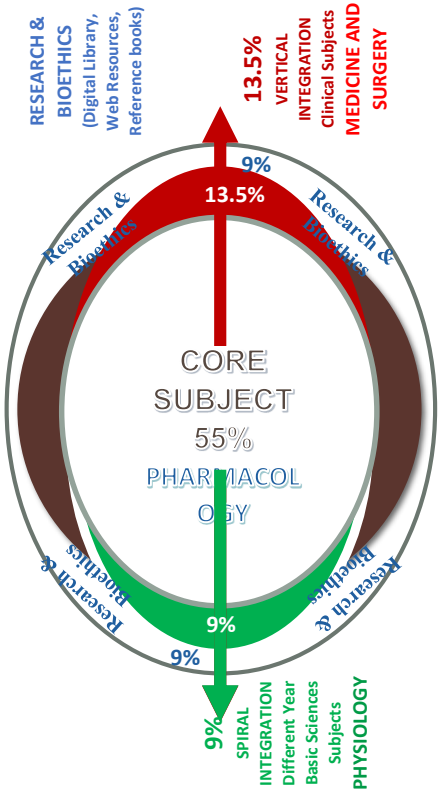

بسم الله الرحمن الرحيم

MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

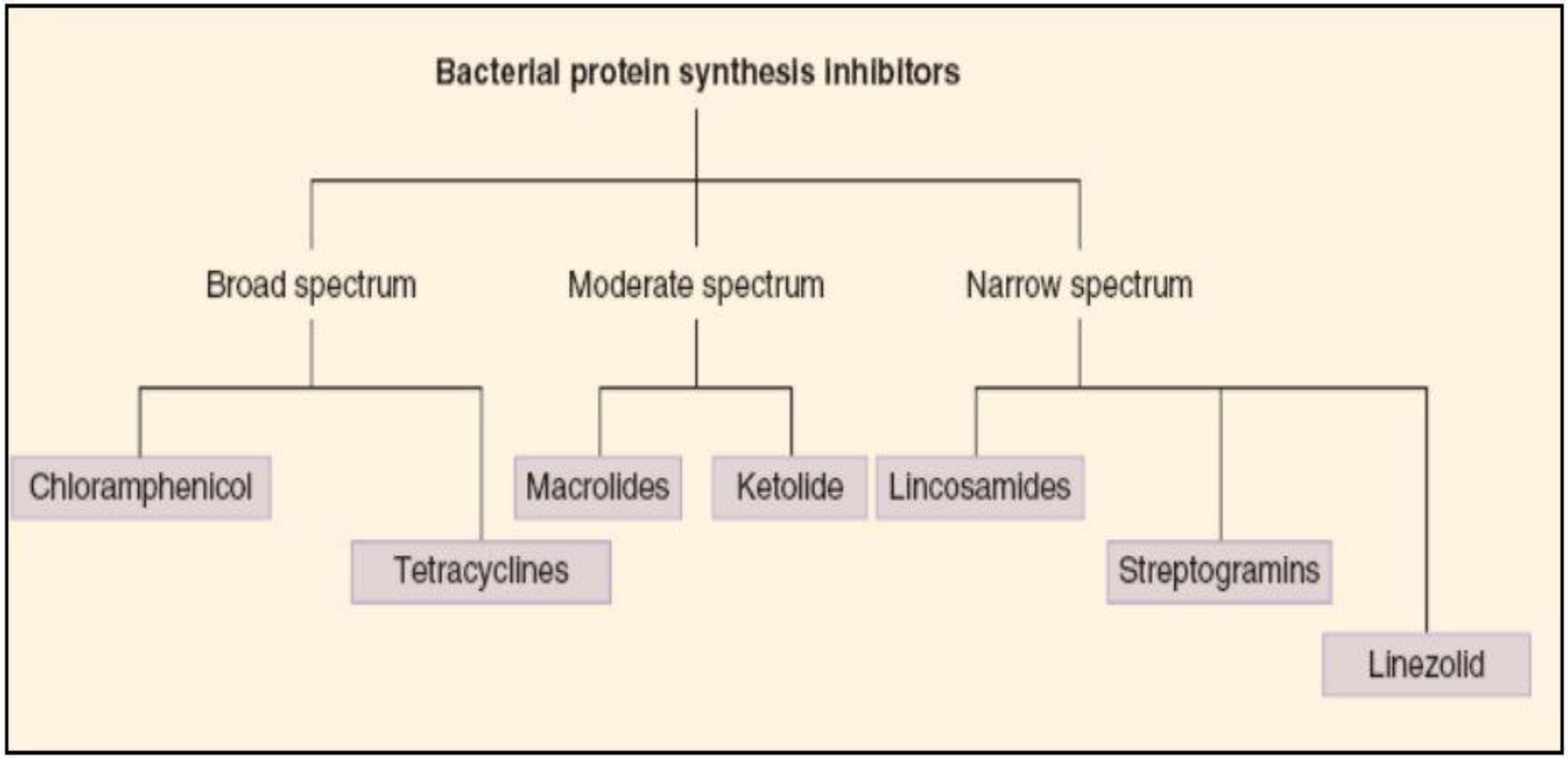
Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



Model 3rd Year Pharmacology (44 slides)	
Core Subject – 70%	
Horizontal Integration – 10%	
Vertical integration (Clinical Subjects)	• Medicine/ surgery (10 %)
Different Year Basic Sciences Subjects	
Research & Bioethics 5%	

PROTEIN SYNTHESIS INHIBITORS

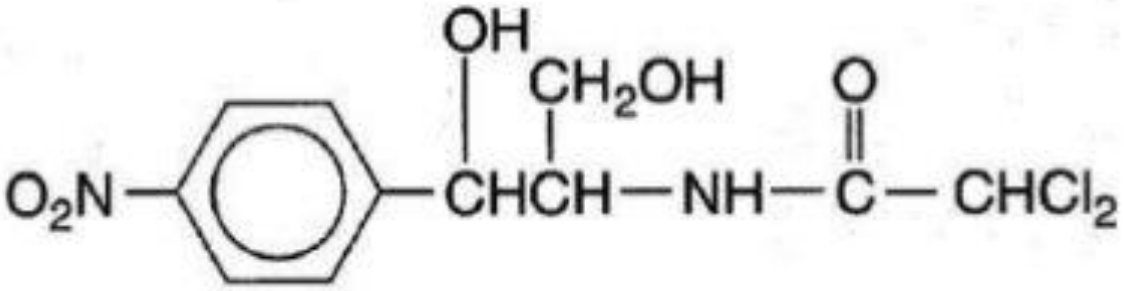
Bacterial protein synthesis inhibitors



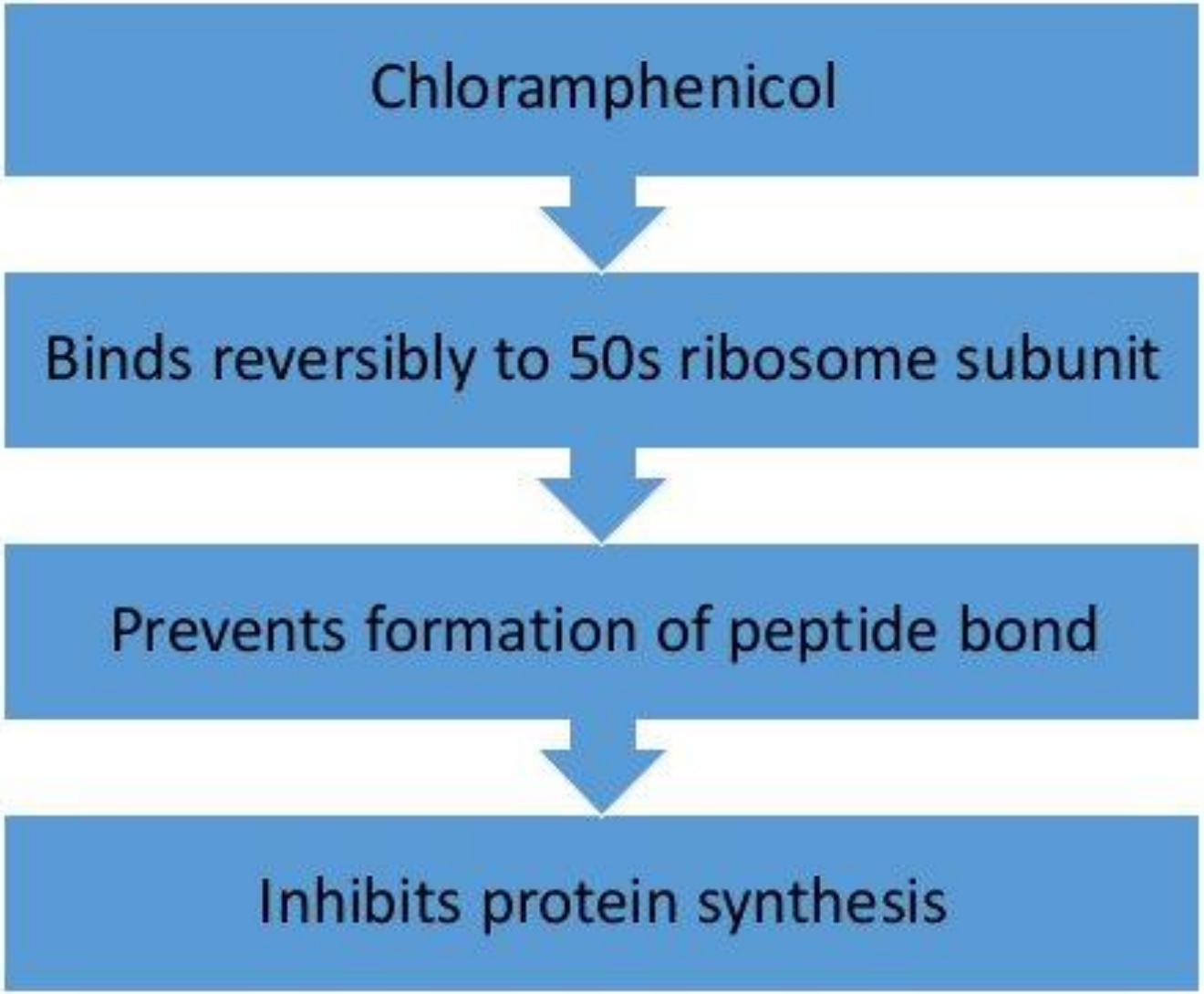
Core subject – Pharmacology

CHLORAMPHENICOL

- Chloramphenicol was initially obtained from Streptomyces venezuelae in 1947.
- It was soon synthesized chemically and the commercial product now is all synthetic.



Mechanism of action



Clinical Pharmacokinetics

- Rapidly & completely absorbed after oral ingestion.
- Crosses placenta and secreted in milk and bile.
- Widely distributed in body compartment as well as in CSF (tetracyclines do not in CSF).
- It undergoes glucoronide conjugation in liver, so *dose needs to be lowered in neonates and cirrhotics*.

Horizontal integration – Microbiology

Antimicrobial Spectrum

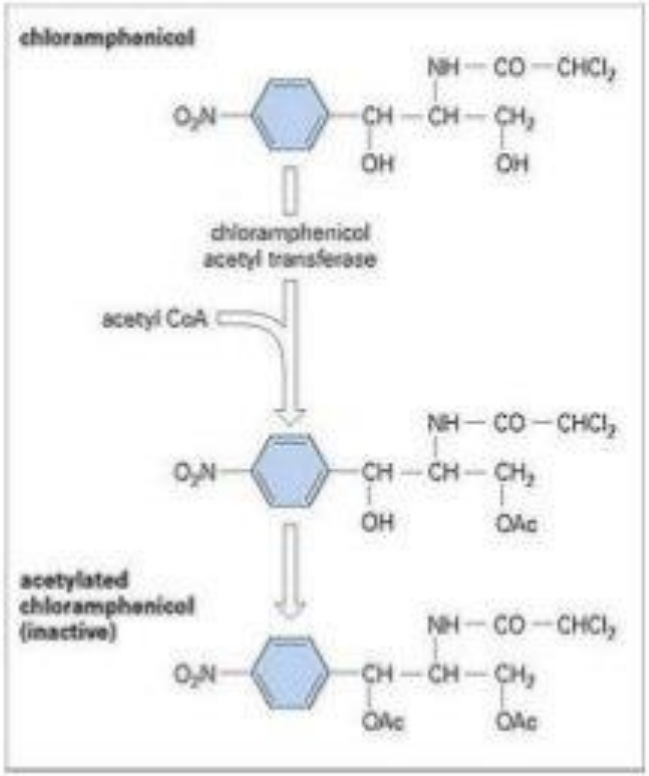
- Broad spectrum antibiotic like tetracyclines.
- Active against *S. typhi, H. influenzae, S. pneumoniae, B. fragilis* and other microbes inhibited by tetracyclines.
- Less active against *Chlamydia*, Spirochetes while more against *Klebsiella, B. pertussis*.
- Ineffective against Proteus, viruses and Pseudomonas just like tetracyclines.

Mechanism of Resistance

- Resistance to chloramphenicol is caused by

Resistance

- Ribosomal mutation
- Decreased permeability of drug to microbial cell wall
- Production of inactivating enzyme, acetlytransferase, e.g. H.influenza, S.typhi S.aureus



- **VERTICLE INTEGRATION MEDICINE/ SURGERY**

USES

1. Enteric fever
2. Pyogenic meningitis
3. Anaerobic infections
4. Intraocular infections
5. As second choice drug
   (a) To tetracyclines
   - For brucellosis and rickettsial infections
   - Especially in young children and pregnant women in whom tetracyclines are contraindicated.

   (b) To erythromycin
   - For whooping cough.
6. Urinary tract infections
7. Topically In conjunctivitis, external ear infection

Clinical uses

Use limited because of potential toxicities

1. Typhoid fever- s. typhi (quinolones are preffered)

2. Meningitis – H.influenzae,N.meningitidis,S.pneumoniae (Ceftriaxone is preffered)

3. Anaerobic infections- B. fragilis (Metronidazole is the drug of choice)

4. Rickettsial infections – Doxycycline is preffered

5. Bacterial conjunctivitis (topical)

Adverse effects

1) Dose related Bone marrow depression: Of all drugs, *chloramphenicol is m. imp. Cause of aplastic anemia, agranulocytosis, thrombocytopenia or pancytopenia.*

- Reversible on discontinuation of drug.
- Seen frequently when dose exceeds 3-4g/day for 1-2 weeks.
- Occurs due to inhibition of host mitochondrial 70 S ribosomes.

- Hepatic/ renal insufficiency predispose to this type of toxicity. Periodic blood counts advised.

2) Idiosyncratic Aplastic Anemia:

- Rare, but serious and often fatal (1 in 40,000).
- Possibly has a genetic cause and occurs commonly after repeated courses or even after a single oral/ocular administration.
- Aplastic anemia: m/c manifestation.
- Many survivors tend to develop leukemias later.

3) Gray Baby Syndrome:

- Neonates lack ability to conjugate chloramphenicol via glucoronidation.
- High levels of chloramphenicol (100mg/kg) may cause fatal neonatal toxicity.
- Abdominal distension, progressive cyanosis (gray body), hypothermia, vomitting, loss of hunger and CV collapse leading to death.

4) Hypersensitivity reactions:

- Rashes, fever, atrophic glossitis, angioedema

5) Irritation:

- N,V,D & pain on injection

6) Superinfection:

- Same as tetracyclines, but are less common

Notable differences between these two are:

(a) Highly active against Salmonella including S. typhi,

(b) More active than tetracyclines against

- H. Influenzae, B. pertussis, Klebsiella, N. Meningitis and anaerobes including Bact. fragilis.

(c) Less active against

- Gram-positive cocci, spirochetes, certain enterobacteriaceae and chlamydia.

- Entamoeba and Plasmodia are not inhibited.
- **Like tetracyclines,** it is ineffective against Mycobacteria, Pseudomonas, many Proteus, viruses and fungi.

Drug Interactions

- Paracetamol enhances bioavailability of Chloramphenicol by 28%.

- Chlorampenicol is a potent enzyme inhibitor and inhibits metabolism of:

  - Morphine (respiratory depression)
  - Chlorpropamide (aggravate hypoglycemia)
  - Warfarin (may cause bleeding)

PRECAUTIONS

- Because of serious bone marrow toxicity:

(a) Never use chloramphenicol for minor infections or those of undefined etiology.

(b) Do not use chloramphenicol for infections treatable by other safer antimicrobials.

(c) Avoid repeated courses.

(d) Regular blood counts may detect dose-related bone marrow toxicity.

Streptogramins

- They affect the Bacterial ribosome.

Core subject – Pharmacology

- Streptogramins are class of natural cyclic peptide antibiotics produced by certain sub-species of Streptomyces .
- They are 2 classes A & B.
- They inhibit bacterial protein synthesis by interfering 50S ribosomal binding sites.
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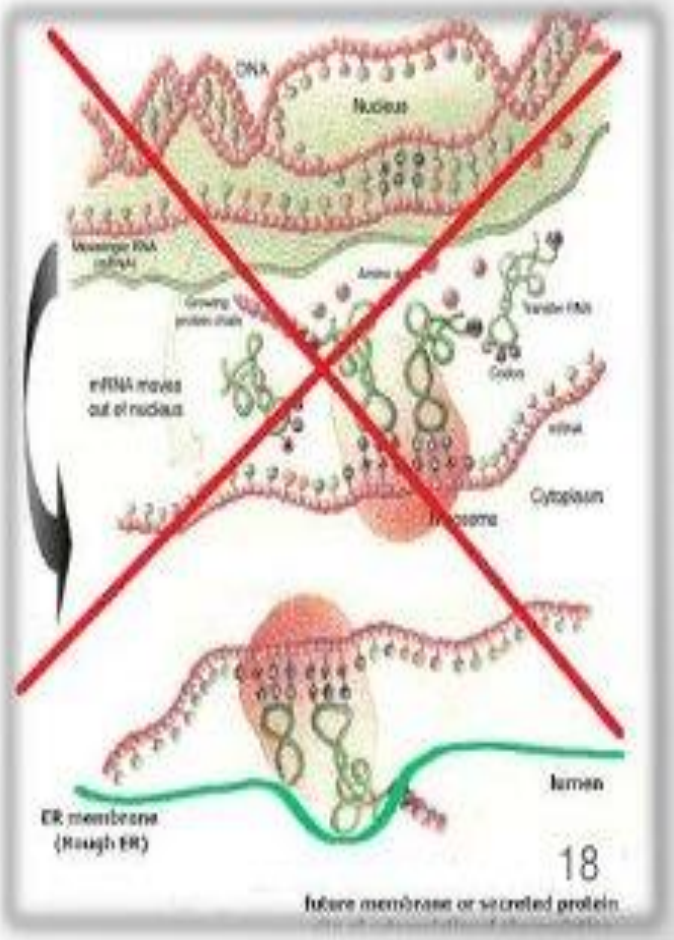


Streptogramins classes

Cyclic peptides include two structurally unrelated components

Group A	Group B
Dalfopristin Inhibit the early phase of protein synthesis	Quinupristin Inhibits the late phase of protein synthesis

Mechanism of action

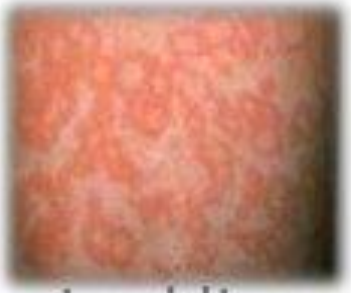
- The individual components are bacteriostatic.
- Their **combination synergistically** is bactericidal combination.
- Quinupristin/dalfopristin are available in combination of 3:7 ratio respectively[1] .

- **VERTICLE INTEGRATION MEDICINE/ SURGERY**

Streptogramins

- Streptogramins are effective in the treatment of vancomycin-resistant *Staphylococcus aureus* (VRSA) and vancomycin-resistant *Enterococcus* (VRE), two of the most rapidly growing strains of multidrug-resistant bacteria. They fall into two groups: streptogramin A and streptogramin B.

Side effects



- Nausea and vomiting
- Skin rash, pruritus
- Hyperbilirubinemia and raised liver enzyme values may occur.
- Arthralgias and myalgias in patients with hepatic insufficiency
  - Managed by reducing the dosing frequency from q. 8hr to q.12 hr

CLINDAMYCIN

Core subject – Pharmacology

CLINDAMYCIN

- Potent lincosamide antibiotic
- Similar in mechanism of action to erythromycin

SPECTRUM:-

- Similar spectrum of activity to erythromycin
- Exhibits partial cross resistance.
- It inhibits most gram-positive cocci (including penicillinase producing Staph., but not MRSA), C. Diphtheriae, Nocardia, Actinomyces, Toxoplasma.
- High activity against a variety of anaerobes, especially Bact. fragilis.
- Aerobic gram-negative bacilli, spirochetes, Chlamydia, Mycoplasma and Rickettsia are not affected.

RESISTANCE:-

- Modification of the ribosomal binding site by constitutive methylase enzyme confirs resistance to both.

PHARMACOKINETICS:-

- Good Oral absorption
- Penetrates into most skeletal and soft tissues, but not in brain and CSF
- Accumulates in neutrophils and macrophages.
- Metabolized by liver
- Excreted in urine and bile.
- The t ½ is 3 hr.

SIDE EFFECTS :-

- Rashes, urticaria, abdominal pain, diarrhoea and pseudomembranous enterocolitis, superinfection.
- Because of potential toxicity,
  - Use of clindamycin is restricted to anaerobic and mixed infections.
- It is generally combined with an aminoglycoside or cephalosporin.
- Metronidazole and chloramphenicol are the alternatives to clindamycin for covering the anaerobes.

- **VERTICLE INTEGRATION MEDICINE/ SURGERY**

INDICATION:-

- Anaerobic streptococcal and Cl. perfringens infections
  - those involving bone and joints respond well.
- For prophylaxis of endocarditis in penicillin allergic patients
  - With valvular defects
  - To prevent surgical site infection in colo rectal/ pelvic surgery.
- In AIDS patients,
  - Combined with pyrimethamine for toxoplasmosis
  - With primaquine for Pneumocystis jiroveci pneumonia.
- Topically :- for infected acne vulgaris.

DRUG INTERACTION:-

- Clindamycin, erythromycin and chloramphenicol can exhibit mutual antagonism
  - Because their ribosomal binding sites are proximal
  - Binding of one hinders access of the other to its target site.
- Clindamycin weakly potentiates neuromuscular blockers.

LINEZOLID

OXAZOLIDINONE

- **Svnthetic AMAs**

SPECTRUM:-

- **Resistant gram positive coccal (aerobic and anaerobic) and bacillary infections.**

ACTIVE AGAINST:-

- MRSA and some VRSA, VRE, penicillin-resistant Strep. pyogenes, Strep. viridans and Strep. Pneumoniae, M. tuberculosis, Corynebacterium, Listeria, Clostridia and Bact. fragilis.
- Primarily bacteriostatic
- Can exert cidal action against some streptococci, pneumococci and B. fragilis.
- Gram negative bacteria are not affected.

MECHANISM OF ACTION:-

- Inhibits bacterial protein synthesis
- By inhibiting at an early
- Binds to the 23 S fraction of the 50S ribosome.
- Interferes with formation of the ternary **N-formylmethionine-tRNA** (t RNA fMet) **initiation complex.**
- Binding of linezolid **distorts the tRNA binding site** overlapping both 50S and 30S ribosomal subunits.
- Stops protein synthesis before it starts.
- No cross resistance with any other class of AMAs

PHARMACOKINETICS:-

- Rapidly and completely absorbed orally
- Excreted in urine.
- Plasma t 1/2 is 5 hrs.

SIDE EFFECTS:-

- Mostly mild abdominal pain and bowel upset
- Occasionally, rash, pruritus, headache, oral/ vaginal candidiasis
- Neutropenia and thrombocytopenia are infrequent.

INDICATIONS:-

- For skin and soft tissue infections
- Pneumonias
- Bacteraemia
- Other drug-resistant gram positive infections.
- Serious hospital-acquired pneumonias,
- Neutropenia,
- Wound infections
- For multidrug-resistant gram positive bacteria, vancomycin resistant-MRSA ,multi-resistant pneumoniae, etc.

FUSIDIC ACID

- Steroidal antibiotic
- Narrow spectrum

MOA:-

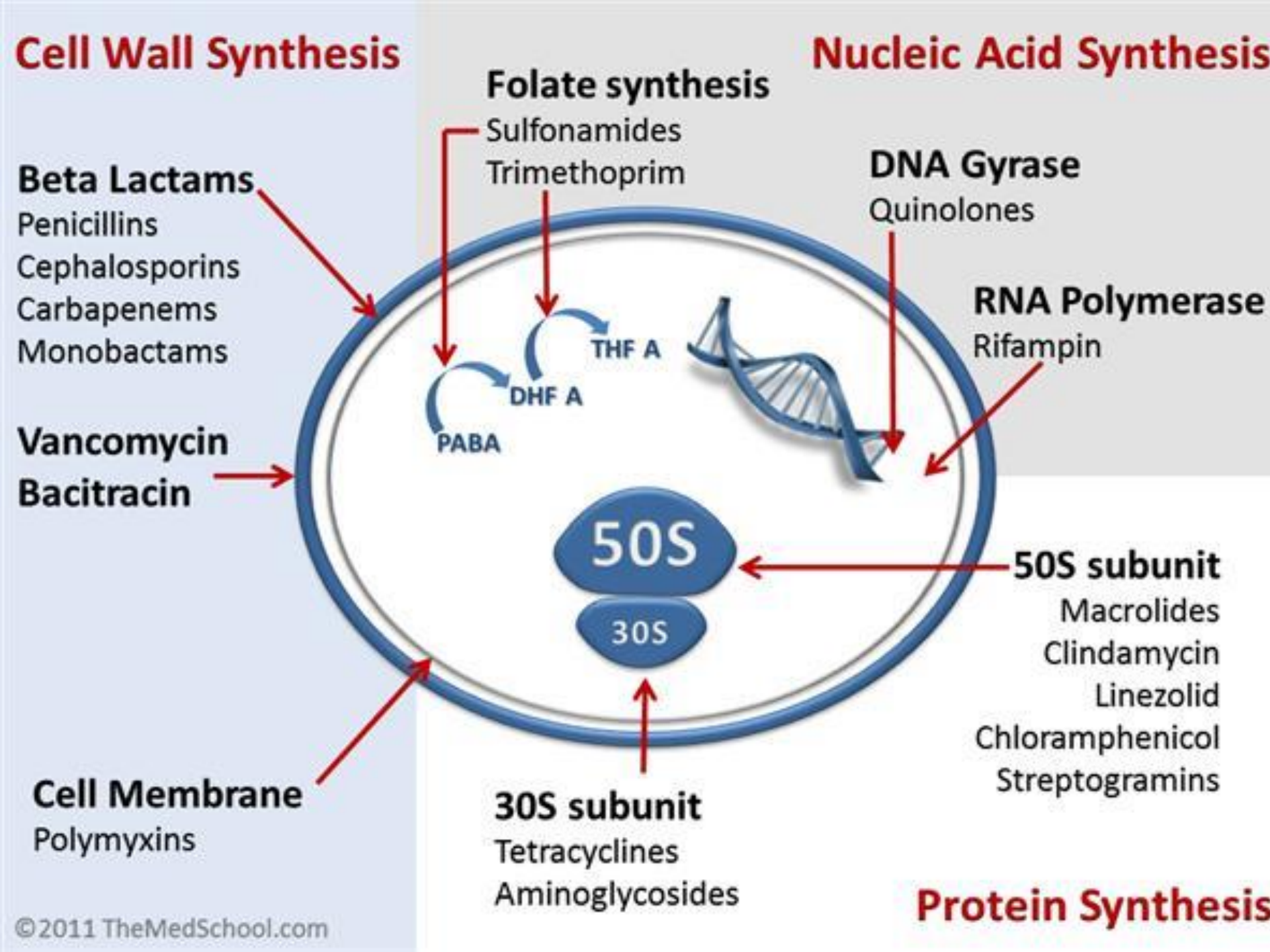
- Blocks bacterial protein synthesis

SPECTRUM:-

- Active against penicillinase producing Staphylococci and few other gram-positive bacteria.

USES:-

- Only topically
  - For boils (Bacterial infections of hair follicles and surrounding skin)
  - Folliculitis (Inflammation or infection of one or more hair follicles)
  - Sycosis barbae
    (A staphylococcal infection and irritation of the hair follicles in the beard region)
  - Other cutaneous infections.


Cell Wall Synthesis
Nucleic Acid Synthesis
Folate synthesis
Sulfonamides
Trimethoprim
Beta Lactams
Penicillins
Cephalosporins
Carbapenems
Monobactams
DNA Gyrase
Quinolones
RNA Polymerase
Rifampin
THF A
DHF A
PABA
Vancomycin
Bacitracin
50S
30S
50S subunit
Macrolides
Clindamycin
Linezolid
Chloramphenicol
Streptogramins
Cell Membrane
Polymyxins
30S subunit
Tetracyclines
Aminoglycosides
Protein Synthesis
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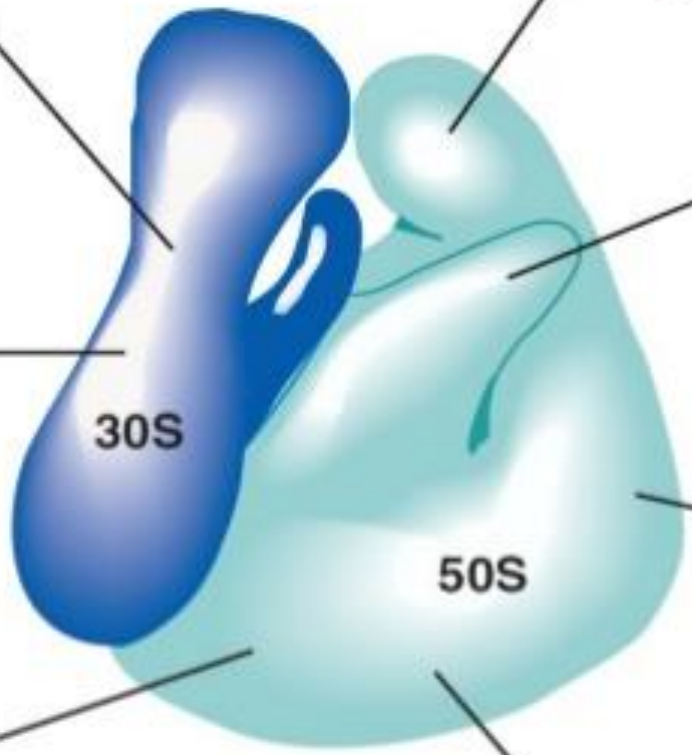
9.GENERAL MECHANISM OF PROTEIN SYNTHESIS INHIBITORS



Aminoglycosides
Block the initiation of translation and causes the misreading of mRNA

Macrolides
Prevent the continuation of protein synthesis

Chloramphenicol
Prevents peptide bonds from being formed

Tetracyclines
Block the attachment of tRNA to the ribosome

Lincosamides
Prevent the continuation of protein synthesis

Streptogramins
Each interferes with a distinct step of protein synthesis

Oxazolidinones
Interfere with the initiation of protein synthesis

Con...

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6. Journals and Researches will appear
7. You can find a Journal by clicking on JOURNALS AND DATABASE and enter a keyword to search for your desired journal.

- A 46 year old female is in ICU for treatment of a VRE caused bacteremia. You want to limit the risk of drug interactions in this pt. who is receiving five other medications. Which of the following antibiotics would you choose?
- Azithromycin
- Clindamycin
- Doxycycline
- Linezolid
- Quinupristin/dalfopristin

- A patient with a gunshot wound to abdomen is brought to ER. Which of the following antibiotics would you select to treat an infection due to bacteriodes fragilis
- Doxycycline
- Clindamycin
- Azithromycin
- Gentamicin
- aztreonam

THANK YOU