Allergic Emergencies in Children: The Pivotal Role of Epinephrine

Twenty minutes ago at school, eight-year-old Brian ate what he thought was a butterscotch cookie. It turns out it was made from peanut butter, and Brian has a history of peanut allergy. He is brought in by basic life support ambulance and is complaining of severe itching. He’s screaming, “It’s hard to breathe!” Vital signs: Blood pressure 90/40 mm Hg, heart rate 120 beats per minute, respiratory rate 30 breaths per minute, and he is afibrile. On exam, he is covered head-to-toe in hives and has audible wheezing on chest auscultation. His oropharynx is clear, but he’s not looking good … how do you proceed?

Perhaps no other diagnostic entity embodies the true essence of emergency care better than anaphylaxis: The rapid and often unpredictable onset of potentially lethal symptoms, the propensity for significant morbidity and mortality if not treated swiftly and aggressively, and the wide availability of highly effective treatment modalities … all frequently occurring in those who are young, otherwise healthy, and in the prime of their lives.

This issue of Pediatric Emergency Medicine Practice will examine the proper evaluation and management of pediatric patients with allergic emergencies, and will tackle many of the controversial issues, including:

1. The use of epinephrine – in which cases, by what route, and when should it be avoided?
2. Antihistamines – H1 and H2 blockers, alone or in combination

CME Objectives

Upon completing this article you should be able to:

1. Understand the epidemiology, pathophysiology, and clinical features of anaphylaxis.
2. Discuss the role of pharmacotherapy, including epinephrine administration, in the management of anaphylaxis.
3. Describe the appropriate ED disposition for patients presenting with allergic symptoms and anaphylaxis.
4. Distinguish true drug “allergies” from non-allergic adverse drug events.

February 2007

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what’s the evidence?

3. Observation of patients with allergic reactions – in what setting and for how long?

In addition, this issue will examine other key related issues, including:

4. The “nightmare” airway - difficult airway management in pediatric anaphylaxis.
5. The use (and misuse) of epinephrine self-administration devices.
6. Special situations, including: Hereditary angioedema, pediatric patients on beta-blockers, and pregnant patients.
7. And, finally, how to distinguish a true drug “allergy” from the far more frequent medication “side effect.”

The first documented case of anaphylaxis was purportedly the death of the Pharaoh Menes in 2640 BC from a wasp sting. However, the seminal work on anaphylaxis did not occur until 1902, when Portier and Richet coined the term “anaphylaxis” derived from the Greek words “a-” (against) and “-phylaxis” (immunity, protection), literally meaning “without protection” (the opposite of prophylaxis). They reported a fatal systemic reaction in a dog within minutes of receiving an injection of a previously tolerated foreign protein (sea anemone venom) while attempting to confer sting prophylaxis. Richet eventually received the Nobel prize for his work.

Anaphylaxis is a severe, life threatening, systemic reaction that can affect all ages. It results from the sudden release of active mediators from mast cells (located in tissues) and basophils (located in the bloodstream). The clinical syndrome is variable and may potentially involve multiple target organs, including the skin, respiratory, gastrointestinal (GI), central nervous, and cardiovascular systems. (Table 1) Respiratory and cardiovascular symptoms cause the greatest concern because they carry the greatest potential for morbidity or mortality. During the second National Institute of Allergy and Infectious Disease (NIAID) / Food Allergy and Anaphylaxis (FAAN) symposium (July 2005), a panel of experts agreed on a broad definition that would be useful to both the medical and lay communities: “Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.”

Viewing anaphylaxis as a continuum of clinical symptoms with varying degrees of severity circumvents the problem of defining a discrete point at which an acute allergic reaction is classified as anaphylaxis. With this said, it is useful to define a point along this spectrum that distinguishes an anaphylactic reaction from other allergic phenomena in order to facilitate communication between practitioners in both clinical and research settings. (Figure 1)

A reasonable working definition of anaphylaxis involves allergic symptoms with one or both of the following features: Respiratory difficulty (due to local tissue edema in the pharynx or hypopharynx, or resulting from bronchospasm) or hemodynamic instability (may present as presyncope, syncope, hypotension, or dysrhythmia). Experts participating in the second NIAID / FAAN symposium proposed revised clinical criteria for diagnosing anaphylaxis. (Box 1)

### Abbreviations Used In This Article

- ADRs: Adverse drug reactions
- ET: Endotracheal
- FAAN: Food Allergy and Anaphylaxis Network
- GI: Gastrointestinal
- IM: Intramuscular
- IO: Intraosseous
- IV: Intravenous
- LMA: Laryngeal Mask Airway
- MBS: Sodium Metabisulfite
- MSG: Monosodium Glutamate
- NIAID: National Institute of Allergy and Infectious Disease
- NSAID: Non-steroidal Anti-inflammatory Drugs
- RCM: Radiographic Contrast Materials
- SQ: Subcutaneous
- WHO: World Health Organization

<table>
<thead>
<tr>
<th>Table 1. Target Organs In Anaphylaxis</th>
</tr>
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<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
</tr>
<tr>
<td>Hypotension, lightheadedness (presyncope), syncope, dysrhythmias, angina</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
</tr>
<tr>
<td>Upper airway - oropharyngeal, hypopharyngeal or laryngeal edema</td>
</tr>
<tr>
<td>Lower airway - bronchospasm</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea, cramping</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
</tr>
<tr>
<td>Flushing, erythema, pruritus, urticaria, angioedema</td>
</tr>
<tr>
<td><strong>Central Nervous System</strong></td>
</tr>
<tr>
<td>Headache, confusion, altered level of consciousness</td>
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Critical Appraisal Of The Literature

Most available literature is from the field of Allergy and Immunology, while a comparatively smaller portion is specialty specific. There are several published guidelines put forth by various Allergy and Immunology specialty societies, including The Allergy Report (www.theallergyreport.com), as well as practice parameters on topics such as anaphylaxis, food allergy, drug hypersensitivity, and stinging insect hypersensitivity (some of which are referenced later in this issue). However, such guidelines are often opinion and consensus based. Overall, there is a paucity of controlled literature on the management of allergic emergencies; hence, therapeutic recommendations are largely based on clinical observation, interpretation of underlying pathophysiology, and, to some extent, animal models. After all, it would be unethical to enroll patients in the placebo arm of an anaphylaxis study, given the substantial morbidity (and potential for mortality) when left untreated!

Pathophysiology

Gell and Coombs first classified types of hypersensitivity reactions. Their original schema has been expanded to include an “idiopathic” category, which accommodates hypersensitivity reactions failing to meet criteria for any of the other classes. (Table 2)

There are three steps of a classic IgE mediated (Gell and Coombs Type I) allergic response: Sensitization, early phase reaction, and late phase reaction. Sensitization occurs when initial exposure to an allergen leads to the production of allergen specific IgE antibodies which are then bound to the surface of mast cells and basophils. The second step is

<table>
<thead>
<tr>
<th>Classification</th>
<th>Effector Mechanism</th>
<th>Typical Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I Immediate</td>
<td>IgE</td>
<td>Anaphylaxis, angioedema, urticaria</td>
</tr>
<tr>
<td>Type II Cytotoxic</td>
<td>IgM, IgG, complement, phagocytosis</td>
<td>Cytopenia, nephritis</td>
</tr>
<tr>
<td>Type III Immune Complex</td>
<td>IgM, IgG, complement, precipitins</td>
<td>Serum sickness, vasculitis</td>
</tr>
<tr>
<td>Type IV Delayed</td>
<td>T-Lymphocytes</td>
<td>Contact dermatitis</td>
</tr>
<tr>
<td>Other Idiopathic</td>
<td>Varies</td>
<td>Non-specific rash</td>
</tr>
</tbody>
</table>

Adapted from J Allergy Clin Immunol, 117(2), Sampson HA et al, Second symposium on the Definition and Management of Anaphylaxis: Summary Report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium, page 393, © 2006, with permission from American Academy of Allergy, Asthma, and Immunology
the early phase reaction, where subsequent exposure to the same allergen causes the IgE mediated release of active substances. As mast cells and basophils degranulate, they release both preformed (i.e., histamine, tryptase, and heparin) as well as newly synthesized (i.e., leukotriene and cytokine) mediators. Finally, the late phase reaction is initiated when the allergen stimulates other immune cells to produce additional inflammatory mediators. The cascade of events results in augmented inflammatory cell influx (neutrophils, basophils, eosinophils), culminating in a vicious cycle of heightened mediator production.

“Allergy” refers to the acquired potential to develop immunologically mediated adverse reactions to normally innocuous substances. “Atopy,” on the other hand, refers to the genetic tendency to develop the classic allergic diseases (allergic rhinitis, asthma, atopic dermatitis). Atopy may be a predisposing factor for anaphylaxis. One review reported an increased prevalence in atopic subjects of anaphylaxis induced by insect stings, latex exposure, and exercise, as well as idiopathic anaphylaxis. In addition, anaphylactoid reactions are more common in atopic individuals.

Urticaria is characterized by cutaneous elevations that are superficial, polymorphic, and pruritic (frequently referred to as “hives”). Urticarial lesions are caused by blood vessel dilatation and edema formation in the dermis and may be acute, subacute, or chronic. Histamine is thought to be the most important mediator. Angioedema is characterized by non-pitting, well-defined swelling, caused by edema of comparatively deeper structures (subcutaneous or submucosal tissues) by similar mechanisms. Areas of angioedema typically have little or no associated pruritis as these deeper layers contain fewer mast cells and fewer sensory nerve endings. Urticaria and angioedema are generally the most common manifestations of anaphylaxis and often occur as the initial signs of severe anaphylaxis. However, such symptoms might be delayed or absent entirely, so their absence certainly does not exclude the diagnosis.

### Anaphylactoid Reactions

An anaphylactoid (“allergic-like”) reaction is an immediate, systemic reaction that mimics anaphylaxis (release of identical mediators from mast cells and basophils), but differs in that it is not an IgE mediated response. (Table 3) Unlike anaphylaxis, adverse reactions may occur on first exposure to allergen, since prior sensitization (resulting in IgE formation) is not required. Reactions are generally dependent on the degree of systemic exposure (i.e., dosage of allergen), typically in amounts greater than those needed to induce anaphylaxis. For instance, reactions to radiographic contrast materials generally result from a comparatively large bolus dosage of iodinated contrast material, especially when compared with the micro-dosage of Hymenoptera venom capable of causing anaphylaxis. It is virtually impossible to distinguish between anaphylactic and anaphylactoid reactions on clinical grounds. Fortunately, however, the distinction is moot in the acute phase as treatments for both syndromes are identical. Differentiation between the two is more important for risk assessment following resolution of the acute, symptomatic phase.

### Hereditary (C1 Esterase Inhibitor Deficiency)

**Angioedema**

C1 esterase inhibitor is a modulator of complement activation; it is also involved in regulating the formation of bradykinin. In hereditary angioedema, inhibition of bradykinin formation results in its over-accumulation. (Figure 2) There are both hereditary and acquired forms of C1 esterase inhibitor deficiency. The hereditary form is a rare autosomal dominant condition. The underlying pathophysiology of bradykinin-mediated angioedema differs from other forms of angioedema. The proposed mechanism involves increased levels of bradykinin (a potent vasodilator), leading to capillary leakage and tissue edema.

Hereditary angioedema is characterized clinically by recurrent episodes of well circumscribed, non-pruritic angioedema. Symptoms are frequently distinguished from allergic phenomena by their charac-

<table>
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<tr>
<th>Table 3. When Is It An Anaphylactic Or Anaphylactoid Reaction?</th>
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<tbody>
<tr>
<td><strong>Is sensitization required?</strong></td>
</tr>
<tr>
<td><strong>Can reaction occur on first exposure?</strong></td>
</tr>
<tr>
<td><strong>How much exposure is needed to elicit reaction?</strong></td>
</tr>
<tr>
<td><strong>Is reaction predicted by allergy skin tests?</strong></td>
</tr>
</tbody>
</table>

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teristic lack of coexisting urticaria. The ensuing angioedema may involve the integument or any part of the GI and respiratory tracts. However, of immediate concern in the ED setting is involvement of the upper respiratory tract, where angioedema may be life threatening. Albeit controversial in the literature, acute treatment generally involves the administration of fresh frozen plasma, which transiently repletes the C1 esterase inhibitor protein.\(^{13}\) There is little evidence that standard treatment modalities for Type I (IgE-mediated) hypersensitivity reactions (including epinephrine) are of any benefit in hereditary angioedema.\(^{12}\)

**Epidemiology**

Several investigations have looked at both the incidence of new cases of anaphylaxis and the prevalence of underlying allergic conditions that predispose patients to the development of anaphylaxis. However, the true incidence and prevalence of anaphylaxis remain elusive as a consequence of several key limitations. First, there is no universally accepted clinical definition of anaphylaxis (i.e., some define a reaction with isolated skin involvement – urticaria for instance – as anaphylaxis, whereas others mandate multi-system physiologic derangements to meet the definition). Second, although there is a lack of data, it has been suggested that anaphylaxis is under-reported overall,\(^{14}\) including under-reporting in the ED setting,\(^{15}\) leading to an underestimation of both its morbidity and mortality. Lastly, there is a widespread lack of required reporting to public health agencies of either serious or fatal episodes.

An Australian study revealed an anaphylaxis presentation incidence in an ED setting of 1 in 439 teenage and adult patients (0.23%), with a 0.7% case-fatality rate.\(^{16}\) Another study revealed an incidence of 0.4% in adult patients presenting to an Italian ED, although a more encompassing definition of anaphylaxis was employed in this investigation.\(^{17}\) A retrospective Australian study of patients less than 16 years old revealed a generalized allergic reaction incidence of 9.3 per 1000 ED presentations (0.93%), and an anaphylaxis incidence of 1 per 1000 ED presentations (0.1%).\(^{18}\) In 2001, Neugut and his colleagues estimated that the risk of death among those who suffer an anaphylactic reaction is about 1%, leading to a total of at least 500 to 1000 deaths annually in the United States.\(^{19}\)

A novel approach to studying the epidemiology of anaphylaxis relies on the examination of data regarding epinephrine self-administration devices dispensed for out-of-hospital use in the community setting. In one such study, dispensing data for all prescribed epinephrine formulations were analyzed through the use of a Canadian insurance claims database.\(^{20}\) During the five year period analyzed, 0.95% of a defined population of 1.15 million persons received prescriptions for epinephrine self-administration devices. Although this information may provide a fresh perspective, the true incidence and lifetime prevalence of anaphylaxis will remain elusive until there are universally accepted diagnostic criteria and standardized reporting of all cases.

**Etiologies**

There are multiple known etiologic culprits. (Table 4) Food induced anaphylaxis is now generally regarded as the most common single cause of anaphylaxis treated in United States ED’s.\(^{21}\) Likewise, food induced anaphylaxis has been reported as the most common etiology among pediatric ED

**Table 4. Etiologies Of Anaphylaxis**

<table>
<thead>
<tr>
<th>Category</th>
<th>Example(s)</th>
</tr>
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<tbody>
<tr>
<td>Foods</td>
<td>- Children: Eggs, milk, soy</td>
</tr>
<tr>
<td></td>
<td>- Adults: Peanuts, tree nuts, fish, shellfish</td>
</tr>
<tr>
<td>Medications</td>
<td>Antimicrobials, anesthetics, insulin, others</td>
</tr>
<tr>
<td>Hymenoptera</td>
<td>- Apid family (honeybee, bumblebee)</td>
</tr>
<tr>
<td></td>
<td>- Vespid family (yellow jacket, hornet, wasp)</td>
</tr>
<tr>
<td></td>
<td>- Formicid family (fire ant)</td>
</tr>
<tr>
<td>Latex</td>
<td>Proteins in natural rubber latex; additives used in processing latex</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Proteins cross-reactive with egg; hydrolyzed gelatin, sorbitol, neomycin</td>
</tr>
<tr>
<td>Blood Components</td>
<td>Packed red blood cells</td>
</tr>
<tr>
<td>Biological Fluids</td>
<td>Human seminal fluid</td>
</tr>
<tr>
<td>Exercise Induced</td>
<td>More than half of cases are associated with ingestion of certain foods prior to exercise</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Diagnosis of exclusion</td>
</tr>
</tbody>
</table>

\(^{12}\)
There is a greater risk of food allergy in atopic individuals, especially children. Overall, the prevalence of food allergies is greatest in the first few years of life, and declines over the first decade. Many infants outgrow their allergies to eggs, milk, or soy products. On the other hand, the most prevalent food allergies in adults (peanuts, tree nuts, fish, and shellfish) are usually not outgrown and may remain problematic for the individual throughout life, even if they first develop during childhood.

Drug (medication) allergies are caused by a wide variety of drug classes, may present in a wide array of clinical syndromes, and are able to affect almost any tissue or organ system. The most common sources of drug-induced anaphylactic and anaphylactoid reactions are beta-lactam antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and aspirin.

Stinging insects capable of causing anaphylaxis are all members of the order Hymenoptera, which includes the apid (i.e., honeybee, bumblebee), vespid (yellow jacket, hornet, wasp) and formicid (fire ant) families. Hymenoptera stings cause painful local reactions in most patients, and, in addition, are capable of causing potentially severe systemic reactions in susceptible individuals.

Latex allergies encompass various reactions to the proteins found in natural rubber latex or to the additives used in processing latex. Such reactions may be IgE mediated or mediated by other immunologic mechanisms (i.e., Gell and Coombs Type IV delayed hypersensitivity reaction causing contact dermatitis). In addition, non-immune (i.e., irritant) reactions can be observed as a result of latex exposure.

The pathogenesis and true incidence of exercise induced anaphylaxis remains unknown. Cases are often unpredictable and can be difficult to diagnose. Exercise induced anaphylaxis has been described in relation to a variety of activities, including running, aerobics, tennis, dancing, bicycling, swimming, and skiing. It has been suggested that more than half of all exercise induced anaphylaxis cases are associated with the ingestion of certain foods in the hours preceding exertion (“food-triggered exercise-induced anaphylaxis”).

Idiopathic anaphylaxis is a diagnosis of exclusion. The true incidence is unknown, but several studies estimate that nearly 20% of all anaphylaxis cases are idiopathic in nature. Importantly, there are no clinically distinguishing features of idiopathic anaphylaxis when compared with anaphylaxis resulting from known antigens.

Other, less frequent causes of anaphylaxis include reactions in patients receiving blood components (“transfusion anaphylaxis”) or in patients exposed to certain biological fluids (i.e., seminal fluid).

Morbidity And Mortality
As mentioned, foods are often cited as the most frequent offending agents, which are closely followed by medications (particularly antibiotics and NSAIDs). Although investigators have attempted to estimate annual U.S. death rates for various allergens, results are not broken-down by age. Foods may account for 100 to 200 fatalities each year in the U.S. The most frequent offenders in severe reactions are peanuts, tree nuts (i.e., almonds, hazelnuts), fish, and shellfish. For medications, beta-lactam antibiotics are alleged to cause 400 to 800 fatal episodes per year. Of note, the majority of deaths reported from penicillin result from its parenteral administration; an older review identified only six reported fatalities attributable to oral penicillin in the worldwide medical literature.

Radiographic contrast materials account for about 900 deaths per year in the U.S.. The true incidence of fatalities from Hymenoptera venom is unknown, although it is suspected to cause about 40 to 100 deaths per year in the U.S. Allergen vaccines, which are administered primarily for desensitization to Hymenoptera venom, rarely result in death: Only one fatality per 2 to 2.5 million injections for allergen immunotherapy has been reported (average of 3.4 deaths per year). Similarly, fatal reactions to allergy skin testing are rare. Only one fatality in the 12 year period spanning 1990 to 2001 was reported. Latex exposure accounts for approximately three deaths per year in the U.S.

It has been suggested that certain factors may be associated with especially severe or even fatal anaphylaxis. In particular, asthma has been shown to be an independent risk factor for death from anaphylaxis. However, this association is based on tenuous data. The most widely referenced study linking asthma to fatal or near fatal anaphylaxis was done by Sampson and his colleagues in 1992. They identified a total of 13 patients (aged 2 to 17 years) by word-of-mouth, and found that all patients had a history of asthma, which was “well-controlled” in all but one of the subjects. A second retrospective study of 19 children (aged 1 to 16 years) mechanically ven-
tilated for an acute asthma exacerbation found that food allergy, along with frequent admissions for asthma, were independently associated with life-threatening asthma.31

Peanuts and tree nuts have also been associated with severe reactions, accounting for the majority of fatal or near-fatal food reactions in the U.S.32 Food allergy is of particular interest because of its prevalence. In addition, unlike drug and sting reactions, those dying from food induced anaphylaxis typically have suffered prior, albeit significantly less severe, reactions to the offending allergen.33 For instance, the majority (about 80%) of patients included in a United Kingdom registry of food related anaphylaxis deaths had suffered only minor prior reactions, underscoring the frequency of previous reactions and suggesting that prior severity cannot be used to identify those at risk for fatal reactions.34 Bock and his colleagues reviewed 32 fatal food anaphylaxis cases (aged 2 to 33 years) reported to a U.S. national registry and determined that peanuts and tree nuts accounted for 94% of fatalities.35 They also found that all but two of the study subjects had a prior history of symptomatic reactions to the specific food that ultimately led to death. Additionally, a history of asthma was present in 24 of the 25 patients for whom such data were available, providing further fuel to the association between asthma and fatal anaphylaxis.

Adverse Drug Reactions
According to the World Health Organization (WHO), adverse reactions to drugs include all non-therapeutic consequences of the drug, with the exception of treatment failures, purposeful or accidental poisoning, and drug abuse.6 Adverse drug reactions (ADRs) are common; however, allergic ADRs only represent somewhere between 5 to 25% of all ADRs.4,6 Allergic ADRs can fall into any of the Gell and Coombs classes (I through IV or idiopathic). Despite this, patients and healthcare providers alike often erroneously misclassify any ADR as a drug “allergy,” and then further presume that such a drug “allergy” is synonymous with an immediate hypersensitivity (Type I) reaction. As a prime example, routinely encountered ADRs (such as nausea, vomiting, diarrhea, weakness, and non-specific rash) are frequently mislabeled as drug “allergies.” Further, development of routine ADRs leads many to erroneously believe that repeat exposure to the same (or similar) agents will place a patient at risk for a potentially fatal anaphylactic reaction. What has been misclassified as an “allergy” in the first place is further misclassified as the most concerning form of allergy: A Type I, immediate hypersensitivity reaction!

Non-immunological reactions (those not classified by the Gell and Coombs hypersensitivity schema) do not invoke a true allergic response, per se. However, these reactions may be difficult to distinguish from Type I hypersensitivity reactions, particularly in the case of drug-induced inflammatory mediator release directly from basophils and mast cells (anaphylactoid reaction). Other examples of non-immunological ADRs specific to certain medications are included in Table 5.

In addition, certain findings suggestive of a med-
ication “allergy” may be entirely unrelated to the drug itself. For instance, some reactions may result directly from the underlying infectious disease (i.e., viral-induced urticaria) that prompted medication use in the first place, or may result from another unrelated cause entirely.

**Differential Diagnosis**

Anaphylaxis must be considered in the differential for any acute onset respiratory distress, bronchospasm, hypotension, or cardiac arrest. However, it is also important to consider other diagnostic possibilities. *(Table 6)* A thorough yet focused history and physical examination is extremely useful to this end. Importantly, vasovagal (neurocardiogenic or vasodepressor) reactions may appear strikingly similar to anaphylaxis. Vasodepressor episodes share many of the characteristic features of anaphylaxis: Hypotension, pallor, weakness, nausea, and emesis. Furthermore, these episodes usually occur with a relatively rapid onset. However, vasovagal reactions can usually be differentiated from anaphylaxis by their lack of characteristic cutaneous findings, such as urticaria, angioedema, flush, or pruritis (although anaphylaxis can occur in the absence of dermatologic manifestations. More on this later…). Also, vasodepressor syndromes will often spontaneously regress after laying the patient in a supine position. Further, vasodepressor reactions are typically associated with bradycardia. Anaphylaxis, on the other hand, is most frequently associated with reflexive tachycardia. Interestingly, bradycardia has been observed in anaphylaxis, possibly resulting from either the direct action of anaphylactic mediators on the heart or nervous system, or via vasodepressor mechanisms. Also, patients taking beta-adrenergic blockers may exhibit a “relative” bradycardia in the setting of anaphylaxis because of a blunted chronotropic response to intravascular volume loss.

Other forms of shock (i.e., hypovolemic, cardiogenic, or endotoxic) may be confused with anaphylaxis. Flush syndromes (such as carcinoid), “restaurant” syndromes (such as scombroid poisoning or a monosodium glutamate (MSG) reaction), or excessive endogenous production of histamine syndromes (such as systemic mastocytosis) may all be confused with anaphylaxis as well. Restaurant syndromes may be particularly difficult to distinguish from food induced anaphylaxis given their shared historical and clinical features. Scombroid poisoning results from the ingestion of fish (typically mackerel or tuna) containing high levels of histamine which accumulates when bacteria metabolize the amino acid histidine found in fish muscle. This atypical foodborne illness is often not reported despite its public health implications, as most episodes are mild in nature or are confused with allergic phenomena. Treatment is with antihistamines. MSG reactions may cause flushing, palpitations, GI symptoms, irritability, and delirium. Treatment is largely supportive and directed towards the alleviation of acute symptoms. Finally, non organic etiologies must always remain a diagnosis of exclusion.

**Prehospital Care**

If necessary and possible, the victim should be protected from further absorption of the implicated antigen. For instance, if a bee stinger remains in the skin, it should be quickly and carefully removed on the scene. A veno-/lymphatic constriction band proximal to the site of sting on an extremity and local application of ice to the wound itself might reduce or delay venom absorption, although specific evidence is lacking.

In all cases, prehospital management of allergic emergencies focuses on the maintenance of airway, breathing, and circulation. Early definitive airway management and the provision of adequate oxygen are paramount. Epinephrine, antihistamines, intravenous (IV) crystalloid infusions, and aerosolized beta-adrenergic agonists can be used in the prehospital setting. Depending on local protocols, other agents may be available for use as well, including glucocorticoids. Studies have investigated the appropriateness of out-of-hospital epinephrine use by both basic and advanced life support providers, and have found that severe allergic reactions can be reliably identified and safely managed by such providers with the use of an epinephrine auto-injector in a discriminating manner that typically agrees with physician judgment after the fact. While use of activated charcoal has been considered in an effort to bind food allergens following accidental ingestion, there is no strong evidence to support its use at this time.

**Emergency Department Evaluation**

**Initial Stabilization**

ED evaluation begins with rapid triage and initial stabilization of the symptomatic patient.
Measurement of vital signs, including pulse oximetry, is critical to appropriate patient placement within the ED. Patients with rapidly progressive symptoms or abnormal vital signs should be taken immediately to an area fully equipped with advanced airway equipment and critical care capabilities. Continuous cardiac and pulse oximetry monitoring are prudent in this scenario. Anaphylaxis is a dynamic process; as such, frequent reassessments are critical. A severe reaction may not require any treatment if improvement occurs prior to ED arrival. Conversely, it should also be appreciated that patients who present with mild allergic symptoms and initially appear stable have the potential for rapid deterioration.

**Important Historical Questions**

Often, the most valuable information comes from those who actually observed an allergic event from its onset. Take the time to interview caretakers, bystanders, friends, other family members, and anyone else who may have witnessed an out-of-hospital episode to elicit specific information regarding the initial presenting signs and symptoms. Anyone who was present at the time should be prompted to give a detailed history of all recent potential allergen exposures, including foods, medications, insect bites or stings, or exercise. Query EMS personnel regarding presenting signs and symptoms (including initial and subsequent prehospital vital sign determinations), and regarding any treatments rendered. However, obtaining an accurate history may be particularly challenging in the non-verbal pediatric patient.

Obtain the patient’s past medical history, focusing on a prior history of allergy, asthma, or any other preexisting atopic conditions. Obtain a detailed list of medications using all available resources (family, friends, EMS, primary care physicians, and medical records), as this information has both diagnostic (i.e., antibiotic that may have led to the episode) and treatment (i.e., coexisting beta-adrenergic blockade) implications. Maintain a particularly high level of vigilance in patients with a history of asthma, especially when it is poorly controlled, as fatal anaphylactic reactions may be more likely to occur in such individuals.23,42

**Important Physical Findings**

The frequency of occurrence of various signs and symptoms of anaphylaxis based on a compilation of nearly 1900 patients representing all ages and reactions resulting from a wide variety of allergens is presented in Table 7.43 Respiratory failure and cardiovascular collapse represent the major life threats. Prior investigations have estimated that, as a result of capillary permeability, losses of up to 35% of the circulating blood volume can occur within 10 minutes of the onset of symptoms.44 The absence of cutaneous findings speaks against the diagnosis of anaphylaxis in general; however, by no means does it exclude this possibility. Moreover, the most severe episodes can occur without any cutaneous manifestations whatsoever.45,46 The cause of large, localized, cutaneous reactions following insect stings remains unclear, but may be related to an IgE-mediated mechanism or localized histamine release. Such reactions do not, however, portend a greater chance of anaphylaxis if the victim is later re-stung.47 Remember that true insect hypersensitivity includes wide ranging systemic manifestations that reach far beyond the entry (bite) site. Anaphylaxis may also rarely present with unusual manifestations, such as seizures.48

It is important to note that it has been suggested that the clinical presentation of anaphylaxis may vary between children and adults, with respiratory symptoms predominating in children and cardiovascular manifestations predominating in adults. This may result from differences in observed responses to

<table>
<thead>
<tr>
<th>Table 7. Frequency Of Occurrence Of Signs And Symptoms Of Anaphylaxis</th>
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<tr>
<td><strong>Cutaneous</strong></td>
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<tr>
<td>Overall</td>
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<td><strong>Respiratory</strong></td>
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<tr>
<td><strong>Cardiovascular</strong></td>
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<td><strong>Abdominal</strong></td>
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<td><strong>Miscellaneous</strong></td>
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Data based on a compilation of 1,865 patients. Percentage approximations.

various allergens, given the comparatively increased frequency of food allergy in the pediatric age group (as compared with drug and insect sting reactions in adults).\(^1\) Advanced age and comorbid disease (which is rarely encountered in the pediatric population) may also help account for these clinical differences.

**Diagnostic Studies**

The diagnosis of anaphylaxis is typically based on clinical grounds. There are few, if any, diagnostic tests that are of value to the emergency physician, as anaphylaxis is a true medical emergency that must be treated swiftly and aggressively in the absence of confirmatory evidence. With this said, the use of diagnostic tests is guided by each individual clinical circumstance, paying particular attention to patient comorbidities or confounding circumstances, such as incidental trauma sustained during an anaphylactic episode.

In terms of diagnosing anaphylaxis itself, serum tryptase and plasma histamine levels may be beneficial as retrospective confirmatory tests when the diagnosis remains uncertain. There is a paucity of data regarding the utility of these tests in the ED setting. One prospective cohort of 97 patients looking at histamine and tryptase levels in ED patients with acute allergic reactions found that elevations of both are frequently found; however, the clinical utility of such findings warrants further investigation.\(^5\) Tryptase is released primarily by mast cells during degranulation in an anaphylactic (or anaphylactoid) reaction. It has a relatively long half-life and can be helpful in retrospectively determining the precise etiology of a patient’s sudden decompensation in such cases. In fatal cases, it can even be used in the post mortem setting to confirm the diagnosis.\(^5\) The half-life of histamine, however, is much shorter, making it of limited to no benefit in investigating such tragic cases.

**Treatment**

**ABC’s**

As with any emergency condition, initial attention must focus on the ABC’s. Definitive airway management is of paramount importance, as the window for effective intervention may rapidly dwindle if decisions are not made swiftly and decisively. Keep in mind that the pediatric airway is smaller in diameter as compared with adults; therefore, airway edema has a more profound effect. The administration of supplemental oxygen along with large-bore vascular access (preferably at two sites) and crystalloid infusion (i.e., 20 mL per kg initially; then titrate to response, with maximum of 80 to 100 mL per kg) is essential in the majority of cases. Monitor for signs of fluid overload, especially in patients with a history of underlying cardiovascular or renal disease. Maintain vigilance for early clinical signs of shock. Compensated pediatric shock can present with tachycardia alone; hypotension may be a late clinical finding. Pediatric patients may be in shock despite a normal blood pressure ([70] plus 2 x [age in years] = systolic blood pressure, if one year or older).

**Pharmacologic Treatments**

*Epinephrine:* Guidelines uniformly recommend epinephrine as the first line treatment for severe allergic reactions.\(^4\) However, in a recent multicenter study of ED visits for food allergies, it was noted that fewer than 25% of patients classified as having severe reactions received epinephrine in the ED, and only 16% of discharged patients were prescribed epinephrine for self-administration.\(^5\) Similarly, a retrospective questionnaire-based study focusing on children less than 12 years old found that only 20% of patients with anaphylactic reactions (and 36% of those with reactions deemed “severe”) received epinephrine, and only 17% overall were prescribed an epinephrine self-administration device after the acute episode.\(^5\) A second pediatric study yielded similar findings.\(^1\)

One could consider this first line therapy as a

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### Table 8. Physiologic Effects Of Epinephrine In Anaphylaxis

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Physiologic Effect</th>
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<tbody>
<tr>
<td>Alpha</td>
<td>Increased peripheral vascular resistance</td>
</tr>
<tr>
<td></td>
<td>Reversal of peripheral vasodilation</td>
</tr>
<tr>
<td></td>
<td>Decreased angioedema and urticaria</td>
</tr>
<tr>
<td>Beta</td>
<td></td>
</tr>
<tr>
<td>(\beta-1)</td>
<td>Positive cardiac inotropic effects</td>
</tr>
<tr>
<td></td>
<td>Positive cardiac chronotropic effects</td>
</tr>
<tr>
<td>(\beta-2)</td>
<td>Bronchodilation</td>
</tr>
<tr>
<td></td>
<td>Increased intracellular cAMP production</td>
</tr>
<tr>
<td></td>
<td>with subsequent reduction of inflammatory</td>
</tr>
<tr>
<td></td>
<td>mediator production and release from</td>
</tr>
<tr>
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<td>mast cells and basophils</td>
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\(^c\)AMP = cyclic-adenosine monophosphate
second “A” (adrenaline) in the “ABCs” (airway, breathing, circulation) prioritization of anaphylaxis management. Epinephrine has numerous identifiable physiologic benefits in the treatment of anaphylaxis (Table 8); although it’s particular indications and dosing regimens still cause confusion. For instance, a study of senior house officers in the United Kingdom found that only 5% of study participants were able to correctly indicate the appropriate route and dosage of epinephrine according to standard published national guidelines.55

**Epinephrine: When Should It Be Given?** Anecdotal consensus, as well as evidence from the literature, suggests that poor outcomes are most often associated with failure to give or delay in administering epinephrine. For example, in a series of 13 fatal or near fatal cases of anaphylaxis in children and adolescents, six patients who died had symptoms within 3 to 30 minutes of ingestion of the allergen, but only two received epinephrine in the first hour.30 Among the seven patients who survived, all but one received epinephrine within 30 minutes of symptom onset. The authors concluded that failure to rapidly recognize symptom severity and failure to promptly administer epinephrine increases the risk of fatal outcome. Current guidelines recommend prompt administration of epinephrine in any case of anaphylaxis.43 However, the issue of what precisely constitutes anaphylaxis (i.e., where a particular patient’s symptoms lie along the anaphylactic spectrum) repeatedly arises, leading to uncertainty regarding epinephrine use not only among health care providers, but also among those prescribed epinephrine self-administration devices for out-of-hospital use.

**Epinephrine: How should it be given?** Epinephrine is typically administered as an intramuscular (IM) or subcutaneous (SQ) injection, as virtually all reported adverse outcomes result from its IV administration (although SQ administration has its own limitations, as discussed below).23

The typical dose for IM (or SQ) administration is 0.01 mg / kg, up to a maximum of 0.3 to 0.5 mg of a 1:1000 dilution. The European literature, however, suggests higher maximal dosages (0.5 to 1 mg) in adult patients.56

Current data supports the use of IM epinephrine. It was once thought that SQ was superior; however, in a randomized, double blind, parallel group study of children at risk for anaphylaxis, it was shown that peak plasma epinephrine levels were achieved significantly faster after an IM injection into the thigh as compared with a SQ injection into the upper arm.57 In a follow-up study of adults, the same investigators performed a prospective, randomized, blinded, placebo-controlled, crossover study of SQ versus IM injection. Similarly, they concluded that IM administration is the superior route of administration, and the lateral thigh is the preferred site of injection.58 These studies showed delayed and variable absorption when the SQ route was utilized compared with IM administration. Peak serum levels are not obtained until 34 minutes via the SQ route, compared to eight minutes via IM, and the levels reached are higher with IM.57,58 Subcutaneous administration of medications is highly dependent on cutaneous blood flow, which is already potentially compromised in anaphylaxis, and can be further aggravated by epinephrine’s potent local vasoconstrictor activity. Therefore, the current data support the IM route over SQ, regardless of age, for routine epinephrine administration.

**What About IV Epinephrine?** Major adverse events have been reported when IV epinephrine is administered too rapidly, as an inadequately diluted solution or in excessive dosage.59 Intravenous epinephrine has also been associated with the induction of fatal cardiac dysrhythmias, myocardial infarction, and intracranial hemorrhage.60-63 However, published reports on the dangers of IV epinephrine consistently fail to emphasize that other factors related to the underlying pathophysiologic process (including hypoxia, acidosis, or the direct effects of inflammatory mediators) may be responsible for the observed complications.64 Taken all together, IV epinephrine should probably be reserved for those patients with severe cardiovascular compromise (i.e., profound decrease in peripheral perfusion where IM absorption will be significantly hampered) or when repeated IM epinephrine fails to alleviate symptoms.

A firm IV dose cannot be recommended – the amount administered depends on the severity of the episode and should be titrated to response. A frequently cited adult IV dosing regimen, originally proposed by Barach and his colleagues in 1984, utilizes a dilute (1:100,000) epinephrine solution, slowly infusing 100 mcg (= 0.1 mg) over 5 to 10 minutes in adults (Box 2).65 Other authors have suggested 0.2 mcg per kg for children (up to 5 to 10 mcg IV bolus
doses in adults) for treatment of hypotension, and 100 mcg to 500 mcg IV bolus doses in adults with severe cardiovascular collapse.66 There are no prospective, controlled studies to support such recommendations. Overall, continuous low dose epinephrine infusion may represent the safest and most effective form of IV delivery, as the dose can be titrated to desired effect while minimizing the potential for accidental administration of large or concentrated bolus doses of epinephrine.3 Intravenous epinephrine in the pediatric patient should be used cautiously, and it is paramount that the weight based dosages are double (and triple!) checked in order to avoid a medication error catastrophe.

Is Epinephrine Safe? Most adverse events related to epinephrine administration occur when it is given intravenously, particularly when IV epinephrine is administered too rapidly, as an inadequately diluted solution, or in excessive dosage. Reservations about using epinephrine by any route are certainly understandable given the potential dangers associated with its IV administration. Although controlled data adequately addressing safety concerns are scarce, some lessons can be gleaned from experience with the use of epinephrine for asthma. A study of SQ epinephrine in asthmatics demonstrated the safety of its administration in a wide age distribution of patients in the ED setting (ages ranged from 15 to 96 years old).67 A recent Australian study of IV epinephrine infusion (average dose of 1.5 mcg per minute) for the treatment of adult asthmatics (aged 18 to 55 years) concluded that “serious” adverse events were uncommon (8 of 220 cases: Two cases of supraventricular tachycardia, two cases of myocardial ischemia, and four cases of hypotension requiring intervention) and of unclear relationship to epinephrine, although “minor” adverse events (sinus tachycardia or other transient, self-resolving cardiovascular or neurologic symptoms) occurred in 67 of 220 (30%) cases.68 Although such asthma data cannot be overly generalized, it suggests a more favorable safety profile of epinephrine (particularly by routes other than IV) than is routinely acknowledged. In addition, children have a more attractive risk-benefit ratio (including fewer comorbid conditions) for epinephrine in general; they will likely tolerate most of the potential complications better than adults.

Antihistamines
Antihistamines are second line agents in the treatment of anaphylaxis as they have a relatively slow onset of action when compared with epinephrine. Antihistamines also have a role in prophylaxing against allergic reactions. However, antihistamines should never be administered as a sole treatment for anaphylaxis.

The role of H1 antihistamines (such as diphenhydramine) is well established. Administer 1 mg / kg IV (up to 50 mg) for children (25 to 50 mg IV for adults). Oral preparations (same dosages) are advocated for milder allergic symptoms. The newer (second generation) H1 antagonists, such as cetirizine (Zyrtec®), fexofenadine (Allegra®) and loratidine (Claritin®), are highly selective for the H1 receptor and are generally well tolerated at doses that produce high levels of antihistaminergic activity.69 One of the primary limitations of their use is that none of these newer generation agents is presently available for intravenous use, which is the preferred route of administration in anaphylaxis. Also, second generation agents have not been widely studied in the treatment or prevention of anaphylaxis in humans. Their use as a substitute for oral diphenhydramine in cases of milder allergic symptoms appears plausible, although clinical trials specifically addressing this topic are lacking. These agents have been well stud-
ied with an established track record in the treatment of chronic urticaria, where they appear to have a similar efficacy when compared with traditional H1 antagonists without the often unwanted side effect of sedation seen with the older agents. 70

The role of H2 antagonists in the treatment of allergic reactions is more controversial when compared to the long established role of H1 antagonists. Reports have demonstrated that the combination of an H1 and H2 antihistamine may be more effective than treatment with an H1 antagonist alone. A randomized, double-blind, placebo-controlled trial of 91 ED patients with acute allergic syndromes demonstrated benefit of the H1 (diphenhydramine) and H2 (ranitidine) antagonist combination, as compared with H1 antagonists alone.71 Similarly, another ED study found that the combination of diphenhydramine (H1 blocker) and cimetidine (H2 blocker) was more effective than diphenhydramine alone for the treatment of acute urticaria.72 Given their potential benefit, combined with a low propensity for adverse events, the adjunctive use of H2 antagonists in the treatment of acute allergic reactions is reasonable. However, there are no available data regarding which particular H2 antagonist is best. Cimetidine has effects on the hepatic p450 system, which may make ranitidine a more attractive alternative, although there are no specific studies to address this. Administer ranitidine intravenously (1 mg / kg, max 50 mg per dose) or orally (1 to 2 mg / kg, max 150 mg per dose, twice daily).

Corticosteroids
Surprisingly, in their 2005 expert consensus practice guidelines, the Joint Task Force on Practice Parameters, composed of members representing the major American Allergy and Immunology specialty societies, stated that “Systemic corticosteroids have no role in the acute management of anaphylaxis because they might have no effect for four to six hours, even when administered intravenously.”63 Their position is largely based on the fact that, although corticosteroids have traditionally been used in the management of anaphylaxis, their effects have never been validated in placebo-controlled trials. However, based on their known beneficial effects in asthma and other allergic diseases, by extrapolation, they may be beneficial in preventing recurrent or protracted anaphylaxis. As such, their administration is indicated in the vast majority of cases. While practice guidelines suggest that the intravenous route is the preferred method of administration when steroids are used for treatment of anaphylaxis, there is no research available supporting any specific dose, route of administration, or particular formulation. Another potential consideration is that there have been scattered reports of anaphylaxis to glucocorticoids themselves.73 Administer methylprednisolone as a 2 mg / kg IV loading dose (max 125 mg). Administer oral steroids 1 to 2 mg / kg daily (max 60 mg).

Other Pharmacologic Treatments
Glucagon may have a role in treating anaphylaxis refractory to standard therapy, especially in the case of coexisting beta-adrenergic receptor blockade (which is fortunately uncommon in the pediatric population).74 The cellular effects of sympathomimetic agents, such as epinephrine, are in part mediated by their stimulation of intracellular cyclic AMP (cAMP) production through interactions with beta-adrenergic receptors. Glucagon exerts its intracellular effects by directly stimulating cAMP production entirely independent of the adrenergic system, thereby bypassing drug-induced adrenergic blockade.75 A recent evidence-based review of the role of glucagon in refractory anaphylaxis suggested that, although there is a physiological rationale for the use of glucagon in anaphylactic patients on beta-adrenergic blockers, the evidence is limited to case reports only. The authors concluded that, despite the limited quality of the evidence, glucagon may benefit patients who are taking beta-blockers when all other, better recognized anaphylaxis treatments have failed.76 The initial pediatric bolus dose is 20 to 30 mcg / kg (maximum dose of 1 mg); the recommended adult dose is 1 to 5 mg IV over five minutes, followed by a continuous IV infusion of 5 to 15 mcg per minute, titrated to clinical response.61 Airway protection should be addressed upfront, as glucagon administration may cause emesis.

Consider the use of alternative vasopressor agents (such as norepinephrine or dopamine) to maintain blood pressure in the event that epinephrine and volume expansion fail to do so. Administer norepinephrine (initial 0.05 to 0.1 mcg / kg per minute; titrate to effect, maximum dose 2 mcg / kg per minute) or dopamine (initial 2 to 5 mcg / kg per minute; titrate to effect, maximum customary dose 20 mcg / kg per minute). In addition, continuous nebulized inhaled bronchodilators (such as albuterol sulfate) may be used for the treatment of anaphylaxis.
induced bronchospasm, either as a routine adjunct or a rescue measure in severe cases that remain refractory to epinephrine treatment. Finally, easily performed, yet frequently overlooked measures, such as removal of the offending allergen (i.e., removal of the stinger in the case of Hymenoptera hypersensitivity), may benefit the patient by curtailing the continued introduction of antigenic material.

Special Circumstances

Relative “Contraindications” To Epinephrine Use

There are no absolute contraindications to epinephrine use. However, there are a few potential confounding circumstances that deserve special attention; the first of which is beta-adrenergic blockade. Its implications in the management of anaphylaxis are two-fold: First, anaphylaxis has the potential to be worse in patients using beta blockers and, second, beta blockers may decrease the effectiveness of the principal treatment, epinephrine.

At the cellular level, there is a dynamic interplay between forces regulating inflammatory mediator formation and release, with beta adrenergic receptor stimulation hampering these processes. Thus, patients taking beta blockers are, in essence, postured towards anaphylactic mediator formation and release at baseline, potentially leading to more severe clinical symptoms. In addition, treatment with epinephrine may be blunted in the case of pre-existing beta adrenergic blockade. Further, epinephrine administration in this setting may lead to unopposed alpha adrenergic receptor stimulation and reflex vagotonic effects, potentially contributing to augmented mediator release, bronchoconstriction, bradycardia, and coronary vasoconstriction.77

Cardioselective (predominately beta-1) blockers cannot be assumed to be free of the increased risk of protracted anaphylaxis, as there are reports of unusually severe symptoms in association with these agents as well.78 Use of topical ophthalmic preparations has also been associated with systemic adverse events.78,79 All of this has led some authors to recommend administration of half-dose epinephrine in the treatment of anaphylaxis for patients who are receiving beta-adrenergic blocking drugs at baseline (including ophthalmic preparations) in order to attenuate these potential untoward effects of epi-

Cost Effective Strategies

1. Confirmatory tests are useless in the majority of patients.

Anaphylaxis is largely a clinical diagnosis and, as such, laboratory, radiographic, or other confirmatory tests generally have no role in its diagnosis.

_Caveat:_ In uncertain or confusing cases, a serum tryptase level may be helpful in confirming (or refuting) the diagnosis. Serum tryptase levels peak 60 to 90 minutes after the onset of anaphylaxis, so there is a relatively brief window to obtain the data that may otherwise be permanently lost in a “crash” ED setting. Therefore, earmark an additional tube of blood specifically for this purpose in unclear cases – your Allergy and Immunology consultants will thank you!

2. Patients with mild reactions (i.e., without any form of respiratory or hemodynamic compromise) can be observed in the ED for several hours for recurrence, and discharged with a reliable caretaker (and possibly two epinephrine self-administration devices dispensed from the hospital pharmacy prior to discharge).

_Caveat:_ Patients with either initially severe symptoms or any recurrent or progressive symptoms require admission to the hospital.

3. Teach patients (and their caretakers) how to properly use their epinephrine self-administration devices.

If used correctly and in the appropriate clinical setting, this simple intervention has the potential to reduce overall healthcare costs, and, in most cases, significantly improve patient outcomes. “Trainer” units are readily available from pharmacies (they come pre-packaged in both EpiPen® and Twinject® twin-packs) or directly from the device manufacturers.

_Caveat:_ Ensure that at-risk patients who are otherwise safe for discharge have the means (24-hour pharmacy and adequate financial resources) to obtain the devices right away. An alternative approach is to have the hospital pharmacy dispense at least two units at the time of patient discharge, especially when you are sending someone home in the middle of the night.
nephrine administration. In addition, glucagon has been recommended as an adjunctive agent for the treatment of anaphylaxis in the setting of coexisting beta-adrenergic blockade.

A second relative contraindication involves epinephrine administration in sulfite allergic patients. Sodium Metabisulfite (MBS) is a commonly used food and drug preservative that is ubiquitously found in commercially available epinephrine preparations. The mechanism of sulfite sensitivity in susceptible individuals typically relates to direct mast cell activation (anaphylactoid), and rarely involves IgE antibodies. There are no good recommendations on how to manage these scenarios (potential administration of a sulfite-containing epinephrine formulation in a sulfite allergic patient experiencing anaphylaxis from another cause) assuming that MBS-free epinephrine is not immediately available. At least one author has recommended epinephrine treatment despite a history of sulfite sensitivity if anaphylaxis is unresponsive to antihistamines, bronchodilators, corticosteroids, and other vasopressors.

A final relative contraindication to the use of epinephrine is in the pregnant patient experiencing anaphylaxis, due to the drug’s adverse effect on placental blood flow. In such cases, ephedrine can be tried (25 to 50 mg SQ or IM every four to six hours, or, if unstable, 5 to 25 mg IV every five to ten minutes until stabilized). Glucagon may also be tried, though there are no data on its use in this setting. However, these alternative treatments may not be readily available in your ED. As such, life saving interventions (including epinephrine) should not be withheld while awaiting medication delivery from the hospital pharmacy!

Controversies / Cutting Edge

Other Potential Routes Of Epinephrine Administration

Alternative routes of epinephrine administration include intraosseous (IO), endotracheal, or inhaled.

Intraosseous epinephrine may be particularly useful in the case of repeated, failed IM administration and difficult vascular access, although there are no studies addressing this specifically. Exercise the same precautions as used when giving IV epinephrine. Endotracheal administration may be a last resort in the case of refractory symptoms and failed IV / IO access.

Use of inhaled epinephrine has been proposed. One study of epinephrine metered-dose inhalers in children found that inhaled epinephrine contributes to relief of respiratory symptoms, but is impractical for the treatment of other systemic effects, which requires 20 to 30 inhalations over a period of four minutes in an adult.

In addition, one recent adult study of fast-disintegrating, sublingual epinephrine tablets (40 mg) showed similar epinephrine plasma concentrations to those achieved with IM injection (0.3 mg, lateral thigh). The authors concluded that the sublingual route may be a feasible alternative to IM administration, but this warrants further study prior to any formal recommendation regarding its use in adults. Oral epinephrine is ineffective owing to both intestinal wall and hepatic metabolism prior to entry into the systemic circulation.

Pediatric Airway Management In Allergic Emergencies

Airway management may be particularly challenging in the child with anaphylaxis. As airway resistance is related to airway radius to the fourth power, edema has a much greater effect on the comparatively small pediatric airway. There is no correct answer to the question of when to intubate. Definitive airway management must be addressed with great care and preferably well before respiratory distress ensues. Several different intubation techniques may be employed, including: “Awake” intubation (i.e., use of nebulized lidocaine topical anesthesia and mild sedation without the use of induction and paralyzing agents), fiberoptic intubation, or placement of a surgical airway (as a back-up to a failed airway or as the primary modality in severe cases). Early mobilization of anesthesiology and surgery for assistance with fiberoptic intubation or surgical airway placement is prudent, if time and circumstances permit. Cricothyroidotomy is relatively contraindicated in children less than approximately eight years of age, due to anatomical considerations. Therefore, surgical options for the emergency physician in such young patients include needle cricothyroidostomy with jet ventilation or emergency tracheostomy by our surgical colleagues.

In order to optimize success, prepare a variety of additional endotracheal (ET) tubes of smaller size than what you would customarily use based on patient age and weight. Caution must be exercised with the decision to utilize sedatives or paralytic agents, as airway compromise may be worse than...
initially anticipated, leaving fewer options for airway management in the case of failed intubation in a patient whom you are unable to effectively ventilate. Customary “rescue” techniques, such as the placement of a laryngeal mask airway (LMA) or esophageal tracheal Combitube®, are unlikely to be effective in the case of significant oropharyngeal angioedema, further limiting options in the case of a failed airway. Small diameter ET tube placement over a gum elastic bougie may serve as a back-up in such cases; a relatively small ET tube is much more preferable to no airway at all. Overall, maintaining a systematic approach to airway management in allergic emergencies, with several contingency plans in the case of failed intubation or ventilation, is most prudent.

Disposition

Recurrent Anaphylaxis

Recurrent (biphasic or multiphasic) anaphylaxis is defined as the reappearance of allergic phenomena following the complete resolution of the original reaction and without re-exposure to the inciting allergen. Recurrence may involve nuisance level symptoms, such as urticaria, or more ominous physiologic derangements, including respiratory compromise or hemodynamic instability. Symptoms experienced during the recurrent phase may be equal to or greater in severity than those seen with the initial reaction. In addition, protracted (prolonged or refractory) anaphylaxis has also been reported. These patients often present with refractory respiratory distress or hypotension. There have also been reports of delayed anaphylaxis specifically in the setting of insect sting injuries, with initial symptom onset hours to days following the initial deposition of venom in the dermis and subcutaneous tissues.

Experimental evidence suggests that an initially strong antigenic stimulus may result in a second, delayed phase of mediator release, corresponding clinically to a second wave of symptoms occurring several hours after the initial manifestations have cleared. Other factors potentially contributing to recurrence include: Large initial antigen exposure, inadequate initial therapy with only transient suppression of the immune response, repeat “internal” exposure (i.e., second wave of absorption following the ingestion of antigenic material), or ongoing accumulation of mediators leading to recurrent clinical symptoms. Rates of multiphasic anaphylaxis have been reported to be as high as 20% In addition, recurrences have been reported up to 72 hours after the inciting event. A study of biphasic reactions in pediatric inpatients (median age: eight years; range: six months to 21 years) found an overall incidence of 6%, with a 3% incidence of severe biphasic reactions, and asymptomatic intervals of 1 to 28 hours.

In a retrospective study of multiphasic anaphylaxis in the ED setting, it was noted that, of the 67 cases (mean age 30 years) included in their analysis, 93% had immediate resolution of symptoms and remained asymptomatic for a mean time of 4.2 hours in the ED. Protracted anaphylaxis requiring hospitalization was noted in five patients (7%), with the majority occurring in patients taking beta-adrenergic blocking agents. Recurrent anaphylaxis was noted in two patients who had been released from the ED, with only minor recurrent allergic manifestations (urticaria) in both cases.

Another study found that biphasic reactions occurred in 18% of 34 ED patients (age 16 to 81 years) with anaphylaxis, with the second phase developing after more than 29 hours in one patient. The authors also noted that patients who went on to develop a multiphasic reaction required significantly more epinephrine to treat their initial symptoms. They concluded that all patients requiring epinephrine should be admitted (or observed) for at least 24 hours.

A recent investigation of 282 ED patients (age 19 to 43 years) with anaphylaxis in Hong Kong found that biphasic symptoms occurred in 15 of 282 patients (5.3%). Interestingly, three of these patients had stable vital signs on initial presentation, yet developed hypotension (two patients) or severe dyspnea and hypoxia (one patient) at the time of recurrence. Overall, the mean time from treatment to onset of the recurrent reaction was eight hours (range of 1 to 23 hours). Further analysis revealed that an observation time of up to eight hours would have missed four patients with biphasic reactions; however, observation for 24 hours after initiation of treatment would have captured all patients with recurrent phenomena. The authors recommended admission or ED observation for at least 24 hours for anyone who requires treatment with epinephrine.

Admission Criteria

One of the most difficult decisions is determining the appropriate ED disposition. Unfortunately, such decisions are readily apparent in only a minority of
Ten Pitfalls To Avoid

1. “It appeared to be an anaphylactic reaction, but I didn’t administer epinephrine because I was worried about its adverse effects.”

Epinephrine is the undisputed first-line agent in the treatment of anaphylaxis. Although careful analysis of risks and benefits should certainly be addressed in all cases, anaphylaxis may lead to significant morbidity or mortality if not treated early and aggressively, and there are no absolute contraindications to epinephrine use.

2. “The patient looked great by the time the paramedics arrived; it seemed like the epinephrine they administered had worked, so I just wrote scripts for antihistamines and corticosteroids and sent her home.”

Recurrent (multiphasic) anaphylaxis occurs more frequently than is generally appreciated. Although there are no good data from the literature regarding the ideal duration of ED observation, practitioners should maintain a lower threshold for prolonged ED observation or hospital admission, particularly when the reactions were severe.

3. “I removed the stinger, treated the patient’s symptoms with all the right things, and sent him to an allergist for follow-up. I didn’t even think to ask if he needed a refill of his epinephrine self-administration device prior to discharge.”

The self-administration of epinephrine is a potentially life-saving intervention. Never forget to prescribe it in at-risk patients, or to inquire about refills that may be needed. Even better, consider having the hospital pharmacy dispense at least two devices for the patient (or caretaker) to carry home.

4. “The patient’s symptoms were unresponsive to epinephrine, antihistamines, and corticosteroids. She was still hypotensive, so I intubated her and admitted her to the pediatric ICU on an IV epinephrine drip.”

Whenever faced with an unresponsive or protracted case of anaphylaxis, entertain the possibility of concurrent beta-adrenergic blockade. An empiric trial of glucagon may be warranted in such recalcitrant cases, as its potential benefits are appreciable without significant downside.

5. “The patient presented with bradycardia; I assumed that it must be vasodepressor syncope causing the patient’s symptoms … how was I supposed to know that it was actually anaphylaxis?”

Patients with anaphylaxis typically present with tachycardia as a reflex response to extravascular volume re-distribution. Although the precise mechanisms involved are speculative, anaphylaxis may also present with bradycardia. In addition, patients taking beta-adrenergic blocking agents may fail to mount a tachycardic response, and present with a relative bradycardia.

6. “There was no rash or any other skin findings … I didn’t even think about the possibility of anaphylaxis!”

Anaphylaxis usually presents with skin findings such as urticaria, angioedema, or flushing. However, it may also occur in the absence of these classic findings. The presence of such dermatologic findings supports the diagnosis, but their absence certainly does not exclude the possibility.

7. “The IV catheter was already in place for us to give the antihistamine and corticosteroid, so I figured I would give the epinephrine through the IV as well.”

The incidence of adverse events from epinephrine increases exponentially when it is administered via the IV route. Reserve IV epinephrine for patients unresponsive to repeated IM epinephrine administration or with rapidly deteriorating respiratory status or significant hemodynamic compromise.

8. “Even though he was ventilating on his own, the patient’s overall condition was worsening, so I performed rapid sequence induction with etomidate and succinylcholine in preparation for intubation … how was I supposed to know that the endotracheal tube would not pass because of the angioedema?”

Exercise extreme caution when deciding on the best approach to manage an airway in anaphylaxis. Definitive management should occur well before it’s too late; however, the use of paralytics carries the potential for making the situation even worse in the case of a failed intubation. Alternatives to rapid sequence intubation include “awake” intubation utilizing topical anesthesia and light sedation without paralysis, preferably with a fiberoptic laryngoscope. In any case, contingency plans for a surgical airway should be in place, with appropriate equipment opened and ready for immediate use at the bedside, and airway consultants (surgeons, anesthesiologists) present if circumstances and time permit.

9. “No one told me about the history of hereditary angioedema … I just placed him on an oral antihistamine and an oral steroid and sent him home.”

Hereditary angioedema is a unique situation that may not be responsive to standard treatments such as epinephrine, antihistamines, and corticosteroids. Albeit controversial in the literature, acute treatment generally involves the administration of fresh frozen plasma in consultation with a pediatric hematologist or other specialist.

10. “The patient had a history of shellfish allergy, so I waited for the ultrasound technician to get here from home instead of immediately doing the CT scan with IV contrast.”

There is no known definitive correlation between a history of shellfish allergy and reaction to iodine-containing radiographic contrast materials (RCM). At-risk patients for RCM reactions include those with a history of prior RCM reaction, a history of atopy, pre-existing coronary artery disease, and use of beta-adrenergic blocking agents.
cases. Patients with a slow response to standard therapies or patients with ongoing, severe reactions certainly require admission. On the other end of the spectrum, patients with clearly mild reactions can be safely discharged home with a responsible adult. However, the majority of patients fall somewhere in between, making disposition more challenging. Although there are no rigorous studies on the subject, factors to consider in determining whether to admit a patient to the hospital are presented in Table 9.

What about the ED observation time for patients who appear safe for discharge? A few considerations deserve mention. First, the incidence of recurrent anaphylaxis is greater than generally appreciated by the medical community. In addition, recurrent reactions have occurred despite the early institution of appropriate treatments, including glucocorticoid therapy. These factors, when combined with the wide range of reported asymptomatic intervals, make it difficult to establish guidelines regarding the appropriate duration of ED observation. Overall, there is not an established time frame. A minimum of several hours post treatment appears reasonable for mild episodes, and admission (or 24 hour observation) appears prudent for severe episodes or patients with any high-risk or otherwise concerning features.

A comprehensive literature review of biphasic anaphylaxis compiled by Lieberman in 2005 concluded that an eight hour observation period is probably sufficient to ensure that the majority of significant recurrences would manifest (as most occur within an eight hour timeframe), whereas a full 24 hours of observation would only benefit a minority of patients. A recent consensus statement recommended four to six hours of post-anaphylactic observation for most patients, with more prolonged observation (or hospital admission) for those with severe or refractory symptoms, and in patients with reactive airway disease. Although these recommendations may appear conservative, practitioners should have a low threshold for prolonged ED observation or hospital admission.

**Epinephrine Self-Administration Devices**

Anaphylaxis often occurs in the out-of-hospital setting in the absence of trained health care professionals. Therefore, the prompt self-administration of epinephrine remains a key to effective management in this setting. There is little disagreement that self-administration devices should be prescribed to individuals who have a prior history of anaphylaxis involving respiratory distress or shock when the triggering allergen may be re-encountered. A more difficult decision involves patients who experienced only minor symptoms after exposure to a known trigger. This has fueled controversy regarding the possible over- or under-prescription of epinephrine self-administration devices. Unfortunately, there are no evidence-based guidelines on the topic. It should be kept in mind, however, that an initial episode, no matter how mild, may not predict the severity of future events, particularly in the case of food induced allergy.

Self-administration epinephrine is currently available in several devices. EpiPen® Jr (Dey, Napa, California) contains 0.3 ml of a 1:2000 solution (0.15 mg of epinephrine) for children, and EpiPen® (Dey, Napa, California) contains 0.3 ml of a 1:1000 solution (0.3 mg of epinephrine) for adults. In addition, the recently released Twinject® (Verus, San Diego, California) is also available in 0.3 mg and 0.15 mg formulations. Given the recommended IM epinephrine dose of 0.01 mg/kg for children, there are currently no clear guidelines on which dose to prescribe to individuals weighing between 15 and 30 kg.

| Table 9. Factors To Consider In Determining Hospital Admission For Patients With Allergic Reactions |
|---|---|
| **Factor Presenting Symptom Severity** | **Comments** |
| Anaphylaxis History | Any history of severe, protracted, or recurrent anaphylaxis |
| Particular Allergen | “Nut” (peanut or tree nut) reactions are associated with especially high morbidity and mortality among food allergens |
| Medical Comorbidities | Conditions such as asthma (particularly high morbidity and mortality in the setting of anaphylaxis), congestive heart failure, or renal disease (at risk for fluid overload with volume resuscitation) |
| Baseline Medications | Particularly beta-adrenergic blocker use (including ophthalmic) |
| Access to Medical Care | Great distance or reduced access to medical care |
| Age | Patients at extremes of age have reduced compensatory abilities |
| Unreliable Home Situation | Including barriers to appropriate discharge instruction and education |
Similarly, there are no pre-measured options available for at-risk children weighing less than 15 kg, leaving the 0.15 mg formulation as the sole option for self-administration (and the traditional, weight-based ampule / syringe / needle technique may be impractical in high-stress medical emergencies such as anaphylaxis).97

One retrospective study concluded that more than 35% of anaphylactic reactions included in their analysis required more than one epinephrine dose in order to reverse symptomatology.98 Therefore, it is frequently recommended that at-risk patients carry two auto-injector units at all times. However, Twinject® allows for administration of a second, follow-up epinephrine dose with use of the same autoinjector device for persistent or worsening allergic symptoms despite initial epinephrine treatment.99 The second dose is available by manual injection following partial disassembly of the autoinjector unit.

Other Discharge Medications
In addition to epinephrine, other recommended discharge medications include: H1 antihistamines, H2 antihistamines, and corticosteroids. Many authors empirically recommend continuation of oral medications for at least 72 hours following ED discharge, as recurrent anaphylaxis can occur up to 72 hours after the initial event.100 It comes as no surprise, however, that the 72 hour recommendation is entirely empiric. Despite limited data, a three day to one week course of oral antihistamines (H1, H2) and oral corticosteroids is unlikely to produce harm, and may prevent or attenuate a recurrence.

Discharge Education
Studies have shown that as few as 30% of patients prescribed epinephrine self-administration devices carry them with them at all times.101 Another study showed that, while 71% of people had their device with them at an office visit, only 55% were unexpired.102 Moreover, studies evaluating patients’ understanding of self-administration technique showed that only 32 to 44% of patients (or caretakers) could correctly demonstrate proper use of their device.103-105

Even more concerning is a study revealing that, among physicians who commonly prescribe self-administration devices (emergency physicians, pediatricians, and family practitioners), only 25% could themselves correctly demonstrate the “three steps” of injection (remove safety cap, grasp device, administer into outer thigh while holding in place for 10 seconds).104 In addition, 76% of participants in this study did not know the two available dosage strengths (0.3 mg and 0.15 mg), which has important treatment implications, particularly in the pediatric population. A second study of practicing pediatricians and pediatric residents showed that only 21% and 36% of participants, respectively, correctly demonstrated the use of EpiPen® or EpiPen® Jr.102 Underscoring the importance of appropriate training is the unique complication of local digital ischemia caused by inadvertent injection of epinephrine into a finger when the device is used incorrectly.103,105 It is vital that the patients’ teachers are adequately instructed in the use of the self-administration device in the event a severe reaction occurs at school or on a field trip.

Patients and caretakers should be instructed to always err on the side of caution, and promptly administer epinephrine even when few or mild symptoms occur after exposure to the individual’s known trigger.95 The potential side effects of IM epinephrine are relatively benign compared to severe, untreated anaphylaxis. In a study of children who had been previously prescribed epinephrine for self-administration, the device was used in only 29% of subsequent anaphylactic reactions.106 The authors noted that parental knowledge was deficient in both recognition of the symptoms of anaphylaxis and in the actual use of the device. Clearly, more education is needed at all levels, including medical practitioners and patients (and their caretakers).

Despite early, aggressive and appropriate treatment, a small proportion of anaphylactic reactions will ultimately prove fatal; therefore, the optimal management of anaphylaxis begins prior to symptom onset, with avoidance of the precipitant whenever possible.107 In addition, MedicAlert® bracelets should be recommended for at-risk individuals. These identifiers provide an invaluable clue for EMS and ED personnel of the need for rapid epinephrine administration in patients with suggestive signs and symptoms who may be unconscious and unable to communicate. If traveling in a foreign country, patients should wear bracelets translated into that country’s native language.

Patients with anaphylaxis should be referred to an allergy-immunology specialist at the time of ED discharge. Allergy-immunology specialists will obtain a detailed allergy history, coordinate both laboratory and allergy testing, evaluate the long-term
Summary

Anaphylactic reactions are life-threatening and are almost always unanticipated. Any delay in the recognition of the initial signs and symptoms may result in a poor outcome. Even when there are only mild symptoms initially, the potential for progression to airway obstruction or vascular collapse must be appreciated, and treatment must be swift and aggressive. Epinephrine is the cornerstone of therapy. Second line pharmacotherapies include H1 and H2 antihistamines and corticosteroids. ED disposition is fraught with potential dangers, given the potential of

<table>
<thead>
<tr>
<th>When Does an Allergic Reaction Become an Anaphylactic Reaction?</th>
<th>There is no universally accepted definition of anaphylaxis. However, most authorities do agree that involvement of the respiratory (upper or lower) or cardiovascular system is necessary to distinguish anaphylaxis from other allergic phenomena.</th>
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<tr>
<td>Epinephrine</td>
<td></td>
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<td><strong>In which cases?</strong></td>
<td>Epinephrine is the undisputed first line agent and treatment of choice for anaphylaxis; despite this, it remains greatly underutilized. Maintain a very low threshold for use, prior to the vicious cycle of inflammatory mediator release spiraling beyond control.</td>
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<tr>
<td><strong>By what route?</strong></td>
<td>IM (particularly in the lateral thigh) is superior to SQ, regardless of patient age. Virtually all adverse events of epinephrine administration related to its IV use; therefore, reserve IV for patients unresponsive to repeated IM dosages or those with profound shock.</td>
</tr>
<tr>
<td><strong>When to avoid?</strong></td>
<td>There are no absolute contraindications. However, exercise caution in patients on beta-adrenergic blockers, patients with severe sulfite sensitivity, and pregnant patients.</td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
<td>H1 plus H2 antihistamine carries potential benefits and has a low propensity for adverse events.</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>Corticosteroids are of benefit as a secondary treatment in Anaphylaxis; extrapolated from known benefit in other allergic diseases, such as asthma; they may play a role in reducing the incidence of recurrent anaphylaxis.</td>
</tr>
<tr>
<td><strong>Disposition</strong></td>
<td>Maintain a low threshold for admission or prolonged ED observation due to the risk of recurrent anaphylaxis. Be especially cautious in asthmatics or in patients with &quot;nut&quot; allergies, as they are at risk for particularly severe symptoms or fatal outcome.</td>
</tr>
<tr>
<td><strong>Adverse Drug Reactions (ADR)</strong></td>
<td>Non-allergic ADRs (nausea, vomiting, non-specific rash) are far more common than allergic ADRs; among all allergic ADRs, true Type I hypersensitivity reactions, which place a patient at risk for anaphylaxis, are relatively infrequent. Probe the authenticity of any reported medication “allergy” before excluding potential treatment options.</td>
</tr>
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recurrent anaphylaxis. It is prudent to maintain a low threshold for hospital admission (or prolonged ED observation) in significant cases or in the presence of other high-risk features, particularly pre-existing asthma, use of beta blockers, or “nut” induced food allergy. Ensuring that patients have continuous access to and familiarity with their epinephrine self-administration device is critical to preventing morbidity and mortality in anaphylaxis. Fortunately, the battle against our own immune systems can, more often than not, be won with such widely available and highly effective treatment modalities.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available.

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<td>88.</td>
<td>Ellis AK, Day JH. Biphasic anaphylaxis: a prospective examination of 103 patients for the incidence and characteristics of biphasic reactivity. <em>J Allergy Clin Immunol</em> 2004;113:5:259. (Abstract; Prospective; 103 subjects)</td>
</tr>
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CME Questions

1. Which of the following represents the recommended epinephrine dilution (weight/volume) for intravenous (IV) use in anaphylaxis?
   a. 1:100,000
   b. 1:10,000
   c. 1:1,000
   d. 1:100
   e. 1:1

2. Which of the following is the preferred initial route and site of epinephrine administration in anaphylaxis?
   a. SQ, deltoid
   b. IM, deltoid
   c. SQ, lateral thigh
   d. IM, lateral thigh
   e. IV, peripheral venous catheter

3. Which of the following is a relative contraindication to epinephrine use in anaphylaxis?
   a. Less than one year of age
   b. Tachycardia on presentation
   c. History of sulfite sensitivity
   d. History of poorly controlled asthma
   e. History of diabetes

4. What is the proper dosage of epinephrine for IM use in a 30 kg child?
   a. 0.01 mg
   b. 0.03 mg
   c. 0.1 mg
   d. 0.3 mg
   e. 3 mg

5. Regarding epinephrine self-administration devices for out-of-hospital use, which of the following is true?
   a. Use it only in patients with a history of severe anaphylaxis.
   b. Do not prescribe it to patients less than three years of age.
   c. Proper instruction is paramount to successful use of the device.
   d. It has no role in the prehospital setting for use by EMS personnel.
   e. It is currently available in only one dosage formulation (0.3 mg of a 1:1,000 dilution).

6. Which of the following is most characteristic of an allergic adverse drug reaction (ADR) as compared with a non-allergic ADR?
   a. Urticaria
   b. Nausea
   c. Lightheaded
   d. Malaise
   e. Vomiting

7. Acute Hymenoptera sensitivity can best be categorized as which of the following Gell and Coombs hypersensitivity reaction types?
   a. Type I reaction
   b. Type II reaction
   c. Type III reaction
   d. Type IV reaction
   e. Idiopathic reaction that does not fit Types I through IV

8. Which of the following regarding recurrent anaphylaxis is true?
   a. By definition, it may only occur within 72 hours of initial symptom onset.
   b. Recurrent symptoms are always less severe than initial symptoms.
   c. It may occur following complete resolution of initial symptoms.
   d. It only occurs in adult patients.
   e. Corticosteroid use reliably prevents recurrence.

9. Which of the following is the best initial route and choice of antihistamines for the treatment of anaphylaxis in the ED setting?
   a. PO diphenhydramine
   b. IV diphenhydramine
   c. PO cetirizine
   d. IM cimetidine
   e. IV ondansetron
10. Which of the following regarding glucocorticoid administration in anaphylaxis is true?
   a. IV administration is clearly superior to IM.
   b. There is no role of PO glucocorticoids in the treatment of anaphylaxis.
   c. Methylprednisolone is superior to hydrocortisone.
   d. Glucocorticoids may be beneficial in preventing recurrent anaphylaxis.
   e. Once initiated, treatment with glucocorticoids should be continued for at least seven days.

11. Which of the following may be beneficial in anaphylaxis unresponsive to repeated epinephrine administration?
   a. Lidocaine
   b. Insulin
   c. Glucagon
   d. Naloxone
   e. Flumazenil

12. What is the most appropriate self-administration epinephrine dose for a 22.5 kg child?
   a. EpiPen® Jr (0.15 mg)
   b. EpiPen® (0.3 mg)
   c. Either EpiPen® Jr (0.15 mg) or EpiPen® (0.3 mg)
   d. “Weight-based” (precise dose) self-administration epinephrine
   e. None of the above

13. When compared with adult presentations, which of the following statements regarding anaphylaxis in pediatric patients is correct?
   a. Cardiovascular symptoms predominate.
   b. Cutaneous manifestations predominate.
   c. Gastrointestinal symptoms predominate.
   d. Respiratory symptoms predominate.
   e. None of the above.

14. Which of the following is the most common etiology of anaphylaxis seen in U.S. EDs?
   a. Medications
   b. Foods
   c. Hymenoptera venom
   d. Radiographic contrast materials
   e. Latex

15. Which of the following distinguishes between an anaphylactic and an anaphylactoid reaction?
   a. Rapidity of onset
   b. Presence of hypotension
   c. Degree of bronchospasm
   d. Response to epinephrine
   e. Involvement of IgE antibodies

16. Which of the following is thought to be a risk factor for particularly severe, or even fatal, anaphylaxis?
   a. Strong family history of atopy
   b. History of asthma
   c. Hymenoptera sting in an at-risk individual
   d. Early onset of symptoms following allergen exposure
   e. Presence of gastrointestinal manifestations

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- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling


Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case-control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

No recommendations until further research

Results inconsistent, contradictory

Results not compelling


Class IV
- Unacceptable
- Use with caution
- Generally higher levels of evidence

Level of Evidence:
- Consistent negative results
- Negative results
- Evidence not available

No recommendations until further research

Results inconsistent, contradictory

Results not compelling


Class V
- Evidence not available

No recommendations until further research

Results inconsistent, contradictory

Results not compelling


Class VI
- No recommendations until further research

No recommendations until further research

Results inconsistent, contradictory

Results not compelling


Class VII
- Unacceptable
- Use with caution
- Generally higher levels of evidence

Level of Evidence:
- Consistent negative results
- Negative results
- Evidence not available

No recommendations until further research

Results inconsistent, contradictory

Results not compelling


Class VIII
- Evidence not available

No recommendations until further research

Results inconsistent, contradictory

Results not compelling


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