Pharmacology

Subject :

Lec no : 26

Done By : Raneem Azzam

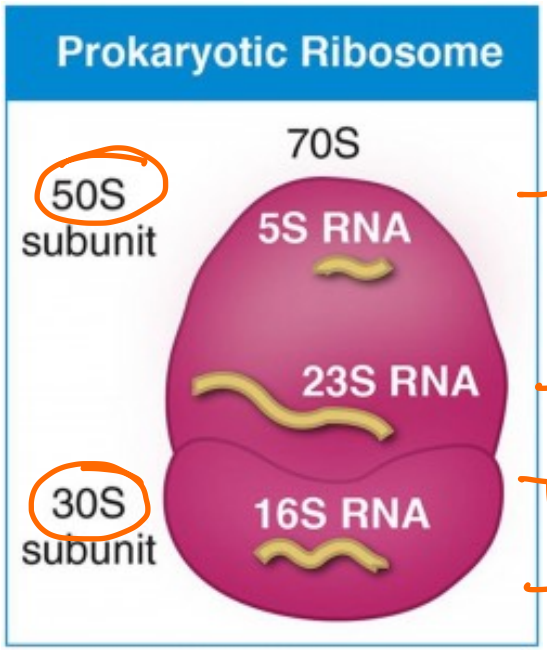
وَقُل رَّبِّ زِدْنِي عِلْمًا

+هاي مقدمة من المحاضرة حتى بعد هيك بكون كل شي واضح .

في المقدمة حكينا انو الي بتعمل protein synthesis inhibitor ← تعتبر bacteristatic بس ممكن لو زدت الدوز تصير bactericidal

طب كيف بيتم الموضوع بشكل عام ؟
احنا بس يضاعف الDNA ،يؤدي الي تكوين ال mRNA حتى نكمل العملية ونعمل transcription وبعدها translation ويصير ال protein synthesis يوصل الرايبوسوم وهاد الحكي الي اخذناه بالجنتكس

← نراجع شكل ال Ribosom لانو كل الشغل عليه ←



العزء الكبير ← أغلبية المضادات بترتبط هون

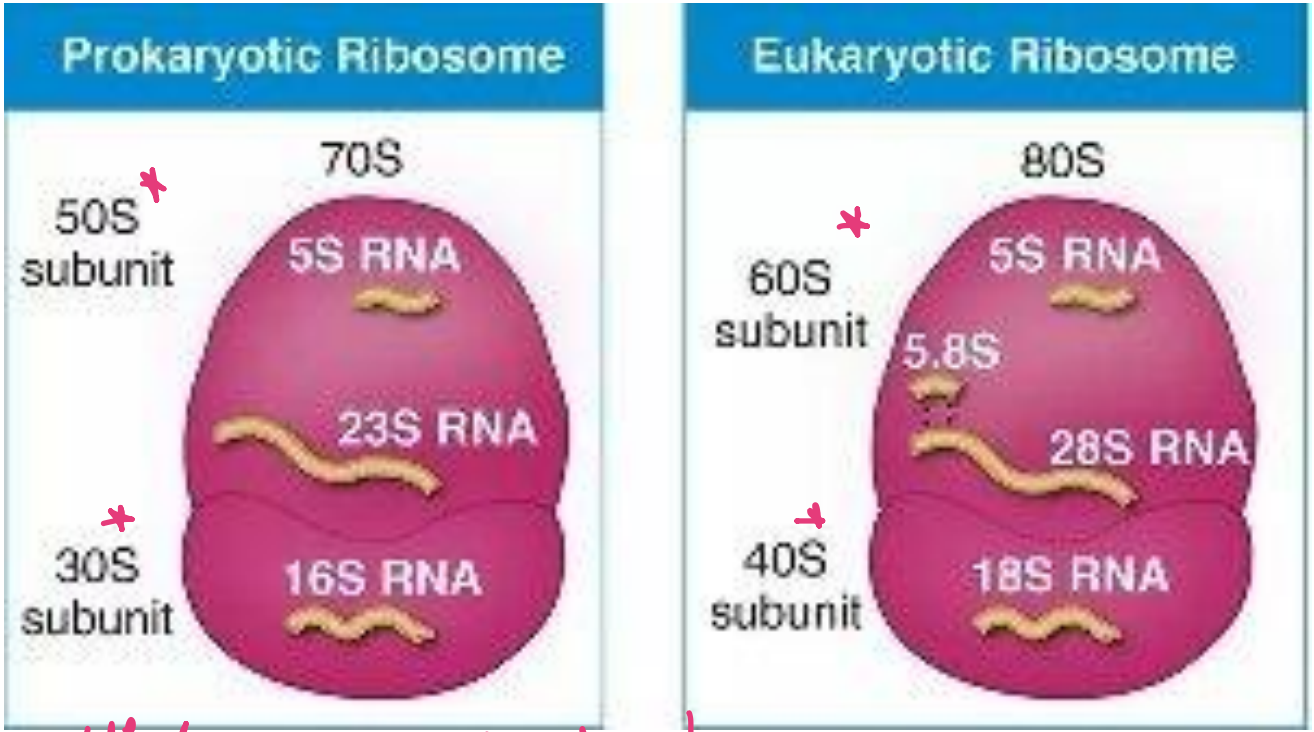
الجزء الصغير ← هون بترتبط مضادين بس لهالتين

Tetracyclines

Aminoglycosides

*طب بعد هيك احنا عنا ٣ مواقع على الرايبوسم الي هما (A,P,E) ،، في عنا مضادات بترتبط عند موقع A وبتمنع تكوين سلسلة a.a peptide chain ،،النتيجة:ثبطت التصنيع
وفيه الي برتبط على 50S فيمنع ارتباط a.a ببعض وما يواصل تصنيع السلسلة
***شو المحصلة : انت منعت تكوين البروتين اللازم لاستمرار انقسام البكتيريا بالتالي اسمو Bacteristatic مثبط لنمو البكتيريا
نتذكر انا بس اثبط نمو البكتيريا،شو بصير :يا جهازي المناعي يقدر يتخلص منها
او فترة حياتها تكون ساعات بس بالتالي تموت من حالها

Bacterial Protein Synthesis



still have different لسه في تشابه بس

**The basis for selective toxicity in cell wall inhibitors is that they are able to target bacterial cell wall which isn't existing in human cells .However, with protein synthesis inhibitors, we have a little bit of problem, why?

Firstly, we target bacterial protein synthesis because it is essential biochemical process required for survival of bacteria (if the bacteria isn't able to synthesis their own proteins, the bacterial cell will either go into growth rest or it will die),so that's the main cause of why we developed protein synthesis inhibitors.

** Protein synthesis inhibitors are effective antibiotics (very wide uses) The problem is : protein synthesis in general as a process isn't limited for bacteria only, it occurs both in prokaryotic bacterial cells and Eukaryotic human cells and there is a risk of lowered selective toxicity .

Protein synthesis inhibitor have ADE more than cell wall inhibitor

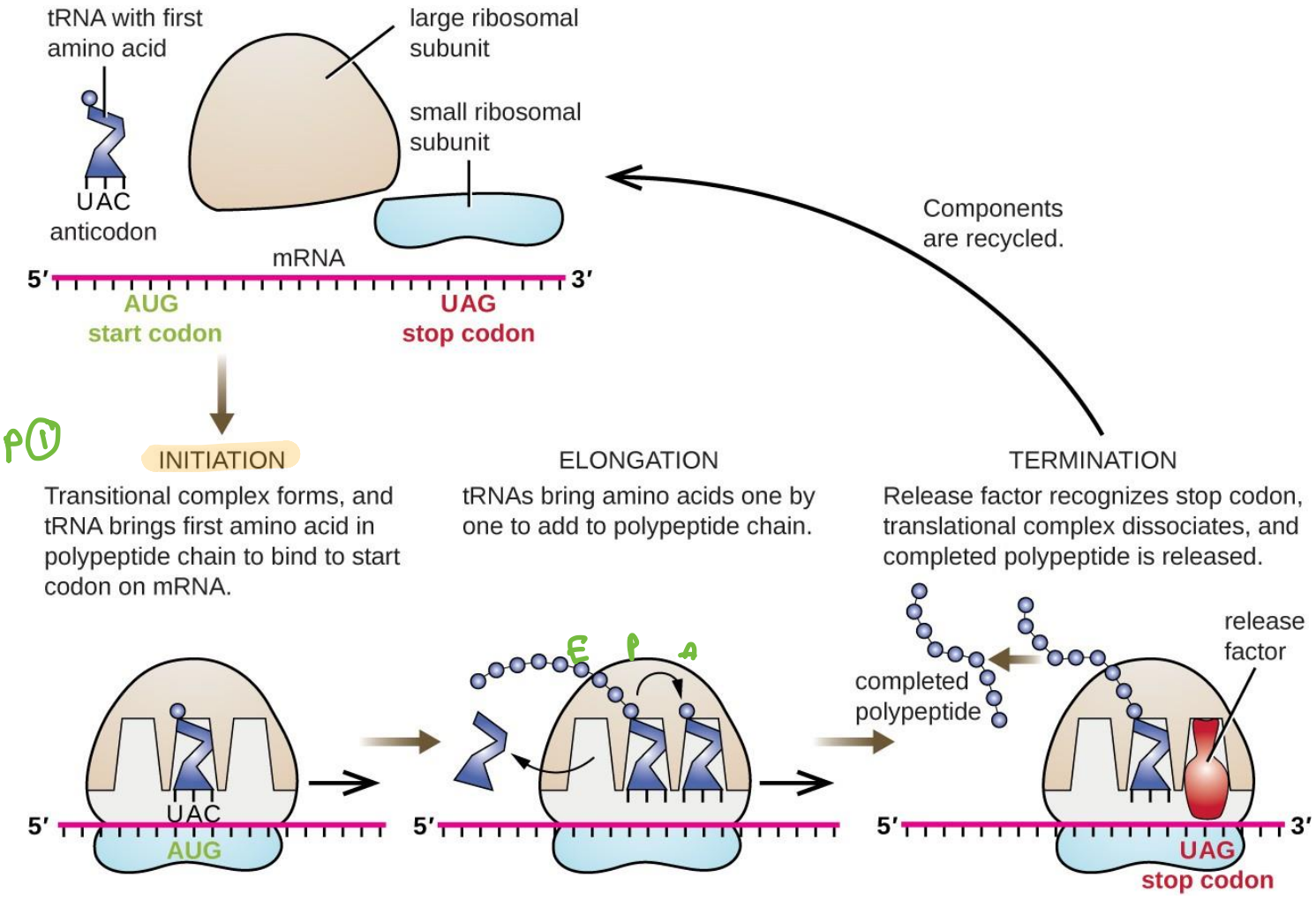
في الوضع العام

كل اغلب اشي ممكن يعمل الحساسية

وهيو عالعلاقة ب Mechanism

ولا specific لا cellwall inhibitor

+لانو ذكونا الدوا إلي مستخلص من الطبيعة طبيعي فلاقي الحساسية ردت فعل لبعض العالات



* الدكتور شرحها زي ما اخذناها بالجدنكس

step①

**Protein synthesis is required a machinery that composed of : ribosome (large subunit 50s , small subunit 30s) , mRNA (which carries the code for the protein to be synthesized) , tRNA (which have anticodon that is responsible to bind to the codon in coding the AA in the mRNA) , initiation and elondation factors that also help in the process.

*Protein synthesis is an energy dependent process , its required lots of energy (anabolic process) ,Steps of protein synthesis :

1)Initiation : it starts by the assembly of the protein synthesis complex (initiated by binding of tRNA with start codon (AUG) and that's recruit the binding of small and large subunits to mRNA.

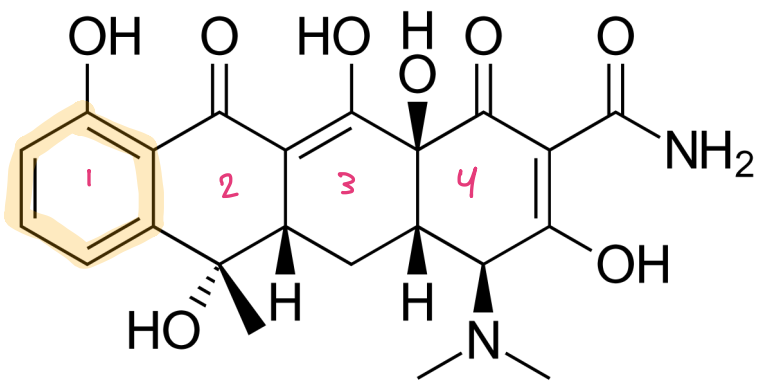
2)Elongation : which is energy dependent , the growing peptide enters certain site in the large subunits of ribosome which called growing polypeptide site (P site) ,while new tRNA enters the A site . during elongation , it happens a shift on mRNA whenever put a new AA on polypeptide by transpeptidation reaction .

3)Termination : release factor binds to stop codon on mRNA resulting in disassembly of the ribosome RNA complex and release of completely synthesized polypeptide So we have multiple target in the protein synthesis machinery that we can target with the drug .

Tetracyclines

Tetracyclines

4 حلقات



Tetracyclines

TETRACYCLINES	
Demeclocycline	DECLOMYCIN
Doxycycline	VIBRAMYCIN
Minocycline	MINOCIN
Tetracycline	

اشهرهم

Tetracycline → هاي تعتبر الطبيعية فيهم إنها استخرجناها من البكتريا

لما ننتبه على انو اسم دوا نفس اسم المجموعة

Tetracyclines

Mechanism of action

Target ال

-bind ***reversibly*** to the **30S** subunit of bacterial ribosomes

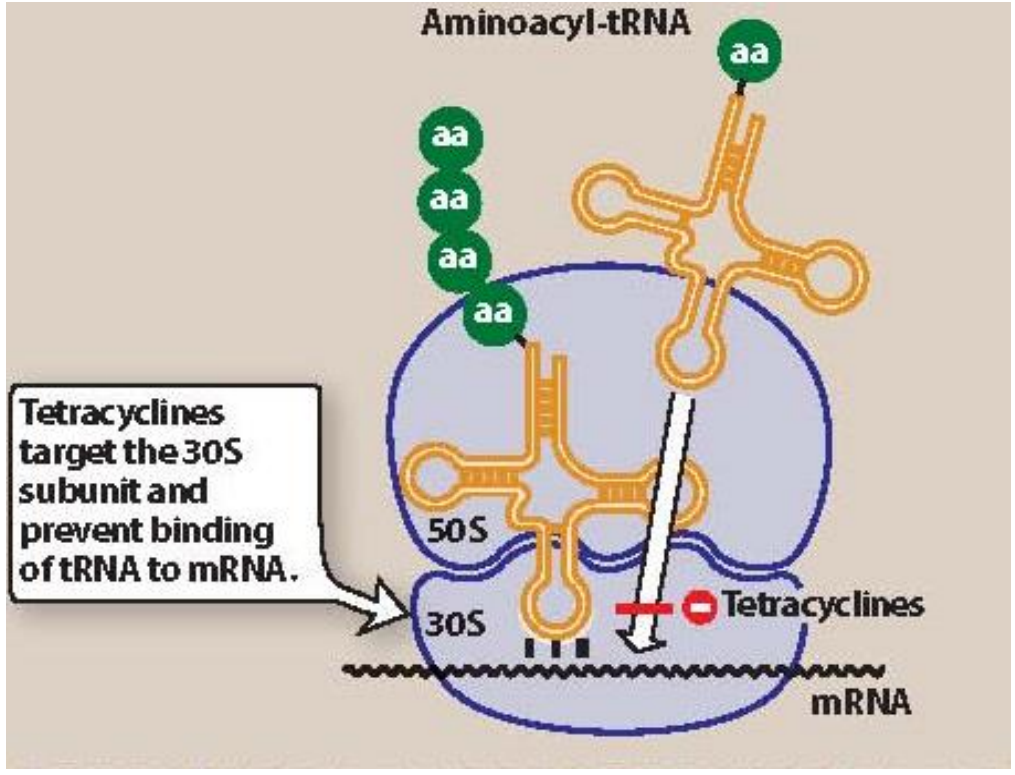
-prevent the binding of tRNA to the mRNA-ribosome complex

يربطوا مكان

ال tRNA

Prevent assembly of tRNA to mRNA ribosom → بالتالي يعطل لتصنيع البروتين

* النتيجة ← تثبيط صناعة البروتين



Tetracyclines

Antibacterial spectrum

- Bacteriostatic → Because of reversible binding
- Effective against gram-positive, gram-negative, protozoa, spirochetes, atypical, etc ال atypical هي لا gram + ولا

Commonly used for the treatment of: Most of are → orally موجودين

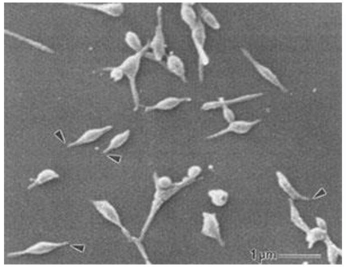
1. Acne (doxycycline) حب الشباب
2. (Chlamydia) (doxycycline) chlamidy can cause sexually transmitted infection and eye infection
3. Peptic ulcer disease (tetracycline) H.pylori which is the bacteria responsible of peptic ulcer disease
4. Lyme Disease (doxycycline) lyme disease is caused by spirochetes called Borrelia burgdorferi
5. Mycoplasma Pneumonia (doxycycline) cause type of lung infection specially in young adult

atypical ← atypical ← لو سببها ال

او لو السبب S.aureus لا يفرق الموضوع

Therapeutic Spectrum of Doxycycline

Intracellular bacteria are generally more difficult to treat compared to extracellular bacteria. This is because intracellular bacteria reside inside host cells, where they are protected from the immune system and difficult for antibiotics to reach. Some examples of bacteria that are known to be intracellular and can be challenging to treat include -



LYME DISEASE

- This is a spirochetal infection caused by Borrelia burgdorferi. The disease is transmitted by the bite of infected ticks.
- Infection results in skin lesions, headache, and fever, followed by meningoencephalitis and, eventually, arthritis.
- A bull's-eye pattern rash with a red outer ring, called erythema migrans is a hallmark of Lyme disease
- *Doxycycline* is one of the preferred therapeutic options.

MYCOPLASMA PNEUMONIAE

- Mycoplasma pneumoniae, or walking pneumonia, is a common cause of community-acquired pneumonia in young adults and in people who live in close confines, such as in military camps.
- Treatment with a macrolide or *doxycycline* is effective.

Gram (+) cocci
- Staphylococcus aureus (including *methicillin*-resistant strains)
- Streptococcus pneumoniae

Gram (+) bacilli
- Bacillus anthracis

Gram (–) cocci

Gram (–) rods
- Brucella species*
- Vibrio cholerae
- Yersinia pestis

*(a tetracycline + *gentamicin*)

Anaerobic organisms
- Clostridium perfringens
- Clostridium tetani

Spirochetes
- Borrelia burgdorferi
- Leptospira interrogans
- Treponema pallidum

Mycoplasma
- Mycoplasma pneumoniae

Chlamydia
- Chlamydia species

Other
- Rickettsia rickettsii

CHOLERA

- Cholera is caused by Vibrio cholerae ingested in fecally contaminated food or water.
- The organism multiplies in the gastro-intestinal tract, where it secretes an enterotoxin that produces diarrhea.
- Treatment includes *doxycycline*, which reduces the number of intestinal vibrios, and fluid replacement.

CHLAMYDIAL INFECTIONS

- Chlamydia trachomatis is the major cause of sexually transmitted disease in the United States. It causes nongonococcal urethritis, pelvic inflammatory disease, and lymphogranuloma venereum.
- Chlamydia psittaci causes psittacosis, which usually takes the form of pneumonia. Other clinical forms include hepatitis, myocarditis, and coma.
- *Doxycycline* or *azithromycin* is used to treat chlamydial infections.

ROCKY MOUNTAIN SPOTTED FEVER

- This disease, caused by Rickettsia rickettsii, is characterized by fever, chills, and aches in bones and joints.
- Response to tetracyclines is prompt if the drug is started early in the disease process.

trachoma →

طه حسين
كان أعمى وانصاب فيها وهو بعمر صغير

12/7/2023

Wolters Kluwer

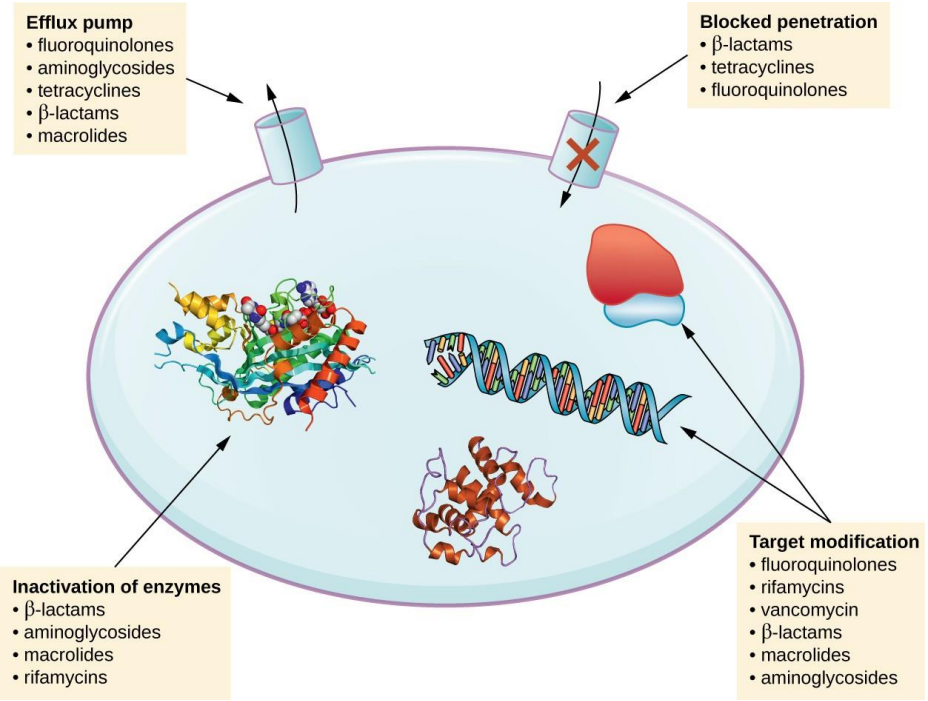
الدكتور راجعنا بنقطة ← β-lactamases, for example, are enzymes that can break down β-lactam antibiotics, including the commonly used protein synthesis inhibitors such as penicillins and cephalosporins. These enzymes hydrolyze the β-lactam ring in the antibiotic, rendering it ineffective in inhibiting bacterial protein synthesis.

بعاد على الـ cell wall اللي بتتضيق
نفس الفكرة هون

Tetracyclines

Mechanisms of resistance

1. Efflux pump (most common) pump the drug out of the cell.
2. Enzymatic inactivation of the drug → التتراسيكلين بيقدر على هذه تعديل فيها Tetracycline انزيم تكسر الـ
3. Interfering with binding to ribosomes → PBP * مثل فكرة تعديل على cell wall في
4. Cross-resistance is *not* common



that's mean resistance to one tetracycline doesn't confer universal resistance to all tetracyclines, and development of cross resistance may be dependent on the mechanism of resistance → عكس β lactams

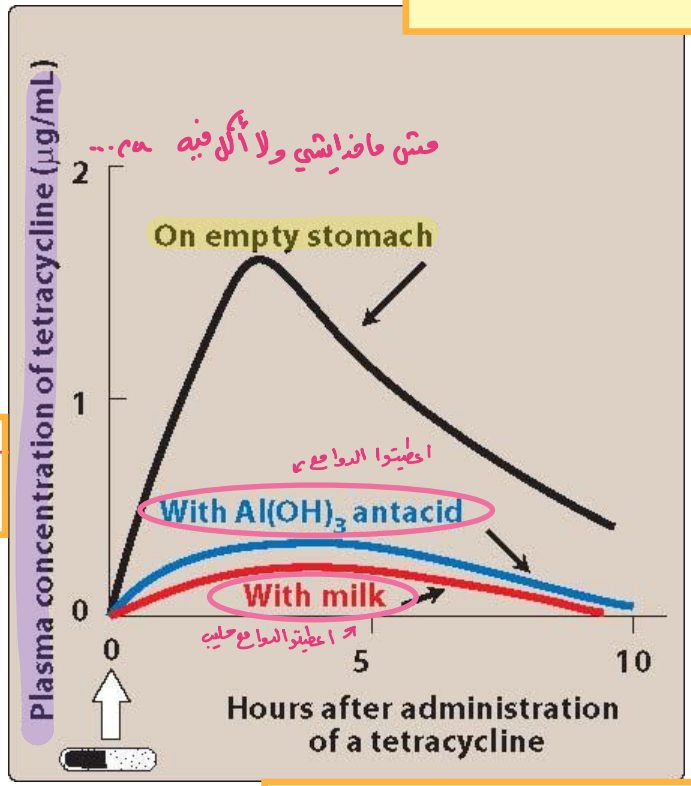
Tetracyclines

Pharmacokinetics

Absorption

- Oral
- Adequately absorbed
- ↓ absorption when administered with dairy (high cations) → formation of nonabsorbable chelates

It will happen an adequate absorption ,reaching to peak in plasma, then it happens metabolism and excretion



it reflect how much of drug is absorbed after oral administration

Administration of tetracyclines with dairy products(high Ca) or other substances that contain divalent and trivalent cations (ex :Mg ,Ca, Al,or iron supplements) decreases absorption , because they form insoluble comple x

Administration of tetracycline with milk is interfere with absorption of it ,resulting in low con.c of drug in plasma ,and the same when give anti acid .

General idea : tetracyclines shouldn't given with dairy product

Tetracyclines

tetracyclines are concentrated in bones

and teeth because they have high content of Ca ,and this actually create a problem because imagine that you give tetracyclines to child that still has bone clacification.,this lead to bone malformation ,so tetracyclines are contraindicated in children younger than 8years

Pharmacokinetics

Distribution

good

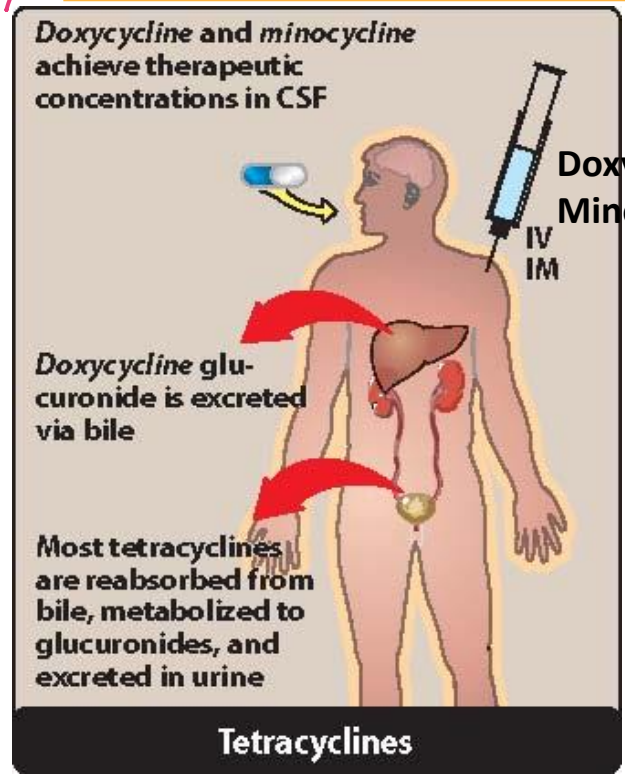
- Distribute well in body fluids, including CSF **We don't use it for meningitis test**
- Bind to tissues undergoing calcification e.g., bones, teeth. *can use it in bones/teeth infection
- Cross placenta and deposit in fetal bones

بعدل تتشوهان

contraindicated in pregnant women

Elimination

- Tetracycline eliminated unchanged in urine
- Doxycycline eliminated in bile/feces



* **Other types of tetracyclines undergo normal hepatic metabolism into inactive metabolites which then eliminated by renal execration.**

Tetracyclines

Alteration of gut microbiota: Tetracycline has a broad-spectrum antibacterial effect, which means it can also affect the normal gut microbiota, the beneficial bacteria that reside in the gastrointestinal tract. Disruption of the natural gut flora can lead to changes in the gastrointestinal environment and increase the risk of gastric irritation and inflammation.

normal flora

بعد اخذو لمدة طويلة ←

Adverse effects

- **Gastric discomfort:**

-irritation of gastric mucosa

-esophagitis if irritation is severe

- **Effects on calcified tissues**

-deposited in tissues undergoing calcification, e.g., bones in children.

-dental hypoplasia characterized by discoloration of teeth and usually mal Growth

-growth problems

-pediatric use is limited

الاطفال

الحل

Irritation is minimized through coadminstration With food other than dairy product (Tetracycline) should be taken on an empty stomach always.

شرط

Tetracyclines الوحيدون عيلة

GI disturbance

Deposition of drug in bones and teeth

Tetracyclines

they increase the sensitivity of skin to sun light so we recommended patient to use tetracyclines with sun protection and avoid unnecessary avoid to sun light

Adverse effects

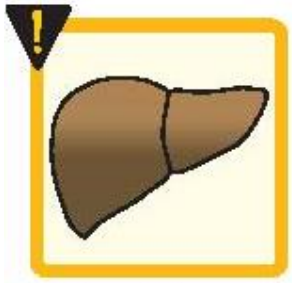
- **Hepatotoxicity**
- **Phototoxicity:**

-severe sunburns (recommended to wear sun protection)

- **Vestibular dysfunction:**

-dizziness, vertigo, tinnitus

- **Pseudotumor cerebri** rarely



Liver failure

Phototoxicity

Vertigo

dizziness

Avoid in pregnancy

1) Hepatotoxicity :Rarely hepatotoxicity may occur with high doses , particularly in pregnant women and those with preexisting hepatic dysfunction

2) Phototoxicity : they increase the sensitivity of skin to sun light so we recommended patient to use tetracyclines with sun protection and avoid unnecessary avoid to sun light

3) Vestibular dysfunction : cochlea and the vestibule of the inner ear are responsible for hearing and balance , tetracyclines may effect of their function and this result in Dizziness , vertigo , tinnitus

4) Pseudotumor cerebri: CSF circulate within CNS through chambers ventricles and spinal canal of spinal cord and , that is closed system In case that volume of CSF is increased or obstruction happened that result in increase intracranial hypertension .

pseudotumor

كاذب / ليس حقيقي

*

خارجي الفهم

Pseudotumor cerebri, also known as idiopathic intracranial hypertension (IIH), is a condition characterized by increased pressure within the skull. Despite the name, it is not a tumor but rather a condition that mimics the symptoms of a brain tumor.

The exact cause of pseudotumor cerebri is unknown, but it is believed to be related to an abnormal accumulation of cerebrospinal fluid (CSF) within the skull, leading to increased pressure on the brain. This condition primarily affects overweight women of childbearing age, but it can also occur in men and children.

Symptoms of pseudotumor cerebri can include severe headaches, ringing in the ears (tinnitus), blurry or double vision, temporary loss of vision, neck and shoulder pain, nausea, and papilledema (swelling of the optic nerve, visible during an eye examination).

Tetracyclines

why?

Because of teratogenic

***

Contraindications

1. Pregnant women
2. Breast-feeding women
3. Pediatric age group <8 years

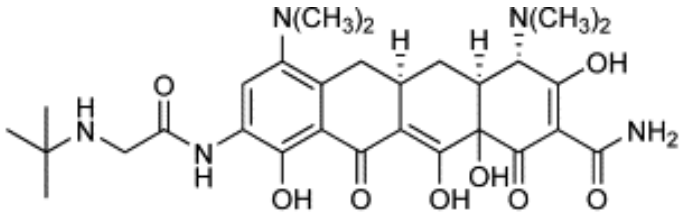
+ موانع الاستخدام

Glycylcyclines

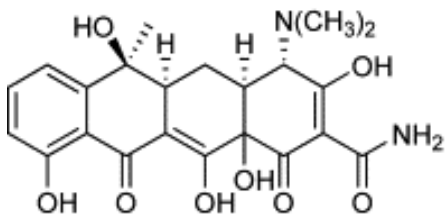
Tigecycline

*very broad specrtrum

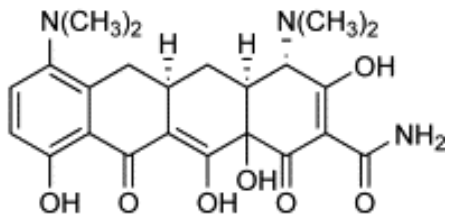
- Derivative of minocycline
- Same mechanism of action as tetracyclines
- Similar mechanisms of resistance



Tigecycline (**58**)



Tetracycline (**59**)



Minocycline (**60**)

← في تشابه →

Tigecycline

Antibacterial spectrum

- Effective against MRSA
- Effective against multi-drug resistant streptococci
- Effective against vancomycin-resistant enterococci (VRE)
- Effective against ESBL gram-negative bacteria
- Effective against Acinetobacter spp
- NOT effective against Pseudomonas

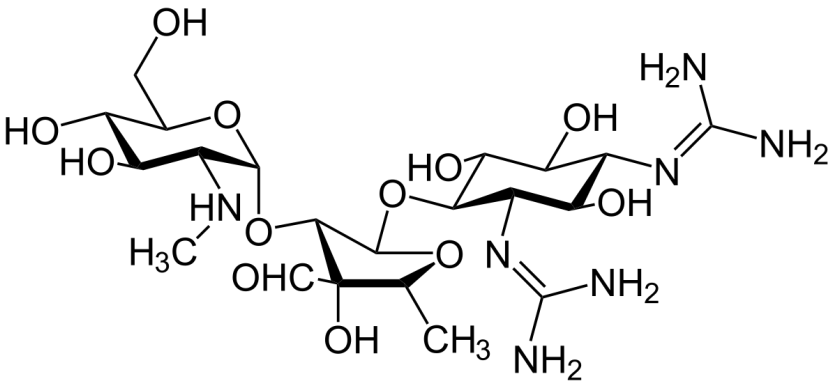
Right ال عشن

kept as last options to treat a resistant infections

* خصوصًا ل MRSA الادوية إلي قبل اخذناها و بيجي هاد بعدها

Aminoglycosides

Aminoglycosides → gram⊖ اربطها بـ



AMINOGLYCOSIDES

- *Amikacin*
- *Gentamicin* GARAMYCIN ← الأبن تبعهم
- *Neomycin* NEO-FRADIN
- *Streptomycin* → Anti TB
- *Tobramycin* TOBREX

for التليف الكيسي → Cystic fibrosis (CF) is a genetic disorder that primarily affects the lungs

+

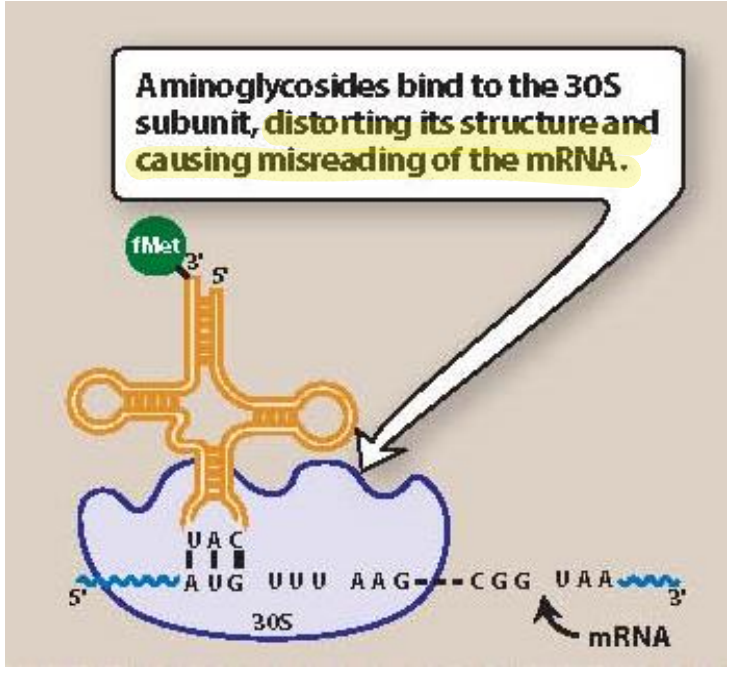
used for treatment of respiratory infections specially those caused by p.aueruginosa

Aminoglycosides

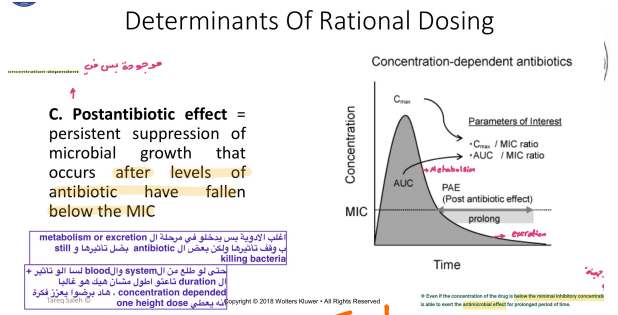
tetracyclines and Aminoglycosides are bind with 30s ribosome but in different binding site And the result of binding also differs

Mechanism of action

- Bind to 30S ribosomal subunit
- Interfere with assembly of the functional ribosomal apparatus
- Cause the 30S subunit of the completed ribosome to misread the genetic code



Aminoglycosides



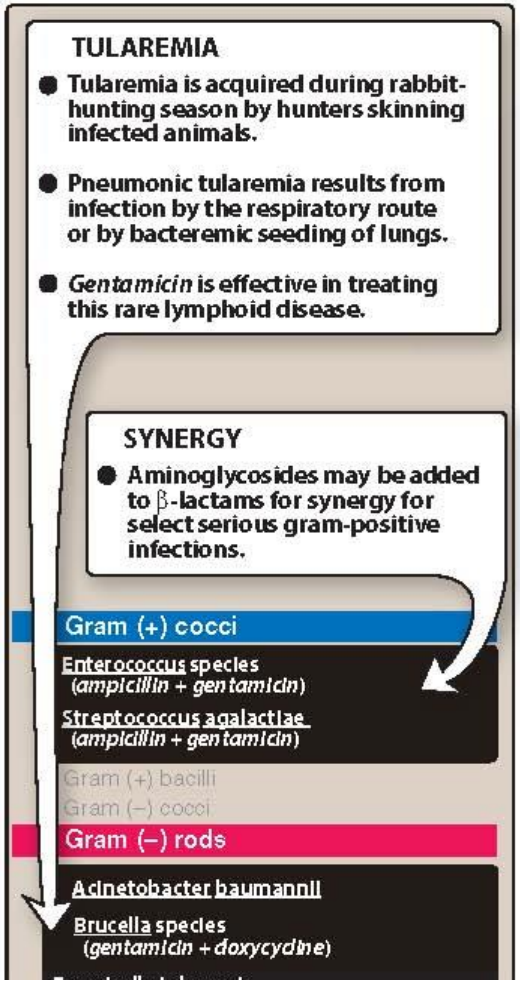
Antibacterial spectrum

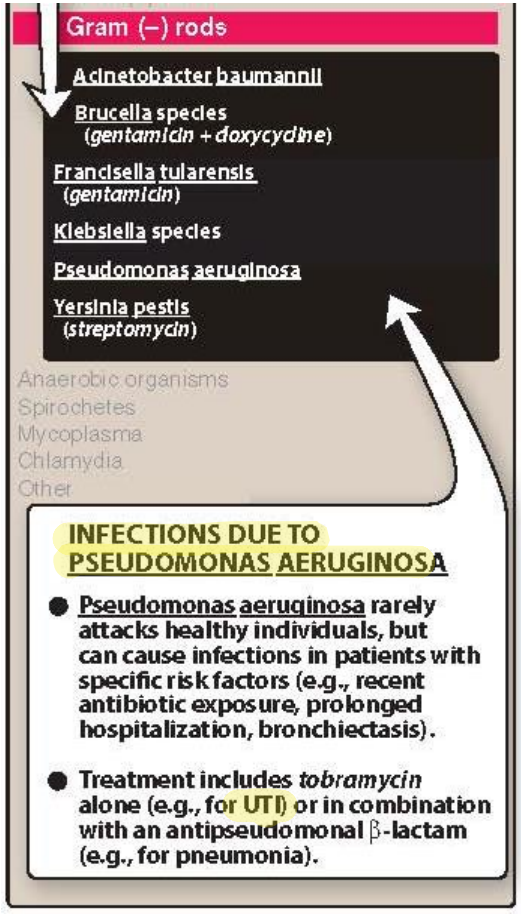
- Bactericidal
- Concentration-dependent → cMax → give it 8 to 10 times the MIC
- Exhibit PAE post anti biotic effect → Irreversible binding
- Effective against gram-negative bacilli (INCLUDING multi-DRUG resistant *P. aeruginosa*) specially tobramycin + remember : tetracyclines and tigecycline don't cover p.aeruginosa
- Used in combination with β-lactams

Gentamycin + ampicillin

cidal + cidal

Ampicillin is a penicillin-type antibiotic that is frequently used in combination with other antibiotics for the treatment of meningitis caused by bacteria called Streptococcus pneumoniae





Urinary tract infection

Some clinical uses of aminoglycosides

Aminoglycosides

Aminoglycosides

Mechanisms of resistance

1) efflux pumps → تدخل لجوا و تطلع بـ pumps
2) decreased uptake by modification of porins in G- bacteria
3) modification and inactivation by plasmid-associated synthesis of enzymes that hydrolyze aminoglycosides

   -Amikacin is less vulnerable to these enzymes

Aminoglycosides

Pharmacokinetics

Absorption

given topical → مثلا قطب كريم

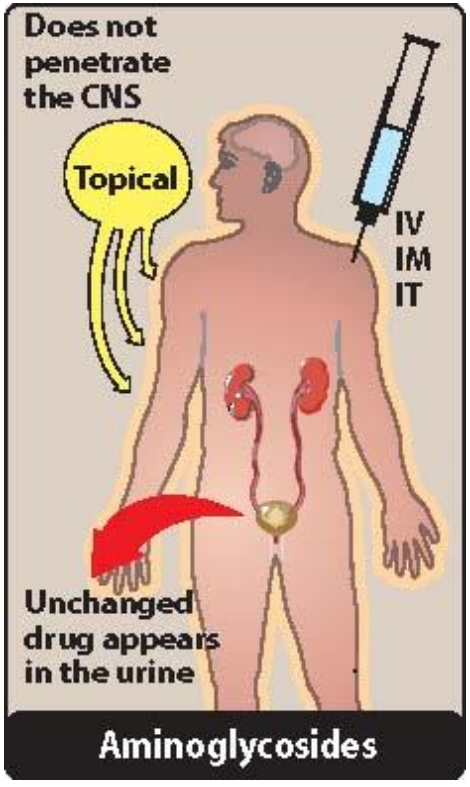
-all are given IV (except neomycin) ممنوع يتعطى systemic

Distribution

-variable distribution in body fluids

-inadequate distribution in CSF → Gentamycin ماعدا ال (قليل)

-cross the placenta **Maybe teratogenic**



Aminoglycosides

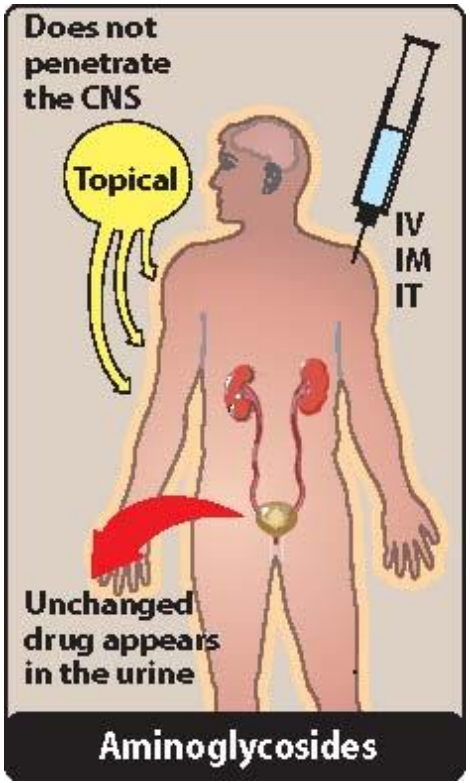
Pharmacokinetics

Elimination

-90% are excreted unchanged in the urine

-accumulation occurs in cases of renal dysfunction

Toxic لانو



Aminoglycosides

Adverse effects

- **Ototoxicity (vestibular and auditory)**

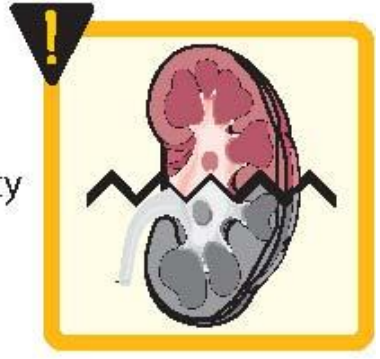
-might cause irreversible deafness

-Vertigo (especially with streptomycin)

- **Nephrotoxicity**

-disrupt Ca^{++}-mediated transport processes

-from mild reversible renal impairment to irreversible acute tubular necrosis



Aminoglycosides

Adverse effects

- Neuromuscular paralysis

-patient with myasthenia gravis are at risk

this disease is characterized by formation autoantibodies directly against ACH receptors

عندهم مشكلة في التوصيل بين الاعصاب والعضلات

- Allergic reaction

- Mostly contact dermatitis with topical neomycin

Paralysis

Skin rash