Drug used in anaphylaxis

EDITING FILE

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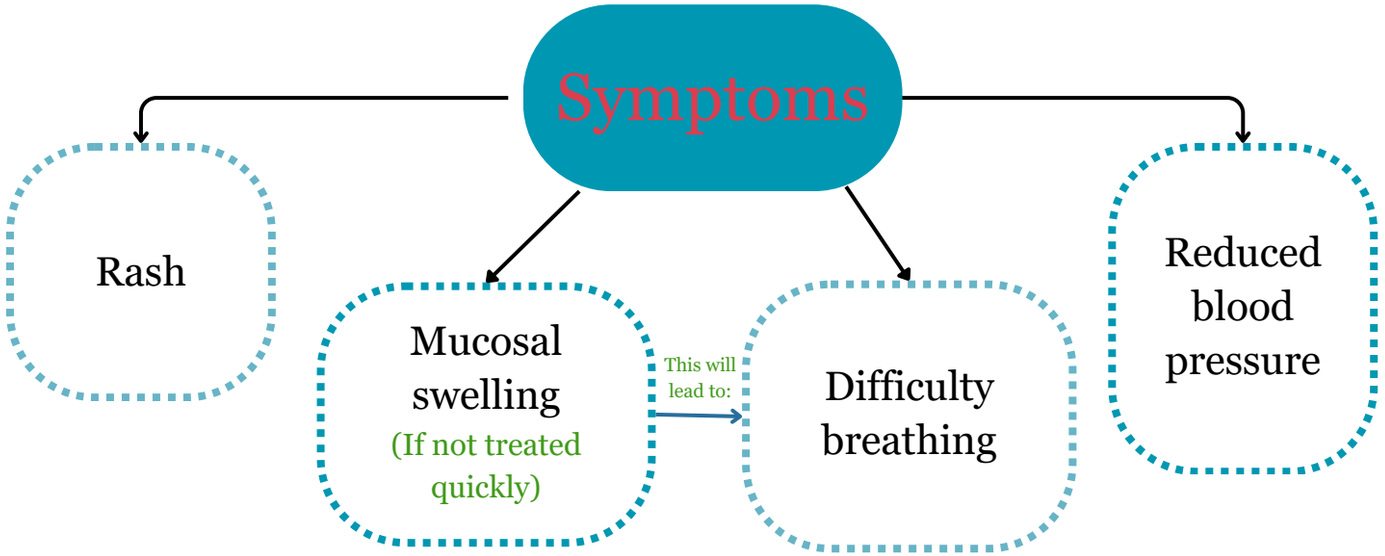
Objectives:

- PERCEIVE THE DIFFERENCES BETWEEN ANAPHYLACTIC SHOCK & OTHER TYPES OF SHOCK
- RECOGNIZE ITS NATURE, CAUSES & CHARACTERISTICS
- SPECIFY ITS DIAGNOSTIC FEATURES
- IDENTIFY ITS STANDARD EMERGENCY MANAGEMENT PROTOCOL
- JUSTIFY THE MECHANISM OF ACTION & METHOD OF ADMINISTRATION OF EACH OF THE DIFFERENT USED DRUGS TO LIMIT ITS MORBID OUTCOMES.

ANAPHYLAXSIS

Anaphylaxis Is an acute & sudden, severe allergic reaction affecting the whole body. (generalized or systemic) in response to antigen or allergen.



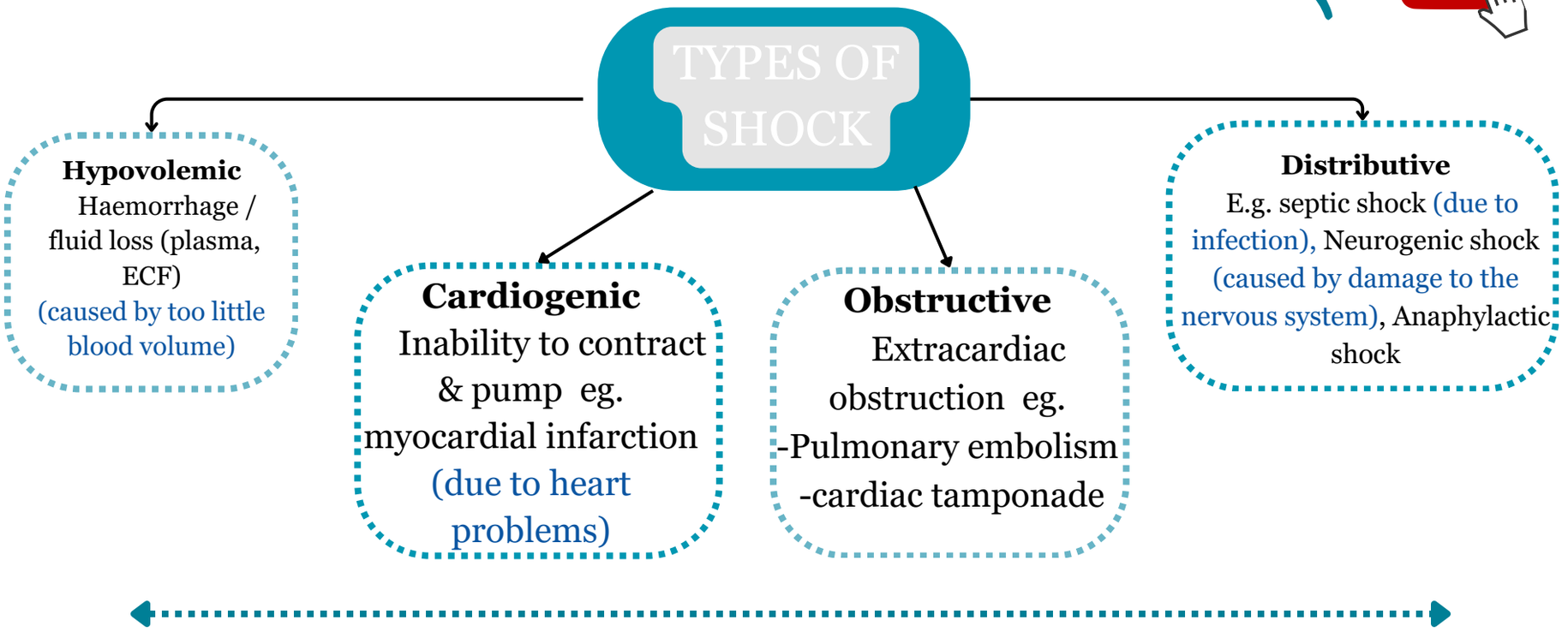
-it is a life-threatening if not treated ⟶ shock (ANAPHYLACTIC SHOCK): hypoperfusion and airway swelling.

shock

Generalized circulatory derangement causing multiple organ HYPOPERFUSION [Inadequate oxygen delivery to meet metabolic demands] & strong sympathetic activation.

when intense or sustained enough, irreversible derangements sets ⟶ permanent functional deficit or death

shock cont..



ANAPHYLACTIC SHOCK

A life-threatening allergic reaction that causes shock (hypoperfusion) and airway swelling.

- Belong to TYPE I HYPERSENSITIVITY REACTION (IgE-mediated reactions affect both the respiratory & the CVS).

-Occurs after exposure to foreign substances [antigen]; food, insect or animal venom, drugs, blood products, ...

(441: Any shock is due to Hypoperfusion) Perfusion means delivery of oxygen to the tissues , Hypoperfusion: decreased O2 delivery to the tissues.

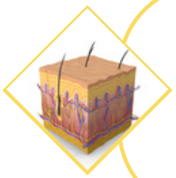
ANAPHYLACTIC SHOCK

The Nature of anaphylactic shock	
Immunologic Anaphylaxis (ANAPHYLAXIS)	Non-Immunologic Anaphylaxis (ANAPHYLACTOID)
أول تعرض لل (allergen) ما يسوي ردة فعل ثاني تعرض هو الي يسوي ردة فعل	ما يحتاج exposer first على طول يسوي ردة فعل
It belongs to type I hypersensitivity reaction	Directly act on mast cells (Not IgE-mediated)
Occurs after exposure to foreign substances (antigen) such as food, insect or animal venom, drugs, blood products	Exogenous substances directly degranulate mast cells.
The immune system will then develop antibodies for this antigen and it will remain in the body for a while Sensitization phase	Radiocontrast dye (enhance the visibility of internal structures in X-ray based imaging techniques) Opiates (such as heroin and morphine, binds to the brain's opioid receptors that is responsible for controlling pain). Depolarizing drugs Dextrans (plasma volume expander made from glucose, restore blood plasma lost through severe bleeding).(Side notes from439)
After a 2nd exposure to the same antigen in previously sensitized persons (antigen-specific IgE are present), IgE binds with mast cell causing its degranulation. Challenge phase	

ANAPHYLACTIC SHOCK

BECAUSE ANAPHYLACTIC AND ANAPHYLACTOID REACTIONS PRODUCE THE SAME CLINICAL MANIFESTATIONS AND ARE TREATED EXACTLY THE SAME WAY. WE USE THE TERM ANAPHYLAXIS TO REFER TO BOTH CONDITIONS. (NOTE FROM 435)

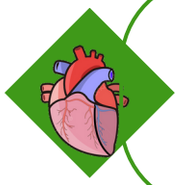
The degranulation of the mast cells will release Histamine, Leukotrienes and other inflammatory substances and will lead to:



Skin:
- Pruritus
- Urticaria
- Edema

Mucus swelling:
- Rhinitis 16%
- Airway 56%
- Angioedema 88%
- GIT 30%

Blood vessels:
- Vasodilation
- leakiness
- Hypoperfusion



Heart:
- Decrease output
- Decrease coronary flow
- Circulatory collapse

Lungs:
- Bronchospasm
- Vasoconstriction
- Shortness in breath

Characters of Anaphylactic Shock:

1. Rapidly developing [5/30 min. → can be hours].
2. Severe, life-threatening.
3. Multisystem involvement.
4. Mortality: due to respiratory (70%) or cardiovascular deficits (25%).

Anaphylactic Shock Therapy Protocol

When the diagnosis is made as an anaphylactic shock (after calling the ambulance), emergency treatment should be immediately start as follows:

Rescue	Life Threatening Problems: 1- Airway: swelling, hoarseness, stridor. 2- Breathing: rapid breathing, wheezing, cyanosis, fatigue, confusion, oxygenated Hb (SpO2) < 92%. 3- Circulation: pale, clammy, low BP, faintness, drowsy /coma.	**Management**: **1- Respiratory support:** Open airway for O2 inhalation. **2- Circulatory support:** Lay down and raise legs up. Fluid replacement.
Important 1st Line Therapy	Adrenaline (give IM unless experienced with IV adrenaline) IM doses of 1:1000 Adrenaline (repeat after 5 min if no better) Adult:500 micrograms (0.5ml)IM Child more than 12 years: 500 micrograms (0.5ml)IM Child 6-12 years:300 micrograms (0.3ml)IM Child less than 6 years: 150 micrograms (0.15ml)IM ***Female dr said numbers for Adrenaline doses are important *** Adrenaline IV to be given only by experienced specialist titrate: Adult 50 micrograms: children 1 microgram/kg Normally no IV to not have an affect on the heart(↑COP ↑ BP) IV fluid challenge: Adult-500-1000ml Child-crystalloid 20 mL/kg, stop IV colloid if this might be the cause of anaphylaxis	
2nd line Therapy	Chlorpheniramine (1st generation H1 blocker) (IM or slow IV) Adult or above 12Y : 10mg Child 6-12Y : 5mg Child 6M to 6Y: 2.5mg Child less than 6M: 250 microgram/Kg	Hydrocortisone (Glucocorticoids) (IM or slow IV) Adult or above 12Y : 200gm Child 6-12Y : 100gm Child 6M to 6Y: 50gm Child less than 6M: 25gm

Anaphylactic Shock Therapy Protocol cont..

When the diagnosis is made as an anaphylactic shock (after calling the ambulance), emergency treatment should be immediately start as follows:

Adjuvant to 2nd line

أدوية مساعدة نستعملها مع 2nd line therapy

- Bronchodilators:

- Salbutamol (nebulizer) -Ipratropium (nebulizer) -Aminophylline (IV).
- **Glucagon**: "to increase cardiac output"

For patients taking beta-blockers & with refractory hypotension, 1 mg IV q 5 minutes until hypotension resolves.

- **H2 blocker:** "we mainly want to block H1
so we give H2 blocker to support the action of H1 antagonist"

Ranitidine: 150mg I.V

Cimetidine: contraindicated in elderly renal/hepatic failure, or if on beta-blockers.

Why do we use the 2nd line adjuvants?

Objective of Therapy:

- To support the respiratory & circulatory deficits.
- To halt (stop) the existing hyper-reaction.
- To prevent further hyper-reaction of immune system
(prevent biphasic phenomenon).

Biphasic Phenomenon:

(only happened in the first day)

- 2nd release of mediators without re-exposure to antigen leukotrienes and
histamines are still active (in up to 20%)
- Clinically evident 3-4h after the initial
manifestations clear.

First Line Therapy Adrenaline (Epinephrine) "Sympathomimetic"

Mechanism	A nonselective adrenergic agonist [α1, α2, β1, β2].
Indication	Drug of choice for anaphylactic shock.
Action	***Important*** **1- As an α-Adrenergic agonist:** • **Reverses peripheral vasodilation (vasoconstriction), thus maintains blood pressure and directs blood flow to major organs.** • **Vasoconstriction leads to decreasing edema → reverse hives swelling around face & lips & angioedema (a swelling of ,(urticaria) .the area beneath the skin) in nasopharynx & larynx** **2- As a β-Adrenergic agonist:** • **β1 effect: ↑ force of myocardial contraction.** • **β2 effect: Dilates bronchial airways + ↓ histamine & leukotriene release from mast cells** *Explanation: There are several substances that have antihistaminergic action despite not being ligands for the histamine receptor. .Thus, despite not being true antihistamines because they do not bind to and block the histamine receptor, epinephrine(adrenaline) and other such substances are physiological antagonists to histamine
ADRs	**Causes dysrhythmias if given IV.** اضطراب نبضات القلب

First Line Therapy Adrenaline (Epinephrine)

Contraindications

Rare in a setting of anaphylaxis Not given for cardiac patient who are older than 40 years
Because it affect β1 and it can cause dysrhythmia

Patients taking β-blockers either are:
A. Refractory not responding as it may antagonize β effect of adrenaline.
B. Rebound hypertension *severe increase in blood pressure* (unopposed α effect), specially when adrenaline is repeated.

Extra :
- Because adrenaline will act only on α receptor because β receptor are blocked by β blocker
- if a patient on a nonselective beta-blocker receives a systemic dose of epinephrine,the beta-blocker prevents the vasodilation, leaving unopposed alpha vasoconstriction. The resulting hypertensive reaction(rebound hypertension) can be large.

Administration

-Best is IM (intramuscular) route in anaphylaxis
why?

1- Easily accessible by using Auto-injectors Kits, they are disposable prefilled, auto devices matically administer a single dose of epinephrine in emergency.

2- Greater margin of safety → no dysrhythmias as with IV.

3- No need to wait for IV line, if present, it should be given by physician under monitoring.

- Repeat every 5-10 min as needed

- Patient should be observed for 4-6 hours Why? Because of fear of biphasic anaphylaxis.

What is biphasic anaphylaxis? After the patient survive the anaphylactic shock it may come back even without any thing to stimulate it, in about 1 hour to 72 hour after the attack occurred, it commonly after 10 hours. for more info about it HERE

GIRLS'S SLIDES

NOTE THAT: IF HYPOTENSION PERSISTS START TO USE DOPAMINE WE USE DOPAMINE TO PROTECT THE KIDNEY

WHY NOT NORADRENALINE?
DOPAMINE (ACT ON D1 R, ADRENERGIC VASOPRESSOR) IS GIVEN IN LOW DOSE TO TREAT BLOOD PRESSURE, COP & BLOOD FLOW.

Second Line Corticosteroid (Anti-Inflammatory)

Mechanism	Non-*genomic action: for acute cases ● Immediate Glucocorticoids actions on Membrane-bound receptors, which leads to modulating 2nd messengers levels (that's why we use it in anaphylactic shock). ● Rapid onset of action (seconds or minutes). That's why we use it in anaphylactic shock. *Genomic action: for chronic treatment because it take time. - Action is slow may take hrs to days. مشكلة الحساسية بسبب الجهاز المناعي شغال بقوة فتعطي كرتزون لأنه مثبط للمناعة فيخفف من كمية الماست سلز الموجودة فيقل الهيستامين الي مسبب الحفلة ذي كلها
Action	**Non-genomic action in anaphylactic shock:** ● Reverse hypotension & bronchoconstriction. ● ↓ Release of inflammatory and allergic mediators (anti-chemotactic & mast cell stabilizing effects). ● ↓ Mucosal swelling and skin reaction. ● May help to limit biphasic reactions by **decreasing allergic mediators.**
Administration	• Given slowly IV or IM. • Not used alone **(not life saving).** So we combine first line drug (adrenaline) with second line drug (corticosteroides). **NOTE: we never combine two 2nd line drugs together.** The best combination of adrenaline from Second Line is corticosteroid

Second Line H Blockers (Antihistamine)

	H1 blockers (2nd line)	H2 blockers (Adjuvant to 2nd line)
Examples	**Pheniramine**	Anaphylactic shock: Ranitidine 150 mg iv *best choice * Cimetidine Git acidity —> **Pantoprazole**
Action	• Though **mast cells** have already de-granulated, yet these drugs can still help to counteract histamine-mediated **vasodilation** & **bronchoconstriction.** • May help to limit biphasic reactions by blocks histamine receptors.	• The significance of H2 blockers is not established (is effective in some patients only), these drugs are associated with serious adverse drug interactions. • *In cases of GIT acidity, pantoprazole is safer than H2 blockers pantoprazole (Proton pump inhibitor) and it gives once
Administration	• Given slowly **I.V** or **I.M** • It can not be used alone (not life saving)	H2 blocker is given only in epigastric pain.
Contraindication	-	Cimetidine a lot of ADRs shouldn't be given to **elderly**, **renal/ hepatic failure**, or if **on b-blockers** Why? Because it inhibits cytochrome P450 which controls drug-drug interactions,So when given it may increase the toxicity of other drugs,therefore it's replaced by ranitidine
combination MALES'S SLIDES	Studies have shown that treatment with a combination of H1 and H2 antagonists is more effective than treatment with H1 antagonists alone.	

Adjuvant to Second Line

Bronchodilators

Drugs	Salbutamol Inhalation(nebulizer)	Ipratropium Inhalation(nebulizer)	AMINOPHYLLINE Parenteral IV
Administration	If there is respiratory obstruction bronchodilators given in Aminophylline If not given inhaled salbutamol or ipratropium		
Pharmacokinetic	Short acting Rapid relief onset of acting	Longer action Less rapid in action	---
Action	β2 agonist : 1.Relaxation of Bronchial smooth muscle (Bronchodilation) 2.Decrease mediators released from mast cell and basophils 3.Inhibit airway Microvascular Leakage (part of inflammation) ● Not effective in patients taking β2 Blockers	Anticholinergic (Antimuscarinic) **1.Decrease secretion** of mucus **2. Bronchodilator** How? *Decreases cGMP, therefore decreases the contractility of smooth muscles	Xanthine preparation 1. May be useful in the **treatment** of **anaphylaxis** when Inhaled bronchodilators are **not effective & bronchospasm is persistent** * Given in hospital setting as levels of drug should be the**rapeutically monitored** because ir has narrow therapeutic index ● increase cAMP ● Smooth muscle relaxation

Adjuvant to Second Line

Glucagon

Mechanism	• Main action: act on **glucagon receptors** in the heart.
ACTION	• Has both **positive inotropic & chronotropic** effect on heart **How?** Glucagon Action increase cardiac cyclic AMP. This effect is completely independent of Adrenergic Receptors. That's why effective in spite of β- adrenergic blockade. • Efficacy of acting on bronchi is less prominent than that of the heart → No evident bronchodilation (that's why we should give bronchodilator with it).
Clinical Uses	• Drug of choice for severe anaphylaxis in patients taking β-blockers & with refractory hypotension → 1 mg IV q 5 minutes until hypotension resolves. Because adrenaline won't be effective. Q:How a patient will benefit if he took beta blockers and developed allergic reaction, what will be the role of glucagon? Glucagon works the same way it increases cAMP BUT it is independent of adrenergic receptors.

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summary

MCQs

1 One of the contraindications of adrenaline is?

- **A** Not given for cardiac patient who are older than 40 years
- **B** Diabetic patients
- **C** Children
- **D** shouldn't be given to elderly, renal/ hepatic failure,

2 1.The Drug of choice for anaphylactic shock is?

- **A** Cimetidine
- **B** Pheniramine
- **C** Ranitidine
- **D** Adrenaline

3 Anaphylactic shock mainly effects?

- **A** Heart only
- **B** Respiratory + CVS
- **C** B- GIT + Respiratory tract
- **D** CNS

4 Drug of choice for people who have anaphlactic shock and use beta blockers?

- **A** Anti-Histamine
- **B** Glucagon
- **C** H1 blockers
- **D** Salbutamol

Answer: 1-A 2-D 3-B 4-B

MCQs

5 A 10 year old patient came to the hospital with rash, difficulty breathing and hypotension. which of the following combainations is the best for his condition?

- **A** adrenalin with H1 & H2 blockers
- **B** adrenalin with H1 blocker
- **C** corticosteroid with H1 blocker
- **D** adrenalin with corticosteroid

6 A patient came to the hospital with anaphylactic shock. which of the following combination is best choice for him?

- **A** adrenalin with H1 blocker
- **B** adrenalin with H2 blocker
- **C** adrenalin with H1 & H2 blockers
- **D** corticosteroid with H1 blocker

7 a patient with anaphylaxis. he had persistent bronchospasm the doctor gave him inhaled bronco-dilator, but he did not respond to it, which of the drug should he give him?

- **A** Salbutamol
- **B** Aminophylline
- **C** Adrenaline
- **D** Glucagon

8 A 20-year-old patient came to clinic, he has history of bee bite. the doctor saw him using β-Blockers. he diagnosed him with sever anaphylaxis. which should the doctor give him?

- **A** Glucagon
- **B** Ipratropium
- **C** adrenalin
- **D** Pheniramine

Answer: 5-D 6-C 7-B 8-A

SAQs

1. what is the definition of anaphylaxis?

an acute sudden, severe allergic reaction affecting the whole body.

2. what is the mechanism of action for adrenaline

β1 effect: ↑ force of myocardial contraction.
β2 effect: Dilates bronchial airways +↓ histamine &
leukotriene release from mast cells.

3. List some of the bronchodilators that can be used as adjuvant to 2nd line therapy?

1-Aminophylline 2-Ipratropium 3-
Salbutamol 4-Glucagon

4. what are the symptoms of anaphylaxis?

1-Rash 2-Mucosal swelling
3-Difficulty breathing 4-Reduced blood pressure

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