ANTIBACTERIAL DRUGS
(INHIBITORS OF PROTEIN SYNTHESIS)

M.Kampamba (DipPharm, Bpharm, MclinPharm) PhD candidate

Clinical Pharmacy Specialist (Specialty: General Pharmacotherapy)

Lecturer University of Zambia
School of Health Sciences
Pharmacy Department

Kampamba .M

Learning Objectives:

At the end of this session, YOU should be able to:

1. Classify inhibitors of protein synthesis antibacterial drugs
2. Explain correctly the mechanism of action of antibacterial drugs
3. Explain correctly the pharmacokinetic considerations & adverse effects of antibacterial drugs

INHIBITORS OF PROTEIN SYNTHESIS

- Aminoglycosides
- Tetracyclines
- Macrolides
- Chloramphenicol
- Linconsamide
- Linezolid

Aminoglycosides

Mode of action:

- Bactericidal
- Bind irreversibly to 30S ribosomal bacterial subunits leading to inhibition of protein synthesis
- Effective bactericidal activity against:
  - Aerobic gram-negative bacilli
  - Few Aerobic gram- positive bacteria
  - Mycobacteria *(streptomycin)*
  - Few Protozoa
  - MDR TB. Kanamycin, Amikacin

Examples

- Gentamicin
- Amikacin (widest antimicrobial activity)
- Neomycin
- Streptomycin
- Tobramycin (preferred for P. Aeruginosa infection)
- Kanamycin
- Netilmycin

Pharmacodynamics

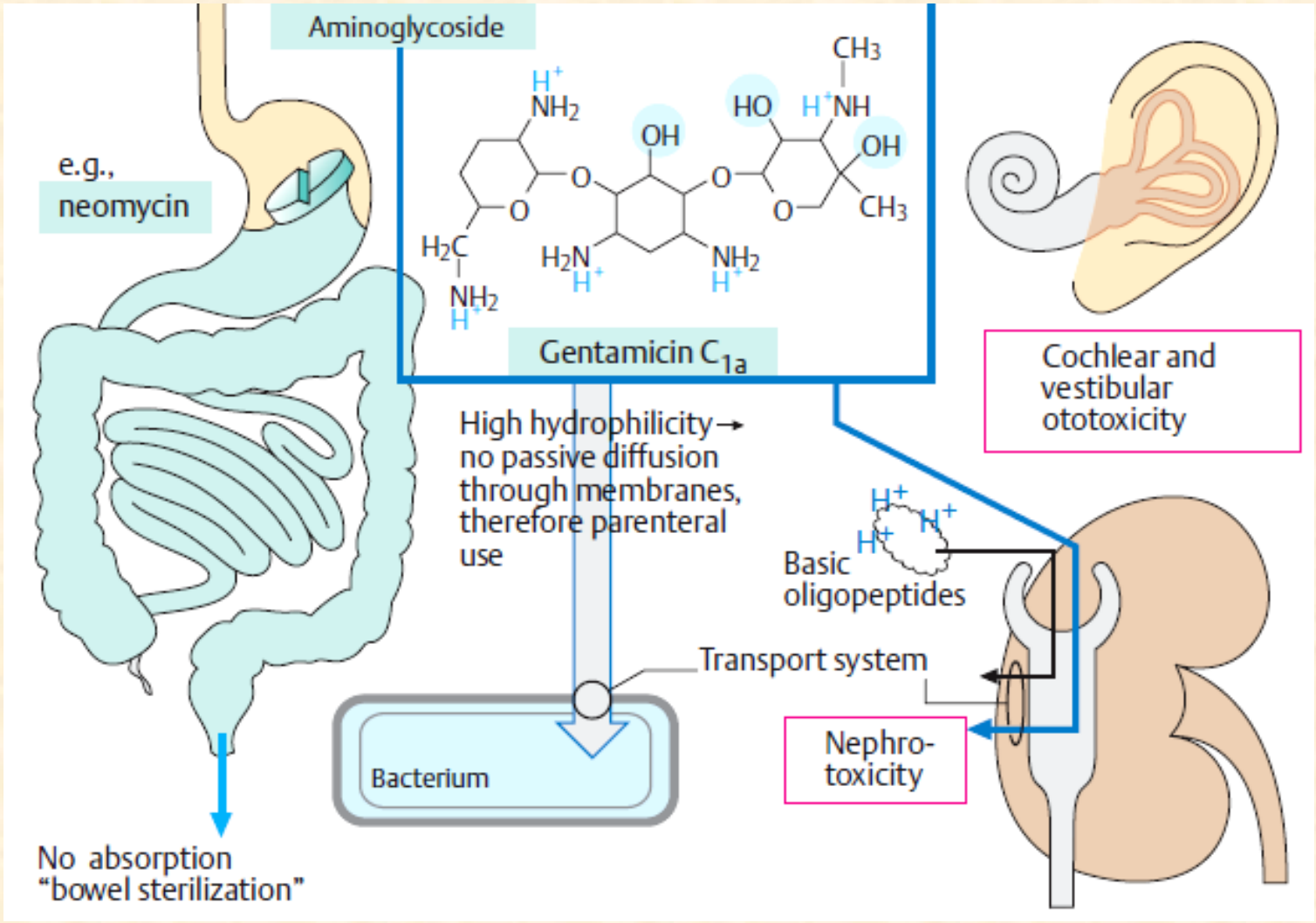
- Resistance associated with drug failure include:
  - Inability to cross cell membrane
    - ❖ May be used with penicillin to aid entry of aminoglycoside
  - Altered ribosomes
  - Destruction of drug by bacterial enzymes

Spectrum of Activity

- Aminoglycosides are most effective against Gram-negative bacteria, including:
- Escherichia coli
- Klebsiella pneumoniae
- Pseudomonas aeruginosa
- Enterobacter species
- Serratia species
- They have limited activity against Gram-positive bacteria and are usually not effective against anaerobic bacteria.

Pharmacokinetics

- Very poor GIT absorption
- Absorption complete and rapid after I.V./I.M administration
- Widely distributed in ECF
  - Rapidly crosses placental barrier not BBB
- Not metabolized
  - Excreted by kidneys unchanged
  - Decreased renal function associated with increase serum $t_{1/2}$



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Clinical Uses

- Treatment of infections by aerobic G(-) bacilli
- Nosocomial infections in critically ill patients
  - Gram negative bacteremia/septicemia
  - Peritonitis
  - Pneumonia
  - Sub-acute bacterial endocarditis
- UTI
  - Enteric bacilli resistant to less toxic antibiotics such as penicillins and cephalosporins
- Eye infections

- Streptomycin used in TB regimens
- Kanamycin used for MDR-TB
- Neomycin used orally (to sterilize the bowel before surgery) and topically in infected wounds. **It is too toxic for systemic use**.

❖ *Because of toxicity, Aminoglycosides are reserved for serious infections and usually combined with Penicillins*

Examples of Bacterial Coverage

Aminoglycoside Agent	Bacteria
Streptomycin	Mycobacteria including mycobacteria tuberculosis Gram- positive bacteria
Amikacin; Gentamicin; Tobramycin	Acinetobacter, Citrobacter, Enterobacter, Klebsiella, Proteus, pseudomonas aeruginosa
Gentamycin; Tobramycin	Used synergistically with penicillins against gram positive organisms such as staphylococci or enterococci

Bacterial spectrum dependent on susceptibility of bacteria (based on culture and sensitivity tests)

Examples of Drug Interactions

Drug	Interacting Drugs	Possible Effects	Monitoring aspects
All aminoglycosides	Antiemetics	Masked vestibular ototoxicity	Hearing loss
	Loop diuretics	Increased ototoxicity	
Amikacin, gentamicin, streptomycin, tobramycin, neomycin,	Neuromuscular blockers	Increased blockade	Administer anticholinesterases and calcium; cautious administration
	Carbapenems;	Decreased effect of aminoglycoside	Do not give together; give at least 1 hour apart
Amikacin, gentamicin, tobramycin	Amphotericin B, cephalosporins, acyclovir	Increased nephrotoxicity	Monitor renal function
	Cyclosporines	Increased nephrotoxicity	Avoid combination; monitor renal function

Adverse Effects

- Most notably: Ototoxicity and Nephrotoxicity
  - Commonly occurs in elderly due to impaired renal function & in patients receiving ototoxic drugs
  - Risk of nephrotoxicity increases with higher doses

  The result, usually irreversible, may manifest as vertigo, ataxia and loss of balance in the case of vestibular damage, and auditory disturbances or deafness in the case of cochlear damage
- Can produce irreversible damage to cranial nerve VIII
- Renal tubular necrosis (↑Serum Cr and BUN)
- Neuromuscular paralysis: - Aminoglycosides inhibit *Acetylcholine* release

- Common adverse effects after oral administration:
  - Nausea, vomiting, diarrhoea
- Allergic reactions rare:
  - Rash, urticaria, stomatitis, fever

Question (True or False)

1. Which of the following aminoglycoside has widest antimicrobial activity?

a. Kanamycin
b. Gentamycin
c. Streptomycin
d. Tobramycin

2.Aminoglycoside that is too toxic for systemic use is

a. Tobramycin
b. Gentamycin
c. Neomycin
d. Kanamycine

3. **Preferred aminoglycosed for P. aeruginosa infections is:**

a. Netilmycin
b. Gentamycin
c. Neomycin
d. Tobramycin

Tetracyclines

Tetracycline

oxytetracycline

Demeclocycline

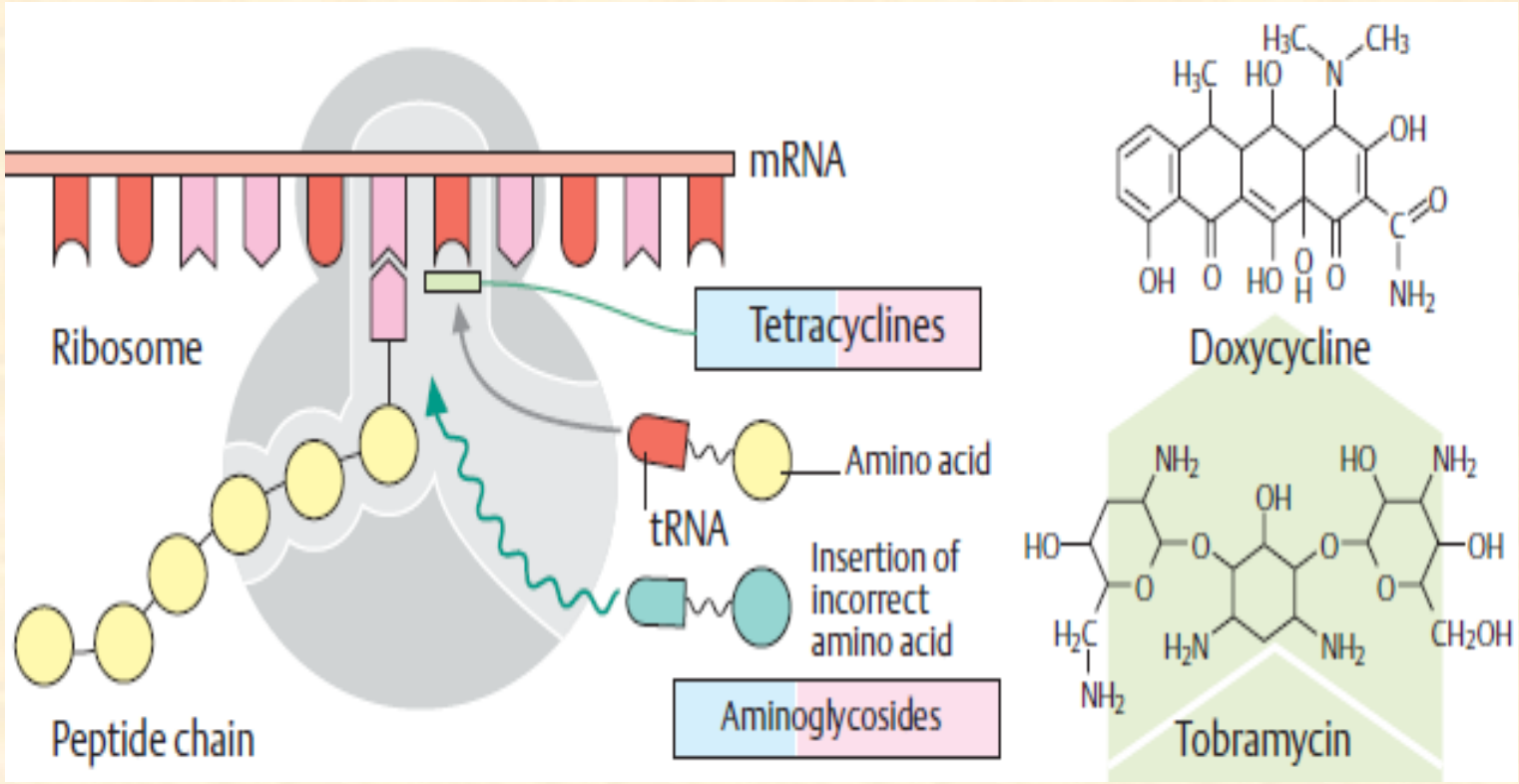
Doxycycline

Minocycline

Limecycline

Pharmacodynamics

- Bacteriostatic
- Penetrate cell wall by energy-dependent processes
- Tetracycline is a short-acting antibiotic that **inhibits bacterial growth by inhibiting translation**.
- It binds to the 30S ribosomal subunit and prevents the amino-acyl tRNA from binding to the A site of the ribosome
  - Prevents addition of new amino acids to peptide chain of bacteria → inhibition of protein synthesis



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Pharmacokinetics

- Well absorbed from duodenum after oral administration
- Absorption impaired by Fe^{3+} preparations, antacids containing Ca^{2+}, Mg^{2+} or aluminum salts
- Distributed widely into body tissue and fluids concentrated in bile , bind to bones due to affinity to calcium
- Excreted primarily by kidneys

Spectrum of activity & Clinical Uses

- Spectrum of Activity:
- Tetracyclines have a broad spectrum of activity
- Activity against G(+), G(-), aerobic and anaerobic bacteria such as rickettsiae and some protozoa
- Activity against atypical bacteria chlamydia, Legionella , mycoplasma and N. Meningitides (Minocycline)
- Brucellosis, lyme disease and anthrax
- Spirochaetes (syphilis) and Coxiella burnetii

Common Drug Interactions

Drug	Interacting Drugs	Possible Effects	Interventions
Doxycycline, minocycline, tetracycline	Antacids-magnesium, aluminum, calcium salts	Inhibited absorption of tetracycline	Administer 1 to 2 hours apart
Doxycycline, minocycline, tetracycline	Iron salts, zinc sulfate, bismuth salicylate	Decreased absorption of tetracycline	Administer 3 hours before or 2 hours after tetracycline
Doxycycline	Barbituates, phenytoin	Increased doxycycline metabolsm	Avoid concurrent use or use different tetracycline
Tetracycline	Oral contraceptives	Altered GI flora decreases OC absorption	Use alternative method of contraception
All tetracycline	Penicillin	Decreased bactericidal activity of penicillin	Administer several hours apart

Adverse Effects

- Superinfection
- GI disturbances
  - Nausea, vomiting, abdominal distress, distension and diarrhoea
  - Prolonged symptoms– pseudomembranous colitis
- Photosensitivity reactions
  - Common in patients receiving demeclocycline but can also occur with other tetracyclines
- Permanent discoloration of teeth during tooth formation
  - Do not administer to children under age 8 (period of tooth enamel formation)

- Hepatotoxicity
  - Lipid infiltration of liver associated with IV administration
- Nephrotoxicity
  - Develops in patients with renal failure
  - Fanconi syndrome-associated with administration of expired tetracycline
- CNS toxicity
  - Vestibular disturbances—primarily with minocycline.
- Dental hypoplasis and bone deformities

4. The Tetracycline of choice in renal failure is :

a. Doxycycline
b. Limecycline
c. Demeclocycline
d. Tetracycline

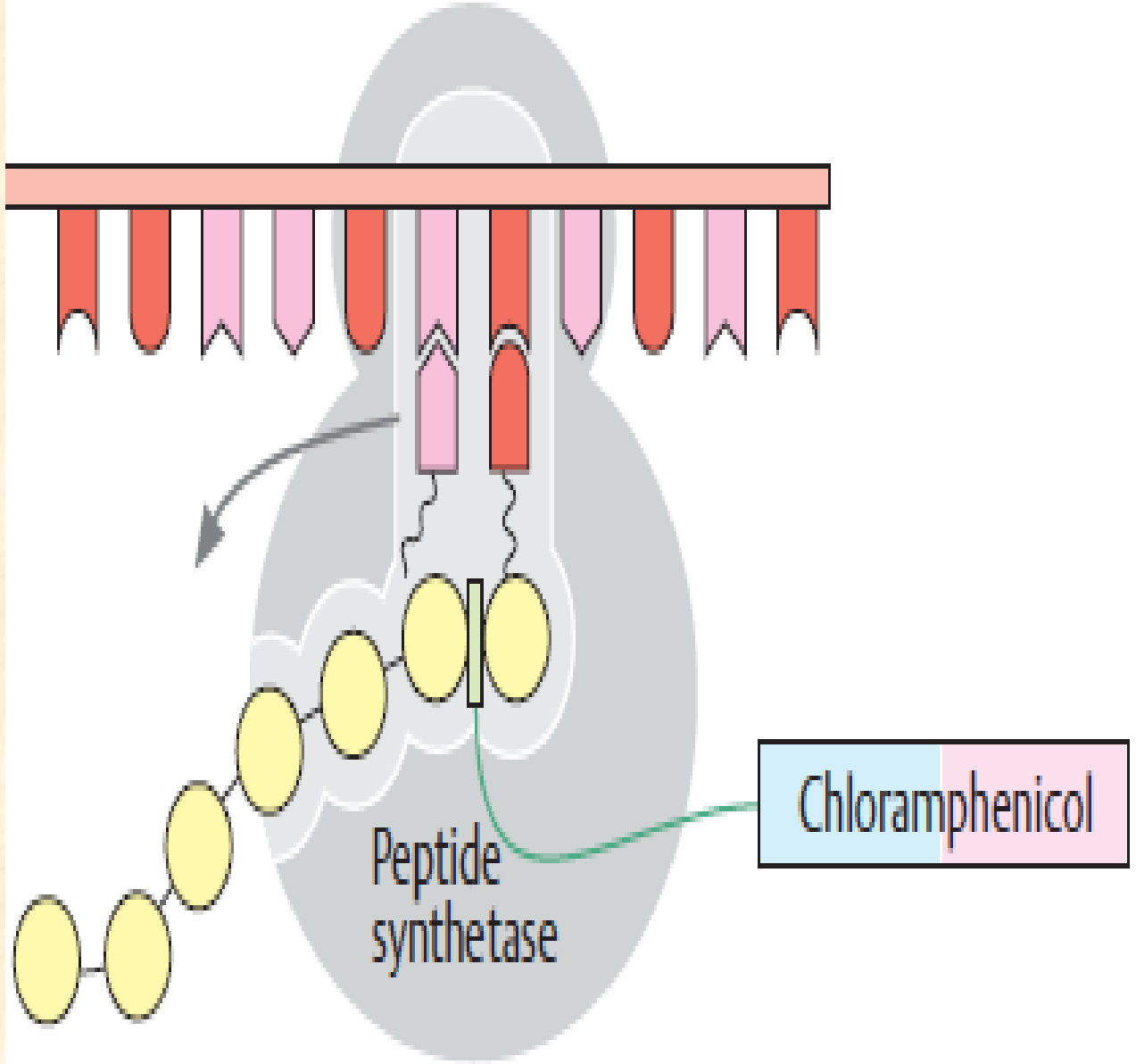
5. The Tetracycline associated with vestibular disturbance is

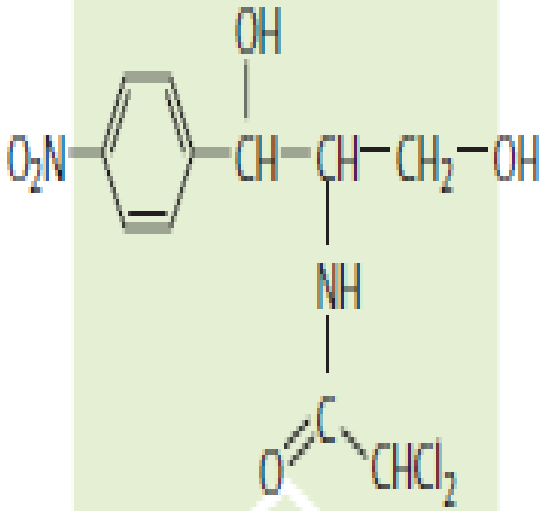
a. Doxycycline
b. Limecycline
c. Demeclocycline
d. Minocycline

AMPHENICOLS

Chloramphenicol

- Limited clinical use due to drug-induced aplastic anaemia
- Reserved for treating serious infections and ampicillin-resistant H. influenzae
- Pharmacokinetics:
  - Absorbed rapidly and completely from GIT
  - Good penetration through biological barriers
  - 10% excreted unchanged in the urine and 90 percent inactivated by the liver
- Pharmacodynamics:
  - Bacteriostatic
  - Binds to 50S ribosome subunit → inhibits peptide synthase → inhibition of protein synthesis in susceptible organisms





Chloramphenicol

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- Overcomes enzymatic acetylation
  - Major mechanism of resistance in most gram-negative bacilli
- Other Uses:
  - Active against various organisms including bacteria, spirochetes, rickettsiae, chlamydiae
  - Very active against anaerobic bacteria
  - DOC for treating ampicillin resistant typhoid fever and other systemic Salmonella infections
  - Quinlones are now mostly used in salmonellosis.

Drug Interactions

- Inhibits metabolism of oral hypoglycaemic agents, anticonvulsants, and oral anticoagulation
  - Symptoms include hypoglycaemia, phenytoin toxicity, haemorrhage
- Bone marrow suppression exacerbated by co-administration of other drugs causing suppression

Adverse Effects

- Bone marrow suppression
- Aplastic anemia
- Grey baby syndrome in neonates *(Vomiting, Flaccidity, Hypothermia, Grey color, Shock and Collapse) resulting from decreased drug clearance due to undeveloped liver and kidney functions in neonates.*
- Optic neuritis
- GIT upset and super-infection

Lincosamide Antibiotic

Members: Clindamycin

- Pharmacokinetics:
  - Absorbed well and distributed widely in body
  - Eliminated primarily via hepatic metabolism including renal metabolism and biliary excretion
- Pharmacodynamics :
  - Bacteriostatic
  - Clindamycin works primarily by **binding to the 50s ribosomal subunit of bacteria**.
  - This agent disrupts protein synthesis by interfering with the transpeptidation reaction, which thereby inhibits early chain elongation.

- Clinical Uses:
  - Activity against aerobic gram-positive organisms including staphylococcus, streptococcus, pneumococci, anaerobes
  - Used for skin and bone infections
  - Used specifically against anaerobic infections

- Drug interactions
  - Enhances action of neuromuscular blockers

- Adverse effects
  - Diarrhoea, stomatitis, nausea and vomiting from oral administration
  - Pseudomembranous colitis
    - Symptoms include severe diarrhoea, abdominal pain, fever, and mucus and blood in stools
  - IV administration may damage tissue
  - IM administration may produce pain, sterile abscess
  - Hypersensitivity
    - Stevens-Johnson syndrome (rare)

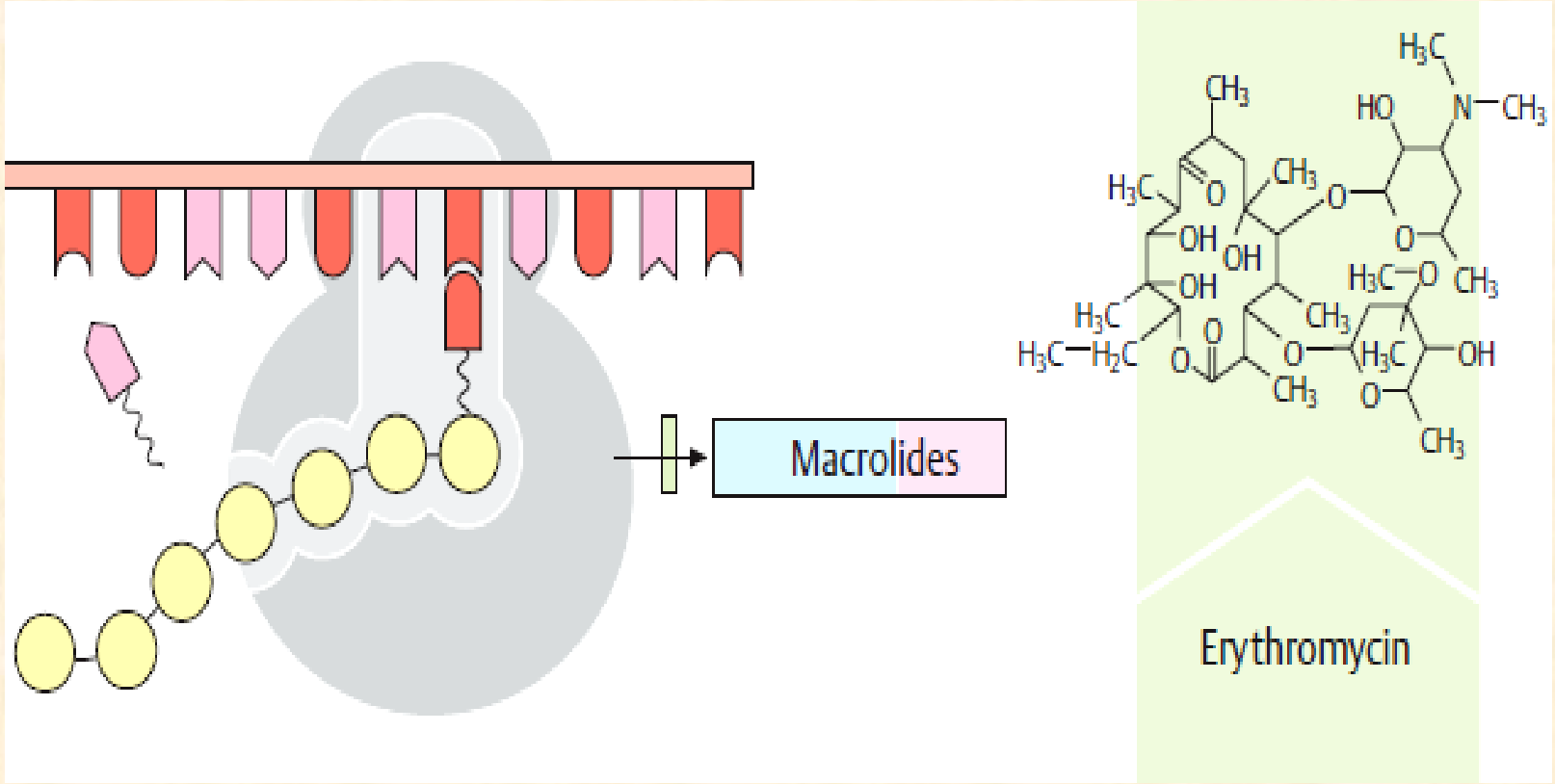
Macrolides

- Members: ***Erythromycin, azithromycin, clarithromycin, roxithromycin, spiramycin and Telithromycin***
- Pharmacokinetics
  - Absorption dependent on type of formulation, influenced by presence of food in GIT
  - Distributed to most tissues and body fluids except cerebrospinal fluid
  - Metabolized by liver

- Erythromycin primarily excreted in faeces; also excreted in urine in small amounts
- Crosses placental barrier and secreted in breast milk

Pharmacodynamics:

- Bacteriostatic
- Inhibits protein synthesis
  - Acts on 50S ribosomal units inhibiting RNA-dependent protein synthesis
    - Block advancement of ribosome unit and translocation of peptides



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Spectrum of activity and clinical use

- Erythromycin is effective against Gram-positive bacteria and spirochaetes, *N. gonorrhoeae* and, to a lesser extent, *H. influenzae.*
- *Mycoplasma pneumoniae*, *Legionella* spp some chlamydial organisms are also susceptible
- Azithromycin is less active agains gram + bacteria than erythromycin but is considerably more effective against *H. influenza, Legionella*.
- It has excellent action against *Toxoplasma gondii*, killing the cysts

- Clarithromycin is as active against *H. influenzae* as erythromycin.
- It is also effective against *Mycobacterium avium-intracellulare*
- it may also be useful in leprosy and against *Helicobacter pylori*
- also effective in Lyme disease.

Common Drug Interactions

- High dose macrolides decreases clearance of theophylline
  - Increases serum levels– requires decrease of theophylline dosage
- Erythromycin lactobionate incompatible with vitamin B complex, vitamin C, tetracycline, heparin, furosemide, metoclopramide
- Clarithromycin increases plasma levels of carbamazepine

Adverse Effects

- GIT disturbances e.g.
  - Epigastric distress, nausea, vomiting and diarrhoea
  - Stomatitis, heartburn, anorexia and melena
- Allergic reactions
  - Rash, fever, eosinophilia, anaphylaxis
- Rare: reversible sensorineural hearing loss
  - Occurs in renally impaired patients receiving high dose erythromycin
- Rare: cholestatic hepatitis
  - Associated with erythromycin ethylsuccinate
  - Characterized by nausea, vomiting, abdominal pain followed by jaundice, fever

Azythromycin

- Less effective against G(+) but more effective against G(-) organisms than *Erythromycin*.
- Potent against Chlamydia.
  - Fewer GI adverse effects than erythomycin
  - Palpitations, chest pain, dizziness, vertigo, fatigue, rash
- **Clarithromycin**
  - Fewer GI adverse effects
  - Dyspepsia, headache

Questions.

6. Macrolyde with activity against Toxoplasma gondii:

a. Talithromycin
b. Erythromycin
c. Clarythromycin
d. Azithromycin

7. Macrolyde with activity against H.pylori and MAC

a. Talithromycin
b. Erythromycin
c. Clarythromycin
d. Azithromycin

4. Inhibitor of protein synthesis through binding to 30S subunit include:

a. Tetracycline
b. Chloramphenical
c. Aminoglycosides
d. Macrolydes

5. Bacteriocidal agent (s) include:

a. Doxycycline
b. Gentamycin
c. Erythromycin
d. Chloramphenicol

Linezolid:

- **Mechanism of Action**: Linezolid is an oxazolidinone antibiotic that inhibits bacterial protein synthesis by binding to the 23S ribosomal RNA of the 50S subunit, preventing the formation of the 70S initiation complex. This action ultimately leads to the inhibition of bacterial protein synthesis, halting bacterial growth.

Spectrum of Activity

- Linezolid is effective against a wide range of Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), Streptococcus pneumoniae, and various other resistant strains.
- It is not effective against Gram-negative bacteria.

Clinical Uses:

- Linezolid is primarily used to treat serious infections caused by resistant Gram-positive bacteria.
- It is often used as a second-line agent for the treatment of MRSA infections when other antibiotics are not effective.
- It is also employed in the treatment of complicated skin and soft tissue infections, pneumonia (including hospital-acquired pneumonia), and bloodstream infections.

Pharmacokinetics:

- Linezolid is available in both oral and intravenous (IV) forms.
- It is well-absorbed orally, allowing for convenient outpatient treatment of certain infections.
- The drug is metabolized in the liver and excreted primarily in the urine.
- Dose adjustments may be necessary in patients with renal impairment.

Adverse Effects:

- Linezolid is generally well-tolerated, but some common side effects include nausea, vomiting, diarrhea, and headache.
- Long-term use or high doses may lead to bone marrow suppression, resulting in anemia, thrombocytopenia, or leukopenia. Regular blood count monitoring is necessary during treatment.
- Peripheral neuropathy has been reported with prolonged use, but it is rare.
- Linezolid has the potential to interact with certain medications, particularly monoamine oxidase inhibitors (MAOIs), as it can increase the risk of serotonin syndrome.
- Therefore, caution should be exercised when combining Linezolid with other serotonergic drugs.

Resistance: Resistance to Linezolid is relatively rare but can occur due to mutations in the 23S rRNA binding site or other mechanisms. Combination therapy or alternative antibiotics may be required in cases of resistance.

Special Considerations:

- Linezolid should be used judiciously due to concerns about the development of antibiotic resistance.
- It is often reserved for severe infections caused by multidrug-resistant Gram-positive bacteria.
- The duration of therapy and choice of oral or IV administration depend on the specific infection being treated.

- END OF LECTURE

Thank you for having me