ANTIBIOTICS

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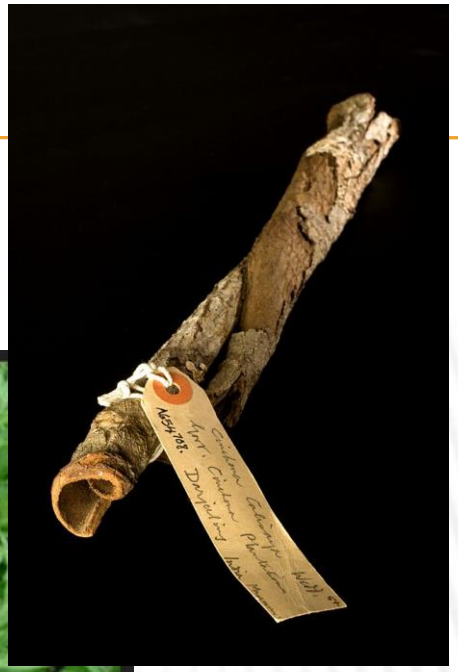
Infekční klinika 2. LF UK
Praha
X/2018

History

- **All living organisms produce substances that improve chance for their surviving**
- **Substances with antiinfetive effect were used for thou sands years**

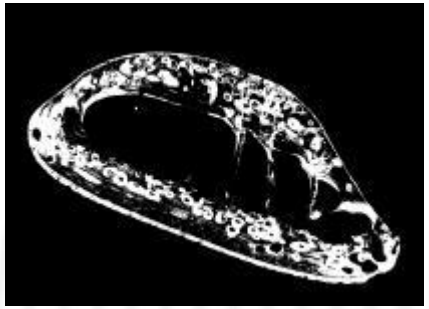
Historie



- **Superstition**
  - **Horn from unicorn**
- **Malaria**

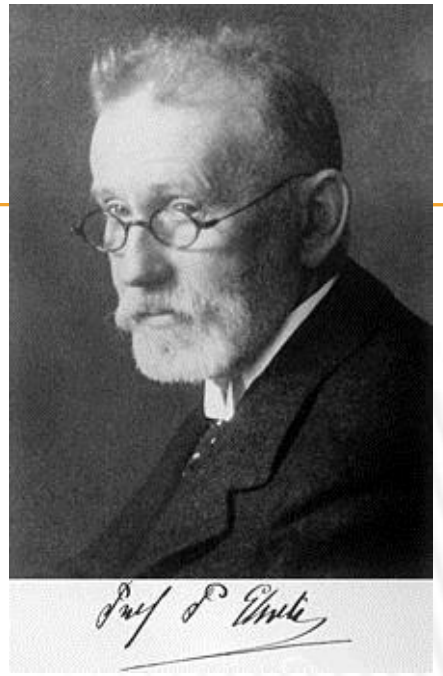
  Cinchoma
  - **Artemissins**

- **Nubia – beer with TTC, depots in bones**

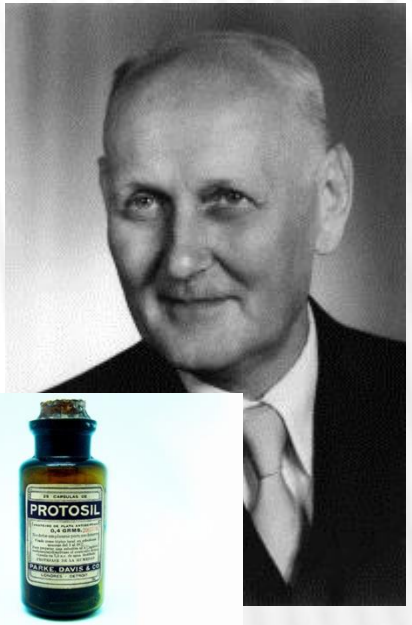


History


Das neue **Ehrlich**'sche
Syphilis-Heilmittel
bringen wir Mitte Dezember 1910 unter der geschützten Marke
„SALVARSAN"
in den Handel.
Wegen Bezuges von „Salvarsan" bitten wir die Herren Apotheker, sich ausschliesslich an die Grossdrogen-Handlungen wenden zu wollen.
Farbwerke vorm. Meister Lucius & Brüning,
Hoechst a. M.



- **1910** salvarsan — P. Ehlich, Hata
  - Arsen, syflilis
- **1932** prontosil — G. Domagk
  - sulfonamidy
- **1928/41** penicillin — Fleming, Chain, Florey
- **1944** streptomycin — Waksmann
- **1945** cephalosporin C — Brotzu
- **1947** chloramphenicol — I. Ehrlich
- **1952** erythromycin — Guire
- **1955** vancomycin — Cormig
- **1957** kanamycin — Umezawa
- **1960** ampicillin
- **2000** linesolid



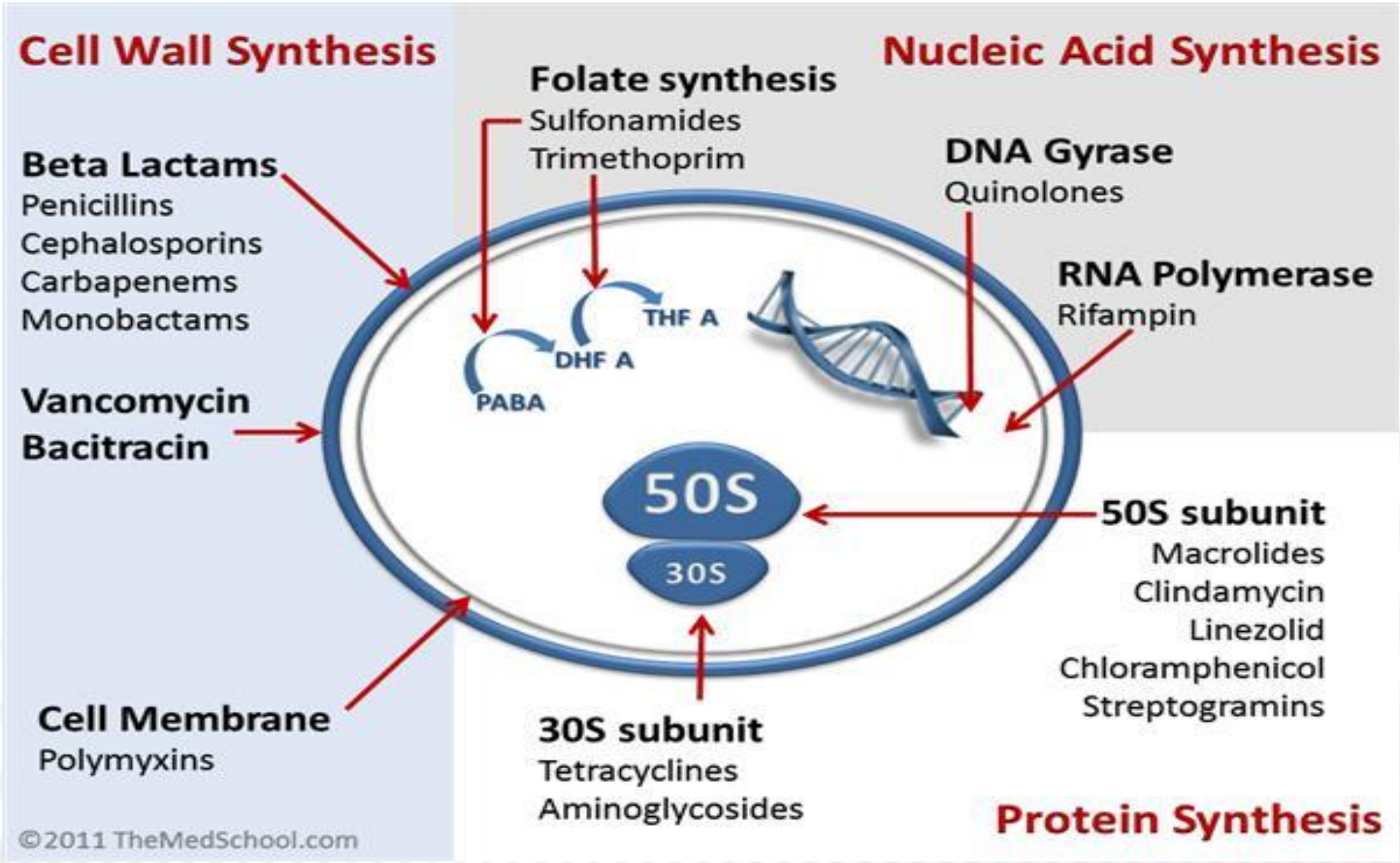
Characteristic of antibiotics

- **Antibiotics**
  - **Natural products form microorganisms**
  - **Bactericidal**
  - **Dosage milligrams**
  - **Toxicity low**
- **Chemotherapeutics**
  - **Chemical synthesis**
  - **Bacteriostatic**
  - **Dosage grams**
  - **Toxicity relatively high**
- **Difference is minimal – semisynthetic ATB**

General characteristic of antibiotics

- **Preparation**
  - Nature products, chemical synthesis
- **Effect**
  - bactericide, bacteriostatic
- **Spectrum**
  - Narrow x broad spectrum
- **Most important effect**
  - Antistaphyloccoci, antipseudomonas, anti-TBC …
- **Chemical structure**
  - peptide, glycopeptide, heterocyklic …
- **Solubility**
  - Hydrophilic – do cross plasmatic membrane, ineffective against intracel. pathogens, low bound to plasma proteins, renal elimination - beta-lactams, glycopeptides, aminoglycosides
  - Lipophillic cross cell membrane, effective againsti IC pathoges, frequent metabolism in liver: fluorochinolons, macrolides, TTC, lincosamides
- **Target place**
  - Bacterial cell wall, membrane, bacterial DNA, disturbance protein synthesis and/or bacterial DNA …
- **Way of application**
  - Oral, parenteral, local, inhalational, intrathecal, in abscess and foci of infection …

General characteristic of ATB – point of the effect



https://www.orthobullets.com/basic-science/9059/antibiotic-classification-and-mechanism

RATIONAL ATB THERAPY

- **Ekonomicaly effective**
- **Maximal antimicrobial effectivity**
- **Maximal clinical effectivity**
- **Minimum adverse events**
- **Maximal epidemiological safety**
- **Maximal reduction of resistance occurance**
- **Early**
- **Optimally dose rate**
- **Minimal treatment length**
- **Minimisation of toxicity**

ANTIBIOTIC STEWARDSHIP - ABS

- **Management, control**
- **Initial ATB treatment spontaneous, often inappropriate**
- **1996 firstly used term stewardship**
- **2014 first CDC guidelines**
- **2017 central organs EU released the first obligatory recommendations**
  - **„ … for prudent using of antimicrobial substances …“**
- **ABS includes scanning:**
    - **ATB prescribing from point of view election, dosing, lenght of treatment and price**
    - **Appearance of bacterial nosocomial rezitance**
    - **Indication in ATB choice**

Performs infectologist, microbiologist, pharmacologist …

Classification of ATB

- **Inhibition of the cell wall**
  - **Beta lactams**
  - **Glycopeptides**
  - **Bacitracin**
- **Lyssis of the cellular membrane**
  - **Lipopeptides**
  - **Polypeptides**
- **Inhibition of the proteosynthesis**
  - **Macrolides**
  - **Lincosamides**
  - **Oxazolidinoides**
  - **Aminoglykosides**
  - **Tetracyclines**
  - **Amphenicols**
  - **Streptogramines**

Classification of ATB

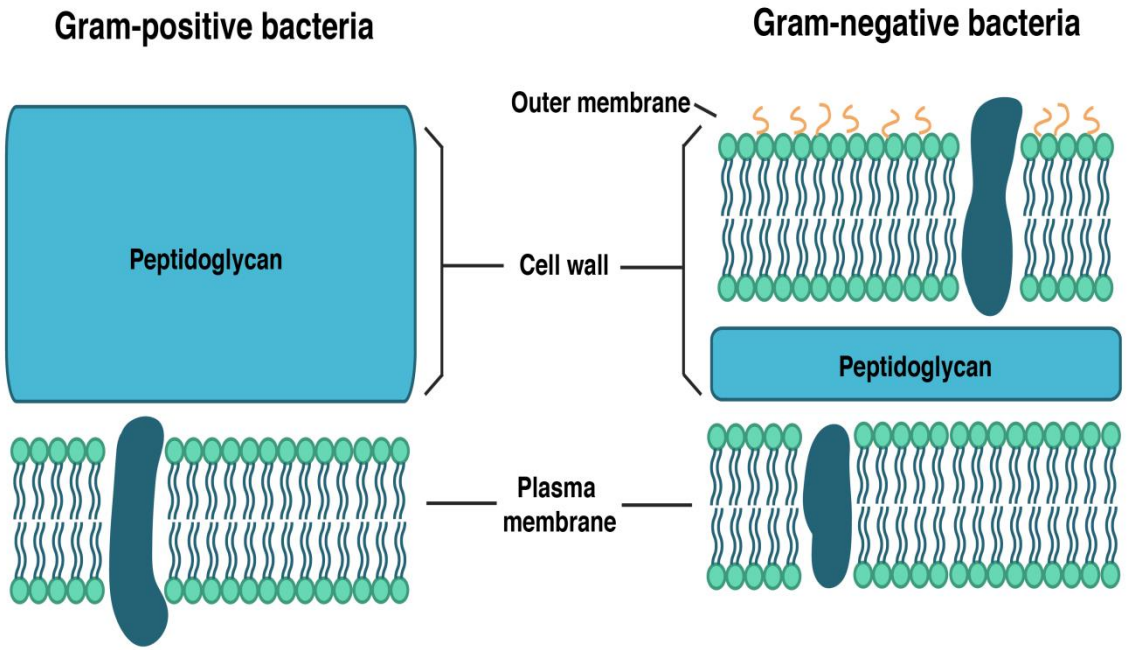
- **Inhibition of the nucleic acid synthesis**
  - **Chinolones**
  - **Ansamycines**
- **Disturbances of bacterial cell metabolism**
  - **Sulfonamides**
  - **Pyrimidines**
  - **Imidazols**
  - **Nitrofurans**

ATB blocking cell wall synthesis

- **Beta-lactams**
  - **Penicillins**
  - **Cephalosporins**
  - **Inhibitors of beta-lactamases**
  - **Monobactams**
  - **Carbapenems**
  - **Glykopeptides and lipoglykopeptides**

ATB blocking cell wall synthesis

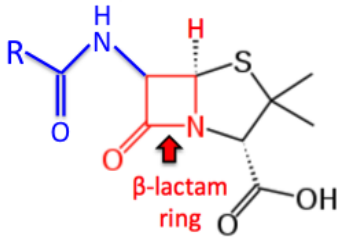
- **Peptidoglycan**
  - **Essential**
  - **Highly conservative**
  - **Open to extracellular surrounding**
  - **Lacking alternative in human cells**



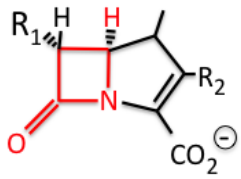
http://www.onlinebiologynotes.com/bacterial-cell-wall-structure-composition-types/

Beta-lactam ATB

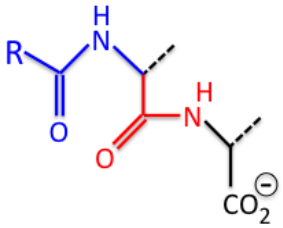
- Beta-lactam ring
- Mechanism of the effect
  - Binding on the PBP
  - Inhibition of transpeptidation in peptidoglycan synthesis
  - Bactericidial effect
- Difference of beta-lactams
  - PBP affinity in different bacteria
  - External membrance penetrating
  - Beta-lactamase resistance
  - Allergy – hapten
- Using
  - Acute and severe infections
    - In blood and well vascularized tissues
  - Well tolerated
  - To keep dosage !!
  - Less effective in:
    - Chronic infection
    - Skin
    - Intracellular pathogens



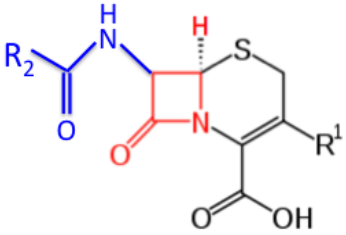
penicillins



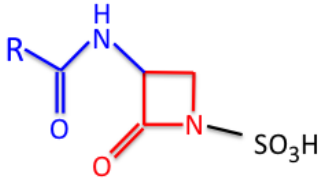
carbapenems



acyl-D-Ala-D-Ala (cell wall precursor)



cephalosporins

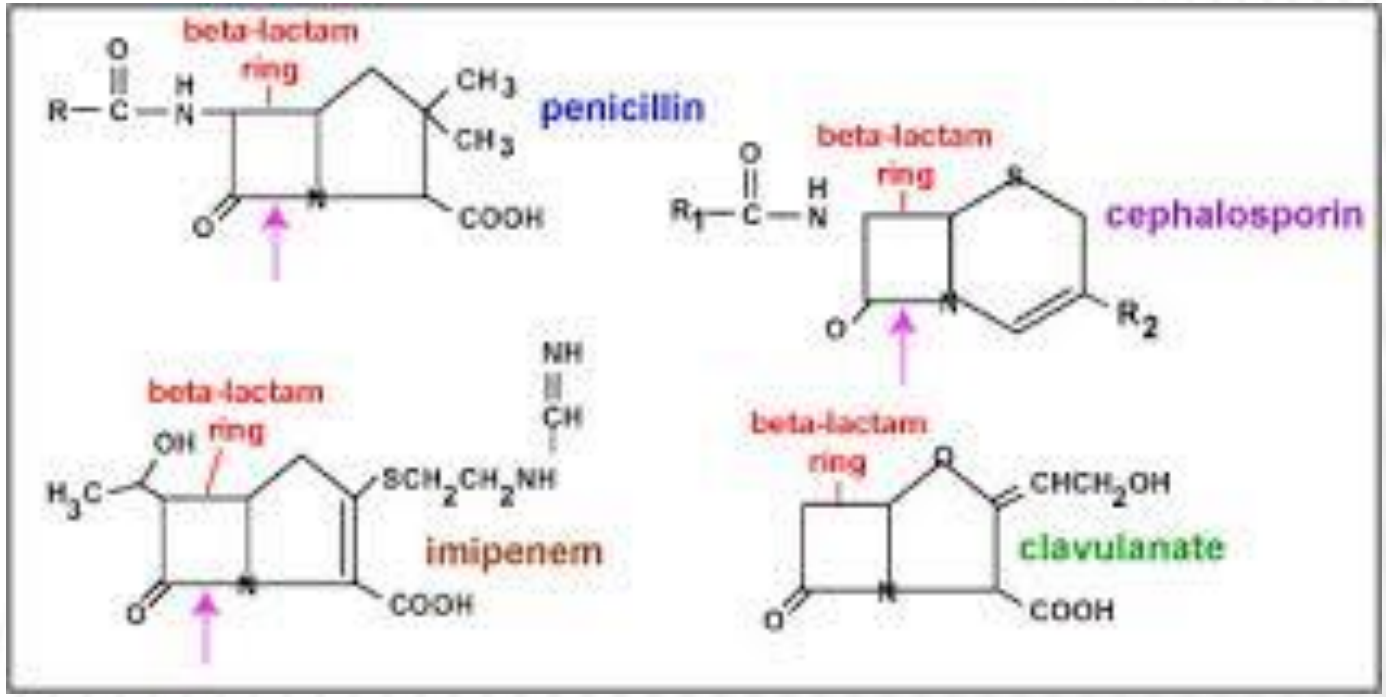


monobactams

https://www.google.cz/search?newwindow=1&tbm=isch&q=beta+lactams&spell=1&sa=X&ved=0ahUKEwj2xtmBq5ndAhWLalAKHbULChMQBQg7KAA&biw=1394&bih=663&dpr=1.25#imgrc=2C9krSDvRLbZ2M:

Beta-lactam ATB

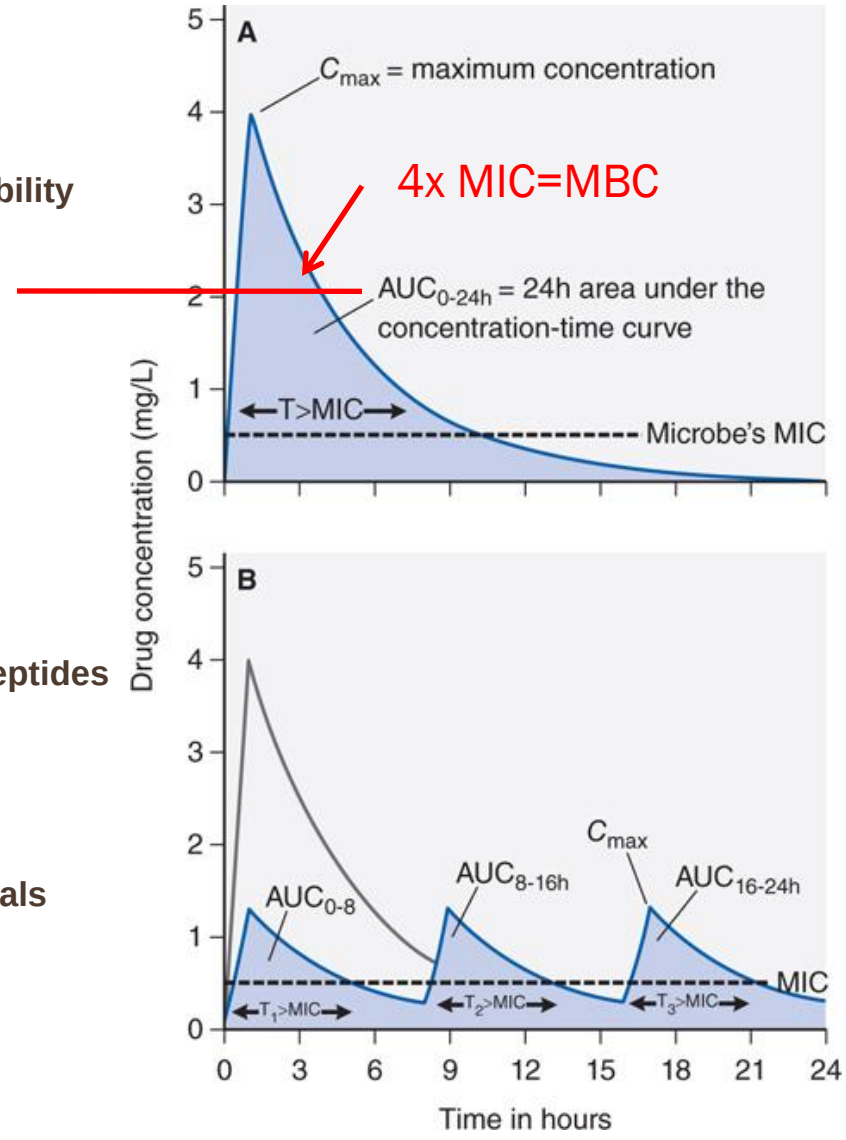
- **Beta-lactamases**
  - **Enzymes splitting beta-lactam ring**
  - **Hundreds, complicated classification**



https://www.google.cz/search?newwindow=1&biw=1394&bih=663&tbm=isch&sa=1&ei=N1eKW9PfB4jSwQK89oQw&q=beta+lactamases&oq=beta+lactamases+&gs_l=img.1.1.0i19k1j0i30i19k1j0i5i30i19k1l5.12820.14392.0.16765.13.8.0.0.0.0.450.898.0j1j1j0j1.3.0....0...1c.1.64.img..11.2.618...0i8i30i19k1.0.EleRylqd-Pk#imgrc=iG2bFMkMsUpqPM:

Beta-lactam ATB

- **Characteristics – time above MIC**
- **Spectrum of effect differs much**
- **Resistance – more mechanisms**
  - **Inactivation ATB, change of the frequency permability of porins …**
- **Pharmacokinetics**
  - **Hydrofillic, distrib. volume = just about ECF**
  - **T1/2 30 min - 8 h.**
  - **Excretion - renal**
  - **Goall only some (cefoperazon, ceftriaxon)**
  - **Practically none postATB effect**
- **Undesirable effect**
  - **Nontoxic; allergy, clostridium difficille diarrhoe**
- **Drug interaction**
  - **Synergy with aminoglykosides sometime glykopeptides**
  - **Combination with fluorochinolones indiferrent**
  - **With bacteriostat. ATB st. antagonistic**
- **Usage**
  - **Acute infection; all patients;**
  - **Dependence on high concentration – short intervals**
  - **Ineffective in non dividing bacteria**
  - **Not in chronic infections**



https://basicmedicalkey.com/general-principles-of-antimicrobial-therapy-3/

Penicillins

- **Basic PNC**
  - **Penicillin G (benzylpenicillin)** — **iv.**
  - **Procain PNC, benzathin PNC** — **im.**
  - **PNC V, (penamecillin)** — **po.**
- **Anti-staphylococcus PNC**
  - **Oxacillin**
    - **Methicilin, cloxacilin - similar effect**
- **Amino PNC**
  - **Ampicillin, amoxicillin** — **i.v., po.**
- **Anti-Pseudomonas PNC**
  - **Piperacillin, carbenicillin, ticarcillin** — **iv.**
- **Next unclassified PNC**

Penicilin G

- **Antibacterial spectrum**
  - ***Str. pyogenes, pneumoniae (different sensitivity), Enterococcus fecalis (high concentration)***
  - ***Bacillus anthracis, Erysipelothirx spp.,Listeria monoc. Corynebact spp.***
  - ***N. menigitidis, Pateurella multocida***
  - ***Acinetobacter, Clostr. perfingens …***
  - ***Trep. pallidum, Leptospira, Borrealia …***
- **Resistance**
  - **S. aureus, Str. pneumoniae, N. gonorh. G – rods**
- **Pharmacokinetics**
  - **i.v.; tissue penetration limited incl. CNS;$T_{1/2}$ = 30 min.; excretion by kidney**
- **Undesirable effects – allergy**
- **Drug interactions – minimal**
- **Recommended dosage – 60-80 MIU/D.**
- **Clinical using:**
  - **Narrow spectrum – but here very effective**
  - **Necessity of frequent application – quick elimination**
  - **Therapy of well perfused tissues**
  - **Some prirlly sensitive bacteria can be resistant (*B. anthracis, Eikenella corrodes, Str. pneumoniae)***
  - ***Inappropriate for intracelullar and chronic infections***

Depot forms of penicillin G

- **Procain-benzyl PNC**
  - For treratment of sensitive infections is more effective than oral PNC
  - Str. pharyngitis, diphteria, purples, skin anthrax
  - Hoigné a Nicolau syndrome
  - Str. pyogenes, pneumoniae
  - Dosing 1-2x 1,2 MIU/24 h.
- **Benzathin-PNC**
  - Long-term leaking from depo – days – 2-3 weeks
  - Possible to combine with proc. PNC
  - Therapy of syphilis prim.
  - Prophylaxis of streptococci inf.
  - Prophylaxis rheumatoid fever
  - Dosing 1x 1,2 MIU/14-21 days

Penicillin V

- **Characteristic**
  - **phenoxymethylPNC; acidostabile, suitable for oral treatment**
- **Spectrum**
  - **Only for microbes with very high sensitivity**
- **Undesirable effects – very good tolerance; allergy, GIT**
- **Drug interactions - minimal**
- **Recommended dosing 3 – 4 times per day**
  - **50 mg V PNC = 400 000 IU PNC**
  - **Adults 3 – 4,5 – (6) MIU/den**
  - **Children 50 – 100 000 IU/den**
- **Using**
  - **Narrow spectrum = selective indications**
  - **Minimum of undesirable interactions**
  - **Low antibacterial effectivity and short $T_{1/2}$**
  - **Str. pyogenes (tonsilopharyngitis, scarlet, impetigo)**
  - **Prophylaxis of str. infections (rheumatic fever)**
  - **Not suitable for pneumococci nor mixed infections with unclear etiology**

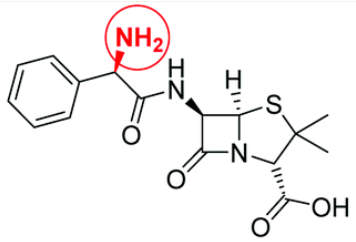
Oxacillin - methicilin

- **Characteristic**
  - The only preparation of anti-staphylococci PNC registered in ČR
  - Resistant against staphylococci penicillasis – not against PNClasis of G - bacteria
- **Spectrum of activity**
  - Similar to PNC G slightly lower effectivity
  - Low effect against listerias, corynebacterias a pneumococci
  - Against enterococci - ineffective
- **Pharmacokinetic**
  - Poor resorbtion from GIT (33 %) – oral preparation is not on market
  - Kinetics similar to PNC G (i.v. 4 times daily)
- **Adverse events**
  - Well-tolerated similar to other PNCs
  - Potentially hepatotoxic (metabolisation in liver)
- **Recommended dosing**
  - Mild infections 250 – 500 mg each 4 – 6 h.
  - Severe inf. 1 – 6 – (12) – (18) g / day

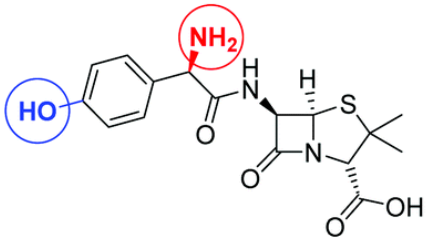
Oxacillin - methicillin

- **Clinical using**
  - **Acute staphylococci infections of blood or well oxygenated tissues**
  - **Endocarditis, sepsis, osteomyelitis, arthritis, mastitis, other infections of soft tissues**
  - **Prophylaxis in orthopedic, neurosurgical, vessel surgery**
  - **Not suitable for treatment of chronic or superficial infections, nor mild infections (because lack of oral form)**
  - **Not suitable for treatment if infections with massive production of toxins (Panton-Valentine leucocidine, toxin of the toxic shock) – a risk of quick releasing of toxins; better ATB which inhibit proteosynthesis (clindamycin, linezolid)**

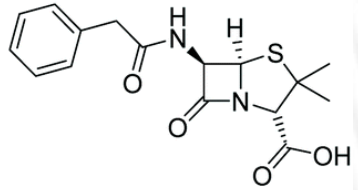
Ampicillin - amoxicillin



Ampicillin



Amoxicillin

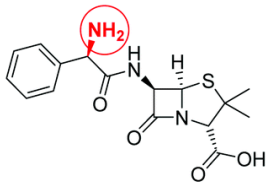


Benzylpenicillin

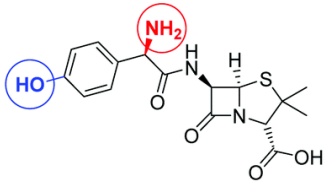
- **Characteristic**
  - **Amox – a hydroxyl added**
  - **The only change – perfect p.o. absorption**
- **Spectrum of activity**
  - **Similar to PNC G**
  - **Moreover G – rods**
    - **hemophilli, *E.coli, Salmonella enterica, Shigella* spp. *Proteus mirabilis***
    - **More effective against *Enterococcus fecalis a Listeria monoc.***
- **Resistance**
  - **Not resistant against betalactamases – combined drugs with inhibitors**
- **Pharmacokinetics**
  - **Both of them are similar instead of resorbtion oral**
  - **Double T1/2 comparing with PNC G; dosing each 6-8 hours**
  - **High concentration in urine**
  - **Meaningful enterohepatal turnover**

https://www.google.cz/search?newwindow=1&biw=1394&bih=663&tbm=isch&sa=1&ei=O2uKW_j2EImkwAL7vp9g&q=ampicilin+amoxicilin+difference&oq=ampicilin+amoxicilin+difference&gs_l=img.3...20039434.20063370.0.20064195.40.26.0.10.10.0.187.1918.22j2.24.0....0...1c.1.64.img..8.21.926.0..0j0i19k1j0i67k1j0i30k1j0i30i19k1j0i10i30i19k1j0i5i10i30i19k1j0i24k1.0.ic29wG1lHss#imgrc=n2dYjGaikyczbM:

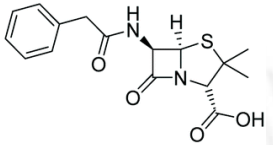
Ampicillin - amoxicillin



Ampicillin



Amoxicillin



Benzylpenicillin

- **Adverse events**
  - **Induction of clostridial colitis**
  - **Allergy**
  - **Aggregates with heterophyllic antibodies**
    - **exanthema – mononucleosis inf., leukemia; allergy on antibodies complexes, different type than in PNC**
- **Drug interaction – rare**
- **Clinical experience**
  - **purulent meningitis, sepsis, tonsilopharyngitis, sinusitis, helicobacter, urinary tract infection**
- **Recommended dosing**
  - **100 – 200 – 400 mg/kg/day**

https://www.google.cz/search?newwindow=1&biw=1394&bih=663&tbm=isch&sa=1&ei=02uKW_j2EImkwAL7vp9g&q=ampicilin+amoxicilin+difference&oq=ampicilin+amoxicilin+difference&gs_l=img.3...20039434.20063370.0.20064195.40.26.0.10.10.0.187.1918.22j2.24.0....0...1c.1.64.img..8.21.926.0..0j0i19k1j0i67k1j0i30k1j0i30i19k1j0i10i30i19k1j0i5i10i30i19k1j0i24k1.0.ic29wG1IHss#imgrc=n2dYjGaikyczbM:

Ampicillin - amoxicillin

- **Using**
  - **parenteral ampi i amox with the same effect**
  - **Orally only amoxicillin**
  - **aminoPNC without beta-lactamase inhibitors:**
    - **listeria, *Enterococcus fecalis,* some hemophilli**
  - **Amoxicillin - sometimes is used in infections where the basic PNCs would be sifficient, the better GIT resorbtion is used in infections is less complicated infecctious but the better pharmacokinetics is used - GIT resorption, longer T1/2**
    - **streptococci (puerperal sepsis)**
    - **pneumococci (mesotitis, sinusitis …)**
    - **spirochetes (lyme bor.)**
    - **actinomycetes**
  - **combination amox + claritromycin – community pneumonia**
  - **Contraindication – in EBV mononucleosis**

Amoxicillin/clavulanic acid – co-amoxicillin

- **Characteristic**
  - **aminoPNC+ inhibitor beta-lactamase – clavulanic acid in proportion ½ to 1/16**
- **Spectrum**
  - **As aminoPNC +**
    - ***S. aureus, E. coli, Salmonella enterica, N. gonorhoae, H. influenzae, Shigella spp., Moxarella carrhalis, Paterella multocida***
- **Pharmacokinetics**
  - **Reduced dosis due to clavulanate – GIT intolerance, with food**
- **Klinical experience**
  - **As amoxicillin + necessity to cover bate-lactamase producing microbes**
- **Dosing**
  - **375 – 625 – 1000 mg/8 hod**
- **Using**
  - **Urinary and biliary tract infections**
  - **Sinusitis, otitis, bronchitis, pneumonia**
  - **Acute mixed infections of skin, bite wounds (possible *Pasteurella multocida*)**
  - **Surgical infections of GIT and urinary tract**
  - **It is not recommended in high susceptible pathogens – strepto, enterococ., spirochetes, listeria, actinomycetes**
  - **Not recommended in hospital infections**

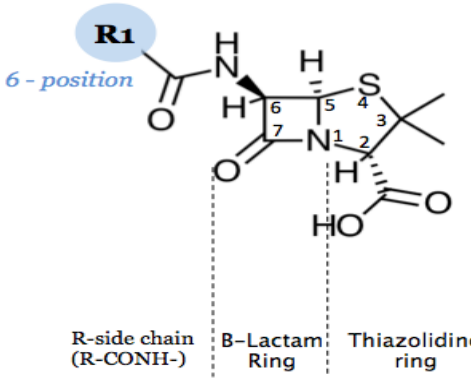
Ampicillin/sulbactam – co-ampicillin

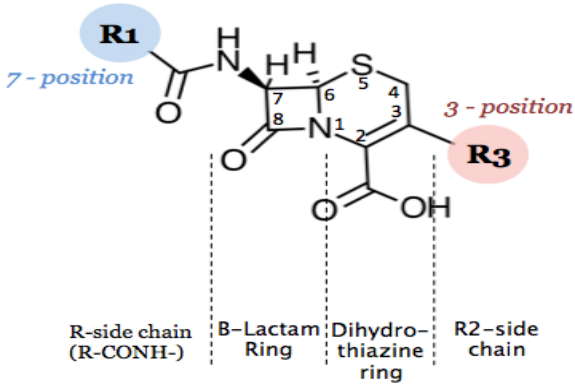
- **Characteristics**
  - **co-ampicillin – for i.v. application**
  - **Sultamicillin – p.o. application**
    - **Molar ratio 1/1; adverse events reduce doses - sulbactam**
  - **Features similar to aminoPNC resp. protected aminoPNC**
- **Dosing**
  - **Co-ampi 1g ampi + 500 mg sulbactam**
    - **Adults 1,5 – 3 g 3 - 4 times daily**
    - **Children 150 mg/kg/day**
  - **Sultamicillin 2-4 tbl - 375 mg each 12 h.**
    - **Children up 30 kg 25-50 mg/kg/day each 12 h.**
- **Using**
  - **Similar to co-amoxicilin**

Piperacillin, piperacillin/tazobaktam

- **Characteristics**
  - Most powerfull from anti-protipseudomonas PNC
  - Single in Czech market (ticarcillin/clavulanate)
- **Spectrum**
  - Same as co-aminoPNC nad moreover:
  - Higher effectivity against G- bacteria and anaerobs
    - *Proteus vulgaris, Citrobacter, Enterobacter, Morganella, Providencia, Serratia*, *Pseudomonas aeruginosa*
    - Anaerobs: peptostr., fusobakterias, klostridias, often also *Bacteriodes fragilis*
- **Resistance – due to beta lactamases**
- **Pharmacokinetics**
  - Low resorbtion from GIT
  - Very similar to other PNCs
- **Adverse events – other PNCs**
- **Clinical experiences**
  - Severe infections - nosocomial pneumonia, abdomen and urinary inf., interstitial inf., decubital sepsis, febrile neutropenia
- **Recommended dosing**
  - Adults 4/0,5 g each 6-8 h.
  - Děti 80/10mg/kg each 6 h. or 100/12,5 mg each 8 h.
- **Using**
  - Very board spectrum – suitable for above mentioned infections with suspected G+ and G- bact.
  - In clearly proven G- bacteria is better to use cephalosporins of the 3rd generation
  - Combination with aminoglykosides is advantageous

Cephalosporins





Penicillins

Cephalosporins

EBM CONSULT

- **Characteristics**
  - With PNC the most frequently used ATBs
  - Isolated decades of molecules
  - Registered 13 in Czech, 17 in USA
- **Systematic**
  - **1st generation**
    - Streptococci incl. pneumcocci, staphyloc. and others G+
    - Spectrum of G- has reduced
    - Some resistance against stph. penicillase
  - **2nd generation**
    - G+ as 1st generation and moreover:
    - Common G-: *E.coli, Klebsiella pn., Heamophylus in., Moxarella cat., N. gonorhoae*
    - Resistant against simple beta-lactamases
  - **3rd generation**
    - Comparing to the 2nd generation 10 times higher effectivity against G-
    - Effectivity against G+ weeker than 1st and 2nd gen.
    - Sometimes classified into groups:
    - Basic cephalosporins (3 gen)
    - Anti-pseudomonas ceph.
    - Cephalosporiny protected by inhibitors of beta-lactamases
  - **4th generation**
    - G+ as 1st gen. + G- as 3. generation
  - **(5th) generation cephalosporins effective against MRSA or pseudomonas**
    - But, they differe in activity against others G- microbes

http://east.keywesthideaways.co/cephalosporins/

Cephalosporinsy – general features

- **Characteristics**
  - **Mostly hydrophile molecules**
  - **Mostly low resorbtion from GIT**
  - **Good penetration in biological fluids**
  - **Low penetration into cells; low distribution volume = ECT**
  - **Mostly short biological half-life (besides ceftriaxon)**
  - **Very good toleration – low toxicity**
  - **Low allergization**
  - **Mostly excreted by kidney**
- **Spectrum !!**
  - **Cephalosporins 1.- 4. generation <u>are not effective</u> against (among others):**
    - ***Enterococcus spp***
    - **MRSA**
    - ***Listeria monoc.***
    - ***Highly resistant* PNC rezistant pneumococci**
    - **Anaerobic bacteria**
    - **ESBL + enterobacterias**

Cephalosporins - 1st generation

- **Characteristics – mostly it is an alternative of other ATB (PNC)**
- **Spectrum**
  - **Not active against hemophillus, moxarella, MRSA stph.**
- **Preparations**
  - **Cefazolin – the only on CZ market**
  - **Cefadroxil – p.o. the same spectrum as cefazolin**
- **Dosing**
- **Using**
  - **Infections of skin and soft tissues**
  - **Wound infection (not animal bite)**
  - **Streptoc. Infections of upper airway tract incl. sensitive pneumococci, scarlet, erysipel as an alternative of PNC, erythema migrans**
  - **Prophylaxis in surgery str. + stph.**
  - **They are not suitable – even in the case of sensitivity for treatment :**
    - **G- a MRSA inf.**
    - **Chronic infections**

Cephalosporins – 2nd generation

- **Characteristics – more meaningful drugs comparing with the first generation**
- **Spectrum**
  - **Practically as the 1st generation**
    - **Additionally: sensitive hemophilli, moxarella, MSSA stph., salmonella, proteus, *N. meningitidis***
- **Drugs**
  - **Cefuroxim i.v., cefuroxim axetil p.o.**
  - **Cefprozil very good resorbtion p.o., recommende dosing is possible to inscrease**
- **Pharmacokinetics**
  - **Cefuroxim good diffusion into CSF**
  - **Dosing**
- **Using**
  - **Acute respiratory infections**
  - **Infections of skin and soft tissues**
  - **Wound infection (except animal bit)**
  - **Strep. infection upper respir. tract and skin, erythema migrans**
  - **Are not suitable for treatment:**
    - **More severe G- inf. - better cphsp. of the 3rd. generation, gonorrhoe (low local concentration)**
    - **Chronic infections**

Cephalosporin 3rd generation

- **Characteristics – the most important drugs against G- bacteria**
- **Spectrum**
  - **The same as cefuroxim**
  - **Additionally 10 time pewerfull against G- bacteria**
  - **Low effect on G+ than 1st and 2nd generation**
- **Preparations**
  - **Cefotaxim i.v. – main drug of the group**
  - **Ceftriaxon i.v.**
  - **Cefoperazon, cefoperazon/sulbaktam i.v.**
  - **Ceftazidim, ceftazidim/avibactam i.v.**
  - **Cefpodoxim-proxetil p.o.**
  - **Cefixim p.o.**
- **Pharmacokinetics**
  - **Hydrophile molecules, distribution in ECF very good, in soft tissues inferior**
  - **Very good penetration into tissues**
  - **Short half-life except of CTX**
  - **Variable binding to blood proteins, only CTX very high**
  - **Excretion mostly by kidney, CTX biliary excretion**
  - **Very safe, low allergization**

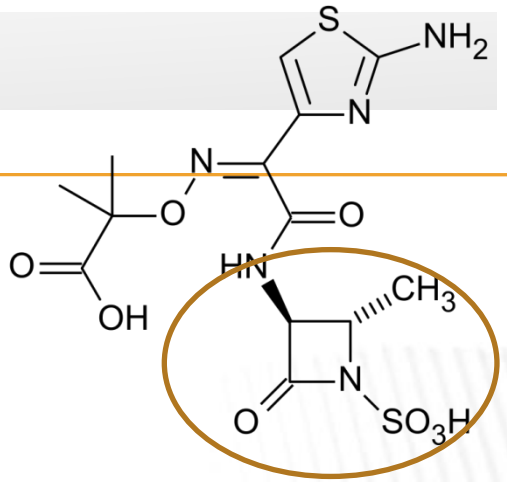
Cephalosporins – 3rd generation, cefotaxim, ceftriaxon

- **Cefotaxim**
  - The most meaningful preparation of the group
  - Good penetration in CNS when in inflammation
  - **Dosing: 1-2 g each 4-6 h. (max 12 g/day); 100-200 mg/kg/day in 3 to 6 separate dose
  - Treatment is possible potentiate by aminoglykosid
- **Ceftriaxon**
  - 90% binding on plasma proteins – small proportion of free fraction
  - Very long biological $T_{1/2}$ 6-9 h.; it can by given in one morning dose
  - Adverse events: GIT dyscomfort, phlebitis, precipitates in gall
  - It can displace other drugs from binding on plasma proteins - albumin – important in neonates (icterus of newborns), precipitates in organs when given contemporary with calcium
  - Dosing: 1-2 g/day in one dose, max 4 g/day in two doses; children 50-100 mg/kg/day
- **Clinical using**
  - Empirical treatment of severe community infections incl. sepsis, septic shock, purulent meningitis
  - Treatment of severe/complicated infections by sensitive bacteria due to high efficacy and good penetration
  - Next bacteria gonococcal arthritis, hemophillus influenzae epiglotitis, endocarditis HACEK, urosepsis
  - Salmonella osteomyelitis, severe pneumonia
  - Neuroboreliosis, neurolues
  - In the case of anaerobic coinfection – metronidazol must be added
  - Not suitable for treatment of staphylococcal inf.
  - The use of ceftriaxon:
    - The same as cefotaxim
    - Limitations above
    - Convenient in biliary inf.

Cephalosporins – 4th + 5th generation

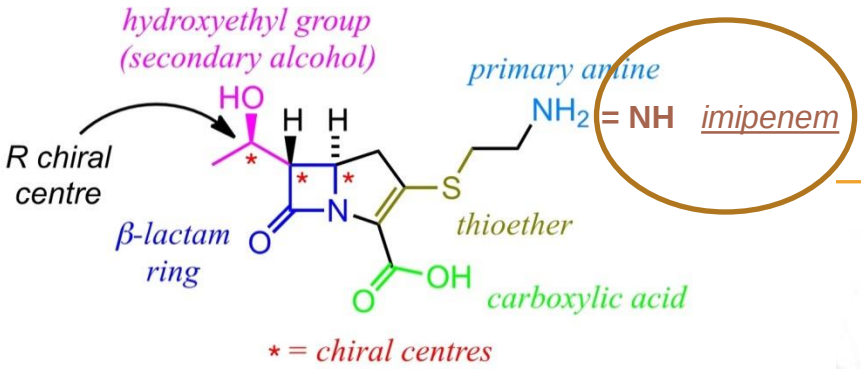
- **Cefepim**
  - **The only cephalosporin of the 4th generation registered in ČR recently**
  - **i.v.**
  - **Widest spectrum towards G+ and G- bacteria**
  - **Resistant against many beta-lactamases incl. some ESBL**
  - **Effective in comunite strains of pseudomonas, clebsiella, staphylococci MSSA**
  - **Two main indications – alternative of carbapenems**
    - **G- bacteria synthesizing ESBL type AmpC**
    - **Severe and life-threatening infections with unknown etiology**
      - **Febrile neutropenia**
      - **Mixed abdominal and gynecological infections (metronidazol added)**
- **Ceftarolin-fosamil (5th generation)**
  - **Prodrug; i.v..**
  - **Effective on stph. MRSA, effectivity on G- bacteria on the level of cephalosporins of the 3rd generation**
  - **Treatment of mixed infections with participation of MRSA**
- **Ceftolozan-tazobactam**
  - **Boosted effect against pseudomonas**

Monobactams - aztreonam



- **Beta-lactam ring solitary – not conjugated other cyclic structure**
- **Similar effect as ceftazidim – the same side chain**
- **Same spectrum – only against aerobic G- bacteria**
- **Pharmacokinetics – i.v.**
- **Adverse effect – minimal toxicity**
- **Drug interactions – minimal**
- **Dosing 3-8 g/day**
- **Using – mostly in combinations**
  - **In CR registered only for patients with cystic fibrosis for inhalational using**

Carbapenems



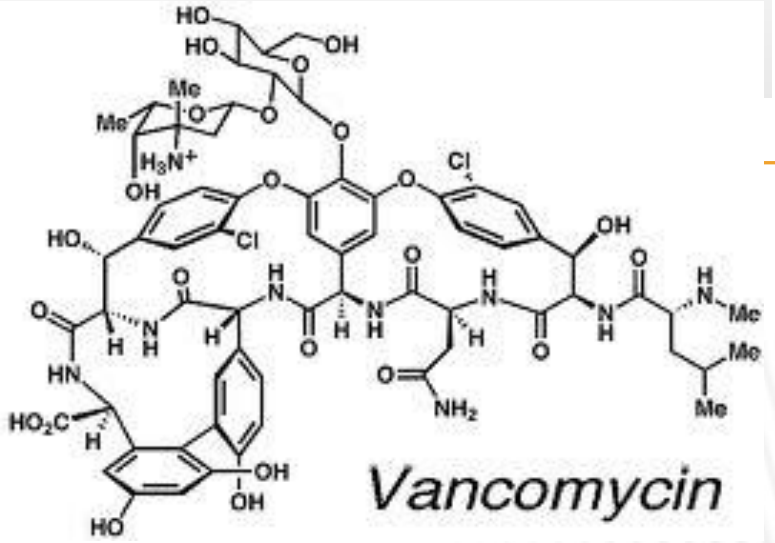
- **Characteristics**
  - Most powerful beta-lactams
  - Extremely resistant against serin beta-lactamases
  - Tienamycin the 70s – non-stable
  - Synthetic: imipenem, meropenem, ertapenem, doripenem
  - Effective against more bacterial enzymes at one time
- **Spectrum**
  - G+ i G- incl. anaerobes
- **Resistance**
  - ertapenem is not effective against pseudomonas
- **Pharmacokinetics**
  - Excretion by kidney
  - Ertapenem very high bind on plasma proteins – long T1/2
- **Adverse events**
  - Non important; rarely spasms – coud by severe
- **Drug interactions**
  - Decrease level of valproic acid – risk of seizures
- **Using**
  - Treatment of severe infections:
    - Beta-lactamase bacteria
    - Severe mixed infections by sensitive microbes - including anaerobes
  - Strongly reserve ATB
  - Not suitable for treatment of pseudomonas infections

https://www.futurelearn.com/courses/everyday-chemistry/0/steps/22316

Carbapenems

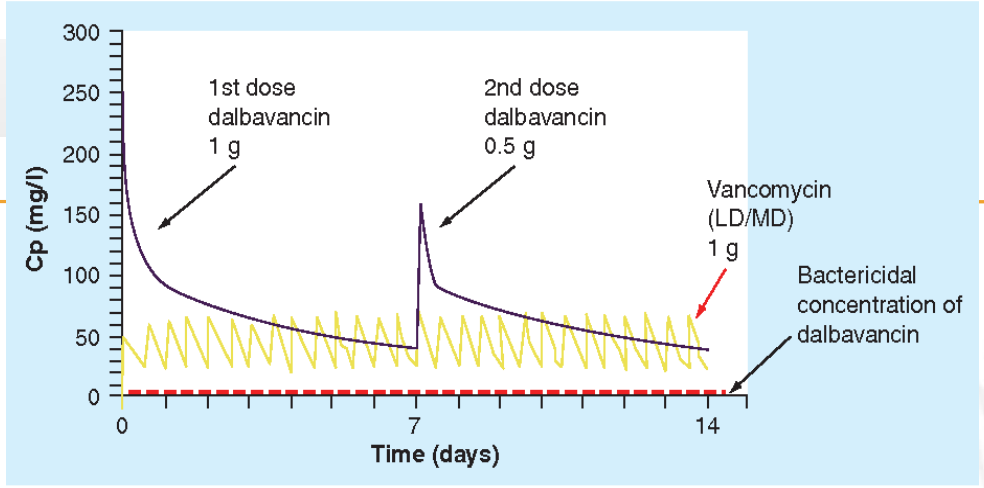
- **Imipenem/cilastatin 1 : 1**
  - **(excreted by kidney)**
  - **Advers events**
    - **Seizures – depend on doses – due to enhanced permeability HEB in neuroinfections**
    - **Not suitable for neuroinfections treatment**
- **Using**
  - **More suitable in some enteral infections**
- **<u>Meropenem</u>**
  - **More convenient than imipenem**
  - **Most powerful beta-lactam**
  - **Dosing 0,5-1 g each 8 h.; meningitis 2 g each 8 h.**
  - **Higher doses are well tolerated**
- **Ertapenem**
  - **Less convenient pharmacokinetics, worse penetration in tissues**
  - **Dosing once time daily**

Glycopeptides



- **Characteristics**
  - Big molecule
  - Inhibition of cell wall synthesis
- **Representatives**
  - Vancomycin
  - Teicoplanin
  - Dalbavancin
- **Spectrum**
  - Majority of G+ including some anaerobes
  - Effect of particular ATB differs considerebly
  - Vanko a teico – effect depends more on the parametre above MIC
- **Resistance**
  - G- naturally resistant

Glycopeptides



- **Pharmacokinetics**
  - i.v. application
  - Long half-time in organism
  - Necessity of saturation doses
  - Excreted by kidney
  - T1/2 (i hours)
    - Vanco 6-8; teico 100-170; dalba 180
- **Adverse events**
  - Allergy, nephrotoxicity, ototoxicity
  - Necessity to give in slow infusion – red man sy – histamine reaction
- **Dosing**
  - Vanco 1g each 12 h. slowly i.v.; monitoring of levels is very advisable
- **Using**
  - **Treatment of infection:**
    - G+ bacteria resistant to beta-lactams
    - more G+ pathogens together
    - Long term intensive treatment of infections in homecare – OPAT
    - Oral treatment – *Cl. difficile*
    - Not suitable for treatment superficial and mild infection
    - Onset of the effect can be slower

https://www.semanticscholar.org/paper/Dalbavancin-(BI-387)-for-the-treatment-of-skin-and-Leuthner-Yuen/34ea3bcacd4339a758db9680cfb1c66d7f03f8e4/figure/2

Cyclic lipopeptides, polypeptides

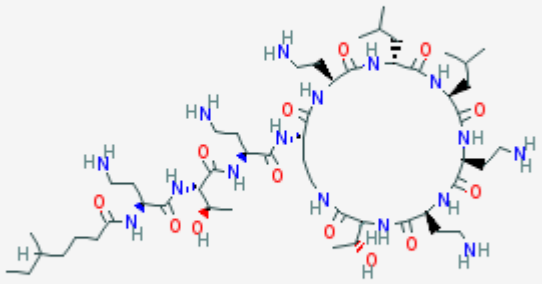
- **Daptomycin, surotomycin**
  - **Modern lipopetides; daptomycin 1 time/d; musculary toxicity**
  - **Reserve drug for treatment of infections caused by sensitive G+ microbes especially staphc.**
  - **Long T1/2 – OPAT**
  - **G- bacteria primarily resistant**
- **Polymyxins**
  - **Colistin**
  - **Polymyxin B**
- **Bacitracin**
- **Characteristic**
  - **Highly effective ATB**
  - **Bactericide**
  - **Kill bacteria in not dividing period as well**
  - **Effect depends more on C_{max} than on t>MIC**
  - **Effective on the majority of multiresistant strains of G- bacteria**
  - **Disadvantages**
    - **i.v. application or local application**
    - **Toxicity**
    - **Complicated to assess dosing, especially in severe infections; saturation dosis**
- **Toxicity on membranes of human cells**
  - **Nephrotoxicity, neurotoxicity, hematotoxicity**
- **Using**
  - **Back-up antibiotics for the treatment of life-threatening infections caused by multiresistant bacteria**

Colistin and polymyxin B; bacitracin

- **Colistin**
- Characteristic
  - Back-up ATB in patients where other drugs are not effective, patients in intensive care
  - Quick and bactericide action
  - Disadvantages
    - Toxicity
    - Troublesome predictable pharmacokinetics
    - Week penetration into tissues
- Indications
  - Sepsis and other complicated infections caused by multiresistant G- bacteria
  - Local application in CNS and lungs possible

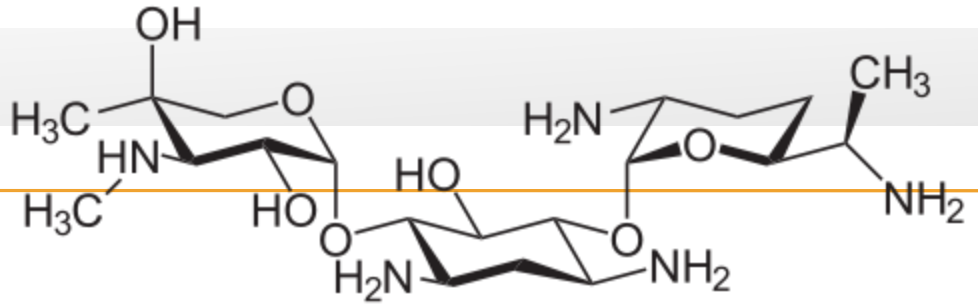
- **Polymyxin B**
- Characteristic
  - Very resembling spectrum to colistin
  - Resembling adverse events – higher toxicity
  - Resistance low
- Local use
- I.v. preparations in other countries
- Using in eye preparations, inhalation
  - Combination with neomycin

- **Bacitracin**
  - Local use



https://pubchem.ncbi.nlm.nih.gov/compound/colistin#section=Top

Aminoglykosides



- **Characteristics**
  - Main actions are two:
    - Ribosomes – 30S subunit
    - Cell wall of bacteria
  - More preparations – very similar features
- **Streptomycin – the first one 1944**
- **Gentamycin the most important**
- **Mechanism of action:**
  - Action more quick than beta-lactams
  - Bactericide
  - Action depends on C_{max}; optimally 6-10 times > MIC
  - Postantibiotic effect only in G- bacteria
- **Spectrum**
  - Main on G- aerobic bacilli
  - Out of G+ mainly Stph. a mycobacteria
  - On streptococci and enterococci- synergic effect
  - Some strains of str. and enterococci have high resistance, here is not measurable synergic effect; in str. highly sensitive to PNC low synergic effect as well
  - <u>Did not influence on:</u>
    - Metabolically nonactive bacteria
    - Anaerobic bacteria
    - Intracellular bacteria
    - Bacteria in biofilm
  - Synergy with betalactams and carbapenems

Aminoglykosides

- **Pharmacokinetics**
  - **Administration i.v.; i.m.; GIT resorption 0**
  - **Good penetration in well vascularised tissues**
  - **CNS besides inflammation only 5 % concentration**
  - **Excretion - active transport renal tubule**
  - **Due to urine levels are 25 – 400 times higher than in blood**
  - **Similar mechanism in inner ear**
- **Adverse events**
  - **Nephrotoxicity - inertia – destruction continues still a few days after removal of ATB from therapy;**
    - **mostly reversible but cummulative effect**
  - **Ototoxicity – primarily vestibular, later cochlear; irreversible**
  - **Neuromuscular blocad – resorption of large amount of substance (lavage of cavities …)**
- **Dosing**
  - **3-5mg or 5 – 7 mg/kg/den respectively, possible to give in one dosis**
  - **Safety – to hydrate patient, measure levels, examine vestibular functions, treat maximally 2 weeks**
  - **Frequently used in local preparations**
  - **Similarly intrathecal and intraventricular application (5-10 mg/d)**
  - **Oral using – some GIT infections – decontamination**

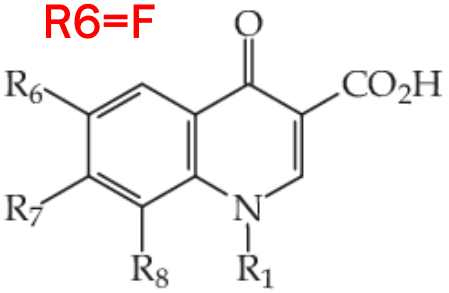
Aminoglykosides

- **Using**
  - **In combination treatment – severe infections (sepsis) enhancement or synergy with other ATB**
    - **Quick reduction of bacterial loading (sepsis …) treatment a few days – without risk of toxicity**
    - **In very resistant bacteria 2 (+) weeks – monitoring of levels**
  - **In monotherapy – sparsely**
  - **Local treatment**
    - **Eye, ear, skin, inhalation (cystic fibrosis, ventilatory pneumonia), lavage, orally (enteral infection with noninvasive pathogens)**
- **Not suitable for:**
  - **Intracellular pathogens**
  - **Anaerobic infections**
  - **Infections in acid pH**
  - **Mucose infections**
  - **Neuroinfections, pneumonia – low levels**

Aminoglykosides

- **Gentamicin**
  - **The most used**
- **Amikacin**
  - **Back up ATB used, where gentam. cannot be used**
- **Streptomycin**
  - **Different chemical structure than others AMG**
  - **TBC a mycobacteriosis**
  - **Controversial indication in zoonoses – probable relict from the 60s**
- **Neomycin**
  - **Local application**
- **Paromomycin**
  - **Not registered in ČR**
  - **Orally – for therapy amoebiasis, cryptosporidiosis**
  - **Locally leishmaniosis**

Fluoroquinolons



- **Characteristics**
  - **Synthesized chemically - 4-chinolon-3 carboxyl acid**
- **Classification - dividing: 3 – 4 generation, not unified, slight differences**
  - **1st nalidixine, oxoline acids …**
    - **Covers *E.coli*, neisseria, hemophilli**
  - **2nd norfloxacin, pefloxacin, cirpofloxacin, levofloxacin, prulifloxacin**
    - **Larger spectrum: pseudomonas, staphylococci, chlamydia, mycoplasma, mycobacteria**
  - **3rd moxifloxacin**
    - **Plus: G+ bacteria – streptococci including pneumococci and some anaerobic**
- **Mechanism of action**
  - **Inhibition of topoisomerase II (gyrase) and IV – blocking of DNA synthesis**
  - **Quick bactericidal effect proportional to C_{max} and AUC as well**
  - **Postantibiotic effect about 2 h.**
- **Resistance**
  - **Unfortunately very frequent and clinically important, can appear during one – the first ATB treatment; 5 mechanism resistance recognized**

https://www.researchgate.net/figure/Structure-of-4-oxo-1-4-dihydro-quinoline-3-carboxylic-acids_fig5_305766354

Fluoroquinolons

- **Pharmacokinetics**
  - **Advantages of small molecule**
  - **Particular drugs differ sometimes but in general:**
  - **Mostly excellent resorption p.o. (sometimes so good as i.v.)**
  - **Contemporary intake of food do not interfere; chelates bind**
  - **Excellent penetration into tissues 50 – 200 % levels of blood (prostata, lungs, kindey)**
  - **Metabolisation and excretion by different paths**
  - **Longer $T_{1/2}$ 3-4 h. cipro, 12 h. peflo**
- **Adverse events**
  - **Frequency and spectrum comparable with others ATB, severe reaction appears in less than 1%** 🙂
  - **But, … severe ones and in special cases are severe:**
    - **Fototoxicity – the late as well and not doses depending**
    - **Neurological – hallucination, depression, seizures – GABA blocking**
    - **Arthropathy (good outcome), tendinitis (can be irreversible, serious)**
    - **Prolonging of QT interval, hypoglycemia …**
- **Adverse events – concerning of ATB interactions**
  - **cytochrome P-450, combinations with different ATB are safe (pharmacological)**

Fluoroquinolons - using

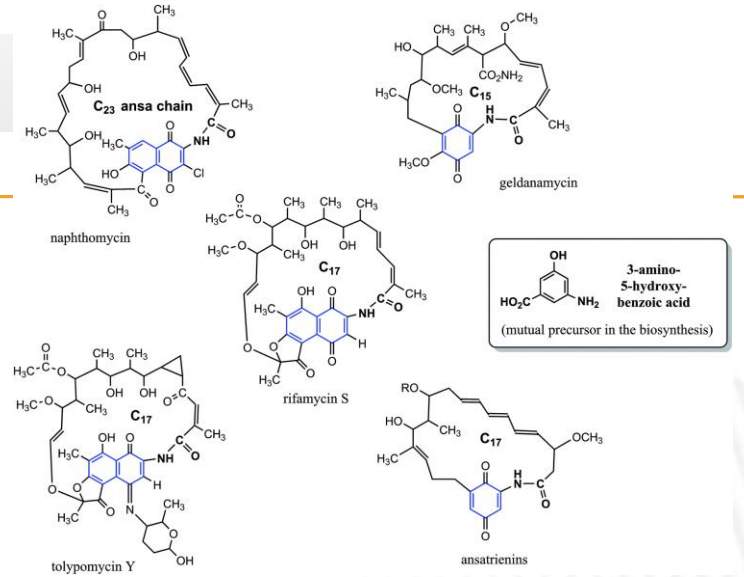
- **1st generation is not registered in ČR**
  - **Reduced effect and risk of induction of resistance to other chinolons**
- **2nd generation**
  - **Treatment of moderate infections by G- bacteria**
  - **Intracelullar pathogens (bartonella, francisela, legionella)**
  - **GIT infections, *Salmonella* Typhi, urogenital, chronic respiratory – exacerbations**
  - **Infections of skeleton, joints**
  - **Mixed infections**
  - **Unreliable for pneumococci, viridans str., enterococci, listeria, spirochetes anaerobes**
- **3rd generation**
  - **Respiratory infections incl. commune pneumonia**
  - **Suitable to cover of more potential respiratory pathogens**
- **Advantages**
  - **Bactericidal effect – high efficiency**
  - **Relatively board bacterial spectrum**
  - **Good penetration in tissues and cells**
  - **Comfortable treatment – dosing two times daily**
  - **Low cost**
- **Disadvantages – cause reducing of board field using**
  - **Increasing resistance**
  - **Unpredictable – although rare – but important side effects**

Fluoroquinolons – drugs

- **2nd Norfloxacin**
  - **Treatment of urinary tract and prostate, (gonorrhoe)**
  - **Not suitable for treatment of systemic infections not event by sensitive pathogens**
  - **Decrement of prescription**
- **2nd Pefloxacin**
  - **As norfloxacin**
  - **Some indiacation additionally:**
    - respiratory infections – acute exacerbated, cystic fibrosis, infection GIT, bones, joints; skin infection including of staphylococci,septicemia, meningitis – when agent sensitive
  - **Its‘ prescribtion is not supported in ČR**
- **2nd Ciprofloxacin**
  - **Etalon of quinolones, most used**
  - **Most wide spectrum of effect, most of all G-**
  - **Most powerful quinolon against *Pseudomonas aeruginosa* and moreover p.o.**
  - **Most clearly defined effects, very good but variable resorption**
  - **Side effect commost with other quinolons incl. arising resistance**
- **2nd Ofloxacin**

  Very similar to ciprofloxacin
- **2(-3?). Levofloxacin**
  - **Purified ofloxacin, lower dosing, indication the same**
- **3rd Moxifloxacin**
  - **Respiratory quinolon – upper and lower airways**
  - **Effective on G+ respiratory pathogens**
  - **Low effective for treatment of urogenital inf. Most powerful quinolon for *Mycobakterium tub., effective on Mycobat . leprae, M. avium***

Rifamycins - ansamycins



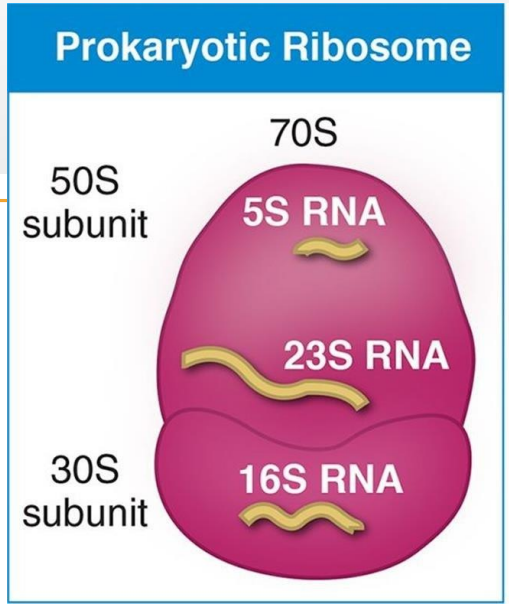
- **Characteristic**
  - Rifamycins – subunit of ansamycins
  - (ansa = bridging, concerning of molecular structure)
  - Action – Inhibition of DNA transcription into mRNA
  - Effect for the most depends on C_{max} ,
  - … but finally on AUC/MIC
  - Long postantibiotic effect – enables intermittent dosing
  - Bactericide
- **Spectrum**
  - G+ bacteria, mycobacteria, intracellular b.
  - Do not influence G- bact. (do not penetrate into their cells)
  - Therapeutically interesting – certain reduced effect on plasmodia, filariasis, mycotic organisms
- **Resistance**
  - Often and therapeutically very important; several mechanisms
- **Pharmacokinetics**
  - Resorption from GIT variable, after it very good penetration follows into tissues and cells including CNS
  - High concentration in gall
  - Induction of liver enzymes
- **Adverse events**
  - Mild and rare
  - GIT, allergy, hepatopathy
  - Red-orange colouring of tissues, fluids and secrets – to warn patient (contact lences)
- **Drug interaction**
  - Very important and frequent, often inconsistent

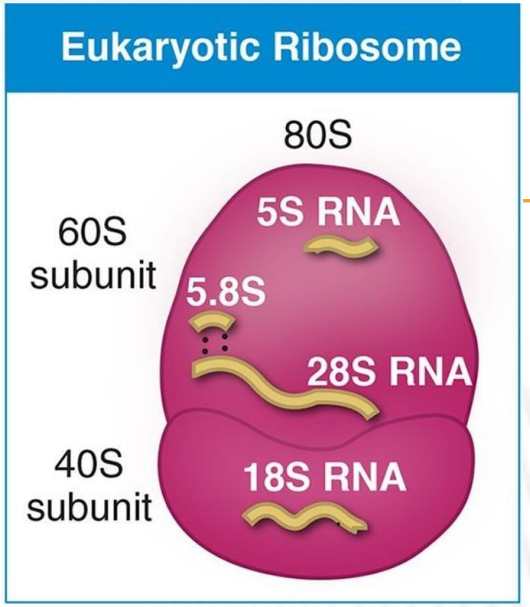
https://pubs.rsc.org/en/content/articlelanding/2016/ra/c6ra22880a/unauth#!divAbstract

Rifamycins - ansamycins

- **Recommended dosing**
  - **P.o.**
- **Using**
  - **Only some indication are used in practice due to fear form resistance. Other indication is recommended to reduce.**
  - **Using always in combination with other ATB**
  - **TBC a mycobacteriosis**
  - **Severe staphylococci infections**
  - **Intracellular bacteria – bartonellosis, brucellosis**
  - **Bacteria in biofilm**
  - **G+ bacteria with consideration the above mentioned remarks**
- **Preparations**
  - **Rifampicin p.o. always on an empty stomach, 1 time daily**
    - **TBC a mykobacteriosis; lepra; indication above + some special (biofilm, chronic infection, foreign body …)**
  - **Rifabutin – similar, less utilized in practice**
  - **Rifaximin – no resorption from GIT – treatment of non-invasive intestinal infections, debacillation of intestine**

Antibiotics acting by ribosomes

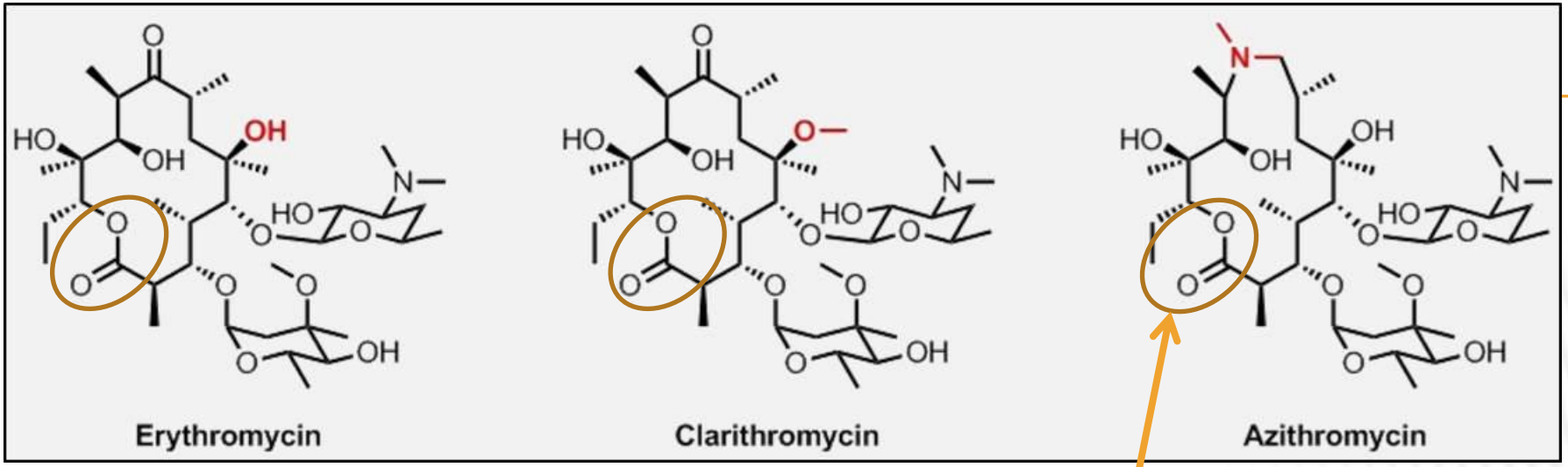




- Characteristics
  - Macrolides
  - Lincosamides
  - Streptogramines
  - Amphenicols
  - Aminoglyosides
  - TTC
- Bacterial ribosomes have a different structure, this enables the therapeutic action
- Inhibition of proteosynthesis on 23SrRNA
  - Action in same place:
    - Macrolides, azalides, ketolides, streptogramins B
    - Probably linesolid, chloramphenicol a lincosamides
  - This results in antagononism when used contemporary
  - Bacteriostatic effect
  - They can disturb ribosomes of eucaryont mitochondria – followed by mitochondrial dysfunction
    - Fatigue during treatment with TTC
    - Myelodysplastic syndrome in treatment CHLF, linezolid

https://www.quora.com/What-are-70S-ribosomes

Makrolides, azalides, ketolides



Lacton group

- **Macrolides**
  - **Natural**
    - **Erythromycin**
    - **Spiramycin**
  - **Semisynthetic**
    - **Claritromycin**
    - **Roxithromycin**
- **Azalides**
  - **azithromycin**
- **Ketolides**
  - **Telithromycin**

Macrolides

- **Spectrum**
  - **Sensitive bacteria**
    - **Most of G+**
    - **Easy cultivated G- rods (bordetella, legionella, campylobacter, helicobacter …)**
    - **Atypical bacteria (mycoplasma, chlamydia)**
    - **Spirochetes**
    - **Some mycobacteria**
    - **Protozoa (coccidia, plasmodia)**

https://www.quora.com/What-are-70S-ribosomes

Macrolides

- **Resistance**
  - **More mechanisms**
  - **Finally resistant: Stph., pneumococci, gonococci, hemophillus …**
  - **Many others are naturally resistant (G-, enterobacteria, enterococcus …)**
- **Pharmacokinetics**
  - **Good penetration**
    - **Into tissues instead of CNS**
    - **Into cells – leucocytes**
    - **On surface of mucosa**
  - **Excretion mostly by liver, gall**
    - **Metabolisation in cytochromes**
- **Adverse events**
  - **Safe drugs**
  - **Emetic effect (ery)**
  - **Influence in metabolism of liver cytochromes**

Macolides - using

- Mild to moderate infections
- Mostly only p.o. forms, dosing 2 times daily (azitro special pattern)
- Impossible to use in severe infections – weak activity
- In children – given where it is not possible to use TTC and quinolons
- They support appearance of resistance due to easy membrane resulting in subtherapeutic serum levels on different places of organism

- Respiratory and ORL infections
- Urogenital – STD infections (chlamydia, mycoplasma …)
- Pertusssis, diphteria (mild forms), legionellosis, chlamydia, mycoplasma
- Campylobacter enterocolitis; helicobacter. infection
- Mycobacteriosis
- Lyme borreliosis – alternative treatment

Macrolides - drugs

- **Erythromycin**
  - **Abandoned – negative side effects (GIT, drug interactions …)**
  - **Dermatological local therapy**
- **Clarithromycin**
  - **Spectrum similar to erythrm.; double effective; successor of erythromycin; frequent drug interactions**
  - **Dosing 2 times d, relatively KI in pregnancy (mitochondr. dysfunction)**
  - **Not suitable (similarly as other EMs) for treatment of severe infections instead of legionella and mycoplasma pneumonia**
- **Roxithromycin**
  - **More suitable kinetics dosing – 1 time daily; weaker effectivity; higher blood level than než azithromycin; possible substitution of PNC for str. infections incl. Long-term prophylaxis**
- **Spiramycin**
  - **Spectrum similar to erythr., less effective against str., more against *Mycopl. hominis* a *Toxopl. gondii; c*ryptosporidia**
  - **Suitable for children and pregnant women; well tolerated**

Macrolides - drugs

- **Azithromycin**
  - **Effect on G+ cocci minor and on some G- better than ery or clari**
  - **Accumulation in tissues – mostly in lymphoreticular – 10 to 100 times higher concentration.**
  - **Dosing – 3 days – levels persist during 7 days (it is possible to give in one doses/one day)**
  - **Main using:**
    - **infections with high tissue infiltration of leukocytes**
    - **intracelluar microorganisms (legionella tularemia, bartonellosis, mycobacterioses)**
  - **Negative sideeffect – induction of selection of resistant strains – due to long persistence of subtherapeutic levels**
- **Telithromycin**
  - **Spectrum the same as ery; efficiency 2 to 10 times stronger**
    - **Spectrum Str. a Stph. and on some G- and intracellular paths.**
  - **Dose dependent effect - can be bactericide**

Lincosamides

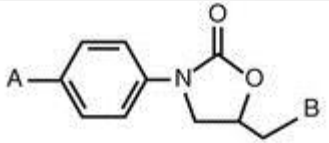
- **Lincomycin, clindamycin**
  - **Narrow spectrum ATB**
    - **G+ bacteria**
    - **Anaerobes**
  - **Clindamycin moreover effective on apicomplexa (*T. gondii, Plasmodium spp., Babesia spp., Pneumocystis jirovecii*)**
- **Mechanism of action**
  - **50S subunit, two independent sites**
  - **Effect most of all bacteriostatic**
  - **Synergy with other ATB week**
  - **Reasonable affinity to leucocytes and macrophages – potentiation**
- **Adverse events rare:**
  - **GIT, dysmicrobia, blocking of neuromuscular synapses**

Lincosamides

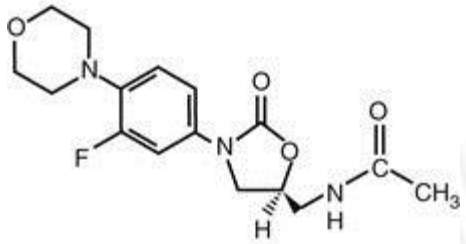
- **Clindamycin**
  - Greater effect on anaerobic infections
  - Mixed G+ and anaerobic infections
  - Protozoa infections
- **Using**
  - Recidiv tonsillitis, odontogenous infections, actinomycosis, subacute infections of soft tissues, osteomyelitis
  - Combination with other ATBs: diabetic foot, intraabdominal infections, abscesses (instead of CNS), necrotizing fasciitis
- **Dosing**
  - P.o. and i.v. 600 – 1200 mg/d in 4 doses; in severe infections 2,7 – 4,7 g/d

- **Lincomycin – is being left with coming of oxazolidinoids**
  - Str. and stph. infections
  - Osteomyelitis !!!
  - Sometimes is advantageous the tolerance of extreme doses

Oxazolidinons



Basic oxazolidinone structure



Linezolid

- **Characteristics**
  - **Linezolid, tedizolid (formerly torezolid)**
  - **Pure synthetic ATBs**
  - **Block proteosynthesis at 50S subunit of ribosome**
  - **Unique mechanism of effect – no crossreactive resistance, allergic reactions**
  - **Primarilly bacteriostatic – activity depends on both AUC/MIC**
  - **No postantibiotic effect**
- **Spectrum**
  - **Recently registered preparations only G+ and mycobacteria**
- **Resistance**
  - **No in ČR, some detection in the world**

https://oncohemakey.com/linezolid-and-other-oxazolidinones/

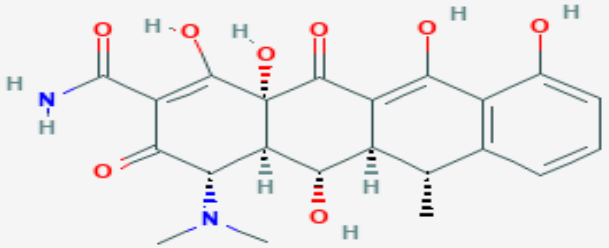
Linezolid

- **Pharmacokinetics**
  - **Excellent resorption from GIT**
  - **Excellent penetration in tissues**
  - **Favorable is quick blocking of proteosynthesis – in infections connected with massive toxin synthesis (diphteria, gas gangrene, toxic shock syndrome)**
- **Side effects**
  - **Myelotoxicity – cumulative, depends on whole dose, reversible, due to mitochondrial toxicity**
  - **Neurotoxicity – after long therapy (months), neuropathy, chills, irreversible**
- **Drug interactions**
  - **Nonselective inhibitor of MAO – appearance of serotonine syndrome (confusion, chills, agitations, delirium)**
- **Recommended dosing**
  - **Similar p.o. and i.v.; dosing 2 times /D 600 mg; or 20 mg/kg/d in 2-3 doses**
  - **Recommended to treat up to 28 days (longer with risk!)**
- **Indications**
  - **Better effect than clindamycine, lesser than beta-lactams or vancomycine**
  - **Better tisssue penetration, effect on multiresistant G+ bacteria (MRSA, VRSA …)**
  - **Infections of skin and hypodermis**
  - **Community and as well nosocomial pneumonia**
  - **Bone and joint infections**
  - **Infections with synthesis of proteinaceous toxins**
  - **Back-up ATB**
    - **For mycobacterioses**
    - **Not optimal fro sepsis, or endocarditis treatment – „only“ bacteriostatic**

Tetracyclines a glycylcyclines

- Characteristic
  - Bacteriostatic
  - Broad-spectrum ATB
  - 30S subunit of ribosome
  - Effect depends lenght of treatment AUC/MIC
  - Certain intiflogistic – immunomodulatory effect (rheumatoid arthritis versus … LB?)
  - 1st generation:
    - chlorTTC
    - oxyTTC
    - TTC
  - 2nd generation
    - Doxycycline
  - 3rd generation
    - Tigecycline
- Adverse events
  - GIT
  - Phototoxicity
  - Colouring of teeth – KI up to 8 years of age
  - Chelates with Ca and Mg ions – reduction of absorption

Doxycycline

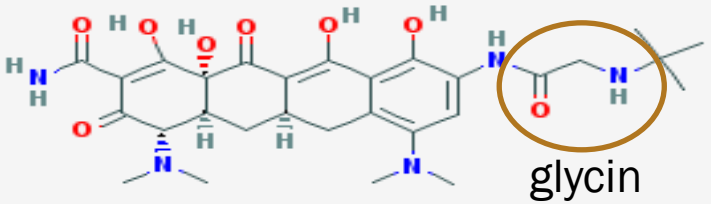


- Long biological half-life
- High binding to proteins
- Intracelullar pathogens
  - Chlamydia, rikettsia, ehrlichia, francisellla,
  - brucella, bartonelly
- Mycoplasma, legionella, leptospira
- Spirochetes – *Treponema pall. B. burgdorferi*
- Anaerobic bacteria (actinomycetes, propionibacteria)
- Atypical pneumonia
- Urogenital infections and sexually transmitted diseases
- Zoonoses
- Against other bacteria in spite of they are sensitive (e.g. Stph, Str., E. coli …) they are less effective and they are not used

- Dosing
  - 200 mg/d in one or 2 doses; max 300 mg/d (off label even more)
  - Reduction of doses in hepatal insuficiency or not to give

https://pubchem.ncbi.nlm.nih.gov/compound/doxycycline#section=Top

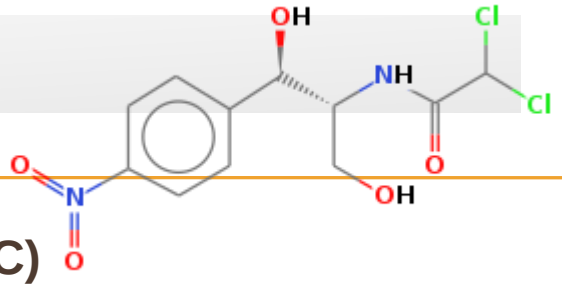
Tigecykline - glycylcyklines



- **Characteristics**
  - Derived of minocycline
  - Resistible against to two strong mechanisms of resistance
    - Efflux, protection of ribosomes
- **Spectrum**
  - Resists to many resistant nosocomial pathogens
  - Good effect on anaerobic bacteria
- **Pharmacokinetics**
  - No resorption from GIT – i.v.
  - Strong bound on plasmatic proteins – slow saturation of tissues
  - Excellent penetration in tissues
- **Adverse events**
  - GIT, skin and liver functions
- **Using**
  - To some extent ATB „of the 2nd line“ – in its‘ indications exist the others – more effective ATB
  - Complicated skin infection, intraabdominal infections
  - = mixed infections by resistant pathogens
  - (+ indication as others TTCs where parenteral application required)
  - (+ as the other TTCs)
  - On many primarily sensitive microbes is unsatisfactorily effective (pseudomonas, proteus …)

https://pubchem.ncbi.nlm.nih.gov/compound/Tigecycline#section=Top

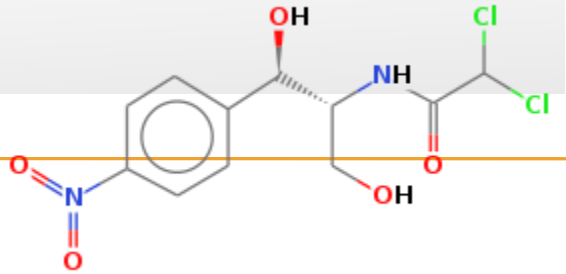
Amphenicols - chloramphenicol



- **Characteristics**
  - **ATBs known for longest time (with PNC and TTC)**
  - **Due to myelotoxicity searched for others derivates, but non was successful**
  - **Small lipophilic molecule – excellent tissue penetration**
  - **Bacteriostatic; against some species bactericide**
  - **Inhibition of proteosynthesis - bound at 50S ribosome subunit**
- **Pharmacokinetics**
  - **Oral preparations have greater biologically effectivity than i.v. (lipophilic molecule is given as prodrug, it has to be split by hydrolases – intestinal, tissue)**
- **Adverse events**
  - **GIT, allergy, dysmicrobia**
  - **Myelotoxicity**
    - **Reversible suppression of bone marrow – dose dependent**
    - **Aplastic anemia – very rare (1 : 25 000 to 1 : 40 000 applications), not dose-dependent**
    - **Neurotoxicity**
    - **Grey baby syndrome, immaturity of liver enzymes – not ability of conjugation – liver excretions of ATB**

https://webbook.nist.gov/cgi/inchi/InChI%3D1S/C11H12Cl2N2O5/c12-10(13)11(18)14-8(5-16)9(17)6-1-3-7(4-2-6)15(19)20/h1-4%2C8-10%2C16-17H%2C5H2%2C(H%2C14%2C18)/t8-%2C9-/m0/s1

Amphenicols - chloramphenicol

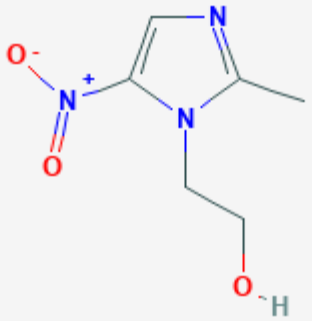


- Recommended dosing
  - 50 – 100 mg/kg/d ((higher as well !!))
- Contraindications
  - Blood disturbances, hematological malignancy, liver and kindney insufficiency, porphyria
- Using
  - Extremely broad spectrum, excellent tissue penetration
  - Classical indications
    - Typhoid fever, paratyphoid, septic salmonellosis, severe hemophillic infections (epiglotitis), severe pertussis, purulent meningitis and <u>especially brain abscesses</u>
  - Recently – alternative, back-up ATB
    - Severe mixed infections with participation of anaerobes and necessity of good tissue penetration (abscesses incl. brain a.)
    - Special indication – atypical pathogens
      - Spotted fever (rikettsial infection), recurrent fever – typhoid, Q-fever, anthrax, pestis, tularemia
  - Not suitable for treatment of sepsis (slowly ongoing action, only average effect of therapy)
  - Only i.v. preparations is registered in ČR

Oxidative acting ATBs

- **Nitroimidazoles**
- **Nitrofurans**
- **Characteristic**
  - **Give as a prodrug – active drug released after entrance into cell**
  - **Nitrocompounds – intracelularly are released very ně vznikají velmi reactive radicals, which act in cells které působí v buňce toxically**
  - **Condition of action is anarerobic – reductive sorroundings; e.g. Intracelullarly or for instance in GIT**
- **Adverse events**
  - **GIT, photosensitivity, allergy, orange coloureing of urine, hepatotoxicity**

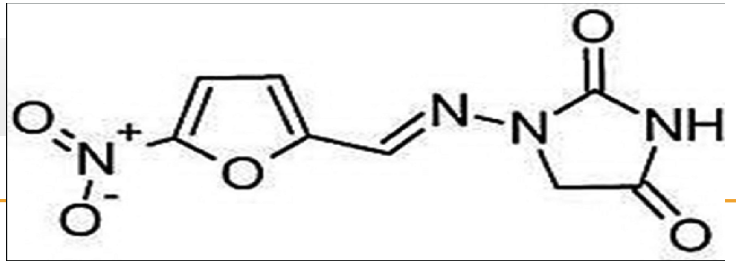
Nitroimidazols



- Metronidazol
- Ornidazol

- Characteristics
  - Bactericidal, high efficiency
  - Very quick start of effect – advantageous pharmacokinetics
  - Postantibiotic effect
  - Low price
- Spectrum of action
  - Some anaerobic G- and G+ bacteria
  - Protozoa *Trichomonas v., Dientamaeba fragilis, Balantidium coli, Blastocystis hominis*
- Resistance
  - Primarily rare at the beginning
- Pharmacokinetics – p.o.; i.v.; very good levels – tissue penetration
- Adverse events
  - GIT
  - Neurotoxicity central and peripheral
  - Disulfiram reaction with alcohol (Antabuse effect) – vomiting
  - Next
- Indication
  - Main using – therapy of mixed aerobic/anaerobic infections when the other ATB is added – imidazol is the supportive drug
    - GIT infections and gynecologic inf.
    - Brain abscess
  - Amebiasis, trochomoniasis, giardiasis
  - Clostridium colitis

Nitrofurantoin



- **Characteristics**
  - Old drugs, low antimicrobial effectivity, reduce tolerance, dysadvantageous pharmacokinetics
  - Relative advantage is low manifestation of resistance.
- **Antibacterial spectrum**
  - G+ and G- bacteria – some out of G- are partially or completely resistant (*Proteus spp, Pseudomonas aer., Acinetobacter spp, Morganella m.*)
- **Pharmacokinetics**
  - Good resorption, good tissue penetrations but short half-life due to quick metabolisation
  - Therapeutic levels only in urine
- **Adverse events**
  - GIT (anorexia, nausea …)
  - Relative frequent and multiple allergic reactions
  - Organ lesions most frequently immunopathological principal (pneumonitis, hepatopathy, neuropathy, hemolytic reaction …)
- **Recommended dosing**
  - Therapy of acute infection – 5-7 days
  - Chronic – preventive therapy – 1 dosis night
- **Using**
  - Long-term prophylaxis of community uroinfections with low probability of development of resistance
  - Treatment of urinary tract infections – urocystitis
  - Not suitable for treatment of tissue infections – kidney, prostate …
  - Handicap for treatment of acute infections is necessity 3-4 doses per day, slow ingoing of effect
  - Not suitable for treatment of acute nosocomial infections

Inhibitors of metabolic pathways - sulfonamides and sulfons

- **Old drugs – Prontosil the first chemotherapeutics**
- **Classification**
  - **1) Generally acting drugs – resorption from GIT**
  - **2) Locally acting in GIT – sulfasalazin**
  - **3) Dermatological preparations – argent-sulfadiazin**
  - **1) Shortly acting – half-time 6-8 h: dosing 2-3times daily – sulfadimidin, sulfisoxazol,**
  - **2) Medium action half time 8-16 h: dosing 2times daily – sulfametoxazol, sulfadiazin**
  - **3) Long acting 1time daily - sulfametoxydiazin**
  - **4) Very long time acting 1time weekly: sulfadioxin (+ pyrimetamin = Fansidar)**
- **Characteristics**
  - **Sulfonamids and sulfons are similar to paraaminobenzooic acid – initial drug for synthesis of acidum folicum**
  - **Bacteriostatic effect**
  - **Depends on time above MIC**
  - **Postantibiotic effect minor**
- **Spectrum of effect**
  - **G+**
  - **G-**
  - **Fungi *Pneumocystis jirovecii, (Histoplasma, Paracoccidioides, Aspegillus)***
  - **Protozoa *Toxoplasma gondii, (Palsmodium, Leishmania, Acathamoeba)***
- **Adverse events**
  - **GIT**
  - **Allergy – very large spectrum of manifestations**
  - **Hepatopathy, nefropathy**
- **Using**
  - **Resistance and adverse events limit the using only on some preparations**

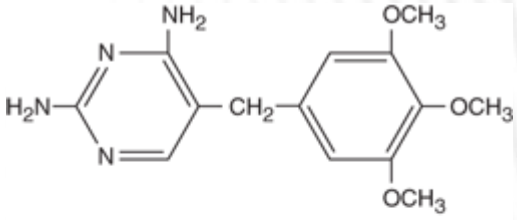
Sulfonamids – other preparations

- **Sulfadioxin, sulfadiazin**
  - **Therapy of malaria, toxoplasmosis**
- **Sulfasalazin**
  - **Immunomodulating features (therapy of colitis ulcerosa)**

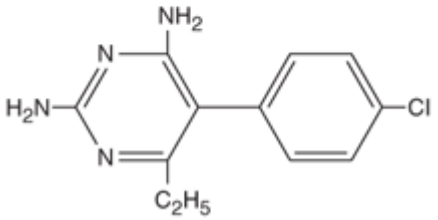
- **Dapson**
  - **Extremely strong drug for therapy *Mycobacterium leprae***
  - **Long-term prophylaxis of pneumocystosis, when cotrimoxazol can not be used**
  - **In other indications is spectrum similar to others SA – is not used for these purposes**

Diaminopyridins

- Characteristics
  - Inhibition of dihydroxyfolat-reductase = blocing of synthesis folic acid
  - Bacteriostatic ATB
- Spectrum
  - The most of pathogenic bacteria
    - Do not act against pseudomonades, mykoplasmata, spirochétes and the most of anaerobes
- Pharmacokinetics
  - Good resorption from GIT
  - Good penetration in tissues
  - Metabolized in liver in part
  - Kidney excretion
- Adverse events
  - Hematotoxicita – mostly cummulative
  - Can be treataed by ac. folicum treatment
- Resistance – frequent manifestations
- Using
  - Pyrimethamin – treatment of malaria and toxopl
  - Trimethoprim
    - Alone seldom
    - Mostly in combination with sulfamethoxasol



Trimethoprim



Pyrimethamine

Cotrimoxazol

- **Trimethoprim alone:**
  - **Only for goal-directed therapy of UTI – when the sensitivity is known**
  - **Prophylaxis in surgery in urynary tract**
- **Cotrimoxazole**
  - **Trimethoprim/sulfamethoxazol 1:5**
- **Characteristics**
  - **Blocking of two steps folic acid synthesis**
  - **Synergy + putting–off resistance**
- **Pharmacokinetics**
  - **Trimethoprim has excellent penetration in tissuaes, sulfametoxazol worse**
- **Drug interactions**
  - **Frequent**
- **Adverse events**
  - **Allergy**
  - **Immunopathological manifestations**
  - **Photosensibilization**
  - **Hematotoxicity**
  - **Nephrotoxicity, hepatotoxicity, porphyria**
- **Recommended dosing - tbl 480 mg**
  - **2 times 2 tbl, enhanced 3 times 2 tbl, high 4 times 2 tbl**

Cotrimoxazol

- **Using**
  - **Acute infection of kidney, urinary tract and prostatitis**
  - **GIT infections – salmonellosis**
  - **Staphylococcal infection of skin, mucosa and tissues including MRSA**
  - **Infections of upper and lower respiratory ways – hemophilic and pneumococcal etiology (not for streptococcal etiology of inf.)**
  - **Infections of sexual organs after of revealing of sensitivity**
  - **Some rare bacterial infections – nocardiosis, brucellosis, *Coxiella burnetti* and others**
  - **Pneumocystis pneumonia, toxoplasmosis**
  - **Contraindications**
    - **Disturbances of liver, kidney, porphyria, gravidity (mostly 1st trimenone), blood diseases, newborns (binding on plasma proteins)**
    - **Not suitable**
      - **for polymorbid persons with multiplex therapy – interference with therapy**
      - **allergy**

Providing of ATB therapy – regimen OPAT

- Outpatient parenteral antibiotic therapy
- Providing specialized center, not general practitioners
- Condition is good contact of patients and physicians in center
- OPAT is not stationery – time of visits is short
  - Treatment is provided in outpatients facilities; patients, attends from home
  - Or treatment provide trained nurse at home
  - Or patient applicate drugs by him/herself
- Choice of ATB
  - Usually drugs with parenteral application and long half-time (teicoplanin, dalbavancin, daptomycin, gentamycin, tigecyclin …)
- Patient has to be in good condition
- Examples of infections
  - Lyme borreliosis, osteomyelitis, infectious endocarditis …)

DĚKUJI ZA POZORNOST

The White Horse, Nr Alton Barnes, Wiltshire
25.5.2017

Oxleaze Copse, Nr Stitchcombe, Wiltshire.
21.5.2017