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Practice Parameter

Emergency department diagnosis and treatment of anaphylaxis: a practice parameter

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This parameter was developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

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Classification of recommendations and evidence

Recommendation rating scale

Statement	Definition	Implication
Strong recommendation	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (grade A or B)*. In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Moderate	A recommendation means the benefits exceed the harms (or that the harms clearly exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (grade B or C).* In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians also should generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Weak	An option means that the quality of evidence that exists is suspect (grade D)* or that well-done studies (grade A, B, or C)* show little clear advantage to one approach vs another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.
No recommendation	No recommendation means there is a lack of pertinent evidence (grade D)* and an unclear balance between benefits and harms.	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit vs harm; patient preference should have a substantial influencing role.

Category of evidence

Ia Evidence from meta-analysis of randomized controlled trials
Ib Evidence from at least 1 randomized controlled trial
IIa Evidence from at least 1 controlled study without randomization
IIb Evidence from at least 1 other type of quasi-experimental study
III Evidence from nonexperimental descriptive studies, such as comparative studies
IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

*Strength of recommendation**

A Directly based on category I evidence
B Directly based on category II evidence or extrapolated recommendation from category I evidence
C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
LB Laboratory based
NR Not rated

Emergency department diagnosis and management of anaphylaxis: a practice parameter

The Joint Task Force on Practice Parameters

The Joint Task Force on Practice Parameters is a 13-member task force consisting of 6 representatives assigned by the American Academy of Allergy, Asthma and Immunology; 6 by the American College of Allergy, Asthma and Immunology; and 1 by the Joint Council of Allergy and Immunology. This task force oversees the development of practice parameters; selects the workgroup chair(s); and reviews drafts of the parameters for accuracy, practicality, clarity, and broad utility of the recommendations for clinical practice.

Protocol for finding evidence

A search of the medical literature was performed for different terms that were considered relevant to this practice parameter. Literature searches were performed on PubMed and the Cochrane Database of Systematic Reviews. All reference types were included in the results. References identified as relevant were searched for relevant references and those references also were searched for relevant references. In addition, members of the workgroup were asked for references that were missed by this initial search.

Preface

This practice parameter is a joint effort between emergency physicians, who are often on the front line in the management of anaphylaxis, and allergists-immunologists, who have a vested interest in how such patients are managed. As recognized by emergency physicians and allergists, the timely administration of epinephrine is essential to the effective treatment of anaphylaxis, and such administration is dependent on correctly diagnosing anaphylaxis. In an emergency department (ED) setting, with the broad and often atypical presentation of anaphylaxis, failure to recognize anaphylaxis is a real possibility. Failure to recognize anaphylaxis inherently leads to undertreatment with epinephrine. Studies have shown that a large percentage of patients (57%) who present to the ED with anaphylaxis can be misdiagnosed.[1–3] Moreover, even when correctly diagnosed, epinephrine, the essential first line in the treatment of anaphylaxis, is frequently (up to 80% of the time) not administered.[4–6] In addition, patients who are treated in the ED for anaphylaxis, frequently do not receive a prescription for auto-injectable epinephrine and usually are not referred for allergy follow-up.[6,7]

The recommendations made in this document about the management of anaphylaxis apply to anaphylaxis that occurs in an ED setting. Some of these recommendations might be different if anaphylaxis occurs in an office setting.

It is important to understand that there is no absolute contraindication to administration of epinephrine in the setting of anaphylaxis. It also is important to recognize that anaphylaxis can progress rapidly from mild manifestations involving 1 organ system to severe involvement of multiple organ systems.

Compilation of summary statements

Summary Statement 1: Base the diagnosis of anaphylaxis on the history and physical examination, using scenarios described by the National Institutes of Allergy and Infectious Disease (NIAID) Panel (Fig 1)[8] but recognizing that there is a broad spectrum of anaphylaxis presentations that require clinical judgment. Do not rely on signs of shock for the diagnosis of anaphylaxis. (Strong Recommendation; C Evidence)

Summary Statement 2: Carefully and immediately triage and monitor patients with signs and symptoms of anaphylaxis in preparation for epinephrine administration. (Strong Recommendation; C Evidence)

Summary Statement 3: In general, place patients in a supine position to prevent or counteract potential circulatory collapse. Place pregnant patients on their left side. (Moderate Recommendation; C Evidence)

Summary Statement 4: Administer oxygen to any patient exhibiting respiratory or cardiovascular symptoms or patients with decreased oxygen saturation and consider for all patients experiencing anaphylaxis regardless of their respiratory status. (Moderate Recommendation; D Evidence)

Summary Statement 5: Expeditiously consider conditions other than anaphylaxis that might be responsible for the patient's condition. Obtain a serum tryptase level to assist in this regard after effective treatment has been rendered. (Moderate Recommendation; C Evidence)

Summary Statement 6: Determine whether the patient has risk factors for severe and potentially fatal anaphylaxis, such as delayed administration of epinephrine, asthma, a history of biphasic reactions, or cardiovascular disease, and consider these in the management and/or disposition of all patients with anaphylaxis. (Moderate Recommendation; B Evidence)

Summary Statement 7: Administer epinephrine intramuscularly in the anterolateral thigh as initial treatment for acute anaphylaxis immediately after the diagnosis of anaphylaxis is made. The first line of treatment for patients experiencing anaphylaxis is epinephrine. (Strong Recommendation; B Evidence)

Summary Statement 8: If the patient is not responding to epinephrine injections, administer an intravenous (IV) infusion of epinephrine in a monitored setting. (Moderate Recommendation; C Evidence)

Summary Statement 9: If IV access is not readily available in patients experiencing anaphylaxis, obtain intraosseous (IO) access and administer epinephrine by this route. (Moderate Recommendation; D Evidence)

Summary Statement 10: Prepare for airway management, including intubation if necessary, if there is any suggestion of airway edema (eg, hoarseness or stridor) or associated respiratory compromise. (Moderate Recommendation; C Evidence)

Summary Statement 11: For patients with circulatory collapse from anaphylaxis, aggressively administer large volumes of IV or IO normal saline through large-bore catheters. (Strong Recommendation; B Evidence)

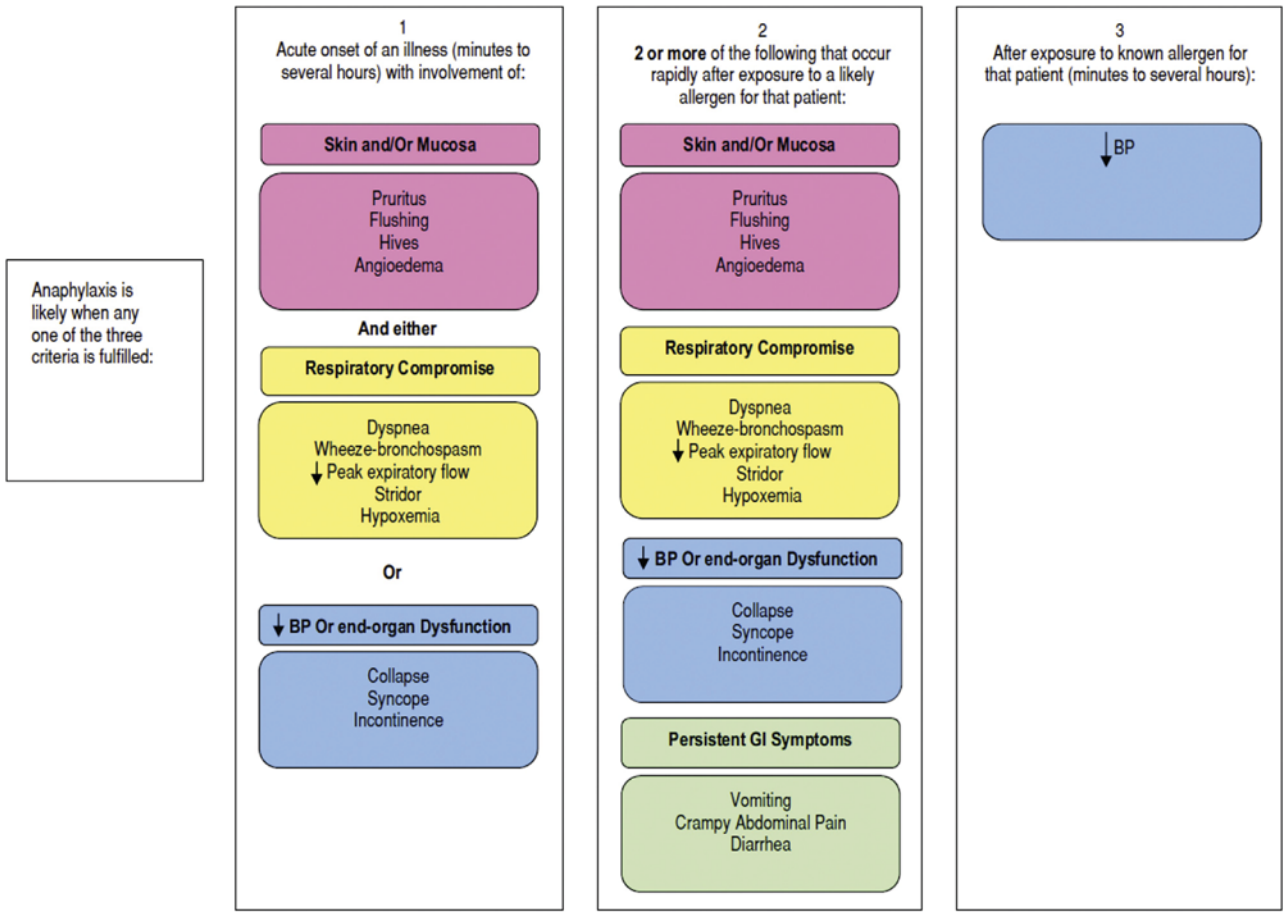

Figure 1. Visual representation of the NIAID/FAAN criteria. Reprinted with permission from the Internal Journal of Emergency Medicine.[8]

Summary Statement 12: Administer additional vasopressors or glucagon (especially if the patient is receiving β-blockers) if parenteral epinephrine and fluid resuscitation fail to restore blood pressure. (Moderate Recommendation; B Evidence)

Summary Statement 13: Administer an inhaled β-agonist if bronchospasm is a component of anaphylaxis. (Moderate Recommendation; B Evidence)

Summary Statement 14: Consider extracorporeal membrane oxygenation in patients with anaphylaxis who are unresponsive to traditional resuscitative efforts. (Moderate Recommendation; D Evidence)

Summary Statement 15: Do not routinely administer antihistamines or corticosteroids instead of epinephrine. There is no substitute for epinephrine in the treatment of anaphylaxis. Administration of H_1 and/or H_2 antihistamines and corticosteroids should be considered adjunctive therapy. (Strong Recommendation; B Evidence)

Summary Statement 16: Identify triggers of anaphylaxis and consider obscure and less common triggers. (Moderate Recommendation; C Evidence)

Summary Statement 17: Strongly consider observing patients who have experienced anaphylaxis for at least 4 to 8 hours and observe patients with a history of risk factors for severe anaphylaxis, such as asthma, previous biphasic reactions, or protracted anaphylaxis, for a longer period (Moderate Recommendation; C Evidence)

Summary Statement 18: Prescribe auto-injectable epinephrine for patients who have experienced an anaphylactic reaction and provide patients with an action plan instructing them on how and when to administer epinephrine. (Strong Recommendation; C Evidence)

Summary Statement 19: Instruct patients who have experienced anaphylaxis when discharged from the ED to see an allergist-immunologist. (Moderate Recommendation; C Evidence)

ED diagnosis and management of anaphylaxis: a practice parameter

Summary Statement 1: Base the diagnosis of anaphylaxis on the history and physical examination, using scenarios described by the NIAID Panel (Fig 1) but recognizing that there is a broad spectrum of anaphylaxis presentations that require clinical judgment. Do not rely on signs of shock for the diagnosis of anaphylaxis. (Moderate Recommendation; C Evidence)

Symptoms of anaphylaxis are usually sudden in onset and can progress in severity over minutes to hours. Typically, at least 2 organ systems are involved, although only 1 organ system might be initially involved. There is a broad spectrum of anaphylaxis presentations that require clinical judgment. Although no set of diagnostic criteria for anaphylaxis will provide 100% sensitivity and specificity, the criteria developed by the NIAID Panel in 2004 have been shown to aid in the diagnosis of anaphylaxis[9] (Fig 1). The accuracy of these criteria were retrospectively evaluated in an ED setting and found to have 97% sensitivity and 82% specificity.[2] The negative predictive value was 98% and the positive predictive value was 69%; the positive likelihood ratio was 5.48, with a negative likelihood ratio of 0.04. Therefore, these criteria are useful but do not replace clinical judgment. It is important for health care providers to recognize the variable presentation and progression of anaphylaxis.[10–12] Recognizing milder anaphylaxis is important not only in preventing progression of a specific event to a more serious outcome but in preventing recurrent episodes in the future. Although anaphylaxis can present as hypotension alone, it frequently presents without hypotension. Studies of fatal and near-fatal anaphylaxis have shown that most of these patients did not have a history of severe reactions.[11] Although most cases of anaphylaxis will include cutaneous manifestations, the absence of skin manifestations does not exclude a diagnosis of anaphylaxis.[12,13]

Summary Statement 2: Carefully and immediately triage and monitor patients with signs and symptoms of anaphylaxis in preparation for epinephrine administration. (Strong Recommendation; D Evidence)

Anaphylaxis can progress rapidly and become life threatening. Therefore, monitoring, preferably continuous hemodynamic monitoring, is essential for patients who are experiencing anaphylaxis. This should include blood pressure, continuous pulse rate, pulse oximetry, and electrocardiographic monitoring. IV access should be obtained as soon as possible. These measures should be used to monitor response to therapy and direct subsequent intervention.

Summary Statement 3: In general, place patients in a supine position to prevent or counteract potential circulatory collapse. Place pregnant patients on their left side. (Moderate Recommendation; C Evidence)

A case series on anaphylactic deaths has suggested an association between upright posture and death.[14] To counteract the circulatory collapse of anaphylaxis, patients generally should be placed in a supine position. However, patients in respiratory distress could benefit from being in a more upright position while they are monitored carefully for any circulatory collapse. Although Trendelenburg positioning has long been proposed to prevent or counteract hypotension, there is no evidence to support Trendelenburg positioning and it might even be counterproductive.[15] Pregnant patients should be placed on their left side to prevent the gravid uterus from compressing the inferior vena cava and obstructing venous return to the heart. Gentle manual displacement of the uterus may be necessary. The patient should not sit or stand suddenly because of the possibility of cardiac arrest caused by the empty inferior vena cava syndrome.[16]

Summary Statement 4: Administer oxygen to any patient exhibiting respiratory or cardiovascular symptoms or patients with decreased oxygen saturation and consider for all patients experiencing anaphylaxis regardless of their respiratory status. (Moderate Recommendation; D Evidence)

Summary Statement 5: Expeditiously consider conditions other than anaphylaxis that might be responsible for the patient's condition. Obtain a serum tryptase level to assist in this regard after effective treatment has been rendered. (Moderate Recommendation; C Evidence)

The differential diagnosis of anaphylaxis is broad. In the study noted in summary statement 1, the negative predictive value of the proposed NIAID criteria was 98%, but the positive predictive value was only 69%, showing that a significant number of patients who meet the criteria might not have anaphylaxis. The physician cannot rely on the presence of shock to make a diagnosis of anaphylaxis. It is important to consider other conditions that could be responsible for the patient's presentation: (1) cardiogenic, distributive, obstructive, or hypovolemic shock; (2) pre-syncope or syncope; (3) hereditary angioedema or angioedema induced by an angiotensin-converting enzyme inhibitor; (4) vocal cord dysfunction; (5) flushing such as occurs associated with metastatic carcinoma or vasoactive intestinal peptide-producing tumor; (6) respiratory distress from asthma, pulmonary embolism, congestive heart failure, or other causes; (7) isolated skin reactions, such as those that can be seen with adverse drug reactions; (8) mast cell disorders, as discussed below; and (9) psychiatric disorders, such as panic attacks.

Serum tryptase is a marker of mast cell degranulation and could be useful for confirming the diagnosis of anaphylaxis. Thus, the ED physician should consider obtaining a tryptase level if appropriate follow-up of the test result can be assured (eg, with the patient's primary care physician or by an allergist who agrees to see the patient in follow-up. Because serum tryptase levels are not rapidly available, management of a patient with possible anaphylaxis should never be based on serum tryptase levels alone. However, when the diagnosis of anaphylaxis is uncertain, a serum tryptase level could aid at follow-up in the diagnosis of anaphylaxis in a given patient. The sensitivity of serum tryptase in patients who present to the ED with acute allergic reactions is low (21% in 1 study).[17] Moreover, serum tryptase level is not elevated in most patients who develop anaphylaxis from foods.[18] However, a small study using serial measurements of tryptase 15 and 60 minutes after a sting challenge found that an increase of at least 2.0 μg/L had a sensitivity of 73% and specificity of 98%.[19] Serum tryptase levels typically begin to increase approximately 30 minutes after the onset of the reaction, peak 1 to 2 hours after the onset of the reaction, and remain elevated for up to at least 6 to 8 hours.[20]

Summary Statement 6: Determine whether the patient has risk factors for severe and potentially fatal anaphylaxis, such as delayed administration of epinephrine, asthma, a history of biphasic reactions, or cardiovascular disease, and consider them in the management and/or disposition of all patients with anaphylaxis. (Moderate Recommendation; B Evidence)

Patients at risk of severe anaphylaxis include those with (1) peanut and tree nut allergy, especially adolescents; (2) pre-existing respiratory or cardiovascular disease; (3) asthma; (4) delayed administration of epinephrine; (5) previous biphasic anaphylactic reactions; (6) advanced age; and (7) mast cell disease.[12,21,22]

Studies of fatal and near-fatal anaphylaxis have identified important risk factors for fatal anaphylaxis. Based on a national registry, several risk factors for fatal anaphylaxis from foods have been identified.[21] Most patients have been shown to be adolescents or young adults, most have been allergic to peanuts or tree nuts, most have had a history of asthma, and very few have had epinephrine administered in a timely manner.[22–26] Causes of fatal anaphylaxis are presented in Table 1.[12,27]

Summary Statement 7: Administer epinephrine intramuscularly in the anterolateral thigh as initial treatment for acute anaphylaxis immediately after the diagnosis of anaphylaxis is made. The first line of treatment for patients experiencing anaphylaxis is epinephrine. (Strong Recommendation; B Evidence)

The decision to initiate specific treatment for anaphylaxis requires clinical judgment. However, when the patient is experiencing ongoing symptoms that are consistent with acute anaphylaxis, the patient should receive epinephrine promptly. In a study of fatal food-induced anaphylaxis in the United Kingdom, the median time to respiratory or cardiac arrest was 30 minutes. The median time to arrest in Hymenoptera venom-induced anaphylaxis has been shown to be 15 minutes and the median time to arrest in medication-induced anaphylaxis in a hospital setting has been shown to be 5 minutes, thus underscoring the need for rapid recognition and management.[11,21] Epinephrine was administered only before arrest in 14% of patients, and overall, only 62% received epinephrine.[11]

Table 1
Causes of fatal anaphylaxis

Study	Food	Insects	Medication	Other (RCM)	Unclear
Liew WK et al[27]	6%	18%	58%	5%	13%
Greenberger et al[12]	16%	24%	28%	24%	0

Abbreviation: RCM, radiocontrast media.

Patients with anaphylaxis can present with symptoms not meeting the criteria for anaphylaxis and yet require administration of epinephrine, such as a patient with a history of near-fatal anaphylaxis to peanut who inadvertently ingests peanut and within minutes is experiencing urticaria and generalized flushing. Delayed administration of epinephrine is associated with poor outcomes and mortality.[24] It is important to recognize that there is a broad spectrum of anaphylaxis presentations that require clinical judgment in any given patient. The management of a patient who presents with symptoms of anaphylaxis 15 minutes after exposure to the suspected trigger might be handled differently than the patient who was exposed 2 hours previously. Because anaphylaxis can be self-limited, patients can present at a point when symptoms have nearly resolved and might no longer require epinephrine for acute management. However, the patient who presents with acute symptoms of anaphylaxis should immediately receive epinephrine even if the initial symptoms are not life threatening, because anaphylaxis can progress rapidly from mild symptoms to severe life-threatening symptoms.

The management of anaphylaxis also can depend on the setting in which symptoms of anaphylaxis develop. For example, the patient who presents to the ED with urticaria 2 hours after eating shrimp might not require an injection of epinephrine. In contrast, a patient known to be allergic to shrimp who presents with symptoms consistent with upper airway obstruction 2 hours after eating shrimp should receive an injection of epinephrine. The recommended dosage of epinephrine in a setting where an exact does can be drawn up is 0.01 mg/kg (maximum dose, 0.5 mg) administered intramuscularly every 5 to 15 minutes as necessary to control symptoms. The 5-minute interval between injections can be liberalized to permit more frequent injections as determined by the clinician.

There are no randomized controlled studies of epinephrine during anaphylaxis, including pharmacokinetic studies. A pharmacokinetic study in children not experiencing anaphylaxis showed that epinephrine administered intramuscularly into the anterolateral thigh resulted in a higher and more rapid peak plasma concentration compared with subcutaneous administration in the arm.[28] A subsequent study in adults not experiencing anaphylaxis showed that peak plasma epinephrine concentrations were higher and achieved faster after administration of epinephrine intramuscularly in the thigh compared with when it was administered intramuscularly or subcutaneously in the arm.[29] Subcutaneous administration in the thigh has not been studied.

The physiologic effects of epinephrine include vasoconstriction, cardiac chronotropic and inotropic effects, bronchodilatation, and suppression of the release of histamine and other mediators form mast cells and basophils, resulting in increased cardiac output, increased peripheral vascular resistance, and decreased mucosal edema and airway resistance.[30]

Complications associated with parenteral administration of epinephrine, other than IV administration, are very rare. There are no absolute contraindications for the administration of epinephrine in the setting of anaphylaxis. Nevertheless, a significant percentage of patients treated for anaphylaxis do not receive epinephrine.[31–33]

Summary Statement 8: If the patient is not responding to epinephrine injections, administer an IV infusion of epinephrine in a monitored setting. (Moderate Recommendation; C Evidence)

If the patient is not responding to epinephrine injections, careful administration of an IV infusion of epinephrine in a monitored setting might be necessary. A 1:1,000,000 infusion solution,

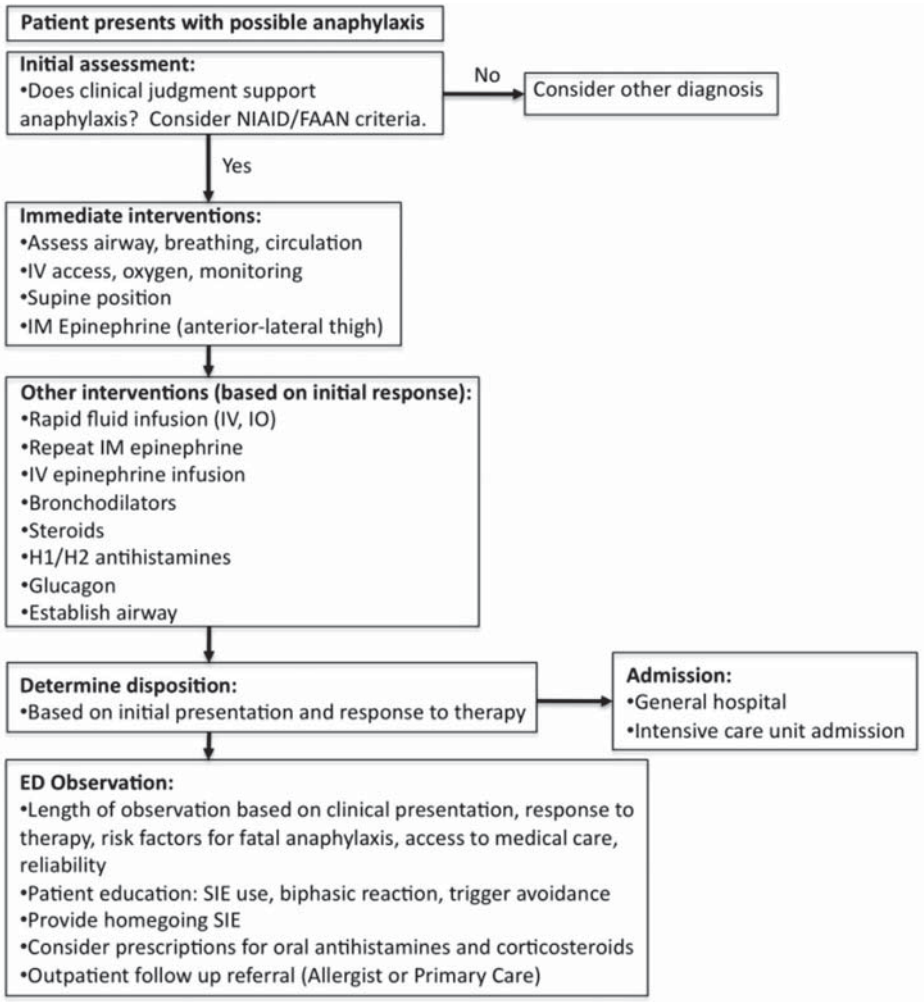

Figure 2. Emergency anaphylaxis management algorithm.

prepared by adding 1 mg (1 mL) of a 1:1,000 concentration of epinephrine to 1000 mL of 5% dextrose in water or normal saline to produce a concentration of 1.0 μg/mL, can be infused at a rate of 1 μg/min and titrated to the necessary hemodynamic response and in adults and adolescents increased to a maximum of 10.0 μg/min. A starting dose of 0.1 μg/kg per minute is recommended for children. Bolus administration of IV epinephrine is associated with an increased risk of cardiac arrhythmias and inappropriate dosing and therefore should be avoided whenever possible.[31,34–37] In patients with actual or impending cardiovascular collapse unresponsive to an epinephrine infusion or when an epinephrine infusion is not immediately available, slow administration of a 50-μg (0.5 mL of 1:10,000) bolus of IV epinephrine might be necessary.

Summary Statement 9: If IV access is not readily available in patients experiencing anaphylaxis, obtain IO access and administer epinephrine by this route. (Moderate Recommendation; D Evidence)

Intraosseous fluid and medication administration is rapid, safe, and effective.[38–42] In animals, minimally delayed but equivalent hemodynamic effects have been seen with IO and IV administrations. Drug delivery appears to be slightly less when IO epinephrine is given in the tibia than when it is given in the sternum. Epinephrine can be infused by an IV or IO route at a rate of 1 μg/min and titrated to the necessary hemodynamic response, increasing to a maximum of 10.0 μg/min for adults and adolescents. A starting dose of 0.1 μg/kg per minute is recommended for children.[43]

Endotracheal administration of epinephrine also can be considered in patients in whom IV access is not possible. Anecdotally, successful reports when using alternative routes have been reported. These include inhaled, sublingual, and endotracheal use of epinephrine.

Summary Statement 10: Prepare for airway management, including intubation if necessary, if there is any suggestion of airway edema (eg, hoarseness or stridor) or associated respiratory compromise. (Moderate Recommendation; C Evidence)

Asphyxia can occur in anaphylaxis because of upper airway swelling or bronchospasm.[15,44] Therefore, it is necessary to prepare for airway management, including intubation when necessary, if there is any suggestion of airway edema (hoarseness or stridor) or associated respiratory compromise. In severe cases of anaphylaxis, airway management is an essential part of the treatment plan. Whether to intubate the patient is a difficult decision. Airway management begins with preoxygenation, an assessment of the level of predicted difficulty of laryngoscopy, and preparation. Various algorithms and scores have been designed to help predict difficult laryngoscopy, but their utility in the ED setting is limited.[45] Although a quick assessment of the airway should occur, given the significant potential for pharyngeal and laryngeal edema, laryngoscopy should be presumed to be difficult. Preparation includes selection and preparation of initial and back-up airway equipment (including suction), optimizing patient positioning, pharmacology,

and the outlining of an initial and back-up airway management plan.[46,47] Upper airway edema can preclude rescue ventilation, so the merits of an awake fiberoptic intubation should be strongly weighed against the benefits and risks of rapid sequence intubation.

When selecting airway management medications, because patients with anaphylaxis requiring intubation are often hemodynamically unstable, medications should be avoided that depress blood pressure. Paralytics should be used with caution, because mask ventilation can be impossible in the setting of upper airway edema. Because the airway should be presumed difficult, optimizing the first look is essential no matter what approach is used. Once the patient is intubated, post-intubation management should continue with sedation and ventilator management. For the wheezing patient with anaphylaxis, minimize breath stacking and barotraumas by allowing adequate exhalation time. In those with bronchospasm, ketamine, a sedative with bronchodilator properties, can be used after intubation. Peri-intubation decompensation has a broad differential diagnosis. Because of the frequency of bronchospasm in anaphylaxis, barotrauma should be considered.

Nebulized epinephrine has been shown to alleviate respiratory distress associated with upper airway obstruction in childhood croup.[48] The vasoconstrictive (α_1) effects likely account for the decrease of upper airway edema. Similarly, and based on anecdotal experience, aerosolized epinephrine also can decrease oropharyngeal edema and make airway management less difficult in anaphylaxis.[49]

Summary Statement 11: For patients with circulatory collapse from anaphylaxis, aggressively administer large volumes of IV or IO normal saline through large-bore catheters. (Strong Recommendation; B Evidence)

Aggressive fluid resuscitation helps to counteract the significant plasma leak associated with anaphylaxis and complement parenteral epinephrine therapy. Children might require successive IV fluid boluses of 20 mL/kg and adults might require successive IV boluses of 1,000 mL to maintain blood pressure in the early stages of anaphylaxis. To overcome venous resistance, fluids administered through IO catheters should be infused under pressure using an infusion pump, pressure bag, or manual pressure. As blood pressure stabilizes, fluid rates should be adjusted. Care should be taken to avoid volume overload in certain patients, such as those with a history of left ventricular failure.

Summary Statement 12: Administer glucagon (especially if the patient is receiving β-blockers) if parenteral epinephrine and fluid resuscitation fail to restore blood pressure. (Moderate Recommendation; B Evidence)

Norepinephrine, vasopressin, and other pressors have been used with success in patients in anaphylaxis with refractory hypotension (see Fig 2).[50,51] Infusions of glucagon have been used to treat anaphylaxis that is refractory to epinephrine in some patients on β-blockers.[52] There are numerous case reports of treatment refractory anaphylaxis in patients on β-blockers.[53,54] There also are case reports of such patients responding favorably to glucagon infusion when standard therapy has failed. Glucagon increases cyclic adenosine monophosphate intracellularly, independent of adrenergic receptors, and might reverse refractory hypotension and bronchospasm.[55,56] Although data are very limited, glucagon infusion should be considered when patients are not responding to traditional management. The recommended dose of glucagon is 1 to 5 mg (20–30 μg/kg [maximum, 1 mg] in children) administered intravenously over 5 minutes and followed by an infusion of 5 to 15 μg/min titrated to clinical response. Airway protection is important because emesis and possible aspiration is a possible side effect of glucagon.

Summary Statement 13: Administer an inhaled β-agonist if bronchospasm is a component of anaphylaxis. (Moderate Recommendation; B Evidence)

Epinephrine has been known for many years to effectively reverse bronchospasm. Sometimes, however, bronchospasm can persist despite treatment with epinephrine. Therefore, current approaches used to treat bronchospasm, such as β-adrenergic agonists, should be readily available if needed. There are no studies evaluating the effectiveness of β-adrenergic agonists in the treatment of bronchospasm occurring as part of anaphylaxis. However, there is no reason to believe that the treatment of bronchospasm during anaphylaxis is different than the treatment of bronchospasm in patients who are not in anaphylaxis. This conclusion has been supported by observation of the effectiveness of inhaled β-adrenergic agonists in treating bronchospasm that occurs during anaphylaxis. A β-agonist, such as albuterol, can be administered by a metered-dose inhaler (2–6 inhalations) or nebulizer (2.5–5 mg in 3 mL of saline and repeated as necessary) for bronchospasm that has not responded to epinephrine.

Summary Statement 14: Consider extracorporeal membrane oxygenation in patients with anaphylaxis who are unresponsive to traditional resuscitative efforts. (Moderate Recommendation; D Evidence)

Extracorporeal membrane oxygenation is becoming more readily available in the ED and can be applied to anyone with reversible causes of pulmonary and/or cardiac failure. Patients with anaphylaxis who are unresponsive to traditional resuscitative efforts should be considered candidates for this potentially life-saving therapy. There are several case reports of successful resuscitation of refractory anaphylaxis involving extracorporeal membrane oxygenation or operative cardiopulmonary bypass.[57,58] The decision to initiate extracorporeal membrane oxygenation can be difficult but should be considered early in patients who are failing to respond to traditional resuscitative measures and before irreversible ischemic acidosis develops.

Summary Statement 15: Do not routinely administer antihistamines or corticosteroids instead of epinephrine. There is no substitute for epinephrine in the treatment of anaphylaxis. Administration of H_1 and/or H_2 antihistamines and corticosteroids should be considered adjunctive therapy. (Strong Recommendation; B Evidence)

Use of antihistamines in anaphylaxis is believed justified based on their mechanism of action and effectiveness in other allergic diseases, such as allergic rhinitis and allergic conjunctivitis. Many clinical manifestations of anaphylaxis, including vasodilatation, increased vascular permeability, bronchial smooth muscle contraction, and increased airway secretions, are mediated by histamine. However, there is no direct evidence to show that antihistamines are effective in anaphylaxis.[59] In fact, their onset of action is not rapid enough to be useful in the acute management of anaphylaxis. Therefore, epinephrine administration should not be delayed in patients with anaphylaxis while the patient is observed for a response to antihistamines. Antihistamines are never a substitute for epinephrine in the treatment of anaphylaxis. The recommended dose for diphenhydramine, an H_1 antagonist, by intramuscular or by slow IV infusion is 25 to 50 mg in adults and 1 to 50 mg/kg 50 mg in children. Oral diphenhydramine and other oral first- or second-generation H_1 antihistamines also can be used. H_2 antihistamines, such as cimetidine, at an IV dose of 4 mg/kg, are used widely in anaphylaxis treatment. They are recommended as second-line medications in the treatment of anaphylaxis in most guidelines and other well-known references.

Corticosteroids also have a slow onset of action (4–6 hours) and therefore, like antihistamines, are not effective in the acute management of anaphylaxis. There is no strong evidence that supports the use of corticosteroids in the management of anaphylaxis.[60,61]

Moreover, there no definitive evidence to indicate that corticosteroids decrease the risk of biphasic reactions, although there is a theoretical possibility, owing to their anti-inflammatory properties, that they could decrease such reactions.[62] Dosing of corticosteroids should be 1.0 to 2.0 mg/kg per dose of methylprednisolone or an equivalent formulation. Oral doses of prednisone also can be considered (1.0 mg/kg, up to 50 mg).

Patients allowed to leave the ED after complete resolution of symptoms of anaphylaxis do not routinely need further treatment with antihistamines or corticosteroids. There are no studies that have evaluated the benefits of these medications *after* patients leave the ED if their symptoms of anaphylaxis have resolved *before* they leave the ED.

Summary Statement 16: Identify triggers of anaphylaxis and consider obscure and less common triggers. (Moderate Recommendation; C Evidence)

There are a myriad of triggers of anaphylaxis. The frequency of specific triggers can vary with age.[63,64] In pediatric patients, the most common cause of anaphylaxis is food ingestion; in adults, the cause of anaphylaxis is not identified approximately 25% of the time.[2] In older adults, medications are the most common cause of anaphylaxis, with antibiotics and nonsteroidal anti-inflammatory drugs topping the list of possibilities.[64,65] The most common cause of drug-induced anaphylaxis is β-lactam antibiotics, although recently there has been an increasing number of reports of anaphylaxis or anaphylactoid reactions from biological modifiers.[66–68] Exercise, latex, and seminal fluid are other causes of anaphylaxis that need to be considered, as do non-IgE–mediated reactions such as to radiocontrast media.

Overall, foods, drugs, and stinging insect venom are the most common causes of anaphylaxis. However, the actual food component causing anaphylaxis might not be readily apparent, resulting in the exact cause of anaphylaxis being missed. In 1 study, 47% of patients with food allergy were not diagnosed with food allergy in the ED.[69] Less apparent triggers of anaphylaxis also should be considered (eg, galactose and $\alpha_{1,3}$ galactose, a carbohydrate found in mammalian meat), particularly in patients who present with delayed anaphylaxis. The allergist-immunologist should play an important role in identifying less readily apparent causes of anaphylaxis at follow-up.

Summary Statement 17: Strongly consider observing patients who have experienced anaphylaxis for at least 4 to 8 hours and observe patients with a history of risk factors for severe anaphylaxis (eg, asthma, previous biphasic reactions, or protracted anaphylaxis) for a longer period. (Moderate Recommendation; C Evidence)

Admission rates for anaphylaxis vary widely from 7% to 41%,[70,71] being somewhat lower in pediatric patients.[72,73] The decision to admit should be based on symptom severity, response to treatment, pattern of previous anaphylactic reactions (eg, a history of protracted or biphasic reactions), medical comorbidities, patient reliability, and access to medical care. If the patient is not being admitted to the hospital, a period of observation should be strongly considered in all patients diagnosed with anaphylaxis. Biphasic reactions occur in up to 20% of patients who develop anaphylaxis and could involve organ systems not affected in the initial reaction.[74,75] There is no evidence that systemic corticosteroids will prevent biphasic reactions. Moreover, as serum epinephrine levels wane, symptoms can recur.[76] Expert consensus opinion has recommended that patients be observed for 4 to 8 hours. However, the time of observation should be individualized based on the same criteria used to determine the need for admission. In addition, longer periods of observation should be considered for patients who have a history of risk factors for more severe anaphylaxis.[71] Longer periods of observation should be considered in patients who ingested the allergen, required more than 1 dose of epinephrine, had hypotension or pharyngeal edema, or have a history of asthma.

Summary Statement 18: Prescribe auto-injectable epinephrine for patients who have experienced an anaphylactic reaction and provide patients with an action plan instructing them on how and when to administer epinephrine. (Moderate Recommendation; C Evidence)

After leaving the ED, patients are at risk for reencountering the allergen that triggered the anaphylactic reaction treated in the ED. As noted under summary statement 16, biphasic reactions can occur in up to 20% of patients who present with an anaphylactic reaction. Therefore, patients need to be prepared for possible recurrent anaphylaxis and should be given 2 auto-injectable epinephrine devices to carry with them at all times. Children weighing 15 to 30 kg can receive a 0.15-mg dose of epinephrine from an auto-injector. Children weighing more than 30 kg and adults can receive a 0.3-mg dose of epinephrine from an auto-injector. Recognize that 0.01 mg/kg, the recommended dose, cannot be exactly administered using the available auto-injector doses, so some judgment is required.

Studies have shown that up to 30% of patients who develop anaphylaxis will have to administer more than 1 dose of epinephrine.[77,78] A large percentage of patients use epinephrine injectors incorrectly and inadvertent injection of epinephrine into the digits has increased significantly in the past decade.[79–81] Therefore, it is essential that health care providers demonstrate for patients the proper use of an epinephrine auto-injector and confirm patient proficiency. Parents of food-allergic children were 4 to 5 times more likely to effectively administer self-injectable epinephrine after a practical demonstration.[82] Patients and caregivers should be instructed to administer epinephrine at the first sign of a generalized reaction or if the patient develops any manifestations that have preceded the development of anaphylaxis. The allergist-immunologist can play an important role in this educational process during follow-up.

Summary Statement 19: Instruct patients who have experienced anaphylaxis when discharged from the ED to see an allergist-immunologist in a timely fashion. (Moderate Recommendation; C Evidence)

The cause of anaphylaxis is frequently unknown at the time of discharge from the ED or at the time of admission to the hospital (see Preface). Therefore, follow-up with a physician with expertise in the diagnosis and management of anaphylaxis, such as an allergist-immunologist, is extremely important.

Anaphylaxis might be the presentation of a mast cell disorder. In a study of patients with a history of anaphylaxis after an insect sting, approximately 8% were found to have an underlying mast cell disease.[83] Mast cell disorders are diverse and can have multiple manifestations and complications affecting essentially every organ system and ranging in severity from indolent cutaneous disorders to rapidly fatal leukemia.

Allergists-immunologists can obtain a detailed history, coordinate additional outpatient testing, provide additional allergen-avoidance counseling, develop a detailed emergency action plan for future reactions, provide the patient with medical identification jewelry, and reinforce the proper use of auto-injectable epinephrine.

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