5. Preventing and Managing Adverse Reactions

Updates

Major changes to the best practice guidance include 1) more descriptive characterization of anaphylactic allergy and 2) incorporation of protocols for managing adverse reactions.

Benefit and Risk Communication

Parents, guardians, legal representatives, and adolescent and adult patients should be informed about the benefits of and risks from vaccines in language that is culturally sensitive and at an appropriate educational level. Opportunity for questions should be provided before each vaccination. Discussion of the benefits of and risks from vaccination is sound medical practice and is required by law.

The National Childhood Vaccine Injury Act of 1986 (1) requires that vaccine information materials be developed for each vaccine covered by the Act (uscode.house.gov). These materials, known as vaccine information statements (VISs), must be provided by all public and private vaccination providers each time a vaccine is administered. Copies of VISs are available from state health authorities responsible for vaccination and from CDC (www.cdc.gov/vaccines/hcp/vis/index.html). Translations of VISs into languages other than English are available from certain state vaccination programs and from the Immunization Action Coalition website (http://www.immunize.org). The act does not require that a signature be obtained; however, documentation of consent might be recommended or required by certain state or local health authorities or school authorities.

Some parents or patients question the need for or safety of vaccinations and want to discuss the risks from and benefits of certain vaccines. Some refuse certain vaccines or reject all vaccinations for personal or religious reasons. Having a basic understanding of how patients and parents of patients view vaccine risk and developing effective approaches to address vaccine safety concerns are imperative for vaccination providers.

Each person understands and reacts to vaccine information on the basis of different factors, including previous experience, education, personal values, method of data presentation, perceptions of the risk for disease and perceived ability to control these risks, and risk tolerance. In some circumstances, decisions about vaccination are based on inaccurate information about risk provided by the media and certain websites. Websites and other sources of vaccine information may be inaccurate or incomplete. Health care providers can be a pivotal source of science-based credible information by discussing with parents and patients the risks from and benefits of vaccines, which helps patients make informed decisions.

When a parent or patient initiates a discussion about a perceived vaccine adverse reaction, the health care provider should discuss the specific concerns and provide factual information, using appropriate language. Effective, empathetic vaccine risk communication is essential in responding to misinformation and concerns, with health care providers recognizing that risk assessment and decision-making can be difficult and confusing. Certain vaccines might be acceptable to a parent who is resistant to other vaccines. This partial acceptance can be used to facilitate additional communication. Their concerns can be addressed using the VIS and offering other resource materials (e.g., vaccination information from CDC: www.cdc.gov/vaccines/hcp/vis/index.html).

The American Academy of Pediatrics (AAP) does not recommend that providers exclude from their practice patients whose parents or guardians question or refuse vaccination. However, an effective public health strategy is to identify common ground and discuss measures that need to be followed if the decision is to defer vaccination (2). Health care providers should reinforce key points about each vaccine, including safety, and emphasize risks for disease among unvaccinated children. Parents should be advised of state laws regarding entry to schools or child-care facilities, which might require that unvaccinated children be excluded from the facility during outbreaks (www.cdc.gov/vaccines/imzmanagers/coverage/schoolvaxview/requirements/index.html). These discussions should be documented in the patient's medical record, including the refusal to receive certain vaccines (i.e., informed refusal). When a vaccine is refused when first offered the provider should take the opportunity to offer the vaccine again at the next visit.

Preventing Adverse Reactions

Vaccines are intended to produce active immunity to specific antigens. An adverse reaction is an undesirable side effect that occurs after a vaccination. Vaccine adverse reactions are classified as 1) local, 2) systemic, or 3) allergic (additional information is available at

https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm09383 3.htm. Local reactions (e.g., redness) are usually the least severe and most frequent. Systemic reactions (e.g., fever) occur less frequently than local reactions, and severe allergic reactions (e.g., anaphylaxis) are the least frequent reactions. Severe adverse reactions are rare (3).

Some of the systemic reactions may be complicated by the onset of syncope. Syncope (vasovagal or vasodepressor reaction) can occur after vaccination and is most common among adolescents and young adults. In 2005, the Vaccine Adverse Event Reporting System (VAERS) began detecting a trend of increasing syncope reports that coincided with the licensure of 3 vaccines for adolescents: human papillomavirus (HPV), MenACWY, and Tdap (4). Of particular concern among adolescents has been the risk for serious secondary injuries, including skull fracture and cerebral hemorrhage. Of 463 VAERS reports of syncope during January 1, 2005, to July 31, 2007, a total of 41 listed syncope with secondary injury with information on the timing after vaccination, and the majority of these syncope reports (76%) occurred among adolescents. Among all age groups, 80% of reported syncope episodes occur within 15 minutes of vaccine administration (additional information is available at <u>www.cdc.gov/vaccinesafety/concerns/fainting.html</u>). Providers should take appropriate measures to prevent injuries if a patient becomes weak or dizzy or loses consciousness. Adolescents and adults should be seated or lying down during vaccination.Vaccine providers, particularly when vaccinating adolescents, should consider observing patients (with patients seated or lying down) for 15 minutes after vaccination to decrease the risk for injury should they faint (4). If syncope develops, patients should be observed until the symptoms resolve.

Although allergic reactions are a common concern for vaccine providers, these reactions are uncommon and anaphylaxis following vaccines is rare, occurring at a rate of approximately one per million doses for many vaccines (5).

Epinephrine and equipment for managing an airway should be available for immediate use (6). The best practice to prevent allergic reactions is to identify individuals at increased risk by obtaining a history of allergy to previous vaccinations and vaccine components that might indicate an underlying hypersensitivity. Acute allergic reactions following vaccinations might be caused by the vaccine antigen, residual animal protein, antimicrobial agents, preservatives, stabilizers, or other vaccine components (7). Components of each vaccine are listed in the respective package insert. An extensive list of vaccine components and their use, as well as the vaccines that contain each component, has been published (8) and also is available from CDC

(www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table- 2.pdf). Additional information and tables of potential allergens in different vaccines are available at (http://www.vaccinesafety.edu/components-Allergens.htm). The allergens identified in the history can be cross-checked against the allergens identified in package inserts.

Managing Acute Vaccine Reactions

Vaccine providers should be familiar with identifying immediate-type allergic reactions, including anaphylaxis, and be competent in treating these events at the time of vaccine administration. Providers should also have a plan in place to contact emergency medical services immediately in the event of a severe acute vaccine reaction.

Allergic reactions can include: local or generalized urticaria (hives) or angioedema; respiratory compromise due to wheezing or swelling of the throat; hypotension; and shock. Immediate-immunoglobulin E (IgE)-mediated (type 1) immune reactions, such as anaphylaxis, usually occur within minutes of parenteral administration and involve specific IgE interactions with discrete antigens (9,10). Rapid recognition and initiation of treatment are required to prevent possible progression to respiratory failure or cardiovascular collapse. It is important to note that urticaria may not be present in all cases of anaphylaxis. For respiratory or cardiovascular symptoms, or other signs or symptoms of anaphylaxis, immediate intramuscular epinephrine is the treatment of choice (11,12). Additional doses of epinephrine as well as other drugs also might be indicated (Tables 5-1 and 5-2) (12). Considering the availability of emergency services, providers should plan for the availability of at least 3 doses of epinephrine (in dosing formulations appropriate to each and every age/group served by the provider) for a General Best Practice Guidelines for Immunization: Preventing and Managing Adverse Reactions 75 hypothetical emergency situation. If hypotension is present, the patient should be placed in a recumbent position with the legs elevated. Maintenance of the airway, oxygen administration, and intravenous normal saline might be necessary.

After the patient is stabilized, arrangements should be made for immediate transfer to an emergency facility for additional evaluation and treatment. Because anaphylaxis may recur after patients begin to recover, monitoring in a medical facility for several hours is advised, even after complete resolution of symptoms and signs. Additional information on management of patients with anaphylaxis has been published (9).

Persons Who Have Had an Allergic Reaction Following a Previous Immunization

For an individual patient who has experienced an immediate reaction to immunization, it is important to identify the type of reaction that occurred, obtain a history of prior allergic reactions, and try to identify the particular agent responsible. An algorithm approach to these patients has been published (13) and additional advice is available for allergists on the evaluation of these adverse events (10). In general, a history of a severe allergic reaction to a vaccine should be considered a contraindication to additional doses of the same vaccine (13). Referral of the individual to an allergist for evaluation is usually indicated to possibly determine the component responsible, before making decisions regarding administration of the additional doses of the same vaccine or other vaccines that have the same components. Patients who have not had a severe allergic reaction following a vaccine, but who have a history of possible allergy to a vaccine component can often be vaccinated safely after careful evaluation (6).

Influenza Vaccination of Persons with a History of Egg Allergy

Severe allergic and anaphylactic reactions can occur in response to a number of influenza vaccine components, but such reactions are rare (6). All but the recombinant inactivated influenza vaccine may have come into contact with egg protein. The use of influenza vaccines for persons with a history of egg allergy has been reviewed recently by ACIP (14).

VAERS data mining did not identify a higher than expected proportion of serious allergic events after influenza vaccination during the 2011-2012 season, relative to all other reported vaccines and adverse events in the database. Persons with a history of egg allergy should receive recombinant inactivated vaccine (if 18 years or older), or IIV.

Other measures, such as dividing and administering the vaccine by a 2-step approach and skin testing with vaccine, are not recommended (*10*).

All vaccines should be administered in settings in which personnel and equipment for rapid recognition and treatment of anaphylaxis are available. ACIP recommends that all vaccination providers be certified in cardiopulmonary resuscitation (CPR), have an office emergency plan, and ensure that all staff are familiar with the plan (6). Some persons who report allergy to egg might not be egg-allergic. Those who are able to eat lightly cooked egg (e.g., scrambled egg) without reaction are unlikely to be allergic.

Egg-allergic persons might tolerate egg in baked products (e.g., bread or cake). Tolerance to egg-containing foods does not exclude the possibility of egg allergy (15). Egg allergy can be confirmed by a consistent medical history of adverse reactions to eggs and eggcontaining foods, plus skin and/or blood testing for IgE antibodies to egg proteins. A previous severe allergic reaction to influenza vaccine, regardless of the component suspected to be responsible for the reaction, is a contraindication to future receipt of the vaccine (14).

Yellow Fever Vaccination of Persons with a History of Egg Allergy

Yellow fever vaccine contains egg protein. There have been insufficient studies to determine which patients with egg allergy may be able to receive yellow fever vaccine, but there are reports of patients with true egg allergy safely receiving yellow fever vaccine after evaluation by specialists with expertise in the management of allergic reactions (16,17). According to the manufacturer, persons who are able to eat eggs or egg products may receive the vaccine (18). However, potential hypersensitivity reactions might occur in persons with a history of minor reactions to eggs. For egg-sensitive persons, a scratch test or intradermal test can be performed before administering the vaccine to check for reactivity.

If a person has a severe egg-sensitivity or has a positive skin test to the vaccine, but the vaccination is recommended because of their travel destination-specific risk, desensitization can be performed under direct supervision of a physician experienced in the management of anaphylaxis.

The desensitization procedure is detailed in the product insert (see yellow fever recommendations at

Vaccines with MMR or Varicella Components and Persons with a History of Egg Allergy

Varicella vaccine is grown in human diploid cell cultures and can safely be administered to persons with a severe allergy to eggs or egg proteins (19). Measles and mumps vaccine viruses are grown in chick embryo fibroblast tissue culture. However, persons with a severe egg allergy can receive measles- or mumps-containing vaccines in the usual manner because the content of these proteins is extremely low (20). The rare severe allergic reactions after measles- or mumps-containing vaccines or varicella are thought to be caused by other components of the vaccine (e.g., gelatin) (21-24). MMR, MMRV, varicella and other vaccines contain hydrolyzed gelatin as a stabilizer.

Vaccines and Persons with a History of Allergy to Substances Other than Eggs

Persons who have had an anaphylactic reaction to gelatin or gelatin-containing products should be evaluated by an allergist prior to receiving gelatin-containing vaccines (6).

Certain vaccines contain trace amounts of antimicrobial agents or other preservatives (e.g., neomycin or thimerosal), although allergies to these are rare. No licensed vaccine contains penicillin or penicillin derivatives. Most often, neomycin hypersensitivity manifests as contact dermatitis, a delayed-type (cell-mediated) immune response rather than immediate-hypersensitivity (IgE-mediated allergy)–type response (25,26). A history of delayed-type reactions to neomycin is not a contraindication for administration of neomycin-containing vaccines. There has only been 1 reported case of immediate hypersensitivity reaction following a neomycin-containing vaccine (27). Persons who have had anaphylactic reactions to neomycin should be evaluated by an allergist prior to receiving vaccines containing neomycin (6).

Thimerosal, an organic mercurial compound in use since the 1930s, is added to certain immunobiologics as a preservative. Since mid-2001, vaccines routinely recommended for infants younger than 6 months of age have been manufactured without thimerosal as a preservative (14). Live, attenuated vaccines have never contained thimerosal. Thimerosalfree formulations of inactivated influenza vaccine are available. Inactivated influenza vaccine also is available in formulations with only trace amounts of thimerosal, which remains as a manufacturing residual but is not added at the higher concentration that would be necessary for it to function as a preservative. Thimerosal at a preservative concentration is present in certain other vaccines that can be administered to children (e.g., Td and DT). Information about the thimerosal content of vaccines is available from FDA at

https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM096 22 8.

Reactions to thimerosal have been described as local delayed-type hypersensitivity reactions with only rare reports of immediate reactions (28-31). Thimerosal elicits positive delayed-type hypersensitivity patch tests in 1%-18% of persons tested; however, these tests have no relevance to acute allergic reactions that might occur within minutes or hours after immunization (32,33). The majority of persons do not experience reactions to thimerosal administered as a component of vaccines even when patch or intradermal tests for thimerosal indicate hypersensitivity (31). A local or delayed-type hypersensitivity reaction to thimerosal is not a contraindication to receipt of a vaccine that contains thimerosal (34).

Latex is sap from the rubber tree. Latex contains naturally occurring plant proteins that can be responsible for immediate-type allergic reactions. Latex is processed to form either natural rubber latex products such as gloves or dry, natural rubber products such as syringe plunger tips and vial stoppers. Synthetic rubber is also used in gloves, syringe plungers, and vial stoppers but does not contain the latex proteins linked to immediatetype allergic reactions. Natural rubber latex or dry, natural rubber used in vaccine packaging generally is noted in the manufacturers' package inserts.

Immediate-type allergic reactions due to latex allergy have been described after vaccination, but such reactions are rare (35).

If a person reports a severe anaphylactic allergy to latex, vaccines supplied in vials or syringes that contain natural rubber latex should be avoided if possible (6). If not, if the decision is made to vaccinate, providers should be prepared to treat immediate allergic reactions due to latex, including anaphylaxis. The most common type of latex hypersensitivity is a delayed-type (type 4, cell-mediated) allergic contact dermatitis (36). For patients with a history of contact allergy to latex, vaccines supplied in vials or syringes that contain dry natural rubber or natural rubber latex may be administered.

Reporting Adverse Events After Vaccination

Modern vaccines are safe and effective; however, adverse events have been reported after administration of all vaccines (3). More complete information about adverse reactions to a specific vaccine is available in the package insert for each vaccine and from CDC at <u>www.cdc.gov/vaccines/vac-gen/side-effects.htm</u>. An adverse event is an untoward event that occurs after a vaccination that might be caused by the vaccine product or vaccination process. These events range from common, minor, local reactions to rare, severe, allergic reactions (e.g., anaphylaxis). Reporting to VAERS helps establish trends, identify clusters of adverse events, or generate hypotheses. However, establishing evidence for cause and effect on the basis of case reports and case series alone is usually not possible, because health problems that have a temporal association with vaccination do not necessarily indicate causality. Many adverse events require more detailed epidemiologic studies to compare the incidence of the event among vaccinees with the incidence among unvaccinated persons. Potential causal associations between reported adverse events after vaccination can be assessed through epidemiologic or clinical studies.

The National Childhood Vaccine Injury Act of 1986 (1) requires health care personnel and vaccine manufacturers to report to VAERS specific adverse events that occur after vaccination. The reporting requirements are different for manufacturers and health care personnel. Manufacturers are required to report all adverse events that occur after vaccination to VAERS, whereas health-care providers are required to report events that appear in the reportable events table on the VAERS website at

https://vaers.hhs.gov/docs/VAERS_Table_of_Reportable_Events_Following_Vaccinat_ ion.pdf.

In addition to the mandated reporting of events listed on the reportable events table, health care personnel should report to VAERS all events listed in product inserts as contraindications, as well as all clinically significant adverse events, even if they are uncertain that the adverse event is related causally to vaccination (6). Persons other than health care personnel also can report adverse events to VAERS.

General information on VAERS is available at <u>https://vaers.hhs.gov/index.html</u>. Specific information for healthcare providers is available

at <u>https://vaers.hhs.gov/resources/infoproviders.html</u>. Reporting to VAERS is fully electronic and can be done using an online reporting tool or a writable PDF; instructions are available at <u>https://vaers.hhs.gov/reportevent.html</u>. Further assistance on VAERS reporting is available through email at <u>info@VAERS.org</u> and the VAERS toll free number 1-800-822-7967.

National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986 (1), is a no-fault system in which persons thought to have experienced an injury or to have died as a result of administration of a covered vaccine can seek compensation. The program became operational on October 1, 1988, and is intended as an alternative to civil litigation under the traditional tort system in that negligence need not be proven. Claims arising from covered vaccines must first be adjudicated through the program before civil litigation can be pursued.

The program relies on the Vaccine Injury Table, which lists the vaccines covered by the program and the injuries (including death), disabilities, illnesses, and conditions for which compensation might be awarded. The table defines the time during which the first symptom or substantial aggravation of an injury must appear after vaccination to be eligible. Successful claimants receive a legal presumption of causation if a condition listed in the table is proven, thus avoiding the need to prove actual causation in an individual case. Claimants also can prevail for conditions not listed in the reportable events table if they prove causation for covered vaccines.

Additional information is available from the Health Resources and Services Administration (HRSA at <u>https://www.hrsa.gov/vaccine-compensation/index.html</u> or by telephone at 800-338- 2382). Persons who would like to file a claim for vaccine injury should contact the U.S. Court of Federal Claims (717 Madison Place, N.W., Washington, DC 20005; telephone: 202-357-6400).

TABLE 5-1: Rapid overview: Emergent management of anaphylaxis in infants and children^(a) The most common signs and symptoms are cutaneous (e.g., sudden onset of generalized Diagnosis is urticaria, angioedema, flushing, pruritus). However, 10 to 20% of patients have no skin made findings. clinically: 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, vomiting, dysrhythmia, hypotension, collapse The first and most important therapy in anaphylaxis is epinephrine. There are NO absolute Acute contraindications to epinephrine in the setting of anaphylaxis. management: 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): Epinephrine 0.01 mg/kg should be injected intramuscularly in the mid-outer thigh. For large children (>50 kg), the maximum is 0.5 mg per dose. If there is no response or the response is inadequate, the injection can be repeated in 5 to 15 minutes (or more frequently). 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 L/minute via facemask or up to 100% oxygen, as needed. Normal saline rapid bolus: Treat poor perfusion with rapid infusion of 20 mL/kg. Reevaluate and repeat fluid boluses (20 mL/kg), 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/kg (minimum dose: 2.5 mg) in 3 mL saline inhaled via nebulizer. Repeat, as needed. H1 antihistamine: Consider giving diphenhydramine 1 mg/kg (max 50 mg) IV given over 5 minutes, or cetirizine (children age 6 months to 5 years can receive 2.5 mg IV, those 6 to 11 years of age can receive 5 or 10 mg IV, over 2 minutes). H2 antihistamine: Consider giving famotidine 0.25 mg/kg (max 20 mg) IV, over at least 2 minutes. Glucocorticoid: Consider giving methylprednisolone 1 mg/kg (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. Epinephrine infusion:^(b) In patients with inadequate response to IM epinephrine and IV saline, Treatment of give epinephrine continuous infusion at 0.1 to 1 mcg/kg/minute, titrated to effect. refractory Vasopressors:^(b) Patients may require large amounts of IV crystalloid to maintain blood symptoms: pressure. 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 and cardiac rate/function monitored continuously and oxygenation monitored by pulse oximetry IM: intramuscular; IV: intravenous. ^(a) A child is defined as a prepubertal patient weighing less than 40 kg. ^(b) 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.

Source: Campbell RL, Kelso JM. Anaphylaxis: Emergency treatment. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on December 9, 2021) Source: (37).

Table 5-2: Rapid overview: Emergency management of anaphylaxis in adults

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% 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), vomiting, 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
Promptly and simultaneously, give:	available. Cricothyrotomy may be necessary.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 (or more frequently), 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.Place patient in recumbent position, if tolerated, and
Adjunctive therapies:	 Place patient in recumbent position, it obstated, and elevate lower extremities. Oxygen: Give 8 to 10 L/minute via facemask or up to 100% 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. Albuterol (salbutamol): For bronchospasm resistant to IM epinephrine, give 2.5 to 5 mg in 3 mL saline via nebulizer. Repeat, as needed. H1 antihistamine:^(a) Consider giving cetirizine 10 mg IV (given over 2 minutes) diphenhydramine 25 to 50 mg IV (given over 5 minutes) (for relief of urticaria and itching only)
	 H2 antihistamine:^(a) Consider giving famotidine 20 mg IV (given over 2 minutes). Glucocorticoid:^(a) 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 ^(b) : For patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion, beginning at 0.1
	mcg/kg/minute by infusion pump(c). Titrate the dose continuously according to blood pressure, cardiac rate and function, and oxygenation.Vasopressors(b): 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 and cardiac rate/function and oxygenation monitored by pulse oximetry.

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	Glucagon: Patients on beta blockers may not respond to epinephrine and can be given glucagon 1 to 5 mg IV over 5 minutes, followed by infusion of 5 to 15 mcg/minute. Rapid administration of glucagon can cause vomiting.
Instructions on how to prepare and administer epinephrine for IV continuous infusions are available as	

Instructions on how to prepare and administer epinephrine for IV continuous infusions are available as separate tables in UpToDate.

IM: intramuscular; IV: intravenous.

^(a) These medications should not be used as initial or sole treatment.

^(b) All patients receiving an infusion of epinephrine and another vasopressor require continuous noninvasive monitoring of blood pressure, heart rate and function, and oxygen saturation.

^(c) For example, the initial infusion rate for a 70 kg patient would be 7 mcg/minute. This is consistent with the recommended range for non–weight-based dosing for adults, which is 2 to 10 mcg/minute. Non–weight-based dosing can be used if the patient's weight is not known and cannot be estimated.

Source: Campbell RL, Kelso JM. Anaphylaxis: Emergency treatment. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on December 9, 2021) **Source:** (*37*).

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