This study material is exclusively for students of general medicine and stomatology in Pharmacology II course. It contains only basic notes of discussed topics, which should be completed with more details and actual information during practical courses to make a complete material for test or exam studies. Which means that without your own notes from the lesson this presentation IS NOT SUFFICIENT for proper preparation for neither tests in practicals nor the final exam.
CLASSIFICATION

1. Chemical structure
   - betalactams, glycopeptides, macrolides, amphenicols etc.

2. Microbial spectrum

3. Extent of the effect

4. Mode of the action
Modes of the action

Target sites

1.
   - G+
   - G-

2.

3.

4.
   a)
   b)
ATB therapy particularities

Selective toxicity

ATB spectrum

MIC, MBC

Postantibiotic effect

Concentration- and time-dependent effect

Resistance
Resistance - mechanisms

1.
   a)
   b)
   c)

2.

3.
Resistance - types

1. Primary
2. Secondary
3. Coupled
4. Crossed
5. Absolute
6. Relative
ATB combinations

Advantages:

1.

2.

3.

4.

Unsuitable combinations
Selection of suitable ATB agent

ATB policy in CZ
• Antibiotic centers, free and bound ATB

ATB prophylactic use
Classification

**Antibiotics**
- β-lactams
- glycopeptides
- polypeptides
  - amphenicols
  - aminoglycosides
  - tetracyclines
  - other ATBs
  - macrolides
  - ATB related macrolides
  - lincosamides

**Chemotherapeutics**
- sulphonamides
- quinolones
- pyrimidines
- nitroimidazoles
  - nitrofurans
β-LACTAMS

- penicillins
- cephalosporins
- monobactams
- carbapenems

- combination with betalactamase inhibitors
β-lactams

MofA: destruction of cell wall, PBP, transpeptidases, autolysis

• baktericidal effect
• peroral and parenteral administration

AE: low toxicity

    well tolerated

    allergic reactions

PK: widely distributed to body fluids, do not penetrate into cells
PENICILLINS

Classification: narrow spectrum
anti-staphylococcus
wide spectrum

Pharmakokinetics: well distributed to different tissues except the brain (increased in meningitis), metabolized in liver, excreted into urine
Narrow spectrum (basic) penicillins

benzylpenicillin (PEN G)
- spectrum G+
- short halftime
- for parenteral use only
- not stable against \( \beta \)-lactamases
- depot forms: prokainpenicillin, benzathinpenicillin

fenoxymethylpenicillin (PEN V)
- for peroral use
- respiratory tract infections and other infections evoked by G+ microbes:
  - streptococci, pneumococci, meningococci, actinomycosis, anaerobic infections (gas gangreene), syphilis, borreliosis
Anti-staphylococcus penicillins

- stable against β-lactamases
- *S. aureus* and streptococcal infections
- basic penicillins resistant infections
  
  cloxacinilin

oxacinilin

- methicillin, dicloxacillin, flucloxacillin
Wide spectrum penicillins

- wider spectrum against G-: enterobacteria (E.coli, Salmonella spp., Shigella spp., Proteus), Haemophilus spp., Enterococcus spp.

aminopenicillins

- ampicillin
- amoxicillin
- otitis media, sinusitis, meningitis, H. pylori

carboxypenicillins

- ticarcillin
- only in comb. with β-lactamase inhibitors

ureidopenicillins

- piperacillin
- serious infections
- combination with aminoglycosides

against P. aeruginosa
Potentiated penicillins

Combination with β-lactamase inhibitors

- **Clavulanic acid** → co-amoxicillin + amoxicillin
- **Sulbactam** → i.e. sultamicillin
- **Tazobactam** → i.e. co-piperacillin

- protections against some types of β lactamases
- co-amoxicilin – drug of choice in otitis media and sinusitides
CEPHALOSPORINS

- more stable against β-lactamases
- classified into 4 generations with regard to their spectrum: increasing G-, decreasing G+ sensitivity

AE: allergy often crossed with penicillines (5 - 10%)

GIT dysmicrobia

disulphiram reaction

changes in the blood counts

Pharmacokinetics: 1st and 2nd generation as in penicillins, 3rd and 4th generation more variable
Cephalosporins

**I\(^{st}\) generation**

- **cefazolin**
- **cefalotin**

\{parent.\}

- **cefalexin**
- **cefadroxil**

\{p.o.\}

- **G+ cocci** (*staphylococci, streptococci*)
- **G-**: *E. coli, Proteus, Klebsiella, Neisserie*, other G- are usually resistant (e.g. *haemophilus*)

**I**: S. aureus infections, prophylaxis in surgery

**II\(^{nd}\) generation**

- **cefuroxim – parent.**
- **cefuroxim axetil**
- **cefaclor**

\{p.o.\}

- wider spectrum against G+ i G- : *H. influ.*, *enterobacterias, Neisseria, Proteus, E. coli, Klebsiella, Bran. catarrhalis, anaerobes* and *B. fragilis*.
- less effective against *S. aureus* than **I\(^{st}\) generation**
Cephalosporins

**III**\(^{rd}\): ceftriaxon  
  cefotaxim  
  ceftazidim  
  cefoperazon (+ sulbaktam)  
  - *enterobacterias*, partially *pseudomonades*  
  - more stable against β-lactamases, higher efficacy (the best for G-)  
  - some agents cross BBB!!!!

**IV**\(^{th}\): cefepim  
  cefpirom  
  - the widest spectrum  
  - *G+ and G- bacteria* (*no anaerobes*)  
  - high stability against β-lactamases, longer half life
MONOBACTAMS
aztreonam
• resistant against β-lactamases
• narrow spectrum
• aerobe G- bacilli
I: in the past sepsis, abdominal infections
today pseudomonas respiratory infections

CARBAPENEMS
• imipenem + cilastatin
• meropenem, doripenem, ertapenem
- reserved for the therapy of life-threatening infections
cauased by mixed or multiresistant flora
GLYCOPEPTIDES

**MofA:** cell wall synthesis inhibition – binding to pentapeptide precursor
- bactericidal
- resistance, VRE

**I:** parenteral – reserve ATB for the serious, resistant G+ infections, local (p.o.) intestinal infections – not absorbed from GIT

**AE:** zarudnutí (red man syndrome)
- ototoxicity
- nephrotoxicity
- **vancomycin**
- **teicoplanin**
POLYPEPTIDES

polymyxin B, colistin (polymyxin E) – G-
MofA: disrupts the plasma membrane by its detergent activity
• toxic after systemic administration = local use (eye infections, ORL, GYN, intestinal decontamination)

bacitracin – G+
MofA: interferes with the cell wall metabolism
• local administration in combination with neomycin, nystatatin or glucocorticoids
AMPHENICOLS

chloramphenicol, tiamphenicol, florphenicol

**MofA:** protein synthesis inhibition, binds to 50S ribosomal subunit, wide spectrum

**Pharmacokinetics:** lipophilic, well absorbed from GIT, widely distributed to tissues and brain, glucuronated in liver, excreted into urine

**I:** is not a drug of choice!

- bacterial meningitis, typhus and paratyphus, serious pneumonia (abscessing forms), anaerobic and mixed flora infections, abdominal and serious invasive haemophilus infections

**AE:** myelosuppression

  a) reversible

  b) irreversible – aplastic anemia

  grey baby syndrome

  neurotoxicity

  • 2% chloramphenicol spirit – obsolete in the acne treatment
TETRACYCLINES

**MofA:** proteosynthesis inhibition – reversible binding to 30S ribosomal subunit

**Pharmacokinetics:** creates unabsorbable complexes with cations in GIT, lipophilic, widely distributed, high conc. in bile → therapy of biliary tract inf., enterohepatic recirculation

**I:** respiratory and urinary tract infections, boreliosis, syphilis, gonorrhea, ureaplasma, leptospirosis, chlamydiosis, mycoplasmosis, acne (minocycline)

**Primary resistant strept. + staph.**!

**AE:** disrupts tooth enamel and bone matrix – interfere with growth → CI in children and in pregnancy
  - phototoxicity
  - dysmicrobia – GIT disturbances, vaginal dysmicrobia

- tetracycline, doxycycline, minocycline

**ATB related to tetracyclines**
- tigecycline
- glycylcyclin ATB for the therapy of resistant infections, i.v. administration
MACROLIDES

**MofA:** reversible binding to 50S ribosomal subunit

**Pharmacokinetics:** CYP3A4 inhibitors (strongest erythromycin, clarithromycin)

**Spectrum:** G+ G- microbes (campylobacters, legionella sp., *Toxoplasma gondii, H. pylori*)

- increase in resistance in streptococci in the last years
  crossed resistance – MLSB phenotype

**AE:** GIT intolerance

  allergies

  prokinetic effect (erythromycin) - diarrheas

- **erythromycin**

- **spiramycin, roxithromycin, clarithromycin,**
ATB related to macrolides

Azalides
- azithromycin – tkáňově orientovaná FK

Streptogramins
- quinupristin
- dalfopristin

Ketolides
- telithromycin

Oxazolidinones
- linezolid
LINCOSAMIDES

**MofA:** proteosynthesis inhibition – reversible binding to 50S ribosomal subunit

**Pharmacokinetics:** well penetrates to teeth and bones

**I:** alternative treatment of beta lactams hypersensitivity, prophylactic use in stomatology, gynecologic infections (can be used in pregnant)

**AE:** - minimal toxicity
   - crossed-resistance with macrolides

- clindamycin, lincomycin
AMINOGLYCOSIDES

**MofA:** proteosynthesis inhibition, irreversible binding to 30S ribosomal subunit (bactericidal effect)
- postantibiotic effect and concentration-dependent effect

**I:**
- sepsis
  - serious uroinfections (pyelonefritis)
  - lower respiratotry infections (in combination)
  - orthopedic and surgical infections (postoperative)

**AE:** nephrotoxicity
  - ototoxicity
  - ↑↑ doses - neurotoxicity

- parenteral: streptomycin, gentamicin, amikacin
- topical: tobramycin, kanamycin, neomycin
Other ATB

Rifampicin
- ansamycin wide spectrum agent
- baktericidal – inhibits synthesis of bacterial nucleic acids (RNA)
- antituberculotic agent
AE: orange color of urine, tears, saliva, sweat

Fusidic acid
- primáry bactericidal
- inhibits synthesis of cell wall
- against staphylococci

Antibiotics for local and topical administration
• mupirocin
• bacitracin
• neomycin
• fusafungin