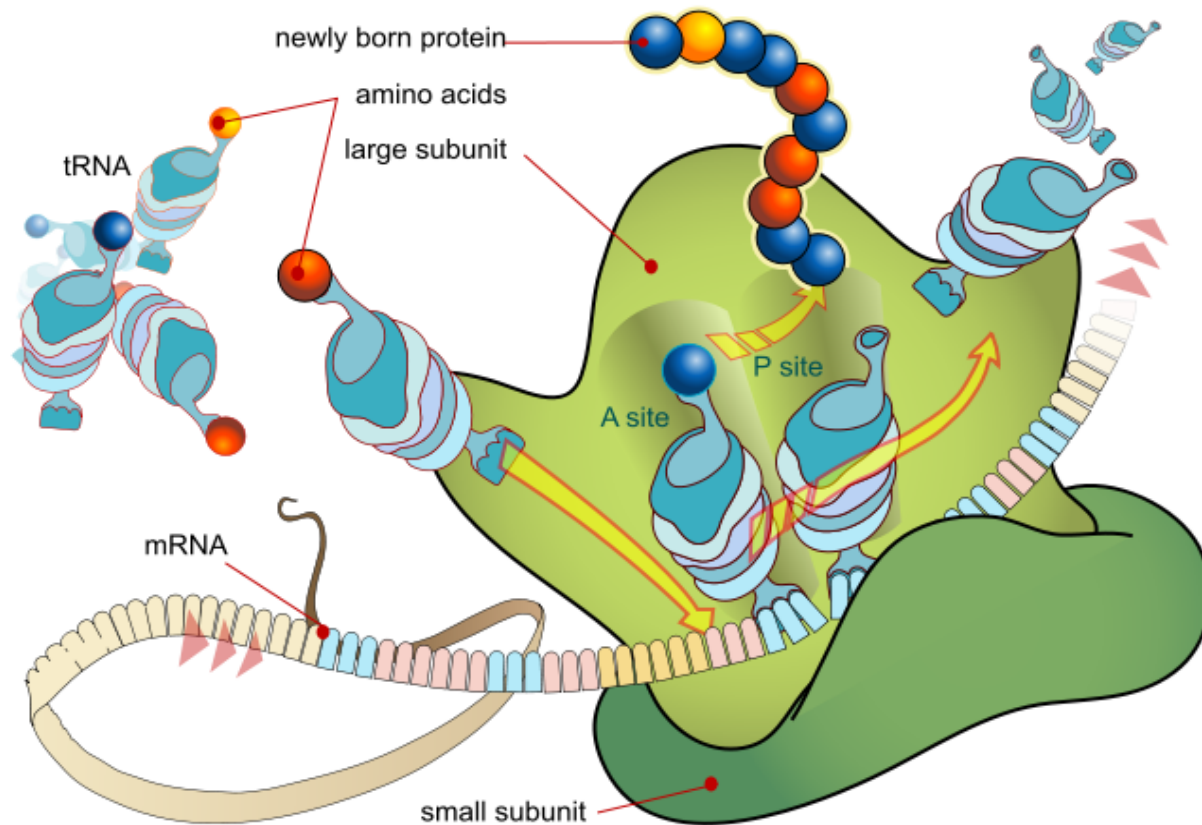


Protein Synthesis Inhibitors

Part 1



Pharmacolgy 3
Dr. Heba Khader

بسم الله الرحمن الرحيم, اللهم لا سهل الا ما جعلته سهلا وانت تجعل الحزن اذا شئت سهلا
اللهم اشرح لي صدري ويسر لي امري واحلل عقدة من لساني يفقهوا قولي, اللهم ارحم شهداءنا في فلسطين
اللهم ارزقهم دارا خيرا من دارهم وارزقهم اهلا خيرا من اهلهم وارزقهم الفردوس الاعلى من الجنة يارب

يلا نبلس...🔥💥

Difference between human and bacterial ribosomes

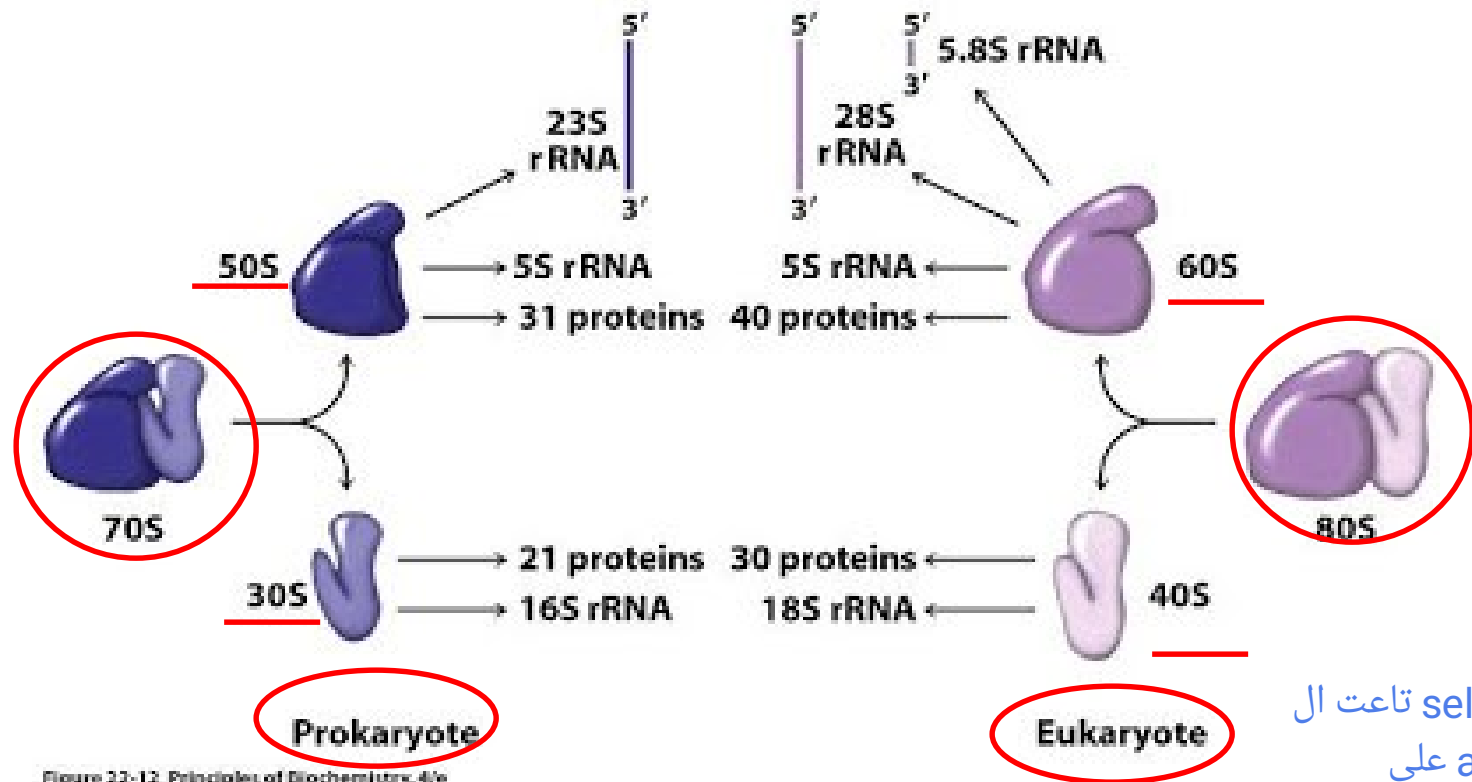
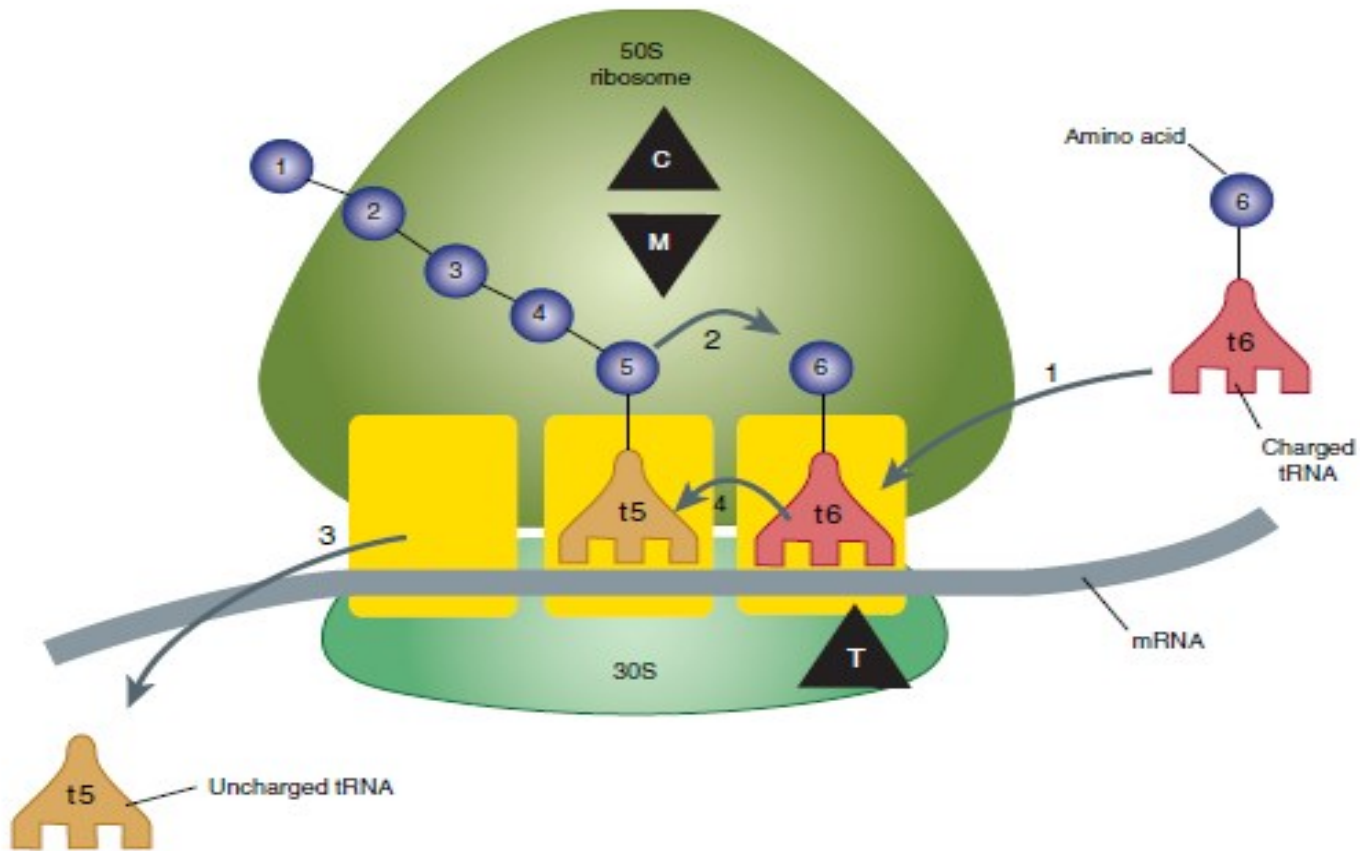


Figure 23-12 Principles of Biochemistry, 4/e
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ال selectivity تاعت ال
antibiotics على
الرايبوسوم تاع البكتيريا
(prokaryotic) مش
تاعت
الانسان (eukaryotic).

Selectivity of antibiotics on bacterial ribosomes.

Protein synthesis steps



Amino acids are shown as numbered circles. In **step 1**, the charged tRNA unit carrying amino acid 6 binds to the acceptor site on the 70S ribosome (**initiation**). The peptidyl tRNA at the donor site, with amino acids 1 through 5, then binds the growing amino acid chain to amino acid 6 (**peptide bond formation or elongation, step 2**). The uncharged tRNA left at the donor site is **released (step 3)**, and the new 6-amino acid chain with its tRNA shifts to the peptidyl site (**translocation, step 4**).

عملية تصنيع البروتين بتمر بمراحل

١- ييجي عنا ال uncharged tRNA unit الي لونها احمر حامل لل amino acid خلينا نحكي ٦
عشان يسهل الشرح لقدام, وبيرتبط بموقع اسمه ال acceptor site على الرايوسوم 70s
المرحلة هاي بنسميها ال initiation.

٢- جنب ال acceptor site في donor site يكون عليه tRNA الحامل لل GROWING
amino acid chain الي لونها اصفر الي بالاخير بده يعطيني peptide وبالاخير بده يعطيني
protein يقوم هاض ال tRNA بعطي ال growing chain لل tRNA الاحمر, بربطوها مع ال
AMINO ACID 6 (PEPTIDATION FORMATION OR) هاي العملية بنسميها
(ELONGATION).

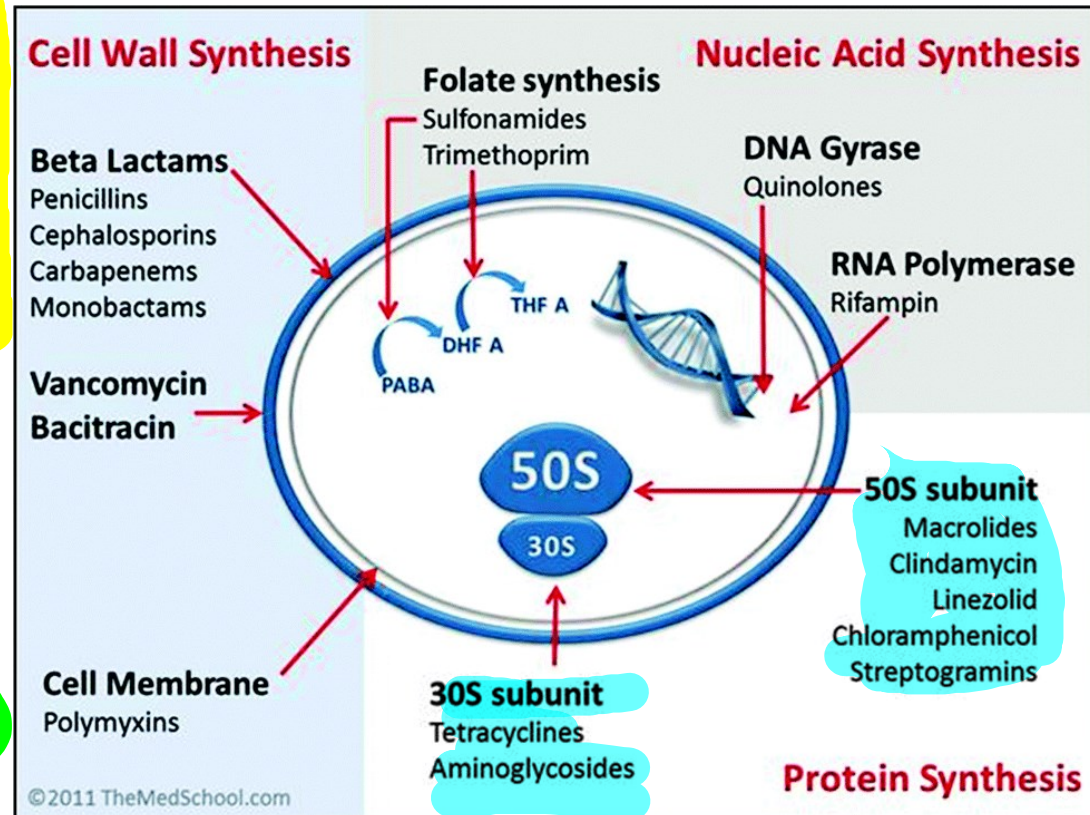
٣- ال uncharged tRNA الي كان موجود على donor site بصيرله release.

٤- ال tRNA الاحمر الي كان موجود على ال acceptor site ييجي محل الاصفر الماضي على
donor site هاي العملية اسمها (translocation).

وبضلها تتكرر هاي العملية حتى يعملوا كل ال amino acid.

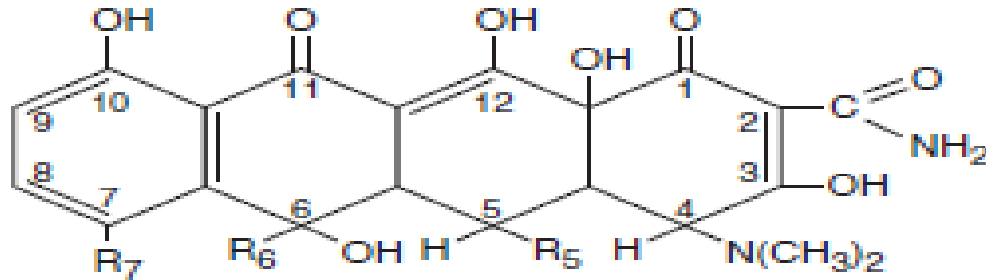
Protein synthesis inhibitors

- Tetracyclines
- Macrolides
- Clindamycin
- Chloramphenicol
- Aminoglycosides



تسميته هيـك لانه عنده 4-cycles , وال different substitution يعني different activity.

Tetracyclines



	R ₇	R ₆	R ₅	Renal Clearance (mL/min)
Chlortetracycline	— Cl	— CH ₃	— H	35
Oxytetracycline	— H	— CH ₃	— OH	90
Tetracycline	— H	— CH ₃	— H	65
Demeclocycline	— Cl	— H	— H	35
Methacycline	— H	= CH ₂ *	— OH	31
Doxycycline	— H	— CH ₃ *	— OH	16
Minocycline	— N(CH ₃) ₂	— H	— H	10

*There is no — OH at position 6 on methacycline and doxycycline.

- Tetracyclines are broad-spectrum bacteriostatic antibiotics that inhibit protein synthesis.
- Tetracyclines enter microorganisms in part by passive diffusion and in part by an energy-dependent process of active transport.

الشفـل كله تصنع الـ protein بصير قاعد جوا الـ cytosol

من الاشياء الي سببتي resistance انه البكتيريا ما تدخل الدوا او تعمله efflux

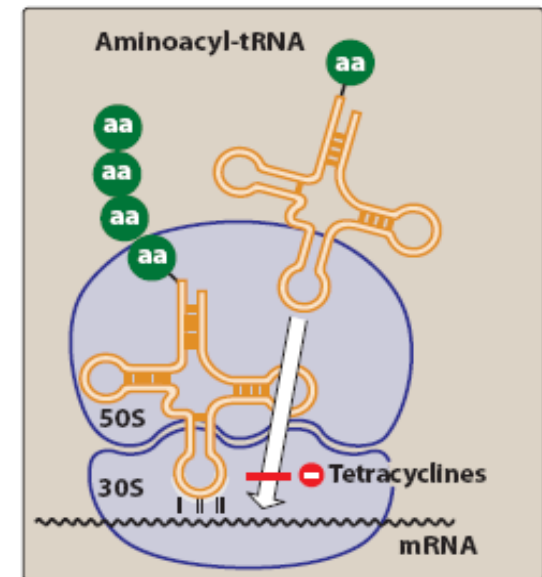
Tetracyclines

بشكل عام ال tetracycline يمنع
ال tRNA بانه يرتبط على ال
acceptor site.

- **Mechanism of action:**

- binds reversibly to the 30S subunit of the bacterial ribosome
- blocking access of the amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site thus inhibiting initiation step in bacterial protein synthesis.

Step 1



Tetracycline indications

- Spectrum of activity:

Bro ad

- A tetracycline is the drug of choice in the treatment of infections caused by rickettsiae.
- Tetracyclines are also excellent drugs for the treatment of *Mycoplasma pneumonia*, *chlamydiae*, and some *spirochetes*.
- They are used in combination regimens to treat gastric and duodenal ulcer disease caused by *Helicobacter pylori*.

الاستخدامات:

ال indication هاي مافي نوع محدد من ال tetracyclin بنستخدمه احنا بنستخدم ال tetracyclin group يعني كلهم يعني مثلاً minocycline او doxycycline.

Tetracycline indications

- **ROCKY MOUNTAIN SPOTTED FEVER**

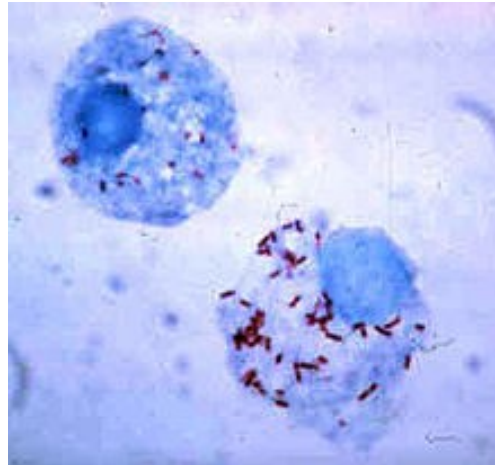
اسباب

– **Caused by Rickettsia rickettsii (G-ve, obligate intracellular parasite)**

اعراض

– **Characterized by fever, chills, and aches in bones and joints**

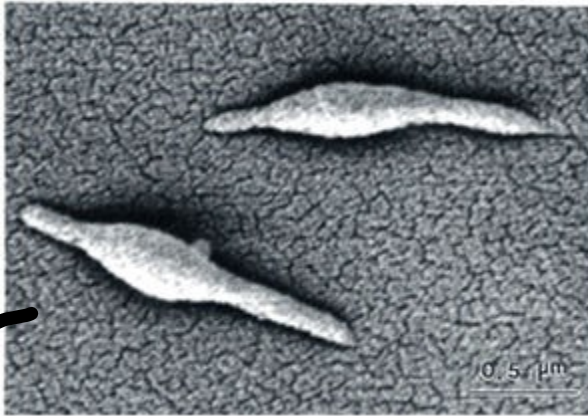
اول ما شخصوا المرض شخصوه بمنطقة اسمها rocky mountain ومن الاعراض كانت الحمة المنقطة زي الصورة تحت



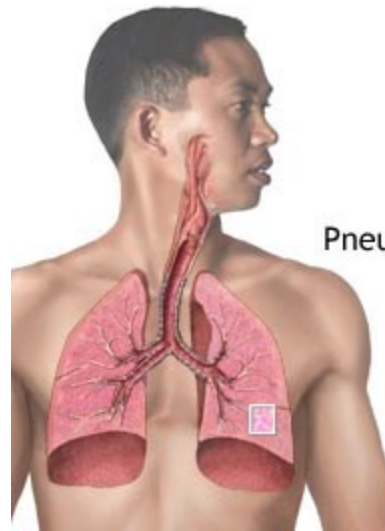
Tetracycline indications

2

• MYCOPLASMA PNEUMONIAE



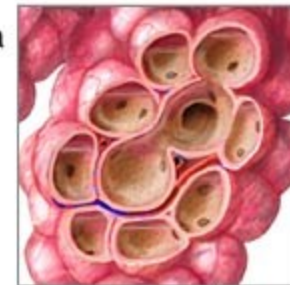
Is a bacterium that lacks cell wall



Normal alveoli



Pneumonia



ADAM.

ال mycoplasma ما عندها cell wall يعني
الادوية الي بتأثر عليه ما رح يكون الها فائدة

Mycoplasma pneumoniae is a common cause of community acquired pneumonia

Tetracycline indications

• LYME DISEASE



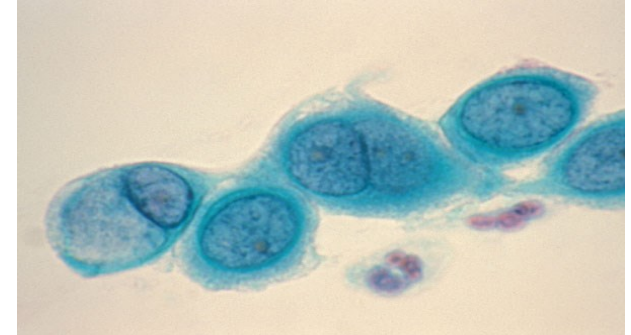
- This is a spirochetal infection caused by *Borrelia burgdorferi* (bor-dor-fry)
- Transmitted by the bite of infected ticks
- Infection results in skin lesions, pain, headache, and fever

Tetracycline indications

• **CHLAMYDIAL INFECTIONS** caused by:

A. **Chlamydia trachomatis** :

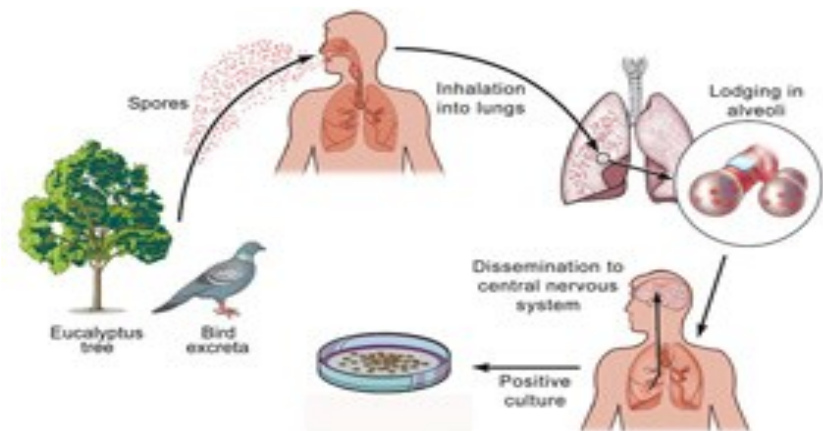
- Sexually transmitted infection
- Chlamydia conjunctivitis



ال chlamydia اذا هي سببت ال pneumonia فال tetracycline هو الي بعالجها

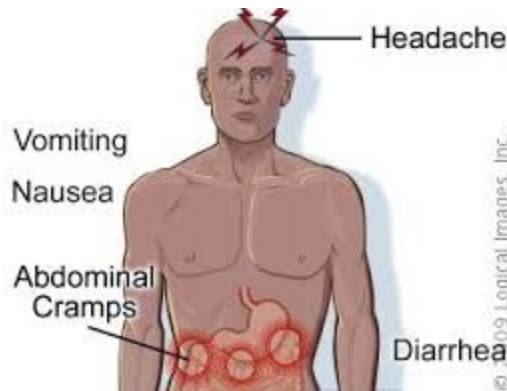
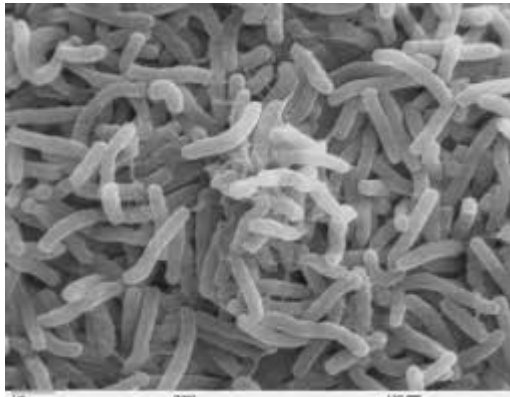
B. **Chlamydia psittaci (sita-si)**

- **causes psittacosis (sitacosis) or called parrot disease which usually takes the form of pneumonia.**



Tetracycline indications

• CHOLERA



- An infection of small intestine
- Caused by **Vibrio cholerae (G-)** ingested in fecally contaminated food or water
شخص بصير عنده vomiting , dehydration فبنقله عوض سوائل ومي كثير
- The organism multiplies in the gastrointestinal tract, where it secretes an enterotoxin that produces diarrhea and vomiting

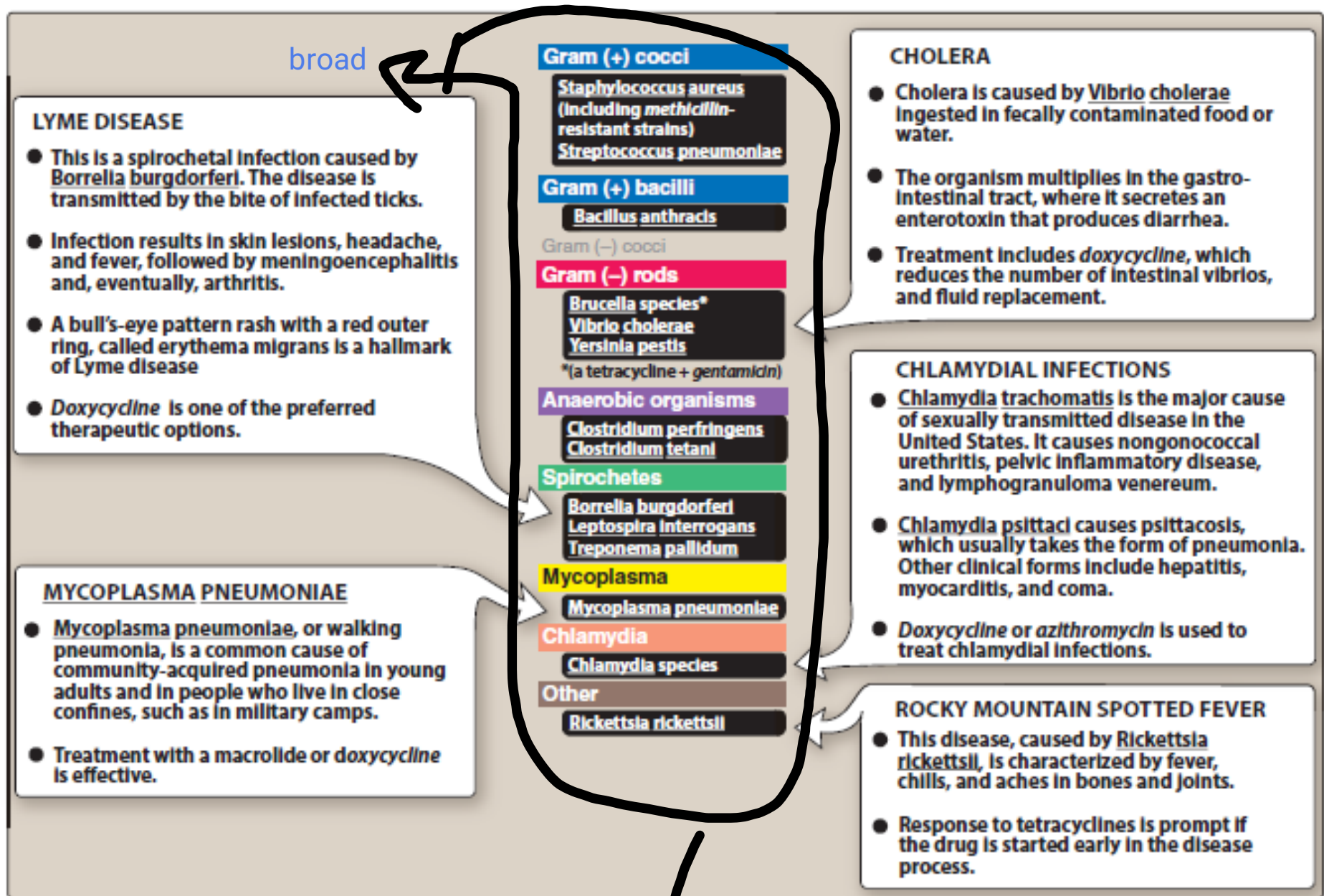


Figure 39.3

Typical therapeutic applications of tetracyclines.

مذكور هون كل الي حكيناه

Secondary uses of Tetracyclines

- Alternative drug for syphilis بدل penicillin g
- Prophylaxis against chronic bronchitis
- Treatment of moderately severe acne

اکثر استخدماته



Resistance to Tetracyclines

- Three mechanisms of resistance to tetracycline analogs have been described:

حكيت عنه فوق يا اما انها بتمنع دخوله او بتخليه يطالع بشكل اكبر

1. **impaired influx or increased efflux** by an active transport protein pump.

2. **ribosome protection** due to production of proteins that interfere with tetracycline binding to the ribosome.

ال rimosomes بتصير تعمل modification لحالها وبتمنع ارتباط الدواء فيها

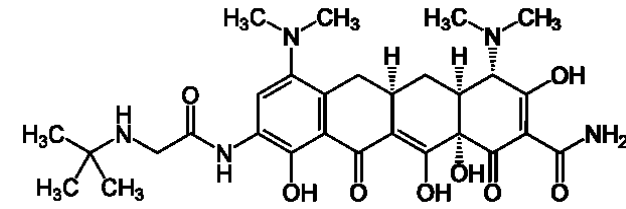
3. enzymatic inactivation.

انه الكثيرا يصير عندها انزايم يحطم نفس فكرة ال b-lactamase وهاي قليلة انه البكتيريا تعملها

The most important of these are production of an efflux pump and ribosomal protection. (but not for tigecycline)

صار عنا resistance للدواء فا شو عملوا الصيادلة والعلماء اخترعوا دواء يقوام مقاومة البكتيريا الي هو ال tigecycline وهو عبارة عن derivative من ال monicycline بمنع مقاومة البكتيريا لل classic tetracycline.

Tigecycline



الـtigecycline من الـdrugs يتوصل تركيز منيح للجلد عشان هيك يستخدم لحب الشباب والـskin infection

- A newer tetracycline analog, **tigecycline**, is a glycylcycline and a semisynthetic derivative of minocycline.
- It is specifically designed to overcome tetracycline resistance, that utilize efflux pumps and/or ribosomal protection.
- It is indicated for the treatment of complicated skin and soft tissue infections, as well as complicated intra-abdominal infections (active against **MRSA**, vancomycin-resistance enterococci (**VRE**)).
- Following IV infusion, tigecycline exhibits a large volume of distribution.
- It penetrates tissues well but has low plasma concentrations. Consequently, tigecycline is a poor option for bloodstream infections.

عشنة بتوزع كويس فالدّم وهاي خاصية كويسة الا انه بضل تركيز قليل فالدّم وهاض الاشّي بخليني ما استخدمه في حال صار عندي infection فالدّم

Pharmacokinetics

Absorption:

- Most tetracyclines are adequately absorbed after oral ingestion (Doxycycline, minocycline)
- Tigecycline is poorly absorbed orally and must be administered intravenously.
- Administration with dairy products or other substances that contain divalent and trivalent cations (for example, magnesium and aluminum antacids or iron supplements) decreases absorption due to the formation of nonabsorbable chelates.
- Tetracycline and demeclocycline should be administered on an empty stomach, while doxycycline and minocycline absorption is not impaired by food.

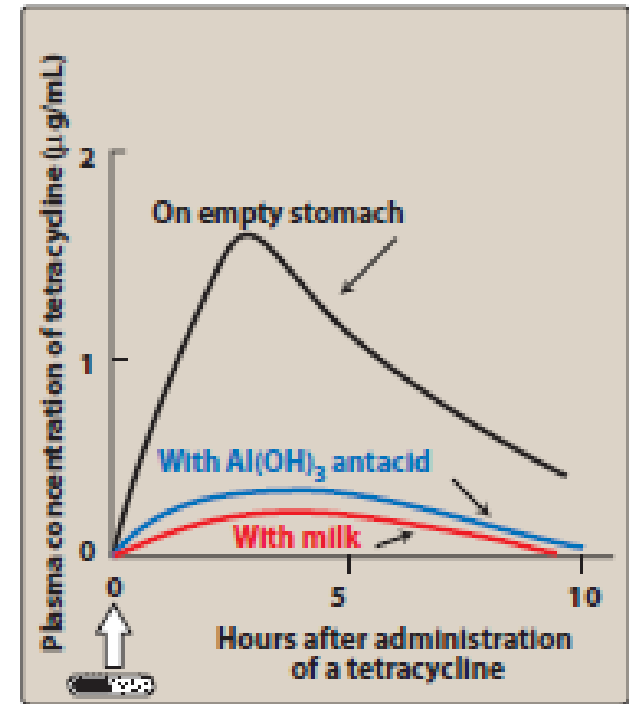
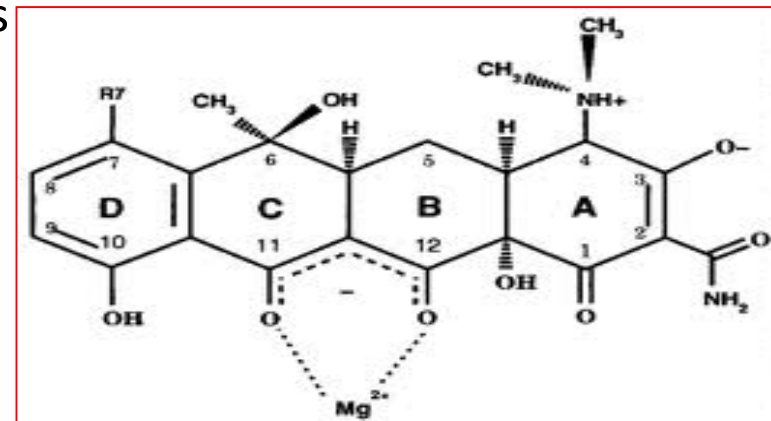


Figure 39.5

Effect of antacids and milk on the absorption of tetracyclines.



al minocycline and doxycycline عادي لو اكلوا اكل مثلا مما يحتوي على divalent or
trivalent, الباقي لا لازم على معدة فاضية

Distribution

- The tetracyclines concentrate in the liver, kidney, spleen, and skin (used for acne).
- Tetracyclines cross the placenta to reach the fetus. As a result of chelation with calcium, tetracyclines are bound to—and damage—growing bones and teeth and are also excreted in breast milk.
- Tetracyclines are distributed widely to tissues and body fluids except for cerebrospinal fluid (only doxycycline and minocycline enters the CSF in sufficient concentrations).

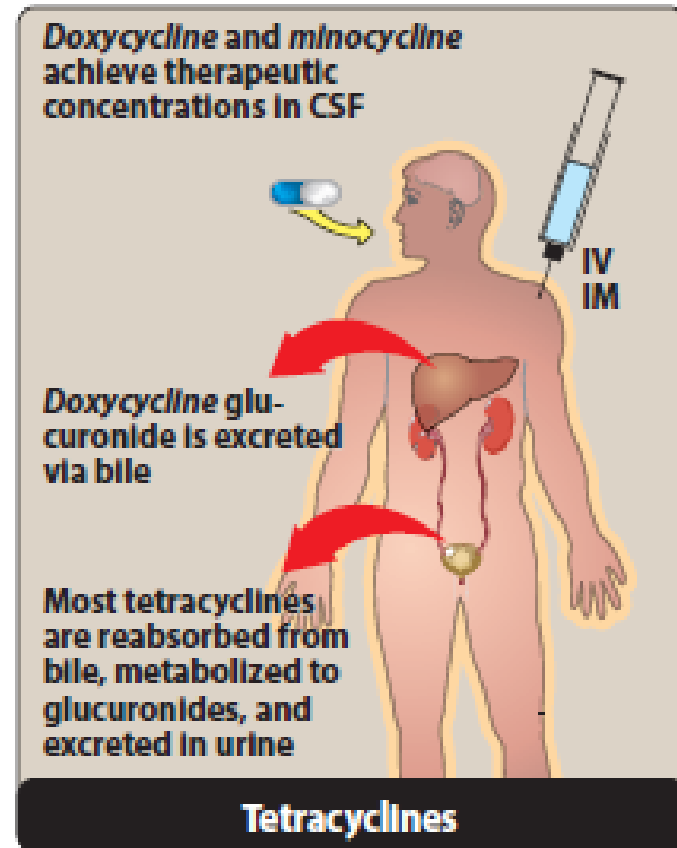


Figure 39.4

Administration and fate of tetracyclines. CSF = cerebrospinal fluid.

ال distribution كويس اله زي ما حكينا قبل

بخترق ال placenta بوصل للعظم والاسنان فا اذا مرأة حامل اخذته الجنين اكل هوا لا مؤاخذه

بالنسبة لل CSF ما بوصلوله الا الدوايين هذول MINOCYCLINE AND DOXYCYCLINE.

Elimination

- Metabolized and conjugated in the liver to form soluble glucuronides.
- Carbamazepine, phenytoin, barbiturates, and chronic alcohol ingestion may shorten the half-life of doxycycline by 50% due to induction of hepatic enzymes that metabolize the drug.
- The parent drug and/or its metabolites are secreted into the bile
- Most tetracyclines are reabsorbed via enterohepatic circulation and enter the urine by glomerular filtration
- Obstruction of the bile duct and hepatic or renal dysfunction can increase their half-lives.
- **Doxycycline and tigecycline**, in contrast to other tetracyclines, are eliminated by **nonrenal mechanisms**, do not accumulate significantly, and require no dosage adjustment in renal failure.

بلفوا بالجسم وبصيرله Metabolite and conjugated داخل ال liver وبصيرلهم excretion بال urine
عشان هيك بدنا functional kidney and functional liver

الا ال doxycycline and tigecycline هم nonrenal mechanism عشان هيك ما بحتاجوا dosage
adjustment في حالة ال renal failure .

Adverse effects

- ✓ **Gastric discomfort** and irritation (can be controlled if the drug is taken with foods other than dairy products)

Note: *Tetracycline* should be taken on an empty stomach.

- ✓ **Effects on calcified tissues:** When a tetracycline is given during pregnancy, it can be deposited in the **fetal teeth**, leading to fluorescence, **discoloration**, and enamel dysplasia. It can also be deposited in bone, where it may cause deformity or growth inhibition. If the drug is given for long periods to children younger than 8 years, similar changes can result.
- ✓ **Hepatotoxicity:** Rarely hepatotoxicity may occur with high doses, particularly in pregnant women and those with preexisting hepatic dysfunction or renal impairment..
- ✓ Systemically administered tetracyclines, especially demeclocycline and tetracycline, can induce **sensitivity to sunlight or ultraviolet light**, particularly in fair-skinned persons. Patients should be advised to wear adequate sun protection.
- ✓ Vestibular problems (dizziness) particularly with minocycline.

Contraindications: The tetracyclines should not be used in pregnant or breast-feeding women or in children less than 8 years of age.

١- الاصل انهم يتأخذوا على معدة فاضية لكن اذا ضايقوا المعدة بنوخذ معها dairy product بس هيك حيقل الامتصاص.

٢- زي ما حكينا انه بدخلوا بتركيبة العظم وبعملي dulgd ,discoloration ويعملي deformity or growth inhibition ولهاض السبب ما يعطيه لمرأة حامل او طفل اقل من ٨ سنين

٣- بعملي hepatotoxicity وهاض نادر لكن بعملي sensitivity to sunlight or ultraviolet light عشان هيك لازم يحط sun protection.

٤- في ناس بصيرلهم dizziness خصوصا من ال minocycline

THE END
DONE BY MOHAMMAD KH