



Emergency Medical Training Services

Emergency Medical Technician – Paramedic Program Outlines

Outline Topic: Allergic Glucagon

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A student asked why give Glucagon to an severe allergic reaction if the patient is on a beta-blocker. What is the connection?

- Glucagon. Understanding the role of glucagon in anaphylaxis requires knowledge of specific cellular biochemistry. Cyclic adenosine monophosphate (cAMP) is a nucleotide (protein molecule) that plays an important role in many biological processes. Located in the cell's fluid, cAMP is a secondary messenger, which means it relays a signal in the cell to transfer effects for a specific hormone. When a large amount of cAMP is produced in the cell's fluid, hormones such as epinephrine or glucagon work more effectively.

Epinephrine acts on beta-2 receptor sites of smooth muscles in the airways. When the beta-2 receptors are stimulated, cAMP is produced, relaxing the smooth muscle cells and opening the airways. If a patient is currently taking a beta blocking agent—especially a noncardioselective type, such as propranolol, naldolol, or sotalol—epinephrine may not effectively utilize beta-2 receptors. In these cases, cAMP is not produced, the bronchial smooth muscle cannot relax, and the patient's airway remains compromised. To achieve bronchodilation and subsequent effective air exchange in a patient on beta blockers, 1 mg of IM or IV glucagon may be administered. Glucagon works by stimulating higher cAMP levels and overrides the alpha and beta receptors so that epinephrine does not require those receptor pathways to work. Glucagon has documented positive inotropic and chronotropic effects on the heart.

Patients treated with glucagon require close monitoring of their blood glucose levels because glucagon elevates serum glucose. Although current research has not directly studied its effects in anaphylaxis, glucagon acts independently of alpha and beta receptors and can counteract the systemic effects of anaphylaxis. Emergency care providers should consider glucagon therapy when treating the anaphylactic patient who is taking a beta blocker or is refractory to epinephrine.

This is some more information found on-line regarding allergic reactions. Read if interested.

Background: Anaphylaxis refers to a severe allergic reaction in which prominent dermal and systemic signs and symptoms manifest. The full-blown syndrome includes urticaria (hives) and/or angioedema with hypotension and bronchospasm. The classic form, described in 1902, involves prior sensitization to an allergen with later re-exposure, producing symptoms via an immunologic mechanism. An anaphylactoid reaction produces a very similar clinical syndrome but is not immune-mediated. Treatment for both conditions is similar, and this article uses the term anaphylaxis to refer to both conditions unless otherwise specified.

Pathophysiology: Rapid onset of increased secretion from mucous membranes, increased bronchial smooth muscle tone, decreased vascular smooth muscle tone, and increased capillary permeability occur after exposure to an inciting substance. These effects are produced by the release of mediators, which include histamine, leukotriene C4, prostaglandin D2, and tryptase.

In the classic form, mediator release occurs when the antigen (allergen) binds to antigen-specific immunoglobulin E (IgE) attached to previously sensitized basophils and mast cells. The mediators are released almost immediately when the antigen binds. In an anaphylactic reaction, exposure to an inciting substance causes direct release of mediators, a process that is not mediated by IgE. Increased mucous secretion and increased bronchial smooth muscle tone, as well as airway edema, contribute to the respiratory symptoms observed in anaphylaxis. Cardiovascular effects result from decreased vascular tone and capillary leakage. Histamine release in skin causes urticarial skin lesions.

The most common inciting agents in anaphylaxis are parenteral antibiotics (especially penicillins), IV contrast materials, Hymenoptera stings, and certain foods (most notably, peanuts). Oral medications and many other types of exposures also have been implicated. Anaphylaxis also may be idiopathic.

Frequency:

- In the US: The true incidence of anaphylaxis is unknown, partly because of the lack of a precise definition of the syndrome. Some clinicians reserve the term for the full-blown syndrome, while others use it to describe milder cases. Fatal anaphylaxis is relatively rare; milder forms occur much more frequently. Some authors consider up to 15% of the US population "at risk" for anaphylaxis. The frequency of anaphylaxis is increasing and this has been attributed to the increased number of potential allergens to which people are exposed. Up to 500-1,000 fatal cases of anaphylaxis per year are estimated to occur in the US.
- Internationally: Reactions to insects and other venomous plants and animals are more prevalent in tropical areas because of the greater biodiversity in these areas.

Mortality/Morbidity: Approximately 1 in 5000 exposures to a parenteral dose of a penicillin or cephalosporin antibiotic causes anaphylaxis. More than 100 deaths per year are reported in the United States. Fewer than 100 fatal reactions to Hymenoptera stings are reported each year in the United States but this is considered to be an underestimate. 1 to 2% of people receiving IV radiocontrast experience some sort of reaction. The majority of these reactions are minor, and fatalities are rare. Low molecular weight contrast causes fewer and less severe reactions.

Race: Well-described racial differences in the incidence or severity of anaphylaxis do not exist. Cultural and socioeconomic differences may influence exposure rates.

Sex: No major differences have been reported in the incidence and prevalence of anaphylactic reactions between men and women.

Age: Anaphylaxis occurs in all age groups. While prior exposure is essential for the development of true anaphylaxis, reactions occur even when no documented prior exposure exists. Thus, patients may react to a first exposure to an antibiotic or insect sting. Adults are exposed to more potential allergens than are pediatric patients. The elderly have the greatest risk of mortality from anaphylaxis due to the presence of preexisting disease.

History:

- Anaphylactic reactions almost always involve the skin or mucous membranes. More than 90% of patients have some combination of urticaria, erythema, pruritus, or angioedema.
- The upper respiratory tract commonly is involved, with complaints of nasal congestion, sneezing, or coryza. Cough, hoarseness, or a sensation of tightness in the throat may presage significant airway obstruction.
- Eyes may itch and tearing may be noted. Conjunctival injection may occur.

- Dyspnea is present when patients have bronchospasm or upper airway edema. Hypoxia and hypotension may cause weakness, dizziness, or syncope. Chest pain may occur due to bronchospasm or myocardial ischemia (secondary to hypotension and hypoxia).
- GI symptoms of cramplike abdominal pain with nausea, vomiting, or diarrhea also occur but are less common, except in the case of food allergy.
- In a classic case of anaphylaxis, the patient or a bystander provides a history of possible exposures that may have caused the rapid onset of skin and other manifestations. This history often is partial; exposure may not be recalled, or it may not be considered significant by the patient or physician. For example, when queried about medications, a patient may not mention over-the-counter (OTC) products. The clinician may not realize that, while reactions are usually rapid in onset, they also may be delayed.

Physical:

- General
- Physical examination of patients with anaphylaxis depends on affected organ systems and severity of attack. Vital signs may be normal or significantly disordered with tachypnea, tachycardia, and/or hypotension.
- Place emphasis on determining the patient's respiratory and cardiovascular status.

- Frank cardiovascular collapse or respiratory arrest may occur in severe cases. Anxiety is common unless hypotension or hypoxia causes obtundation. Shock may occur without prominent skin manifestations or history of exposure; therefore, anaphylaxis is part of the differential diagnosis for patients who present with shock and no obvious cause
- General appearance and vital signs vary according to severity of attack and affected organ system(s). Patients commonly are restless due to severe pruritus from urticaria. Anxiety, tremor, and a sensation of cold may result from compensatory endogenous catecholamine release. Severe air hunger may occur when the respiratory tract is involved. If hypoperfusion or hypoxia occurs, the patient may exhibit a depressed level of consciousness or may be agitated and/or combative. Tachycardia usually is present, but bradycardia may occur in very severe reactions.
- Skin
- The classic skin manifestation is urticaria (ie, hives). Lesions are red and raised, and they sometimes have central blanching. Intense pruritus occurs with the lesions. Lesion borders usually are irregular and sizes vary markedly. Only a few small or large lesions may become confluent, forming giant urticaria. At times, the entire dermis is involved with diffuse erythema and edema. Hives can occur anywhere on the skin.
- In a local reaction, lesions occur near the site of a cutaneous exposure (eg, insect bite). The involved area is erythematous, edematous, and pruritic. If only local skin reaction (as opposed to generalized

urticaria) is present, systemic manifestations (eg, respiratory distress) are less likely. Local reactions, even if severe, are not predictive of systemic anaphylaxis on re-exposure.

- Lesions typical of angioedema also may manifest in anaphylaxis. The lesions involve mucosal surfaces and deeper skin layers. Angioedema usually is nonpruritic and associated lesions are nonpitting. Lesions most often appear on the lips, palms, soles, and genitalia.
- Pulmonary
- Upper airway compromise may occur when the tongue or oropharynx is involved. When the upper airway is involved, stridor may be noted. The patient may have a hoarse or quiet voice and may lose speaking ability as the edema progresses. Complete airway obstruction is the most common cause of death in anaphylaxis.
- Wheezing is common when patients have lower airway compromise due to bronchospasm or mucosal edema.
- In angioedema, due to ACE inhibitors, marked edema of the tongue and lips may obstruct the airway
- Cardiovascular
- Cardiovascular examination is normal in mild cases. In more severe cases, compensatory tachycardia occurs due to loss of vascular tone.
- Intravascular volume depletion may take place as a consequence of capillary leakage. These mechanisms also lead to development of hypotension.

- Relative bradycardia has been reported.

Causes:

- A wide variety of substances can cause anaphylaxis. Anaphylaxis also may be idiopathic.
- In the classic form of anaphylaxis, a foreign protein is the inciting agent (eg, antigen). On initial exposure, the antigen elicits generation of an IgE antibody. The antibody residue binds to mast cells and basophils. On re-exposure, the antigen binds to the antibody, and the receptors are activated. Clinical manifestations result from release of immune response mediators such as histamine, leukotriene's, tryptase, and prostaglandins. The same mechanism occurs when a non immunogenic foreign substance binds as a so-called hapten to a native carrier protein, creating an immunogenic molecule. Factors influencing severity of a reaction include degree of host sensitivity and dose, route, and rate of administration of the offending agent.
- Parenteral exposures tend to result in faster and more severe reactions. Most severe reactions occur soon after exposure. The faster a reaction develops, the more severe it is likely to be. While most reactions occur within hours, symptoms may not occur for as long as 3-4 days after exposure.
- Drugs
- Penicillin and cephalosporin antibiotics are the most commonly reported medical agents in anaphylaxis. This prevalence is a function of the immunogenicity and overuse of these agents. Because of their

molecular and immunologic similarity, cross-sensitivity may exist. Reports often assert that 10% of patients allergic to a penicillin antibiotic are allergic to cephalosporins. A recent report suggests that actual incidence of cross-reactivity is lower (perhaps 1%), with most reactions considered mild. A more recent review indicated that patients with a history of allergy to penicillin seem to have a higher risk (by a factor of about 3) of subsequent reaction to any drug and that the risk of an allergic reaction to cephalosporins in patients with a history of penicillin allergy may be up to 8 times as high as the risk in those with no history of penicillin allergy (ie, at least part of the observed "cross reactivity" may represent a general state of immune hyperresponsiveness, rather than true cross-reactivity).

- Reactions tend to be more severe and rapid in onset when the antibiotic is administered parenterally.
- Anaphylaxis may occur in a patient with no prior history of drug exposure.
- History of penicillin or cephalosporin allergy often is unreliable and is not predictive of future reactions.

Up to 85% of patients reporting an allergic reaction to penicillin do not react on subsequent exposure.

When a drug in either class is the drug of choice for a patient with a life-threatening emergency, a number of options exist. When the history is indefinite, the drug may be administered under close observation; however, when possible, obtain the patient's informed consent. Immediate treatment measures for anaphylaxis should be available. Alternatively, when the history is more convincing, a desensitization or prophylactic pretreatment protocol may be instituted or another agent selected.

- Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) commonly are implicated in allergic reactions and anaphylaxis. Bronchospasm is common in patients with reactive airway disease and nasal polyps. Cross-reactivity may occur between the various NSAIDs.
- Intravenous radiocontrast media
- IV administered radiocontrast media causes an anaphylactoid reaction that is clinically identical to true anaphylaxis and is treated in the same way. The reaction is not related to prior exposure. Shellfish or "iodine allergy" is not a contraindication to use of IV contrast and does not mandate a pretreatment regimen. As with any "allergic" patient, give consideration to use of low molecular weight (LMW) contrast.
- The term iodine allergy is a misnomer. Iodine is an essential trace element present throughout the body. No one is allergic to iodine. Patients who report iodine allergy usually have had either a prior contrast reaction or a shellfish allergy. Manage these patients as indicated earlier.
- Approximately 1-3% of patients who receive hyperosmolar IV contrast experience a reaction. Use of LMW contrast decreases incidence of reactions to approximately 0.5%. Personnel, medications, and equipment needed for treatment of allergic reactions always should be available when these agents are administered. Obtain consent before administration.
- Reactions to radiocontrast usually are mild (most commonly urticarial), with only rare fatalities reported. Risk of a fatal reaction has been estimated at 0.9 cases per 100,000 exposures.

- Mucosal exposure (eg, GI, genitourinary [GU]) to radiocontrast agents has not been reported to cause anaphylaxis; therefore, a history of prior reaction is not a contraindication to GI or GU use of these agents.
- Pretreatment with antihistamines or corticosteroids and use of LMW agents lead to lower rates of anaphylactoid reactions to IV contrast. Consider these measures for patients who have prior history of reaction, since rate of recurrence is estimated at 17-60%. Patients who are atopic and/or asthmatic also are at increased risk of reaction. In addition, allergic reaction is more difficult to treat in those taking beta-blockers.
- Hymenoptera stings
- Hymenoptera stings are a common cause of allergic reaction and anaphylaxis. An uncertain but enormous number of exposures occur; accurate reaction rates are difficult to estimate. In the United States, Hymenoptera envenomations result in fewer than 100 reported deaths per year.
- Local reaction and urticaria without other manifestations of anaphylaxis are much more common than full-blown anaphylaxis. Generalized urticaria is a risk factor for subsequent anaphylaxis; but a local reaction, even if severe, is not a risk factor for anaphylaxis.
- Caution patients treated and released from the ED after an episode of anaphylaxis or generalized urticaria from Hymenoptera envenomation to avoid future exposure when possible. Consider referral to an allergist for desensitization, particularly when further exposure is likely. Additionally, consider

prescribing a treatment kit with an epinephrine auto-injector and oral antihistamine. Both are effective measures in preventing or ameliorating future reactions.

- Allergies
- Food allergy is common. Symptoms usually are mild and limited to the GI tract, but full-blown anaphylaxis can occur. Fatalities are rare compared to number of exposures; however, the number of exposures is so high that foods may be the commonest cause of anaphylaxis. Anaphylaxis due to foods may be an underrecognized cause of sudden death and an unappreciated cause of diagnosed anaphylaxis. Commonly implicated foods include nuts (especially peanuts), legumes, fish and shellfish, milk, and eggs.
- Latex allergy is an increasingly recognized problem in medical settings, where use of gloves and other latex products is ubiquitous. Most reactions are cutaneous or involve the mucous membranes. Anaphylactic reactions occur and have been reported with seemingly benign procedures (eg, Foley catheter insertion, intraperitoneal exposure to gloves during surgery).

Prehospital Care:

- Prehospital patients with symptoms of severe anaphylaxis should first receive standard interventions. Interventions include high-flow oxygen, cardiac monitoring, and IV access. These measures are appropriate for an asymptomatic patient who has a history of serious reaction and has been re-exposed

to the inciting agent. Additional treatment depends upon the condition of the patient and the severity of the reaction. Measures beyond basic life support (BLS) are not necessary for patients with purely local reactions.

- Immediately assess airway patency due to the potential for compromise secondary to edema or bronchospasm. Active airway intervention may be difficult due to laryngeal or oropharyngeal edema. In this circumstance, it may be preferable to defer intubation attempts, and instead ventilate with a bag/valve/mask apparatus while awaiting medications to take effect. In extreme circumstances, cricothyrotomy or catheter jet ventilation may be lifesaving. Inhaled beta-agonists are used to counteract bronchospasm and should be administered to patients who are wheezing
- The IV line should be of large caliber due to the potential requirement for large-volume IV fluid resuscitation. Isotonic crystalloid solutions (ie, normal saline, Ringer lactate) are preferred. A keep vein open (KVO) rate is appropriate for patients with stable vital signs and only cutaneous manifestations. If hypotension or tachycardia is present, administer a fluid bolus of 20 mg/kg for children and 1 L for adults. Further fluid therapy depends on patient response. Large volumes may be required in the profoundly hypotensive patient.
- Administer epinephrine to patients with systemic manifestations of anaphylaxis. With mild cutaneous reactions, an antihistamine alone may be sufficient, thus the potential adverse effects of epinephrine can be avoided. Patients on beta-blocker medications may not respond to epinephrine. In these cases,

glucagon may be useful. The Medication section describes dosage, routes of administration, and contraindications for medications discussed in this section. Antihistamines (eg, H1 blockers), such as diphenhydramine (Benadryl) are important and should be administered for all patients with anaphylaxis or generalized urticaria.

- Corticosteroids are used in anaphylaxis primarily to decrease the incidence and severity of delayed or biphasic reactions. Corticosteroids may not influence the acute course of the disease; therefore, they have a lower priority than epinephrine and antihistamines.

Emergency Department Care:

- ED care begins with standard monitoring and treatment, including oxygen, cardiac monitoring, and a large-bore IV with isotonic crystalloid solution. Further intervention depends on severity of reaction and affected organ system(s).
- Rapidly assess airway patency in patients with systemic signs or symptoms. If required, intubation may be difficult to achieve because of upper airway or facial edema. Standard rapid sequence induction (RSI) techniques can be used but may cause loss of the airway in a patient whose airway anatomy is altered by edema. Epinephrine may rapidly reverse airway compromise, and bag/valve/mask ventilation may be effective in the interim when intubation is not possible. Surgical airway intervention using standard cricothyrotomy is an option when orotracheal intubation or bag/valve/mask ventilation is not effective.

- Wheezing or stridor indicates bronchospasm or mucosal edema. Treatment with epinephrine and inhaled beta-agonists is effective for these indications.
- Recommendations to treat refractory bronchospasm with corticosteroids have been made because of their effectiveness in reactive airway disease. As in asthma therapy, onset of action is delayed for several hours. Aminophylline also has been recommended for bronchospasm in anaphylaxis and may be more rapidly effective than corticosteroids.
- Hypotension in anaphylaxis usually is due to vasodilatation and capillary fluid leakage. Epinephrine is the primary pharmacologic treatment for these findings. H1-blocking antihistamines also may have a role in reversing hypotension. Some authors also recommend H2-blocking agents. Large volume fluid resuscitation with isotonic crystalloid often is needed to support the circulation in patients with cardiovascular manifestations of anaphylaxis.
- Refractory hypotension first should be treated with large volumes of crystalloid and repeated doses of epinephrine or a continuous epinephrine infusion. If this is not effective, other pressors with alpha-adrenergic activity, such as levarterenol (Levophed) or dopamine, may be considered. Cases of effective use of military antishock trousers (MAST) for refractory hypotension have been reported.
- Mediators of anaphylaxis are not considered to have direct myocardial toxicity. In patients with preexisting heart disease, ischemic myocardial dysfunction may occur due to hypotension and hypoxia. Epinephrine still may be necessary in patients with severe anaphylaxis, but remember the potential for

exacerbating ischemia. If pulmonary congestion or evidence of cardiac ischemia is present, fluid

resuscitation should be approached more cautiously.

- Patients taking beta-blockers may be resistant to the effects of epinephrine. Larger than usual doses may be needed. Glucagon may be effective in this circumstance, because it increases intracellular cyclic adenosine monophosphate (cAMP) levels by a mechanism that does not depend upon beta-receptors.
- Cutaneous effects of anaphylaxis are uncomfortable but not life threatening. Patients often respond promptly to epinephrine and H1 antihistamines. Some authors state that corticosteroids help prevent recurrence of symptoms (both cutaneous and systemic) that may occur 6-8 hours after successful treatment (so-called biphasic reaction). H2 blockers may have an added effect.
- GI symptoms in anaphylaxis respond to H1 antihistamines and epinephrine.