INTRODUCTION — Anaphylaxis is a potentially fatal disorder. The rate of occurrence is increasing in industrialized countries [1-6]. Anaphylaxis is not always recognized as such because it can mimic other conditions and is variable in its presentation. This topic will review the recognition and treatment of anaphylaxis by healthcare professionals working in settings such as an emergency department (ED), surgical unit, hemodialysis facility, hospital ward, clinic, or clinician’s office [7-11]. Unique features of anaphylaxis in pregnant women and infants are presented separately, as is the pathophysiology of anaphylaxis. (See "Anaphylaxis in pregnant and breastfeeding women" and "Anaphylaxis in infants" and "Pathophysiology of anaphylaxis".)

DEFINITION AND DIAGNOSIS — Anaphylaxis is defined as a serious allergic or hypersensitivity reaction that is rapid in onset and may cause death [12,13]. The diagnosis of anaphylaxis is based primarily upon clinical symptoms and signs, as well as a detailed description of the acute episode, including antecedent activities and events occurring within the preceding minutes to hours.

Anaphylaxis is underrecognized and undertreated [1-3,5]. This may partly be due to failure to appreciate that it can present without obvious skin symptoms and signs and without shock. Anaphylaxis is a much broader syndrome than “anaphylactic shock,” and the goal of therapy should be early recognition and treatment with epinephrine to prevent progression to life-threatening respiratory and/or cardiovascular symptoms and signs, including shock.

Diagnostic criteria — Diagnostic criteria for anaphylaxis were published by a multidisciplinary group of experts in 2005 and 2006 [12,13]. These criteria were intended to help clinicians recognize the full spectrum of symptoms and signs that comprise anaphylaxis. Recognition of the variable and atypical presentations of anaphylaxis is critical to providing effective therapy in the form of epinephrine, as well as reducing overreliance on less effective medications such as antihistamines and glucocorticoids [14]. In a retrospective cohort study of 214 emergency department patients, these criteria were found to have a sensitivity of 97 percent compared with an allergist’s diagnosis upon review of the case, as well as a specificity of 82 percent, a positive predictive value of 69 percent, and a negative predictive value of 98 percent [15]. There are three diagnostic criteria, each reflecting a different clinical presentation of anaphylaxis (table 1) [12]. Anaphylaxis is highly likely when any ONE of the following three criteria is fulfilled:

**Criterion 1** — Acute onset of an illness (minutes to several hours) involving the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia). OR
- Reduced blood pressure (BP) or associated symptoms and signs of end-organ dysfunction (eg, hypotonia [collapse] syncope, incontinence). (See ‘Criterion 3’ below.)

Note: Skin symptoms and signs are present in up to 90 percent of anaphylactic episodes. This criterion will therefore frequently be helpful in making the diagnosis.

**Criterion 2** — Two or more of the following that occur rapidly after exposure to a LIKELY allergen for that patient (minutes to several hours):

- Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).
- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).
Note: Skin symptoms or signs are absent or unrecognized in up to 20 percent of anaphylactic episodes. Criterion 2 incorporates symptoms and signs in other organ systems and is applied to patients with exposure to a substance that is a likely allergen for them.

**Criterion 3 — Reduced BP after exposure to a KNOWN allergen for that patient** (minutes to several hours):
- Reduced BP in adults is defined as a systolic BP of less than 90 mmHg or greater than 30 percent decrease from that person's baseline.
- In infants and children, reduced BP is defined as low systolic BP (age specific)* or greater than 30 percent decrease in systolic BP.
- Low systolic BP for children is defined as:
  - Less than 70 mmHg from 1 month up to 1 year
  - Less than (70 mmHg + [2 x age]) from 1 to 10 years
  - Less than 90 mmHg from 11 to 17 years

Note: Criterion 3 is intended to detect anaphylactic episodes in which only one organ system is involved and is applied to patients who have been exposed to a substance to which they are known to be allergic, for example, hypotension or shock after an insect sting.

There will occasionally be patients who do not fulfill any of these criteria, but for whom the administration of epinephrine is appropriate. As an example, it would be appropriate to administer epinephrine to a patient with a history of near-fatal anaphylaxis to peanut who presents with urticaria and flushing that developed within minutes of a known unintentional ingestion of peanut [13].

**Symptoms and signs** — Anaphylaxis may present with various combinations of approximately 40 potential symptoms and signs (table 2) [7-13,16-24].

Common symptoms and signs of anaphylaxis include the following:
- Skin symptoms and signs, which occur in up to 90 percent of episodes, including generalized hives, itching or flushing, swollen lips-tongue-uvula, periorbital edema, conjunctival swelling.
- Respiratory symptoms and signs, which occur in up to 70 percent of episodes, including nasal discharge, nasal congestion, change in voice quality, sensation of throat closure or choking, stridor, shortness of breath, wheeze, cough.
- Gastrointestinal symptoms and signs, which occur in up to 45 percent of episodes, including nausea, vomiting, diarrhea, and crampy abdominal pain.
- Cardiovascular symptoms and signs, which occur in up to 45 percent of episodes, including hypotonia (collapse), syncope, incontinence, dizziness, tachycardia, and hypotension.

Anaphylaxis may be mild and resolve spontaneously due to endogenous production of compensatory mediators (eg, epinephrine, angiotensin II, endothelin, and others) or it may be severe and progress within minutes to respiratory or cardiovascular compromise and death [18]. The factors that determine the course of anaphylaxis in an individual patient are not fully understood. At the onset of an anaphylactic episode, it is not possible to predict how severe it will become, how rapidly it will progress, and whether it will resolve promptly and completely or become biphasic or protracted.

Death from anaphylaxis usually results from asphyxiation due to upper airway edema or respiratory failure due to bronchial obstruction, and less commonly, from cardiovascular collapse [14,25-32]. (See "Fatal anaphylaxis".)

Unique aspects of the clinical manifestations of anaphylaxis in infants, and in women in labor and delivery, are reviewed separately. (See "Anaphylaxis in infants" and "Anaphylaxis in pregnant and breastfeeding women".)

**Time course** — Anaphylaxis is usually characterized by a defined exposure to a potential trigger, followed by rapid onset, evolution, and resolution of symptoms and signs within minutes to hours.
Biphasic anaphylaxis — Biphasic anaphylaxis is defined as a recurrence of symptoms that develops following the apparent resolution of the initial anaphylactic episode with no additional exposure to the trigger. Biphasic reactions have been reported to develop in up to 23 percent of anaphylactic episodes in adults and up to 11 percent of episodes in children. They typically occur within 8 to 10 hours after resolution of the initial symptoms, although recurrences up to 72 hours later have been reported [33,34]. (See "Biphasic and protracted anaphylaxis").

Protracted anaphylaxis — Protracted anaphylaxis is defined as an anaphylactic reaction that lasts for hours, days, or even weeks in extreme cases [25].

Pitfalls in making the diagnosis — Anaphylaxis is not always easy to recognize clinically. The patterns of target organ involvement are variable and may differ among individuals, as well as among episodes in the same individual. Anaphylaxis is likely underdiagnosed and underreported for a variety of reasons [3,7-10,19-23,35]:

- Some healthcare professionals remain reluctant to diagnose anaphylaxis in the absence of hypotension or shock, even though changes in blood pressure are not required for the diagnosis according to Criterion 1 or Criterion 2 [12]. (See 'Diagnostic criteria' above.)
- Hypotension may go undetected when the initial blood pressure measurement is obtained after epinephrine administration, or when an inappropriately small blood pressure cuff is used. In infants and young children, normal blood pressure is lower than it is in teenagers and adults.
- Many of the dramatic physical signs associated with hypoxia and hypotension in anaphylaxis are nonspecific, such as dyspnea, stridor, wheeze, confusion, collapse, unconsciousness, and incontinence (table 2).
- Skin symptoms and signs (such as hives, itching, flushing, and angioedema), which are helpful in making the diagnosis, are absent or unrecognized in up to 20 percent of all episodes. Skin symptoms and signs may be absent if a patient has taken an H1 antihistamine. They may also be missed if an individual cannot describe itching or is not undressed and fully examined during the episode, or in patients who are draped during surgery [18]. (See "Perioperative anaphylaxis: Clinical manifestations, etiology, and diagnosis").
- Anaphylaxis may be difficult to recognize in certain clinical situations; for example, hemodialysis, surgery, or childbirth when, for other reasons, patients may experience dramatic physiologic shifts with consequent changes in vital signs [7-11,18,35,36]. In addition, inability of the patient to communicate the presence of early symptoms (eg, if dysphonic, dyspneic, in shock, unconscious, or anesthetized) also impedes prompt recognition of anaphylaxis.
- Anaphylaxis in a known asthmatic may be mistaken for an asthma exacerbation if accompanying skin symptoms and signs such as itching and hives, or dizziness suggestive of impending shock, are overlooked [18].
- Patients experiencing their first episode may not recognize the symptoms as anaphylaxis. As a result, they may not report symptoms fully, or may focus on one prominent symptom (eg, unless specifically asked, a patient presenting with vomiting may not report that the episode was preceded by diffuse itching).
- The above factors are further compounded in patients with neurologic, psychiatric, or psychologic problems, or those who take medications or substances such as a sedating H1 antihistamine, ethanol, or recreational drugs that potentially impair cognition and judgment, making anaphylaxis symptoms difficult to recognize (table 3) [18,22].

TRIGGERS AND MECHANISMS — Most anaphylaxis episodes are triggered through an immunologic mechanism involving IgE. Foods are the most common trigger in children, while medications and insect stings are more common triggers in adults than in children. The table provides a more comprehensive list of potential anaphylaxis triggers, categorized by causative mechanism (table 4) [12,13,16,19-23].

In this review, the term anaphylaxis applies to all of the following:

- Acute systemic reactions involving IgE-dependent mechanisms.
- Acute systemic reactions involving other immunologic mechanisms (formerly called anaphylactoid reactions).
- Acute systemic reactions that occur independently of any immunologic mechanism due to direct release of histamine and other mediators from mast cells and basophils, eg, after exercise or exposure to cold or (ultraviolet), ingestion of opioids, etc.
- Acute systemic reactions without any obvious trigger or mechanism (idiopathic anaphylaxis).
The acute management of anaphylaxis is the same, regardless of the trigger or mechanism involved [12,13,16].

CONTRIBUTORY FACTORS — Comorbidities and concurrent medications may impact the severity of symptoms and signs and response to treatment in patients with anaphylaxis (table 5) [19-23,37].

Comorbidities — Asthma and cardiovascular disease are the most important risk factors for a poor outcome from anaphylaxis. Other disorders may also increase risk.

- Persistent asthma is a risk factor for anaphylaxis [38,39]. Asthma is also associated with increased risk of death from anaphylaxis, especially in adolescents and young adults with poorly controlled disease [14,25-29].
- Cardiovascular disease is an important risk factor for death from anaphylaxis in middle-aged and older individuals [30].
- Other respiratory diseases, eg, chronic obstructive pulmonary disease (COPD), interstitial lung disease, or pneumonia are also risk factors for severe or fatal anaphylaxis in older adults [30,40].
- Acute infection such as an upper respiratory tract infection, fever, emotional stress, exercise, disruption of routine, and premenstrual status may also increase the risk. With the exception of exercise, these amplifying factors have not been systematically studied in the context of anaphylaxis [20].

Concurrent medications — Concurrent administration of certain medications, such as beta-adrenergic blockers, angiotensin-converting enzyme inhibitors, and alpha-adrenergic blockers may increase the likelihood of severe or fatal anaphylaxis, and may also interfere with the patient's ability to respond to treatment and with the patient's compensatory physiologic responses (table 5) [41-44].

- Beta-adrenergic blockers, administered orally, parenterally, or topically (eg, eye drops) are sometimes associated with severe anaphylaxis and may also potentially make anaphylaxis more difficult to treat by causing unopposed alpha-adrenergic effects. They also can worsen hypotension, as well as reduce the bronchodilator and cardiovascular response to the beta-adrenergic effects of endogenous or exogenous epinephrine [45]. (See 'Glucagon for patients taking beta-blockers' below.)
- Alpha-adrenergic blockers may decrease the effects of endogenous or exogenous epinephrine at alpha-adrenergic receptors, potentially making anaphylaxis less responsive to the alpha-adrenergic effects of epinephrine [43].
- ACE inhibitors are of particular importance in regards to patients who have experienced anaphylaxis to Hymenoptera venom [44,45]. They not only block the effect of angiotensin, a compensatory response, but also block the degradation of kinins which are active in the production of symptoms and signs.
- In an emergency department study, use of any antihypertensive medication (beta-blockers, ACE inhibitors, calcium channel blockers, angiotensin-receptor blockers, or diuretics) by patients with anaphylaxis was associated with increased organ system involvement and increased odds of hospital admission, independent of age, gender, suspected trigger, or preexisting lung disease [46].

LABORATORY TESTS — The clinical diagnosis of anaphylaxis can sometimes be supported by documentation of elevated concentrations of serum or plasma total tryptase or plasma histamine [37,47-49]. It is critical to obtain blood samples for measurement of these mast cell and basophil mediators soon after the onset of symptoms, because elevations are transient. Instructions for proper collection of samples are provided in the table (table 6).

- Serum or plasma total tryptase - The standardized assay for measurement of total serum or plasma tryptase is widely available in clinical laboratories (normal range 1 to 11.4 ng/mL, Phadia AB, Uppsala, Sweden). In infants under age six months, normal baseline total tryptase concentrations are higher than they are in older infants, children, and adults. Optimally, the blood sample for tryptase measurement needs to be obtained from 15 minutes to 3 hours of symptom onset. Tryptase elevations are more likely to be detected in anaphylaxis from stinging insect venoms or medications, and following reactions that involve hypotension [48-50].

A tryptase level that is within normal limits cannot be used to refute the clinical diagnosis of anaphylaxis [37]. The history trumps the test results. As an example, in individuals with food-induced anaphylaxis, or in patients who are normotensive, tryptase levels are seldom elevated, even in optimally-timed blood samples obtained within 15 minutes to 3 hours of symptom onset [25].

Serial measurements of total tryptase in serum or plasma over several hours may increase the sensitivity and the
DIFFERENTIAL DIAGNOSIS — Approximately 40 other diseases and conditions might need to be considered in the differential diagnosis of anaphylaxis ([table 7][54-61]). The most common disorders in the differential diagnosis include acute generalized urticaria and/or angioedema, acute asthma exacerbations, syncope/faint, and anxiety/panic attacks. These are reviewed in detail elsewhere. (See "Differential diagnosis of anaphylaxis in children and adults" and "Anaphylaxis in pregnant and breastfeeding women", section on 'Differential diagnosis' and "Anaphylaxis in infants", section on 'Differential diagnosis'.)

IMMEDIATE MANAGEMENT — The tables provide rapid overviews of the initial assessment and emergency management of anaphylaxis in adults ([table 8][114]) and children ([table 9][214]).

Prompt assessment and treatment are critical in anaphylaxis, as respiratory or cardiac arrest and death can occur within minutes [14,25-32]. The cornerstones of initial management are the following [62-67]:

- Removal of the inciting antigen, if possible (eg, stop infusion of a suspect medication)
- Call for help (summon a resuscitation team in a hospital setting, or call 911 or an equivalent emergency medical services number in a community setting)
- Intramuscular injection of epinephrine
- Placement of the patient in the supine position with the lower extremities elevated, or if dyspneic or vomiting, placement of
In a series of 164 fatalities due to anaphylaxis, the median time interval between onset of symptoms and respiratory or cardiac arrest was 5 minutes in iatrogenic anaphylaxis, 15 minutes in stinging insect venom-induced anaphylaxis, and 30 minutes in food-induced anaphylaxis [14]. A more detailed review of fatal anaphylaxis is presented elsewhere. (See "Fatal anaphylaxis").

**Initial assessment** — A number of critical components in the initial management need to be instituted concomitantly [19-23]:

- Initially, attention should focus on airway, breathing, and circulation, as well as adequacy of mentation. The skin should be examined.

- **Epinephrine** should be injected intramuscularly into the mid-outer aspect of the thigh (table 8 and table 9) [63-70]. If symptoms are severe, an intravenous epinephrine infusion should be prepared. (See 'Dosing and administration' below.)

- The patient should be placed in the recumbent position with the lower extremities elevated to maximize perfusion of vital organs. This also helps prevent the "empty ventricle syndrome," in which severe hypotension leads to inadequate cardiac filling and pulseless cardiac activity. In this syndrome, death can occur within seconds [67]. Individuals with respiratory distress or vomiting may not tolerate the recumbent position and should be placed in a position of comfort, with lower extremities elevated. Empty ventricle syndrome is discussed in greater detail separately. (See "Fatal anaphylaxis").

- Supplemental oxygen, 8 to 10 liters by facemask, up to 100 percent, should be administered.

- Two large-bore intravenous catheters (ideally 14 to 16 gauges for most adults) should be inserted in preparation for rapid administration of fluids and medications.

- In normotensive adults, isotonic (0.9 percent) saline should be infused at a rate of 125 mL per hour to maintain venous access. In normotensive children, isotonic saline should be infused at an appropriate maintenance rate for weight, in order to maintain venous access. (See "Maintenance fluid therapy in children").

- Continuous electronic monitoring of cardiopulmonary status, including blood pressure, heart rate, and respiratory rate, and monitoring of oxygen saturation by pulse oximetry is required for the duration of the episode.

**Airway management** — As noted above, the initial steps in anaphylaxis management involve a rapid assessment of the patient's airway [19-23]:

- Intubation should be performed immediately if marked stridor or respiratory arrest is present.

- Preparations for possible intubation should be made if there is any airway involvement or significant edema of the facial or neck tissues.

- In a minority of cases, an emergency cricothyroidotomy may be required to secure the airway.

Intubation may be difficult in individuals in whom edema distorts the upper airway anatomical landmarks. Failed attempts can lead to complete airway obstruction and fatality. Therefore, upper airway closure in the setting of anaphylaxis should be managed by the most experienced clinician available. This may require immediate collaboration between an emergency medicine specialist and an anesthesiologist, otolaryngologist, or intensivist with training and experience in the management of the difficult airway. Hospitals and other healthcare facilities should have clear, written policies about how such situations will be handled.

**Intravenous fluids** — Intravenous access should be obtained in case fluid resuscitation is required. Massive fluid shifts can occur rapidly in anaphylaxis due to increased vascular permeability, with transfer of up to 35 percent of the intravascular volume into the extravascular space within minutes [63]. Any patient whose hypotension does not respond promptly and completely to injected epinephrine should be assumed to have intravascular volume depletion causing persistent hypotension despite maximum vasoconstriction. These patients should receive large volume fluid resuscitation [19-23]. The following principles should guide therapy:

Fluid resuscitation should be initiated immediately in patients who present with orthostasis, hypotension, or incomplete response to intramuscular epinephrine.
Normal saline is preferred over other solutions in most situations, because other solutions have potential disadvantages:

- Patients should be monitored carefully and continuously for clinical response and for volume overload. (See "Treatment of severe hypovolemia or hypovolemic shock in adults" and "Hypovolemic shock in children: Initial evaluation and management".)

Pregnant women — Additional precautions and considerations are important in the management of anaphylaxis in pregnant women; for example during labor and delivery, positioning of the patient on her left side, providing high-flow supplemental oxygen, and maintaining a systolic blood pressure of at least 90 mmHg, as well as continuous fetal monitoring are critically important [20]. (See "Anaphylaxis in pregnant and breastfeeding women", section on 'Management'.)

PHARMACOLOGIC TREATMENTS — In humans experiencing anaphylaxis, randomized, placebo-controlled trials that meet current standards have not yet been performed for any pharmacologic intervention. Epinephrine is the best studied medication in anaphylaxis. The evidence for its use comes from observational studies during anaphylaxis, randomized controlled clinical pharmacology studies at baseline, studies of anaphylaxis in animal models, and epidemiologic studies, including fatality studies. The evidence for use of H1-antihistamines in anaphylaxis is extrapolated from their use in urticaria. The evidence for the use of beta-2 adrenergic agonists and glucocorticoids in anaphylaxis is extrapolated from their use in acute asthma.

In the future, it is possible that randomized controlled trials will be conducted in anaphylaxis with glucocorticoids, H1 antihistamines, or H2 antihistamines; however, placebo-controlled trials with epinephrine will never be performed, due to ethical considerations: anaphylaxis can kill within minutes [14,25-30] and delayed epinephrine injection is associated with fatalities [70,72-76].

Epinephrine — Epinephrine is the drug of choice for anaphylaxis. The pharmacologic actions of this agent address the pathophysiologic changes that occur in anaphylaxis better than any other medication. It decreases mediator release from mast cells [77]. Moreover, it is the only medication that prevents or reverses obstruction to airflow in the upper and lower respiratory tracts, and prevents or reverses cardiovascular collapse (table 8 and table 9).

Therapeutic actions and adverse effects — The therapeutic actions of epinephrine include the following (table 10) [64,70,73-76,78]:

- Alpha-1 adrenergic agonist effects: increased vasoconstriction, increased peripheral vascular resistance, and decreased mucosal edema (eg, in the upper airway).
- Beta-1 adrenergic agonist effects: increased inotropy and increased chronotropy.
- Beta-2 adrenergic agonist effects: increased bronchodilation and decreased release of mediators of inflammation from mast cells and basophils.

In patients of all ages, epinephrine administered in therapeutic doses by any route often causes mild transient pharmacologic effects, such as anxiety, restlessness, headache, dizziness, palpitations, pallor, and tremor [64,75,76,78]. These symptoms and signs are similar to those occurring during the physiologic "fight or flight" response and are due to endogenous epinephrine that occurs normally in sudden frightening or life-threatening situations.

Rarely, and especially after overdose, epinephrine may lead to ventricular arrhythmias, angina, myocardial infarction, pulmonary edema, sudden sharp increase in blood pressure, and intracranial hemorrhage. Serious adverse effects occur most commonly after an intravenous bolus injection or an overly rapid intravenous infusion in patients without continuous noninvasive monitoring of blood pressure and heart rate and function. They also occur after erroneous intravenous injection of a 1 mg/mL (1:1000) epinephrine solution instead of an appropriately diluted 0.1 mg/mL (1:10,000) or 0.01 mg/mL epinephrine solution [70,75,79]. (See 'Situations requiring caution' below.)
Anaphylaxis itself can lead to angina, myocardial infarction, and cardiac arrhythmias in the absence of any exogenous epinephrine or before exogenous epinephrine is administered [80].

**Dosing and administration** — Confusion persists among clinicians regarding the optimal epinephrine dose and route of administration for the initial treatment of anaphylaxis [79].

- **Intramuscular injection** — Intramuscular injection is recommended over subcutaneous injection because it consistently provides a more rapid increase in the plasma and tissue concentrations of epinephrine [65,66]. Epinephrine is commercially available in several dilutions, and great care must be taken to use the correct dilution [19-23]. The epinephrine dilution for intramuscular injection contains 1 mg per mL and may also be labeled as 1:1000.

  For adults, the recommended dose of epinephrine (1 mg per mL) is 0.3 to 0.5 mg per single dose, injected intramuscularly into the mid-outer thigh (vastus lateralis muscle). Based on clinical experience and consensus opinion, this dose may be repeated at 5 to 15 minute intervals [20-22,78]. Typically, only one or two additional doses are needed.

  For infants and children, the recommended dose of epinephrine (1 mg per mL) is 0.01 mg per kilogram (up to 0.5 mg per dose in a child weighing 50 kg or more), injected intramuscularly into the mid-outer thigh (vastus lateralis muscle). The dose should be drawn up using a 1 mL syringe. This treatment may be repeated at 5 to 15 minute intervals [64,70,81].

  Epinephrine can also be administered into the mid-thigh using an autoinjector. These are available only in 0.15 mg and 0.3 mg doses. Children weighing less than 25 kilograms should receive the 0.15 mg dose [64]:

  The adult dose is Auvi-Q 0.3 mg, EpiPen 0.3 mg, Jext 0.3 mg, or other autoinjectors as available, including Adrenaclick, Anapen, or Twinject.

  The pediatric dose is Auvi-Q 0.15 mg, EpiPen Jr 0.15 mg, Jext 0.15 mg, or other, including Adrenaclick, Anapen, or Twinject.

  The needle used in adults and children should be long enough to penetrate the subcutaneous adipose tissue over the vastus lateralis muscle. Realistically, however, intramuscular injection into the thigh may be impossible in some patients, especially those who are overweight or obese [82,83]. Although the best approach in this situation has not been studied, we suggest as deep an injection as possible into the muscle.

- **Intravenous infusion and indications** — Patients who do not respond to intramuscular injection of epinephrine and fluid resuscitation may not be adequately perfusing muscle tissues, as most commonly occurs in individuals presenting with profound hypotension or symptoms and signs suggestive of impending shock (dizziness, incontinence of urine and/or stool).

  Such patients should receive epinephrine by SLOW intravenous infusion, with the rate titrated according to response and the presence of continuous hemodynamic monitoring. Slow continuous infusion is preferred over an intravenous bolus dose as the latter is associated with more dosing errors and more adverse effects [21,70,84]. An intravenous infusion of epinephrine should preferably be given by clinicians who are trained, skilled, and experienced in its use and can titrate the rate of infusion (and therefore the epinephrine dose) using continuous noninvasive monitoring of blood pressure, heart rate and function.

  As noted above, epinephrine is commercially available in several dilutions, and great care must be taken to use the correct dilution in order to avoid overdosing the patient [79].

  The epinephrine dilution for intravenous infusion contains 0.1 mg/mL and may also be labeled 1:10,000.

  - For adults, the initial dose for intravenous epinephrine infusion is 2 to 10 micrograms per minute, titrated to effect on blood pressure with continuous noninvasive monitoring [19].

  - For infants and children, the dose for intravenous infusion of epinephrine is 0.1 to 1 microgram per kilogram per minute, titrated to effect on blood pressure with continuous noninvasive monitoring.

To reduce the risk of making a medication error, we suggest that centers have available a protocol that includes steps on how to prepare and administer epinephrine infusion. Examples of adult (table 11) and pediatric infusions (table 12 and table 13) are provided.

**Efficacy** — Several case series have implicated the failure to administer epinephrine early in the course of treatment as a consistent finding in anaphylaxis deaths [14,25-30,85].
In a series of 13 fatal and near fatal food-induced anaphylactic reactions in children and adolescents, six of the seven patients (86 percent) who received epinephrine within 30 minutes of symptom onset, survived. In contrast, only two of the six patients (33 percent) who received epinephrine one hour or more after symptom onset, survived [25].

In a series of anaphylactic deaths occurring from 1992 to 1998, only 20 percent of 24 patients were given epinephrine at any point in their treatment [26].

In the fatality series described previously, only 14 percent of the 164 patients dying from anaphylaxis received epinephrine before respiratory or cardiac arrest, although 62 percent of the 164 patients eventually received it before demise [14].

In addition, anaphylaxis occurring during evaluation of venom immunotherapy has been investigated prospectively. In one study, 68 patients with a history of anaphylaxis to insect stings were randomly assigned to venom immunotherapy or placebo immunotherapy [63]. Following this, all were stung in a controlled, monitored setting and treated if needed with a standardized protocol of high flow oxygen, epinephrine infusion, and normal saline rapid infusion. Nineteen of the 21 patients in the placebo group developed anaphylaxis and received epinephrine. Symptoms responded within five minutes in all but one patient. In nine patients, an initial attempt to stop the epinephrine infusion was followed by a return of symptoms, which subsided again once the epinephrine infusion was restarted.

Finally, there is extensive clinical experience among allergy practitioners with giving epinephrine to treat anaphylaxis occurring in response to immunotherapy. This is a unique situation, because allergy clinic staff observe patients closely for the symptoms and signs of anaphylaxis and reactions are detected at very early stages. Over the past few decades, consensus has been reached that even mild systemic reactions are best treated immediately with epinephrine, as this appears to prevent progression to more severe symptoms more effectively than any other available therapies. As a result, successive guidelines for treatment of immunotherapy reactions have called for epinephrine to be given as soon as a systemic reaction of any severity is detected [86]. In studies in which all or most patients who developed anaphylaxis after allergen immunotherapy were treated promptly with epinephrine injections, symptoms were mild and no additional injections of epinephrine were given, even in the 10 to 23 percent of reactions that were biphasic [34].

**Situations requiring caution** — There are NO absolute contraindications to epinephrine use in anaphylaxis [19-23,70,73-76,78].

Subgroups of patients might theoretically be at higher risk for adverse effects during epinephrine therapy. Formal risk-benefit analyses are not possible.

- **Patients with cardiovascular diseases:** reluctance to administer epinephrine due to fear of adverse cardiac effects should be countered by the awareness that the heart is a target organ in anaphylaxis. In the healthy human heart, mast cells are present throughout the myocardium and in the intima of coronary arteries. In patients with coronary artery disease, mast cells are found in atherosclerotic lesions and contribute to atherogenesis. Anaphylaxis can unmask subclinical coronary artery disease, and myocardial infarction and/or arrhythmias can occur during anaphylaxis, even if epinephrine is not injected [42,87]. Moreover, anaphylaxis itself can cause vasospasm, arrhythmias, and myocardial infarction in patients, including children, with healthy hearts as confirmed by normal electrocardiograms, echocardiography, and other studies after resolution of anaphylaxis [88].

- **Patients receiving monoamine oxidase inhibitors** (which block epinephrine metabolism), or tricyclic antidepressants (which prolong epinephrine duration of action).

- **Patients with certain preexisting conditions**, such as recent intracranial surgery, aortic aneurysm, uncontrolled hyperthyroidism or hypertension, or other conditions that might place them at higher risk for adverse effects related to epinephrine.

- **Patients receiving stimulant medications** (eg, amphetamines or methylphenidate used in the treatment of attention deficit hyperactivity disorder) or abusing cocaine that might place them at higher risk for adverse effects from epinephrine.

To reiterate, there are no absolute contraindications to the use of epinephrine in the treatment of anaphylaxis. The risk of death or serious disability from hypoxic-ischemic encephalopathy due to inadequately treated anaphylaxis usually outweighs other concerns [19-23,70,73-76,78]. Existing evidence clearly favors the benefit of epinephrine administration in anaphylaxis. Sound clinical judgment is essential.

**Glucagon for patients taking beta-blockers** — Patients receiving beta-blockers may be resistant to treatment with epinephrine and can develop refractory hypotension and bradycardia. In this situation, glucagon should be administered because...
it has inotropic and chronotropic effects that are not mediated through beta-receptors [89]. A dose of 1 to 5 mg in adults (in children, 20 to 30 micrograms per kilogram to a maximum of 1 mg) administered intravenously over 5 minutes is recommended. This dose may be repeated or followed by an infusion of 5 to 15 micrograms per minute. Rapid administration of glucagon can induce vomiting; therefore, protection of the airway, for example, by placement in the lateral recumbent position, is important in drowsy or obtunded patients.

**Adjunctive agents** — Adjunctive therapies for the treatment of anaphylaxis include antihistamines, bronchodilators, glucocorticoids, and other vasopressors in addition to epinephrine.

**H1 antihistamines** — Epinephrine is first-line treatment for anaphylaxis and there is no known equivalent substitute. A systematic review of the literature has failed to retrieve any randomized controlled trials that meet current standards and support the use of H1 antihistamines in anaphylaxis [72]. Despite this, H1 antihistamines are the most commonly administered medications in the treatment of anaphylaxis. This suggests overreliance on these agents, which should be considered adjunctive to epinephrine for the purpose of relieving itching and hives [90-93].

- H1 antihistamines relieve itch and hives. These medications DO NOT relieve upper or lower airway obstruction, hypotension or shock, and in standard doses do not inhibit mediator release from mast cells and basophils. It is probable that the improvement in noncutaneous symptoms that is sometimes attributed to antihistamine treatment occurs instead because of endogenous production of epinephrine and other compensatory mediators, including other catecholamines, angiotensin II, and endothelin I [18]. In addition, the onset of action of antihistamines, even diphenhydramine given by injection, is too slow to provide any immediate benefit [94]. H1-antihistamines administered intravenously may increase hypotension [95].

For parenteral treatment, only first-generation agents are available:

- For adults: consider diphenhydramine 25 to 50 mg intravenously; may be repeated up to a maximum daily dose of 400 mg per 24 hours.

- For children weighing less than 40 kg: consider diphenhydramine 1 mg per kg (maximum 40 mg) intravenously, which may be repeated up to a maximum daily dose of 5 mg per kg or 200 mg per 24 hours.

For oral treatment, second-generation H1 antihistamines (eg, cetirizine) offer certain advantages over first-generation agents (eg, diphenhydramine, chlorpheniramine, hydroxyzine, and promethazine). Second-generation H1 antihistamines are less likely to impair cognition or psychomotor performance (eg, the ability to drive safely), or to cause sedation [72,76,96]. Orally-administered cetirizine acts within one hour. However, second-generation H1 antihistamines are not available in parenteral formulations.

**H2 antihistamines** — There is minimal evidence to support the use of H2 antihistamines in conjunction with H1 antihistamines in the emergency treatment of anaphylaxis. Most guidelines do not include these medications.

If used, ranitidine (50 mg in adults) (12.5 to 50 mg [1 mg per kilogram] in children), may be diluted in 5 percent dextrose to a total volume of 20 mL and injected intravenously over five minutes. Rapid infusion of cimetidine can cause hypotension.

**Bronchodilators** — For the treatment of bronchospasm not responsive to epinephrine, inhaled bronchodilators, such as albuterol should be administered by nebulizer/compressor as needed. They are adjunctive treatment to epinephrine because they do not prevent or relieve mucosal edema in the upper airway or shock, for which the alpha-1 adrenergic effects of epinephrine are required [19-23].

**Glucocorticoids** — The onset of action of glucocorticoids takes several hours; therefore, these medications do not relieve the initial symptoms and signs of anaphylaxis. The rationale for giving them is to prevent the biphasic or protracted reactions that occur in up to 23 percent of adults with anaphylaxis, and up to 11 percent of children with anaphylaxis. A systematic review of the literature failed to retrieve any randomized controlled trials in anaphylaxis that confirmed the effectiveness of glucocorticoids [33,97].

If given, a dose of methylprednisolone of 1 to 2 mg per kilogram per day is sufficient. If glucocorticoid treatment is instituted, it can be stopped after three days without a taper, since all biphasic reactions reported to date have occurred within 72 hours [33]. (See 'Time course' above.)

**Refractory anaphylaxis** — Admission to an intensive care unit should occur without delay. There are no published prospective
studies on the optimal management of refractory anaphylaxis. The management of severe forms of these types of shock is discussed separately. (See "Systemic inflammatory response syndrome (SIRS) and sepsis in children: Definitions, epidemiology, clinical manifestations, and diagnosis" and "Hypovolemic shock in children: Initial evaluation and management" and "Evaluation and management of severe sepsis and septic shock in adults", section on 'Vasopressors' and "Treatment of severe hypovolemia or hypovolemic shock in adults".)

One theory about the pathogenesis of refractory anaphylaxis proposes that the clinical manifestations may become refractory to further catecholamine administration, perhaps due to saturation or desensitization of adrenergic receptors [98]. The use of nonadrenergic vasopressors, such as vasopressin, in the management of anaphylaxis refractory to intravenous epinephrine in adults is discussed elsewhere. (See "Use of vasopressors and inotropes", section on 'Vasopressin and analogs'.)

Vasoplegia (profound vasodilation) may be present in some cases of refractory anaphylaxis. A few case reports and other publications support the use of methylene blue, an inhibitor of nitric oxide synthase and guanylate cyclase, in severe anaphylaxis and other forms of vasodilatory shock [99-101]. The ideal dose of methylene blue is unknown, but a single bolus of 1 to 2 mg/kg has been used. This drug should not be given to patients with pulmonary hypertension, underlying glucose-6-phosphate dehydrogenase deficiency (G6PD), or acute lung injury. We also advise caution given drug interactions with serotonergic agents. (See "Postoperative complications among patients undergoing cardiac surgery", section on 'Vasodilatory shock'.)

**TREATMENT ERRORS** — Important errors in the treatment of anaphylaxis include failure to administer epinephrine promptly, and delay in epinephrine injection due to overreliance on antihistamines, albuterol, and glucocorticoids. (See 'Adjunctive agents' above.)

- **Epinephrine** should be administered as soon as possible once anaphylaxis is recognized. Delayed administration has been implicated in contributing to fatalities [14,25-30,85]. As noted above, a study of 13 fatal or near-fatal food-induced anaphylactic reactions in children reported that six of the seven children who survived received epinephrine within 30 minutes of ingesting the allergen, whereas only two of the six children who died received epinephrine within the first hour [25].

- H1 antihistamines are useful for relieving itching and urticaria, as mentioned previously. They do NOT relieve stridor, shortness of breath, wheezing, gastrointestinal symptoms and signs, hypotension or shock, and should not be substituted for epinephrine [19,20,23,72,96].

- Bronchodilator treatment with nebulized albuterol should be given in individuals with severe bronchospasm, as an adjunctive treatment to epinephrine. However, albuterol does NOT prevent or relieve upper airway edema, hypotension or shock and should not be substituted for epinephrine in the treatment of anaphylaxis.

- Glucocorticoids theoretically reduce the late phase response. They do not relieve the initial symptoms of anaphylaxis.

**CARE UPON RESOLUTION** — To reduce the risk of recurrence, patients who have been successfully treated for anaphylaxis subsequently require confirmation of the anaphylaxis trigger, as well as anaphylaxis education. (See "Anaphylaxis: Confirming the diagnosis and determining the trigger(s)" and "Long-term management of patients with anaphylaxis".)

**Observation** — There is no consensus regarding the optimal observation period for a patient who has been successfully treated for anaphylaxis in a healthcare facility. We suggest the following:

- Patients with moderate anaphylaxis who do not respond promptly to epinephrine, and all patients with severe anaphylaxis, should be admitted to an observation unit or to a hospital.

- For patients with anaphylaxis that resolved promptly and completely with treatment, we suggest a minimum observation period of a few hours, and prefer a period of 8 to 10 hours, if possible. We also suggest that if patients are sent home after only a few hours, they should be trained to use an epinephrine autoinjector and should actually be supplied with one, rather than simply handed a prescription for one. As noted previously, up to 23 percent of adults may experience a biphasic reaction [33,34]. (See 'Biphasic anaphylaxis' above.)

**Discharge care** — All patients who have experienced anaphylaxis should be sent home with an anaphylaxis emergency action plan, one or more epinephrine autoinjectors, a plan for arranging further evaluation, and printed information about anaphylaxis and its treatment.
Anaphylaxis emergency action plan — Before discharge, patients should be given a written personalized anaphylaxis emergency action plan that lists the common symptoms and signs of anaphylaxis and contains information about prompt self-injection of epinephrine (Anaphylaxis Emergency Action Plan - English) (Anaphylaxis Emergency Action Plan - Spanish) [18].

**Epinephrine autoinjector** — Ideally, patients should be supplied with an epinephrine autoinjector directly. Instructions in the proper use of epinephrine autoinjectors should be reviewed verbally and they should be given a DVD and/or written material and directed to a manufacturer's website video providing relevant information (see 'Information for patients' below). If this is not possible, they should be instructed in how to use an epinephrine autoinjector correctly, provided with a prescription for it, and advised to fill the prescription immediately. In a survey of 1885 patients who survived anaphylaxis, 28 percent of those who did not inject epinephrine during anaphylaxis reported that they had never received a prescription for an autoinjector [102].

**Counseling** — The mnemonic "SAFE" was developed to remind clinicians of the four basic action steps suggested for patients with anaphylaxis who have been treated and are subsequently leaving the emergency department or hospital [103]. The SAFE counseling is outlined below and has been incorporated into printable patient information materials. (See 'Information for patients' below.)

- **Seek support** — Advise the patient that:
  - They have experienced anaphylaxis or "killer allergy," which is a life-threatening condition.
  - Symptoms of the current episode may recur up to three days after the initial onset of symptoms.
  - They should self-inject epinephrine, and call emergency medical services or get to the nearest emergency facility at the first sign of recurrence of symptoms.
  - They are at risk for repeat episodes of anaphylaxis in the future.
  - Refer the patient to resources. (See 'Information for patients' below.)

- **Allergen identification and avoidance** — Before the patient is discharged, an effort should be made to confirm the anaphylaxis trigger suspected from the patient’s history (by measuring specific IgE to the allergen identified by the history). If the patient has received volume resuscitation, IgE levels might be falsely absent or undetectable due to the potential dilutional effects on circulating IgE, and it might be necessary to recheck the levels four to six weeks after the anaphylactic episode.

  - Emphasize the importance of subsequent allergy skin testing to confirm the trigger, so that it can be successfully avoided in the future.

- **Follow-up with specialty care**

  - Advise the patient to follow-up with his or her primary care clinician and obtain a referral to an allergist or to seek consultation directly with an allergist for testing and ongoing management.

- **Epinephrine for emergencies**

  - Provide the patient with an epinephrine autoinjector or with a prescription for self-injectable epinephrine, as well as verbal plus written or DVD instructions for use.
  - Explain the importance of carrying the epinephrine autoinjector at all times.
  - Advise the patient to make sure that family and friends are aware of the risks of anaphylaxis, the triggers, and how to administer epinephrine. The correct injection technique is important to avoid unintentional injection into fingers, thumbs, or other body parts [104].

**LONG-TERM PROGNOSIS** — Patients who have experienced anaphylaxis are at risk for recurrent episodes unless long-term risk reduction measures are implemented [19,20]. Specifically, the trigger for the anaphylactic episode should be verified. In addition, anaphylaxis education is required in order to help patients successfully avoid their confirmed trigger(s), and self-inject epinephrine promptly and confidently in the event of a recurrent anaphylactic episode. For these reasons, patients with anaphylaxis benefit from referral to an allergy specialist.

**INFORMATION FOR PATIENTS** — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer...
the four or five key questions a patient might have about a given condition. These articles are best for patients who want a
general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more
sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who
want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your
patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the
keyword(s) of interest.)

- Basics topics (see "Patient information: Anaphylaxis (The Basics)" and "Patient information: Epinephrine auto-injectors
(The Basics)"
- Beyond the Basics topics (see "Patient information: Anaphylaxis symptoms and diagnosis (Beyond the Basics)" and
"Patient information: Anaphylaxis treatment and prevention (Beyond the Basics)" and "Patient information: Use of an
epinephrine autoinjector (Beyond the Basics)"

Other sources of accurate patient information, accessible through the Internet, include the American Academy of Allergy,
Asthma and Immunology (www.aaaai.org) and the American College of Allergy, Asthma and Immunology (www.acaai.org)
[103,105].

SUMMARY AND RECOMMENDATIONS

- Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. (See 'Definition and diagnosis'
above.)

- There are three clinical criteria for the diagnosis of anaphylaxis, which reflect the different ways in which anaphylaxis may
present (table 1). Anaphylaxis is highly likely when any ONE of the three criteria is fulfilled. (See 'Diagnostic criteria'
above.)
  - Recognition is not always easy, because anaphylaxis can mimic many other disorders and can be variable in its
  presentation. Anaphylaxis may present with various combinations of as many as 40 potential symptoms and signs
  (table 2). (See 'Symptoms and signs' above.)
  - Patients and healthcare professionals commonly fail to recognize and diagnose anaphylaxis in its early stages,
  when it is most responsive to treatment. In particular, there is a reluctance to diagnose anaphylaxis in the absence
  of hypotension, even though this sign is not required for the diagnosis and occurs late or not at all in a food-induced
  anaphylactic episode. (See 'Pitfalls in making the diagnosis' above.)

- Anaphylaxis most often results from an IgE-mediated allergic reaction. Common triggers include foods, insect stings, and
medications. There is a rapidly expanding list of novel and/or unusual triggers (table 4). (See 'Triggers and mechanisms'
above.)

- The clinical diagnosis of anaphylaxis may or may not be confirmed by measurement of elevated concentrations of plasma
histamine or serum or plasma total tryptase. Elevations in these mediators are transient (table 6). Serum tryptase is
seldom elevated in food-triggered anaphylaxis or in normotensive patients with anaphylaxis. (See 'Laboratory tests'
above.)

- Prompt recognition and treatment are critical in anaphylaxis. In fatal anaphylaxis, median times to cardiorespiratory arrest
are 5 minutes in iatrogenic anaphylaxis, 15 minutes in stinging insect venom-induced anaphylaxis, and 30 minutes in food-
induced anaphylaxis. (See 'Time course' above.)

- Initial management is summarized in a rapid overview table for adults (table 8) and children (table 9). (See 'Immediate
management' above.)

- Epinephrine is lifesaving in anaphylaxis. It should be injected as early as possible in the episode in order to prevent
progression of symptoms and signs. There are no absolute contraindications to epinephrine use, and it is the
 treatment of choice for anaphylaxis of any severity. We recommend epinephrine for patients with apparently mild
symptoms and signs (eg, a few hives and mild wheezing) (Grade 1B) and for patients with moderate to severe symptoms
and signs (Grade 1A).

- The route of epinephrine administration depends upon the presenting symptoms. For patients who are not profoundly
hypotensive or in shock or cardiorespiratory arrest, intramuscular (IM) injection into the mid-outer thigh as the initial route
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REFERENCES


# Diagnostic criteria for anaphylaxis

Anaphylaxis is highly likely when any ONE of the following three criteria is fulfilled:

1. **Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)**

   **AND AT LEAST ONE OF THE FOLLOWING:**
   - A. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
   - B. Reduced BP* or associated symptoms of end-organ dysfunction (eg, hypotonia, collapse, syncope, incontinence)

2. **TWO OR MORE OF THE FOLLOWING that occur rapidly after exposure to a LIKELY allergen for that patient (minutes to several hours):**
   - A. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   - B. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
   - C. Reduced BP* or associated symptoms (eg, hypotonia, collapse, syncope, incontinence)
   - D. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. **Reduced BP* after exposure to a KNOWN allergen for that patient (minutes to several hours):**
   - A. Infants and children: low systolic BP (age specific)* or greater than 30 percent decrease in systolic BP
   - B. Adults: systolic BP of less than 90 mmHg or greater than 30 percent decrease from that person's baseline

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**BP:** blood pressure.

* Low systolic blood pressure for children is defined as:
  - less than 70 mmHg from one month to one year,
  - less than (70 mmHg + [2 x age]) from 1 to 10 years, and
  - less than 90 mmHg from 11 to 17 years

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Graphic 72225 Version 8.0
### Symptoms and signs of anaphylaxis

<table>
<thead>
<tr>
<th>Skin</th>
<th>Oral</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling of warmth, flushing (erythema), itching (may occur in areas, such as external auditory canals, palms, soles, or groin), urticaria, angioedema, morbilliform rash, and &quot;hair standing on end&quot; (pilor erection)</td>
<td>Itching or tingling of lips, tongue, or palate</td>
<td>Nose - Itching, congestion, rhinorrhea, and sneezing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laryngeal - Itching and &quot;tightness&quot; in the throat, dysphonia, hoarseness, stridor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower airways - Shortness of breath (dyspnea), chest tightness, deep or repetitive cough, wheezing, and cyanosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea, abdominal pain (colic, cramps), vomiting (large amounts of &quot;stringy&quot; mucus), diarrhea, and dysphagia (difficulty swallowing*)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiovascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feeling of faintness or dizziness; syncope, altered mental status, chest pain, palpitations, tachycardia, bradycardia or other dysrhythmia, hypotension, tunnel vision, difficulty hearing, urinary or fecal incontinence, and cardiac arrest</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurologic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxiety, apprehension, sense of impending doom, seizures, headache*, and confusion; children may become irritable, cease to play, or have other sudden behavioral changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ocular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Periorbital itching, erythema and edema, tearing, and conjunctival erythema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uterine cramps and bleeding in women and girls</td>
</tr>
</tbody>
</table>

* Often occurs in association with throat tightness and other upper airway symptoms.
• Not common in anaphylaxis overall; however, reported in up to 30 percent of patients with exercise-induced anaphylaxis.

Graphic 66333 Version 11.0
Anaphylaxis: Comorbidities and concurrent medications that might interfere with recognition of trigger or symptoms

<table>
<thead>
<tr>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment of vision or hearing</td>
</tr>
<tr>
<td>Neurologic disease</td>
</tr>
<tr>
<td>Psychiatric illness (eg, depression, ADHD, autism spectrum disorder, cognitive disorder, substance abuse)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concurrently administered medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedatives (eg, impairing sedating H₁-antihistamines)</td>
</tr>
<tr>
<td>Hypnotics</td>
</tr>
<tr>
<td>Ethanol</td>
</tr>
<tr>
<td>Recreational drugs</td>
</tr>
</tbody>
</table>

ADHD: attention deficit-hyperactivity disorder.


Graphic 53777 Version 12.0
### Triggers of anaphylaxis

#### Allergen triggers (IgE-dependent immunologic mechanism)
- Foods, especially peanut, tree nut, shellfish, fish, milk, egg
- Insect stings (eg, Hymenoptera venom) and insect bites (eg, kissing bugs, mosquitoes)
- Medications (eg, beta-lactam antibiotics, some nonsteroidal antiinflammatory drugs [NSAIDs])
- Biological materials, including allergens, allergen immunotherapy, monoclonal antibodies, vaccines to prevent infectious disease, and hormones (eg, progesterone)
- Natural rubber latex
- Food additives, including spices, insect-derived colorants (eg, carmine), and vegetable gums
- Inhalants (rare), eg, horse dander
- Human seminal fluid (rare trigger of anaphylaxis in women)
- Occupational allergens (eg, stinging insects, natural rubber latex)

#### Immunologic triggers (IgE-independent mechanism)
- IgG-dependent (rare) eg, to high molecular weight dextran, infliximab
- Coagulation system activation

#### Idiopathic anaphylaxis
- Consider the possibility of a hidden or previously unrecognized trigger
- Consider the possibility of mastocytosis or a clonal mast cell disorder

#### Nonimmunologic triggers (direct activation of mast cells and basophils)
- Physical factors (eg, exercise*, cold, heat, sunlight/ultraviolet radiation)
- Medications (eg, opioids, some NSAIDs)
- Alcohol (ethanol)

Any food, insect sting or bite, or medication or biological, can potentially trigger anaphylaxis. Novel or unusual allergen triggers include foods, such as vegetables, fruits, lupin flour, bird's nest soup, seal, whale, and kangaroo meats, and storage mite-contaminated flour. They also include saliva from kissing bugs, mosquitoes, pigeon ticks, green ants, and pharaoh ants, and venoms from jellyfish, scorpions, and snakes. Medications include taxanes, platins, and other chemotherapy drugs; biologic agents, including monoclonal antibodies, such as rituximab, cetuximab, infliximab, and uncommonly, omalizumab. Other injectants and ingestants, including Botox, bee products, and herbal formulations are also implicated. Some triggers, such as insect venoms, medications, and radiocontrast media (such as nonsteroidal antiinflammatory drugs [NSAIDs]) can act through more than one mechanism.

* Usually involves a co-trigger, such as a food, medication (eg, an NSAID), or exposure to cold air or water.
## Comorbidities and concurrent medications that might impact the severity and treatment of anaphylaxis

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>Other pulmonary diseases (eg, COPD, interstitial lung disease)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseases (eg, ischemic heart disease, hypertensive vascular disease, cardiomyopathy)</td>
<td></td>
</tr>
<tr>
<td>Mastocytosis and clonal mast cell disorders</td>
<td></td>
</tr>
</tbody>
</table>

### Concurrently administered medications

<table>
<thead>
<tr>
<th>Medications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>β-adrenergic blockers*</td>
<td></td>
</tr>
<tr>
<td>α-adrenergic blockers*</td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitorsΔ</td>
<td></td>
</tr>
<tr>
<td>Angiotensin II receptor blockersΔ</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants◊</td>
<td></td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors§</td>
<td></td>
</tr>
<tr>
<td>ADHD medications¥ (eg, stimulants such as methylphenidate and amphetamines)</td>
<td></td>
</tr>
<tr>
<td>Recreational use of cocaine‡</td>
<td></td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; ADHD: attention deficit-hyperactivity disorder.

* Beta-adrenergic blockers, administered orally or topically (eg, eye drops) may be associated with severe anaphylaxis and may also make anaphylaxis more difficult to treat by causing unopposed alpha-adrenergic effects, hypertension, and reduced bronchodilator response to the beta-adrenergic effects of endogenous or exogenous epinephrine.

• Alpha-adrenergic blockers may decrease the effects of endogenous or exogenous epinephrine at alpha-adrenergic receptors, potentially making patients less response to the alpha-adrenergic effects of epinephrine.

Δ Potential interference with endogenous compensatory responses.

◊ Potential increase in adverse effects of epinephrine because of prevention of epinephrine uptake at adrenergic receptors.

§ Potentiate epinephrine's effects by inhibiting its metabolism by monoamine oxidase.

¥ Side effects are similar to those of epinephrine.

‡ Potentiates epinephrine's effects, especially cardiovascular effects, by preventing its re-uptake into adrenergic neurons.


Graphic 65161 Version 13.0
Instructions for optimal collection and handling of blood samples for measurement of tryptase and histamine following suspected anaphylaxis

<table>
<thead>
<tr>
<th><em><em>Tryptase</em> (serum or plasma)</em>*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When to collect the sample:</strong></td>
</tr>
<tr>
<td>Blood should be collected between 15 minutes and 3 hours after symptom onset whenever possible; samples collected &lt;15 minutes or &gt;3 hours after symptom onset are less likely to be informative.</td>
</tr>
<tr>
<td><strong>How to collect the sample:</strong></td>
</tr>
<tr>
<td>Blood can be drawn using standard technique. Collect blood for serum (red top tube) or plasma (tube with heparin, citrate or EDTA). A minimum of 1 mL is recommended.</td>
</tr>
<tr>
<td>For postmortem samples, collect blood from the femoral artery or vein, not the heart.</td>
</tr>
<tr>
<td><strong>How to process the sample:</strong></td>
</tr>
<tr>
<td>Serum or plasma should be placed on ice and frozen as soon as possible. Samples should be shipped frozen by overnight courier if the assay cannot be performed on site.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Histamine (plasma)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When to collect the sample:</strong></td>
</tr>
<tr>
<td>Plasma for histamine levels should be collected between 5 and 15 minutes after symptom onset; samples collected &lt;5 minutes or &gt;15 minutes after symptom onset are less likely to be informative.</td>
</tr>
<tr>
<td><strong>How to collect the sample:</strong></td>
</tr>
<tr>
<td>Pull blood manually (DO NOT use vacuum tubes) under gentle pressure through a 20 gauge or larger needle into a syringe containing either citrate or EDTA.</td>
</tr>
<tr>
<td><strong>How to process the sample:</strong></td>
</tr>
<tr>
<td>Anticoagulated blood should be placed on ice and centrifuged to separate plasma from cells as soon as possible, and then the plasma frozen until ready to be analyzed.</td>
</tr>
</tbody>
</table>

The assay for total tryptase is standardized. The assay for histamine is not standardized.

EDTA: ethylenediaminetetraacetic acid.


- Plasma is used to avoid the artifactual release of histamine from basophils that can occur during blood clotting.

Graphic 72041 Version 19.0
### Differential diagnosis of anaphylaxis

#### Common disorders
- Acute asthma*
- Acute generalized urticaria*
- Acute angioedema
- Syncope (faint)
- Panic attack/acute anxiety attack
- Aspiration of a foreign body
- Cardiovascular events (myocardial infarction*, pulmonary embolus)
- Neurologic events (seizure, cerebrovascular event)

#### Post-prandial syndromes
- Scombroidosis
- Pollen-food allergy syndrome
- Monosodium glutamate
- Sulfites
- Food poisoning

#### Excess production of endogenous histamine
- Mastocytosis and other clonal mast cell disorders
- Basophilic leukemia

#### Flush syndromes
- Peri-menopause
- Carcinoid syndrome
- Autonomic epilepsy
- Medullary carcinoma of the thyroid

#### Other non-organic disease
- Vocal cord dysfunction
- Hyperventilation
- Psychosomatic episode

#### Shock
- Hypovolemic
- Cardiogenic
- Distributive*
- Septic

#### Other
- Non-allergic angioedema (hereditary angioedema types I, II, & III, ACE inhibitor-associated angioedema)
- Systemic capillary leak syndrome
The differential diagnosis in children and adults is shown. In infants, the differential diagnosis of anaphylaxis is unique.

* Acute asthma symptoms, acute generalized urticaria, or myocardial infarction symptoms can also occur during an anaphylactic episode.
  - In anaphylaxis, shock is distributive and hypovolemic. Distributive shock may be due to anaphylaxis or to spinal cord injury.

Graphic 65677 Version 12.0
### Rapid overview: Emergent management of anaphylaxis in adults

**Diagnosis is made clinically:**

The most common signs and symptoms are cutaneous (e.g., sudden onset of generalized urticaria, angioedema, flushing, pruritus). However, 10 to 20 percent of patients have no skin findings.

**Danger signs: Rapid progression of symptoms, respiratory distress (e.g., stridor, wheezing, dyspnea, increased work of breathing, persistent cough, cyanosis), abdominal pain, hypotension, dysrhythmia, chest pain, collapse.**

### Acute management:

The first and most important treatment in anaphylaxis is epinephrine. There are **NO absolute contraindications** to epinephrine in the setting of anaphylaxis.

**Airway:** Immediate intubation if evidence of impending airway obstruction from angioedema; delay may lead to complete obstruction; intubation can be difficult and should be performed by the most experienced clinician available; cricothyrotomy may be necessary.

**Promptly and simultaneously, give:**

**IM epinephrine (1 mg/mL preparation):** Give epinephrine 0.3 to 0.5 mg intramuscularly, preferably in the mid-outer thigh; can repeat every 5 to 15 minutes as needed. If epinephrine is injected promptly IM, most patients respond to one, two, or at most, three doses. If symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion (see below).

**Place patient in recumbent position,** if tolerated, and elevate lower extremities.

**Oxygen:** Give 8 to 10 liters per minute via facemask, or up to 100 percent oxygen as needed.

**Normal saline rapid bolus:** Treat hypotension with rapid infusion of 1 to 2 liters IV; repeat as needed; massive fluid shifts with severe loss of intravascular volume can occur.

**Also consider administration of:**

**Albuterol:** For bronchospasm resistant to IM epinephrine, give 2.5 to 5 mg in 3 mL saline via nebulizer; repeat as needed.

**H1 antihistamine:** Consider giving diphenhydramine 25 to 50 mg IV (for relief of urticaria and itching only).

**H2 antihistamine:** Consider giving ranitidine 50 mg IV.

**Glucocorticoid:** Consider giving methylprednisolone 125 mg IV.

**Monitoring:** Continuous noninvasive hemodynamic monitoring and pulse oximetry monitoring should be performed; urine output should be monitored in patients receiving IV fluid resuscitation for severe hypotension or shock.

### Treatment of refractory symptoms:

**Epinephrine infusion**: For patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion, 2 to 10 micrograms per minute by infusion pump. Titrate the dose continuously according to blood pressure, cardiac rate and function, and oxygenation.

**Vasopressors**: Some patients may require a second vasopressor (in addition to epinephrine). All vasopressors should be given by infusion pump, with the doses titrated continuously according to blood pressure, cardiac rate and function, and oxygenation.

**Glucagon:** Patients on beta-blockers may not respond to epinephrine and can be given glucagon 1 to 5 mg IV over five minutes, followed by infusion of 5 to 15 micrograms per minute. Rapid administration of glucagon can cause vomiting.

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IM: intramuscular; IV: intravenous.
All patients receiving an infusion of epinephrine and another vasopressor require continuous noninvasive monitoring of blood pressure, heart rate and function, and oxygen saturation.
Rapid overview: Emergent management of anaphylaxis in infants and children*

**Diagnosis is made clinically:**

The most common signs and symptoms are cutaneous (e.g., sudden onset of generalized urticaria, angioedema, flushing, pruritus). However, 10 to 20 percent of patients have no skin findings.

**Danger signs:** Rapid progression of symptoms, evidence of respiratory distress (e.g., stridor, wheezing, dyspnea, increased work of breathing, retractions, persistent cough, cyanosis), signs of poor perfusion, abdominal pain, dysrhythmia, hypotension, collapse.

**Acute management:**

The first and most important therapy in anaphylaxis is epinephrine. There are **NO absolute contraindications** to epinephrine in the setting of anaphylaxis.

**Airway:** Immediate intubation if evidence of impending airway obstruction from angioedema; delay may lead to complete obstruction; intubation can be difficult and should be performed by the most experienced clinician available; cricothyrotomy may be necessary.

**IM epinephrine (1 mg/mL preparation):** Give epinephrine 0.01 mg per kilogram intramuscularly (maximum per dose: 0.5 mg), preferably in the mid-anterolateral thigh, can repeat every 5 to 15 minutes as needed. If epinephrine is injected promptly IM, patients respond to one, two, or at most, three injections. If signs of poor perfusion are present or symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion (see below).

**Place patient in recumbent position,** if tolerated, and elevate lower extremities.

**Oxygen:** Give 8 to 10 liters per minute via facemask, or up to 100 percent oxygen as needed.

**Normal saline rapid bolus:** Treat poor perfusion with rapid infusion of 20 mL per kilogram; reevaluate and repeat fluid boluses (20 mL per kilogram) as needed; massive fluid shifts with severe loss of intravascular volume can occur; monitor urine output.

**Albuterol:** For bronchospasm resistant to IM epinephrine, give albuterol 0.15 mg per kilogram (minimum dose: 2.5 mg) in 3 mL saline inhaled via nebulizer; repeat as needed.

**H1 antihistamine:** Consider giving diphenhydramine 1 mg per kilogram (max 40 mg) IV.

**H2 antihistamine:** Consider giving ranitidine 1 mg per kilogram (max 50 mg) IV.

**Glucocorticoid:** Consider giving methylprednisolone 1 mg per kilogram (max 125 mg) IV.

**Monitoring:** Continuous noninvasive hemodynamic monitoring and pulse oximetry monitoring should be performed; urine output should be monitored in patients receiving IV fluid resuscitation for severe hypotension or shock.

**Treatment of refractory symptoms:**

**Epinephrine infusion:** Patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion at 0.1 to 1 microgram per kilogram per minute, titrated to effect.

**Vasopressors:** Patients may require large amounts of IV crystalloid to maintain blood pressure; if response to epinephrine and saline is inadequate, dopamine (5 to 20 micrograms per kilogram per minute) can be given with the dose titrated to effect on continuously monitored blood pressure, cardiac rate, and function.

IM: intramuscular; IV: intravenous.

* A child is defined as a prepubertal patient weighing less than 40 kg.

**All patients receiving an infusion of epinephrine and/or another vasopressor require continuous noninvasive monitoring of blood pressure, heart rate and function, and oxygen saturation. We suggest that pediatric centers provide instructions for preparation of standard concentrations and also provide charts for established infusion rate for epinephrine and other vasopressors in infants and children.
### Beneficial effects and adverse effects of epinephrine in the treatment of anaphylaxis

#### Beneficial effects

<table>
<thead>
<tr>
<th>At alpha-1 receptor:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased vasoconstriction (at low doses)</td>
<td></td>
</tr>
<tr>
<td>Increased peripheral vascular resistance</td>
<td></td>
</tr>
<tr>
<td>Increased blood pressure</td>
<td></td>
</tr>
<tr>
<td>Decreased mucosal edema (eg, in larynx)</td>
<td></td>
</tr>
<tr>
<td>At beta-1 receptor:</td>
<td></td>
</tr>
<tr>
<td>Increased heart rate (chronotropy)</td>
<td></td>
</tr>
<tr>
<td>Increased force of cardiac contraction (inotropy)</td>
<td></td>
</tr>
<tr>
<td>At beta-2 receptor:</td>
<td></td>
</tr>
<tr>
<td>Decreased mediator release from mast cells and basophils</td>
<td></td>
</tr>
<tr>
<td>Increased bronchodilation</td>
<td></td>
</tr>
<tr>
<td>Increased vasodilation</td>
<td></td>
</tr>
</tbody>
</table>

#### Adverse effects* •Δ

<table>
<thead>
<tr>
<th>Common and transient</th>
<th>Anxiety, palpitations, pallor, tremor, fear, restlessness, dizziness, headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon (typically occur after overdose)</td>
<td>Ventricular arrhythmias, angina, myocardial infarction, pulmonary edema, sudden sharp increase in blood pressure, intracranial hemorrhage</td>
</tr>
</tbody>
</table>

* Risk of adverse effects may be increased in the following conditions:
- Use of tricyclic antidepressants, monoamine oxidase inhibitors, or cocaine.
- Some preexisting cardiovascular, central nervous system, or thyroid diseases. Examples include intracranial surgery, acute aneurysm, or untreated hyperthyroidism.

• Serious adverse effects such as those listed in the table potentially occur when epinephrine is given in overdose by any route, most commonly after an intravenous bolus injection, an overly rapid intravenous infusion, or an erroneous intravenous injection of a 1 mg/mL (1:1000) epinephrine solution instead of an appropriately diluted 0.1 mg/mL (1:10,000) or a 0.01 mg/mL epinephrine solution.

Δ Anaphylaxis can present as an acute coronary syndrome (ACS), arrhythmias, myocardial infarction, or angina, before or in the absence of epinephrine injection. This potentially occurs in patients with known coronary artery disease, patients in whom subclinical coronary artery disease is unmasked, and patients (including children) with transient coronary artery vasospasm in whom no cardiovascular abnormalities can be detected by electrocardiogram or echocardiography after recovery from anaphylaxis.
Example of preparation of epinephrine infusion for refractory symptoms of anaphylaxis (adult patient) for emergency/critical care units

**Epinephrine 4 micrograms/mL (0.004 mg/mL)**

Add 1 mg (1000 micrograms) of epinephrine to 250 mL of 5 percent dextrose water (D5W).

Resulting concentration is 4 micrograms per milliliter (mL).

### Preparation

1. **CHECK** vial strength.

2. To prepare epinephrine infusion for a final concentration of 4 micrograms per mL, dilute 10 mL of **0.1 mg/mL** epinephrine (also labeled 1:10,000) **OR** 1 mL of 1 mg/mL epinephrine (also labeled 1:1000) in 250 mL of D5W.*

### Administration

Infuse an initial dose of 2 to 10 micrograms per minute using a programmable infusion pump and titrate as needed while continuously monitoring the patient's cardiac rhythm and blood pressure.

### Adult dose^A^  

<table>
<thead>
<tr>
<th>Micrograms per minute</th>
<th>mL per minute</th>
<th>mL per hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>0.75</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>1.25</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>1.75</td>
<td>105</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>120</td>
</tr>
<tr>
<td>9</td>
<td>2.25</td>
<td>135</td>
</tr>
<tr>
<td>10</td>
<td>2.5</td>
<td>150</td>
</tr>
<tr>
<td>11</td>
<td>2.75</td>
<td>165</td>
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<tr>
<td>12</td>
<td>3</td>
<td>180</td>
</tr>
<tr>
<td>13</td>
<td>3.25</td>
<td>195</td>
</tr>
<tr>
<td>14</td>
<td>3.5</td>
<td>210</td>
</tr>
<tr>
<td>15</td>
<td>3.75</td>
<td>225</td>
</tr>
<tr>
<td>16</td>
<td>4</td>
<td>240</td>
</tr>
</tbody>
</table>

* To reduce the risk of making a medication error, we suggest that centers have available an institutionally approved protocol for epinephrine infusion that includes steps on how to prepare and administer the infusion and standard concentration(s).

* The above table is provided as an example; there are other acceptable concentrations.
Intravenous epinephrine, like all vasopressors, can cause life-threatening hypertension, cardiac ischemia, and ventricular arrhythmias. It should be administered ONLY by clinicians trained and experienced in dose titration of intravenous epinephrine using continuous non-invasive electronic monitoring of heart rate and blood pressure.

Epinephrine is an ischemia causing agent and peripheral venous irritant. Monitor infusion site for extravasation. See Lexicomp drug reference for information on managing extravasation including infiltration of phentolamine. Central line administration is preferred when available.

* Unused diluted solutions should be discarded within 24 hours or less of preparation depending on local standards.

Δ To calculate the adult dose based on body weight, initial dose range is 0.03 micrograms/kg of body weight per minute to up to 0.14 micrograms/kg of body weight per minute.

References:

Example of preparation of epinephrine infusion for refractory symptoms of anaphylaxis for pediatric patient of 10 kg body weight for emergency/critical care units

Epinephrine 10 micrograms/mL (0.01 mg/mL)

Add 1 mg (1000 micrograms) of epinephrine to 100 mL of 5 percent dextrose water (D5W). Resulting concentration is 10 micrograms per milliliter (mL).

### Preparation

1. **CHECK** vial strength.

2. To prepare epinephrine infusion for a final concentration of 10 micrograms per mL, dilute 10 mL of 0.1 mg/mL epinephrine (also labeled 1:10,000) in 100 mL of D5W OR 1 mL of 1 mg/mL epinephrine (also labeled 1:1000) in 100 mL of D5W.*

### Administration

Infuse an initial dose of 0.1 micrograms per kg per minute using a programmable infusion pump and titrate as needed while continuously monitoring the patient's cardiac rhythm and blood pressure.

<table>
<thead>
<tr>
<th>Pediatric dose for 10 kg child</th>
<th>1 milligram epinephrine diluted in 100 mL D5W</th>
<th>Administration rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Micrograms per kg per minute</strong></td>
<td><strong>Micrograms per minute</strong></td>
<td><strong>mL per minute for 10 kg child</strong></td>
</tr>
<tr>
<td>0.05</td>
<td>0.5</td>
<td>0.05</td>
</tr>
<tr>
<td>0.1</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>0.2</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>0.3</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>0.4</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>0.5</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>0.6</td>
<td>6</td>
<td>0.6</td>
</tr>
<tr>
<td>0.7</td>
<td>7</td>
<td>0.7</td>
</tr>
<tr>
<td>0.8</td>
<td>8</td>
<td>0.8</td>
</tr>
<tr>
<td>0.9</td>
<td>9</td>
<td>0.9</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

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- The above table is provided as an example; there are other acceptable concentrations.
- Intravenous epinephrine, like all vasopressors, can cause life-threatening hypertension, cardiac ischemia, and ventricular arrhythmias. It should be administered ONLY by clinicians trained and experienced in dose titration of intravenous epinephrine using continuous non-invasive electronic monitoring of heart rate and blood pressure.
Epinephrine is an ischemia causing agent and peripheral venous irritant. Monitor infusion site for extravasation. See Lexicomp drug reference for information on managing extravasation including infiltration of phentolamine. Central line administration is preferred when available.

* Unused diluted solutions should be discarded within 24 hours or less of preparation depending on local standards.

References:
Example of preparation of epinephrine infusion for refractory symptoms of anaphylaxis for pediatric patient of 20 kg body weight for emergency/critical care units

Epinephrine 10 micrograms/mL (0.01 mg/mL)
Add 1 mg (1000 micrograms) of epinephrine to 100 mL of 5 percent dextrose water (D5W). Resulting concentration is 10 micrograms per milliliter (mL).

**Preparation**

1. **CHECK** vial strength.
2. To prepare epinephrine infusion for a final concentration of 10 micrograms per mL, dilute 10 mL of 0.1 mg/mL epinephrine (also labeled 1:10,000) in 100 mL of D5W OR 1 mL of 1 mg/mL epinephrine (also labeled 1:1000) in 100 mL of D5W.*

**Administration**

Infuse an initial dose of 0.1 micrograms per kg per minute using a programmable infusion pump and titrate as needed while continuously monitoring the patient's cardiac rhythm and blood pressure.

<table>
<thead>
<tr>
<th>Pediatric dose for 20 kg child</th>
<th>Administration rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 milligram epinephrine diluted in 100 mL D5W</strong></td>
<td><strong>10 micrograms per milliliter</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Micrograms per kg per minute</th>
<th>Micrograms per minute</th>
<th>mL per minute for 20 kg child</th>
<th>mL per hour for 20 kg child</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>1</td>
<td>0.1</td>
<td>6</td>
</tr>
<tr>
<td>0.1</td>
<td>2</td>
<td>0.2</td>
<td>12</td>
</tr>
<tr>
<td>0.2</td>
<td>4</td>
<td>0.4</td>
<td>24</td>
</tr>
<tr>
<td>0.3</td>
<td>6</td>
<td>0.6</td>
<td>36</td>
</tr>
<tr>
<td>0.4</td>
<td>8</td>
<td>0.8</td>
<td>48</td>
</tr>
<tr>
<td>0.5</td>
<td>10</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>0.6</td>
<td>12</td>
<td>1.2</td>
<td>72</td>
</tr>
<tr>
<td>0.7</td>
<td>14</td>
<td>1.4</td>
<td>84</td>
</tr>
<tr>
<td>0.8</td>
<td>16</td>
<td>1.6</td>
<td>96</td>
</tr>
</tbody>
</table>

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References:
Disclosures

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