BROAD SPECTRUM ATB

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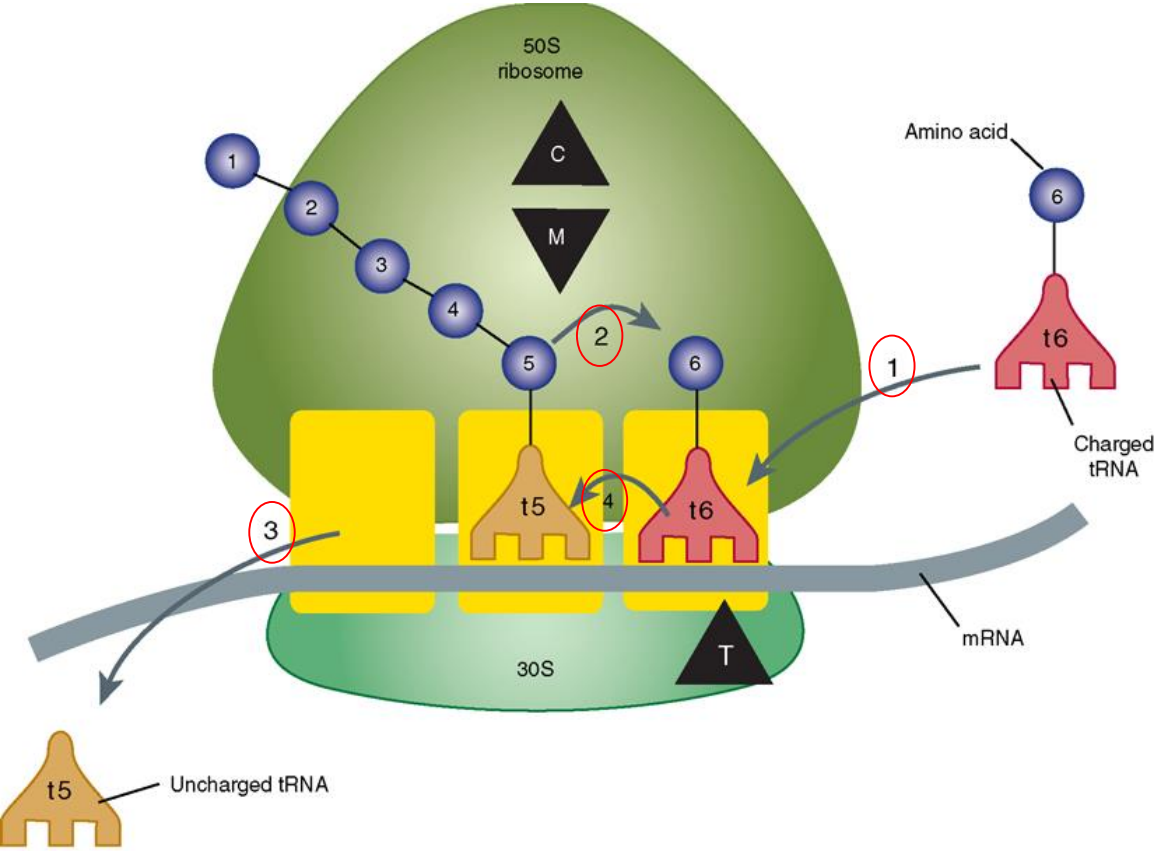
Primarily bacteriostatic ATB

MoA

The ATB-binding sites:
Macrolides (M)
Tetracyclines (T)
Chloramphenicol (C)



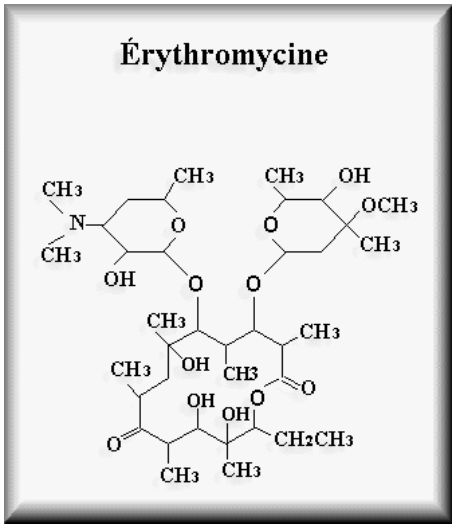
Source: Trevor AJ, Katzung BG, Kruidering-Hall M, Masters SB: *Katzung & Trevor's Pharmacology: Examination & Board Review*, 10th Edition: www.accesspharmacy.com

The 70S ribosomal mRNA complex (its 50S & 30S subunits):

- **Step 1:** The charged tRNA unit carrying amino acid 6 binds to the acceptor site (on the 70S ribosome)
- **Step 2:** The peptidyl tRNA at the donor site, with 5 amino acids then binds the growing amino acid chain to amino acid 6 (transpeptidation)
- **Step 3:** The uncharged tRNA left at the donor site is released
- **Step 4:** The new 6-amino acid chain with its tRNA shifts to the peptidyl site (translocation)

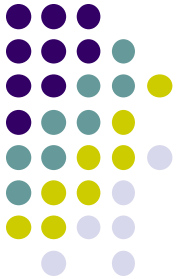
Macrolides
Active agents

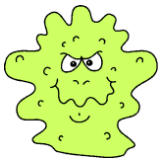
- ***erythromycin***
- ***azithromycin***
- ***roxithromycin***
- ***clarithromycin***
- ***spiramycin***
- ***josamycin***
- ***telithromycin***



- Produced by various strains of *Streptomyces*
- Macrocyclic lacton ring
- Reversible 50S subunit binding:
  - ⇓ of peptidyl transferase (peptidic bonds between aminoacids)
  - **⇓ of protein chain elongation**
  - **bacteriostatic**

Macrolides
Antimicrobial spectrum - general





- **G+**
  Staphylococcus aureus
  Streptococcus pneumoniae
  Streptococcus pyogenes...
- **G-**
  Haemophilus influenzae
  Haemophilus parainfluenzae
  Moraxella catarrhalis
- Other microorganisms - **intracellular**
  Mycoplasma pneumoniae
  Chlamydia pneumoniae...
- **Mycobacteria**
  Mycobacterium avium complex

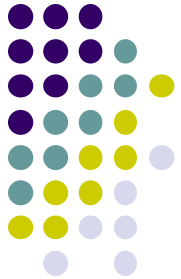
- **Resistance**
  - ***Enterobacteriaceae***
    Pseudomonas
    (***ery*** can not diffuse into bacterial cells)
  - most isolates of ***methicillin-resistant*** & ***oxacillin-resistant staphylococci***

- β-lactamase production should have no effect on ***macrolide*** activity

Macrolides
General PK

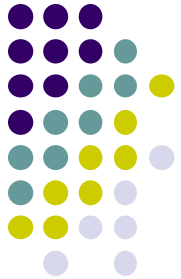
- **Acid stability** of individual agents differs: e.g. *erythromycin < azithromycin < clarithromycin*
- Absorption (p.o.) also differs & may result from application form, number of doses, GI filling
- **Excellent passage into tissues & body fluids (except CNS),** enter & are concentrated within phagocytes (PMNL & macrophages)
- ⇑ **concentrations in liver** (some *macrolides* - ***clarithromycin & erythromycin,*** **not *azithromycin*** are potent **inhibitors of the cytochrome P450 system)**
- Primarily bile & stool excretion
- **Non-dialysable**

Macrolides
Therapeutic use - general



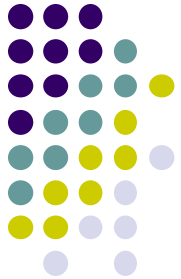
- **Pneumonia** *(mycoplasma, legionella)*
- **Streptococci & sensitive staphylococci**
  (alternative to PNC - ENT, skin)
- **Dental infections** *(spiramycin* enters saliva)
- ***Chlamydia trachomatis & rickettsia*** (alternative to *TTC*)
- **Toxoplasmosis in primary infections & immunocompromised patients** *(spiramycin)*
- ***HP* eradication**
  (clarithromycine in combination with *amoxicillin & PPI)*
- ***Mycobacterium avium*** infections - usually treated with a three-drug regimen of either *clarithromycin* or *azithromycin* (plus *rifampicin & ethambutol*)
- **Formerly** - prophylaxis in colorectal surgery (plus *neomycin)*

Macrolides
SE - general



- Adverse reactions are primarily gastrointestinal (nausea, diarrhea, abdominal pain)
- GI tolerance is better than that of *erythromycin* with minimal laboratory abnormalities reported (like ⇑ transaminases, immunoallergic hepatitis)
- **Ototoxicity** *(erythromycin* & high doses of *clarithromycin)*
- **Skin allergic reactions** (rare)
- **Interactions** with *theophylline (erythromycin)* & *cyclosporine* (all *macrolides)*
- **„Torsades de pointes“** (combination of *erythromycin* + *disopyramide* or *terfenadine)*

Spiramycin
Spectrum & PK



- **Broad antibacterial spectrum** comprises:
  - G+ cocci & rods, G-cocci & also *legionellae, mycoplasmas, chlamydiae,* some types of *spirochetes, Toxoplasma gondii* & *Cryptosporidium* species
  - *Enterobacteria, pseudomonads* & pathogenic moulds are resistant

- *Spiramycin* is rapidly but **incompletely absorbed** (oral bioavailability ranges from 30 - 39%) & not modified by food intake:
  - tissue & saliva diffusion is excellent (lungs: 20 - 60 µg/g, tonsils: 20 - 80 µg/g, infected sinuses: 75 - 110 µg/g, bones: 5 - 100 µg/g)
  - plasma half-life is about 8 h
  - it does not enter the CSF & is excreted into breast milk

Azithromycin
Spectrum & PK

- An **azalide** antimicrobial agent (structurally related to the *erythromycin)*
- Although slightly less potent than *erythromycin* against G+ organisms, *azithromycin* demonstrates superior activity *in vitro* against a wide variety of G- bacilli (including *Haemophilus influenzae)*
- Absorption is ~ 37% (after a 500 mg oral dose, coadministration with a large meal may reduce absorption by up to 50%)
- The large volume of distribution (23 l/kg) & low peak serum level (0.4 µg/ml) are consistent with extensive tissue distribution & intracellular accumulation
- Metabolism is predominantly hepatic (to inactive metabolites), with biliary excretion (terminal half-life of up to 5 days)
- The **plasma half-life** of is 8 to 16 times longer than that of *erythromycin's* 90 min (the longest in macrolide group)

Azithromycin
Principal indications

- Oral *azithromycin* is effective in:
  - acute bacterial exacerbations of COPD, community-acquired pneumonia
  - acute otitis media, acute bacterial sinusitis, pharyngitis/tonsillitis, uncomplicated skin infections
  - acute pelvic inflammatory disease
  - genital ulcer disease (chancroid - G- streptobacillus *Haemophilus ducreyi*)
  - uncomplicated gonococcal infections, non-gonococcal urethritis & cervicitis due to *Chlamydia trachomatis*
  - ***Mycobacterium avium* complex**

(see antituberculotics)

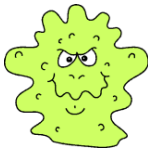
Clarithromycin
Spectrum & PK

- A **semisynthetic *macrolide***
- It is lipophilic & achieves concentrations in tissue generally 10x greater than concentrations in serum
- Oral bioavailability of 55% (25% for *erythromycin)*
- The **plasma half-life** of *clarithromycin* is 3x longer than that of *erythromycin*

- It has activity against a variety of G+ & G- bacteria *(Mycoplasma, Chlamydia &* it has activity against **atypical mycobacteria)**
- The major metabolite *(14-hydroxyclarithromycin)* is generally as active as *clarithromycin* against these organisms but is more active than *clarithromycin* against *Haemophilus influenzae*

Clarithromycin
Principal indications

- It is **primarily used** to treat:
  - a number of bacterial upper & lower respiratory tract infections including pneumonia & as an alternative to *penicillin* in strep throat
  - *Helicobacter pylori* infections (associated with duodenal ulcers) & skin & soft tissue infections
- **Other uses** include:
  - MAC, cat scratch disease (other infections due to bartonella, cryptosporidiosis), as a second line agent in Lyme disease & toxoplasmosis
  - it may be used to prevent bacterial endocarditis (in *penicillin* contraindication)
- **Organisms resistant to** *erythromycin (macrolide-lincosamide-streptogramin B - MLSB)* are also resistant to *clarithromycin*



Telithromycin
MoA & principal indications

- The first **ketolide** (a new class related to the macrolides, designed to overcome *erythromycin* resistance within G+ cocci)
- Structural modifications permitting **dual binding** to bacterial ribosomal RNA → so that activity is retained against *Streptococcus pneumoniae* with *MLSB resistance*
- Oral *telithromycin* 800 mg once daily for 5 - 10 days is effective for the treatment of community-acquired upper & lower respiratory tract infections:

Streptococcus pneumoniae,

Haemophilus influenzae,

Staphylococcus aureus

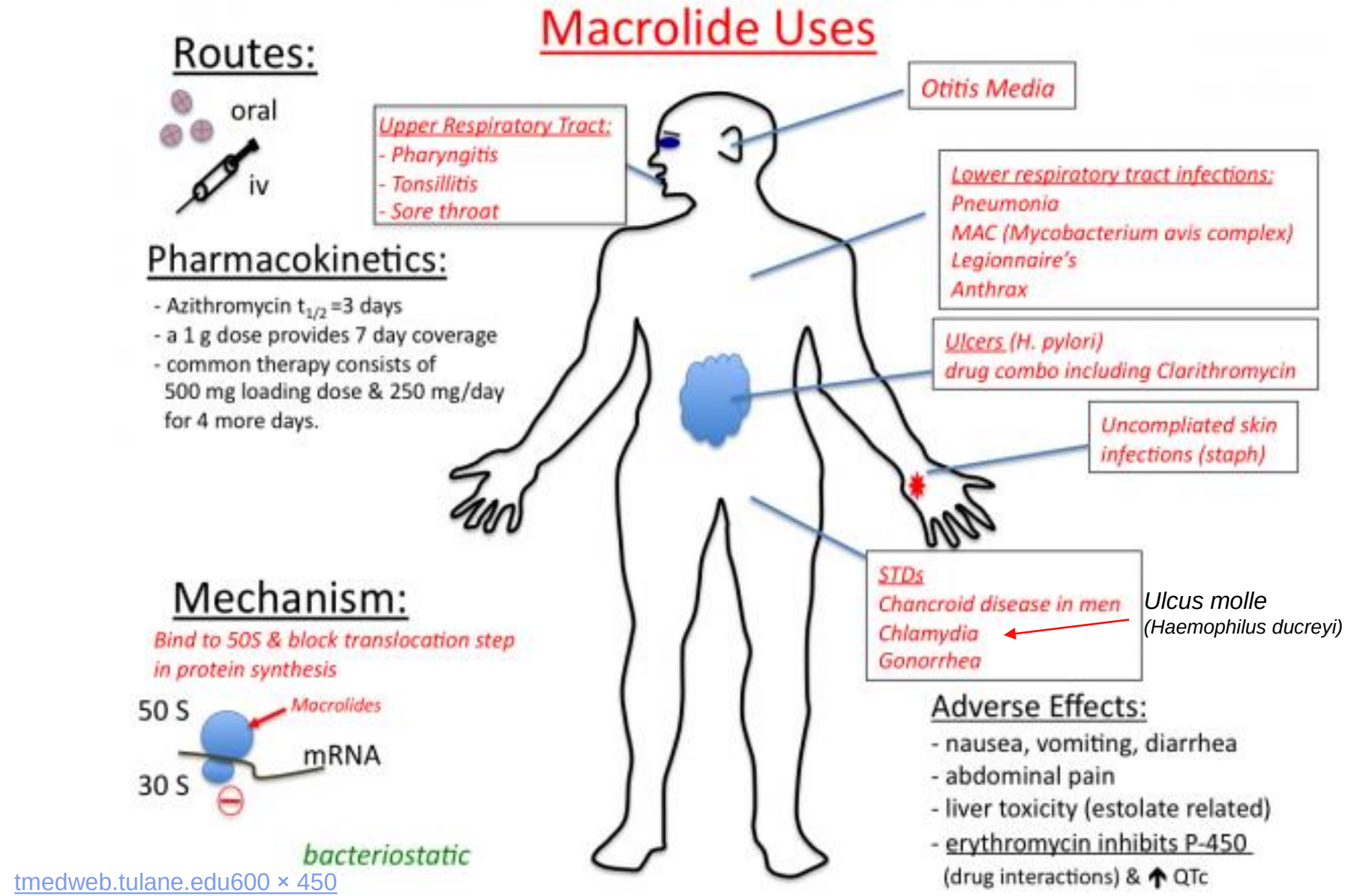
Telithromycin
PK

- **Absorption** in humans is estimated to be > or = 90%:
  - it undergoes first-pass metabolism (mainly by the liver) → its absolute bioavailability is 57% & is **unaffected by food**
- It is 60 - 70% bound to serum proteins & has extensive diffusion into a range of target biological tissues (concentrations above its MIC against key respiratory pathogens throughout the dosing interval)
- It is eliminated by multiple pathways (7% by biliary and/or intestinal excretion, 13% by renal excretion & 37% by hepatic metabolism - CYP3A4 & non-CYP pathways)
- **Plasma** concentrations show a biphasic ⇓ over time:
  - an initial disposition **half-life** of 2.9 hours
  - a terminal **elimination half-life** of ~ 10 h after multiple doses

Telithromycin
Interactions

- Dosage ⇓ may be recommended in patients with severe renal impairment
- ⇓ of CYP3A4 by potent inhibitors *(itraconazole & ketoconazole)* results in a 54% & 95% ⇑ in AUC
- The potential to ⇓ the CYP3A4 pathway is similar to that of *clarithromycin:*
  - *+ loperamide* → ⇑ blood levels of *loperamide* → irregular heart rhythms
  - *+ hydrocodone* → ⇑ blood levels of *hydrocodone* → drowsiness & light headedness
- Once-daily administration is likely to limit the potential for drug interactions

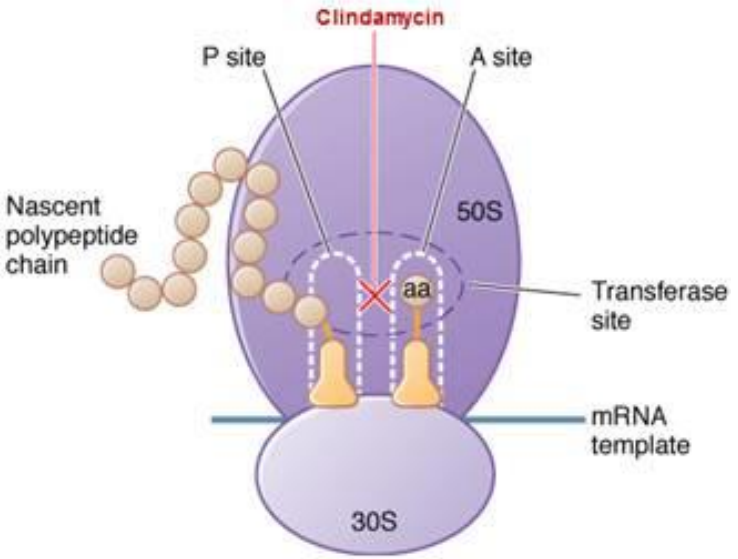
Macrolides
Summary

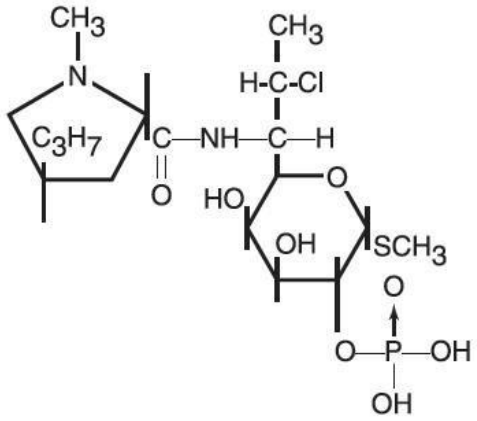


Lincosamides
Bacteriostatic

- ***Clindamycin*** **– more effective than** *lincomycin:*
  - *clindamycin* belongs to the MLSB ATB - all share an overlapping binding site in 23S rRNA of the **50S subunit of bacterial ribosome**
  - they interfere with the development of initiation complexes & with aminoacyl **translocation reactions**
  - **protein synthesis ⇓**

(at ⇑ concentration may be bactericidal)

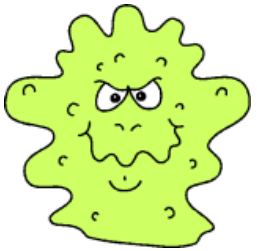




Lincosamides
Antimicrobial spectrum

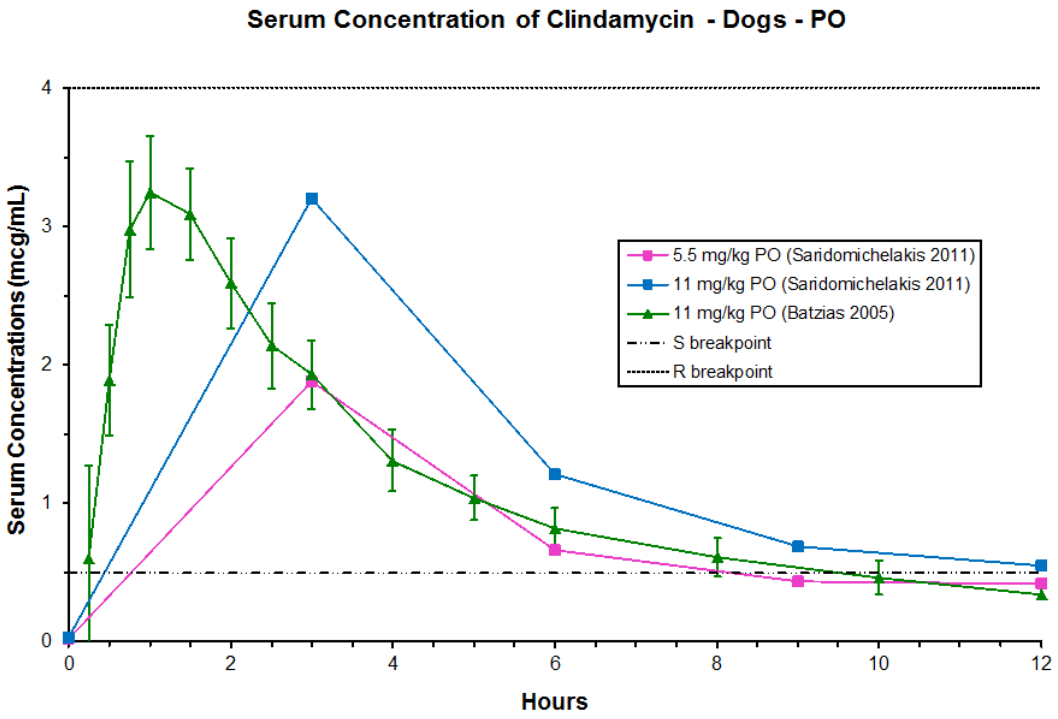
- **Broad spectrum ATB:**
  - majority of **aerobic G+**
    (good antistaphylococcal & antistreptococcal activity)
  - **anaerobic G–** (*Bacterioides fragilis*...)
  - **some *protozoa*** (toxoplasmosis, malaria, babesiosis)

- **Resistance:**
  - **majority of G- aerobic** *(Pseudomonas aeruginosa...)*
  - ***staphylococci*** *(methicilline*-resistent)



Clindamycin
PK

- ***Clindamycin:***
  - better GIT absorption **(90%)**
  - good tissue & body fluid penetration **(except CNS)**
  - active transport in PMNL & macrophages (facilitates opsonization, phagocytosis & intracellular killing of bacteria)

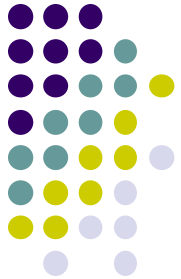


- primarily metabolized in liver
- renal, bile & stool excretion

Clindamycin
Therapeutic use

- **Principal indications:**
  - very good effect in **anaerobic** infections
  - **alternative to *PNC*** or *cephalosporines* for G+ cocci infections
  - soft tissue infections (MRSA)
  - necrotizing fasciitis; suppurative osteomyelitis (i.v. then p.o. 4-6 weeks)
  - oral infections (dentistry)
  - formerly: prophylaxis in surgery (+ *aminoglycoside)*
  - topically to treat infected acne vulgaris
  - **no value in CNS infections**

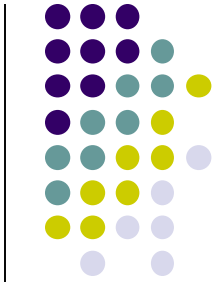
Lincosamides
Resistance & SE



- **Resistance:**
  - MLSB resistance: target site modification (the ribosomal methylation) - the **most widespread mechanism** of *macrolides & lincosamides*
  - non-MLSB type of resistance results from inactivation of *lincomycin & clindamycin* (e.g. the last one through its conversion to clindamycin 4-(5'-adenylate)

- **SE:**
  - **diarrhea or pseudomembranous collitis** (*Clostridium difficile* infection - CDI)
  - nausea, vomiting
  - hypersensitivity
  - transient leukopoenia & eozinophilia
  - change in liver tests

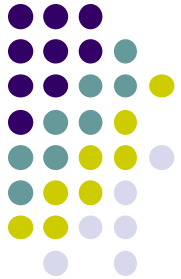
Lincosamides
CDI incidence



- ATB-associated diarrhea is not that uncommon during a course of ATB therapy
- It becomes a more significant event if it is the result of *C. difficile* infection (a common nosocomial anaerobic bacillus)
- Intestinal flora normally prevent colonization by *C. difficile* (it is present in only 1 – 4% of the general population, but 20% in those admitted to health care facilities for a week or more)
- When normal flora is altered by ATB therapy & the patient either harbors or comes into contact with *C. difficile*, colonization ⇑
- Colonization may be enhanced by most ATB (*clindamycin, amoxicillin, 2nd- & 3rd-generation cephalosporins* & the *fluoroquinolones* are most often implicated)

- Once *C. difficile* infection occurs, the consequences range from **diarrhea** to **pseudomembranous colitis**

Lincosamides
CDI treatment



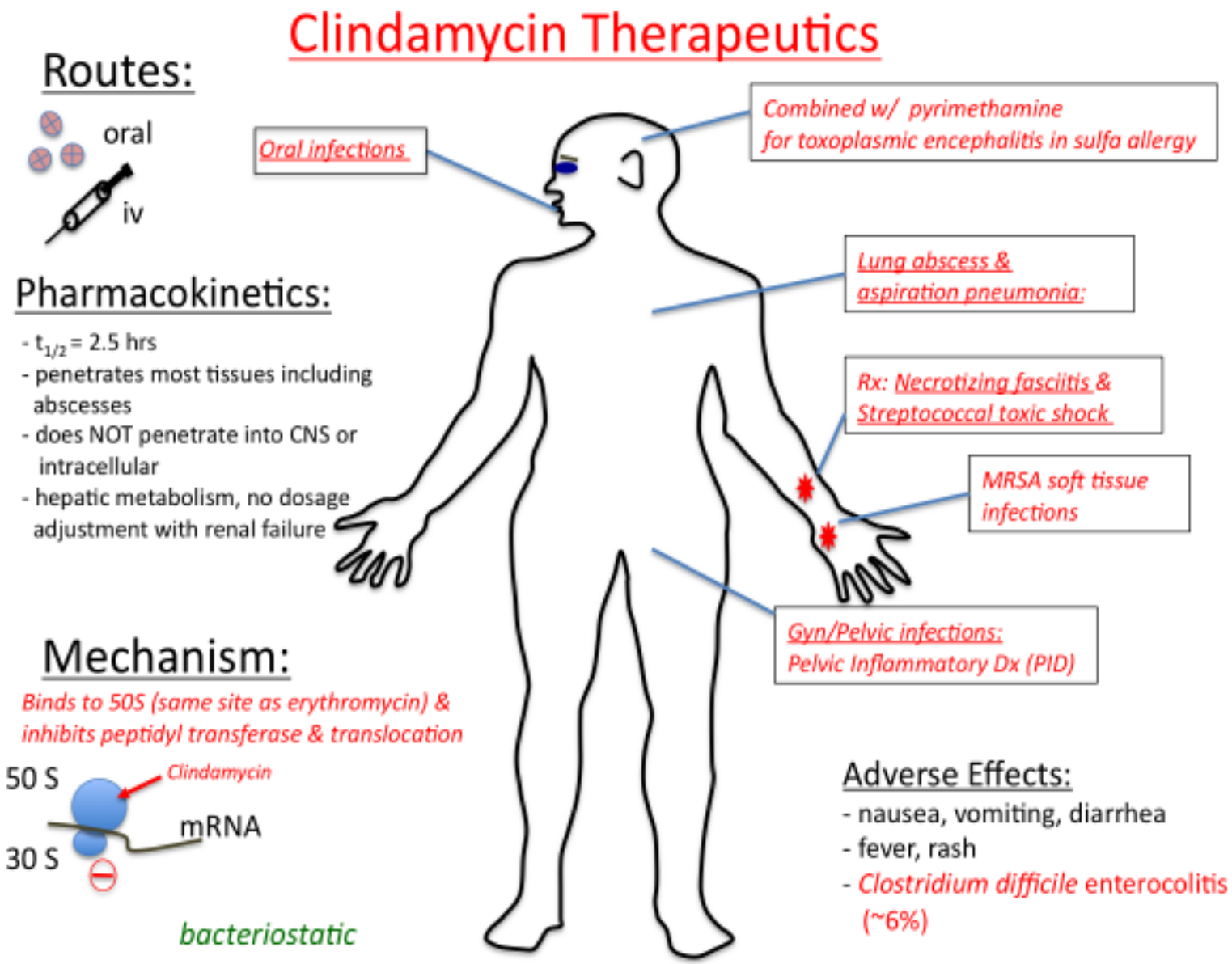
- **Typical sequence of events leading to *C. difficile* infection are as follows:**

1. The patient is currently colonized with *C. difficile* (most likely if the patient has recently visited, has been a patient, or is a health care provider in a hospital or nursing home)
2. Colonization is then ⇑ by an ATB altering intestinal flora (*clindamycin* or *amoxicillin* are most likely)
3. Patient-related factors determine risk for actual infection *&* subsequent severity (older age, poor immune status, use of acid-reduction drugs are most significant)
4. Mild diarrhea may be managed using antiperistaltics *&* changing the ATB to a narrower spectrum if possible

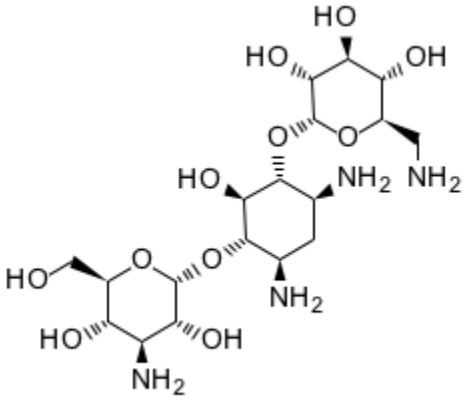
- **If diarrhea is severe *& C. difficile* infection is suspected:**

1. **Avoid antiperistaltics** (accumulation of toxin can worsen the infection)
2. Stop the current ATB *&* prescribe *metronidazole* (500 mg TID 10 – 14 days)
3. If there is no improvement after 2 – 3 days (based on severity), or diarrhea subsides *&* recurs, switch to oral *vancomycin* (not absorbed but provides its action locally within the colon; however, it is shockingly expensive *&* will be initiated only in extreme cases)

Clindamycin
Summary



Aminoglycosides
Active agents



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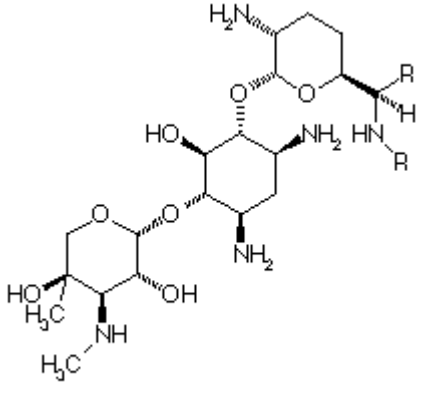

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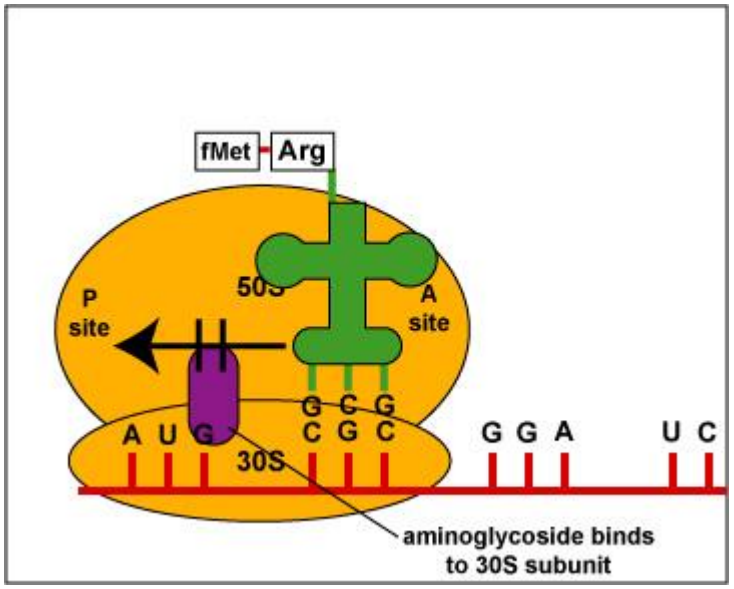
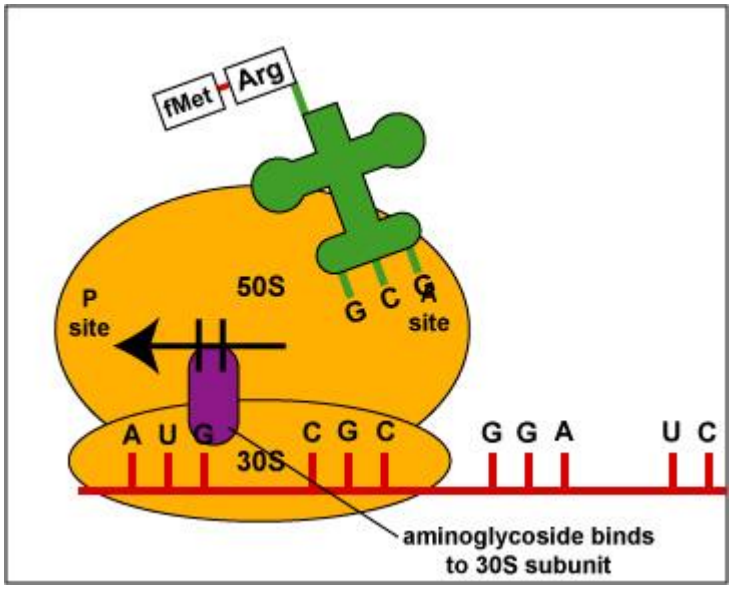
- ***Kanamycin***
- ***Streptomycin***
- ***Tobramycin***

- ***Gentamicin***
- ***Amikacin***
- ***Netilmicin***
- ***Spectinomycin***

(closely related to *aminoglycosides)*

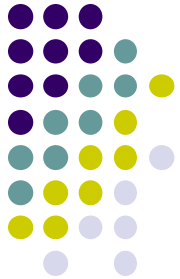
Aminoglycosides
Bactericidal





- **Irreversible binding** to 30S subunit:
  - interfere with tRNA translocation
  - ⇓ of polypeptide chain elongation
  - however, their effect is **bactericidal**
    (because they halt protein synthesis **rapidly & irreversibly** & make bacterial **cell membrane more leaky)**

Aminoglycosides
Resistance



- **Ribosome alteration -** single step mutations in chromosomal genes encoding ribosomal proteins *(streptomycin & spectinomycin)*

- ⇓ **permeability -** absence of or alteration in the *aminoglycoside* transport system can result in a cross resistance to all *aminoglycosides*

- **Inactivation of *aminoglycosides* -** 3 major enzyme classes:

  - AAC (acetyltransferases)
  - ANT (nucleotidyltransferases or adenyltransferases)
  - APH (phosphotransferases)

Aminoglycosides
PK

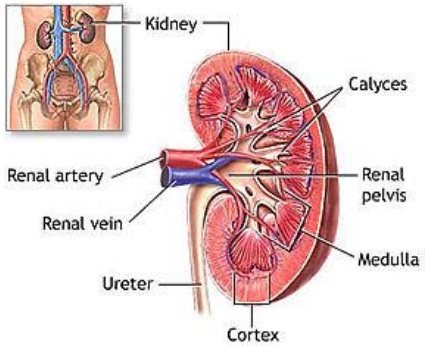
- Very low oral absorption (e.g. *streptomycin* is highly ionized at a wide range of pH values in the gut):
  - *i.m.* or *i.v.* application (oral – only for local GI effect)
- Good tissue distribution except CNS
- Excretion - **glomerular filtration**
- *Aminoglycosides* are actively transported into a bacterial cell by an **oxygen-dependent enzyme system**

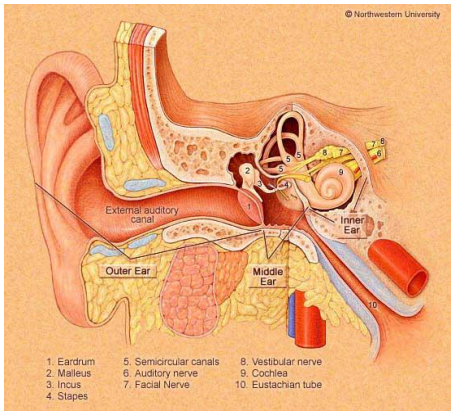
Aminoglycosides
Antimicrobial spectrum

- **Only aerobic bacteria are sensitive** to these drugs
- Majority of **G– bacilly** (e.g. *gentamicin - Pseudomonas...)*
- Some **G+ bacteria** (including **severe *enterococcal* endocarditis** in combination with **cell wall–active agent** e.g., *ampicillin* or *vancomycin)*
- ***Mycobacterium tuberculosis*** *(streptomycin)*
- Treatment of gonorrhea infections ***(****spectinomycin -* given by i.m. inj., especially in patients allergic to *penicillins)*

Aminoglycosides
SE

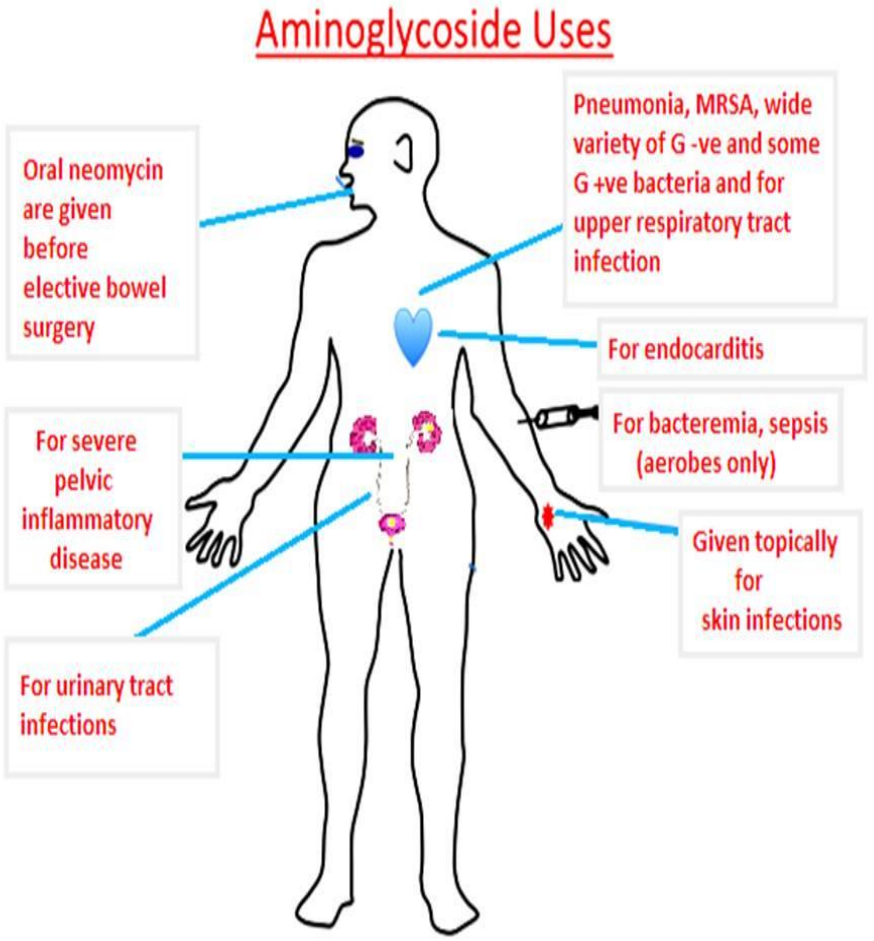
- **Nefrotoxicity** (interferrence with tubular function – excess loss of Mg^{2+} & Ca^{2+}; **generally reversible)**
  - ⇑ with concurrent use of *loop diuretics, vancomycin, amphotericin*...
- **Ototoxicity** **(irreversible;** auditory & vestibular)
- **„Curare-like“ effect** (binding Ca^{2+} in presynaptic region; **reversible with calcium gluconate)**
- Hypersensitivity





Aminoglycosides
Therapeutic use

- **Severe G-, *staphylococal* & mixed infections**
- **Formerly -** prophylaxis of intestine infections (surgery – *oral neomycin)*
- **Formerly -** hepatic encephalopathy *(neomycin -* oral)
- **Local** - eye drops, skin, etc. *(kanamycin, neomycin)*
- **TBC** *(streptomycin)*

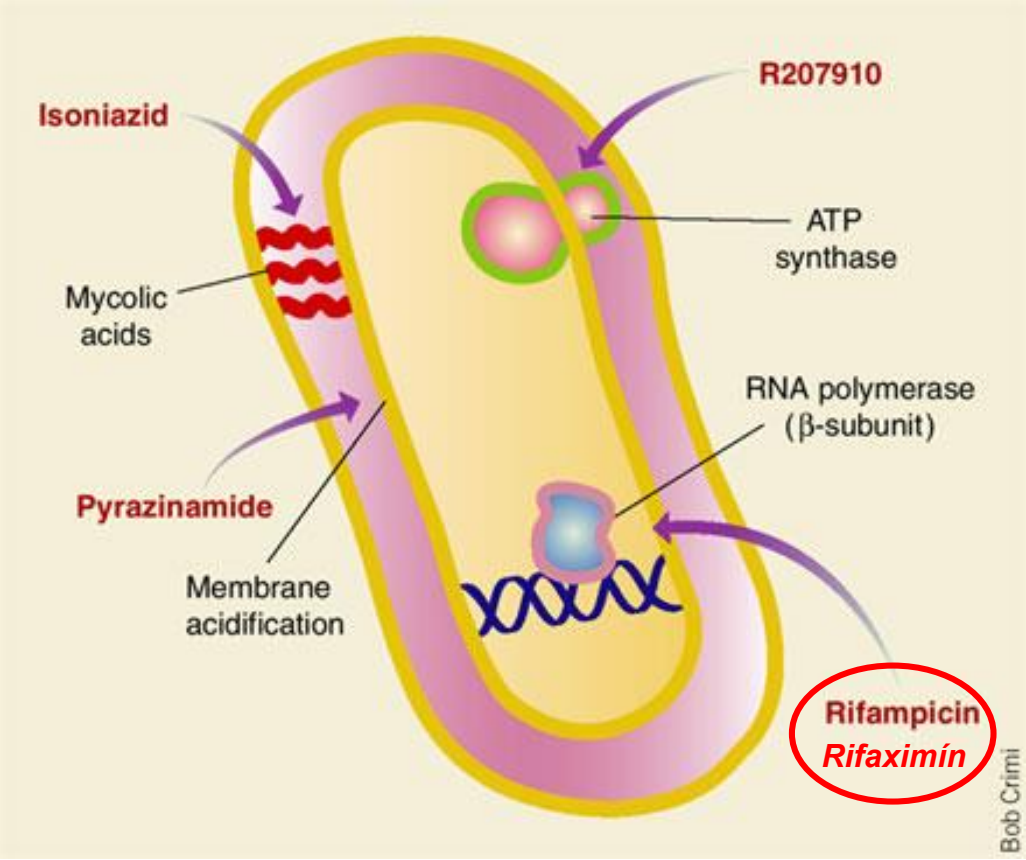


www.webmedcentral.com

Rifaximin
MoA

- An antibacterial drug of ***rifamycin class*** (like ***rifampicin***)

- **Irreversibly** binds:
  - β-subunit of the bacterial enzyme - DNA-dependent RNA polymerase &
  - subsequently ⇓ bacterial RNA synthesis



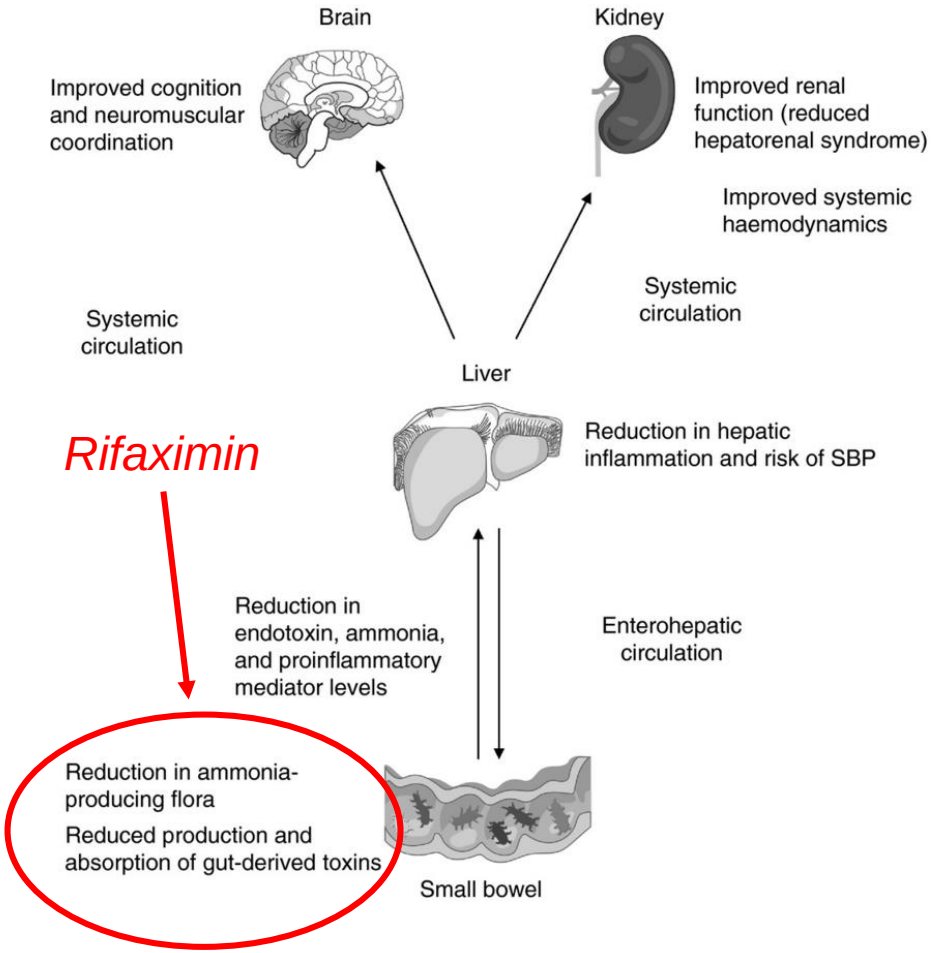
www.nature.com

Rifaximin
Antibacterial spectrum

- **Broad antimicrobial spectrum** - most of the:
  - **G+** & **G-**
  - **aerobic** & **anaerobic**

(including ammonia producing species)

- may ⇓ the division of urea-deaminating bacteria thereby
- ⇓ the production of ammonia & other compounds that are believed to be important to the pathogenesis of **hepatic encephalopathy**



Rifaximin
PK

PK:

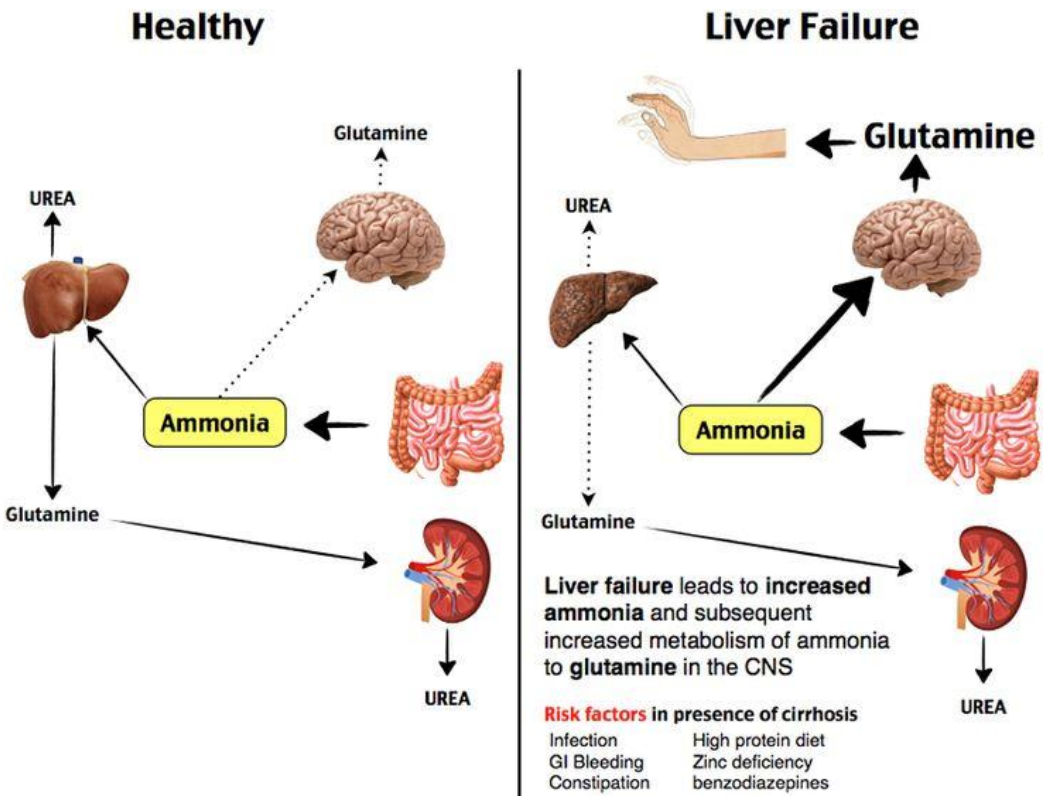
- After oral administration *rifaximin* is poorly absorbed (< 1%)
- It is neither degraded nor metabolised during its passage through the GIT
- It is almost exclusively & completely excreted in faeces (96.9 % of the administered dose)

- **Common SE** (≥1/100 to <1/10):
  - upper abdominal pain, abdominal distension, diarrhoea, nausea, vomiting, ascites
  - dizziness, headache, depression
  - dyspnoea
  - rashes, pruritus
  - muscle spasms, arthralgia
  - peripheral oedema

Rifaximin

Indications

- For the ⇓ in recurrence of episodes of overt **hepatic encephalopathy**
- In irritable bowel syndrome (it may be efficacious in relieving chronic functional symptoms of bloating & flatulence that are common)
- May be used to treat & prevent traveler's diarrhea
- May also be a useful addition to ***vancomycin*** when treating patients with relapsing *Clostridium difficile* infections
- Prophylaxis in colorectal surgery



Tetracyclines

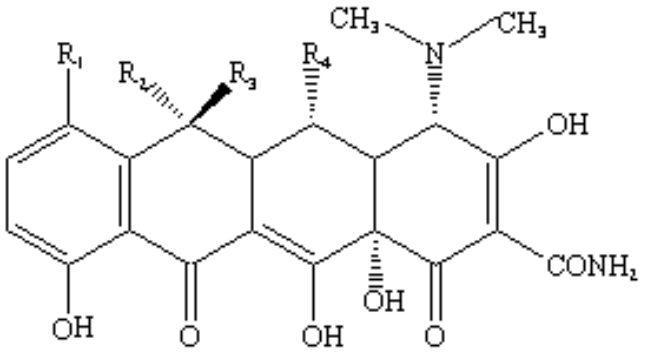
Active agents

Group 1:

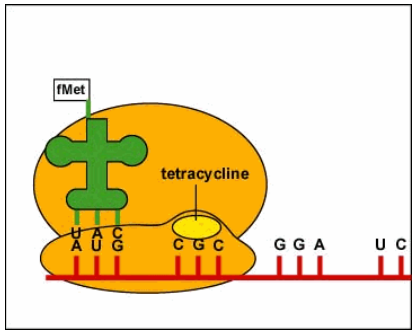
- ***Tetracycline***
- ***Chlortetracycline***
- ***Oxytetracycline***
- ***Rolitetracycline***

Group 2:

- ***Doxycycline***
- ***Minocycline***
- ***Tigecycline***



- Produced by various strains of ***Streptomyces***
- **Macrocyclic lacton** ring
- Reversible tRNA binding to 30S ribosomal subunit:
  - block bacterial translation
  - ⇓ **of protein synthesis**
  - **bacteriostatic**



Tetracyclines
PK – Group 1

- **Group 1:**
- older agents
- reduced GI absorption (25 - 60%)
- less lipophilic
-  - except ***rolitetracycline*** (i.v. only) 
- none of these agents undergoes metabolism (except tetracycline - 5%)
- unchanged drugs are excreted by renal & bilary routes (in the urine <50%; biliary concentrations can exceed blood by a factor of 5)

Tetracyclines
PK – Group 2

- ***Doxycycline:***
- almost completely absorbed (80% with an average of ~95%)
- 5x more lipophilic (than Group 1)
-  &  (i.v.)
- ***doxycycline*–metal** ion complexes are unstable at acid pH (more *doxycycline* enters the duodenum for absorption compared with the earlier compounds)
- food has less effect on absorption (than in earlier drugs)
- no metabolites have been found in man
- renal (35 - 60%) & biliary elimination (bile concentrations may be 10 - 25x those in serum)
- **long elimination half-life** (12 to 25 h)

Tetracyclines
PK – Group 2

- ***Minocycline:***
- almost completely absorbed (95-100%)
- 10x more lipophilic (than Group 1)
-  &  (i.v.)
- food does not appear to have an effect (on either the C_{max} or AUC)
- concentrations of < 50% serum in CSF have been reported
- **it has a variety of metabolites** (faecal elimination accounts for about 20 – 35% of the dose)
- C_{max} after 2-3 h post-oral dose with a **prolonged serum half-life** (12 – 18 h)

Tetracyclines
PK – common

- **Ca^{2+}** & other **di- & tri-valent ions ⇓ absorption** (milk...)
- **Good tissue distribution**, even in necrotic tissues
- **Bacteriostatic levels** are achieved in pleural & synovial fluids, aqous humor, abscess fluid
- Penetration into **CSF is poor** & insufficient to render *TTCs* useful in meningeal infection **(it does not ⇑ significantly in the presence of meningeal inflammation)**
- Do not bind to bone that is already formed but are **incorporated into calcifying tissue** as a *TTC-Ca* orthophosphate complex (bone & teeth accumulation - chelating properties)

Tetracyclines
Antimicrobial spectrum

- **Broad spectrum ATB against G+ & G- bacteria**
- **Very active against intracellular parasites**

  (mycoplasma, ricketsia, chlamydia, brucella)

- *TTC* are **rarely the drugs of first choice** for common bacterial infections (resistance & availability of less toxic ATB)
- Valuable alternatives to drugs of first choice *(penicillin G & aminopenicillins, streptomycin, macrolides, chloroquine-resistant Plasmodia)*

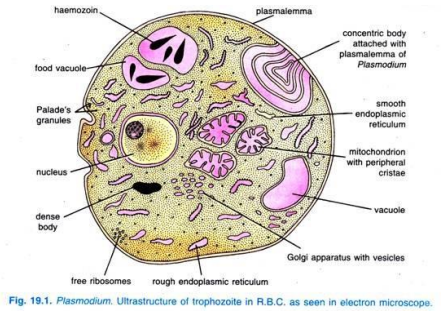
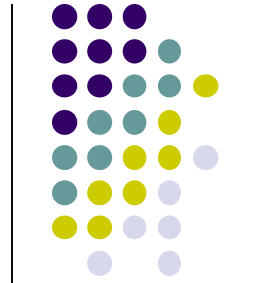


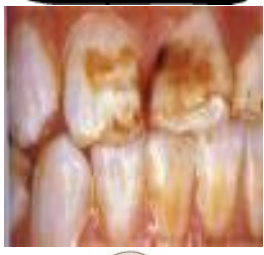
Fig. 19.1. *Plasmodium*. Ultrastructure of trophozoite in R.B.C. as seen in electron microscope.

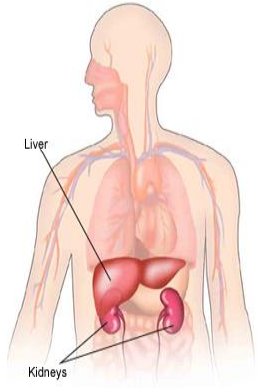
Plasmodium vivax

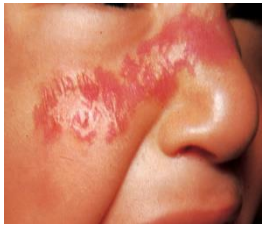
Tetracyclines
SE

- **Irritative substances** (thrombophlebitis, nausea, vomiting, diarrhea – rarelly with well-absorbed *TTC)*
- **Superinfections** (drug-resistant bacteria - *C. difficile* or *Staphylococcal* enterocolitis & yeasts - *Candida)*
- **Long bone growth in premature infants, teeth discoloration** (contraindicated in pregnancy & children up to 8 years of age)
- **Hepatotoxicity** (pregnant & postpartum women with renal disease are especially vulnerable)
- **Renal toxicity** *(TTC* accumulate to toxic levels except *doxycycline)*
- **Skin (phototoxicity;** more frequently for *doxycycline > tetracycline > minocycline – the least phototoxic)*

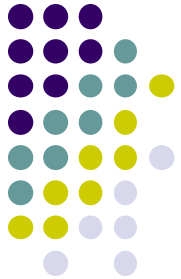








Tetracyclines
Therapeutic use



- **Intracellular parasites** *(mycoplasma, chlamydia, rickettsia, legionella, leptospira, toxoplasma)*

- **ENT infections**
- **Acute exacerbations of chronic respiratory infections**
- **Gall bladder & biliary infections**
- **Urogenital infections – in syphilis,** regimens of:
  - ***doxycycline*** (100 mg orally 2x daily for 14 days) or
  - *TTC* (500 mg 4x daily for 14 days - compliance is likely to be better with *doxycycline* than *TTC*, because *TTC* can cause GI side effects & requires more frequent dosing)

- **Skin infections**