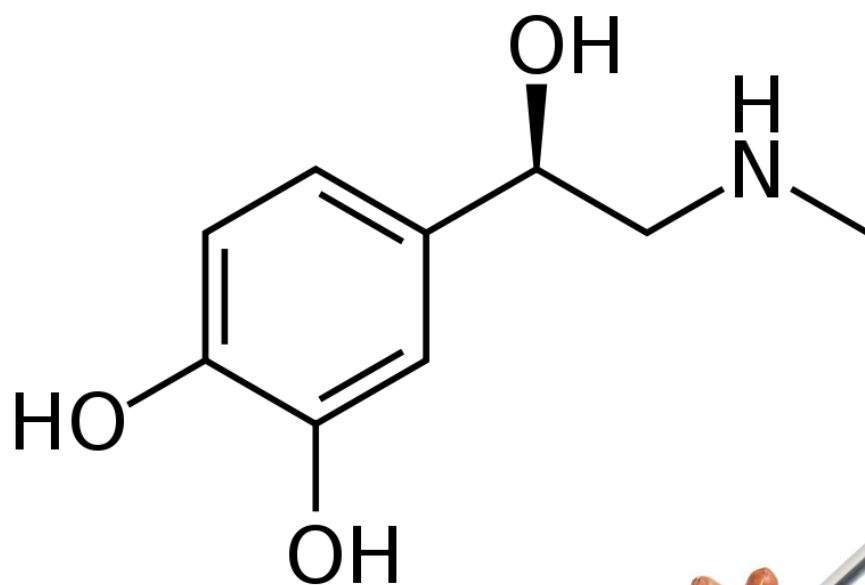


Epinephrine in Anaphylaxis





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“Seek simplicity, and mistrust it.”
Alfred North Whitehead



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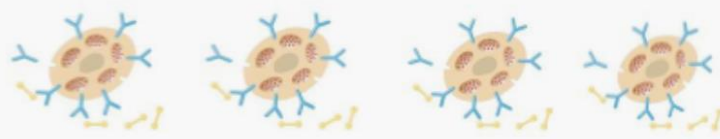


Introduction

- Anaphylaxis is a severe, life-threatening hypersensitivity reaction.
 - It is characterized by rapidly developing, life-threatening problems involving:
 - The airway (pharyngeal or laryngeal edema)
 - Breathing (bronchospasm with tachypnea)
 - Circulation (hypotension and/or tachycardia)
 - The gastrointestinal tract (nausea, vomiting, diarrhea)
 - In most cases, there are associated skin and mucosal changes.
- People who have had a mild or moderate allergic reaction are at risk of, and may subsequently present with anaphylaxis.
- Certain groups may be at higher risk, either because of an existing co-morbidity (e.g. asthma) or because they are more likely to be exposed to the same allergen again (e.g. people with venom allergies or reactions to specific food triggers).
- Fatalities do occur and reactions presenting with mild symptoms can rapidly progress to cardiovascular and respiratory arrest.
- Anaphylaxis may be an allergic response that is immunologically mediated, or a non-immunologically mediated response, or idiopathic. See Figure 1 page 5.
 - Certain foods, insect venoms, some drugs and latex are common precipitants of allergic anaphylaxis.
 - Food is a particularly common trigger in children, while medicinal products are more common triggers in older people.¹
 - Many drugs can also act through non-allergic mechanisms.
 - A significant proportion of anaphylaxis is classified as idiopathic, in which there is no readily identifiable cause.
- Reviews of epidemiological studies for anaphylaxis established that the lifetime prevalence of anaphylaxis is in the range of 0.05% to 2%.^{2,3}
 - Most data for the incidence of anaphylaxis has been derived from hospital databases; however, the exact incidence is difficult to estimate because anaphylaxis is not a reportable event and hospital coding systems for acute allergic reactions are not standardized.^{2,3}
 - It is widely believed that anaphylaxis is under-recognized and under-reported and that the incidence of anaphylaxis is increasing.^{3,4}



Figure 1: Anaphylaxis Triggers¹

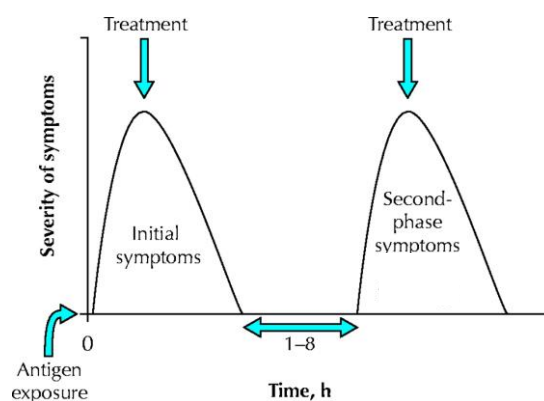
IMMUNOLOGIC MECHANISMS									
   									
PeanutTree NutShellfishFish					Stinging Insects		B-lactam antibiotics		
    							 		
MilkEggSoybeanPeachSesame							NSAIDsBiologic agents		
FOODS					VENOMS		MEDICATIONS		
									
Natural Rubber Latex		Occupational Allergen		Seminal Fluid		Aeroallergens		Radiocontrast Media	
NONIMMUNOLOGIC MECHANISMS									
									
Physical Factors (e.g. exercise, cold, heat)				Ethanol		Medications (e.g. opioids)			
IDIOPATHIC ANAPHYLAXIS									
									
PREVIOUSLY UNRECOGNIZED ALLERGEN				MASTOCYTOSIS/CLONAL MAST CELL DISORDER					

Adapted from the World Allergy Organization 2011



- Reactions may be immediate or delayed in onset (several hours later).
- Most anaphylactic reactions occur in a single phase (uniphasic) and generally resolve within 2 hours of treatment.
- Two phase anaphylactic reactions (biphasic) can occur where symptoms return 1 hour to 72 hours (most within 8 hours) after resolution of the initial phase. This occurs in the absence of a re-exposure to the anaphylaxis trigger.^{5,6}

Figure 2: Representation of biphasic anaphylactic reactions⁷



- The estimated prevalence of biphasic reactions is 1% to 20%.
 - The second phase of symptoms does not necessarily resemble the first and the severity could be equal to, less than or greater than the original reaction.⁵
 - One cohort study found that a delay in administration of epinephrine might predispose patients to a biphasic response while another cohort study reported that a decrease in epinephrine (total dose) was associated with biphasic reactions.⁶
 - Other cohort studies have not established that epinephrine treatment has an impact on the incidence of biphasic reactions.⁶



- American and International Guidelines specific to the assessment and treatment of anaphylaxis are available.

World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis: <http://www.worldallergy.org/anaphylaxis/>

Anaphylaxis – a practice parameter update 2015:

<https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/2015-Anaphylaxis-PP-Update.pdf>

Epinephrine for First-aid Management of Anaphylaxis

<http://pediatrics.aappublications.org/content/pediatrics/early/2017/02/09/peds.2016-4006.full.pdf>

Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology

<http://onlinelibrary.wiley.com/doi/10.1111/all.12437/abstract>

Define/diagnose anaphylaxis

- Anaphylaxis can sometimes be difficult to diagnose. The pattern (onset, number, and course) of signs and symptoms differs from one patient to another, and even in the same patient from one anaphylactic episode to another.
- The clinical criteria for diagnosing anaphylaxis according to treatment guidelines are presented in Table 1:^{1,8,9,10,11}



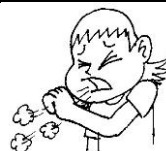
Table 1: Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:^{1,8,9,10,11}

1

Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucosal tissue or both (e.g. generalized hives, swollen tongue, lips or uvula, itching or flushing)



And at least one of the following:



Shortness of breath, wheeze, cough, stridor, hypoxemia



Sudden ↓ BP, collapse, fainting, incontinence

OR

2

Two or more of the following that occur suddenly after exposure to a likely allergen or trigger:



Hives, itching, flushing, swollen tongue, lips or uvula



Shortness of breath, wheeze, cough, stridor, hypoxemia



Sudden ↓ BP, collapse, fainting, incontinence

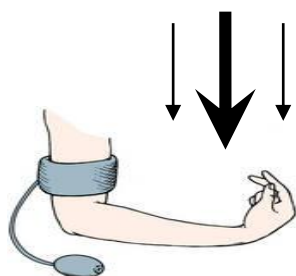


Sudden abdominal cramps, vomiting, diarrhea

OR

3

Rapid decrease in blood pressure (BP) after exposure to a known allergen for that patient (minutes to several hours):



Low systolic BP (definition age specific) or > 30% decrease from baseline systolic pressure.

Low systolic BP defined as

- < 70 mmHg from age 1 month to 1 year
- < 70 mmHg + [2 X age] from age 1 to 10 years
- < 90 mmHg from age 11

Other age specific notes:

- Normal heart rate (beats/min) is 80-140 at age 1-2 years; 80-120 at age 3 and 70-115 after age 3.
- In infants and children, respiratory compromise is more likely than hypotension or shock, and shock is more likely to be manifest initially by tachycardia than by hypotension.



- At the beginning of an episode, it can be difficult to predict the rate of progression or the ultimate severity.
 - Cardiorespiratory arrest from anaphylaxis occurs in a median time of 15 minutes from an insect sting and 30 minutes after ingestion of food to which the patient is sensitized.^{12,13}
 - Fatality can occur within minutes. **When in doubt treat!**
- Patient factors that increase the risk for an anaphylactic event, increase its severity or complicate its treatment include the following:
 - Age
 - The elderly are at increased risk because of co-morbidities (i.e. cardiovascular disease)¹³ and increased use of medications.
 - Infants are at high risk of complications because the manifestation of anaphylaxis may not be detected.
 - Teenagers are at risk because of “risky behaviour”.
 - Atopic Diseases (asthma, eczema and allergic rhinitis)
 - There is an association between the presence of atopic disease and the severity of allergic reactions.
 - The presence of asthma increases the risk of fatal anaphylactic events.^{14,15,16}
 - Drugs
 - Drugs may increase the severity of an anaphylactic reaction such as ACE inhibitors and beta-blockers.⁴⁸
 - Decreased vascular resistance occurs during anaphylaxis which leads to activation of the renin-angiotensin system. ACE inhibitors block this compensatory system, theoretically leading to intensified anaphylaxis.
 - Histamine release also increases cardiac rate, cardiac contractility and bronchoconstriction. Beta-blockers may mask cardiac signs of anaphylaxis and lead to unopposed alpha adrenergic activity causing severe bronchoconstriction.
 - Most of the medical literature evaluating the impact of ACE inhibitors and beta-blockers on the severity of anaphylaxis is limited to case reports or retrospective studies; however,
 - One prospective study in patients with Hymenoptera venom allergy found there was no statistical difference in the severity of venom allergy in patients taking cardiovascular medications (including ACE inhibitors and beta-blockers) versus those not taking cardiovascular medications.



- Drugs can complicate therapy by interfering with the action of epinephrine (e.g. beta-blockers).⁴⁸
 - The response to epinephrine during anaphylaxis may be reduced in patients treated with beta-blockers.
 - Higher doses of epinephrine may be needed to overcome beta-blockade; however, beta-blockade prevents vasodilation, leaving unopposed vasoconstriction that may result in a hypertensive reaction.
 - If epinephrine is ineffective in treating anaphylaxis in patients taking beta-blockers, then glucagon administration may be necessary.
- Food is a particularly common trigger in children, while medicinal products are more common triggers in older people.¹

Treatment

- The goal of therapy is early recognition of anaphylaxis and treatment with epinephrine to prevent progression to cardiorespiratory arrest.
- Initial management involves:
 - Removal of the trigger (if possible)
 - Immediately administer IM epinephrine
 - Call 911
 - Provide the ABCs of resuscitation (Airway, Breathing, and Circulation)
 - Place the patient in supine position with or without leg elevation. If breathing is difficult or they are vomiting place the patient on their side. Place pregnant patients on their left side.¹⁷
 - Do not change the position of the patient until symptoms have resolved.¹⁷
 - Vasodilation and increased capillary permeability result in reduced blood volume during an anaphylactic reaction. Compensatory mechanisms may maintain an adequate venous return when the patient is supine. However, moving a patient into an upright position can cause the venous return to stop leading to a lack of coronary artery perfusion which can result in cardiac arrest.

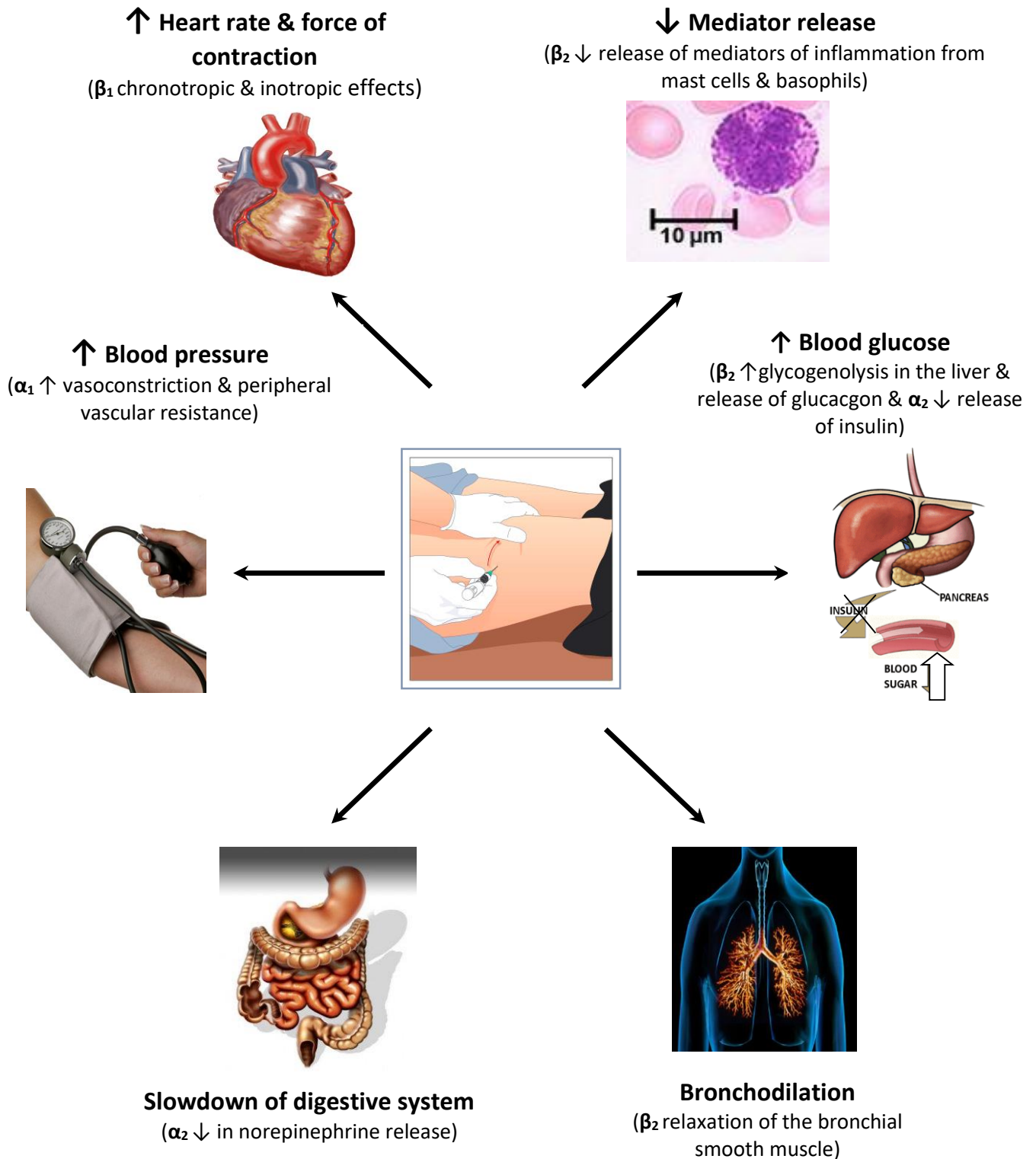


Epinephrine

- 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.
 - There are no prospective, randomized or quasi-randomized trials on the effectiveness of epinephrine for the management of anaphylaxis;^{18,19} however, based on its mechanism of action, epinephrine is the **only medication** that can **resolve** upper and lower respiratory tract edema, and prevent cardiovascular collapse.
 - The adrenergic effects of epinephrine are depicted in Figure 3.
- Epinephrine should also be administered to patients who have signs or symptoms consistent with impending anaphylaxis, and **the clinical suspicion for anaphylaxis is high, even if formal diagnostic criteria are not met.**¹⁰
 - Early administration is associated with improved survival. This is based on several retrospective database analyses.
 - These evaluations found the majority of anaphylactic fatalities were in patients who either did not receive epinephrine or received it late in the reaction.^{12,20,21,22}
 - One analysis also found that in the majority of patients with serious anaphylactic reactions (i.e. required intubation) who survived the event received epinephrine early in the reaction.²²
 - Epinephrine reduces the rate of hospitalization.
 - A retrospective chart review of 234 children who received epinephrine for food-induced anaphylaxis found that treatment with epinephrine prior to arrival to the emergency department was associated with a significantly lower risk of hospitalization.²³



Figure 3: The adrenergic effects of epinephrine





Route of Administration

- Intramuscular (IM) injection is the preferred route for initial administration of epinephrine for anaphylaxis in most settings and in patients of all ages.^{1,2,10,24,25}
- IM injection is recommended over subcutaneous injection because it consistently provides a more rapid increase in the plasma and tissue concentrations of epinephrine.
 - One prospective RCT in children with a history of anaphylaxis found
 - The time to maximum epinephrine concentrations was 8 ± 2 minutes after injection of 0.3 mg of epinephrine intramuscularly in the **vastus lateralis**.
 - The time to maximum plasma peak epinephrine concentration was 34 ± 14 minutes (range 5-120 minutes) after an injection of 0.01 mg/kg of epinephrine subcutaneously in the **deltoid region**.²⁷
 - A prospective RCT in adults with a history of anaphylaxis found peak plasma epinephrine concentrations were higher after epinephrine was injected intramuscularly into the thigh than after epinephrine was injected intramuscularly or subcutaneously into the upper arm.²⁸
- IM injection is also recommended over intravenous (IV) bolus because it is safer (i.e. lower risk of cardiovascular complications, such as severe hypertension, ventricular arrhythmias, or cardiogenic shock).
 - Serious adverse events have been described in adult patients with anaphylaxis who received overdoses of IV epinephrine (cardiac resuscitation doses of 1 mg of 1:10 000 IV push bolus was given), or when rapid IV infusions were given.^{24,25,29}
- If the anaphylactic reaction occurs as a result of immunization, administer IM into an unimmunized thigh site.³⁰

Dose of Epinephrine

- 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).^{1,10,11}
- The strength of epinephrine for IM injection is 1 mg/mL which is available in 1 mL ampoules. Historically these were labeled as 1:1000 but are now only labeled as 1 mg/mL.
- The dose should be drawn up using a **1 mL syringe** using the **1 mg/mL** formulation of epinephrine.



Table 2: Appropriate Dose of Epinephrine 1 mg/mL^{1,10,11,45}

Weight (kg)	Weight (lbs)	Dose (0.01 mg/kg to max 0.5 mg)	Volume of 1mg/mL solution	Auto Injector Dose ^a
5 - 10 kg	11 - 22 lbs	0.05 - 0.10 mg	0.05 - 0.10 mL	Off label ^b
10 - 14.5 kg	22 - 32 lbs	0.10 - 0.15 mg	0.10 - 0.15 mL	Off label ^b
15 - 20 kg	33 - 44 lbs	0.15 - 0.20 mg	0.15 - 0.20 mL	0.15 mg
20 - 25 kg	44 - 55 lbs	0.20 - 0.25 mg	0.20 - 0.25 mL	0.15 mg
25 - 30 kg	55 - 66 lbs	0.25 - 0.30 mg	0.25 - 0.30 mL	0.15 or 0.3 mg
30 - 40 kg	66 - 88 lbs	0.30 - 0.40 mg	0.30 - 0.40 mL	0.3 mg
40 - 50 kg	88 - 110 lbs	0.40 - 0.50 mg	0.40 - 0.50 mL	0.3 mg
50 + kg	110+ lbs	0.50 mg	0.50 mL	0.3 mg

a. Auto Injectors are currently only available in two doses: 0.15 mg/dose and 0.3 mg/dose.

b. The Canadian Society for Allergy and Clinical Immunology suggest for the infant less than 15 kg, the potential consequences of not administering epinephrine to a child with anaphylaxis outweigh the potential consequences of administering higher than recommended doses of epinephrine.

- Infants and small children weighing <15 kg should be given **an exact weight based dose** (not estimated), whenever possible.
 - If drawing up an **exact dose** will cause delay in a rapidly deteriorating patient, the administration of a 0.15 mg via an auto-injector may be considered.
 - The Canadian Society for Allergy and Clinical Immunology suggest for the infant less than 15 kg the potential consequences of not administering epinephrine to a child with anaphylaxis outweigh the potential consequences of administering higher than recommended doses of epinephrine.³¹



Practice Points:

Anaphylaxis can sometimes be difficult to diagnose.

- The signs and symptoms of an anaphylactic reaction can vary from one event to another, even in the same patient.
- Always consider uncommon triggers when evaluating a patient for anaphylaxis.
- There are no absolute contraindications to epinephrine.
- **When in doubt treat!**

The **appropriate treatment** of an acute anaphylactic event requires planning and preparation.

- Where is your epinephrine?
- What needle do you have with it?
- What is the expiry date of your epinephrine?

Plan for an appropriate response to anaphylaxis by:

- Educating all staff (including administrative staff) on the signs and symptoms of anaphylaxis
- Preparing an anaphylaxis emergency kit
- Developing an office action plan for anaphylaxis management to maintain proficiency

Sample Anaphylaxis Kit:

- 3 x 1 mL ampoules of epinephrine 1 mg/mL aqueous solution
- 3 x 1 mL syringe with safety needle (25 gauge, 1"). **Note:** Consider the size of needle to be included in the kit based on the medical practice. A 1.5" needle may be required in obese patients. A 5/8" needle is too short for IM administration
- Extra syringes and needles
- Alcohol swabs
- Cotton swabs or bandage

Inject epinephrine **IM** into the **mid outer thigh** (vastus lateralis muscle).

- If the anaphylactic reaction occurs as a result of immunization, administer IM into an unimmunized thigh site.



How Many Doses?

- Most patients respond to a single dose of IM epinephrine, particularly if it is given promptly after the onset of symptoms.^{32,33,34,35,36}
- IM epinephrine results in increased serum levels for approximately 1 hour.
- 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).^{4,10,26,42}
- When additional IM doses are required, typically one or rarely two additional doses are needed (e.g. in patients with severe anaphylaxis and those who cannot access emergency care promptly).^{32,33,34,35,36}
 - Retrospective studies indicate that a second dose is necessary in 12% - 36% of cases.^{33,34,36,37}
 - In an observational cohort study, 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.³⁵

What to do after Epinephrine?

- When epinephrine is administered out of hospital, contact 911, and the patient should be taken to a hospital for further evaluation.^{1,5,10,11}
- Epinephrine is always first line in the treatment of anaphylaxis.^{1,5,10,11}
- H1-antihistamines (e.g. diphenhydramine, fexofenadine, cetirizine), H2-antihistamines (e.g. ranitidine) and inhaled beta 2- agonists (e.g. salbutamol) **may** be considered as optional or adjunctive therapy to manage symptoms only, **after** the use of epinephrine.
 - H1-antihistamines, H2-antihistamines, corticosteroids, and inhaled beta-2 agonists **have not been shown to reverse anaphylaxis**. These medications should not be used as the sole treatment of anaphylaxis because they do not relieve upper or lower respiratory tract obstruction, hypotension or shock.
 - Two systematic reviews failed to find any RCT evidence for H1-antihistamines and corticosteroids and concluded there is no evidence to support their use in the emergency management of anaphylaxis.^{38,39}



- The onset of antihistamines and corticosteroids are slow compared to epinephrine.
 - For example, the time to 50% reduction in histamine-induced flare is 52 minutes for IM diphenhydramine, 80 minutes for oral diphenhydramine, and 101 minutes for oral fexofenadine.⁴⁰
- Corticosteroids have historically been used in the treatment of anaphylaxis based upon the theory that they may prevent or reduce the later inflammatory changes that follow.
 - An observational study of emergency department patients with anaphylaxis or allergy found that corticosteroid use was **not associated** with a decrease in relapses or the need for additional care including biphasic reactions.⁴¹

IM dosing fails...what next?

- If there has been no response or an insufficient response after 3 to 4 IM doses, moving to IV administration of epinephrine in an emergency setting where continuous monitoring can be performed is required.⁵
 - A cause of this problem is that the patient may be hypotensive or the patient may be in vasogenic shock.

Adverse effects of IM epinephrine

- Epinephrine in therapeutic doses when administered by any route can cause mild transient adverse effects such as pallor, tremor, dizziness, anxiety, restlessness, headache and palpitations.^{26,42}
 - These symptoms are similar to those that occur in response to endogenous epinephrine during the physiologic “fight or flight” response.
 - These symptoms indicate that a **therapeutic dose has been given**.
- Serious adverse effects may occur which include ventricular arrhythmias, hypertensive crisis and pulmonary edema.
 - The pharmacologic effect of epinephrine with the increase in vasoconstriction, vascular resistance, heart rate and force of contraction may be detrimental in patients with heart disease. However;
 - Serious adverse effects are rare and occur most often following an IV bolus injection, especially if inappropriately large doses are administered.^{24,25,29,43}
 - Anaphylaxis itself can lead to angina, myocardial infarction and cardiac arrest in the absence of exogenous epinephrine. There are abundant mast cells in the human heart and the mediators of anaphylaxis can produce coronary artery vasospasm and infarction can occur as part of the natural history of an anaphylactic reaction.⁴⁴



- There are no absolute contraindications to epinephrine administration in anaphylaxis.

Care following an anaphylactic event

Observation

- After the treatment of an acute anaphylactic reaction an observation period should be considered because the reaction might re-occur when the effect of epinephrine wears off, and because of the risk of biphasic reactions.⁸
 - There are no reliable predictors to identify patients at increased risk of a biphasic reaction.
- There is **no consensus** about the optimal observation period following successful treatment of anaphylaxis. Often the severity of the initial anaphylactic reaction is used to determine the duration of observation. Recommendations generally range from 4 hours to 8 hours.^{5,10}
- Longer durations of observation should be considered if there are risk factors for more severe anaphylaxis (e.g. history of severe asthma), the allergens have been ingested, more than one dose of epinephrine was required, pharyngeal edema is present and severe or prolonged symptoms are noted (e.g. prolonged wheezing or hypotension).^{5,10}
- If the duration of observation is only a few hours, patients should have at least one auto-injector with them and should be instructed to fill their prescription immediately upon leaving the medical facility.
- Patients should be informed that there is a possibility of a recurrent reaction up to 3 days following the initial reaction and should stay close to a hospital during that time.⁶

Anaphylaxis Emergency Action Plan

- Patients who have experienced an anaphylactic reaction should be prescribed self-injectable epinephrine and should have an emergency action plan detailing its use and follow up management.^{5,10,11}
- Patients at an increased risk for anaphylaxis should be educated on the signs and symptoms of anaphylaxis as subsequent events may present differently.^{1,5,10,11}
- Patients should receive information on how to avoid the inciting allergen.^{1,5,10,11}
- All patients should be instructed on how and when to use the auto-injector.^{1,5,10,11}



- All patients should be instructed to obtain medical identification jewelry identifying risk for anaphylaxis. ^{1,5,10,11}

Epinephrine Auto-injector

- People at risk of anaphylaxis in the community need to be equipped and trained to self-inject epinephrine. ^{1,5,10,11}
- Fixed doses of epinephrine are available as auto-injectors in two doses, 0.15 mg and 0.3 mg.
 - The Canadian Society for Allergy and Clinical Immunology recommend prescribing the 0.15 mg epinephrine auto-injector for children weighing less than 15 kg. ³¹
 - European guidelines, the Canadian Pediatric Society and the American Academy of Pediatrics recommend the use of the 0.15 mg epinephrine auto-injector for children weighing 7.5 kg to 25 kg. ^{11,45}
 - Children can be switched to the 0.3 mg auto-injector dose when they weigh 25 kg - 30 kg. ^{11,45,46}
 - Patients weighing between 30 and 50 kg can be given 0.3 mg by auto-injector. ⁴⁷
- Epi-pen is the only auto-injector **currently** available in Canada. Patient information for the use of the Epi-pen auto-injector is as follows. ⁴⁷
 - Use the auto-injector at the first sign of a severe allergic reaction.
 - Epi-Pen is administered by
 - Holding the device with the orange tip pointing down and removing the blue safety cap by pulling straight up without bending or twisting.
 - Swing and push the orange tip firmly into the mid outer thigh until a click is heard.
 - Hold for several seconds
 - Epi-pen may be administered through clothing if necessary
 - Pull straight out of the thigh
 - The orange needle cover will extend to cover the needle. The needle is not visible before, during, or after use.
 - An extended orange needle cover along with a black indicator in a window on the device will show that the Epi-pen has delivered its epinephrine.
 - If an auto-injector is administered **call 911** as the effects of epinephrine may wear off or a second reaction can occur.
 - If the reaction continues or symptoms return before medical attention is received another dose can be administered until the symptoms stop.



- Bring used auto-injectors to the hospital to give to a health care provider for inspection and disposal.
- Get a new prescription for an auto-injector before leaving the hospital.
- After getting medical attention stay close to a hospital for the next 48 hours.
- Patients should make sure the color of the liquid within the injector remains clear (discard if not clear), and know when it expires.⁴⁷
- Epinephrine auto-injectors are the preferred method of administering epinephrine due to ease of use and accuracy of dosing.^{1,5,10,11}
 - Ampoules and syringes may be considered by a physician and patient/family as a reasonable compromise in the event an epinephrine auto-injector is cost prohibitive. When this method is chosen it is important that patients/families are appropriately trained.¹

Counselling and referral to an allergy specialist

- Provide the patient with information on how to obtain identification pertaining to their risk for anaphylaxis, either as identification jewelry or an anaphylaxis wallet card.^{1,5,10}
- Refer patient to an allergy specialist to identify anaphylaxis triggers.^{5,10,11}
- Regular follow up visits (i.e. yearly) are ideal to review self-injection of epinephrine and to discuss allergen avoidance strategies.¹



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