MED441
KING SAUD UNIVERSITY

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5&6.
Drug therapy for heart failure

Pharmacology
TEAM 441

Objectives:

- Describe the different classes of drugs used for treatment of acute & chronic heart failure & their mechanism of action
- Understand their pharmacological effects, clinical uses, adverse effects & their interactions with other drugs.

HELPFUL VIDEOS:

- **Pathophysiology of Heart failure**
- **Cardiac Glycosides-Digoxin**
- **Other drugs of HF**

Editing file

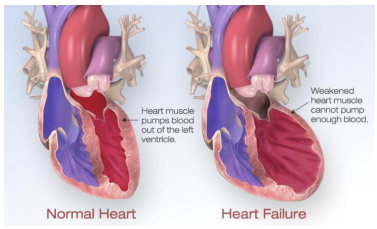
Color index:
Important
In male's slides only
In female's slides only
Extra information
Doctors notes

What is Heart Failure?

Inability of the heart to maintain an adequate cardiac output to meet the metabolic demands of the body.

Causes (acute or chronic)

- Heart valve disorder.
- High blood pressure.
- Cardiomyopathy.
- Abnormal heart rhythm.
- Disorder of coronary arteries



Symptoms:

- Tachycardia
- Cardiomegaly.
- Decrease exercise tolerance(Rapid Fatigue).
- Peripheral edema.
- Dyspnea
- (Pulmonary congestion).

Pathophysiology of CHF

When there is low. Co it will cause The heart to undergo compensatory responses

↓Force of contraction
Low C.O & arterial pressure (BP)

↓ **Renal Blood flow**

Activate renin-angiotensin Aldosterone system

ALDOSTERONE

Ang II

Remodeling

Salt and water retention, thus volume expansion

↓ **Carotid sinus firing**

Activate sympathetic system ↑Sympathetic discharge

↑**Force of cardiac contraction**

↑HR

Vasoconstriction

Venous VC

Arterial VC

↑**Preload**
Venous return

↑**Afterload**
Arterial pressure

Factors affecting cardiac output and heart failure:
الادوية اللي بناخذها كلها راح تأثر على هذه العوامل

1-Preload.
2-Afterload.
3-Cardiac contractility.

Drugs used in treatment of HF

(Overview)

I-Drugs that decrease **preload**:	
1 - Diuretics	Chlorothiazide , Furosemide
2 - Aldosterone antagonists	Spironolactone, Eplerenone
3-Venodilators	Nitroglycerine, Isosorbide dinitrate
II-Drugs that decrease **afterload**:	
1-Arteriodilators	Hydralazine
III Drugs that decrease both **preload & afterload**: (Combined arteriolo- & venodilators)	
1-Angiotensin converting enzyme (ACE) inhibitors	Captopril, Enalapril, Ramipril
2-Angiotensin receptor antagonists	Losartan, Valsartan, Irbesartan
3-α1-adrenoceptor antagonists	Prazosin
4-Direct vasodilators	Sodium nitroprusside
IV- Drugs that increase heart contractility:	
1-Cardiac glycosides (digitalis)	Digoxin
2- β- adrenoceptor agonists	Dobutamine
3-Phosphodiesterase inhibitors	Milrinone, Enoximone, Vesnarinone
β-adrenoceptor blockers in heart failure	
Second generation	Bisoprolol, Metoprolol
Third generation	Carvedilol, Nebivolol
New drugs for heart failure	
Natriuretic Peptides	Nesiritide
Calcium sensitisers	Levosimendan

1-Drug that decrease Preload:

1 **Diuretics**

2 **Venodilators**

3 **Aldosterone antagonists**

Diuretics (↓congestion & edema)

Drug	Chlorothiazide	Furosemide (lasix)
Subgroup	Thiazides	Loop diuretics
M.O.A In HF	-reduce salt and water retention(↑excretion)→ decrease ventricular preload and venous pressure → reduction of cardiac size → Improvement of cardiac performance. -different diuretics function on different parts of a nephron of the kidney, and because each part is responsible for a certain percentage of salt & water excretion, the part a diuretic drug functions on determines how strong it is (its efficacy). Therefore, a drug that works on a part that secretes 60% of salt & water is strong , but a drug that works on a part that secretes 5% is weak.* -a nephron is divided into 4 parts: proximal convoluted tubule→loop of henle→thick ascending limb of loop of henle→distal convoluted tubule.*	
M.O.A	Works on distal convoluted (secretion of 5% of water & salt). Not a strong diuretics (mild).*	Works on Na-K-Cl cotransporter in cells of. the **thick** ascending limb of loop of henle (secretion of 25% of water & salt).* A potent diuretic.
Use	-**First-line agent in heart failure Therapy** -Used in volume overload (Pulmonary and/or peripheral edema) (↓pulmonary congestion). -Used in **mild** congestive heart failure (بالبداية فقط لما تكون حالة المريض مستقرة وليست طارئة).	Used in emergency - Used for immediate reduction of pulmonary congestion (edema) & severe edema associated with: 1- **Acute** heart failure. 2- Moderate & **severe** chronic failure. -↑ urine output,cause hypotension and hypokalemia. -loop is better than thiazide in HF.

Venodilators

Drug	Nitroglycerine	Isosorbide dinitrate
PK	- Can be given IV. -Used in emergency.	
M.O.A	↑cGMP in smooth muscles of vessels→ Dilates venous blood vessels & reduce preload.	
Use	- Used I.V. for severe heart failure when the main symptom is dyspnea due to pulmonary congestion *Dyspnea is often a symptom associated with increased preload. (Venodilators are used in Angina too)	

1-Drug that decrease Preload:

Aldosterone antagonists & potassium sparing diuretics		
Drug	**Spironolactone** (most famous)	**Eplerenone**
M.O.A	Non-selective Antagonist of aldosterone receptor. (non-selective:it can bind to other steroid hormones receptors, like androgen & estrogen) - A potassium sparing diuretic (K+ is not excreted→ **hyperkalemia**) so it's drug of choice when the patient has hypokalemia.	- A new selective aldosterone receptor Antagonist does not inhibit other hormones such as estrogens & androgens.
Use	Improves survival in advanced heart failure.	Indicated to improve survival of stable patients with congestive heart failure.

2.Drug that decrease Afterload

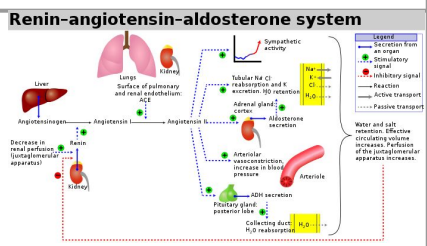
Arteriodilators (mainly used in hypertension & HF)	
Drug	**Hydralazine**
M.O.A	Reduces peripheral vascular resistance.
Use	Used when the main symptom is rapid fatigue due to low cardiac output.

3.Drug that decrease both Afterload & Preload

1. (ACE) inhibitors
2. (ARBs)
3. (a-Adrenoceptor BLOCKERS)
4. Direct acting vasodilators

Angiotensin converting enzyme (ACE) inhibitors (ACEI)

Drug	Captopril *prototype*	Enalapril	Ramipril
Uses	- Considered as first-line drugs for chronic heart failure along with diuretics. - First-line drugs for hypertension therapy. Better taken on empty stomach.		
P.K	- Rapidly absorbed from GIT after oral administration. - Food reduce their bioavailability.		
		- Prodrugs, converted to their active metabolites in liver. - Have long half-life & given once daily	
RAAS system effects	Plasma protein **Angiotensinogen** (synthesized in the liver) is converted to angiotensin I by renin (enzyme in juxtaglomerular cells of the kidney & then released in the circulation). ACE enzyme converts Angiotensin 1→ Angiotensin 2 **Angiotensin II effects:** ➔ extremely powerful vasoconstrictor (constriction of arterioles →↑ total peripheral resistance→↑arterial pressure) (mild constriction of veins →↑venous return). ➔ stimulating secretion of aldosterone (sodium and water retention). ➔ stimulating secretion of vasopressin (Antidiuretic hormone)→ water retention. ➔ stimulating the sympathetic system. ➔ Causes hypertrophy of vascular & cardiac cells & increases synthesis & deposition of collagen by cardiac fibroblasts (remodeling). - Increased renin in the body is mainly responsible for cardiac & vascular remodeling. - ACE (kininase II) is also essential for the the breakdown of Bradykinin. (additive vasodilating effect.)		
M.O.A	Inhibiting ACE, will achieve the opposite of all angiotensin II normal actions in This results in increase in CO.		
Pharmacological actions	1- Decrease peripheral resistance (Afterload) (arteriodilation). 2- Decrease Venous return (Preload) (venodilation). 3- Decrease sympathetic activity 4- Inhibit cardiac and vascular remodeling associated with chronic heart failure (protect to the heart) → **decrease in mortality rate.**		
ADRs	- Acute **renal failure**, especially in patients with renal artery stenosis. - **Hyperkalemia** especially in patients with renal insufficiency or diabetes. - Severe **hypotension** in hypovolemic patients —> hypovolemic due to diuretics, salt restriction or gastrointestinal Fluid loss e.g. severe vomiting or diarrhea). - **Dysgeusia** (reversible loss or altered taste). (reversible: if we stop the drug the side effect will disappear). **The last 2 ADRS are associated with bradykinin accumulation:-** - **Dry cough** sometimes with wheezing - **Angioneurotic edema** (swelling in the nose, throat, tongue, larynx.		
Contra-indication	- During the second & third trimesters of pregnancy (not recommended for the first trimester too) (due to the risk of : fetal hypotension, renal failure and malformations). - **Renal** artery stenosis, due to the low angiotensin II levels. (will cause renal failure)		



3.Drug that decrease both Afterload & Preload

Angiotensin receptor blockers (ARBs) **Used if ACE inhibitors are contraindicated or untolerated.** (just affect receptor not production)	
Drug	**Losartan** **Valsartan** **Irbesartan**
M.O.A	- **Block angiotensin 1 (AT1) receptors** (angiotensin production is not effected & there is no accumulation of bradykinin). Less ADRs due to bradykinin accumulation - **Decrease action of angiotensin II.** - AT1 mediates most of the known actions of Ang & predominate in vascular smooth muscle → renal sodium reabsorption, vasoconstriction, cell growth and proliferation (remodeling). - AT2 → natriuresis, vasodilation, anti proliferation.

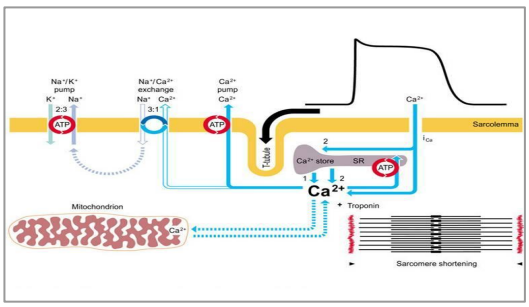
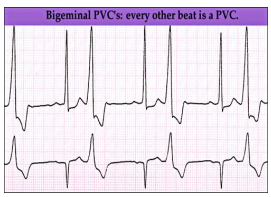
α-Adrenoceptor BLOCKERS	
Drug	**Prazosin**
M.O.A	- blocks α- receptors in arterioles and venules. - decrease both afterload & preload.

Direct acting vasodilators (by ↑ cGMP)	
Drug	**Sodium nitroprusside**
P.K	- Acts immediately and **effects lasts for 1-5 min** **not for chronic use** (it doesn't affect the receptors it acts directly on blood vessels , so the action will be very fast)
Uses	- Given I.V. for acute or severe heart failure used in emergencies

4.Drugs that increase contractility

1. Cardiac glycosides (digitalis)
2. B-Adrenoceptor AGONIST
3. Phosphodiesterase - III inhibitors

Cardiac glycosides (digitalis)

Drug	Digoxin
M.O.A	1- Inhibits Na+ / K+ ATPase enzyme (the sodium pump)⟶ Inhibiting the transport of Na & K against their concentration gradient , will result in high intracellular Na concentration and high extracellular K High intracellular Na will result in an increase in Ca. How ? 1-↑Na reverses the function of Na - Ca exchanger : resulting in high intracellular Ca. 2- ↑Ca will further increase Ca concentration by Calcium induced Calcium release. ↑Ca binding to troponin C will : Increase the force of myocardial contraction (+ve inotropic effect). Normal function of pumps: • Na/K pump, works during repolarization: K in, Na out (against gradient) • Na/Ca pump : Ca out, Na in Abnormal function of pumps due to presence of Digoxin : 1. Blocked Na/K channels 2. Reversed Na/Ca pumps (Na out ,Ca in) 
Uses	- Congestive heart failure ONLY if patient has decrease in contractility (438). - Has narrow therapeutic index.
ADRs	**Cardiac:** **digitalis-induced arrhythmias:** - Extrasystoles. - Coupled beats (Bigeminal rhythm). - Ventricular tachycardia or fibrillation. - Cardiac arrest (toxic dose).  **Non-cardiac:** **-GIT** anorexia (loss of appetite), nausea, vomiting, diarrhea **-CNS:** headache, visual disturbances, drowsiness. yellow vision indication of cardiac toxicity
Factors that Increase its toxicity (check for ion balance before starting therapy	1. -Renal diseases (because it's excreted through it & because the kidney is responsible for ion balance in the body and any imbalance in ions will affect digoxin toxicity). 2. Electrolyte disturbances: • - Hypokalemia (↓K so easier binding of digoxin,could happen by taking non-K sparing diuretics). • - Hypomagnesemia (Mg is cofactor of sodium pump so if it not present the pump won't function achieving what digoxin is already trying to achieve). • - Hypercalcemia (↑↑ intracellular Ca).

4.Drugs that increase contractility

Beta-Adrenoreceptor Agonist	
Drug	**Dobutamine**
M.O.A	Selective B1 agonist
Uses	Treatment of acute heart failure in cardiogenic shock

Phosphodiesterase-III inhibitors		
Drug	**Milrinone**	**Enoximone** **Vesnarinone**
M.O.A	Inhibit phosphodiesterase -III (cardiac & B.vessels) →↑cAMP. -↑cAMP in cardiomyocytes → increase **cardiac contractility.** -↑cAMP in vascular smooth muscles→ Dilatation of arteries & veins **(reduction of preload & afterload).** **Better than digoxin since it works on heart and vessels. (less ADRs)**	
Uses	- Used in emergency. -Used only **IV** for management of acute heart failure. -Not safe for effective in the longer (**>48 hours**) treatment of patients with heart failure.	New drugs in clinical trials.
ADRs	- **Hypotension and chest pain (angina)** (so it's not use at more than 2 days)	-
Chemical interactions	- Furosemide shouldn't be administered in IV lines containing milrinone due to formation of a precipitate. (It affects their absorption because they are not in their dissolved form)	-

5.The use of B-adrenoceptor blockers in heart failure

B-adrenoceptor blockers			
The chronic elevated adrenergic activity in chronic heart failure patients cause structural remodeling of the heart (cardiac dilatation hypertrophy).			
Generation	**Second generation**	**Third generation**	
Drug	**Eg:** **Bisoprolol** **Metoprolol**	**Eg:** **Carvedilol**	**Eg:** **Nebivolol**
	Cardioselective (B1-receptor)	Beta blockers with additional cardiovascular actions Non selective vasodilators (alpha and beta blocker) (a1, B2) (selective a and non selective B-blocker). B-1 receptor blocker + have vasodilator action (a blocking effect)	B1- selective with vasodilating properties not mediated by a blockade due to increase in endothelial release of NO via indication of eNOS.
M.O.A in HF	1- Attenuate/slows down cardiac remodeling. 2- Slow heart rate, which allows the left ventricle to fill more completely. 3- Decrease renin release → reduce mortality & morbidity of patients with HF.		
Use	-Reduce the progression of chronic heart failure. -NOT used in acute heart failure. تذكروا انهم يضحكون بصوت عالي ذا يعني أنهم قليلين ادب علشان كذا أمنعهم من التعامل الكيوت (acute)		

{ لَا يُكَلِّفُ اللَّهُ نَفْسًا إِلَّا وُسْعَهَا }

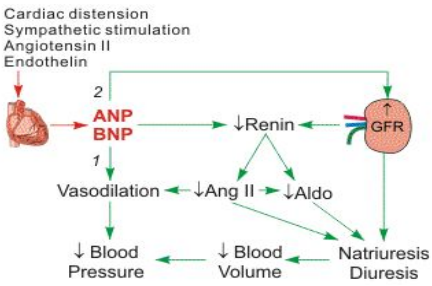
الأمر الذي تظن أنّه فوق طاقتك،
لم يضعه أمامك إلا وجعل بيديك القدرة على تجاوُزه .. استعن بالله ولا تعجز

New drugs for heart failure

1 Natriuretic Peptides

2 Calcium sensitisers

1- Natriuretic Peptides

Drug	Nesiritide
Definition	A purified preparation of human BNP, manufactured by **recombinant DNA technology** -BNP is hormone secreted by cardiomyocyte in the heart ventricles in response to stretch caused by increased ventricular blood. -Elevated BNP and ANP are associated with advanced HF (It is a compensatory mechanism of the heart in heart failure). 
M.O.A	- Physiological effects of ANP and BNP: - Vasodilation. - Natriuresis (excretion of sodium in urine) - Inhibition of RAAS (inhibitory effects on renin secretion, inhibit the action of ANG II & aldosterone). -↑cGMP in vascular smooth muscle leading to: - smooth muscle relaxation (vasodilation). -Reduction of preload and afterload.
Uses	Indicated (IV) for the treatment of patients with (ADHF "acute decompensated heart failure") who have dyspnea at rest or with minimal activity (not given in stable cases).

2- Calcium sensitisers

Drug	Levosimendan
M.O.A	-Calcium sensitization (improves cardiac contractility **Without** increasing oxygen consumption) (no extra work on heart). -Potassium-ATP channel opening (cause vasodilation, improving blood flow to vital organs). -These effects reduce the risk of worsening ADHF or death compared with dobutamine.
Uses	Used in management of ADHF (not given in stable cases).

Non-pharmacological management of Chronic Heart Failure

- Reduce workload of the heart:
  -Limit patient activity.
  -Reduce weight
  -Control hypertension

- Restrict sodium because ↑sodium →↑BP →↑edema.

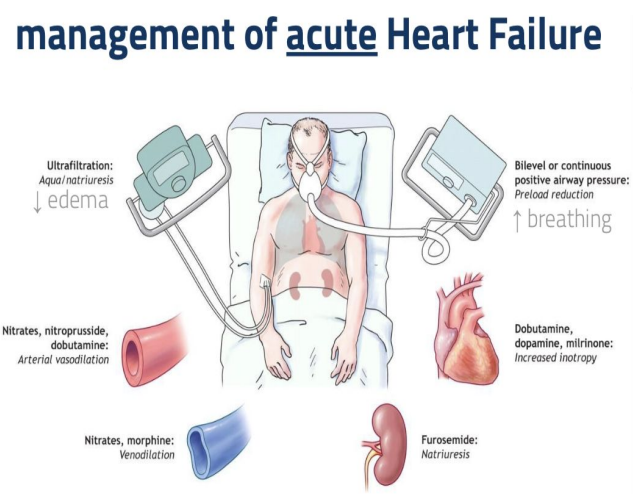
- Stop smoking.

Management of Acute Heart Failure

ADHF is a common and potentially serious cause of respira distress.

Acute Decompensated Heart failure (ADHF): A sudden worsening of signs and symptoms of heart failure, which typically includes:

1- dyspnea 2- leg or feet swelling 3- fatigue



Congestive heart failure in black patients

Hydralazine (Arterial Dilator)/ **isosorbide dinitrate** (venodilators) **fixed dose combination.**

- **FDA** approved to add to standard therapy for black Americans with Congestive heart failure (due to poor response to ACE inhibitors).
- Should be considered for patient intolerant to ACE inhibitor & ARBs due to renal dysfunction.

Heart failure functional Classification and management of Chronic heart failure

The severity of heart failure is usually described according to a scale devised by the New York Heart Association (NYHA):

	Functional classification	Management of chronic HF	
NYHA class:	**Symptoms**	**For survival/Morbidity**	**For symptoms**
I	Cardiac disease, but no symptoms & no limitation in ordinary physical activity, eg: no shortness of breath when walking, climbing stairs etc. -symptoms occur only with greater than ordinary exercise.	Continue ACE inhibitor/ARB if ACE inhibitor intolerant, continue aldosterone antagonist If post-MI and add **beta-blocker if post MI**	Reduce/stop diuretic
II	Mild symptoms (mild shortness of breath &/or angina), slight limitation during activity which result in fatigue and palpitations.	ACE inhibitor as first-line treatment/ARB if ACE inhibitor intolerant add beta blocker and aldosterone antagonist if post-MI.	+/- diuretic depending on fluid retention
III	Marked limitation in activity due to symptoms (fatigue,etc), even during less-than-ordinary activity, eg: walking short distance. Comfortable only at rest (no symptoms).	ACE inhibitor + ARB or ARB alone if ACE intolerant Beta blocker Add aldosterone	+diuretic -Digitalis if still symptomatic
IV	Severe limitation, experiences symptoms even while at rest. Mostly bed bound patients.	-Continue ACE inhibitor/ARB -Beta blocker -aldosterone antagonist	+Diuretic +Digitalis +Consider temporary inotropic support

The End! But don't forget to see the **extra slide**

روي في الحديث عن النبي صلى الله عليه وسلم

"أحبُ الناس إلى اللهِ أنفَعُهُم لِلنَّاس، و أحبُ الأعمال إلى اللهِ عزَ وجلَّ سُرورٌ يدخِلُهُ على مسلمٍ، أو يكشِف عنهُ كُربَةً، أو يقضِي عنهُ دَينا، أو تطردُ عنهُ جوعًا، **و لأن أمشِي مع أخ لي في حاجَةٍ أحبُ إلَيَ من أن اعتكِفَ في هذا المسجدِ**، يعني مسجدَ المدينةِ شهرًا، و مَن كفَّ غضبَهُ سترَ اللهُ عَورَتهُ، و مَن كَظَمَ غَيظَهُ، و لو شاءَ أن يُمضِيَهُ أمضَاهُ مَلأ اللهُ قلبَهُ رَجَاءً يومَ القيامةِ، **و مَن مَشَى مع أخِيهِ في حاجَةٍ حتى تتهَيأ لهُ أثبَت اللهُ قدَمَهُ يومَ تزُول الأقدَامِ**، [وإنَّ سُوءَ الخلق يُفسِدُ العَمَلَ، كما يُفسِدُ الخَلُّ العَسَلَ]"

حديث صحيح -

EXTRA SLIDE

Foursemide :

٤ سميد

(صاحب الربط كان جوعان أو شي)

Nesiritide :

نصير تايد

Not that Levosimenden also use in ADHF

Carvedilol :

الكار في التلال

Hydralazine

حيدر؟ إلا زين

Thanks Rahaf Alrayes

Losartan, Valsartan, Irbesartan :

فقدت الفلوس (قرب) لان بتفاهم معك، طيب ليش؟

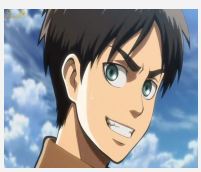
لانه سرق مني فلوس و هو بس يشتغل على الريسيبتورز

👐 ،بس، مو البرودكشن

طبعاً الي سرقها حاط تان

Enalapril , Ramipril, Captopril :

اينال رامي صار كابتن بأبريل



Eplerenone :

ايرين ياكل تفاحة وحدة

Thanks yara

Nebivolol :

احنا : نبي فل مارك

الكلية : لول

Levosimendan :

الحب سم

Dobutamine :

Do it but be amine (الامانه)

الامانه مكانها القلب

Thanks 39

Vesnarinone :

في السيناريو الأول

Enoximone :

قررنا أن نقسم على واحد

α1-adrenoceptor antagonists : prazosin

ألفا بالبرازيل

SAQs:

Q1: A 55 years old patient has been diagnosed with heart failure, which drug is going to decrease heart rate and renin release?

Q2: Enumerate four side effects of (ACE) inhibitors ?

Q3: Describe the mechanism of action of milrinone in Heart failure?

Click here!

SUMMARY

A1:
Metoprolol

A2:
Dry cough.
hyperkalemia
Acute renal failure
Loss of taste (Dysgeusia)

A3:
Inhibit phosphodiesterase -III (cardiac & B.vessels) →↑cAMP.
-↑cAMP in cardiomyocytes → increase **cardiac contractility.**
-↑cAMP in vascular smooth muscles→ Dilatation of arteries & veins **(reduction of preload & afterload).**

Test yourself
From our amazing Qbank team

Good luck!

Pharmacology
TEAM 441

Team leaders

Alanoud Alhaider **Faisal Alhussaini**

Subleader

Leen Alhadlaq

NOTE TAKER

Arwa Almobeirek

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