

## **Lecture 14: Tetracyclins, Chloramphenicol and Macrolides**

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### **Knowledge Objectives**

1. Know the basic processes of bacterial protein synthesis.
2. Know the mechanism of antimicrobial activity for tetracyclines, chloramphenicol and the macrolides.
3. Know the most common adverse effects of these drugs.
4. Know the mechanisms of bacterial resistance for these drugs.
5. Know the most common applications of these antibiotics for the treatment of disease. Which drugs are broad spectrum, and which have specific or unique uses.

### **Drug List**

tetracycline  
doxycycline

polymyxin  
chloramphenicol  
erythromycin  
clindamycin  
clarithromycin  
azithromycin

## Macrolides

**Erythromycin**

**Clarithromycin (Biaxin)**

**Azithromycin (Zithromax; Zitromax)**

**Roxithromycin (Rulid)**

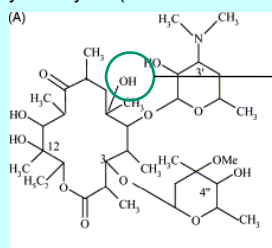
**Dirithromycin (Dynabac)**

} semi-synthetic  
derivatives of  
erythromycin

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

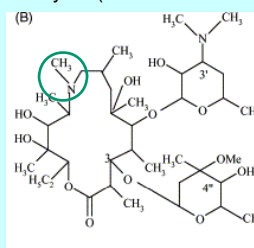
**Ketolides (Telithromycin)**

Erythromycin (14-membered macrolide)

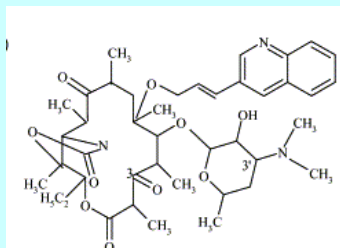


→ OCH<sub>3</sub>  
Clarithromycin

Azithromycin (15-membered macrolide)

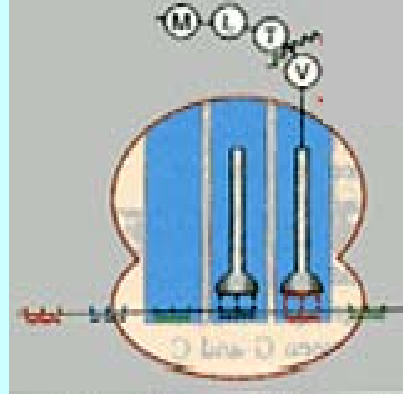


Ketolides (Telithromycin) Cladinose → 3-keto gr

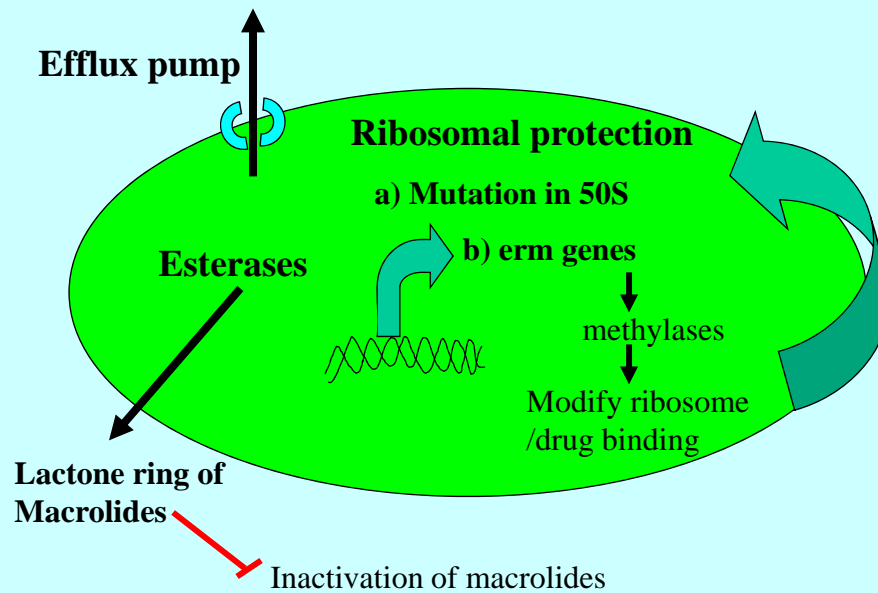


## Mechanism of action

- 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<sub>B</sub> (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)

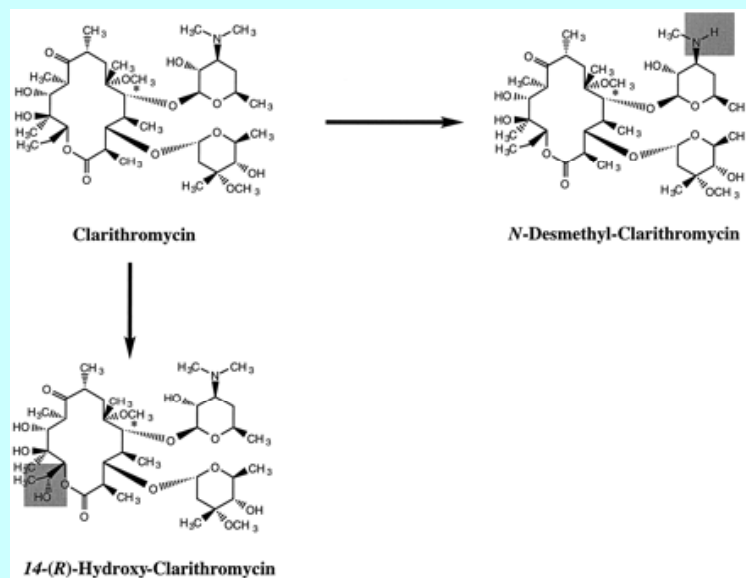
### Clarithromycin:

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<sup>+</sup> current (human ether-a-go-related gene HERG)

~less with azithromycin at clinical doses

hypersensitive reactions such as skin rashes

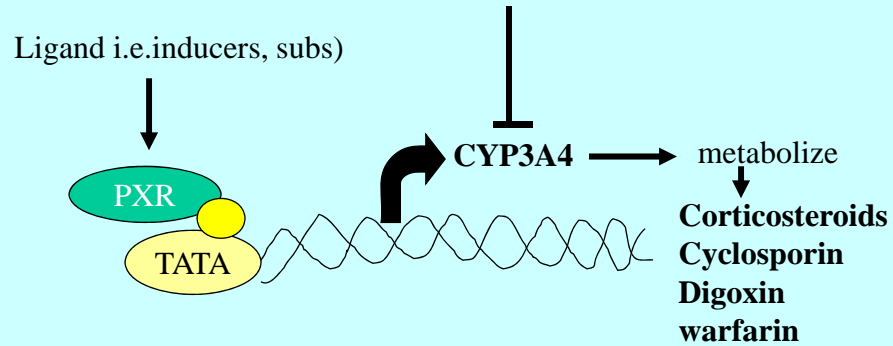
transient hearing disturbances

**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

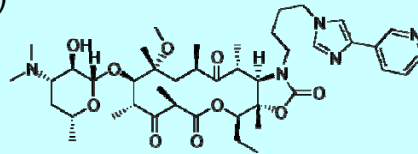
Campylobacter/ Helibacter Infections

**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

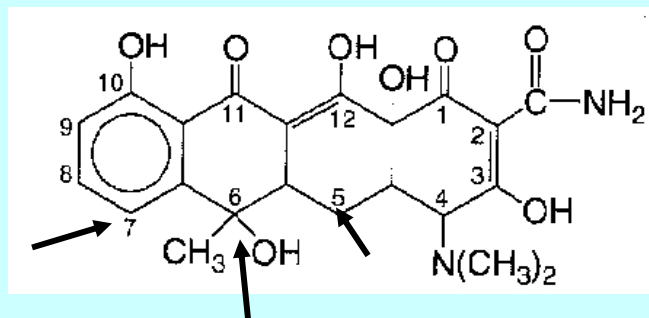
Well-tolerated

Orally bioav

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

## TETRACYCLINES AND CHLORAMPHENICOL

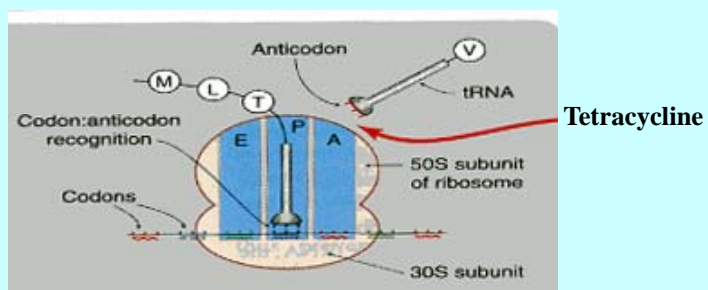
### Tetracyclines



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

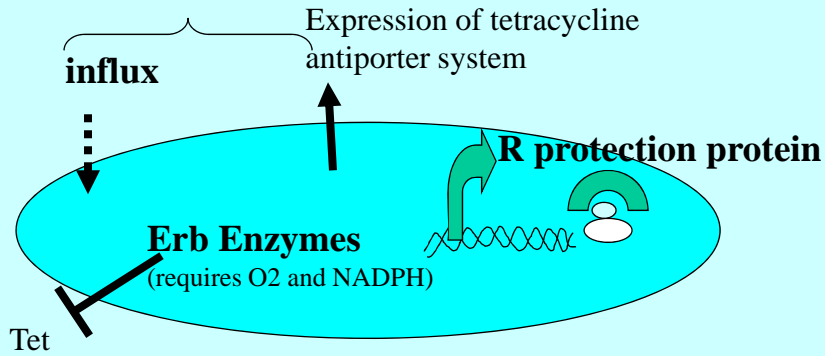
CONGENER	SUBSTITUENT(S)	POSITION(S)
Chlorotetracyclin	-Cl	(7)
Oxytetracycline	-OH, -H	(5)
Demeclocycline	-OH, -H; -Cl	(6; 7)
* Methacycline	-OH, -H; =CH <sub>2</sub>	(5; 6)
Doxycycline	-OH, -H; -CH <sub>3</sub> ; -H	(5; 6)
Minocycline	-H, -H; -N(CH <sub>3</sub> ) <sub>2</sub>	(6; 7)

### I. Mechanism of antimicrobial activity:

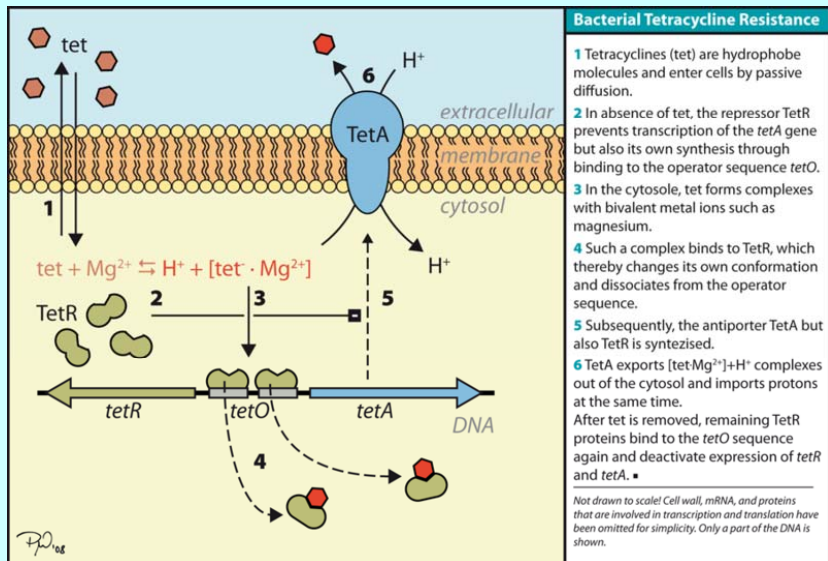


competes with tRNA for the **A site** on 30s ribosome

### 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;

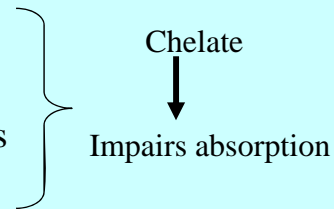
However, induction of tetM imposes cross-resistance to doxycycline and minocycline

## 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

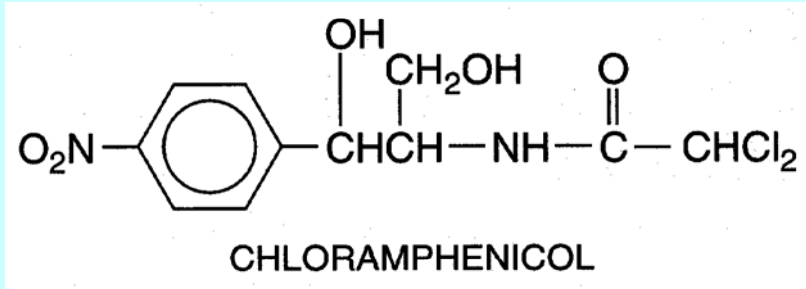
Superinfection with yeast or resistant pathogenic bacteria may occur

### 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,

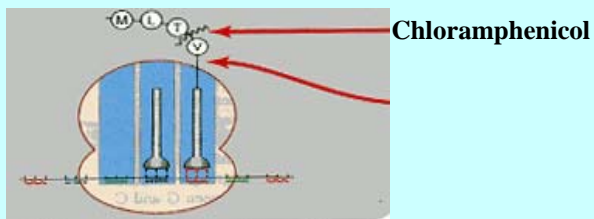
Minocycline: Skin and soft tissue infections

## Chloramphenicol (Chloromycetin)



Rapidly penetrates in bact cell (facilitative diffusion)

### I. Mechanism of action:

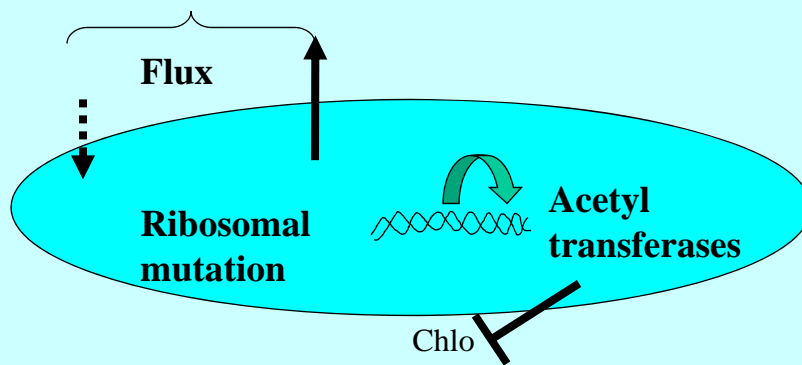


Binds reversibly with 50S ribosome; Inhibits peptidyltransferases

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**

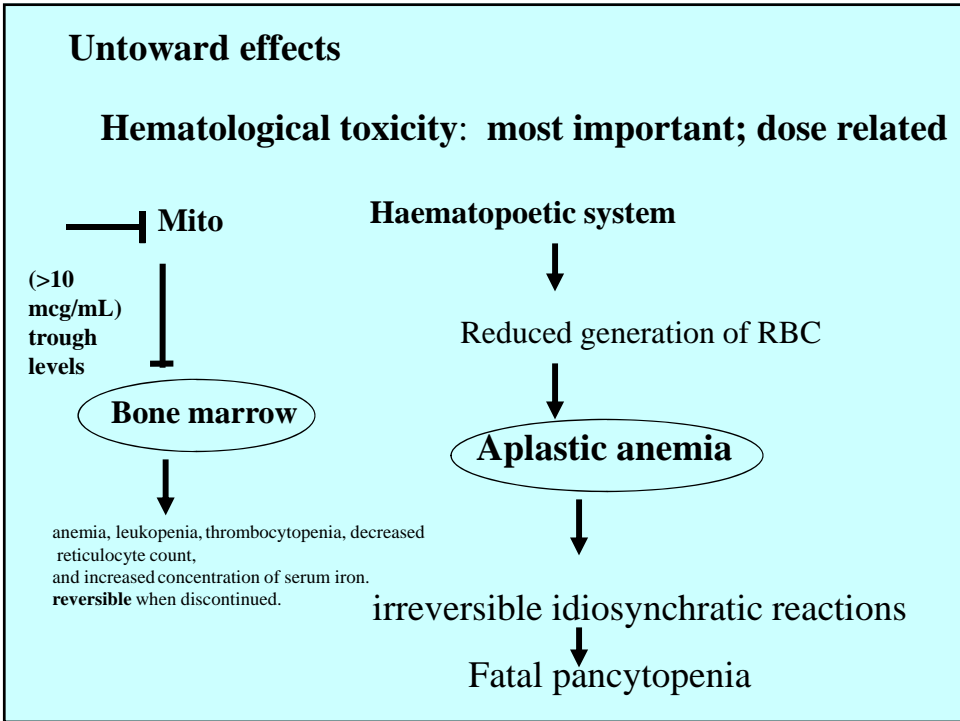
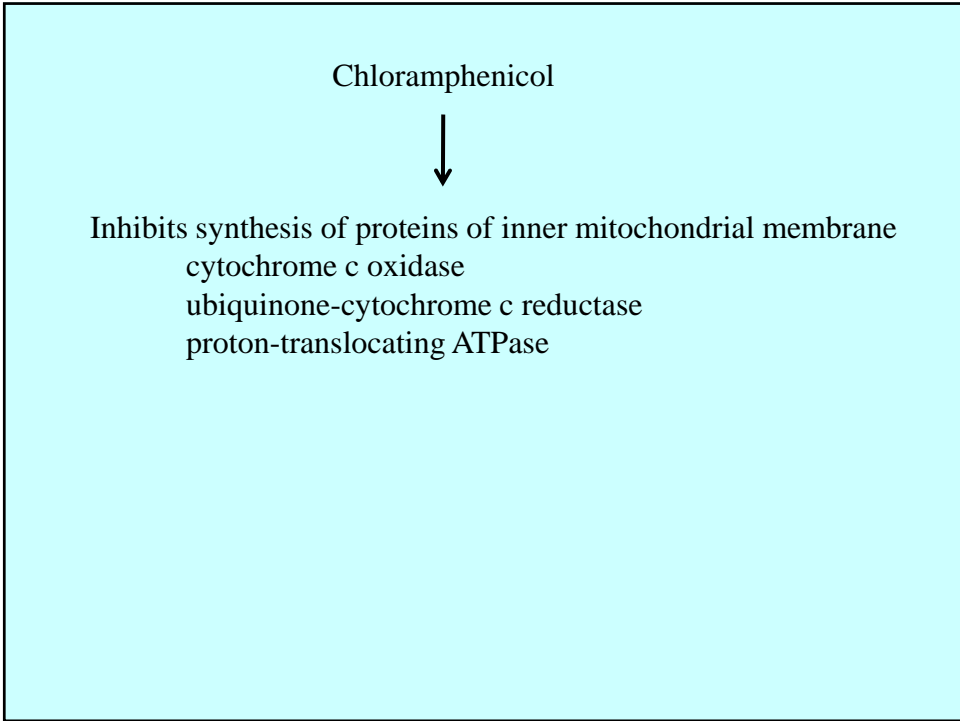
### **Therapeutic use of Chloramphenicol**

**(ONLY WHEN OTHER REGIME FAILS)**

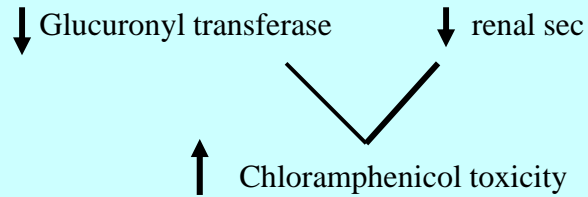
- i. Typhoid fever
- ii. Bacterial Meningitis
- iii. Certain anaerobic infections
- iv. Rickettsial diseases, e.g., epidemic, murine, scrub and recrudescent typhus, Rocky Mountain spotted fever and Q fever
- v. Brucellosis (tetracycline-sensitive patients)

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**).



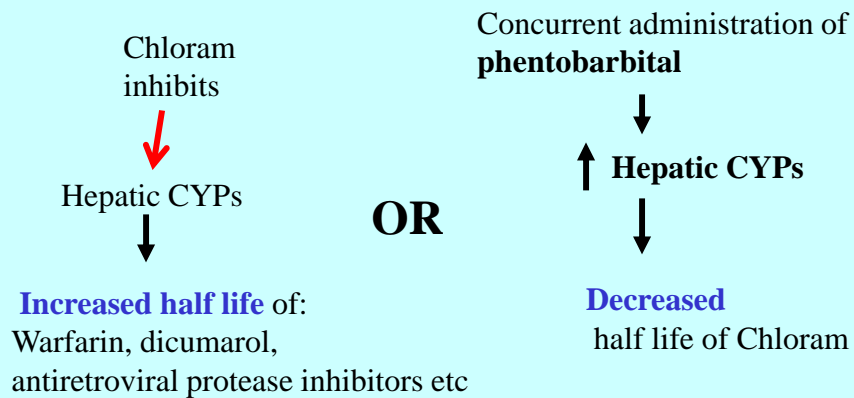
### Neonatal toxicity: "gray baby syndrome"



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