dr. Wignyo Santosa, SpAn, KIC, FIPM
Anesthesiology Departemen
Medical Faculty Unissula

ANAPHYLACTIC REACTION

DEFINITION

- A serious, **rapid onset life threatening** generalized or systemic hypersensitivity reaction
- Severe cases:
  - Complete airway obstruction
  - Cardiovascular collapse
  - Death
- Prevalence 0.05-2%

ETIOLOGY

- Hypersensitive reaction mediated by IgE and IgG
- Prior sensitizations to an allergen
- Subsequent re exposure
  - Food: children, teens and young adults
  - Insect stings and medications: middle ages and elderly adults

TRIGGERS

- Antibiotics, antimicrobal, antiviral, antifungal
- Aspirin, NSAIDS
- Chemotherapeutic agents
- IV contrast agents
- Anesthetic agents: muscle relaxants, opioids, propofol
- Natural Rubber Latex (NRL) in healthcare equipment, gloves, condoms, toys
- Stinging insects
- Foods: cow milk, egg, peanuts, shellfish, fish, peach, etc

TIME COURSE FOR REACTION

- fatal food reactions cause respiratory arrest typically after 30–35 minutes
- insect stings cause collapse from shock after 10–15 minutes
- and deaths caused by intravenous medication occur most commonly within 5 minutes.

PATHOPHYSIOLOGY

- Allergen binds to antigen specific IgE from previously sensitized basophils and mast cells.
- Release mediators: histamines, leukotrines, prostaglandin, tromboxanes and bradykinin

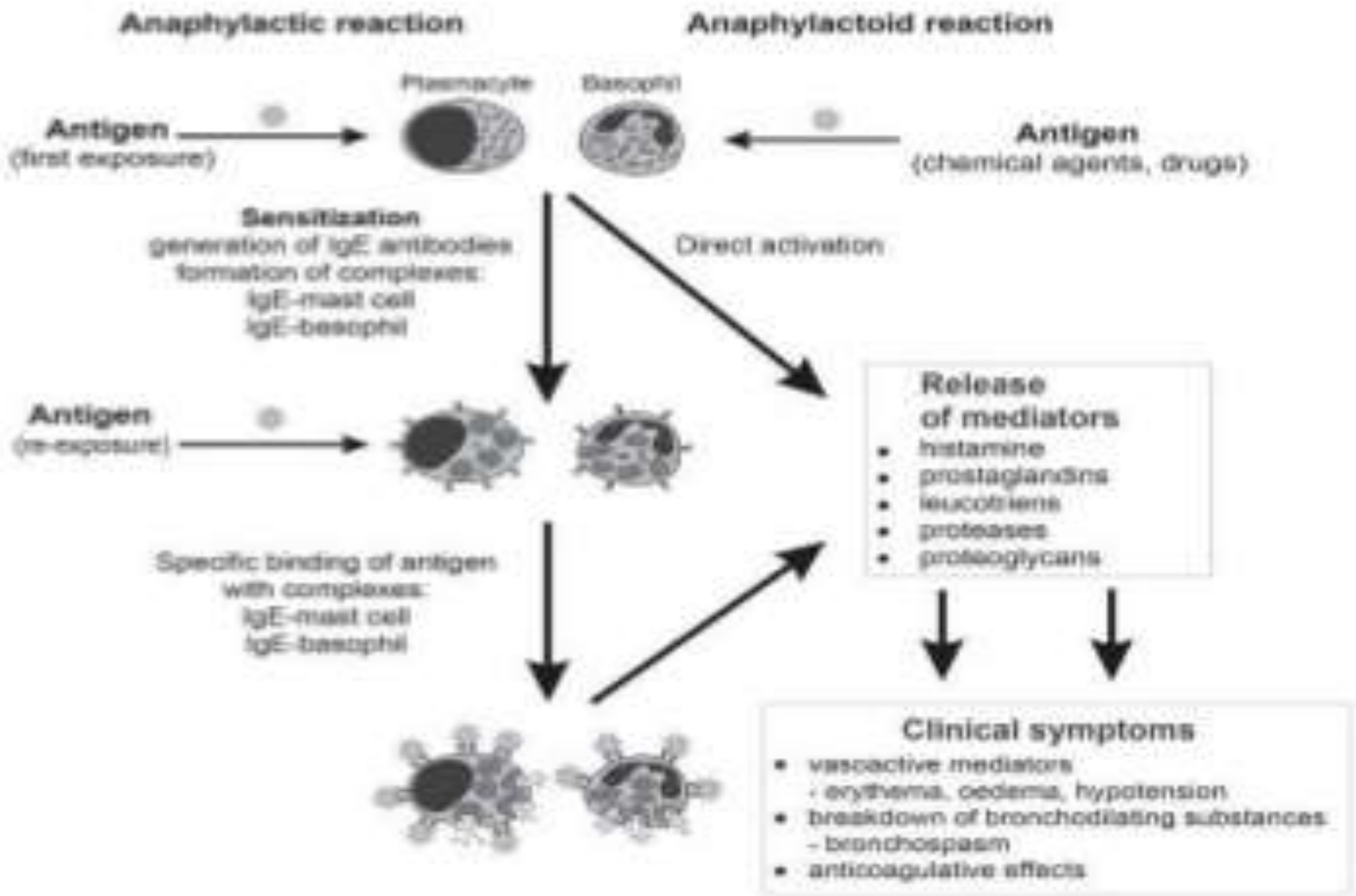
➔Increased mucous membrane secretions

➔Increased capillary permeability and leak

➔**Vasodilation**

- **Patofisiologi**
  Reaksi anafilaksis timbul bila sebelumnya telah terbentuk IgE spesifik terhadap alergen tertentu. Alergen yang masuk kedalam tubuh lewat kulit, mukosa, sistem pernafasan maupun makanan, terpapar pada sel plasma dan menyebabkan pembentukan IgE spesifik terhadap alergen tertentu. IgE spesifik ini kemudian terikat pada reseptor permukaan mastosit dan basofil. Pada paparan berikutnya, alergen akan terikat pada Ige spesifik dan memicu terjadinya reaksi antigen antibodi yang menyebabkan terlepasnya mediator yakni antara lain histamin dari granula yang terdapat dalam sel. Ikatan antigen antibodi ini juga memicu sintesis SRS-A (Slow reacting substance of Anaphylaxis) dan degradasi dari asam arachidonik pada membrane sel, yang menghasilkan leukotrine dan prostaglandin. Reaksi ini segera mencapai puncaknya setelah 15 menit. Efek histamin, leukotrine (SRS-A) dan prostaglandin pada pembuluh darah maupun otot polos bronkus menyebabkan timbulnya gejala pernafasan dan syok. (2)
  Efek biologis histamin terutama melalui reseptor H1 dan H2 yang berada pada permukaan saluran sirkulasi dan respirasi. Stimulasi reseptor H1 menyebabkan peningkatan permeabilitas pembuluh darah, spasme bronkus dan spasme pembuluh darah koroner sedangkan stimulasi reseptor H2 menyebabkan dilatasi bronkus dan peningkatan mukus dijalan nafas. Rasio H1 – H2 pada jaringan menentukan efek akhirnya. (2,3)
  Aktivasi mastosit dan basofil menyebabkan juga respon bifasik dari cAMP intraselluler. Terjadi kenaikan cAMP kemudian penurunan drastis sejalan dengan pelepasan mediator dan granula kedalam cairan ekstraselluler. Sebaliknya penurunan cGMP justru menghambat pelepasan mediator. Obat-obatan yang mencegah penurunan cAMP intraselluler ternyata dapat menghilangkan gejala anafilaksis. Obat-obatan ini antara lain adalah katekolamin (meningktakan sintesis cAMP) dan methyl xanthine misalnya aminofilin (menghambat degradasi cAMP). Pada tahap selanjutnya mediator-mediator ini menyebabkan pula rangkaian reaksi maupun sekresi mediator sekunder dari netrofil,eosinofil dan trombosit,mediator primer dan sekunder menimbulkan berbagai perubahan patologis pada vaskuler dan hemostasis, sebaliknya obat-obat yang dapat meningkatkan cGMP (misalnya obat cholinergik) dapat memperburuk keadaan karena dapat merangsang terlepasnya mediator.(2,3,4)

- **Reaksi Anafilaktoid**
  Reaksi anafilaktoid adalah reaksi yang menyebabkan timbulnya gejala dan keluhan yang sama dengan reaksi anafilaksis tetapi tanpa adanya mekanisme ikatan antigen antibodi. Pelepasan mediator biokimiawi dari mastosit melewati mekanisme nonimunologik ini belum seluruhnya dapat diterangkan. Zat-zat yang sering menimbulkan reaksi anafilaktoid adalah kontras radiografi (idionated), opiate, tubocurarine, dextran maupun mannitol. Selain itu aspirin maupun NSAID lainnya juga sering menimbulkan reaksi anafilaktoid yang diduga sebagai akibat terhambatnya enzim siklooksgenase.


Anaphylactic reaction
Anaphylactoid reaction
Plasmacyte
Basophil
Antigen
(first exposure)
Antigen
(chemical agents, drugs)
Sensitization
generation of IgE antibodies
formation of complexes:
IgE-mast cell
IgE-basophil
Direct activation
Antigen
(re-exposure)
Release
of mediators
histamine
prostaglandins
leucotriens
proteases
proteoglycans
Specific binding of antigen
with complexes:
IgE-mast cell
IgE-basophil
Clinical symptoms
vascactive mediators
- erythema, oedema, hypotension
breakdown of bronchodilating substances
- bronchospasm
anticoagulative effects

SIGNS & SYMPTOMPS

- Two or more body systems involved
- Time interval between exposure and reactions: shorter interval, more severe reactions
- Skin, subcutaneous tissue and mucosa: flushing, itching, urticaria,angioedema, periorbital itching, conjungtival erythrema, itching of lips, tongue, palate, swelling of lips, tongue, uvula, itching of genitalia
- Airway edema, asthma, stridor, wheezing, rhinitis

- Gastrointestinal: abdominal pain, nausea, vomiting, diarrhea, dysphagia
- Central Nervous System (CNS): headache, altered mental status, dizziness, confusion
- Respiratory: nasal itching, congestion, rhinorrhea, sneezing, throat itching and tightness, hoarness, stridor, increased respiratory rate, shortness of breath, chest tightness, wheezing/ bronchospasm, cyanosis, respiratory arrest
- Cardiovascular: chest pain, agitated, anxious, pale, tachycardia, palpitations, vasodilation, relative hypovolemia, increased capillary permeability, hypotension, cardiac arrest.
- Other: metallic taste in the mouth

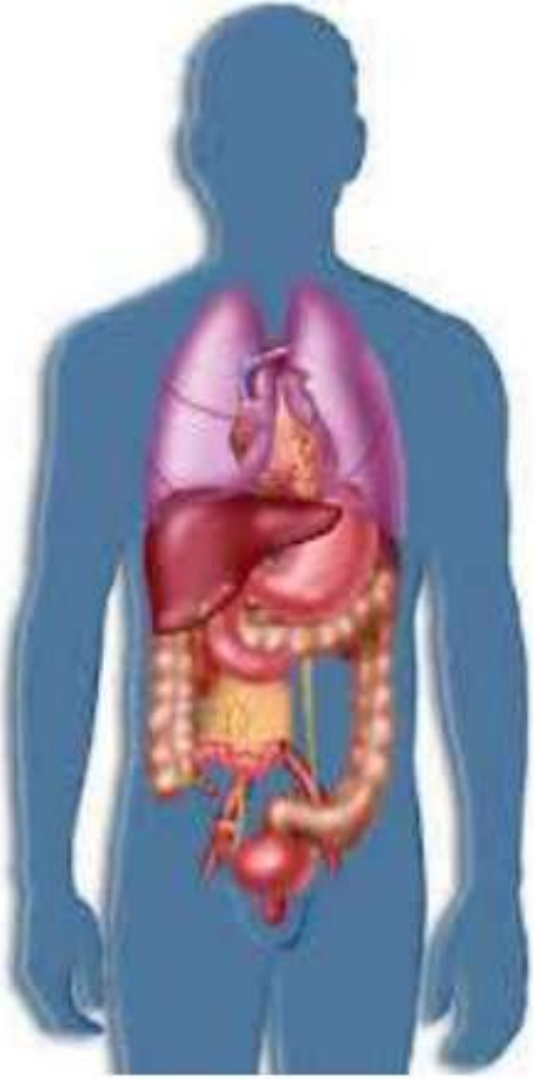


Table 1. Target Organs In Anaphylaxis	
Cardiovascular	Hypotension, lightheadedness (pre-syncope), syncope, dysrhythmias, angina
Respiratory	Upper airway - oropharyngeal, hypopharyngeal or laryngeal edema Lower airway - bronchospasm
Gastrointestinal	Nausea, vomiting, diarrhea, cramping
Skin	Flushing, erythema, pruritis, urticaria, angioedema
Central Nervous System	Headache, confusion, altered level of consciousness

DIAGNOSIS

Anaphylaxis: diagnosis and treatment

WAO
WORLD ALLERGY ORGANIZATION
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Clinical criteria for diagnosis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

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

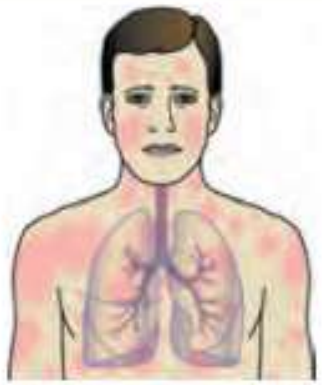
And at least one of the following:

Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)

Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)

Or **2** **Two or more of the following that occur suddenly after exposure to a *likely allergen or other trigger** for that patient* (minutes to several hours):**

Sudden skin or mucosal symptoms and signs (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)



Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)

Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)

Sudden gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

Or **3** **Reduced blood pressure (BP) after exposure to a *known allergen*** for that patient (minutes to several hours):**

Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP***

Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

* For example, immunologic but IgE-independent, or non-immunologic (direct mast cell activation)

** For example, after an insect sting, reduced blood pressure might be the only manifestation of anaphylaxis; or, after allergen immunotherapy, generalized hives might be the only initial manifestation of anaphylaxis.

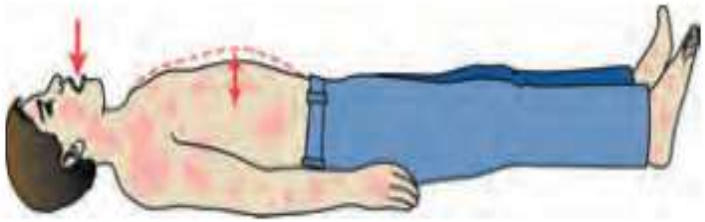
*** Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year less than (70mmHg + [2 × age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years. Normal heart rate ranges from 80–140 beats/minutes at age 1-2 years; from 80–120 beats/minute at age 3 years; and from 70–115 beats/minute after age 3 years. In infants and chilren, respiratory compromise is more likely than hypotension or shock, and shock is more likely to be manifest initially by tachycardia than by hypotension.

Initial treatment

1 **Have a written emergency protocol** for recognition and treatment of anaphylaxis and rehearse it regularly.

2 **Remove exposure to the trigger** if possible, e.g. discontinue an intravenous diagnostic or therapeutic agent that seems to be triggering symptoms.

3



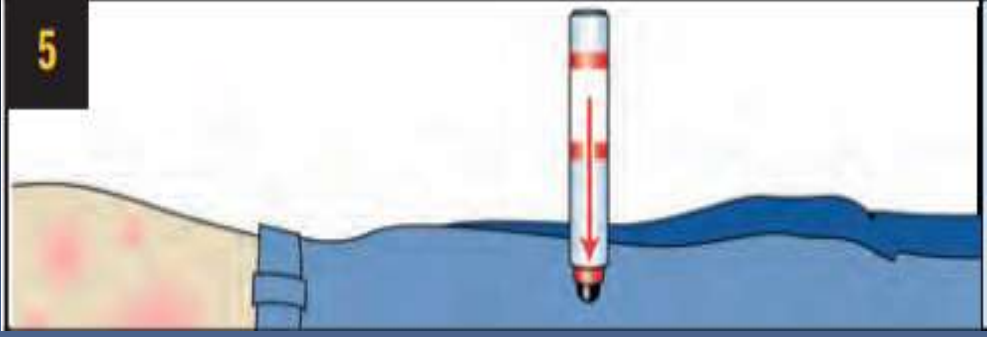
Assess the patient's circulation, airway, breathing, mental status, skin and body weight (mass).

Promptly and simultaneously, perform steps 4, 5 and 6.

4

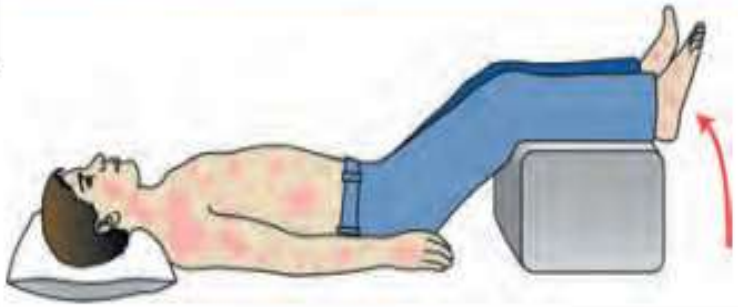
Call for help: resuscitation team (hospital) or emergency medical services (community) if available.

5



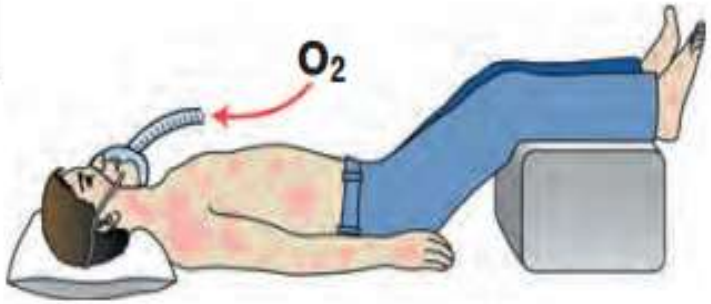
Inject epinephrine (adrenaline) intramuscularly in the mid-anterolateral aspect of the thigh, 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution, maximum of 0.5 mg (adult) or 0.3 mg (child); **record the time of the dose and repeat it** in 5–15 minutes, if needed. Most patients respond to 1 or 2 doses.

6



Place patient on the back or in a position of comfort if there is respiratory distress and/or vomiting; **elevate the lower extremities;** fatality can occur within seconds if patient stands or sits suddenly.

7



When indicated, give high-flow supplemental oxygen (6-8 L/minute), by face mask or oropharyngeal airway.

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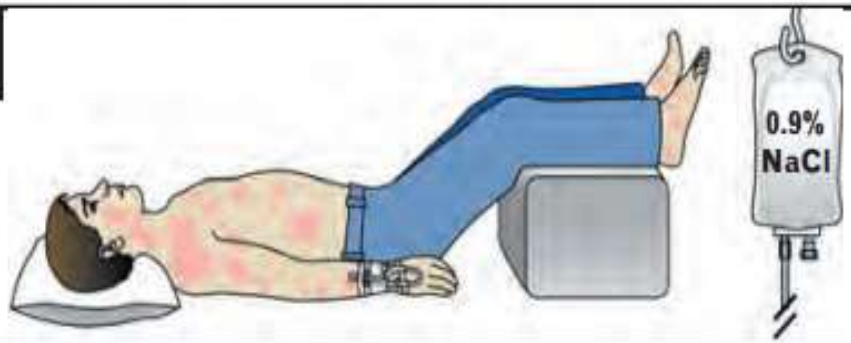


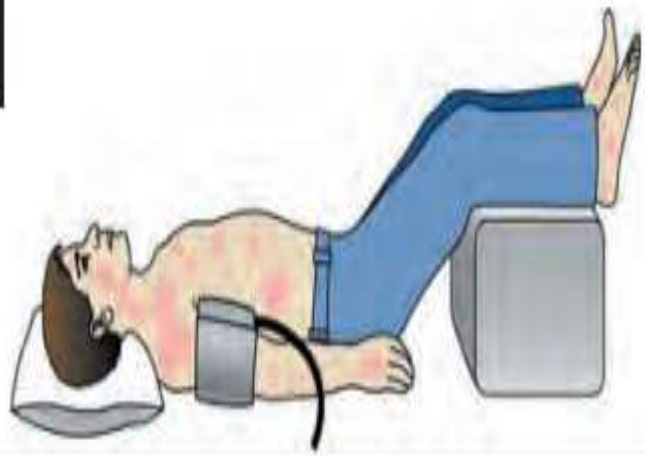
Establish intravenous access using needles or catheters with wide-bore cannulae (14 - 16 gauge): **When indicated, give 1–2 litres of 0.9% (isotonic) saline rapidly** (e.g. 5-10 ml/kg in the first 5-10 minutes to an adult; 10 ml/kg to a child).

9

When indicated, at any time, perform cardiopulmonary resuscitation with continuous chest compressions and rescue breathing.

In addition.

10



In addition,

At frequent, regular interval, monitor patient's blood pressure, cardiac rate and function, respiratory status, and oxygenation (monitor continuously, if possible).

References: Simons FER et al, for the WAO. J Allergy Clin Immunol 2011;127:587-93.e22 and WAO Journal 2011;4:13-36. Illustrator: J Schaffer

EPINEPHRINE

Pharmacologic effects of epinephrine injection:

- Alpha-1 adrenergic receptor:
  - Increases vasoconstriction and vascular resistance
  - Increases blood pressure
  - Decreases mucosal edema in the airways
- Beta-1 adrenergic receptor:
  - Increases cardiac contraction force
  - Increases heart rate
- Beta-2 adrenergic receptor:
  - Decreases mediator release
  - Increases bronchodilation

LIFE SAVING PROPERTY

- Increases blood pressure and prevents and relieves hypotension and shock
- Decreases upper airway obstruction (laryngeal edema)
- Decreases wheezing
- Decreases urticaria and angioedema

DOSING & ROUTING

- Intramuscular injection in the mid-anterolateral thigh as soon as anaphylaxis is diagnosed or strongly suspected
- Dose: 0.01 mg/kg of 1:1000 solution, to a max dose in adults 0.5 mg(in children 0.3 mg) intramuscular
- Effective and safe initial treatment
- Peak plasma will be achieved rapidly
- Do not inject subcutaneously
- Can be repeated every 5-15 minutes, as needed.
- Most patient respond to 1 or 2 dose

- If anaphylaxis appears to be severe with immediate life threatening manifestations:
  - Epinephrine (1: 10.000) 0.1 mg IV slowly over 5 minutes
- An IV infusion at rates of 1-4 microgram (mcg)/minutes to prevent repeated IV injections frequently.

Epinephrine 1:1000. What does it mean?

- In a 1:1000 epinephrine ampoule, there is one part adrenaline to 1000 parts solutions

- 1:1000 solution epinephrine:

= 1 gram epinephrine in 1000 ml solution

= 1000 mg epinephrine per 1000 ml solution

= 1 mg per ml

- Intramuscular injection (I.M):
  - Withdraw 1 ml of epinephrine with 3 cc syringe, inject 0.5 ml (adult), 0.3 ml (children)
- Intravenous bolus dose: 0.1 mg slowly in 5 minutes:
  - 0.1 mg = 100 mcg = 10 cc solution
  - Withdraw 10 ml from the solution with 10 cc syringe, inject IV slowly in 5 minutes

- Intravenous drip dose: 1-4 mcg/minutes
  - 0.5 ml of epinephrine, dilute in 500 ml of NaCl
  - 0.5 ml epinephrine = 500 mcg
  - 500 mcg in 500 ml NaCl = 1 mcg/ml solution
- Intravenous drip dose: 1-4 mcg/minutes
  - 1-4 mcg/minutes = 1-4 cc/ minutes
  - 1 cc = 15 drops (macro set infusion)
  - 1-4 mcg/minutes = 15-60 drops/minutes infusion

SECOND LINE TREATMENT

- **Antihistamines**
  - Relieve itching, flushing, urticaria, angioedema, nasal and eye symptoms.
  - Can not substitutes for epinephrine
  - Do not prevent or relieve airway obstruction , hypotension or shock
  - Slow onset of action relative to epinephrine
- **Beta-2 Adrenergic Agonist**
  - Salbutamol (albuterol) as additional treatment for wheezing, coughing and shortness of breath not relieved by epinephrine.
  - Minimal alpha-1 adrenergic agonist vasoconstrictor effect
  - Do not prevent or relieve laryngeal edema and upper airway obstruction hypotension and shock

Adverse Effects of Epinephrine

Transient pharmacological effects:

- Pallor, tremor, anxiety, palpitations, dizziness, headache
- Overdose: Typically after repeated intravenous dosing/ dosing error
- Ventricular arrhytmia, hypertensive crisis, pulmonary edem

Dosing Error !!!!

Always remember to dilute epinephrine to 1:10.000 solutions before inject intravenously for anaphylaxis treatment

TERIMA KASIH