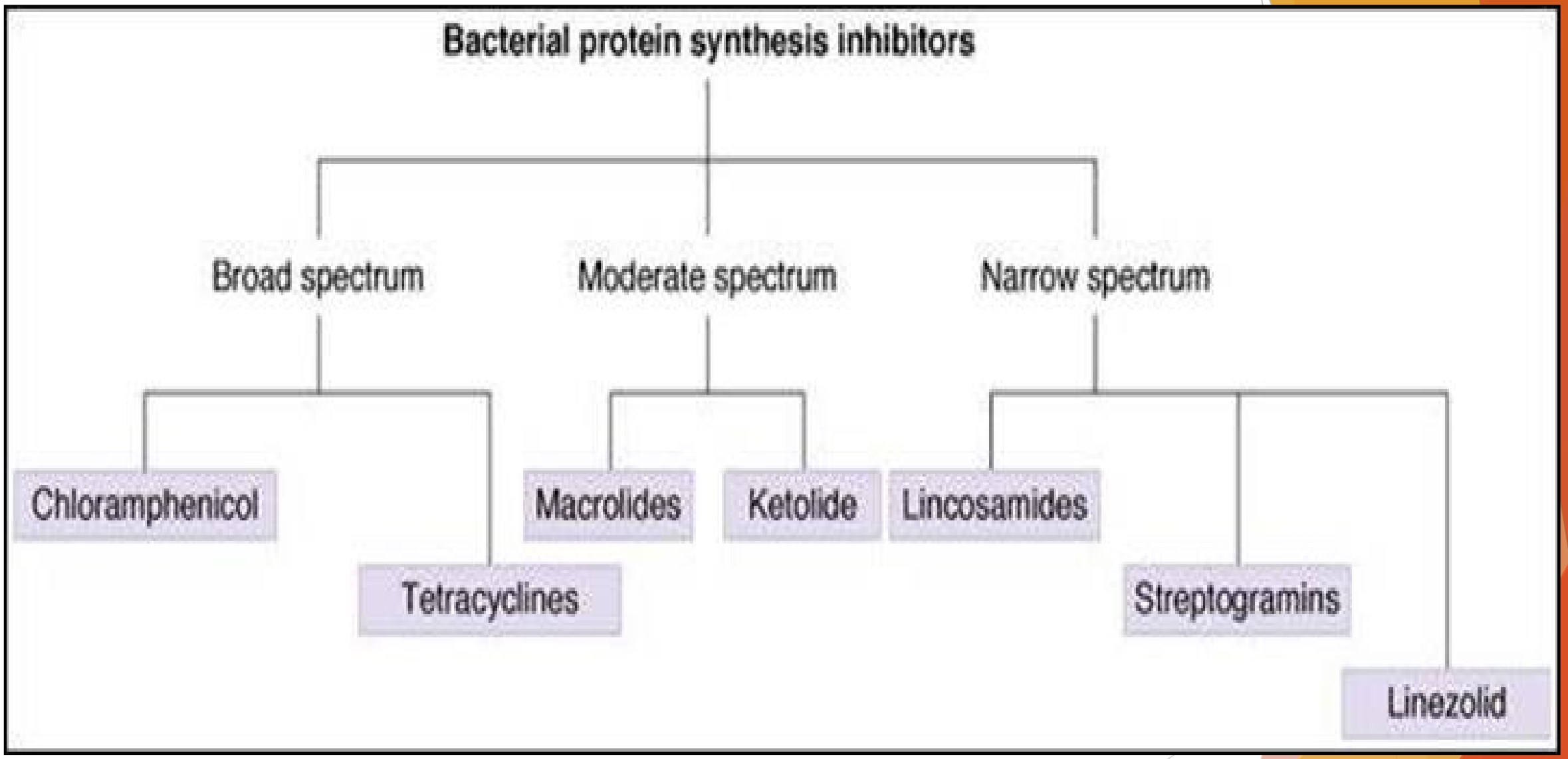

Protein Sy esis
with the A eba Sisters

Protein Synthesis Inhibitors

Tetracycline's

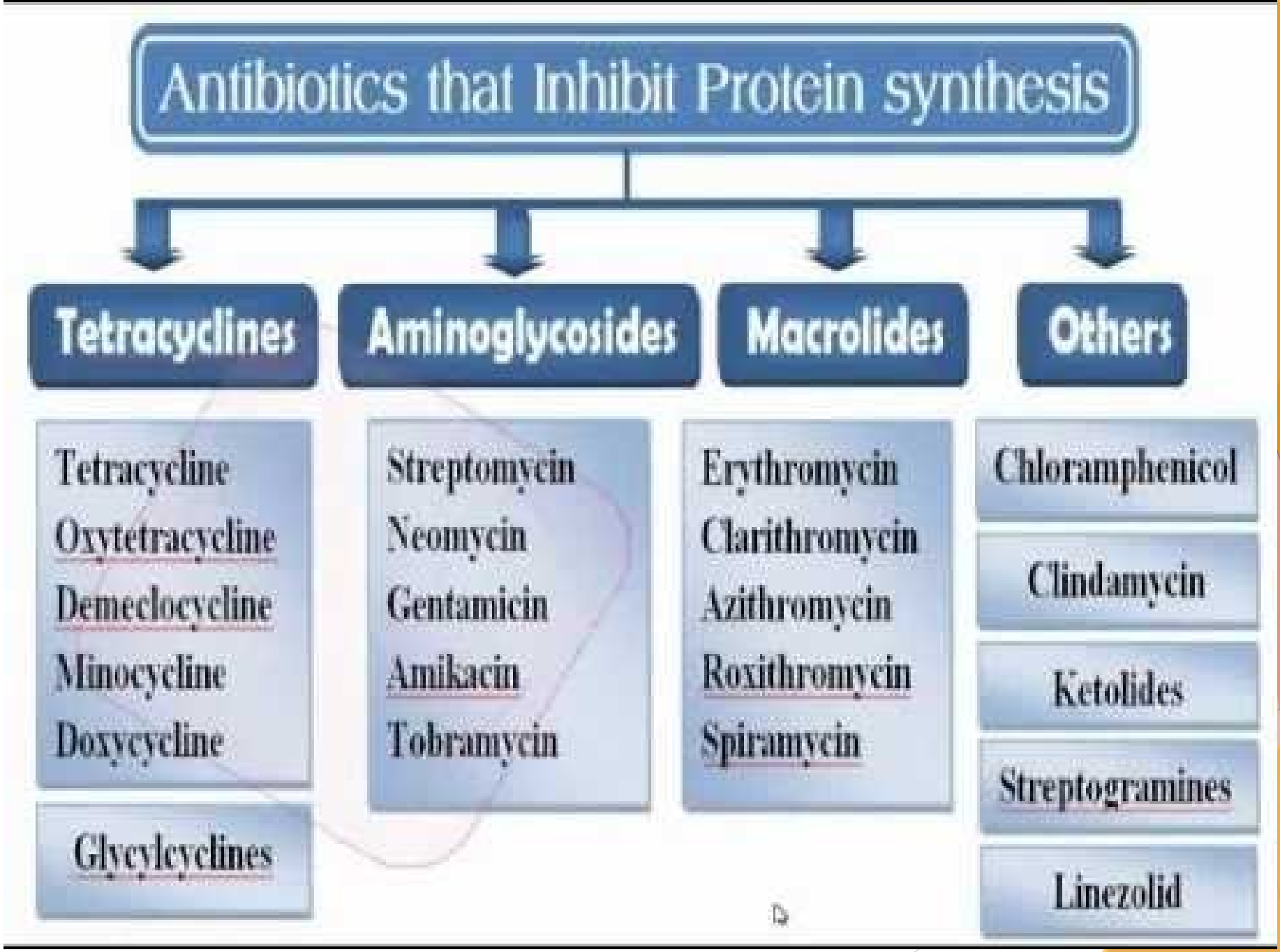
Aims and objectives

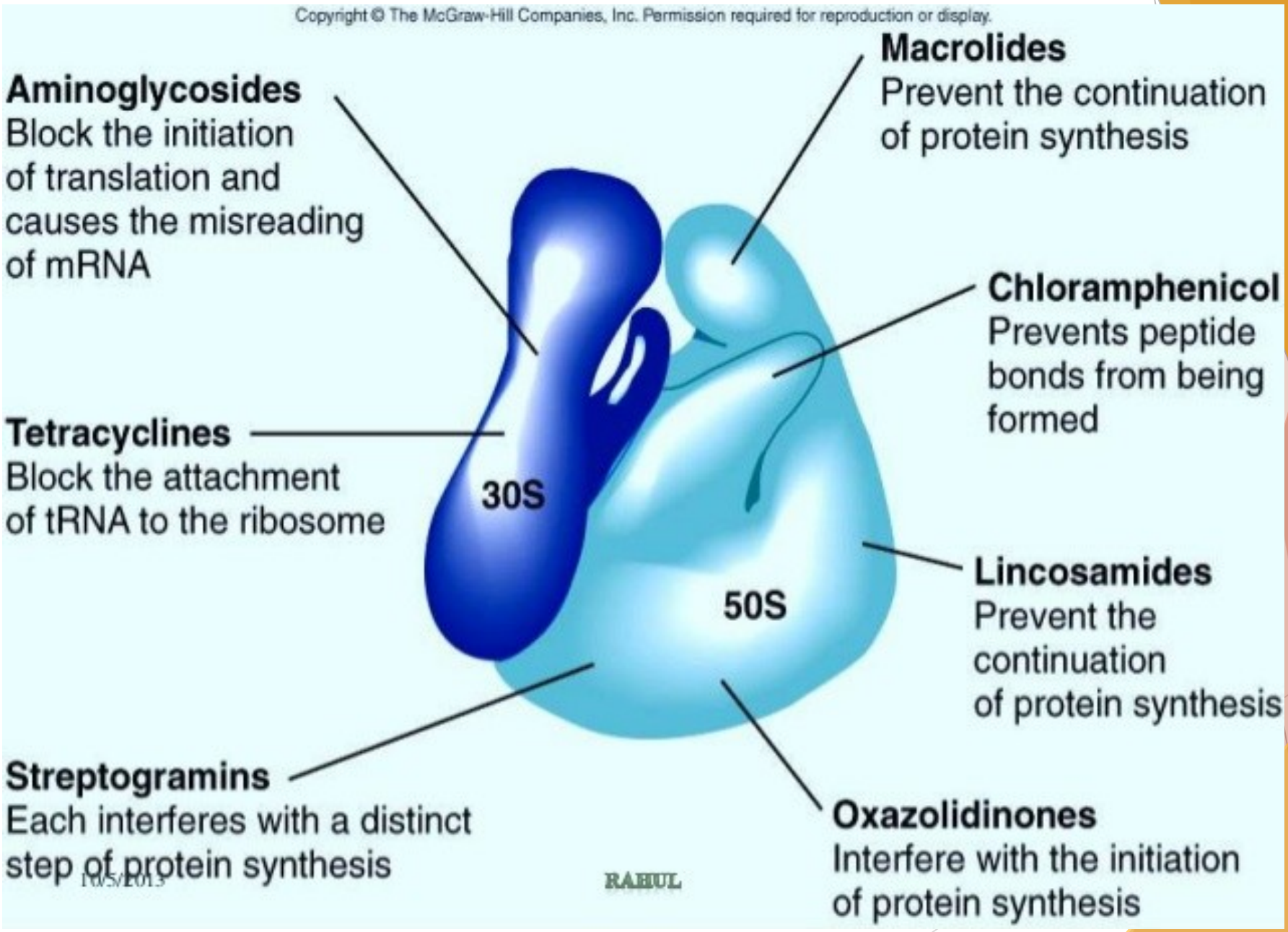
- By the end of this interactive long group discussion the student should be able to
- Classify protein synthesis inhibitors
- Classify tetracycline's
- Describe the mechanism id action of tetracycline's
- Describe the mechanism of resistance of tetracycline's
- Enlist the antibacterial spectrum of tetracycline's
- Enumerate the therapeutic uses of tetracycline's
- Enlist the adverse effects and drug interactions of tetracycline’s
- Briefly describe the contra-indications of tetracycline’s


Bacterial protein synthesis inhibitors
Broad spectrum
Moderate spectrum
Narrow spectrum
Chloramphenicol
Tetracyclines
Macrolides
Ketolide
Lincosamides
Streptogramins
Linezolid

Introduction

- A number of antibiotics exert their antimicrobial effects by targeting the bacterial ribosome, which has components that differ structurally from those of the mammalian cytoplasmic ribosome. In general, the bacterial ribosome is smaller (70S) than the mammalian ribosome (80S) and is composed of 50S and 30S subunits (as compared to 60S and 40S subunits).


Antibiotics that Inhibit Protein synthesis
Tetracyclines
Aminoglycosides
Macrolides
Others
Tetracycline
Oxytetracycline
Demeclocycline
Minocycline
Doxycycline
Glycylcyclines
Streptomycin
Neomycin
Gentamicin
Amikacin
Tobramycin
Erythromycin
Clarithromycin
Azithromycin
Roxithromycin
Spiramycin
Chloramphenicol
Clindamycin
Ketolides
Streptogramines
Linezolid



RAHUL

Classification :

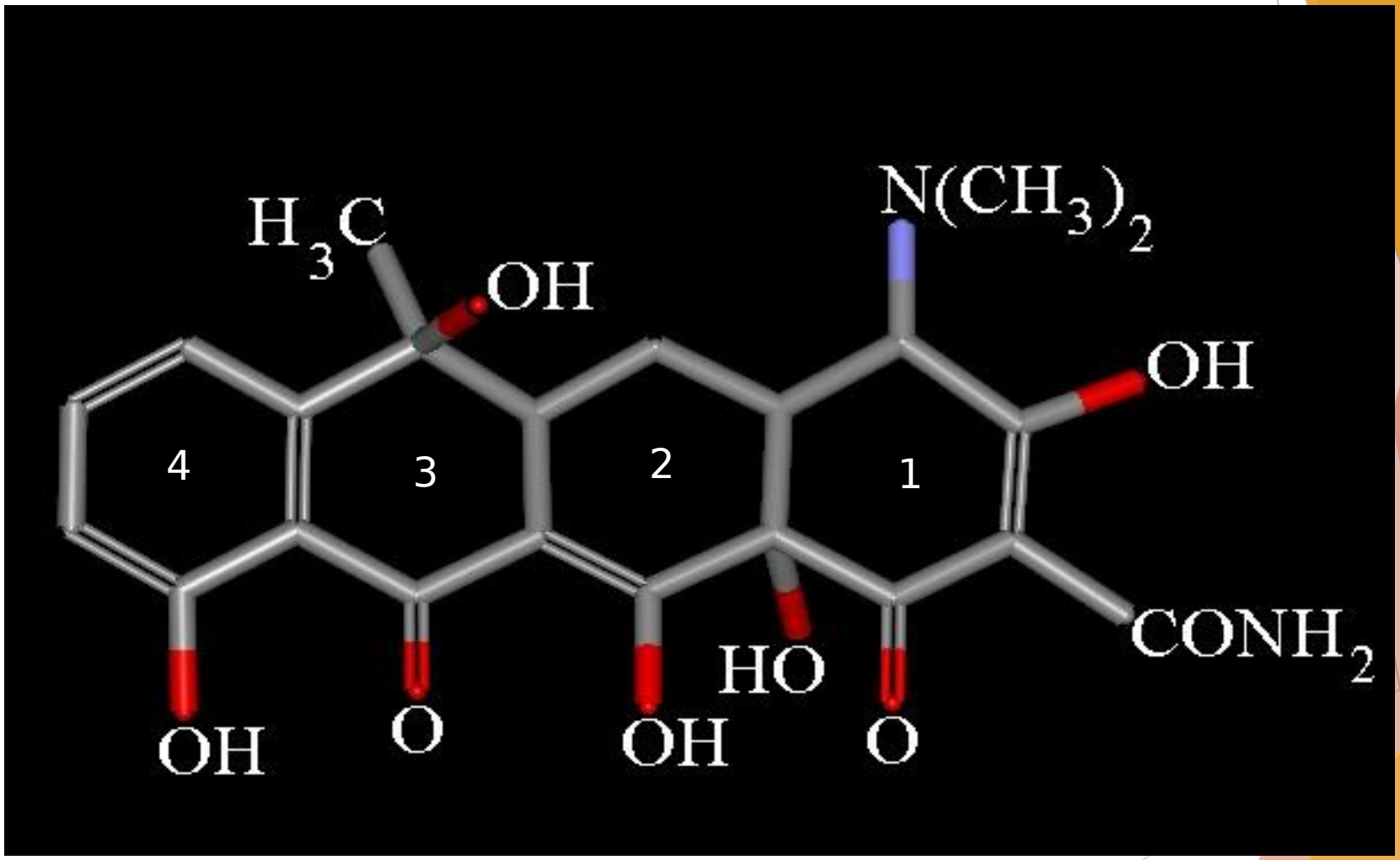
Based on

Duration of action :

- Short acting(half-life 6-8hrs)
  - Tetracycline
  - Chlortetracycline
  - Oxytetracycline
- Intermediate acting(half-life12hrs)
  - Demeclocycline
  - Methacycline
- Long acting(half-life is 16hrs)
  - Doxycycline
  - Minocycline
  - Tigecycline

Structure

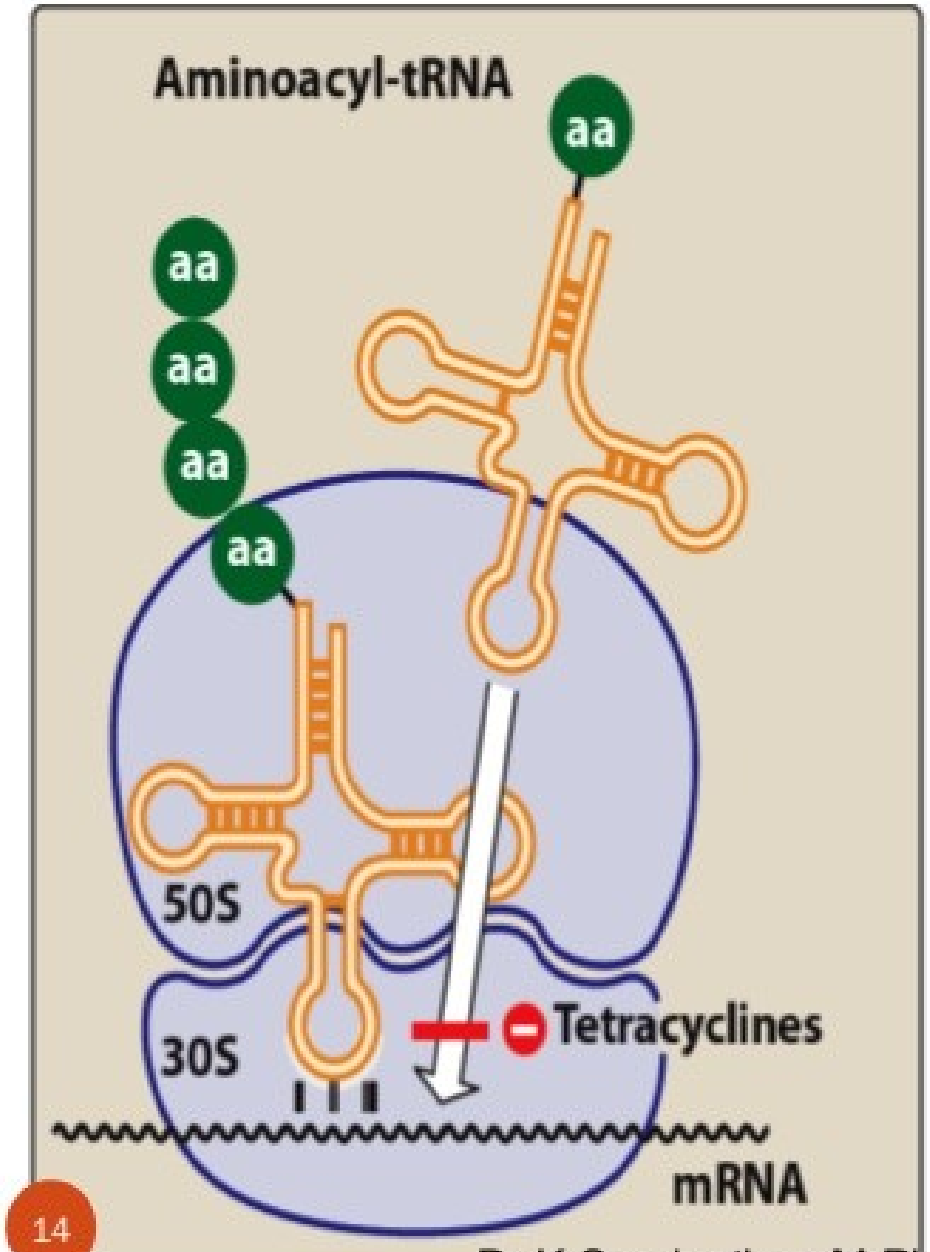
- The tetracycline's are a group of closely related compounds that, as the name implies, consist of four fused rings with a system of conjugated double bonds. Substitutions on these rings are responsible for variation in the drugs' individual pharmacokinetics, which cause small differences in their clinical efficacy


H3C
OH
N(CH3)2
OH
4
3
2
1
CONH2
HO
OH
O
OH
O

Mechanism of action

- Tetracycline's enter microorganisms in part by passive diffusion and in part by an energy-dependent process of active transport. Susceptible cells concentrate the drug intracellularly. Once inside the cell, tetracycline's bind reversibly to the 30S subunit of the bacterial ribosome, blocking the binding of aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex .
- This prevents addition of amino acids to the growing peptide.

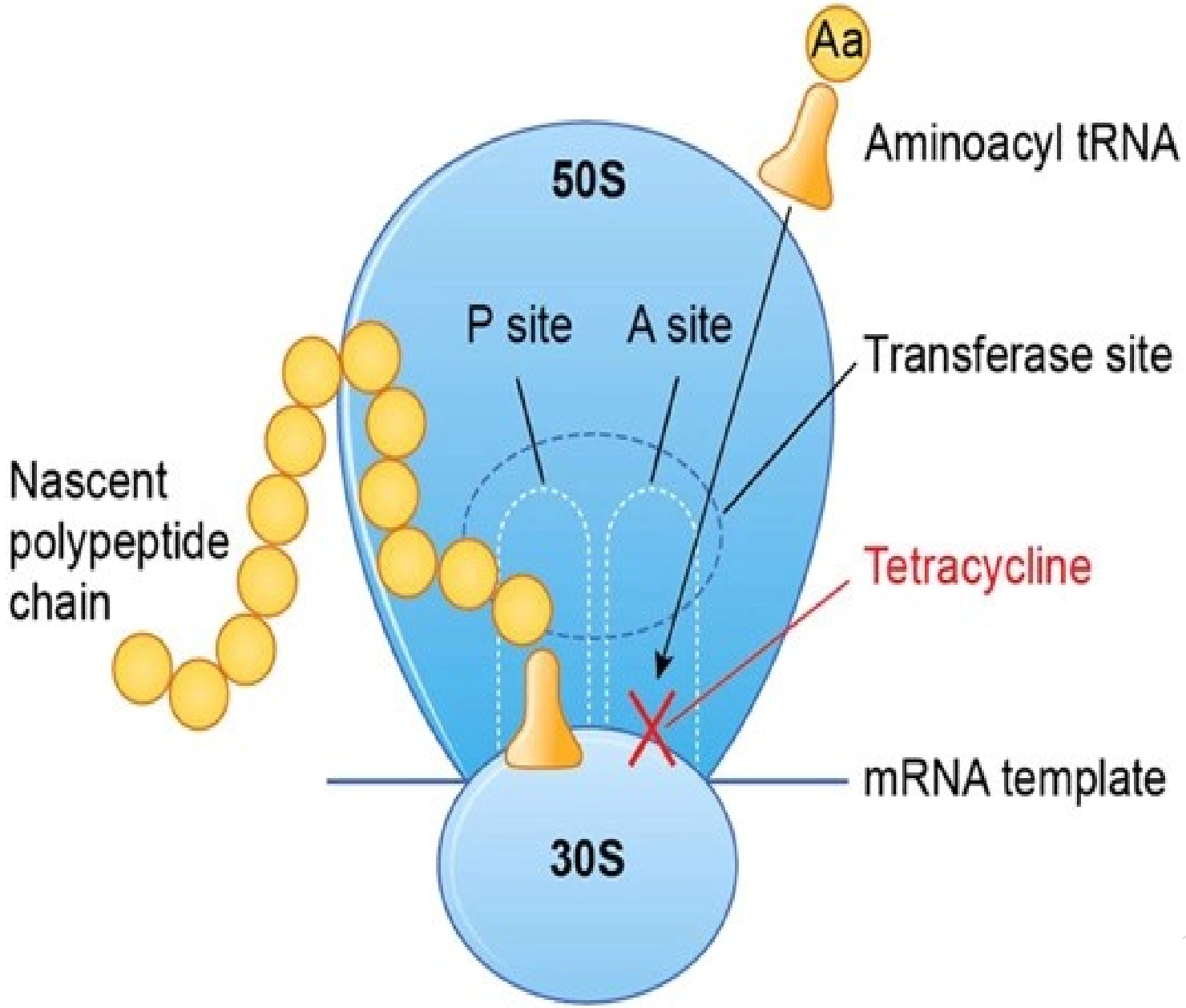
10. MECHANISM OF TETRACYCLINES

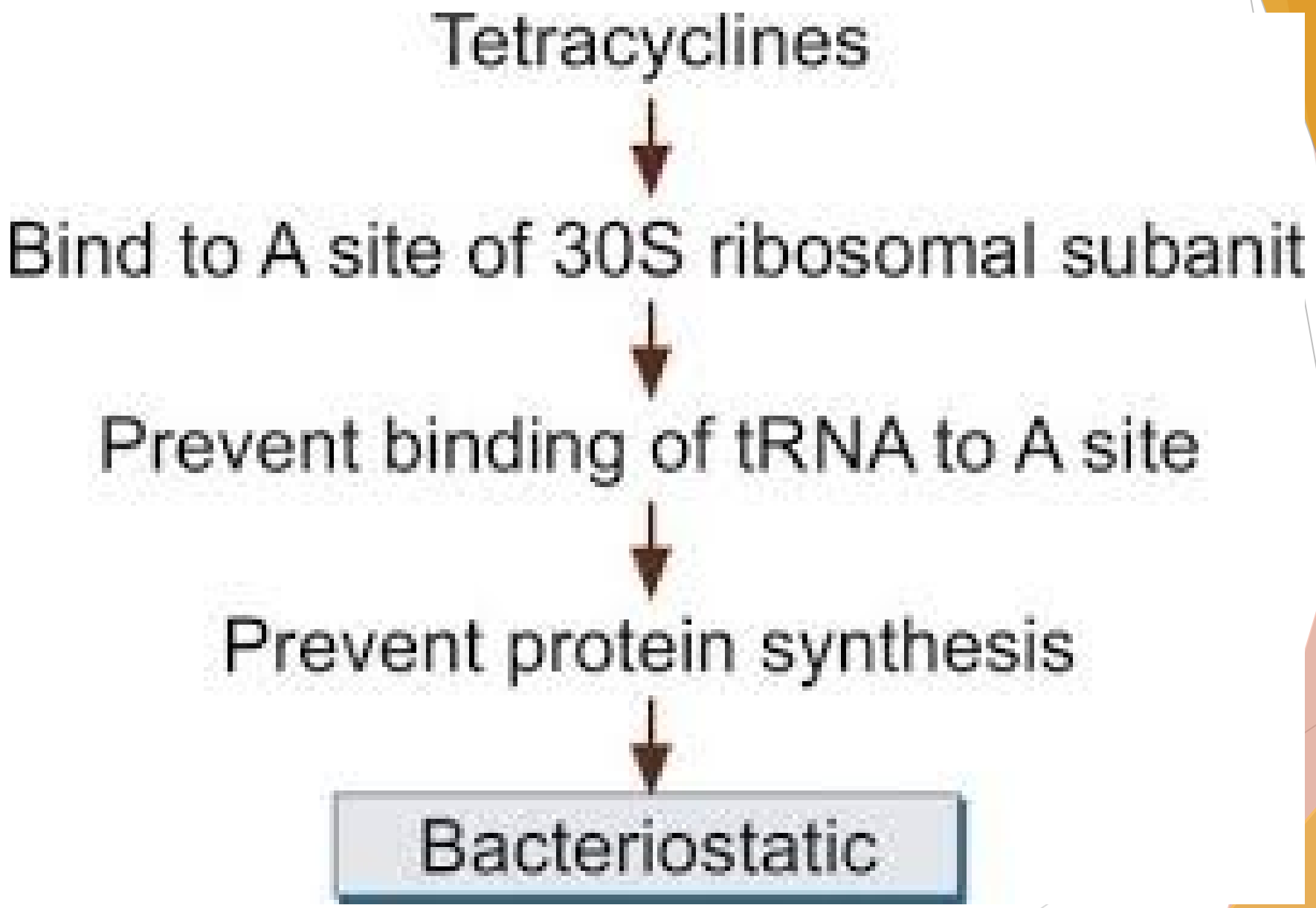


Tetracyclines binds reversibly to the 30S subunit of the bacterial ribosome, thereby blocking access of the amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site.

By this mechanism, bacterial protein synthesis is inhibited

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


Aa
Aminoacyl tRNA
50S
P site
A site
Transferase site
Nascent
polypeptide
chain
Tetracycline
mRNA template
30S


Tetracyclines
Bind to A site of 30S ribosomal subanit
Prevent binding of tRNA to A site
Prevent protein synthesis
Bacteriostatic

Spectrum & Clinical Uses

-Tetracyclines are active against many Gram-positive and Gram-negative bacteria, including anaerobes, rickettsiae, chlamydiae, mycoplasmas, and against some protozoa, as amebas.

-Minocycline is usually the most active followed by doxycycline.

-Tetracyclines remain effective in most chlamydial infections, including sexually transmitted diseases.

-Tetracyclines are effective in treatment of Rocky Mountain spotted fever by rickettsia rickettsii.

-Other uses include treatment of acne, exacerbations of bronchitis & community-acquired pneumonia

-They are used in combination regimens to treat gastric and duodenal ulcer disease caused by *H. pylori*.

- Although all tetracyclines enter the (CSF), levels are insufficient for therapeutic efficacy, except for *minocycline* enters the brain in the absence of inflammation and also appears in tears and saliva so it is useful in eradicating the meningococcal carrier state, *but not effective for central nervous system infections.*

Pharmacokinetics

- **Absorption:** All tetracyclines are adequately but incompletely absorbed after oral ingestion However, taking these drugs concomitantly with dairy foods in the diet decreases absorption due to the formation of nonabsorbable chelates of the tetracyclines with calcium ions.

Doxycycline and minocycline are almost totally absorbed on oral

administration.

Distribution: tetracyclines concentrate in liver, spleen, kidneys skin and in the parts of the body where there is high calcium content like bones and teeth and in tumors with high Calcium content like gastric carcinoma.

Well distributed in all the body fluids and also can go to CSF.

Minocylines can concentrate in CSF in the absence of inflammation, it also appears in the tears and saliva.

All the tetracyclines can cross the placental barrier and concentrate in fetal bones and dentition.

Pharmacokinetics

- **Elimination:** in part metabolized in the liver forming soluble glucoronides and secreted in the bile. The parent drug and the metabolites are reabsorbed by the enterohepatic ciculation thereby entering the glumerolar filtration . Doxycycline can be safely used in renaly compromised patients as it is mainly secreted in the bile and excreted in the feces. Tetracyclines are also excreted in breast milk.

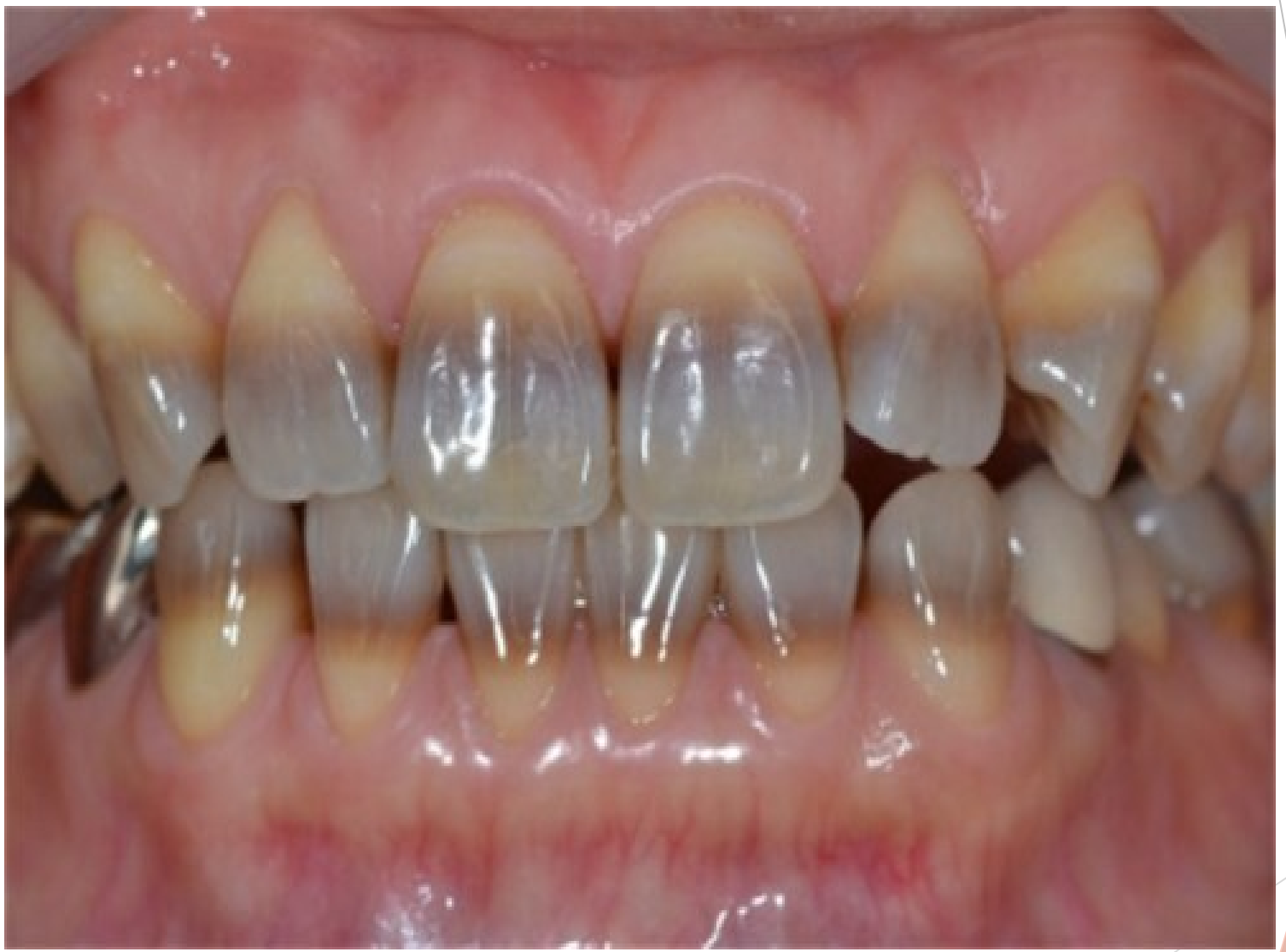
Resistance

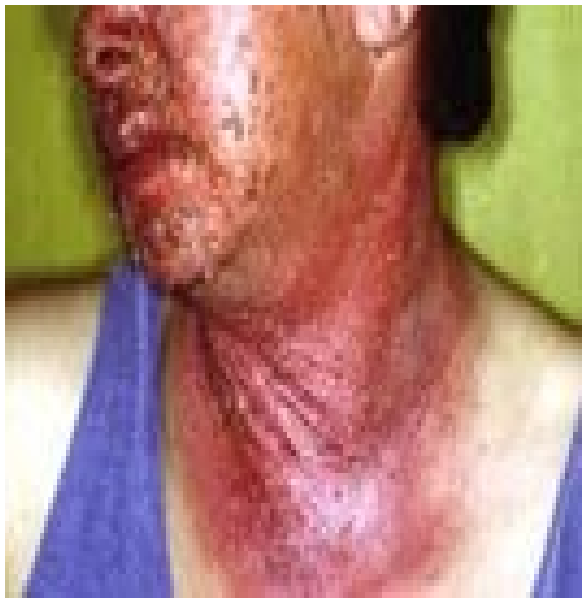
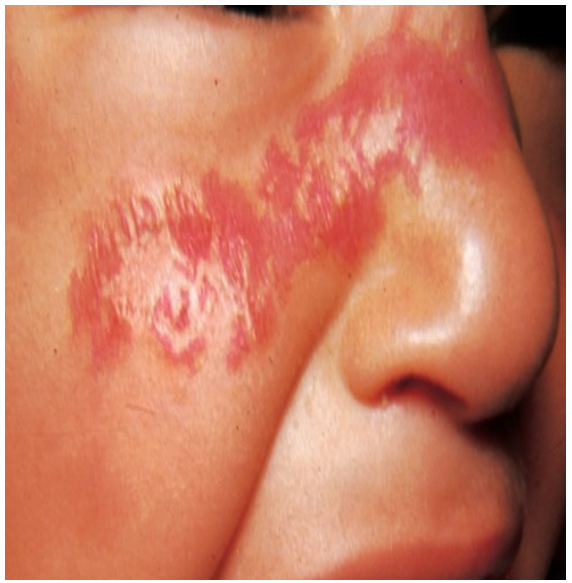
- Resistance is plasmid mediated.

1. Plasmid encodes a resistance protien TetA. TetA results in the formation Mg^{+2} dependent efflux pumps. These efflux pumps renders the organism incapable of concentrating the drug inside(inside the bacteria).
2. Sometimes the bacteria starts enzymatic degradation or inactivation of the drug.
3. In some cases the bacteria starts producing proteins that inhibit the binding of tetracycline's to the bacteria.

Adverse effects

- **Gastric discomfort:** Epigastric distress commonly results from irritation of the gastric mucosa and is often responsible for noncompliance in patients treated with these drugs. The discomfort can be controlled if the drug is taken with foods other than dairy products.
- **Effects on calcified tissues:** Deposition in the bone and primary dentition occurs during calcification in growing children. This causes discoloration and hypoplasia of the teeth and a temporary stunting of growth.
- **Fatal hepatotoxicity:** This side effect has been known to occur in pregnant women who received high doses of tetracyclines, especially if they were experiencing pyelonephritis.
- Fanconi syndrome may occur due to intake of expired tetracyclines.
- **Photosensitization**
- Systemic tetracycline administration, especially of demeclocycline, can induce sensitivity to sunlight or ultraviolet light, particularly in fair-skinned persons.



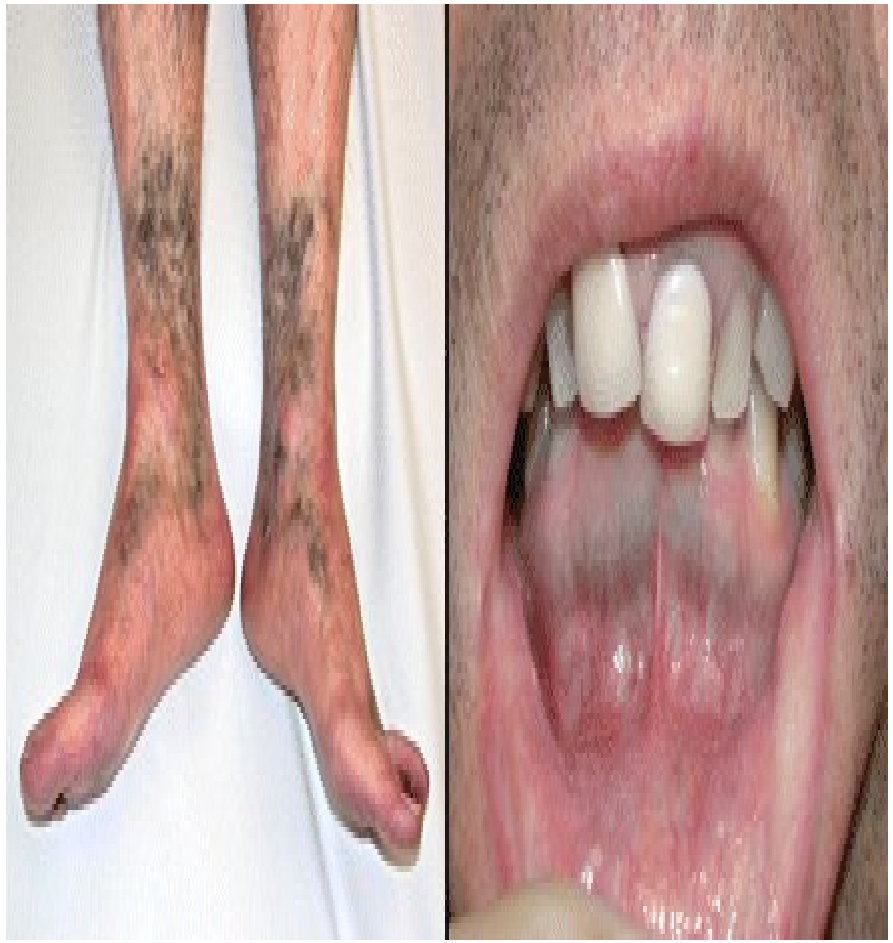



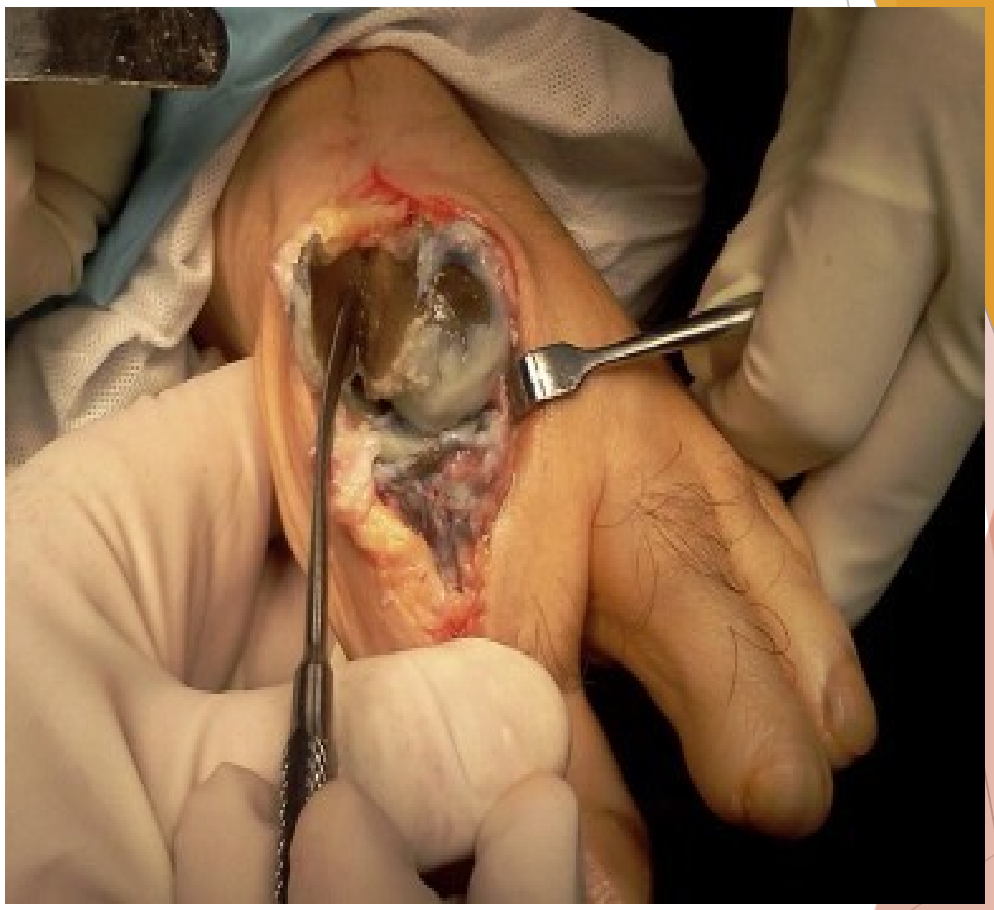

Adverse effects

- **Vestibular Reactions**
- Dizziness, vertigo, nausea, and vomiting have been particularly noted with doxycycline at doses above 100 mg. With dosages of 200–400 mg/d of minocycline, 35–70% of patients will have these reactions.
- **Local Tissue Toxicity:** Intravenous injection can lead to venous thrombosis. Intramuscular injection produces painful local irritation and should be avoided.
- **Medical & Social Implications of Overuse**
- Tetracyclines have been extensively used in animal feeds to enhance growth.
- **Superinfections:** Overgrowths of Candida (for example, in the vagina) or of resistant staphylococci (in the intestine) may occur. Pseudomembranous colitis due to an overgrowth of Clostridium difficile has also been reported.

Black Bone Disease

- As compared to the other tetracycline's, Minocycline it is more lipophillic therefore, has greater volume of distribution and penetration.
- Black Bone Disease is likely caused by the deposition in the scars of pigmented granules, thought to be iron chelates of minocycline
- Pigmentation caused by minocycline has been reported not only in the skin, but in other soft tissues including the thyroid gland, mucosa, and eyes,in the breast milk secretions, and in hard tissues, including teeth, nails and bones.





Minocycline induced Black Bone Disease

Fanconis syndrome

This syndrome occurs due to the use of expired tetracyclines

Fanconi syndrome is a disorder of the kidney tubes in which certain substances normally re-absorbed into the bloodstream by the kidneys are released into the urine instead

They may exhibit symptoms such as:

Unexplained fatigue.

Recurrent colds or

viral infections.

Recurrent nosebleeds.

Easy bruising.

Blood in the stool or urine.

Shortness of breath.

Poor growth / short stature

Contraindications:

- In renally compromised patients they should be avoided other than doxycycline as it is excreted mainly in the feces.
- They may worsen azotemia interfering with protein synthesis and so this may lead to massive breakdown of amino acids.
- Better avoided in lactating as well as in pregnant women.
- Also should be avoided in children less than 8 years of age.

Thank You