vaccine contained between 0.02 and 1.2 μg/mL of egg protein. In the American Academy of Pediatrics Red Book, skin testing prior to administration of yellow fever vaccine to egg hypersensitive individuals is advocated; and administration of influenza vaccine to individuals with severe anaphylactic reactions to eggs is not recommended.[20,25]

LATEX

Latex was used as early as 1600 BC, and use of latex surgical gloves began to proliferate in the early part of the 20th century. Natural rubber latex is derived from the sap of the rubber tree (*Hevea brasiliensis*). Although hypersensitivity attributed to latex was first reported in the late 1920s, latex has become an increasingly important cause of allergy and anaphylaxis over the last 2 decades. The advent of the human immunodeficiency virus (HIV) epidemic in the early 1980s and the institution of the universal precautions policy in the late 1980s are commonly cited contributors to latex hypersensitivity.[26] Furthermore, changes in the manufacturing process of latex gloves driven by increased demand may have led to production of latex products with increased allergenicity. The first reported case of anaphylaxis attributed to latex was published in 1984, and by the end of the decade, reports of anaphylaxis to latex were commonplace.[26]

Risk groups for latex hypersensitivity include patients with spina bifida, patients who have had multiple catheterizations of the genitourinary system such as patients with congenital genitourinary abnormalities, patients who have undergone multiple surgical procedures, people working in the manufacture of latex or latex products, atopic individuals, and health care workers.[27,28] Although controversial, a recent study has suggested that health care workers are not clearly at increased risk for latex sensitization and type I hypersensitivity compared with the general population.[28–31]

Contact with latex is common; it is estimated that as many as 40,000 household products contain latex[27] (Table 3). In addition, it appears that certain fruits and vegetables cross-react with latex, and patients that have an allergy to a particular fruit have subsequently developed an allergy to latex, and conversely, patients with a latex allergy have subsequently developed an allergy to particular fruits. This has been termed the latex–fruit syndrome or the latex–food allergy syndrome.[27,32] It has been noted that 30 to 80% of people who have latex allergy also suffer from food allergy.[27] Commonly implicated foods include banana, kiwi, avocado, and chestnuts; however, others have been implicated as well. It appears that proteins from these natural food products have epitopes that cross react with latex epitopes.[27,32] This, of course, begs the question as to whether sensitization to latex is attributable to the latex itself, the foods just listed, or a combination of both.

Table 3 Items Containing Latex

HOME
Bandages, balloons, condoms, diaphragms, elastic bands in clothing, rubber balls, pacifiers, hand grips, shoes, hot water bottles, shower curtains, toys, waterproofing paints (not all latex paints)
HOSPITAL
Catheters of various types (Foley, nasogastric, intravenous, etc.), gloves, endotracheal tubes, masks, shoe covers and caps, oxygen masks, Ambu®-bags, reflex hammer, stethoscope, syringes

Adapted from Condemi[27] and Nettis et al.[32]

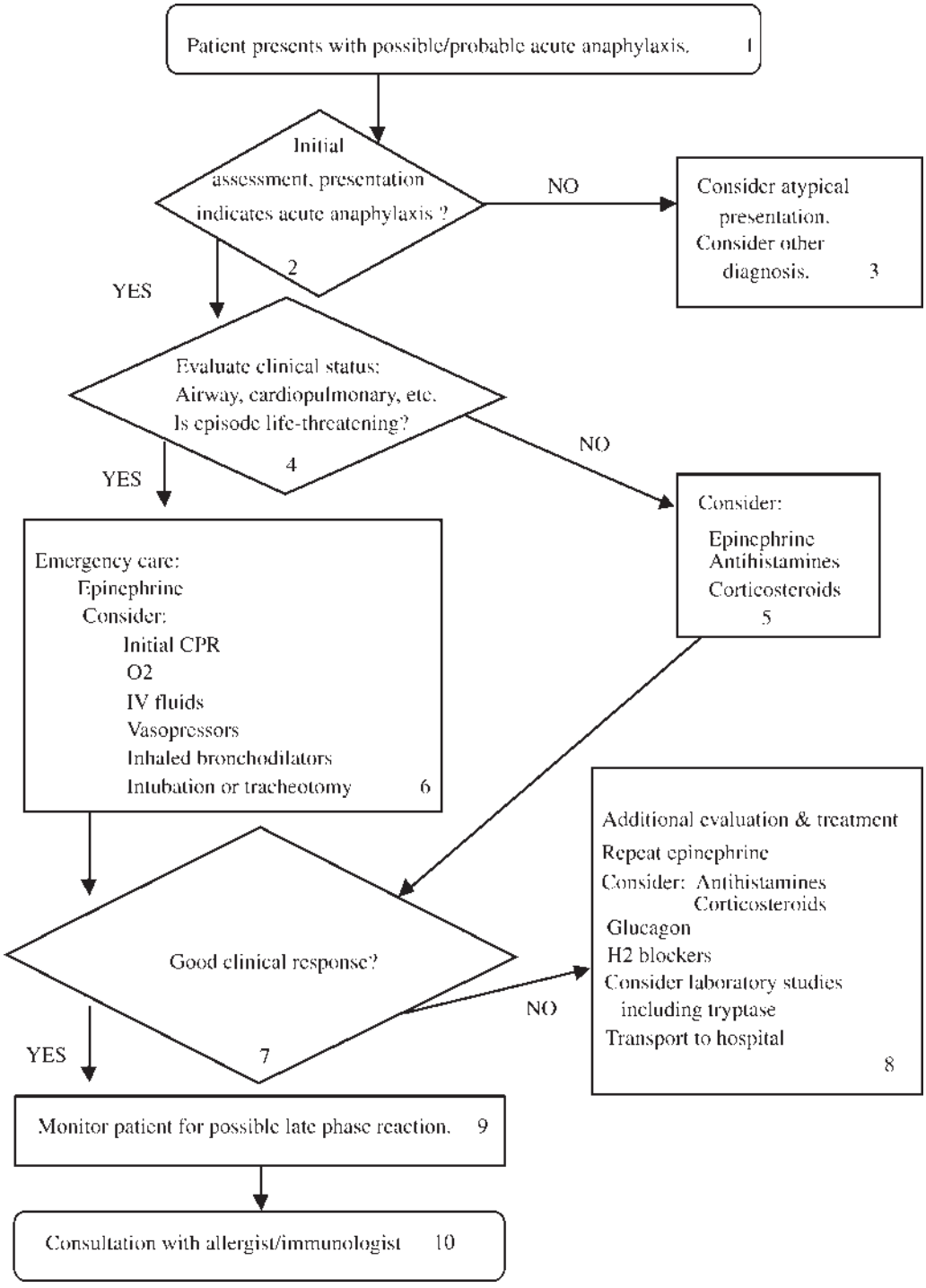

Figure 1 Acute management of anaphylaxis. Reproduced with permission from Joint Task Force on Practice Parameters.[5]

TREATMENT

Once the diagnosis of anaphylaxis is believed likely, immediate administration of epinephrine should occur. A management algorithm is shown in Fig. 1 and an explanation of the medications used in the treatment of anaphylaxis is shown in Table 4. Diphenhydramine and corticosteroids as well as H_2 blockers are also advocated as adjunctive treatments in the management of anaphylaxis; however, they are no substitute for prompt administration of epinephrine.[5] It should be noted that patients can progress from being relatively stable to a state of extremis in a very short time. Biphasic or late phase reactions, in which patients have a recrudescence of anaphylactic signs and symptoms several hours after the anaphylactic episode, have been described in up to 20% of cases.[5,11,12] Patients should therefore be observed for at least 4 hours because 90% of biphasic reactions occur within this time period.[11] Observation for as long

Table 4 Treatment of Anaphylaxis

Therapy	Indication	Dosage	Goals
AIRWAY OR CUTANEOUS REACTIONS			
Epinephrine	Bronchospasm, laryngeal edema, hypotension, urticaria, angioedema	0.3–0.5 mL of 1:1,000 solution IM, every 10 minutes as needed	Maintain airway patency, reduce fluid extravasation
Oxygen	Hypoxemia	Up to 100%	Maintain $SaO_2 > 90\%$
Albuterol	Bronchospasm	0.5 mL of 0.5% solution in 2.5 mL of isotonic saline by nebulizer, or two puffs by metered-dose inhaler every 15 minutes, up to three doses	Maintain airway patency
Diphenhydramine	Urticaria	1 to 2 mg/kg or 25–50 mg parenterally	Reduce pruritis and antagonize histamine effects
Methylprednisolone	Bronchospasm	125 mg IV every 6 hours	Reduce late-phase reactions
CARDIOVASCULAR REACTIONS			
Epinephrine	Hypotension	1:10,000 solution given IV at 1 μg/min initially, then 2–10 μg/min	Maintain systolic blood pressure > 90 mm Hg
Intravenous fluids	Hypotension	1 L of isotonic saline (0.9% normal saline) every 20–30 minutes as needed	Maintain systolic blood pressure > 90 mm Hg
Ranitidine[4,12]	Hypotension	50 mg in 20 mL D_5W infused over 10–15 minutes	Can be used in addition to epinephrine and IV fluids to maintain systolic blood pressure > 90 mm Hg
Secondary Therapy			
Norepinephrine	Hypotension	4 mg in 1 L D_5W at 2–12 μg/min	Maintain systolic blood pressure > 90 mm Hg
Glucagon	Refractory hypotension	1 mg in 1 L D_5W at 5–15 μg/min	Increase heart rate and cardiac output

IM, intramuscular; SaO_2, oxygen saturation; D_5W, 5% dextrose in water.
Adapted from Rusznak and Peebles.[41]

as 24 hours has been advocated[12]; however, we advocate monitoring for no more than 10 hours after severe, life-threatening episodes of anaphylaxis. Biphasic reactions can be treacherous because they often occur after symptoms of anaphylaxis have completely resolved. Biphasic reactions are poorly understood; however, some data suggest that they tend to occur in cases of more severe initial presentations and in instances when treatment with epinephrine has been delayed.[11] Others, however, suggest that it is not possible to predict the occurrence of biphasic reactions based on initial presentation.[4,12] Furthermore, biphasic reactions can be more difficult to treat than the initial episode, often requiring intubation.[11] Persistent anaphylaxis, anaphylaxis that continues for a protracted period of time, has also been described in the literature.[4,8,12] Some authors have observed rates as high as 28%, whereas data from others suggest that persistent anaphylaxis is rare.[4,12] Persistent anaphylaxis, similar to biphasic anaphylaxis, is impossible to anticipate based on initial patient presentation.[12]

There are no absolute contraindications to using epinephrine in the context of anaphylactic shock, and failure to do so promptly can lead to adverse outcomes.[4] This is illustrated by a study in dogs in which treatment with epinephrine at maximal hypotension produced no benefit in hemodynamic recovery in a canine model of anaphylaxis.[33] It is also important to point out that proper dose and route of administration are essential because both over- and underdosage may be life threatening.[13,34] The proper dose of epinephrine in adults is 0.3 to 0.5 mL of a 1:1000 solution given intramuscularly. Some authors advocate 0.1 mL of 1:1000 epinephrine IV for the treatment of hypotensive patients or those refractory to IM dosing; however, intravenous dosing may be associated with more side effects. Repeat dosing may be necessary to reverse anaphylaxis. Many health

care providers do not recognize the difference between epinephrine given for treatment of anaphylaxis and epinephrine given for resuscitation with respect to dose, route, and rapidity of infusion.[13] It has also been reported that some proportion of patients die regardless of treatment with epinephrine.[11,13]

Recent data have come to light regarding the preferred method of administering epinephrine. Simons et al performed a study in children in which they reported that IM injection of epinephrine is superior to subcutaneous administration.[35] This conclusion was based in delayed epinephrine absorption with subcutaneous compared with IM administration. The difference was hypothesized to be due to the cutaneous vasoconstrictive properties of epinephrine. They extended their findings to adults and further defined that IM injection into the thigh (vastus lateralis) is preferred to IM injection into the deltoid.[36] This conclusion is based on the superior serum levels of epinephrine achieved by this method in comparison to subcutaneous injection as well as IM injection into the deltoid. Superiority of blood flow to the vastus lateralis is hypothesized to account for this difference.[36]

It has been suggested that patients taking beta blockers may be at increased risk for severe reactions during anaphylaxis.[4,5] Beta blockers administered orally and even topically may interfere with epinephrine treatment by antagonizing its effects at the beta adrenergic receptor.[4,12] In experimental models, an 80-fold increase in dose of isoproterenol was required to overcome the effects of beta blockade.[4,12] Similarly, angiotensin converting enzyme (ACE) inhibitors may also be problematic during anaphylaxis.[12,37] During anaphylaxis, fluid shifts occur such that up to 50% of the plasma volume may be lost from the circulation in as little as 10 minutes.[4,37] To compensate for this, angiotensin, a potent vasoconstrictor, is released by the action of the renin–angiotensin–aldosterone system. Blockade of ACE prevents this compensatory response from taking place.[4,12,37]

An important aspect of treatment is prevention of further events. This includes, of course, avoidance of the allergen and education of the patient regarding strategies for allergen avoidance. It is also important for patients to be aware of potential cross-reacting allergens, particularly drugs and nuts.[13] Education of teachers and staff at schools and other child care venues is also important.[6] Patients prone to anaphylaxis should also be advised to wear MedicAlert® bracelets.

In addition, patients prone to anaphylaxis should be provided with one or more autoinjector kits (EpiPen® or EpiPen Jr®) and should be instructed on their use. This should take place with an EpiPen® demonstrator in the physician's office. It has been reported that physicians are deficient in teaching patients to use autoinjectors, and in some cases, the physicians themselves are unsure of how to properly use the device.[38,39] Patients with a history of anaphylaxis should be advised to carry the autoinjector kit on their person at all times. Patients should be instructed to seek medical attention, especially if they have had a reaction serious enough to require use of an epinephrine autoinjector. Ideally, EpiPen® or EpiPen Jr® should be used before its expiration date, and this is recommended because epinephrine from outdated autoinjectors has considerably reduced bioavailability.[40] If, however, a patient is suddenly in need of epinephrine, it has been shown that outdated epinephrine autoinjectors have a percent of labeled epinephrine content inversely proportional to months past expiration date. The authors of this study concluded that outdated EpiPen® and EpiPen Jr® can be used if no discoloration or precipitate is present. The basis of their conclusion is that if a life-threatening anaphylactic episode occurs, the potential benefits of using outdated autoinjectors outweigh potential risks.[40] In patients who are taking beta-blockers and who suffer anaphylaxis, some case reports suggest glucagen may be effective in those patients who fail to respond to other therapies listed in Table 4.[41]

CONCLUSION

Anaphylaxis is a systemic, type I allergic reaction that often has fatal consequences. Anaphylaxis has a variety of causes including foods, latex, drugs, and hymenoptera venom. Epinephrine given early is the most important intervention in the treatment of anaphylaxis. Other adjunctive treatments include H_1 and H_2 receptor antagonists, corticosteroids, and bronchodilators; however these do not substitute for epinephrine. Patients with a history of anaphylaxis should be educated about their condition, especially with respect to trigger avoidance. These patients should also be instructed on the correct use of epinephrine autoinjector kits and be counseled to keep these kits on their person at all times.

FUNDING

This work was supported by T32 HL07123, the American Academy of Allergy, Asthma, and Immunology ERT Award, RO1 HL 069949, RO1 AI 054660, RO1 AI 45512.

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