Antibiotics – agents – II

glycopeptides, macrolides, lincosamides, …, antimycotics

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Oddělení klinické mikrobiologie a antibiotická stanice

Nemocnice Na Homolce, Praha

Classification of antibiotics

main groups of antibacterial agents

NEMOCNICE NA HOMOLCE

betalactams

aminoglycosides

quinolones

glycopeptides

macrolides, azalides

ketolides

lincosamides

streptogramines

oxazolidinones

chloramphenicol

tetracyclines

rifamycines

co-trimoxazole

polypeptides

nitroimidazoles

nitrofurans

Antibiotics – antimicrobial agents

NEMOCNICE NA HOMOLCE

GLYCOPEPTIDES

Glycopeptides
agents

- **vancomycin**
- **teicoplanin**

- **avoparcin** veterinary use

Glycopeptides
characteristics

- cell wall synthesis inhibitors
- activity against grampositive bacteria
- bactericidal effect
- time-dependent action
- higher toxicity (vancomycin - ototoxicity, nephrotoxicity)
- resistance – change of target structure (VRE, VISA, VRSA)

Glycopeptides
antimicrobial spectrum

NA HOMOLCE NEMOCNICE

susceptibility

- staphylococci (S.aureus incl. MRSA, CoNS)
- enterococci (E.faecalis, E.faecium)
- streptococci
- Listeria, Clostridium, ...

natural resistance

- gramnegative bacteria
- lactobacilli, Leuconostoc, Erysipelothrix

Glycopeptides - vancomycin
characteristics, pharmacokinetics and dosing

- characteristics:
  - parenteral glycopeptide antibiotic, non-absorbable from gut
- pharmacokinetic parameters:
  - C_{max} (i.v. 500 mg) 10-25 mg/l 1 hour after infusion
  - biological half-life 5 - 11 h
  - protein binding 55%
  - volume of distribution 0,6 l/kg
- dosing (adults):
  - daily dose: 2 - 3 g dosing interval: 6 - 12 h
  - single dose: 0,5 - 1,0 - 1,5 g

Glykopeptides - teicoplanin
characteristics, pharmacokinetics and dosing

- characteristics:
  - parenteral glycopeptide antibiotic
- pharmacokinetic parameters:
  - C_{max} (i.v. bolus 400mg) 25 - 40 mg/l after 1 hour
  - biological half-life 90 h
  - protein binding >90%
  - volume of distribution 0,9 - 1,6 l/kg
- dosing (adults):
  - daily dose: 200 - 400 - 600mg dosing interval: 24 h

Glycopeptides
priorities of clinical use

- infections due to staphylococci resistant to oxacilin (MRSA, MRSE)
- pneumococcal and streptococcal infections resistant to betalactams
- grampositive infections in patients with alergy to betalactams
- infective endocarditis (combination with aminoglycosides)
- peritonitis as complication of peritoneal dialysis
- postantibiotic colitis (oral administration)
- empiric treatment of febrile neutropenia

MLS - group

macrolides, azalides and ketolides

lincosamides

streptogramines

MACROLIDES
AZALIDES
KETOLIDES

Macrolides, azalides and ketolides
characteristics

- 14 and 16-membered ring macrolides, azalides, ketolides
- proteosynthesis inhibitors
- bacteriostatic action
- time-dependent action (cumulation in tissues)
- excellent intracellular penetration
- low toxicity
- resistance – enzymatic (inducible or constitutive MLS type), active efflux, …

Antimicrobial action of macrolides

	ERY	ROX	CLA	SPI	AZI	TEL
S. pyogenes	++	++	++	++	++	++
S. pneumoniae	+	+	+	+	+	+
E. faecalis -	-	-	-	-	-	
St. aureus	+	+	+	+	+	+
H. influenzae	-	-	+	-	+	-
G – rods	-	-	-	-	-	-
legionellae +	+	+	+	+	+	
Mycoplasma	+	+	+	+	+	+
chlamydiae	+	+	+	+	+	+
anaerobes V	V	V	V	V	V	

++ highly effective, **+** effective, **–** no or low effect, **V** variable , **ERY** – erythromycin, **ROX** - roxithromycin, **CLA** - clarithromycin, **SPI** - spiramycin, **AZI** - azithromycin, **TEL** - telithromycin

Antimicrobial spectrum of macrolides

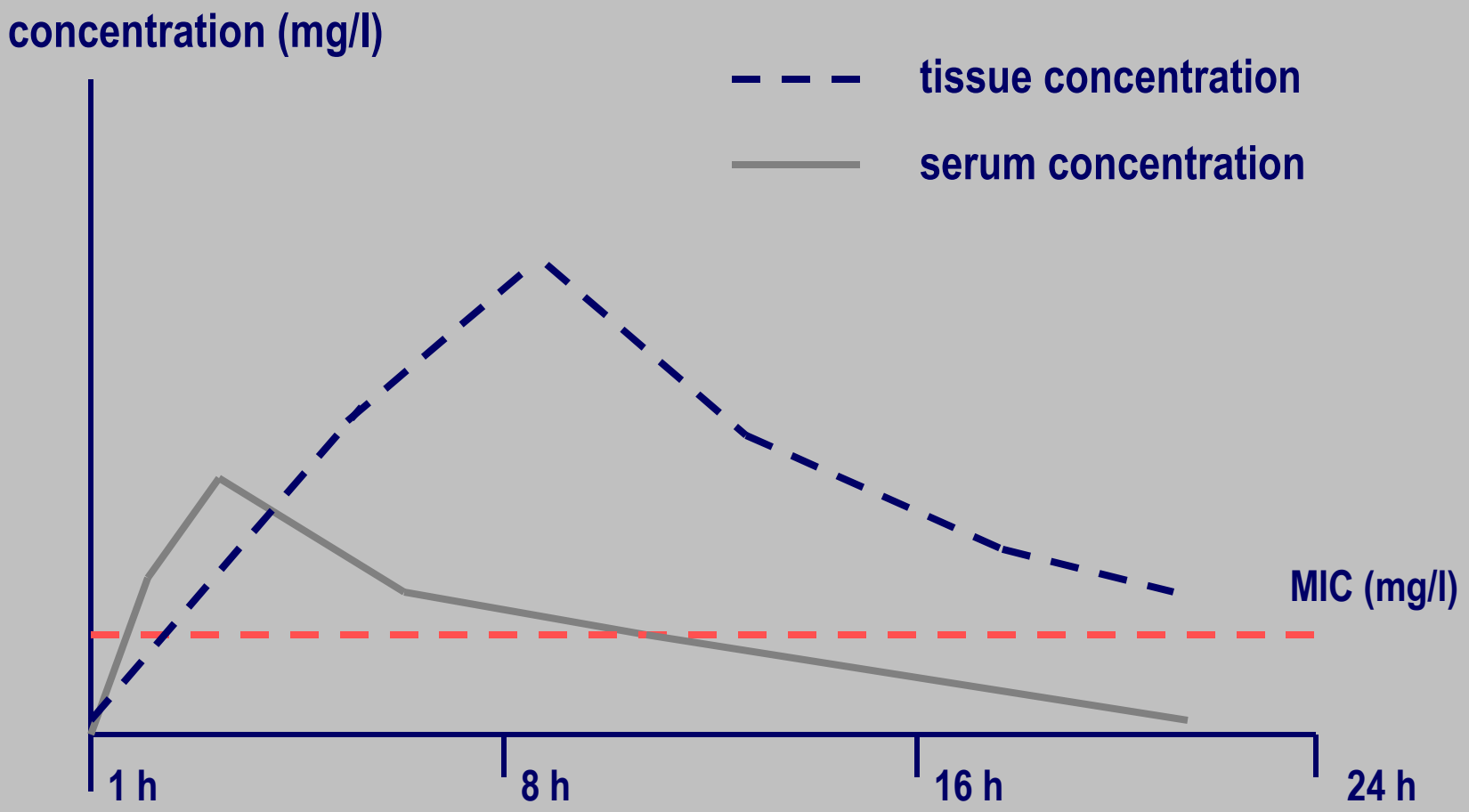
- **grampositive cocci** (staphylococci, streptococci, pneumococci)
- **grampositive rods** (C. diphteriae, Clostridium spp., Listeria)
- **mycobacteria (atypical mycobacteria)**
- **Neisseria spp.** (N.gonorrhoae, N.meningitidis, M. catarrhalis)
- **Bordetella spp.**
- **Campylobacter spp., Helicobacter pylori**
- **Mykoplasma, Chlamydia, Legionella**
- **Borrelia burgdorferi, Treponema pallidum**

Macrolides, azalides and ketolides
agents

- 14 – membered ring macrolides
  - erythromycin, roxithromycin, clarithromycin
- 16 – membered ring macrolides
  - spiramycin
- azalides
  - azithromycin
- ketolides
  - telithromycin

Time-dependent action with tissue cumulation

macrolides



Macrolides, azalides and ketolides
dosing (adults)

	single dose	interval
erythromycin p.o.	250 - 500 - 1000 mg	6 h.
erythromycin p.e.	600 - 1200 mg	6 h.
roxithromycin	150 - 300 mg	12 h.
clarithromycin p.o.	250 - 500 mg	12 h.
clarithromycin p.e.	500 - 1000 mg	12 h.
spiramycin	500 mg - 1 g	8 h.
azithromycin	500 mg	24 h.
telithromycin	800 mg	24 h.

Erythromycin
clinical use

- upper respiratory tract infections (acute tonsillopharyngitis, sinusitis, otitis media – allergy to betalactams)
- tonsillopharyngitis due to *Arcanobacterium haemolyticum*
- lower respiratory tract infections (community acquired pneumonia, atypical pneumonia, AECB)
- skin and soft tissue infections
- urogenital infections (Mycoplasma spp., Chlamydia trachomatis, gonococci)
- legionelosis (combination with rifampicin)
- pertussis, diphteria
- campylobacteriosis
- syphilis (allergy to penicillin)

Clarithromycin
clinical use

- **same as erythromycin and:**

- infections due to *Helicobacter pylori* (in combination)
- disseminated mycobacteriosis (in combination)

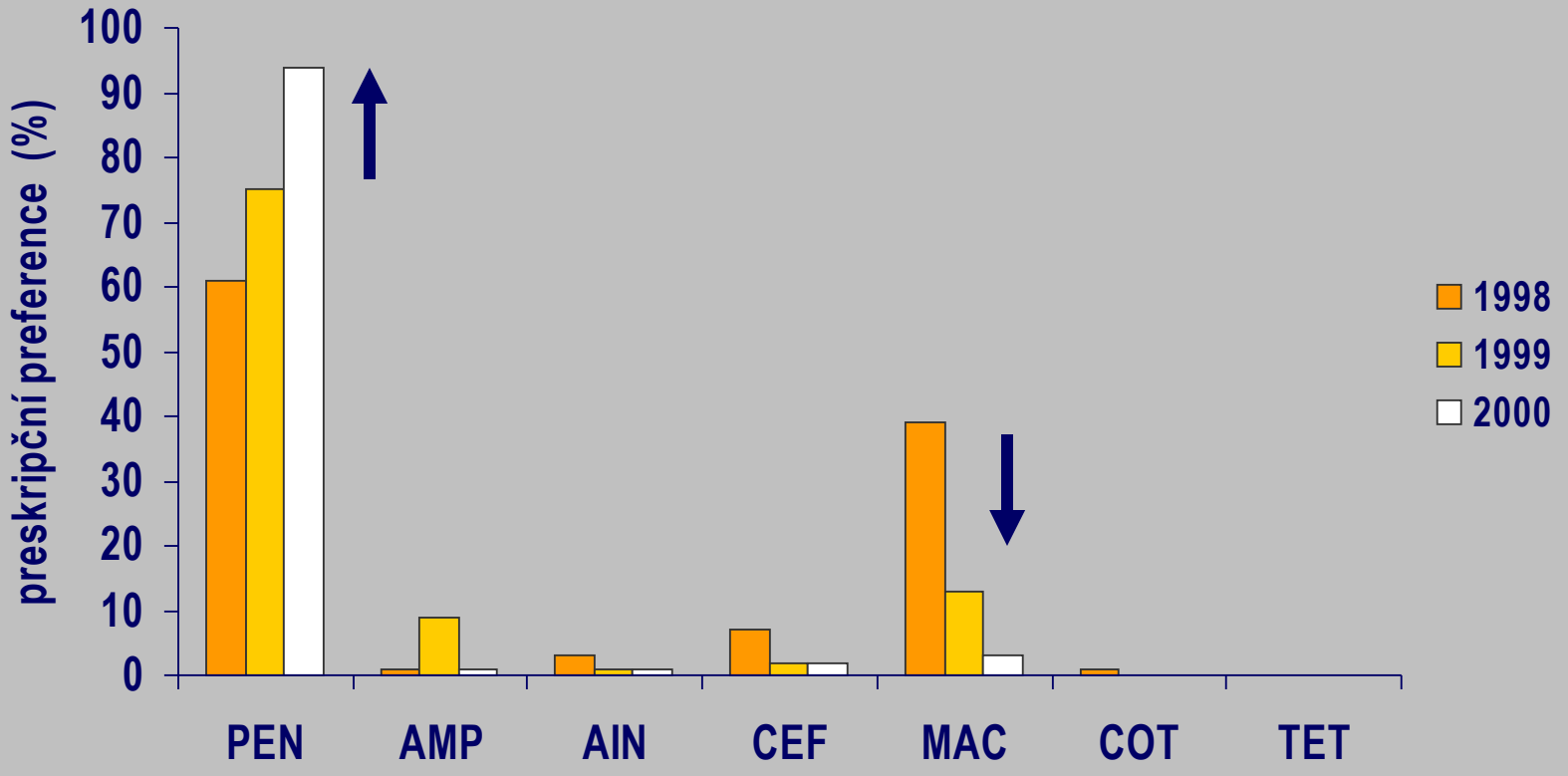
Spiramycin
clinical use

- **same as erythromycin and:**

- toxoplasmosis (primary, in pregnancy, congenital)
- macrolide of choice in patients with asthma treated with theophyllin and transplant patients treated with cyclosporin (interactions)
- stomatological infections

Changes of prescribing in acute tonsillopharyngitis

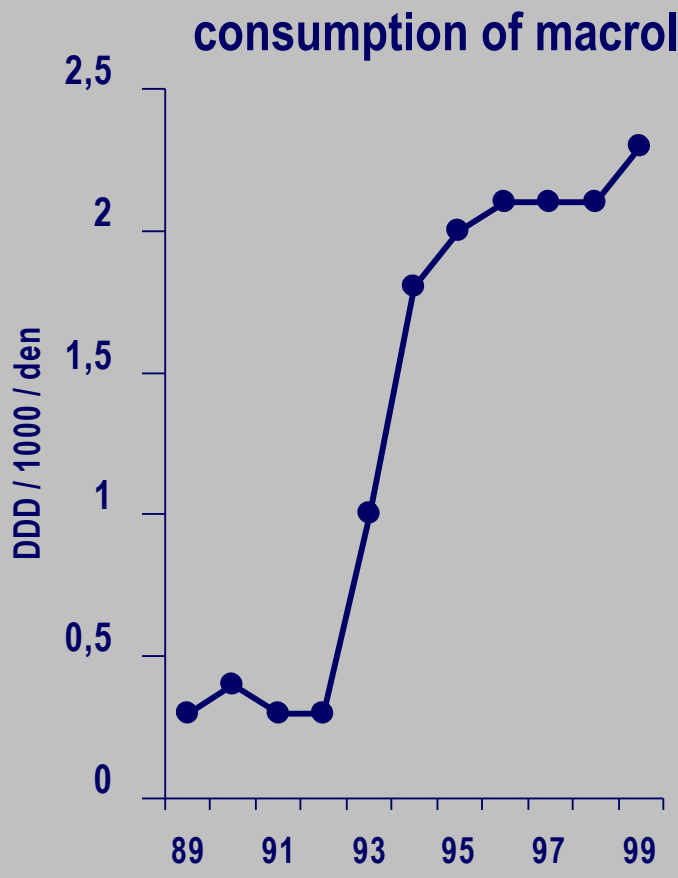
repeated prescribing audit in 10 pediatricians (1998-99-2000)

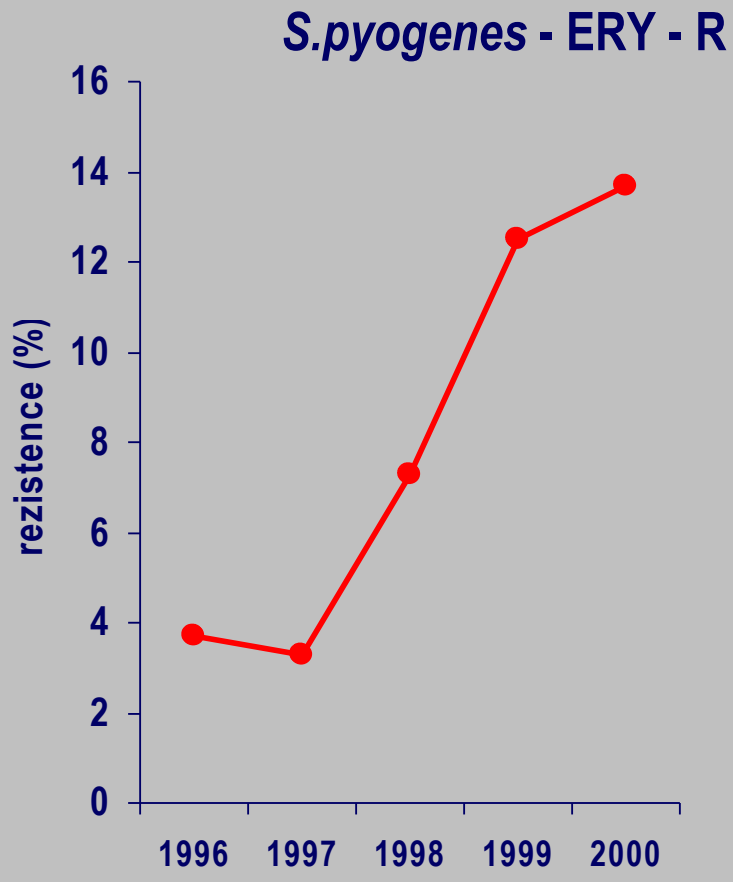


PEN - penicilin, **AMP** - aminopeniciliny, **AIN** - ko-aminopeniciliny, **CEF** - cefalosporiny, **MAC** - makrolidy, **COT** - co-trimoxazol, **TET** - tetracykliny

Consumption of macrolides and resistance

Streptococcus pyogenes in the Czech republic





LINCOSAMIDES

Lincosamides
agents

- **lincomycin**
- **clindamycin**

Lincosamides
charakteristika skupiny

- proteosynthesis inhibitors
- bacteriostatic action
- time-dependent action
- good tissue and intracellular penetration
- low toxicity
- resistance – enzymatic (inducible or constitutive MLS type)

Lincosamides - clindamycin
characteristics, pharmacokinetics and dosing

- characteristics:
  - lincosamide antibiotic for oral and parenteral use
- pharmacokinetic parameters:
  - biological availability 80 - 90%
  - biological half-life 2 - 3 h
  - protein binding 94%
  - volume of distribution 43-74 l/m^2
- dosing (adults):
  - single dose p.o.: 150 - 300 - 450 mg interval: 6 h
  - single dose p.e.: 300 - 1200 mg interval: 6 h
  - maximum daily dose: 4,8 g

Lincosamides - lincomycin
charakteristics, pharmacokinetics and dosing

- characteristics:
  - lincosamide antibiotic for oral and parenteral use
- pharmacokinetic parameters:
  - biological availability 20 - 35%
  - biological half-life 4 - 6 h
  - protein binding 72%
- dosing (adults):
  - single dose p.o.: 500 mg interval: 6-8 h
  - single dose p.e.: 600 - 2400 mg interval: 6-8 h
  - maximum daily dose: 8,0 g

Lincosamides
priorities of clinical use

- skin and soft tissue infections (staphylococcal, streptococcal)
- bone and joint infections (osteomyelitis, arthritis, spondylodiscitis)
- streptococcal infections (allergy to penicillin, invasive infections)
- infections due to anaerobes
- actinomycosis (alternative to penicillin)
- bacterial vaginosis
- acne
- toxoplasmosis

STREPTOGRAMINES

Streptogramines - quinopristin / daphlopristin
characteristics

- **peptide antibiotics**
- **group A and B streptogramines (synergy)**
- **pristinamycin IIA, pristinamycin IA**

- infections due to *Enterococcus faecium* resistant to vancomycin
- infections due to multi-drug resistant staphylococci (MRSA)
- infections due to multi-drug resistant pneumococci (PEN, ERY)

Streptogramines - quinopristin / daphlopristin
administration, dosing, use

- parenteral use (i.v.)
- 7,5 mg / kg every 8 h

- **serious infections due to multi-drug resistant strains of *Enterococcus faecium*, staphylococci and pneumococci**

OXAZOLIDINONES

Oxazolidinones
characteristics

- unique chemical structure
- proteosynthesis inhibitors
- mostly bakteriostatic action
- time-dependent action (important PAE)
- excellent tissue and intracellular penetration
- unique pharmacokinetics, excellent biological availability
- same kinetic parameters for p.o. and p.e. administration
- low toxicity
- resistance – very rare

Oxazolidinones - linezolid
antimicrobial action

grampositive bacteria

- **staphylococci** (incl. strains resistant to oxacillin - MRSA)
- **streptococci, pneumococci** (incl. strains resistant to penicillin)
- **enterococci** (incl. strains resistant to glykopeptides)

Oxazolidinones - linezolid
dosing and priorities of clinical use

dosing

- **oral** 600 mg every 12 h
- **parenteral** 600 mg every 12 h

main indications

- **serious infections due to multi-drug resistant G+ patogens**
  - community acquired and nosocomial pneumonia (G+ patogens)
  - skin and soft tissue infections
  - other serious grampositive infections (not approved)

CHLORAMPHENICOL

Chloramphenicol
characteristics

- the first broad-spectrum antibiotic
- proteosynthesis inhibitor
- bacteriostatic action
- time-dependent action
- excellent tissue and intracellular penetration
- excellent CSF penetration
- high toxicity (aplastic anemia, gray baby syndrome)
- resistance – enzymatic

Chloramphenicol
antimicrobial spectrum

- staphylococci, streptococci and pneumococci
- enterobacteria, non-fermentative G- rods
- salmonelae incl. S. typhi, shigelae
- Bordetella, Haemophilus, Neisseria
- anaerobes incl. Actinomyces spp.
- Rickettsia spp.

Chloramphenicol
dosing and priorities of clinical use

- **dosing (adults):**
  - 50 mg / kg and day in 4 single doses (interval 6 h)

- **infections due to S. typhi and other serious Salmonella inf.**
- **infections due to Rickettsia spp.**
- **bacterial meningitis**
- **invasive Haemophilus infections, pertussis**
- **destructive lung lesions due to anaerobic bacteria**
- **eye infections (local treatment)**

TETRACYCLINES

Tetracyclines
characteristics

- broad-spectrum antibiotics
- proteosynthesis inhibitors
- bacteriostatic action
- time-dependent action
- excellent tissue and intracellular penetration
- moderate toxicity
- resistance – active efflux, change of target structure

Tetracyclines
antimicrobial spectrum

- **grampositive cocci**
  - staphylococci, streptococci (excl. S.agalactiae, enterococci),
- **grampositive rods**
  - Actinomyces, Listeria, Clostridium, B.anthracis
- **gramnegative bacteria**
  - Haemophilus, Neisseria, Moraxella, Legionella, Brucella, Francisella, Vibrio, Campylobacter, Helicobacter, Aeromonas, Plesiomonas,
- **others**
  - Mycoplasma, Chlamydia, Rickettsia, Coxiella, Treponema, anaerobes

Tetracyclines
priorities of clinical use

- **respitatory tract infections**
  - atypical pneumonia (infection due to *Mycoplasma pneumoniae* or *Chlamydia pnemoniae*)
- **gastrointestinal infections**
  - cholera, prophylaxis in travellers diarrhoea
- **urogenital infections**
  - non-gonococcal uretritis, cervicitis (infections due to Chl.trachomatis, Mycoplasma hominis, Ureaplasma urealyticum)
  - Lymphogranuloma venereum
  - pelvic inflammatory disease

Tetracyclines
priorities of clinical use

- **another indications**
  - lyme borreliosis
  - brucelosis
  - trachoma
  - Q fever
  - relapsing fever
  - acne

Tetracyclines - doxycyclin
dosing

- common dosing
  - 200 mg 1st day, then 100 mg once daily
- serious infections
  - 200 mg once daily (100 mg every 12 h)
- acne vulgaris
  - 50 mg daily during 6 weeks

RIFAMYCINES

Rifamycines - rifampicin
characteristics

- inactivation of bacterial DNA-dependent RNA polymerase
- bactericidal action
- excellent tissue and intracellular penetration
- frequent occurence of resistance (use in combinations is necessary)

Rifamycines - rifampicin
antimicrobial spectrum

- *Mycobacterium tuberculosis* and other mycobacteria
- staphylococci (*St. aureus* and CoNS)
- streptococci and pneumococci
- gonococci, meningococci

Rifamycines - rifampicin
priorities of clinical use and dosing

- tuberculosis and mycobacterial infections (incl. lepra)
- serious multi-drug resistant staphylococcal infections (endocarditis, …) in combinations with glycopeptides (event. with oxacillin)
- prophylaxis in occurence of invasive meningococcal disease (elimination in nasopharyngeal carriers)

- oral and intravenous administration
- dosing 300 - 600 mg every 12 h

CO-TRIMOXAZOLE

Co-trimoxazole
characteristics

- combination of sulphonamide (sulfametoxazole - 400 mg) and diaminopyrimidine (trimethoprime - 80 mg) - ratio 5:1
- bacteriostatic, event. bactericidal action
- good penetration to body fluids and tissues (incl. CNS)
- relatively broad spectrum incl. some protozoa (*Pneumocystis carinii*)
- resistence mainly in sulphonamide part

Co-trimoxazole
antimicrobial spectrum

- staphylococci and pneumococci
- Haemophilus spp.
- enterobacteria (incl. salmonellae and shigellae)
- acinetobacters, *B. cepacia*, *S. maltophilia*
- *Nocardia asteroides*
- *Pneumocystis carinii*

Co-trimoxazole

priorities of clinical use and dosing

- pneumocystis pneumonia
- nocardiosis
- urinary tract infections
- acute exacerbation of chronic bronchitis
- acute otitis media

- dosing (adults): 960 - 1440 mg every 12 h

POLYPEPTIDES

Polypeptides
characteristics

- polypeptide antibiotics (polymyxins)
- effective against gramnegative rods
  - enterobacteria, pseudomonads, acinetobacters
- high toxicity (nephrotoxicity, neurotoxicity)

- polymyxin B - local use
- polymyxin E (colistin) - local and systemic use

Polypeptides - colistin
priorities of clinical use and dosing

- **nosocomial multi-drug resistant gramnegative infections**
- **cystic fibrosis (inhalation therapy)**
- **selective bacterial decontamination**

- dosing (adults) 2 MIU every 8 h (i.v., i.m.)

NITROIMIDAZOLES

Nitroimidazoles
characteristics

- **metronidazole, ornidazole** (p.e., p.o. and local use)

- **antiparasitic agents** (protozoal infections)
- **antibacterial agents** (anaerobes)

- **common dosing** 500 mg every 8 h
- **main indications**
  - anaerobic infections of different localisation
  - postantibiotic colitis - CDAD (oral administration of solution)
  - bacterial vaginosis

NITROFURANS

Nitrofurans
characteristics

- **nitrofurantoin (oral administration)**

- urinary tract infection chemotherapeutic agent
- relatively broad-spectrum (*E.coli*, enterococci, …)
- treatment of uncomplicated UTI's, especialy community acquired (acute cystitis)
- long-term prophylaxis of recurrent UTI's

- **dosing (therapy)** — **100 mg every 6 h**
- **dosing (prophylaxis)** — **100 mg once daily ("evening dose")**

ANTIMYCOTICS
AZOLES

Antimykotika
azoles

- **ketoconazole (oral treatment of mucous membrane candidasis)**

azoles for treatment systemic mycoses:

- **fluconazole** **(C. albicans)**
- **itraconazole** **(C. albicans, non-albicans candida)**
- **voriconazole** **(C. albicans, non-albicans candida, aspergillosis)**

Antimycotics
azoles - dosing

- **fluconazole (C. albicans)**
  - p.o.: 150 mg single dose, 50-100 mg every 24h
  - p.e.: 200 - 400 mg every 24 h
- **itraconazole (C. albicans, non-albicans candida)**
  - p.o.: 100 - 200 mg every 12 - 24 h
  - p.e.: 200 mg every 24 - 12 h
- **voriconazole (C. albicans, non-albicans candida, aspergilosis)**
  - p.o.: 200-400 mg every 12 h 1st day, then 100-200 mg every 12 h
  - p.e.: 6mg / kg every 12h. 1st day, then 4mg / kg every 12h

Azoles
main indications

	FLU	ITR	VOR
mucous membr. or skin candidasis	+	+	+
systemic, invasive candidasis	+	+	+
candidasis FLU resistant		+	+
aspergillosis		+	+

ANTIMYCOTICS
POLYENES

Antimycotics
polyenes

- nystatine (local polyene antimycotic agent)

- amphotericin B (systemic polyene antimycotic agent)
- liposomal amphotericin B preparations (lower toxicity)

- dosing
  - 0,25 - 1,0 - 1,5 mg / kg daily
  - lipid preparations 1 - 5 mg / kg daily