Macrolides, Ketolides, Lincosamides, Streptogramins, Linezolid, Chloramphenicol

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Macrolides

History

- Erythromycin - 1952- penicillin allergy
- 1970- ***ATYPICAL*** pathogens (Legionella, Chlamydia, Mycoplasma)

Natural

- Erythromycin
- Spiramycin
- Josamycin

Semisynthetic

- Roxithromycin
- Clarithromycin
- Azithromycin

Mechanism of action

- Inhibition of protein synthesis via binding to the 50S ribosomal RNA
- Bacteriostatic (sometimes bactericid)
- Time dependent effect

Resistance

- Mechanisms:
  - Modification of the ribosomal binding site (MLS_B – Macrolides-Lincosamides-Streptogramin B)
  - Inactivation (esterases)
  - Decreased permeability – efflux

Antibacterial activity

- **G +** : Streptococci sp., Staphylococci sp., Corynebacterium diphteriae, Listeria monocytogenes, Bacillus Anthracis
- **G -** : Neisseria sp., Bordetella pertussis, Hemophylus sp., (Azithromycin) Campylobacters, H. pylori (Clarithromycin)
- **Atypical organisms**: Chlamydia sp., Legionella sp., Mycoplasma sp., Ureaplasma urealyticum
- Spirochetes: Treponema pallidum, Borrelia burgdorferi
- Toxoplasma gondii (Spiramycin)

Resistant bacterias

- Gram-negativ GI tract bacterias → natural resistance
- Pneumococci strains – many of them might be resistant
- MRSA
- Enterococci
- Pseudomonas
- Acinetobacter
- Bacteroides fragilis

Pharmacokinetics

- Well absorbed given orally (exception – Erythromycin)
- Good distribution
- Excretion mainly in the bile (erythromycin) or by the urine (clarythromycin)
- Taken up by **ACTIVE TRANSPORT** into macrophages (IC effectivity!!!)

Adverse effects

- **NON TOXIC**, safe in pregnancy (exception Clarithromycin- might be teratogenic)

- Gastrointestinal (nausea, vomit, diarrhea) – mainly Erythromycin (motilin), the others cause less.

- Erythromycin and Clarithromycin inhibit the cytocrome P450 enzymes, Azithromycin does not.

Indications

- Upper respiratory tract infections in case of penicillin allergy
- Atypical pneumonias
- Chlamydia urethritis (Azithromycin)
- Toxoplasmosis in pregnancy (Spiramycin)
- Campylobacter jejuni gastroenteritis
- H. pylori erradication (Clarythromycin)
- Diphteria, whooping cough, early Lyme syndrome (Azithromycin)

Ketolides - Telithromycin

- Semisynthetic macrolide antibiotic
- Differences:
  - Binds with a higher affinity to the 50S subunit
  - Bactericid, concentration dependent effect
  - Antibacterial activity is similar to the activity of macrolides but can be effective in case of macrolide resistant strains as well
  - hepatotoxicity (rare)

Lincosamides - Clindamycin

Mechanism of action

- Inhibition of protein synthesis via binding to the 50S ribosomal RNA
- Bacteriostatic

Resistance

- Mechanisms:
  - Modification of the ribosomal binding site (MLS_B – Macrolides-Lincosamides-Streptogramin B)
  - Efflux

Antibacterial activity

- **G +** : Streptococci sp., Staphylococci sp.
- **Anaerobs**: Gram-positive > Gram-negative
  - Gram-pozitive: Clostridium sp., (exception Clostridium difficile), Actinomyces sp.
  - Gram-negative: Bacteroides sp., Fusobacterium sp., Prevotella sp.,
- Chlamydia trachomatis
- Some protozoons: Plasmodium falciparum, Toxoplasma gondii, Pneumocystis jiroveci (carinii)

Resistant bacterias

- Gram-negative aerob bacterias → natural resistance
- Enterococci strains
- Staphylococci – many resistant strains
- Mycoplasma pneumoniae
- Clostridium difficile

Pharmacokinetics

- Well absorbed given orally
- Good distribution, into abscesses, **BONES** as well! Does not enter CNS
- Metabolized in the liver
- Accumulates intracellularly

Adverse effects

- Nausea, diarrhea
- Pseudomembranosus colitis caused by Clostridium difficile → treatment Metronidazol or Vancomycin
- Skin rashes
- Neutropenia (rare)

Indications

- **Odontogenic infections! – ex. periodontitis, periodontal abscess**
- Osteomyelitis
- Aspiration pneumonia, lung abscess
- Polymicrobial abdominal infections (in combination with antibiotics active against Gram negative aerobs)
- Skin and soft tissue infections (diabetic foot, gangrene)
- Toxic shock syndrome

Streptogramins

Compounds

- We use a fix combination of Dalfopristin (A) and Quinupristin (B)
- They have **synergic** effect in combination
- Inhibit protein synthesis via binding to the 50S ribosomal RNA
- Bactericid effect

Resistance

- Mechanisms:
  - Modification of the ribosomal binding site in case of Quinupristin (MLS$_B$ – Macrolides-Lincosamides-Streptogramin B)
  - Enzymatic inactivation of Dalfopristin
  - Efflux

Antimicrobial activity

- Effective **„ONLY”** against **G +** cocci
  - Streptococci sp., PRSP
  - Staphylococci sp., MRSA, VRSA
  - Enterococci sp., VRE

Resistant bacterias

- Gram-negative bacterias
- Enterococci faecalis

Pharmacokinetics

- Administered intravenously
- Do not cross blood brain barrier
- Metabolized in the liver, eliminated mainly through the biliary tract

Adverse effects -rare

- Phlebitis
- Arthralgia – Myalgia syndrome
- Inhibit CYP3A4

Indications

Severe infections caused by multiresistant Gram-positive bacterias (staphylococci, streptococci, enterococci)

Linezolid (Oxazolidinone)

Mechanism of action

- Inhibit protein synthesis
- it binds on 23S ribosomal RNA of the 50S subunit (*no cross resistancy!*)

- Primarily bacteriostatic, also bactericidal against *streptococci*

Resistance

- Modification of the ribosomal binding site

Antimicrobial activity

- Effective against **G +** cocci:
  - Streptococci sp., PRSP
  - Staphylococci sp., MRSA, VRSA
  - Enterococci sp., VRE
- Gram positive anaerobs and rods (Corynebacterias)
- Mycobacterium tuberculosis

Resistant bacterias

- Gram-negative bacterias

Pharmacokinetics

- Good oral availability, intravenous administration is also possible
- CNS effect (!)
- Metabolized in the liver
- no interaction with cytochrom P450 enzymes

Adverse effects -rare

- Mainly hematologic (thrombocytopenia, neutropenia)
- peripheral neuropathy at long administration
- Serotonin Syndrome (co-administered with serotonergic drugs)

Indications

- Severe infections caused by multiresistant Gram-positive bacterias (staphylococci, streptococci, enterococci- especially Vancomycin resistant E. faecium)

- pneumonia
- skin and soft tissued infections
- multidrug resistant tuberculosis (off label)

Chloramphenicol

Mechanism of action

- Inhibits protein synthesis via binding to the 50S ribosomal RNA
- bacteriostatic, in case of highly susceptible strains (H. influenzae, Neisseria, Bacteroides) bactericidal

Resistance

- inactivation by acetyl transferase

Antimicrobial activity

- Broad spectrum (!)
- Effective against
  - anaerobic **G +** and **G-** organisms
  - Rickettsiae

Pharmacokinetics

- Good oral availability, intravenous administration is also possible
- excellent tissue and body fluid distribution
- Metabolized in the liver by glucuronide conjugation

Adverse effects

- gastrointestinal (nausea, vomit, diarrhea), alteration of the microbial flora
- dose related reversible suppression of red cell production
- aplastic anemia (idiosyncratic reaction)
- gray baby syndrome

Indications

- severe rickettsial infection below the age of 9
- meningitis (if there is allergy to penicillins, cephalosporins)
- brain abcess (if metronidazole + cephalosporines are not effective)