Anaphylaxis: Emergency treatment

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INTRODUCTION — Anaphylaxis is a potentially fatal disorder that is under-recognized and undertreated. This may partly be due to failure to appreciate that 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.

This topic will discuss the treatment of anaphylaxis. The clinical manifestations and diagnosis of anaphylaxis, pathophysiology, and unique features of anaphylaxis in specific patient groups are reviewed separately:

- (See "Anaphylaxis: Acute diagnosis".)
- (See "Pathophysiology of anaphylaxis".)
- (See "Fatal anaphylaxis".)
- (See "Anaphylaxis: Confirming the diagnosis and determining the cause(s)".)
- (See "Anaphylaxis in infants".)
- (See "Anaphylaxis in pregnant and breastfeeding women".)

Recommendations for dosing and prescribing epinephrine for use by patients and caregivers in the community setting are provided separately. (See "Prescribing epinephrine for anaphylaxis self-treatment", section on 'Dosing'.)

IMMEDIATE MANAGEMENT — Prompt assessment and treatment are critical in anaphylaxis, as respiratory or cardiac arrest and death can occur within minutes [1-9]. It is also important to treat anaphylaxis promptly because it appears to be most responsive to treatment in its early phases, based on the observation that delayed epinephrine injection is associated with fatalities [10-15].

The tables provide rapid overviews of the initial assessment and emergency management of anaphylaxis in adults (table 1) and in children (table 2).

The cornerstones of initial management are the following [16-21]:

- ●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 (IM) injection of epinephrine at the earliest opportunity, followed by additional epinephrine by IM or intravenous (IV) injection.
- ●Placement of the patient in the supine position with the lower extremities elevated, unless there is prominent upper airway swelling prompting the patient to remain upright (and often leaning forward). If the patient is vomiting, placement of the patient semi-recumbent with lower extremities elevated may be preferable. Place pregnant patients on their left side.
- ●Supplemental oxygen.
- ●Volume resuscitation with IV fluids.

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 [1]. A more detailed review of fatal anaphylaxis is presented elsewhere. (See "Fatal anaphylaxis".)

Initial assessment and management — A number of critical components in the initial management needs to be instituted concomitantly [22-27]. Rapid overview tables that summarize important interventions in the first few minutes of management are provided for adults (table 1) and for infants and children (table 2):

- ●Initially, attention should focus on airway, breathing, and circulation, as well as adequacy of mentation. The lips, tongue, and oral pharynx are assessed for angioedema, and the patient is asked to speak his or her name to assess peri-glottic or glottic swelling. The skin is examined for urticaria or angioedema, which (if present) is helpful in confirming the diagnosis.
- ●Epinephrine should be injected intramuscularly into the mid-outer aspect of the thigh (table 1 and table 2) [10,17-21,28,29]. If symptoms are severe, an IV epinephrine infusion should be prepared. (See 'Intramuscular epinephrine injection (preferred)' below.)
- ●If the upper airway is not edematous, the patient should be placed in the recumbent position with the lower extremities elevated to maximize perfusion of vital organs (and pregnant patients on their left side to minimize compression of the inferior vena cava by the gravid uterus) [30]. The recumbent position also helps prevent severe hypotension, subsequent inadequate cardiac filling, and pulseless cardiac activity. In this situation, death can occur within seconds [21]. 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, if possible. (See "Fatal anaphylaxis".)

- ●Supplemental oxygen, initially using a nonrebreather mask at 15 liters/minute flow rate or commercial masks providing at least 70 percent and up to 100 percent oxygen, should be administered.
- ●Two large-bore IV catheters (ideally 14 to 16 gauge for most adults) should be inserted in preparation for rapid administration of fluids and medications. Intraosseous access should be obtained if IV access is not readily obtainable.
- ●In normotensive adults, isotonic (0.9 percent) saline should be infused at a rate of 125 mL/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 frequent measurements of blood pressure (BP), heart rate, and respiratory rate, as well as monitoring of oxygen saturation by pulse oximetry, is required for the duration of the episode.

Airway management — The initial steps in anaphylaxis management involve a rapid assessment of the patient's airway [22-26]:

- ●Intubation should be performed immediately if marked stridor or respiratory arrest is present.
- ●Preparations for early intubation should be made if there is any airway involvement or significant edema of the tongue, oropharyngeal tissues, including the uvula, or if voice alteration has occurred, especially if only a small amount of time has elapsed since the exposure. Early presence of upper airway edema represents rapidly developing airway compromise, requiring prompt action.
- ●In a minority of cases, an emergency cricothyroidotomy may be required to secure the airway if upper airway edema prevents access to the glottic aperture.

Intubation may be difficult in individuals in whom edema distorts the upper airway anatomical landmarks. Early awake flexible scope intubation or awake intubation using a rigid video laryngoscope with sedation and topical anesthesia/vasoconstriction are the methods of choice, unless intubation occurs early when there is minimal disruption of upper airway anatomy. In this latter case a "double set-up" rapid sequence intubation, preferably with a video laryngoscope and surgical airway backup are reasonable alternatives. Failed attempts at intubation can lead to complete airway obstruction and fatality. Therefore, upper airway closure in the setting of anaphylaxis should be managed by the most proficient 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, but delay should not occur while seeking consultation. If airway assistance is not immediately available, intubation should ensue. (See "Flexible scope intubation for anesthesia" and "Approach to the difficult airway in adults outside the operating room" and "The difficult pediatric airway".)

Intravenous fluids — Intravenous (IV) access should be obtained in all cases of anaphylaxis. Massive fluid shifts can occur rapidly due to increased vascular permeability,

with transfer of up to 35 percent of the intravascular volume into the extravascular space within minutes [17]. Any patient whose hypotension does not respond promptly and completely to IM epinephrine should receive large volume fluid resuscitation [22-26]. The following principles should guide therapy:

Fluid resuscitation should be initiated immediately in patients who present with orthostasis, hypotension, or incomplete response to IM epinephrine.

- Adults should receive 1 to 2 liters of normal saline at the most rapid flow rate possible in the first minutes of treatment. Large volumes of fluid (eg, up to 7 liters) may be required.
- Children should receive normal saline in boluses of 20 mL/kg, each over 5 to 10 minutes, and repeated, as needed. Large volumes of fluid (up to 100 mL/kg) may be required [31].

Normal saline is preferred over other solutions in most situations because other solutions have potential disadvantages:

- Lactated Ringer's (LR) solution can potentially contribute to metabolic alkalosis, although large volumes of normal saline can cause hyperchloremic metabolic acidosis, so some clinicians change from normal saline to LR if very large volumes are proving necessary.
- Dextrose is rapidly extravasated from the circulation into the interstitial tissues.
- Colloid solutions (eg, albumin or hydroxyethyl starch) confer no survival advantage in patients with distributive shock and are more costly [32].

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

Pregnant women: Additional considerations — 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 BP of at least 90 mmHg, as well as continuous fetal monitoring, are critically important [23]. (See "Anaphylaxis in pregnant and breastfeeding women", section on 'Management'.)

PHARMACOLOGIC TREATMENTS — The tables provide rapid overviews of the emergency management of anaphylaxis in adults (table 1) and children (table 2). The treatment recommendations in this section are consistent with available practice parameters [22,23,25-27,33]. Each pharmacologic therapy is discussed further below.

Anaphylaxis is variable and unpredictable. It may be mild and resolve spontaneously due to endogenous production of compensatory mediators or it may be severe and progress within minutes to respiratory or cardiovascular compromise and death [34]. 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 not, because the factors that determine the course of anaphylaxis in an individual patient are not fully understood. Because of these variables, it is important to administer intramuscular (IM) epinephrine early to prevent the possible progression to life-threatening manifestations.

Epinephrine — Epinephrine is the first and most important treatment for anaphylaxis, and it should be administered as soon as anaphylaxis is recognized to prevent the progression to life-threatening symptoms. Delayed epinephrine injection is associated with fatalities [10-15]. Epinephrine should also be administered to patients who have symptoms or signs consistent with impending anaphylaxis, and the clinical suspicion for anaphylaxis is high, even if formal diagnostic criteria are not met.

Dosing and administration — Epinephrine is commercially available in different concentrations. Great care must be taken to use the correct dilution in order to avoid inducing cardiac complications [22-26]. Confusion persists among clinicians regarding the optimal epinephrine dose and route of administration for the initial treatment of anaphylaxis [35,36]. Recommendations for dosing and prescribing epinephrine for use by patients and caregivers in the community setting are provided separately. (See "Prescribing epinephrine for anaphylaxis self-treatment", section on 'Dosing'.)

Intramuscular epinephrine injection (preferred) — Intramuscular (IM) injection is the preferred route for initial administration of epinephrine for anaphylaxis in most settings and in patients of all ages [37,38]. IM injection is recommended over subcutaneous injection because it consistently provides a more rapid increase in the plasma and tissue concentrations of epinephrine [19,20]. IM injection is also preferred over intravenous (IV) bolus because it is faster in many situations and safer (ie, lower risk of cardiovascular complications, such as severe hypertension and ventricular arrhythmias).

The epinephrine dilution for IM injection contains 1 mg/mL and ampules may also be labeled as 1:1000. To help prevent medication errors, ratio expressions are being removed from epinephrine labels in the United States; only amount per mL will be listed [39].

- **IM dosing** – For situations where an exact dose can be drawn up and administered, the recommended dose of epinephrine for patients of any age is 0.01 mg/kg (maximum dose of 0.5 mg) per single dose, injected intramuscularly into the mid-outer thigh (vastus lateralis muscle). The dose should be drawn up using a 1 mL syringe using the 1 mg/mLformulation of epinephrine.

  In health care settings where use of an autoinjector is preferred or estimating the dose helps to avoid delays, the following approach may be used:

  - Infants weighing <7.5 kg should be given an exact weight-based dose (not estimated), whenever possible. However, if drawing up an exact dose is likely to cause a significant delay in a rapidly deteriorating patient, the 0.15 mg dose can be given by autoinjector or by drawing up 0.15 mL of the 1 mg/mL solution. It is expected that the side effects of epinephrine would be mild and transient at the plasma concentrations achieved [40].

- Infants and children weighing from 7.5 kg to 25 kg can be given 0.15 mg by autoinjector or by drawing up 0.15 mL of the 1 mg/mL solution. We prefer use of the autoinjector in these patients for speed, reliability, and ease of use [41].
- Patients weighing 25 to 50 kg can be given 0.3 mg by autoinjector or by drawing up 0.3 mL of the 1 mg/mL solution. We prefer use of the autoinjector in these patients for speed, reliability, and ease of use [41].
- Patients who weigh >50 kg can be given 0.5 mg (0.5 mL of the 1 mg/mL solution). If the patient is obese, this can be administered using a 1.5 inch needle to penetrate the subcutaneous fat. However, if drawing up an exact dose is likely to cause a significant delay in a rapidly deteriorating patient, the 0.3 mg dose can be given by autoinjector.

The needle used in adults and children should be long enough to penetrate the subcutaneous adipose tissue over the vastus lateralis muscle. Realistically, however, IM injection into the thigh may be impossible in some patients, especially those who are overweight or obese [42,43]. Although the best approach in this situation has not been studied, we suggest as deep an injection as possible into the muscle.

● **Assessing response to IM** epinephrine – Most patients respond to a single dose of IM epinephrine, particularly if it is given promptly after the onset of symptoms. However, when epinephrine is administered in an out-of-hospital area, emergency response (911 service or the equivalent) should be activated, and the patient should be taken to a hospital for further evaluation. **IM epinephrine may be repeated at 5 to 15 minute intervals if there is no response or an inadequate response or even sooner if clinically indicated** [10,18,23-25,27,44,45]. When additional IM doses are required, typically one or rarely two additional doses are needed (eg, in patients with severe anaphylaxis and those who cannot access emergency care promptly) [46,47]. Retrospective studies indicate that a second dose is necessary in 12 to 36 percent of cases [48-54]. Patients with a history of previous anaphylaxis and those presenting with flushing, diaphoresis, or dyspnea were more likely to require multiple doses of epinephrine to control symptoms in an observational study [55].

In patients who continue to be hypotensive after initial IM epinephrine, IV fluids should be administered. It is also prudent to begin preparing an epinephrine solution for slow, continuous infusion early, so that it is ready in case the patient fails to respond to IM epinephrine and IV fluids. (See 'Intravenous fluids' above and 'Intravenous epinephrine continuous infusion and indications' below.)

Intravenous epinephrine by slow bolus (avoid or use only with caution) — Intravenous (IV) bolus epinephrine is associated with significantly more dosing errors and cardiovascular complications than intramuscular (IM) epinephrine and should be avoided when possible [10,14,35,37,38]. Slow, continuous infusion is preferred if patients have not responded to IM injections [24,56]. In an observational study of 362 doses of epinephrine administered to 301 patients for the emergency management of anaphylaxis, there were four overdoses, all of which occurred with IV bolus administration [37]. Adverse cardiovascular events were significantly more likely with IV bolus compared with IM administration (3 of 30 versus 4 of 316, respectively).

Nonetheless, there may be situations in which a slow IV bolus of epinephrine is indicated, such as when a patient is suffering cardiovascular collapse or impending cardiovascular collapse that is refractory to IM epinephrine and volume resuscitation, and an epinephrine infusion is not yet available.

- In such cases in an adult or adolescent, this is accomplished by the slow administration of a 50 to 100 mcg (0.05 to 0.1 mg) IV bolus of epinephrine, ideally with hemodynamic monitoring. This is best administered by slow push of 0.5 to 1 mL of 0.1 mg/mL (1:10,000) epinephrine solution ("cardiac" epinephrine, available in 10 mL prefilled syringes, containing 1 mg of epinephrine, and stocked on resuscitation carts). **Note that for anaphylaxis, the dose is 1/10th or less of the IV epinephrine dose used in cardiac arrest (advanced cardiac life support).** The administration of 0.5 to 1 mL (ie, maximum 1/10th of the total syringe volume) provides a dose of 50 to 100 mcg and is given over one to three minutes, followed by at least three minutes of observation before considering repeat dosing. Usually, a response is observed after a single dose, providing sufficient time to prepare an infusion. If the patient remains severely hypotensive or has shown little response in either heart rate or blood pressure to the first dose, a second dose is administered in the same way. As soon as infusion is available, bolus injection is discontinued and replaced by titration of the solution [27,57,58].
- We avoid the use of IV epinephrine boluses in infants and children, because data are sparse on the efficacy of safety of this approach and dosing is not well-established. Children who are not responding to initial IM epinephrine and fluid resuscitation should be treated with a slow IV infusion of epinephrine.

Intravenous epinephrine continuous infusion and indications — Patients who do not respond to several intramuscular (IM) injections of epinephrine AND aggressive 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 (IV) infusion, with the rate titrated according to response and the presence of continuous electronic hemodynamic monitoring. IV infusions of epinephrine should preferably be given by clinicians who are trained and experienced in the administration of vasopressors and can titrate the rate of infusion (and therefore the epinephrine dose) using continuous noninvasive monitoring of blood pressure (BP), heart rate, and function.

- **Preparing infusion solutions** – Epinephrine is commercially available in several dilutions. Great care must be taken to use the correct dilution in order to avoid overdosing the patient [35]. To prepare an epinephrine IV maintenance infusion, the commercially available epinephrine solution (eg, ampule, syringe) must be further diluted. To reduce the risk of making a medication error, we suggest that centers have a protocol available that includes steps on how to prepare and administer an epinephrine infusion.

- A simple method for quickly preparing a solution of 1 mcg/mL for adults and adolescents is to add the entire 10 mL contents of a 0.1 mg/mL (1:10,000) prefilled "cardiac" epinephrine syringe (1 mg) to a 1000 mL (1 liter) bag of normal saline. The resultant solution of 1 mcg/mL delivers 1 mcg/minute of epinephrine for each 60 mL/hour of solution infused. Therefore, 120 mL/hour will deliver 2 mcg/minute and so forth (table 3).
- For adolescent/adult patients who have already received large quantities of IV fluids (four or more liters), a more concentrated solution (4 mcg/mL) is preferable. Using a more concentrated solution allows titration of epinephrine infusion and administration of bolus crystalloid solution to be done independent of one another. To prepare a 4 mcg/mL solution, add the entire 10 mL contents of one 0.1 mg/mL (1:10,000) epinephrine syringe to a 250 mL bag of normal saline. The resultant solution delivers 1 mcg/minute of epinephrine for each 15 mL/hour of infusion. Therefore, 30 mL/hour delivers 2 mcg/minute, 45 mL/hour delivers 3 mcg/minute, and so forth (table 4).
- For infants and children, a more concentrated solution of 10 mcg/mL is more appropriate to avoid excessively large infusion volumes.

- **Initial infusion rates**:
  - **Adults** – Start the IV epinephrine infusion at **0.1 mcg/kg/minute**, and increase it every two to three minutes by 0.05 mcg/kg/minute until blood pressure and perfusion improve. The maximum dose is not known and will be different for every patient, but rarely will a patient require a dose exceeding 1 mcg/kg/minute. As an example, for a 70 kg patient, the starting dose is 7 mcg/minute, so either 420 mL/hour of the 1 mcg/mL dilute solution described above or 105 mL/hour of the 4 mcg/mL solution. The infusion rate is increased by one-half of that starting rate every few minutes (in this example, by 210 mL/hour of the dilute solution or 52 mL/hour of the more concentrated solution). The dose is titrated to effect on BP with continuous noninvasive monitoring. When blood pressure (BP) increases by 10 to 15 percent, the infusion rate is held at that level for three to five minutes to see if improvement continues, and the infusion rate is then adjusted accordingly [22]. If there is a risk of volume overload, the more dilute solution should only be used as a temporizing measure until a more concentrated solution is available. To reduce the risk of making a medication error, we suggest that centers have a protocol available that includes steps on how to prepare and administer epinephrine infusion.
  - **Infants and children** – The dose for IV infusion of epinephrine is **0.1 to 1 mcg/kg/minute** with use of an infusion pump, titrated to effect on BP with continuous cardiac monitoring and frequent noninvasive BP monitoring. To reduce the risk of making a medication error, we suggest that centers have a protocol available that includes steps on how to prepare and administer epinephrine infusion. Examples of pediatric infusions are provided (table 5 and table 6).

Epinephrine is a vesicant, and central line administration is preferred, although central line insertion should not delay the initiation of IV epinephrine infusion [59,60]. When a patient does not have a central venous catheter, epinephrine can be temporarily administered

through an appropriately positioned, large bore, peripheral venous catheter until a central venous catheter is inserted. Closely monitor the catheter site throughout the infusion to avoid extravasation injury.

Epinephrine mechanisms of action — The pharmacologic actions of epinephrine address the pathophysiologic changes that occur in anaphylaxis better than any other medication. It decreases mediator release from mast cells [61], prevents or reverses obstruction to airflow in the upper and lower respiratory tracts, and prevents or reverses cardiovascular collapse (table 1 and table 2).

The therapeutic actions of epinephrine include the following (table 7) [10,12-15,18,44]:

- 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.

Adverse effects — 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 [14,15,18,44]. These symptoms and signs are similar to those occurring during the physiologic "fight or flight" response due to endogenous epinephrine that occurs normally in sudden frightening or life-threatening situations.

Rarely, epinephrine may lead to ventricular arrhythmias, angina, myocardial infarction, pulmonary edema, sudden sharp increase in BP, and intracranial hemorrhage. However, anaphylaxis itself can lead to angina, myocardial infarction, and cardiac arrhythmias in the absence of any exogenous epinephrine or before exogenous epinephrine is administered [62].

Serious adverse effects occur most commonly after an IV bolus injection, particularly if an inappropriately large dose is administered [10,14,35,37]. (See 'Situations requiring caution'below.)

Situations requiring caution — There are **no** absolute contraindications to epinephrine use in anaphylaxis [10,12-15,22-26,44]. The risk of death or serious neurologic sequelae from hypoxic-ischemic encephalopathy due to inadequately treated anaphylaxis usually outweighs other concerns [10,12-15,22-26,44]. Existing evidence clearly favors the benefit of epinephrine administration in anaphylaxis. However, formal risk-benefit analyses are not possible, and sound clinical judgment is essential.

Subgroups of patients might theoretically be at higher risk for adverse effects during epinephrine therapy:

●Patients with cardiovascular diseases – The small number of studies examining epinephrine use in older adults with anaphylaxis suggests that while intravenous epinephrine is associated with more adverse cardiovascular effects, intramuscular injection is well-tolerated [37,38]. 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 [63,64]. Moreover, anaphylaxis itself can cause vasospasm, arrhythmias, and myocardial infarction in patients, including children, with healthy hearts as confirmed by normal electrocardiograms, echocardiograms, and coronary angiograms after resolution of anaphylaxis [65].

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

●Patients with certain pre-existing 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.

Efficacy — Epinephrine is the best studied medication in anaphylaxis, although randomized, placebo-controlled trials of epinephrine in humans experiencing anaphylaxis have never been performed for ethical reasons. The evidence for its use comes from observational studies, randomized, controlled clinical pharmacology studies in patients not experiencing anaphylaxis, studies of anaphylaxis in animal models, and epidemiologic studies, including fatality studies. Several case series have implicated the failure to administer epinephrine early in the course of treatment as a consistent finding in anaphylaxis deaths [1-7,66].

●In a series of 13 fatal and near-fatal food-induced anaphylactic reactions in children and adolescents, the six patients who died had symptom-onset within one to five minutes after ingestion of the culprit food, but did not receive their first dose of epinephrine until 25, 60, 80, 90, 125, and 180 minutes after the food was ingested. The authors concluded that the failure to recognize severity of the reactions and to administer epinephrine promptly increased the risk of a fatal outcome [2].

●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 [3].

●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 [1].

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 [17]. 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.

In a retrospective chart review of 234 children who received epinephrine for food-induced anaphylaxis, treatment with epinephrine prior to arrival to the emergency department was associated with a significantly lower risk of hospitalization [67]. Although the time between food exposure and administration of epinephrine could not be precisely determined, children who received epinephrine earlier (often because they had an epinephrine autoinjector) were released from the emergency department sooner and were less likely to require hospital admission compared with those who received it only after arrival (17 versus 43 percent).

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. At the time the autoinjector is used or epinephrine is administered in another form, 911 response should be initiated, with the clear complaint of "anaphylaxis," without waiting to see if the reaction worsens. The 911 call can always be aborted if the patient recovers or the patient can be assessed by paramedics and not transported. 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 [68]. 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 [69].

Glucagon for patients taking beta-blockers — Patients receiving beta-blockers may be resistant to treatment with epinephrine and can develop refractory hypotension. In this situation, glucagon should be administered because it has inotropic and chronotropic effects that are not mediated through beta-receptors [70,71].

- Adult dosing is 1 to 5 mg slow IV bolus over five minutes. May be followed by an infusion of 5 to 15 mcg/minute titrated to effect.

- ●Pediatric dosing is 20 to 30 mcg/kg (maximum 1 mg) slow IV bolus over five minutes. May be followed by an infusion of 5 to 15 mcg/minute titrated to effect (ie, not weight-based).

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.

Bronchodilators — For the treatment of bronchospasm not responsive to epinephrine, inhaled bronchodilators (eg, albuterol, salbutamol), should be administered by mouthpiece (or facemask for those whose age or condition requires) and nebulizer/compressor, as needed. Bronchodilators 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 [22-26]. The evidence for the use of beta-2 adrenergic agonists in anaphylaxis is extrapolated from their use in acute asthma.

Adjunctive agents — Agents that may be given as adjunctive therapies to epinephrine in the treatment of anaphylaxis include H1 antihistamines, H2 antihistamines, bronchodilators, and glucocorticoids. None of these medications should be used as initial treatment or as sole treatment because they do not relieve upper or lower respiratory tract obstruction, hypotension, or shock and are not life-saving.

H1 antihistamines — Epinephrine is first-line treatment for anaphylaxis, and there is no known equivalent substitute. H1 antihistamines relieve itching and urticaria, and their use in anaphylaxis is extrapolated from the studies of urticaria. A systematic review of the literature failed to retrieve any randomized, controlled trials that meet current standards and support the use of H1 antihistamines in anaphylaxis [11]. Despite this, H1 antihistamines are the most commonly administered medications in the treatment of anaphylaxis, which suggests over-reliance on these agents [72-75].

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 [34]. In addition, the onset of action of antihistamines, such as cetirizine or diphenhydramine, takes 30 to 40 minutes and is too slow to provide any immediate benefit [76]. Only first-generation H1 antihistamines are available in parenteral formulations, and rapid IV administration may increase hypotension [77].

- ●For adults, diphenhydramine 25 to 50 mg can be administered intravenously over five minutes, which may be repeated up to a maximum daily dose of 400 mg per 24 hours.
- ●For children weighing less than 50 kg, diphenhydramine 1 mg/kg (maximum 50 mg) can be administered intravenously over five minutes, which may be repeated up to a maximum daily dose of 5 mg/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 [11,15,78]. Orally-administered cetirizine acts within 30 to 40 minutes and lasts for 24 hours. However, second-generation H1 antihistamines are not available in parenteral formulations.

H2 antihistamines — An H2 antihistamine given with an H1 antihistamine may provide some additional relief of hives [79].

Although H2 antihistamines are sometimes administered in anaphylaxis treatment, H2 antihistamines **do not** relieve upper or lower airway obstruction or shock. Systematic reviews have not identified any randomized, controlled trials that support the use of these agents in anaphylaxis or urticaria [80,81].

If used, ranitidine (50 mg in adults) (12.5 to 50 mg [1 mg/kg] in children), may be diluted in 5 percent dextrose to a total volume of 20 mL and injected intravenously over five minutes.

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 theoretically prevent the biphasic or protracted reactions that occur in some cases of anaphylaxis. However, a systematic review of the literature failed to retrieve any randomized, controlled trials in anaphylaxis that confirmed the effectiveness of glucocorticoids [82]. In addition, a study of emergency department patients with allergic reactions or anaphylaxis failed to find a decrease in return emergency department visits or biphasic reactions among patients treated with glucocorticoids [83].

If given, a dose of methylprednisolone of 1 to 2 mg/kg/day is sufficient. If glucocorticoid treatment is instituted, it should be stopped after one or two days without a taper.
(See "Anaphylaxis: Acute diagnosis", section on 'Time course'.)

REFRACTORY ANAPHYLAXIS — For patients who are not responding to initial measures, admission to an intensive care unit should occur without delay. There are no published prospective studies on the optimal management of refractory anaphylaxis.

Anaphylactic shock displays features of both distributive (vasodilatory) and hypovolemic shock. 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 suspected sepsis and septic shock in adults", section on 'Vasopressors' and "Treatment of hypovolemia or hypovolemic shock in adults".)

Other vasopressors — The addition of another vasopressor should be considered if the patient continues to be hypotensive despite maximal epinephrine and fluid therapy. It is

unclear if the addition of other pressors is superior to epinephrine alone, but 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 [84]. The use of nonadrenergic vasopressors, such as vasopressin, in the management of anaphylaxis refractory to intravenous (IV) epinephrine in adults is discussed elsewhere. Other adrenergic vasopressors can also be considered, such as norepinephrine and dopamine. An emergency medicine practice parameter states, "Norepinephrine, vasopressin, and other pressors have been used with success in patients in anaphylaxis with refractory hypotension" [27]. (See "Use of vasopressors and inotropes", section on 'Vasopressin and analogs'.)

Methylene blue — 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, mostly in perioperative settings [85-87]. The efficacy and ideal dose of methylene blue is unknown, but a single bolus of 1 to 2 mg/kg given over 20 to 60 minutes has been used in cardiac surgery. Improvement of vasoplegia (eg, increased systemic vascular resistance, reduced vasopressor dose) has been observed within one to two hours in the setting of cardiac surgery, but few data are available about anaphylaxis. 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 regarding potential drug interactions with serotonergic agents. Methylene blue and other vital dyes are also rarely the cause of perioperative anaphylaxis. (See "Postoperative complications among patients undergoing cardiac surgery", section on 'Vasodilatory shock'.)

Extracorporeal membrane oxygenation — Patients suffering from refractory anaphylaxis have been resuscitated with extracorporeal membrane oxygenation (ECMO) or operative cardiopulmonary bypass [88,89]. ECMO is becoming increasingly available in emergency departments and should be considered in patients unresponsive to complete resuscitative efforts in institutions with experience in this technology. The decision to initiate ECMO should be considered early in patients unresponsive to traditional resuscitative measures, before irreversible ischemic acidosis develops. (See "Extracorporeal membrane oxygenation (ECMO) in adults".)

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

- Epinephrine should be administered as soon as possible once anaphylaxis is recognized or if impending anaphylaxis is suspected, even if patients do not yet meet diagnostic criteria. Delayed administration has been implicated in contributing to fatalities [1-7,66]. 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 [2].

●H1 antihistamines are useful for relieving itching and urticaria. They do NOT relieve stridor, shortness of breath, wheezing, gastrointestinal symptoms and signs, hypotension or shock, and should not be substituted for epinephrine [11,22,23,26,78].

●Bronchodilator treatment with nebulized albuterol (salbutamol) 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.

CARE UPON RESOLUTION — To reduce the risk of recurrence, patients who have been successfully treated for anaphylaxis subsequently require confirmation of the anaphylaxis cause as well as anaphylaxis education. In a study of emergency department patients with suspected anaphylaxis who followed up with an allergist/immunologist, 35 percent of patients had an alteration in the diagnosis or suspected cause, underscoring the importance of follow-up evaluation [90]. (See "Anaphylaxis: Confirming the diagnosis and determining the cause(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 health care 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 hospital.

●We suggest a minimum observation period of four to eight hours for patients at risk for severe anaphylaxis (ie, asthma, those for whom more than one dose of epinephrine was required to treat the initial reaction, or if symptoms persist).

●For patients with anaphylaxis that resolved promptly and completely with treatment, we suggest that observation times be customized based on the severity of the reaction and access to emergency care.

●Patients should be prescribed an epinephrine autoinjector and trained in its use. The importance of filling the prescription immediately should be stressed. From 1 percent to 21 percent of patients may experience a biphasic reaction [91,92]. (See "Anaphylaxis: Acute diagnosis", section on 'Biphasic anaphylaxis'.)

Discharge care — All patients who have experienced anaphylaxis should be sent home with the following:

●An anaphylaxis emergency action plan

●A prescription for more than one epinephrine autoinjector

●Printed information about anaphylaxis and its treatment

●(Documented) advice to follow-up to an allergist, with a referral if possible

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 recognition of anaphylaxis and self-injection of epinephrine.

An action plan that can be personalized is available online through the American Academy of Allergy, Asthma, and Immunology (AAAAI) [34].

- English – Anaphylaxis Emergency Action Plan
- Spanish – Anaphylaxis Emergency Action Plan

Anaphylaxis action plans specifically designed for patients with food allergy are available through the organization Food Allergy Research & Education (FARE). FARE is a trusted source of information about food allergies:

- English – Food Allergy and Anaphylaxis Emergency Care Plan
- Spanish – Food Allergy and Anaphylaxis Emergency Care Plan

Epinephrine autoinjector — Patients should be instructed in how to use an epinephrine autoinjector correctly, provided with a prescription for it, and advised to fill the prescription immediately. Ideally, two epinephrine autoinjectors should be prescribed because up to 20 percent of patients require more than one dose of epinephrine for the treatment of their anaphylactic reaction [50,51,55]. Instructions in the proper use of epinephrine autoinjectors should be reviewed verbally, and patients should be given a DVD and/or written material or directed to a manufacturer's website video providing relevant information. Patient information that can be printed or accessed online is provided. These steps prior to discharge are often overlooked. In a survey of 1885 patients who survived anaphylaxis, 28 percent of those who did not self-administer epinephrine reported that they had never received a prescription for an autoinjector [93]. (See 'Information for patients' below.)

Counseling and referral to an allergist — 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 [94,95]. These steps are: **S**eek support, **A**llergen identification and avoidance, **F**ollow-up for specialty care, and **E**pinephrine for emergencies. 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 (without further exposure to the causal agent) 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.
- They should learn about anaphylaxis (refer the patient to resources).

(See 'Information for patients' below.)

- **Allergen identification and avoidance**
  - Emphasize the importance of avoiding the suspected cause [90]. If the cause is unclear, which is not unusual, it is especially important to refer the patient to an allergist for further evaluation.
- **Follow-up for 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 to confirm the cause and for ongoing management. Specifically, the suspected cause for the anaphylactic episode should be verified. In one study of over 500 patients with anaphylaxis, evaluation by an allergist/immunologist resulted in an alteration to the diagnosis or suspected cause in more than one-third [90]. The evaluation of a patient following anaphylaxis is reviewed separately.

    (See "Anaphylaxis: Confirming the diagnosis and determining the cause(s)".)
  - For anaphylaxis caused by stinging insects, a course of immunotherapy can dramatically reduce the risk of a recurrent reaction. (See "Hymenoptera venom immunotherapy: Efficacy, indications, and mechanism of action".)
  - Comorbidities, such as asthma, other chronic pulmonary disease, and cardiovascular disease, should be optimally controlled, as these can increase the risk of fatal anaphylaxis. (See "Fatal anaphylaxis".)
- Epinephrine **for emergencies**
  - Provide the patient with a prescription for two epinephrine autoinjectors and demonstrate proper use. In addition, give the patient written information about how to recognize anaphylaxis and how to use an epinephrine autoinjector, and provide directions to appropriate websites for video demonstrations of autoinjector use.

    (See 'Information for patients' below.)
    - 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 causes, and how to administer epinephrine. The correct injection technique is important to avoid unintentional injection into fingers, thumbs, or other body parts [96].

RISK OF RECURRENCE — Patients who have experienced anaphylaxis are at risk for recurrent episodes unless long-term risk reduction measures are implemented. The risk of recurrence has been estimated in several retrospective studies of different patient populations [22,23,97,98]. In a prospective study of nearly 300 children with anaphylaxis requiring acute medical care (predominantly caused by foods), the annual recurrence rate was 18 percent [99]. Concomitant asthma and the need for epinephrine to treat the initial episode further increased the risk of recurrence. Thus, it is important to equip patients with

epinephrine autoinjectors and arrange appropriate referrals in a timely manner after the initial event.

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Anaphylaxis".)

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 education: Anaphylaxis (The Basics)" and "Patient education: Epinephrine autoinjectors (The Basics)")
- Beyond the Basics topics (see "Patient education: Anaphylaxis symptoms and diagnosis (Beyond the Basics)" and "Patient education: Anaphylaxis treatment and prevention of recurrences (Beyond the Basics)" and "Patient education: 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 (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) [100,101].

SUMMARY AND RECOMMENDATIONS

- Patients with anaphylaxis should be assessed and treated as rapidly as possible, as respiratory or cardiac arrest and death can occur within minutes. Anaphylaxis appears to be most responsive to treatment in its early phases, before shock has developed, based on the observation that delayed epinephrine injection is associated with fatalities. (See 'Immediate management' above.)
- Initial management is summarized in rapid overview tables for adults (table 1) and children (table 2). (See 'Immediate management' above.)
- Epinephrine is life-saving 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),

as well as for patients with moderate-to-severe symptoms and signs (Grade 1A). (See 'Epinephrine'above.)

●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 of administration is advised, in preference to subcutaneous administration or intravenous (IV) administration. (See 'Intramuscular epinephrine injection (preferred)' above.)

- When an exact dose can be drawn up and administered, 0.01 mg/kg (maximum of 0.5 mg) should be administered in the mid-outer thigh every 5 to 15 minutes or more frequently if necessary.
- When an autoinjector is used, children weighing less than 25 kg should receive the 0.15 mg dose, and those weighing over 25 kg should receive the 0.3 mg dose administered to the outer thigh every 5 to 15 minutes or more frequently if necessary. Autoinjector use must be carefully considered in infants and children weighing under 7.5 kg. However, the benefits likely outweigh the risk if this is the only source of epinephrine available.

●Massive fluid shifts can occur in anaphylaxis, and all patients with orthostasis, hypotension, or incomplete response to epinephrine should receive large volume fluid resuscitation with normal saline. Normotensive patients should receive normal saline to maintain venous access in case their status deteriorates. (See 'Intravenous fluids' above.)

●Supplemental oxygen and bronchodilators should be administered to patients with respiratory signs or symptoms. (See 'Initial assessment and management' above.)

●IV epinephrine is indicated for patients with profound hypotension or symptoms and signs suggestive of impending shock (dizziness, incontinence of urine or stool) who do not respond to initial IM injections of epinephrine and fluid resuscitation. For these patients, we suggest that epinephrine be administered by continuous slow IV infusion rather than by intermittent IV bolus (Grade 2C). Slow IV infusion is less likely to cause extreme hypertension or ventricular arrhythmias. Epinephrine infusion should be accompanied by continuous electronic hemodynamic monitoring. Specific guidance for creating the proper epinephrine solutions is provided. (See 'Intravenous epinephrine continuous infusion and indications' above.)

●Patients successfully treated for anaphylaxis should be discharged with a personalized written anaphylaxis emergency action plan, an epinephrine autoinjector, written information about anaphylaxis and its treatment, and a plan for further evaluation by an allergist. (See 'Care upon resolution' above and 'Information for patients' above.)

●Patients should be evaluated further to confirm the cause, as specific avoidance measures are useful in reducing the risk of recurrence. (See 'Risk of recurrence' above.)

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