passion ACADEMIC team.

YU-Medicine

Sheet #18

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Lec. Title : Protein Synthesis inhibitors antibiotics .

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Protein Synthesis inhibitors antibiotics

General Pharmacology
M212

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PROTEIN SYNTHESIS INHIBITORS

- **Tetracyclines**
  - Demeclocycline
  - Doxycycline
  - Minocycline
  - Tetracycline
- **Aminoglycosides**
  - Amikacin
  - Gentamicin
  - Neomycin
  - Netilmicin
  - Streptomycin
  - Tobramycin

Consist of : Amine group & Glyosidic acid

*ملاحظة مهمة :

هاي الأدوية مش Orally بالمرة , كلهم IV .

أسماءهم فيها mycin و micin ما عدا الـAmikacin

- **Macrolides**
  - Azithromycin
  - Clarithromycin
  - Erythromycin
  - Telithromycin

Orally

هذول اللي بميزهم عن الـAminoglycosides إنه فيهم مقطع ithro قبل الـmycin

- **Chloramphenicol**
- **Clindamycin**
- **Quinupristin/Dalfopristin**
- **Linezolid**

Sheet 1

Synercid (Quinupristin / Dalfopristin) : One of them associate with 30s subunit , & the other associate with 50s subunit , & they do additive & protein inhibitor & reach to the Bactericidal .

For patient who have allergic to penicillin , they can take Macrolides drugs (Erythromycin , Azithromycin , ... etc.) .

Linezolid prevents the association between 30s & 50s together .

Chloramphenicol group is just a one drug , it has a limited use , & it's for emergency cases .

Sheet 2

Clindamycin has very narrow spectrum , it's used only for Bacteroide fragilis – which is anaerobic - & a little Methicillin resistance Staphylococcus (little Gram-Positive) .

الـClindamycin لا يستخدم لعلاج الـClostridium لإنه ممكن يعمل pseudomonas membritess

The second mechanism of action

Protein Synthesis inhibitors

- **Targeting the bacterial ribosome (50S, 30S),**
  - bacterial ribosome is smaller (70S) than the mammalian ribosome (80S)
  - bacterial ribosome composed of **50S** and **30S** subunits (as compared to 60S and 40S subunits).
- The

Human ribosomes found free in the cytoplasm

- **!!!! Human mitochondrial ribosome**
  - more closely resembles the bacterial ribosome.
  - Most drugs that interact with the bacterial target usually spare the host cells,
  - high levels of drugs such **as chloramphenicol** or the **tetracyclines**
    - may cause toxic effects as a result of interaction with the mitochondrial ribosomes.

Sheet 3

-This mechanism group work mostly on ribosomes .

-The human ribosomes is different than bacterial ribosomes .

-أول شرط في ال Anti-Bacterial هو ال Selective toxicity.

-SO , the Anti-Bacterial must act on some thing available in the bacterial cell & not available in our human cell which is mostly the cell wall (it's in the bacterial & not in the human) .

-Most of drugs are minor toxicity on human cells ; because we don't have cell wall .

-The difference between human ribosome & bacterial's :

Human's : consist of two subunits (large (60s),& small (40s) & they equal together 80s molecular weight, when they Associate together for protein synthesis & they called after association ATS).

Sheet 4

-Bacterial ribosomes : 50s & 30s , they equal together 70s in molecular weight , & they differ in structure from human's ribosomes .

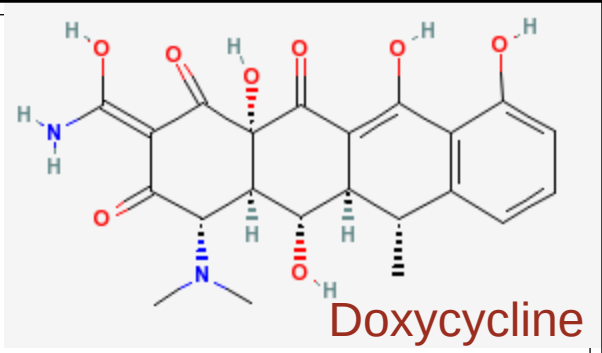
chloramphenicol

-do gray baby syndrome ; because the baby doesn't have Glucunidation .

-& do toxicity in bone marrow ; because of the interaction with the mitochondrial ribosomes & that may lead to anemia ; because the chloramphenicol & the tetracyclines affect on bone marrow which Manufactures the RBCs or may lead to Thrombocytopenia or Leukopenia (WBCs deficiency) .

Tetracyclines

كلهم بنتهوا بـ cycline يعني كلهم فيهم 4 حلقات .
الـ tetracycline هو الماستر تبعهم و الباقيين كلهم derivative .


Doxycycline

- **Tetracycline: orally**
- **Doxycycline:** orally and intravenously
- **Minocycline:** intravenously
- **demeclocycline**

الـHalf-Life قليلة , و الـSpectrum إله قليلة , و هيك دايما الـOld Drugs .

- **Tigecycline (the final generation to the tetracycline)**
- **Structure:** consist of 4 fused rings with a system of conjugated double bonds.
- **MOA**:
  - bind reversibly to the **30S** subunit of the bacterial ribosome
  - block access of the aminoacyl-tRNA to the mRNA-ribosome complex at the acceptor site.
  - Inhibit protein synthesis

- Entry into susceptible organisms
  - by passive diffusion and by an energy-dependent transport protein mechanism.
  - Non-resistant strains concentrate the tetracyclines intracellularly.

Sheet 5

-Tetracycline : its half life is 6 hours .

-Doxycycline : used once daily for Acne (long half life) & have enterohepatic circulation .

الـtetracycline drugs بشتغلوا عالـ30s .

ما بصير نعطي دواءين بشتغلوا عالـ30s مع بعض ؛ لإنه ممكن واحد يرتبط بالـ30s و يثبط الدواء الثاني (Antagonize each other) .

So , Tetracycline drugs are 30s subunit inhibit protein synthesis .

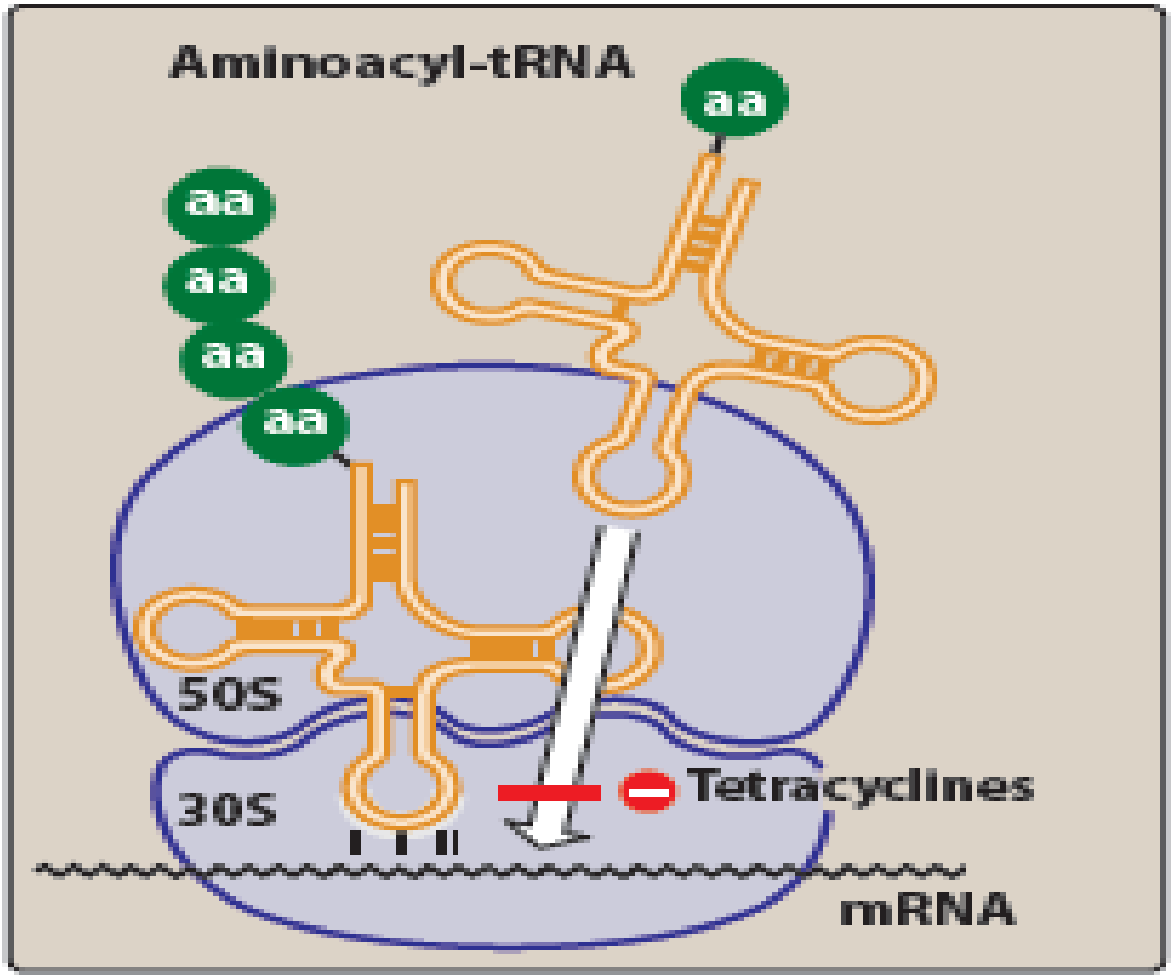


Figure 32.2

Tetracyclines bind to the 30S ribosomal subunit, thus preventing the binding of aminoacyl-tRNA to the ribosome. aa = amino acid.

Tetracyclines – clinical uses

- **Broad spectrum antibiotics G+ and G-**
- **drugs of choice for**

1. **Cholera** → Food poisoning ينتقل عن طريق الـ
2. **intracellular organisms**
   - **Rickettsia**
   - **Mycoplasma Pneumoniae** → Cell wall ليس لديه / cell wall ماكو
   - **Chlamydia**
3. **Mycobacteria** (second line resistant)

First line resistant

- Antibiotics of first choice
  - for **Rickettsia , Mycoplasma and Chlamydial** infections,
  - cholera, and Lyme disease.
  - They are commonly used in the treatment of **acne** (doxycycline).
- Second choice
  - useful in mixed infections of the respiratory tract
  - Tuberculosis

Tetracyclines - PK

- Completely absorbed
  - Altered by dairy foods or antacids
    - Nonabsorbable chelates formed with divalent and trivalent cations Al3+, Ca2+, Mg2+
      - problem if the patient self-treats the epigastric upsets caused by tetracycline ingestion with antacids.
- Widely distributed
  - Soft tissues – liver, spleen, skin
  - Teeth/bones – Calcification
  - Placenta – high penetration – FDA category D
    - Teratogens – bones and teeth development
  - CSF – insuficient
    - **Minocycline may be used for eradication of meningococcal carrier state**

Sheet 6

ممنوع إعطاء Tetracycline للأطفال أقل من 8 سنوات (و إذا قدرت أقل من 12 سنة بكون أفضل) ؛ لإنه الـtetracycline برتبط مع الـ divalent and trivalent cations مثل الكالسيوم , واللي هو موجود في الأسنان , و بالتالي إذا أعطيناهم هذا الدواء راح يرتبط بالكالسيوم , ولما يبدل الطفل أسنانه راح يطلّع أسنان ضعيفة (very soft) , و بأثر على العظام كمان .

و ممنوع يعطى للمرأة الحامل ؛ لإنه ابنها راح يطلع ب أسنان (very soft)

Tetracycline is Contraindicated below 8 years & below 12 years with caution .

Tetracyclines - PK

Metabolism isn't in the kidney

- **Metabolism – it is lipophilic**
  - Concentrate in liver, conjugated by glucuronidation,
  - Excreted to bile – enterohepatic recycling
    - Especially doxycycline
  - Renal excretion limited ← لإنه Urinary tract infection لا يستخدم كـ
    - Dose reduction required only in severe renal insufficiency
    - Not effective in UTIs
- Excreted also in breast milk: C/I

Tetracyclines - Adverse effects

1. Epigastric distress

إذا بتأثر بالـAbsorption منوخذه قبل الأكل ,
أما إذا بسبب آلام بالمعدة منوخذه بعد الأكل

   – irritation of the gastric mucosa
     - Relieved if the drug is taken with foods other than dairy products.
2. Deposition in the bone and primary dentition
     - during calcification in growing children
     - discoloration and hypoplasia of the teeth and a temporary stunting of growth.
   – C/I - pregnancy and in children younger than 8 years
     - or before the **second dentition**
3. Hepatotoxicity
4. Phototoxicity: most frequently with doxycycline and demeclocycline plague

Sheet 7

لازم تحذّر اللي بوخذ الـdemeclocycline و الـDoxycycline اللي بوخذوه عشان حب الشباب , ممنوع تطلع بالشمس بدون واقي للشمس (والأحسن يكون عالي تركيزه (أكثر من 50)) ؛ لإنه بعمل Phototoxicity و بعمل Sun burn .

استخدام الـtetracycline لفترة طويلة ممكن يعمل diarrhea .

- كيف منعرف إنه الشخص عنده pseudomembranous colitis ؟

لما يصير عنده diarrhea ؛ لإنه بصير تكاثر للـClostridium difficile داخل الـGIT و ذلك بسبب قتل الـNormal Flora

(this is called super infection)

-كيفية علاج الـpseudomembranous colitis ؟

عن طريق إعطاء الـVancomycin أو الـmetronidazole

Tetracyclines - Adverse effects

5. Superinfections:
   - Pseudomembranous colitis due to an overgrowth of Clostridium difficile

It's an anaerobic bacteria

6. Vestibular problems:
   - (e.g., dizziness, nausea, vomiting) occur with minocycline, which concentrates in the endolymph of the ear and affects the function

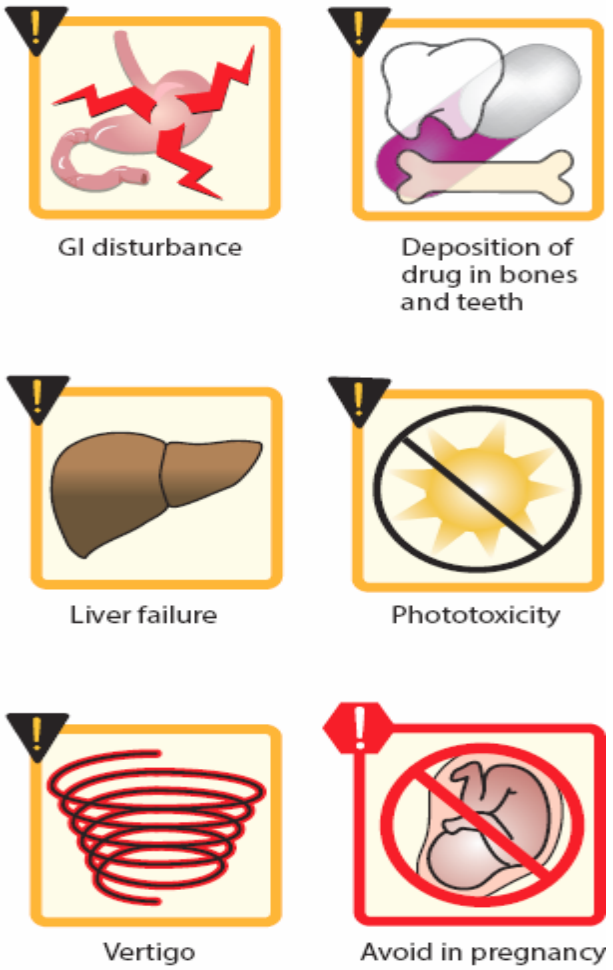


Figure 39.6
Some adverse effects of tetracyclines.

Resistance

- Widespread cross resistance
- inability of the organism to accumulate the drug by active efflux of the drug
- Any organism resistant to one tetracycline is resistant to all.
- The majority of penicillinase-producing staphylococci are now also insensitive to tetracyclines
- Tigecycline develop to overcome Tetracycline resistance

Sheet 8

الـtetracycline لازم يدخل للـintracellular عشان يعمل Action .

و لازم يرتبط بالـribosome لإنه هو شغله عليها أصلا .

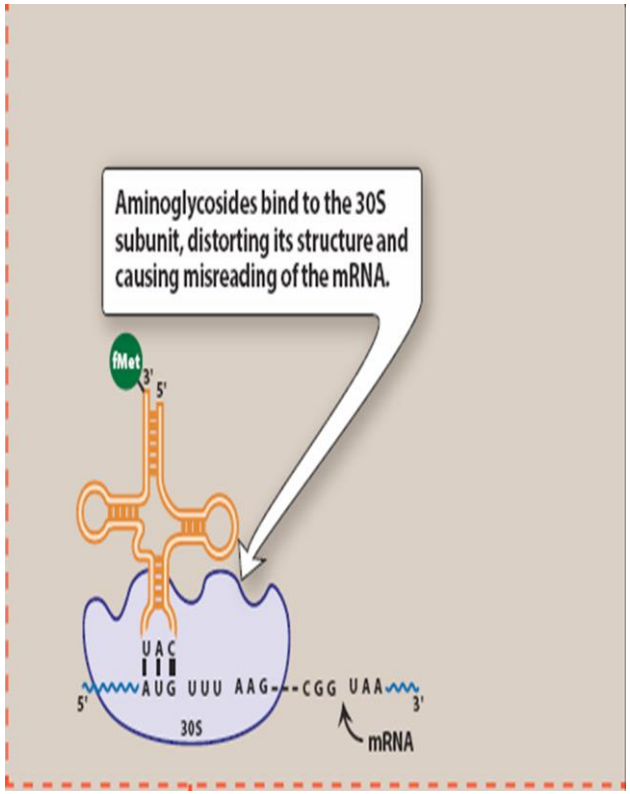
أول شرط عشان يشتغل الدواء :

It must be accumulated inside with certain concentration (if it's less than that certain concentration , the drug will not work & it will not do the inhibition action) .

Aminoglycosides

- Streptomycin, Amikacin, Gentamicin, Tobramycin
- Neomycin, Netilmicin, Kanamycin

- **MOA: inhibit bacterial protein synthesis**
  - bind to the isolated **30S** ribosomal subunit
  - Susceptible gram-negative organisms allow aminoglycosides to diffuse through porin channels in their outer membranes.



Sheet 9

Aminoglycosides

The Aminoglycoside drugs do Nephrotoxicity & Autotoxicity & they are only Gram-Negative .

It's an important drug in ICU , emergency cases & hospital acquired pneumonia .

Aminoglycosides

Spectrum:

For serious infections due to aerobic gram-negative bacilli including *Pseudomonas aeruginosa* , *Klebsiella pneumoniae and Enterobacter sp* (they are gram negative)

- Use is limited by the occurrence of serious toxicities
  - Partially replaced by safer ATB : 3rd generation cephalosporins, fluoroquinolones, carbapenems
- Streptomycin – second line, used to treat Mycobacterium tuberculosis (TB) (kanamycin also effective)

Sheet 10

Klebsiella pneumoniae is a penicillin resistance bacteria , it prevents penicillin to get inside the bacteria ; because it has a high efflux .

Aminoglycosides has a narrow spectrum for Gram Negative (we can say that they are very specific) .

The patient must have a good renal function , if he doesn't , you mustn't give him any Aminoglycosides drug ; because that will cause Nephrotoxicity .

Streptomycin is an old drug and it cause nephrotoxicity , so we replace it with amikacin , Gentamicin or Tobramycin .

Neomycin can't be given IV , we give it Orally just for local effect (local in GIT) , for surgery as example to prevent post GIT infection .

Aminoglycosides

1. The bactericidal effect of aminoglycosides is concentration dependent; the target Cmax is eight to ten times the MIC.
2. They also exhibit a post antibiotic effect (PAE), which is continued bacterial suppression after drug levels fall below the MIC. The larger the dose, the longer the PAE.
3. Because of these properties, extended interval dosing (a single large dose given once daily) is now more commonly utilized than divided daily doses. This reduces the risk of nephrotoxicity and increases convenience
4. The exceptions are pregnancy, neonatal infections, and bacterial endocarditis - administered every eight hours.

Sheet 11

Aminoglycosides is concentration dependent , that means ---> higher than minimum inhibitory concentration ---> more effects .

→FROM THE PREVIOUS SLIDE :

The concentration of the drug in the plasma to inhibit the growth of the Microorganism (MIC) .

الدواء عشان يشتغل لازم يكون من 8 إلى 10 أضعاف الـ(MIC) .

The dose = concentration × volume .

- Post antibiotic effect : that means even if the drug concentration less than the MIC , it still have antibacterial activity .

So , these kind of drugs can be given once daily & that's very good for kidney (to protect the kidney from nephrotoxicity) .

Penicillins and aminoglycosides

- synergize with beta-lactams or vancomycin

- synergistic
  - enhanced antimicrobial activity
- facilitate the entry of aminoglycosides
  - Because cell wall synthesis inhibitors alter the permeability of bacterial cells,
- should never be placed in the same infusion fluid,
  - the positively charged aminoglycosides form an inactive complex with the negatively charged PNCs.

Sheet 12

الدكتور الشاطر بس يعطي Aminoglycoside لازم يعطي معه دواء فيه Cell wall inhibitor بعرف إنه هذا رائع بالفارما و بنقذ المرضى بشكل سريع؛ لإنه الـcell wall inhibitor بعمل pores بالـcell wall , بالتالي بدخل الدواء داخل البكتيريا و بعمل الـAction (synergism) , لكن ممنوع نخلطهم بنفس العلبة أو المحلول ، لإنه الـAminoglycoside عنده شحنة موجبة (positive +) , أما الـpenicillin عند شحنة سالبة (negative -),فإذا خلطناهم بعملوا complex وهيك انت بتموّت المريض ---> راح يصير لـهذا الـcomplex ---> Precipitation ---> و راح يسكروا كل الـBlood Vessels .

Aminoglycosides - PK

- must be given **parenterally** - highly polar - not absorbed orally
- **NEOMYCIN** – only **topical** – because severe nephrotoxic
  - application for skin infections or oral administration to prepare the bowel prior to surgery

- **Extracellular distribution**
  - Poor penetration to CSF even when the meninges are inflamed!.
  - **Except for neomycin, they may be administered intrathecally.**

- **nephrotoxicity and ototoxicity**
  - Accumulate in the renal cortex and in the endolymph and perilymph of the inner ear

Sheet 13

الـVancomycin و الـAminoglycoside لازم نعمللهم Therapeutic drug monitoring بالمستشفى .

ممنوع الـPlasma concentration تزيد عن 40 على سبيل المثال , إذا زاد عن هذا العدد (طبعا كل دواء إله رقم معين) يؤدي إلى ototoxicity .

دايما قبل ما نعطي الجرعة الثانية منقيس تركيز الدواء اللي ضل من الجرعة الأولى , إذا كان عالي (أكثر من حد معين) ---> راح يعمل Nephrotoxicity .

بعد ما نعطي الـAminoglycoside منعمل "TDM Center" <--- منعمل تحليل عشان نعرف تركيز الدواء بالبلازما بعد ساعتين من إعطاء الجرعة الأولى (Serum Concentration) , بتقارن نتائج التحليل مع الـ Therapeutic Range و لازم ما تكون النتائج أعلى منه .

و قبل الجرعة الثانية بنص ساعة منرجع منقيس (على فرض إنه الدواء جرعة وحدة باليوم يعني الـHalf life 24 ساعة) المفروض يكون التركيز نصف الـ40 اللي ذكرناها قبل واللي هو 20 أو أكثر شوي أو أقل من هيك , أما إذا كان أكثر بكثير (مثلا 30) , بكون هذا دليل على إنه الجرعة الأولى اللي أعطيتها كبير , فلازم نقلل الجرعة الثانية .

Aminoglycosides - PK

- **Teratogenic** لا يعطى للمرأة الحامل أبدا (X)
  - All cross the placental barrier - accumulate in fetal plasma

- **All rapidly excreted into the urine**
  - by glomerular filtration
  - short t1/2
  - Accumulation occurs in patients with renal failure and requires dose modification.

Aminoglycosides

Resistance

Rapid onset mostly, three following mechanisms:

1. - Decreased uptake: The oxygen-dependent transport system for aminoglycosides or porins is absent.

1. - Altered receptor: The 30S ribosomal subunit binding site has a lowered affinity for aminoglycosides.

Aminoglycosides Adverse effect

1. **Ototoxicity:**
   - directly related to high peak plasma levels and the duration of treatment.
   - Deafness may be irreversible (it affects on Vestibular and cochlear), it is known to affect fetuses in utero.
   - Vertigo and loss of balance

2. **Nephrotoxicity:** C_{trough} : pre the second dose .
   - directly related to high tough plasma levels
   - Retention of the aminoglycosides by the proximal tubular cells
   - disrupts calcium-mediated transport processes
   - this results in kidney damage
   - from mild, reversible impairment to severe, acute tubular necrosis, which can be irreversible).

3. **Allergic reactions**
   - Contact dermatitis - a common reaction to topically applied neomycin

Gram Negative (diplococcus) --- > Neisseria gonorrhoeae

Spectinomycin

- structurally related to aminoglycosides,
- **MOA: interacts with the 30S ribosomal subunit** inhibit protein synthesis.
- only for treatment of **acute gonorrhea :** caused by penicillinase-producing Neisseria gonorrhea in patients who are allergic to PNC.
  - Administered as a single I.M. injection
- S/e: Hypersensitivity reactions can develop

The first line of Neisseria gonorrhoeae is penicillin
The first alternative to penicillin is the 3rd generation of cephalosporin & the second alternative to penicillin is spectinomycin .

Synercid ®
Quinupristin/Dalfopristin combination

دوبين بدواء واحد
تركيبه وحده
باودر واحد

- They are derived from a streptomycete
- reserved - vancomycin-resistant Enterococcus (VRE) and G+

#هذا ال combination هو البديل الوحيد للي عنده resistance ل vacomycin

- **MOA:**
  - Each component of this combination drug binds to a separate site on the **50S** bacterial ribosome, they synergistically interrupt protein synthesis.
  - The combination drug is bactericidal and has a long postantibiotic effect
  - They synergistically interrupt protein synthesis.
- injected intravenously: I.V. in 5% dextrose solution (incompatibility with **normal saline**).
- PK:
  - **undergo metabolism – further via biliary excretion to feces**
  - **Urinary excretion is secondary.**

- Synercid is the brand name.
- New drug ,from 2006.
- Similar to Aminoglycosides but the **Antibacterial spectrum is** different
- MOA:

▪ Inhibit both ribosome structure (they have Synergism :one drug inhibit 30S and other inhibit 50S)

- Adminstertion: IV

▪Don't use with normal saline (.90% NaCl) because it cause crystallization.

▪Very very irritant drug

▪ with slow infusion through 60 min to decrese irritation.

▪administered through a peripheral rather than a central line

- Very important in emergency cases.

المريض بشعر بحكة باشي عم يدخل الB.V فلما نعطيه ب Slow infusion ومع dextrose solution لتخفيفه ، فبقل التهيج

quinupristin/dalfopristin

Adverse effects

- **Venous irritation**: common when administered through a peripheral line.
- **Arthralgia,**
- **Myalgia**

Interactions

- Ability of quinupristin/dalfopristin to inhibit CYP3A4 isozyme - concomitant administration with drugs metabolized by this pathway may lead to toxicities.
- Interaction with digoxin ?? Eubacterium lentum??? erythromycin and tetracycline ??

- Eubacterium lentum and erythromycin and tetracycline , we cant use these drugs with digoxin because interaction between them causes digoxin toxicity.
- Digoxin is a constant drug and uses for cardiomyopathy while we change the drug that uses for infection.

كطبيب لازم أثبت دواء ، مثلا هون ثبتت ال(DIGOXIN) و بنغير

الدواء المستخدم لل (INFECTION)...

- When digoxin metabolism , large amount of it destructs in liver
- Eubacterium lentum is the 10% of normal flora in our body and metabolism of digoxin in GIT .

- Sypotoms: (are reversible)
  - Joints pain
  - Muscle pain

Macrolide antibiotic

- ATBs with a macrocyclic lactone structure

1. Erythromycin → Very old , the first generation , has less spectrum

2. Roxithromycin
3. Azithromycin
4. Clarithromycin
5. Telithromycin

→ Are more commonly used than Erythromycin

MOA: binding irreversibly to a **50S** subunit of the bacterial ribosome - inhibition of the translocation step of protein synthesis - **bacteriostatic**

mostly as an alternative to penicillin in allergy to beta-lactam ATBs.

- If befor 3 months , I had tonsillitis and used cell wall inhibitor group and it comes back again I prefer using this group(**Macrolide**) to avoid develop resistance.

#معلومة مهمة :
* إذا عنا
Allergic to penicillin
بنستثني كل مجموعة ال
cell wall inhibitor
و بننتقل على مجموعة ال
.Macrolide

- **Azithromycin**
  - has long t1/2 (more than 30-40 h)
  - Once daily - {كورسه٣ حبات ل٣ أيام}

- **Clarithromycin**
  - From Helicobactor pylori (H.pylori is a type of bactera.)
  - Causes peptic ulcer and to treat it we use 3 drugs :

1)Amociiclin 2) clarithromycin - it is very core in the treatment

3) protein pump inhibitor- دواء للحموضة

  - We can use it in Haemophilus influenzae but we prefer using it to treat peptic ulcer.

Macrolide antibiotic

- Erythromycin
  - as PNC : especially G + bacteria and spirochaetes, N.gonorrhoae
  - used in patients allergic to the PNCs
  - intracellular - Chlamydia, Mycoplasma,Legionella, Corynebacterium diphterie
  - Antistaphylococcal antibiotic – not MRSA

- Clarithromycin:
  - high activity against **Helicobacter pylori**
  - similar to erythromycin, but it is also effective against **Haemophilus influenzae.**

- Azithromycin:
  - more active against respiratory infections due to H. influenzae and Moraxella catarrhalis.
  - The preferred therapy for urethritis caused by Chlamydia trachomatis.

- Old Erythromycin is very similar to penicillin.

(اللي بشتغل عليه ال natural penicillin ،بشتغل عليه ال erythromycin فعشان هيك بشبهه بالدرجة الأولى بكل ال spectrum.)

- بالدرجة الثانية بشبه ال tetracyclin

- Nonadherence to the medication because it is taken every 6 hs

- Azithromycin:

- Especially In cases of RS infection it is similar to penicillin .
- H.influenzae and Moraxella catarrhalis are responsible to tonsilitis and inflammation of the upper respiratory and if the patient is allergic to penicillin or used it befor 3 months we prefer using Azithromycin .
- Urethritis caused by Chlamydia_trachomatis :

من أصعب الالتهابات البولية لأنه صعب جدا علاجها ،بتكون رائحة ال urine غريبة ، ممكن المريض يستخدم مجموعة أدوية ل UTI ولكنه يظل موجود ف البديل هواستخدام Azithromycin.

Macrolide antibiotic

- Resistance to erythromycin - a serious clinical problem.
  - Most strains of staphylococci in hospital isolates are resistant to this drug.
- Several mechanisms:
  - presence of an efflux pump
  - a decreased affinity of the 50S ribosomal subunit for ATB;
  - erythromycin esterase.

- **Telithromycin** can be effective against macrolide-resistant organisms.

➢ Telithromycin

- Very very important for those resistance to other Macrolide.
- New , expensive –

بندوّر على البديل اله لأنه غالي لا المريض بشتريه و لا المستشفى بوفره.

Macrolide antibiotic

- Administration:
  - Absorbed orally
    - Azithromycin available for IV infusion,
  - Food interferes with absorption of Erythro and Azithromycin but can increase that of clarithromycin.

كلهم ال Absorption بقل ، ما عدا Clarithromycin بزيد امتصاصه مع الطعام .

- Distribution:
  - Distributed well in all body fluids **except the CSF**.
  - Erythromycin - one of the few ATBs that **diffuses into prostatic fluids**
  - All drugs concentrate in the liver.
  - **azithromycin has the longest half-life and largest Vd. (OD)**

و(لا يكرر خلال 6 أشهر)

- In prostate infection (and using antibiotics) you must use drug reaches prostate .
- A prerequisite in antibiotics is its presence in the area of treatment and very few antibiotics can reach prostate .

- All macrolide drugs and especially Erythromycin are found in prostste.

Macrolide antibiotic

- Metabolism:
  - are extensively metabolized with exception of Azithromycin.
  - **inhibit the oxidation of CYP-450 system.**

Azithromycin exists in urine and its conc is in active , so you can use it in Urethritis

- Excretion:
  - Erythromycin and azithromycin
    - concentrated and excreted in an active form in the bile.
    - Inactive metabolites are excreted into the urine.
    - Partial reabsorption occurs via enterohepatic circulation.
  - clarithromycin and its metabolites
    - are eliminated by the kidney as well as the liver (adjust dosage in compromised renal function!).

Macrolide antibiotic - AE →

مشابهه لل
Tetracyclin

1. Epigastric distress:
   - common - it can lead to poor compliance for erythromycin.
   - Clarithromycin and azithromycin - better tolerated by the patient

2. Cholestatic jaundice:
   - especially with the estolate form of erythromycin, presumably as the result of a hypersensitivity reaction

3. Ototoxicity:
   - Transient deafness - erythromycin, especially at high dosages.

اذا شعر ب
طنين بأذنه ،
مباشرة بنوّقفه .

4. Telithromycin – hepatotoxicity, prolongation of QTc interval

- **Contraindications**: Patients with hepatic dysfunction

✓If it causes stomach pain , take it after eating .

- This AE happen with very long duration and high doses
  - It is not necessary to tell the patient about it from the beginning .

- Erythromycin :

بتحطم لمادة ال estolate ، وهي بتحطّم ال RBCs ، و بتعمل Hyperbilirubinemia ، زي صفار .

* Bilirubin=مادة الهيم ،

لما تتحطم ال RBCs بتكوّن مادة صفراء بتطلع بال urine و بتعمل صفار ، فبتعمل Cholestatic jaundice .

*وهاي مش دائما الا اذا كان sensitive .

- If the drug metabolize in the liver and goes through the kidneys and the patient has renal failure you have not give this drug
- Like : Cephalosporin and penicillin .
- But we give the patient drugs like Macrolide
  والعكس صحيح....
- if patient has liver problem or toxicity or hepatitis
  , you have not give drug metabolize in the liver like Macrolide but you give Cephalosporin and penicillin .

- When you give antibiotics to patient uses digoxin , you must keep in your mind that digoxin don't metabolize in the liver alone , 70% of digoxin metabolize in GIT by bacteria.

- And this bacteria dies if you give Macrolide and tetracycline. When you kill bacteria , digoxin not metabolize and its conc will increase (digoxin is narrow therapeutic index) and cause arrhythmia and increase heart contractility.

Macrolide antibiotic - interactions

- Erythromycin, telithromycin, and clarithromycin **inhibit the hepatic metabolism** of a number of drugs, which can lead to toxic accumulations of these compounds.
  - E.g., theophylline, warfarin, carbamazepine, cyclosporine

✓ These drugs are narrow therapeutic index.
✓ Macrolide drugs with warfarin cause increase conc of warfarin and bleeding because its inhibit metabolism of warfarin .....
✓ هذا يحدث إذا تعدّى استخدام الدواء أكثر من 3 أيام

- Interaction with digoxin may occur in some patients - ATB eliminates a species of intestinal flora that ordinarily inactivates digoxin so greater reabsorbtion?

linezolid

- **Bacteriostatic - Inhibits of bacterial protein synthesis**
  - **MOA:** block the formation of the 70S initiation complex by binding to **50**S subunit.

- New ATB; against resistant G+ organisms
  - methicillin- and vancomycin-resistant S. aureus
  - vancomycin-resistant Enterococcus faecium
  - Enterococcus faecalis

- **Pharmacokinetics**
  - Completely absorbed on oral administration. I.v. is also available.
  - Two metabolites (oxidation products) - one has antimicrobial activity.
  - Excretion - both by renal and nonrenal routes.

- **Adverse effects**
  - nausea, and diarrhea
  - headache and rash
  - Thrombocytopenia - Very toxic

- Binds with 50S and prevents binding 50S with 30S thus inhibit 70S formation.

- Contraindicator : For patient that has problems in the kidney because it is mainly excretion by renal .

Chloramphenicol

- **Broad-spectrum**
  - wide range of G+ and gram– organisms;
  - also some intracellular - e.g. **rickettsiae.**
    - P. aeruginosa is **not** affected, **nor** are the chlamydiae.
  - Excellent activity against **anaerobes.**
- use is restricted to life-threatening infections because of its toxicity
- mostly bacteriostatic

- **MOA**: inhibit bacterial **50S r**ibosomal subunit
  - inhibit protein synthesis at the peptidyl transferase reaction.
  - Toxicity? - similarity of mammalian mitochondrial ribosomes to those of bacteria,
    - protein synthesis in these organelles may be inhibited at high circulating chloramphenicol levels - producing **bone marrow toxicity**!!

- BUT is not the first line , always chloramphinicol is the last line .
- It is as Eye ointment (once at night) and eye drops (every 6 hs) for severe eye infections.

- Absorbtion of it is less than 10% thus its effect is topical and does not affect
- Very limited use ….Why?
- Because it is not selective toxicity , affects ribosome in mitochandria of our body and bone marrow .
- With long usage time it causes thrombocytopenia , anemia and grey baby syndrome , so it is used for emergency cases.

Chloramphenicol

- Administered intravenously or orally
- Widely distributed including the CSF
- glucuronidation in the liver - primary route
  - Glucuronide is then secreted by the renal tubule.
  - Only about 10% of the parent compound are excreted by glomerular filtration
  - inhibits the hepatic CYP450.
  - also secreted into breast milk. C/I in breastfeeding mother
- USES: - serious life-threatening infections
  - **H. influenzae, Bacteroides fragilis and meningitis** where PNCs cannot be used.
  - **In typhoid fever**: 2nd line after amoxycillin and cotrimoxazole less toxic.

➢ In specific states when you can't use penicillin and other drugs you use it.

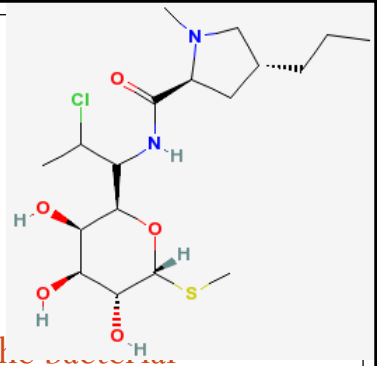
Chloramphenicol – side effects

Side effects make it limited to use , and be the 2nd line

1. Hemolytic anemia
2. Bone marrow suppression (Aplastic anemia , pancytopenia),
3. teratogenic effects
4. GIT: GIT disturbances, diarrhea, hypovitaminosis B and K
5. Gray baby syndrome:
   - Low capacity to glucuronate chloramphenicol drug, which accumulates to levels that interfere with the function of mitochondrial ribosomes
   - poor feeding, depressed breathing, cardiovascular collapse, cyanosis (hence the term "gray baby") and death.

- Interactions
  - inhibits some hepatic P450 and blocks the metabolism of drugs (warfarin, phenytoin, tolbutamide.

Clindamycin



- mechanism as macrolides MOA: binding irreversibly to a 50S subunit of the bacterial ribosome
  - antagonism when co-administered.
- infections caused by **anaerobic bacteria** (e.g. **Bacteroides fragilis).**
  - Note: Clostridium difficile is resistant to clindamycin.

- orally (well absorbed) or parenterally.
- Distributes well into all body fluids except the CSF.
- Penetration into bone occurs even in the absence of inflammation.
- It undergoes extensive oxidative metabolism (to inactive products),
- Accumulation
  - in patients with either severely compromised renal function or hepatic failure.

- If it is used for long time, Clostridium difficile becomes resistant.
- In this case we use vancomycin and Metronidazole instead of clindamycin.

- Very limited use to **Bacteroides fragilis** ,very selective .
- Very similar to Macrolide.
- Binds with 50S.
- For anaerobic bacteria ,but not all anaerobic bacteria , just Bacteroides fragilis.
- When do you expect they are these bacteria (Bacteroides fragilis)?

– when you have 2 infections and we use Augmentin + Amoxicllin + Clindamycin.

(هذه خلطة يستخدمها أطباء الأسنان)

Clindamycin

- Side effects
  - skin rashes
  - GIT disturbances
  - impaired liver function
  - the most serious adverse effect is potentially fatal **pseudomembranous colitis** !! (caused by overgrowth of Clostridium difficil) بسبب الاستخدام الطويل
  - – treated by **vancomycin or metronidazole** … مهم

*ابصموا هاد السلايد بصم.

Metronidazol and tinidazol

- **MOA**: Inhibition of DNA replication in microorganism
- **Spectrum and Uses:**
  - For infections caused by **Anaerobes:** Bacteroides fragilis, anaerobes in abdominal cavity, diarhea by C. difficile
  - **Trichomonas vaginalis**
  - **Entamoeba histolytica**
  - cerebral abscesses
  - Drug of Choice for **tetanus**.

- **PK**
  - Orally . excellent absorption, penetrate bones teeths, CNS abscesses/CSF; placenta milk.
  - Metabolized in liver and kidney excretion.
- **Side effects:**
  - **Metalic taste, dark urine, dissulfiram like effect, depression**

C/I: alcohol drinker

✓Very smart combination for areas that don't reach it any drug except these drugs.

✓ to treat rare cases that caused by protozoa,parasites and anarrobic.

- **dissulfiram like effect:**

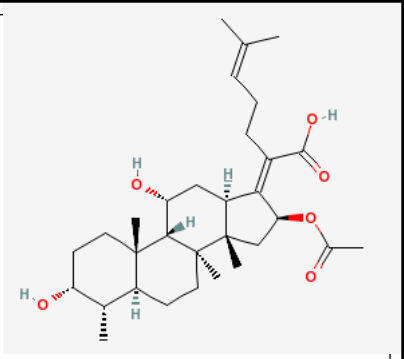
Alcohol drinker to treat it we give it dissulfiram , when he is back to drink , he suufers from headache,vomting and nausea then hates alcohol .

- Alcohol in normal converts to aldehyde but in this case it converts to acetic acid and cause gastric pain .

- اللي بوخذ Metronidazol and tinidazol بصير معاه أعراض زي اللي بشرب كحول مع dissulfiram ، عشان هيك سمّينا هاد ال SE :

dissulfiram like effect.

fusidic acid



- steroid structure
- against G+ bacteria by inhibiting protein synthesis
- registered for **topical** treatment (acne vulgaris and wound infection)
  - Used mainly in resistant staphylococcal infections

✓ Ointments for acne , wound infection and the 2nd line for burn infection .

✓Topical not orally

THANK YOU

DONE

Alhamdulillah

اللهم إنا نستودعك كل ما درسنا و حفظنا بحفظك و رعايتك يا من لا تضيع عنده الودائع رده إلينا عند حاجتنا إليه و زدنا علما .. ☺