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Acute anafylaxie en quincke oedeem.

Dr. T. Issaev
Spoedarts

Definition: Anaphylaxis

Life-threatening systemic or hypersensitivity **reaction** with **sudden onset**. (1)

1) World Allergy organization.

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Anaphylaxis

History

- First death from anaphylaxis in 2641 BC (Pharaon Menes)

Figure 1. Detail from plate no. 1. The 'wasp' appears as a semi circle on the bottom left (6).

Figure 2. Detail from plate no. 2. The bottom of the plate is better preserved. Three 'wasps' are now seen (6).

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Anaphylaxis

History

- First described in the modern medical literature in 1902 by two French physiologist, Charles Richet and Paul Portier
  - Involving protocols fot immunizing dogs with jellyfish toxin
  - Rapid onset of fatal or near-fatal symptoms

- "L'anaphylaxie" a- against and phylaxis - protection

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Anaphylaxis

We don ’t know.

- Who
- Predictability
- Prognosis

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Anaphylaxis

We know that…

- Diagnosis
- Epinephrine
- Biphasic

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Anaphylaxis

Terminology

- “Anaphylaxis” for Ig E-dependent events
- “Anaphylactoid reaction” for Ig E-independent events

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Anaphylaxis

Terminology

- Immunologic
  - IgE-mediated reaction
  - IgG-mediated reaction
  - Immune complex/complement-mediated reaction

- Non-immunologic

Caused by agents or events that induce sudden, massive mast cell or basophil degranulation in the absence of immunoglobulins.

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Anaphylaxis

Causes

Causes of anaphylaxis

Allergens (IgE-dependent immunologic mechanism)
Foods, especially peanut, tree nut, crustacean shellfish, finned fish, milk, egg
Insect stings (eg, Hymenoptera venom) and insect bites (eg, kissing bugs)
Medications (eg, antibiotics, NSAIDs)
Biologic materials, including allergen immunotherapy, monoclonal antibodies, chemotherapy agents, and vaccines*
Natural rubber latex
Food additives, including spices, insect-derived colorants (eg, carmine), and vegetable gums
Inhalants (rare) (eg, horse dander, cat dander, grass pollen)
Human seminal fluid (rare trigger of anaphylaxis in women)
Occupational allergens (eg, stinging insects, natural rubber latex)
Immunologic triggers (IgE-independent mechanism)
IgG-dependent (rare) (eg, to high-molecular weight dextran, infliximab)
Coagulation system activation (eg, heparin contaminated with oversulfated chondroitin sulfate)
Idiopathic anaphylaxis
Consider the possibility of a hidden or previously unrecognized trigger
Consider the possibility of a mast cell activation syndrome, including systemic mastocytosis
Nonimmunologic triggers (direct activation of mast cells and basophils)
Physical factors (eg, exercise¶, cold, heat)
Medications (eg, opioids, NSAIDs)
Radiocontrast agents
Alcohol (ethanol) (may augment, rarely induces)

Any food, insect sting or bite, or medication or biologic can potentially trigger anaphylaxis. Novel or unusual allergen triggers include storage mite-contaminated flour and saliva from kissing bugs. They also include mosquitoes, pigeon ticks, green ants, and pharaoh ants and venoms from jellyfish, scorpions, and snakes. Medications include taxanes, platins, and other chemotherapy drugs, biologic agents, including monoclonal antibodies, such as rituximab, cetuximab, infliximab, and uncommonly, omalizumab. Some triggers, such as radiocontrast media, insect venoms, and medications (such as NSAIDs) can act through more than one mechanism.

IgE: immunoglobulin E; NSAIDs: nonsteroidal anti-inflammatory drugs; IgG: immunoglobulin G.
* Reactions to vaccines are rare and typically involve an excipient, such as gelatin, rather than microbial content.
¶ Often involves a cofactor, such as a food, medication (eg, an NSAID), or exposure to cold air or water.

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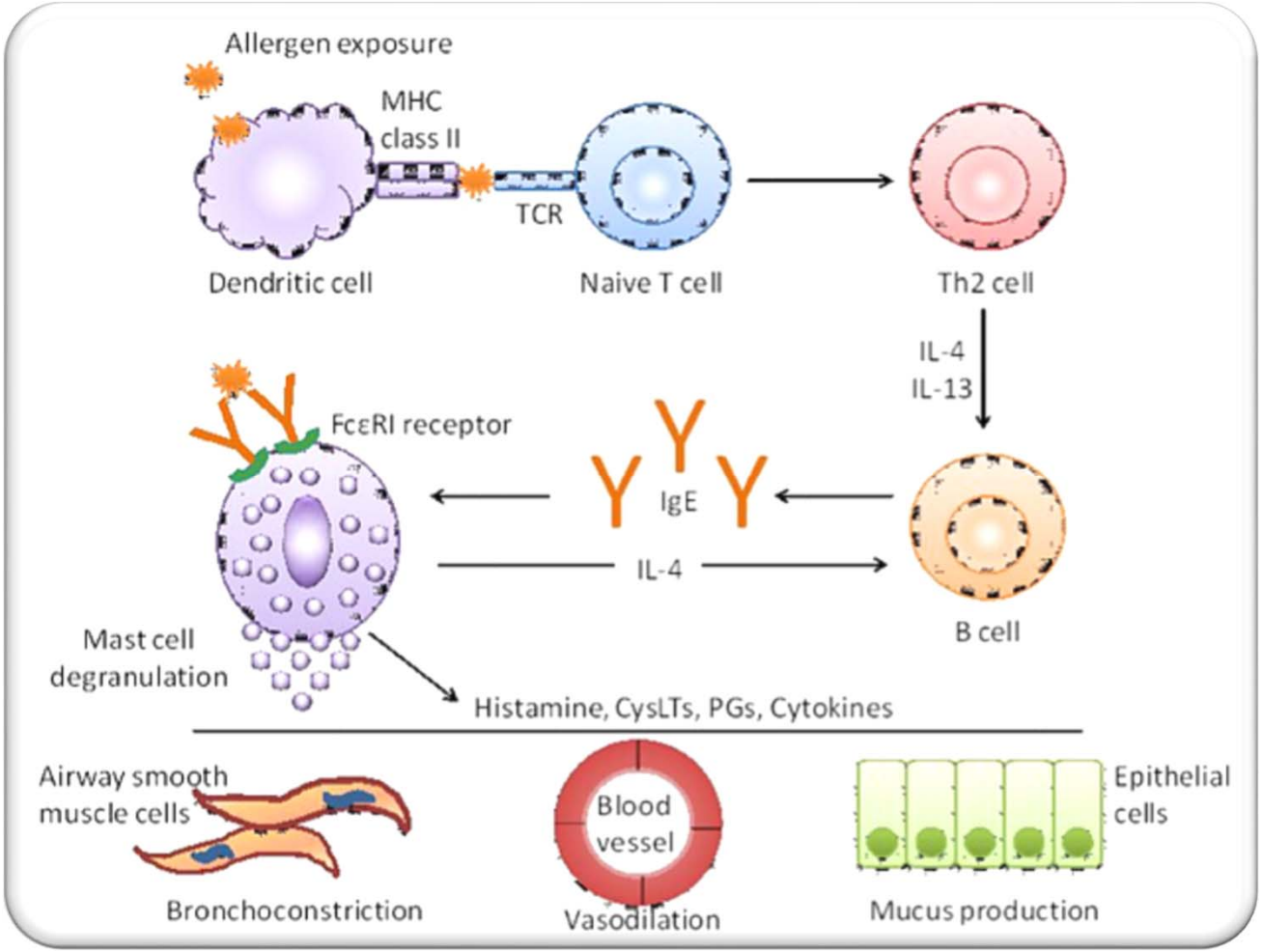
Anaphylaxis

Mechanism



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Anaphylaxis

Amplifying co-factors

- Beta-blocker (metoprolol)
- ACE inhibitor (ramipril)
- …anaphylaxis was exacerbated and mediator release was increased when these medication were given concurrently. (1)

1) Nassiri M et all: Ramipril and metoprolol intake aggravate human and murine anaphylaxis: Evidence for direct mast cell priming. J Allergy Clin Immunol. 2015;135:491-9.

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Anaphylaxis
Symptoms

Symptoms and signs of anaphylaxis

Skin
Feeling of warmth, flushing (erythema), itching, urticaria, angioedema, and "hair standing on end" (pilor erection)
Oral
Itching or tingling of lips, tongue, or palate
Edema of lips, tongue, uvula, metallic taste
Respiratory
Nose - Itching, congestion, rhinorrhea, and sneezing
Laryngeal - Itching and "tightness" in the throat, dysphonia, hoarseness, stridor
Lower airways - Shortness of breath (dyspnea), chest tightness, cough, wheezing, and cyanosis
Gastrointestinal
Nausea, abdominal pain, vomiting, diarrhea, and dysphagia (difficulty swallowing)
Cardiovascular
Feeling of faintness or dizziness; syncope, altered mental status, chest pain, palpitations, tachycardia, bradycardia or other dysrhythmia, hypotension, tunnel vision, difficulty hearing, urinary or fecal incontinence, and cardiac arrest
Neurologic
Anxiety, apprehension, sense of impending doom, seizures, headache and confusion; young children may have sudden behavioral changes (cling, cry, become irritable, cease to play)
Ocular
Periorbital itching, erythema and edema, tearing, and conjunctival erythema
Other
Uterine cramps in women and girls

Original figure modified for this publication. Simons FER. Anaphylaxis. J Allergy Clin Immunol 2010; 125:S161. Table used with the permission of Elsevier Inc. All rights reserved.

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Anaphylaxis

Symptoms

- Respiratory 94 %
- Cutaneous 80-90 %
- GI: 10-46 %
- Cardiovasculair: 30%

1) Russel et all, Pediatric Emergency Care, 2010

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Anaphylaxis

The predominant shock organs

- Heart: myocardial ischemia, conduction defects, coronary artery vasospasm
- Vasculature: increased vascular permeability
- Lungs: - Smaller airway: bronchospasm and mucus plugging

  - Upper airway: laryngeal edema and asphyxiation.

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Anaphylaxis

Diagnostic criteria

Diagnostic criteria for anaphylaxis

Anaphylaxis is highly likely when any ONE of the following three criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:
A. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
B. Reduced BP* or associated symptoms of end-organ dysfunction (eg, hypotonia, collapse, syncope, incontinence)
2. TWO OR MORE OF THE FOLLOWING that occur rapidly *after exposure to a LIKELY allergen for that patient* (minutes to several hours):
A. Involvement of the skin mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
B. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
C. Reduced BP* or associated symptoms (eg, hypotonia, collapse, syncope, incontinence)
D. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP* *after exposure to a KNOWN allergen for that patient* (minutes to several hours):
A. Infants and children - Low systolic BP (age-specific)* or greater than 30% decrease in systolic BP
B. Adults - Systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

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

Adapted with permission from: Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391. Copyright © 2006 The American Academy of Allergy, Asthma, and Immunology.

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Anaphylaxis

Laboratory tests

- Anaphylaxis is a clinical diagnosis, and treatment cannot await laboratory confirmation.
- Elevation is transient.
- Serum or plasma total **tryptase**:
  - When to collect: between 15 minutes and 3 hours after symptom onset.
  - How to collect: standard technique for serum (red top tube) or plasma (tube with EDTA)
  - How to process the sample: place on ice ASAP. Should be shipped frozen.
  - If level of tryptase is still elevated > 24 u -> allergy specialist evaluation of possible **systemic mastocytosis**
- **Plasma histamine**: typically peak within 5 to 15 minutes.

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Anaphylaxis
Differential diagnosis

Differential diagnosis of anaphylaxis
Common disorders
Acute generalized urticaria and/or angioedema*
Acute asthma exacerbation*
Vasovagal syncope (faint)
Panic attack/acute anxiety attack
Other respiratory events
Pulmonary embolism
Pneumothorax
Foreign body aspiration (especially in children)
Vocal cord dysfunction
Epiglottitis
Hyperventilation
Cardiac events
Myocardial infarction*
Dysrhythmia
Acute symptoms related to structural disorders (eg, aortic stenosis, hypertrophic cardiomyopathy)
Shock
Hypovolemic¶ (eg, gastrointestinal bleed, ruptured ectopic pregnancy, ruptured aortic aneurism, systemic capillary leak syndrome)
Cardiogenic
Distributive¶ (eg, sepsis, spinal cord injury)
Obstructive (eg, pulmonary embolism, tension pneumothorax, cardiac tamponade)
Flushing
Perimenopause
Carcinoid syndrome
Autonomic epilepsy
Medications
Alcohol
Medullary carcinoma of the thyroid
Red man syndrome (vancomycin)
Postprandial syndromes
Scombroidosis
Anisakiasis
Pollen-food allergy syndrome
Food poisoning
Caustic ingestion (especially in children)
Neurologic events
Seizure
Cerebrovascular event (stroke)
Nonorganic disease
Munchausen syndrome
Psychosomatic episode

The differential diagnosis in children and adults is shown. In infants, the differential diagnosis of anaphylaxis is unique.
* Acute asthma symptoms, acute generalized urticaria, or myocardial infarction symptoms can also occur during an anaphylactic episode.
¶ In anaphylaxis, shock is distributive and hypovolemic. Distributive shock may be due to anaphylaxis or to spinal cord injury.
Original figure modified for this publication. Simons FER. Anaphylaxis. J Allergy Clin Immunol 2010; 125:S161. Table used with the permission of Elsevier Inc. All rights reserved.

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Anaphylaxis

- It is important to treat anaphylaxis promptly because it appears to be most responsive to treatment in its early phases based on observation that delayed epinephrine injection is associates with fatalities.

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Anaphylaxis
Anaerobic metabolism

- Skeletal muscle maintains high rates of oxygen utilization during anaphylaxis compared with other forms of distributive shock -> anaerobic metabolism ⬆ (1) .

- Dewachter P, Jouan-Hiraex V, Franck P, et al. Anaphylactic shock: a form of distributive shock without inhibition of oxygen consumption/ Anesthesiology 2005; 103:40

Anaphylaxis

Fatal reactions

- 164 fatalities
- Iatrogenic anaphylaxis **5 minutes**
- Stinging-insect venom-induced anaphylaxis **15 min**
- Food-induced **30 min**

- Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000; 30:1144

Anaphylaxis

Initial assessment

- ABCD
- Angioedema! -> The lips, tongue, and oral pharynx. Ask the patient to speak his or her name to assess periglottic or glottic swelling.
- Skin examination

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Angioedema

- Angioedema typically affects the skin and mucosal tissues of the face, lips, mouth, and throat, larynx, extremities, and genitalia, often in an asymmetric pattern. Angioedema can also affect the bowel wall and present as colicky abdominal pain.

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Angioedema

- Mast cell-mediated angioedema (eg, allergic reactions)
- Bradykinin-mediated angioedema (eg, angiotensin-converting enzyme [ACE] inhibitor-induced angioedema, hereditary angioedema [HAE], acquired C1 inhibitor deficiency).

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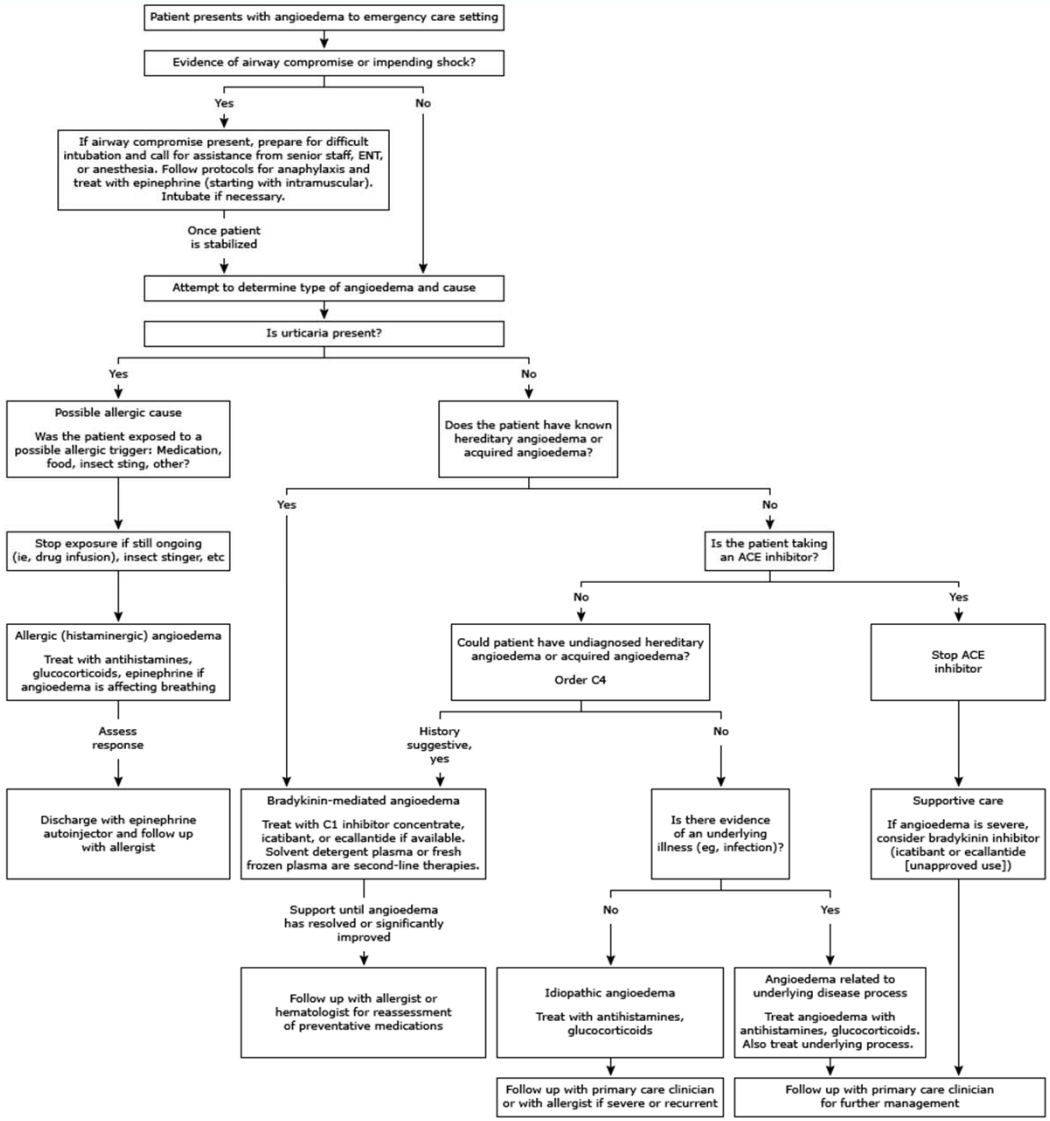
Anaphylaxis
Angioedema

Algorithm for evaluation and management of angioedema in the urgent care setting



ENT: ear, nose, and throat or otolaryngology; ACE: angiotensin-converting enzyme; C4: complement component 4.

Modified from: Jaiganesh T, Wiese M, Hollingsworth J, et al. Acute angioedema: Recognition and management in the emergency department. Eur J Emerg Med 2013; 20:10.

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Anaphylaxis

Acute management

- Removal of the inciting cause, if possible
- Call for help
- IM **epinephrine** (1 mg/ml preparation): 0,3-0,5 mg IM. Can repeat every 5 to 15 min, as needed (prepare IV epinephrine for infusion).
- Place patient in **recumbent postion** and elevate lower legs (“empty ventricle syndrome”).
- **Oxygen**
- **Normal saline rapid bolus**: treat hypotension with rapid infusion of 1-2 L IV. Repeat as needed.
- **Salbutamol**: for bronchospasm resistant to IM epinephrine (2,5-5 mg in 3 ml saline via nebulazer).

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Acute management: adjunctive therapies

- **H1 antihistamine**: PO: Cetirizine (Zyrtec) of IV: Diphenhydramine (Nustasium) 25-50 mg (for relief of urticaria and itchy only).
- **H2 antihistamine**: Ranitidine (Zantac) 50 mg IV
- **Glucocorticoid**: methylprednisolone (Solu-Medrol) 125 mg IV

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Anaphylaxis

Use of Tranexamic acid

- An analysis of 202 anaphylaxis fatalities over a 10-year period in the UK determined that 8 percent of deaths were attributable to DIC. (1)
- Successful treatment with tranexamic acid has been reported. (2)

1) Pumphery R. Anaphylaxis: can we tell who is at risk of a fatal reaction? Curr Opin Allergy Clin Immunol 2004; 4:285
2) De Souza RL, Short T, Warman GR, et al Anaphylaxis with associated fibrinolysis , reversed with tranexamic acid and demonstrated by thromboelastography. Anesth Intensive Care 2004; 32:580

Anaphylaxis

Epinephrine injection

- **IM injection is the preffered route for initial administration**

- IM recommended over SC because
  A. More rapid increase in the plasma and tissue concentration
  B. Faster in many situation and safer

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Anaphylaxis
Epinephrine injection

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Anaphylaxis

Epinephrine injection

- Infants < 10 kg **0.1 mg** by autoinjector (0.1 ml of the 1mg/ml solution)
- 10 -25 kg **0.15 mg** by autoinjector (0.15 ml of the 1 mg/ml solution)
- >25 kg – 50 kg **0.3 mg** by autoinjector (0.3 mL of the 1mg/ml solution)
- > 50 kg **0.5 mg** (0.5 ml of the 1 mg/Ml solution)

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Anaphylaxis

Epinephrine mechanisms of action

- **Alpha-1-adrenergic** agonist effects - ⬆ vasoconstriction, ⬆ peripheral vascular resistance, and ⬇ mucosal edema (eg, in the upper airway).
- **Beta-1-adrenergic** agonist effects - ⬆ inotropy and chronotopy
- **Beta-2-adrenergic** agonist effects - ⬆ bronchodilatation and ⬇ release of mediators of inflammation from mast cells and basophils.

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Observation

- 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.
- Observation period of at least **4 hours** from the last IM dose of epinephrine.
- For patients with anaphylaxis that resolved promptly and completely with treatment, observation times based on the severity of the reaction and access to ER.

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Anaphylaxis

Atypical patterns

- Uniphasic
- Biphasic
- Protracted

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Anaphylaxis

Atypical patterns

- Biphasic reactions occur in up to 23 percent of cases of anaphylaxis.
- The severity of recurrent symptoms is unpredictable.
- Risk factors for biphasic anaphylaxis have not been established.

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Discharge care

- An anaphylaxis emergency action plan (should be informed about the possibility of recurrent symptoms for up to three days after the initial symptoms)
- 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 refferal if possible.

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Anaphylaxis

Penicillin “allergy”

- Important health consequences.
- Significant longer admissions, greater use of broad-spectrum AB
- Increased prevalence of Clostridium difficile, MRSA, vancomycin-resistant enterococcal infections
- Total cost of antibiotics was 1.8-2.6-fold higher.

1) Macy E et all: Health care use and serious infection prevalence associated with penicillin “allergy” in hospitalized patients: A cohort study. J Allergy Clin Immunol. 2014;133:790-6
2) Li M et all: A real-time prospective evaluation of clinical pharmaco-economic impact of diagnostic label of “penicillin allergy” in a UK teaching hospital. J Clin Pathol. 2014;67:1088-92