

Macrolides

Erythromycin

Clarithromycin (Biaxin)

Azithromycin (Zithromax; Zitromax)

Roxithromycin (Rulid)

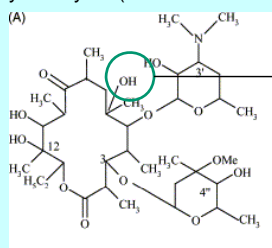
Dirithromycin (Dynabac)

} semi-synthetic
derivatives of
erythromycin

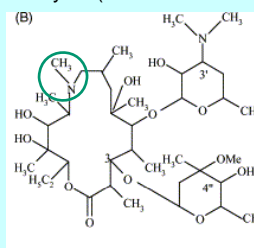
5% of penicillin susceptible strains are macrolides resistant;
50% penn-resistant strains may be resistant to macrolides

Ketolides (Telithromycin)

Erythromycin (14-membered macrolide)

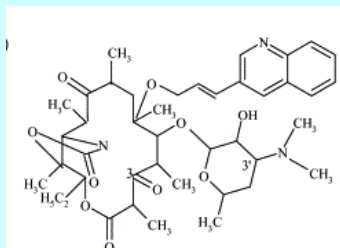


Azithromycin (15-membered macrolide)



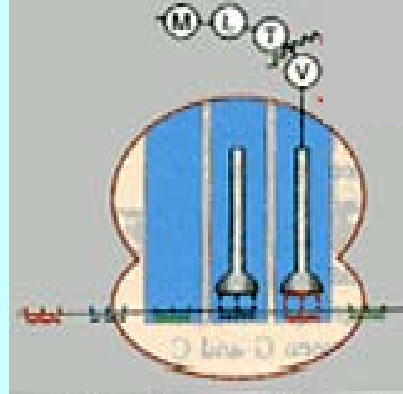
→ OCH₃
Clarithromycin

Ketolides (Telithromycin) Cladinose → 3-keto gr

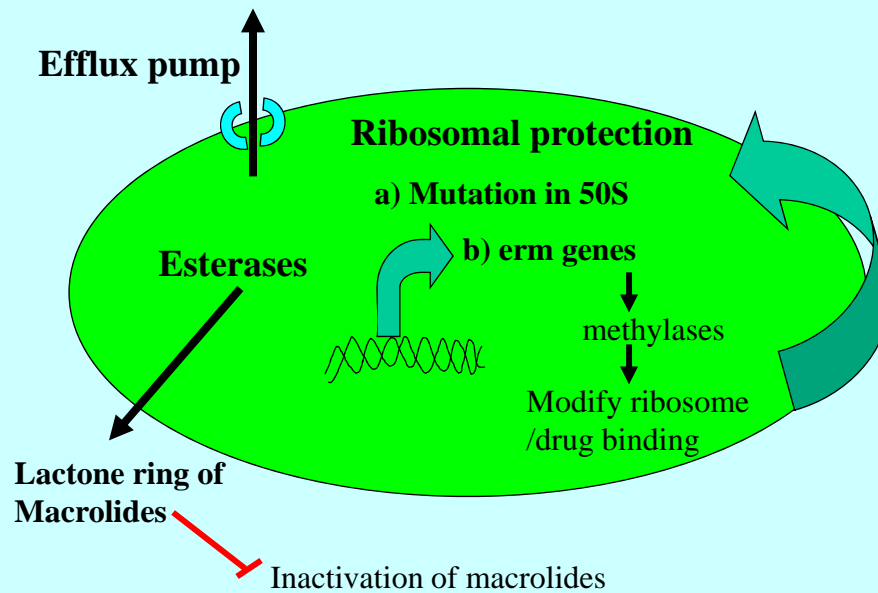


Mechanism of action

- a) Binds reversibly with 50S
- b) Inhibit **translocation** of peptide chain to P site



Mechanism of Resistance



Efflux pumps

requires energy

coded by mrsA genes (Group A staphylococci)

mefA genes (Group A streptococci)

or mefE genes S. pneumoniae)

Methylases (decreases drug binding)

Inducible or constitutive

coded by ermA, ermB and ermC

- Inducible erm will provide to resistance to only macrolides

- constitutive expression of erm leads to :

MLS_B (macrolide-lincosamide-streptogramin B)

ABSORPTION

Erythromycin: Incompletely but adequately absorbed
sensitive to Gastric acid; administered as enteric-coated tablets

Clarithromycin: Acid stable, Oral dose rapidly absorbed;
but **FIRST-PASS** metabolism reduces its bioavailability by 50%;
One of the metabolite 14-hydroxy clarithromycin is twice as **active**

Azithromycin: Oral dose rapidly absorbed; antacids decreases
peak serum drug concentration but NOT overall-
bioavailability ; the metabolites are **not** active; Should **NOT** be
given with food

DISTRIBUTION

Erythromycin:

- distributes readily in intracellular bodily fluids and tissues **except** brain and CSF
- concentration (protein binding 70-80%)
 - in prostatic fluid ~40% of serum
 - in middle ear ~50% of serum
- crosses placenta (5-20% of maternal plasma in fetal plasma) 50% of serum can be in milk

Clarithromycin:

- distributes widely and achieve high intracellular concentration; phagocytes
- Protein binding ranges from 40-70%.
- Tissue concentration > serum concentration
 - in middle ear conc is 50% higher than that in of serum

Azithromycin:

- extensive tissue distribution
 - Protein binding is 50% at low plasma conc and less at higher concentrations
 - Tissue concentration > serum concentration
 - in middle ear conc is 50% higher than that in of serum
- Tissue fibroblasts act as a natural reservoir

Elimination

Erthromycin:

only 2-5% of oral drug is excreted in urine;
concentrated and metabolized in liver CYP's → demethylation →
excreted in bile;
short half life (1.6 hr) may prolong in anuria (dose adjustment not
necessary)

Clarithromycin:

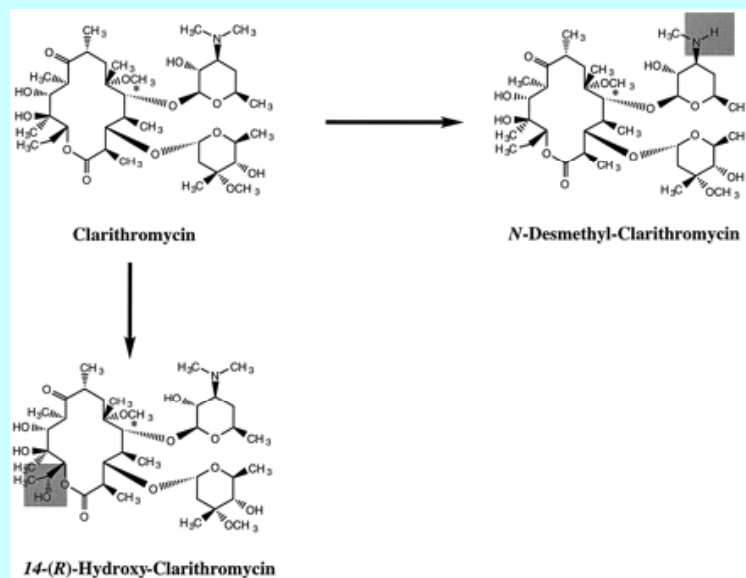
Both renal and non-renal

liver CYP induces N-demethylation and hydroxylation;

20-40% excreted unchanged in urine

half life (3-7); 14-hydroxy metabolite (5-9 hr) may prolong in anuria
(dose adjustment not necessary; only if high creatinine levels)

Metabolism



Azithromycin:

Some hepatic metabolism to inactive metabolite; excreted by bile;
12% by urine
half life 48-68 hrs; because of extensive tissue sequestration and
binding

Spectrum of Activity

Erythromycin: widely prescribed for gram (+) infections caused by
staphylococcal and streptococcal species
also effective against Legionella and Mycoplasma species.

Clarithromycin

Gram-positive activity superior than erythromycin and azithromycin,
especially against Streptococcus pyogenes and Streptococcus
pneumoniae.

Gram-negative coverage is also increased with clarithromycin.

Better than erythromycin against Legionella and Mycoplasma species.

Azithromycin

increased gram-negative coverage than erythro or clarithromycin.

more active than clarithromycin against *H. influenzae*

Salmonella and *Shigella* species are susceptible, as have other diarrheal pathogens such as *Yersinia* and *Campylobacter*.

also has good activity against *Legionella* and *Mycoplasma* species.

excellent activity against *Chlamydia trachomatis*.

Untoward effect

GI irritation common and unpleasant

Prolong QT interval → ventricular arrhythmias due to blockage of K⁺ current (human ether-a-go-related gene HERG)

~less with azithromycin at clinical doses

hypersensitive reactions such as skin rashes

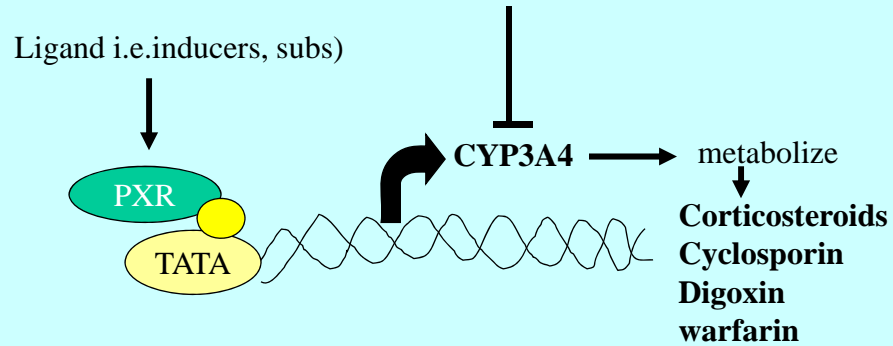
transient hearing disturbances

Cholestatic Hepatitis primarily by erythromycin estolate

Pyloric stenosis in children of mother who took erythromycin during late pregnancy/nursing

Drug Interactions of Macrolides

Mainly Erythromycin
and (to a lesser extent Clarithromycin)
(use caution with Azithromycin)



Therapeutic Use

Mycoplasma pneumoniae infections

Legionnaires Disease

Chlamydial infections (any macrolides)

Diphtheria

Pertussis (erythromycin)

Strep/Staph Infections; alternatives in patients allergic to
Penn

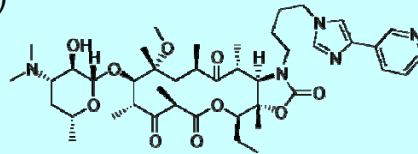
Campylobacter/ Helibacter Infections

Tetanus: in patients allergic to Penn

Mycobacterial Infections: **Clathri/Azithro** Ist choice
in **AIDS or in non-HIV**

Prophylactic use: erythromycin can be used for rheumatic fever
bacterial endocarditis, RTI in patients allergic to Pennicillin

Ketolides: Telithromycin (Ketek)



Mechanism of action:

target is the ribosome;
structural modification **neutralizes** the common resistance
mechanisms that makes macrolide ineffective such as
methylases (**inducible**), drug efflux pumps

Absorption, distribution, elimination

well-absorbed, 60-70% bound to proteins, penetrates
well in tissues (2-20 times more in tissue than plasma); Half
life~9.8 hrs; Cleared by hepatic mechanism; 50% by CYP3A4
and 50% by hepatic-independent mechanism

Therapeutic Use

RTI; pneumococcal pneumonia

Untoward effect

Significant prolongation of QTc; risk of ventricular arrhythmia

drug interaction may be less than other macrolides

Summary

50S Ribo, inhibits transferases

Bact develops resistance by modifying ribosomal target, increased efflux and hydrolysis,

Useful for RTI

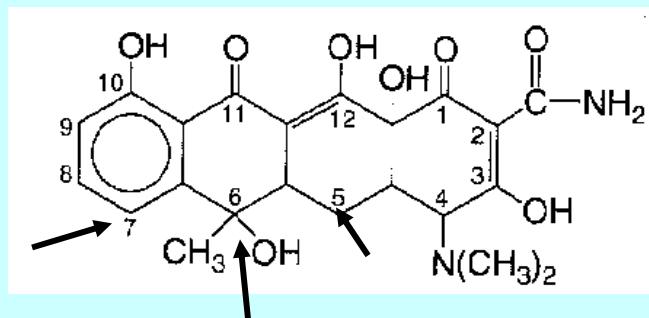
Well-tolerated

Orally bioavl

All except **azithro** have drug interactions as inhibit hepatic CYPs

TETRACYCLINES AND CHLORAMPHENICOL

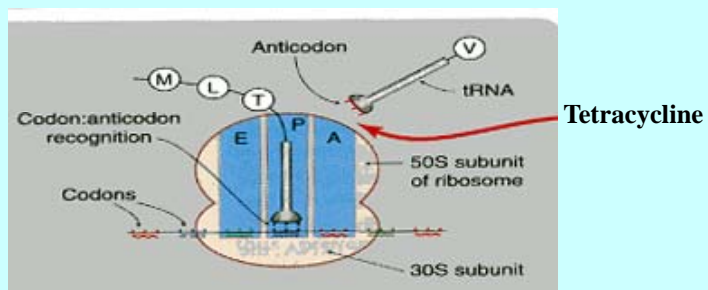
Tetracyclines



Sumycin®
Tetracycl®
Panmycin® etc
Actisite® dental applications.

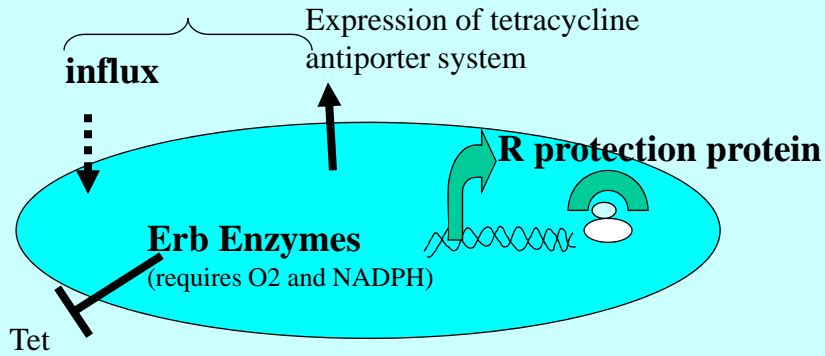
CONGENER	SUBSTITUENT(S)	POSITION(S)
Chlorotetracyclin	-Cl	(7)
Oxytetracycline	-OH, -H	(5)
Demeclocycline	-OH, -H; -Cl	(6; 7)
* Methacycline	-OH, -H; =CH ₂	(5; 6)
Doxycycline	-OH, -H; -CH ₃ ; -H	(5; 6)
Minocycline	-H, -H; -N(CH ₃) ₂	(6; 7)

I. Mechanism of antimicrobial activity:

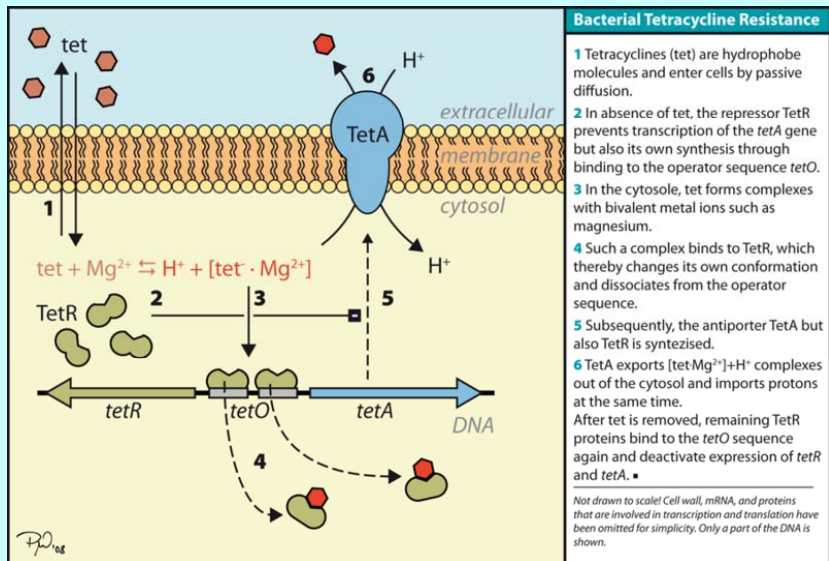


competes with tRNA for the **A site** on 30s ribosome

III. Resistance to antimicrobial activity:



Increase activity of antiporter system: by encoding a resistance operon



R protection protein

Tet(O) and Tet(M) (75% sequence similarity)

soluble cytoplasmic proteins (72 kDa)

display sequence similarity to the ribosomal elongation factors, EF-G and EF-Tu

can dislodge tetracycline from the ribosome

Cross-resistance among Tetracyclines depend on resistance mechanisms i.e.:

Mutation in efflux pumps that renders resistance to tetracycline may still be sensitive to minocycline;

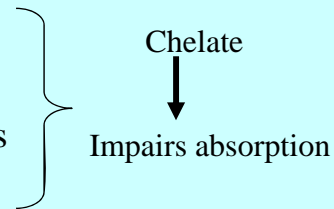
However, induction of tetM imposes cross-resistance to doxycycline and minocycline

Absorption

Incomplete oral absorptions

Chlor (30%) < oxy/deme/tetra (60-80%) < doxy (95%) < **mino** (100%)

Dairy products
aluminum hydroxide gels,
calcium and magnesium salts
iron preparations



Distribution

ready accessible to most tissues

cross placental barrier and enter fetal circulation
and amniotic fluid

high concentration can appear in breast milk

significant concentrations found in CSF after I.V.

accumulate in:

dentine and enamel of unerupted teeth

reticuloendothelial cells of liver, spleen, bone marrow
and bone

Excretion

primary route of elimination is kidney; may be concentrated in liver and excreted in bile; **doxycycline (fecal)**

After biliary excretion (except minocycline), they are partially reabsorbed via enterohepatic circulation

doxycycline does not accumulate in patients with renal failure

can be of value in treating patients with **impaired renal function**

Bacterial Susceptibilities

Intrinsically more active agnst Gram (+) than Gram (-)
i.e. Brucella, Vibrio cholerae etc

Effective agnst Anerobic/ facultative bact Actinomyces

Minocycline is also effective against N.meningitidis

Therapeutic Use

Rickettsial infections (i.e. Rocky Mountain spotted fever, typhus, Q fever)

Mycoplasma infections

Chlamydia infections

Trachoma

Anthrax

Cholera

Brucellosis (Tetra + rifampin/streptomycin)

Acne (Tetra)

DOXYCYCLINE

Side Effects:

Gastrointestinal: lessen by concurrent food intake

pseudomembranous colitis (overgrowth of c.difficile)

Photosensitivity: more particularly with demeclocycline and doxycycline

hepatic toxicity: Oxytetra and tetra are least hepatotoxic (Pregnant women more susceptible)

renal toxicity: aggravate azotemia;

All but less with **doxycycline**

Outdated TETRACYCLINE → Fanconi syndrome

High doses of tetracycline can decrease protein synthesis in the host cells- an **anti-anabolic effect**

Effect on teeth:

chelation property
formation of tetracycline-Ca-orthophosphate complex

long-short--permanent discoloration of teeth

- in children (upto 8yrs);
- risk highest if neonates and babies recv it before **first** dentition
- can effect the baby of pregnant patients

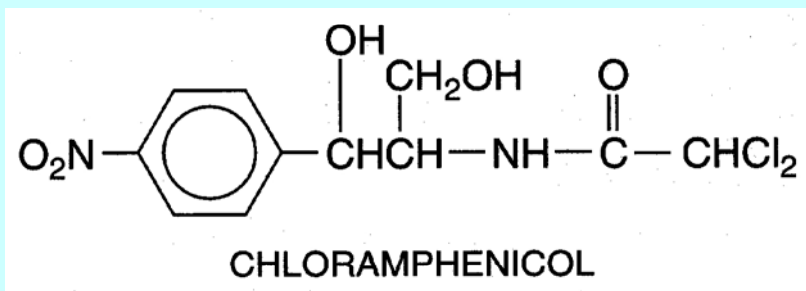
Superinfection with yeast or resistant pathogenic bacteria may occur

Summary

- Enter by porins/active transport sys in an energy-dependent Manner
- Inhibit tRNA binding to A site
- Bact develop resistance by generating ribosomal protection protein, altering fluxes, enzyme inactivation
- Inactivated by Chelating agents
- Gastrointestinal, discoloration of teeth, photosensitivity, hepatic and renal toxicity
- Doxycycline**, most important member,
broad spectrum
STDs, rickettsial infections, plague,
brucellosis, RTI,

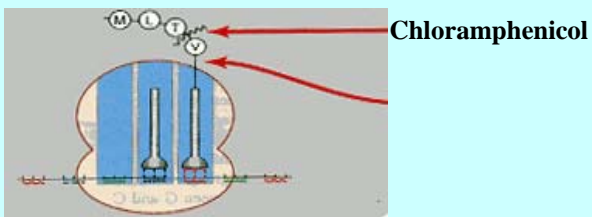
Minocycline: Skin and soft tissue infections

Chloramphenicol (Chloromycetin)



Rapidly penetrates in bact cell (facilitative diffusion)

I. Mechanism of action:

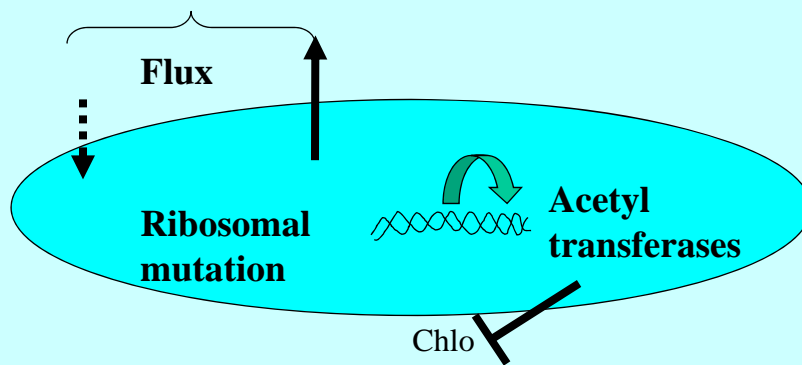


Binds reversibly with 50S ribosome; Inhibits peptidyltransferases

can also block **mitochondrial protein synthesis** in **mammalian** cells, especially in erythropoietic cells

Toxicity : due to blood dyscrasias
use limited in well defined and indicated conditions.

Mechanism of Resistance:



Absorption, Distribution and Excretion

parent drug readily absorbed in GI tract 10-13ug/ml
~2hr after 1g dose

prodrug (chloramphenicol palmitate) hydrolyzed in
duodenum

chloramphenicol succinate used for parenteral
administration

Antibacterial activity

- Broad; Gram (-) e.g., *H. influenzae* (bacteriocidal),
N. meningitidis
- anaerobic bacteria
- Gram (+) cocci; clostridium
- Gram(-) rods: *E. coli*, *V. cholerae*, *Shingella*,
Chlamydia and *Mycoplasma*
- **not effective** against *pseudomonas*, *histolytica*,
Entamoeba

readily accessible to tissues and bodily fluids

high concentration achieved in brain

enters CSF at therapeutic concentrations

Present in bile, milk, and placental fluid

metabolized in liver and inactive glucuronide
metabolite excreted in urine

caution in treating patients with **hepatic cirrhosis**

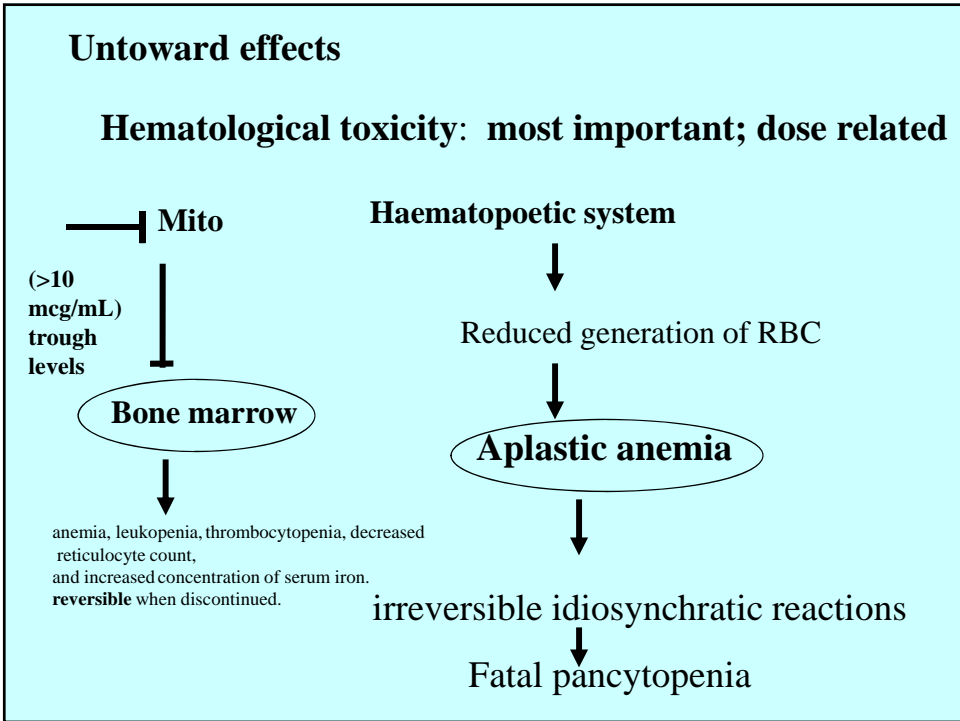
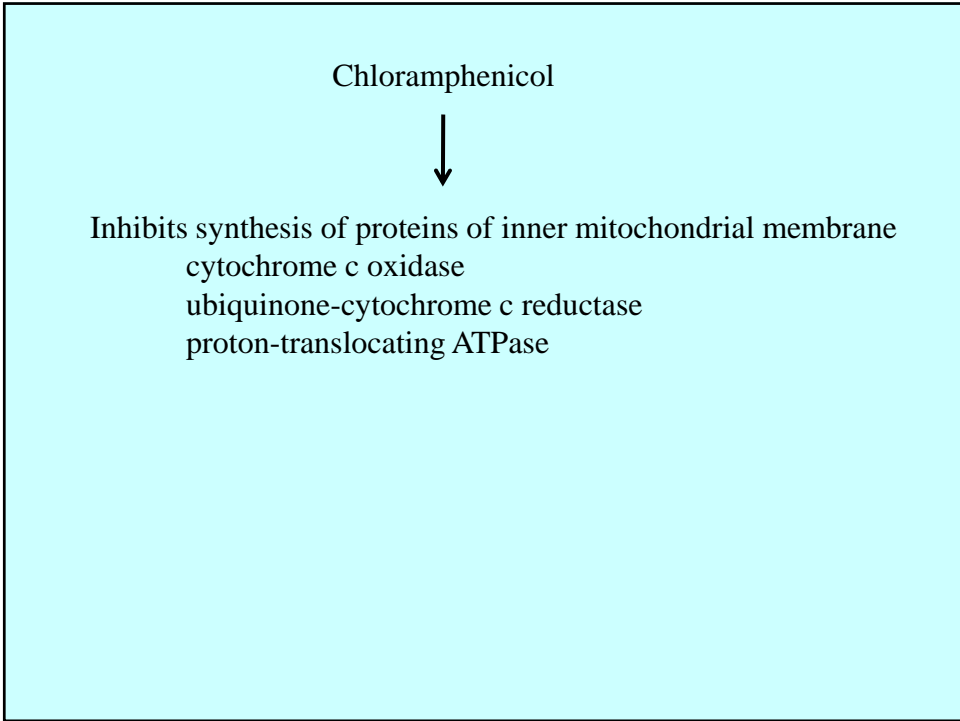
Therapeutic use of Chloramphenicol

(ONLY WHEN OTHER REGIME FAILS)

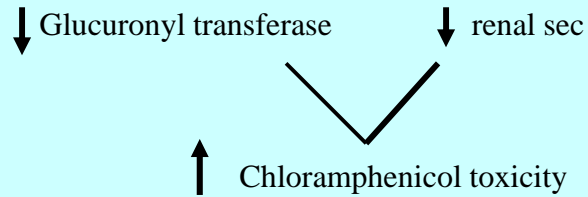
- i. Typhoid fever
- ii. Bacterial Meningitis
- iii. Certain anaerobic infections
- iv. Rickettsial diseases, e.g., epidemic, murine, scrub and recrudescent typhus, Rocky Mountain spotted fever and Q fever
- v. Brucellosis (tetracycline-sensitive patients)

chloramphenicol may become an important agent in the treatment of:

multiple drug-resistant organisms such as vancomycin-resistant *Enterococcus* (VRE) or methicillin-resistant *Staphylococcus aureus* (**MRSA**).



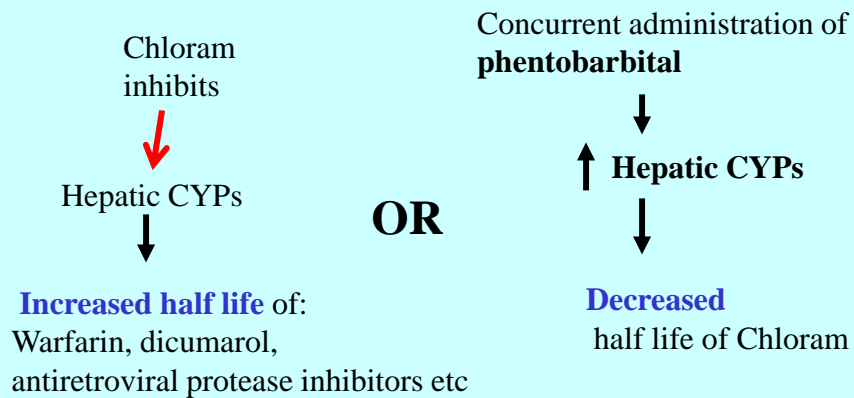
Neonatal toxicity: "gray baby syndrome"



Toxicity observed even in the newborn
when mother receives 1g/2hr during labor

Can be removed by exchange transfusion or charcoal hemoperfusion

VIII. Drug Interactions



Summary

- Enters bact by facilitative transport
- Inhibits transferases
- Bact develops resistance by altering permeability of drug, ribosomal mutation, generation of acetyl transferases
- Induces hematological toxicity, gray baby syndrome
- rarely used in US, Europe due to toxicity
- Developing nations still use it:
cheap and treat broad range of infections