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Antibacterial drugs

Department of Pharmacology, 2020

Notes for Pharmacology II practicals

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.

Terminology

Selective toxicity

Antiseptics vs disinfectants

Antimicrobial spectrum

Post-antibiotic effect

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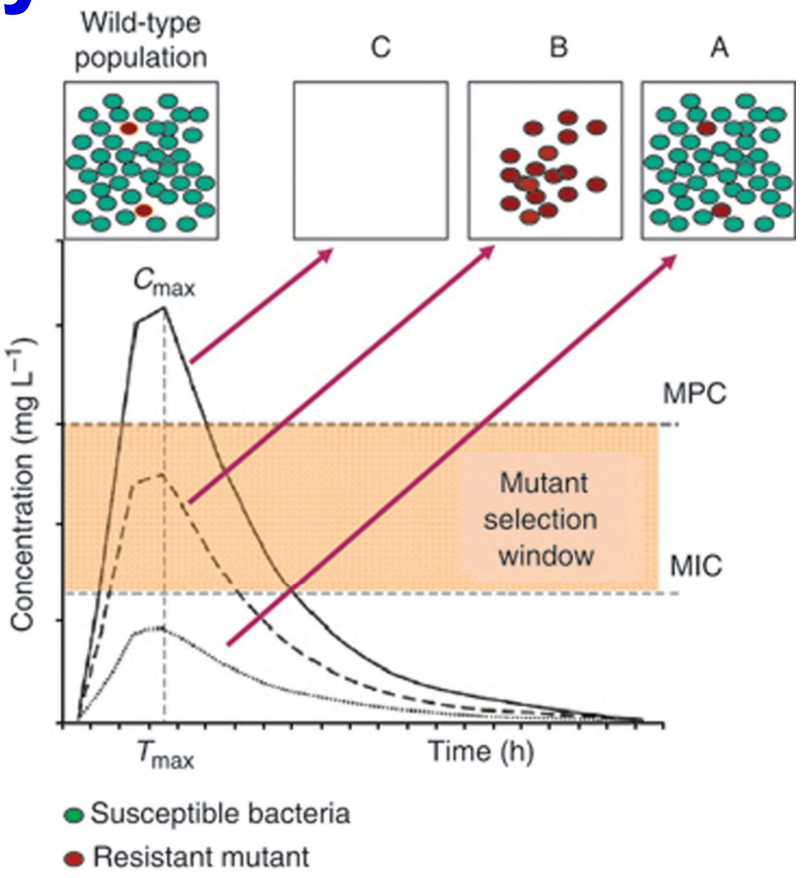
Terminology

MIC (*minimum inhibitory concentration*) – the minimum concentration of antibiotic to inhibit the growth of an organism

MAC

MPC - mutant prevention concentration (e.g. quinolones)

MSW - mutant selection window



Emergence and spread of antibiotic resistance following exposure to antibiotics
Rafael Cantón , María-Isabel Morosini
FEMS Microbiology Reviews Sep 2011, 35 (5) 977-991; DOI: 10.1111/j.1574-6976.2011.00295.x

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Terminology

Resistance to antibiotics

- chromosomal determinants
- extrachromosomal determinants: genes for resistance to antibiotics („r genes“) – R plasmids

Drug resistance can be spread:

- from person to person by bacteria
- from bacterium to bacterium by plasmids
- from plasmid to plasmid (or chromosomes) by transposons

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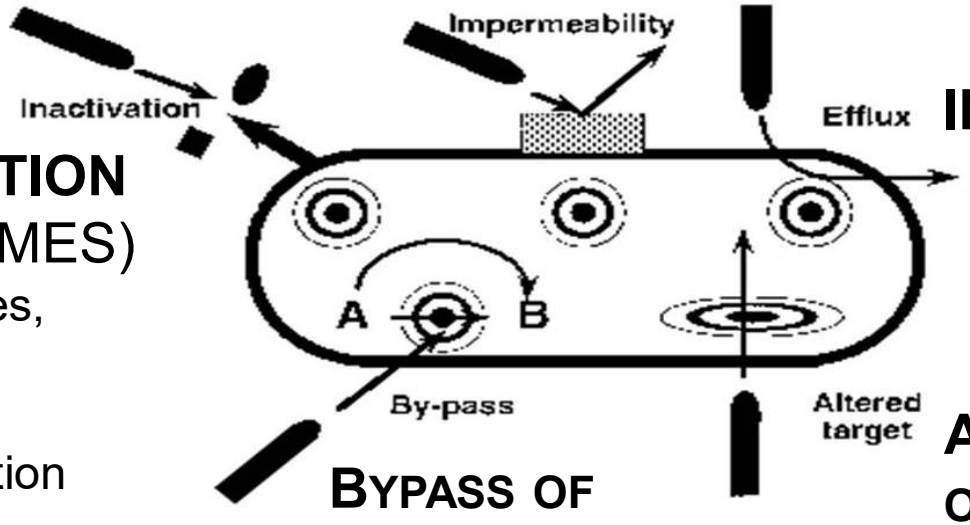
Mechanisms of resistance to antibiotics

DECREASED PERMEABILITY
(AMG, peptides, chloramphenicol)



INACTIVATION (BY ENZYMES)
(β-lactamases, acetylation, adenylation, phosphorylation etc.)

INCREASED EFFLUX (TTC, macrolides)

BYPASS OF TARGET SITE
(trimetoprim)

ALTERATION OF TARGET SITE
(AMG, erythromycine)

Possible combination of mechanisms!

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Resistance - types

1. Primary (innate)
2. Secondary (acquired)

3. Coupled
4. Crossed

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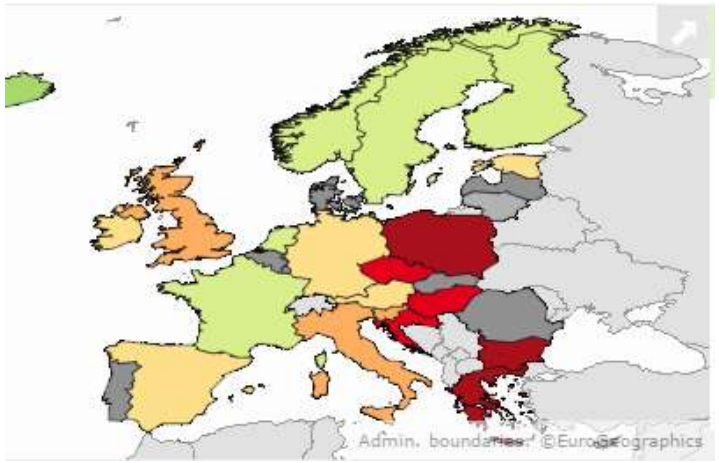
Resistance to 3rd. gen of. cephalosporines III. in *Klebsiella pneumoniae*



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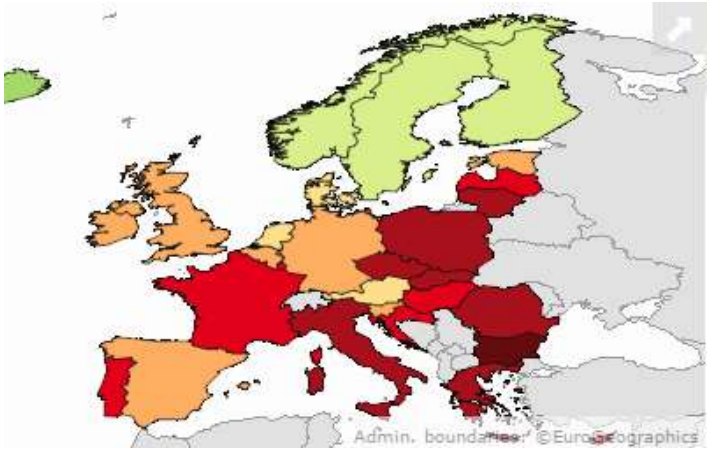

2015

European Centre for Disease Prevention and Control, EARS-Net

https://ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc

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Terminology

Pharmacodynamic index	Definition	Effect	Examples
T>MIC	Once the concentration of an antibiotic is above the MIC (typically 3-5 times greater than the MIC), there is not an increased rate of killing with increasing concentrations of antibiotic	**Time dependent**	beta-lactams
Cmax/MIC	As the concentration of an antibiotic increases, its rate of killing increases	**Concentration dependent**	aminoglycosides
AUC 0-24/MIC	The rate of bacterial killing is both related to the amount of time above the MIC and the total exposure of antibiotic to the organism	**AUC dependent**	glycopeptides

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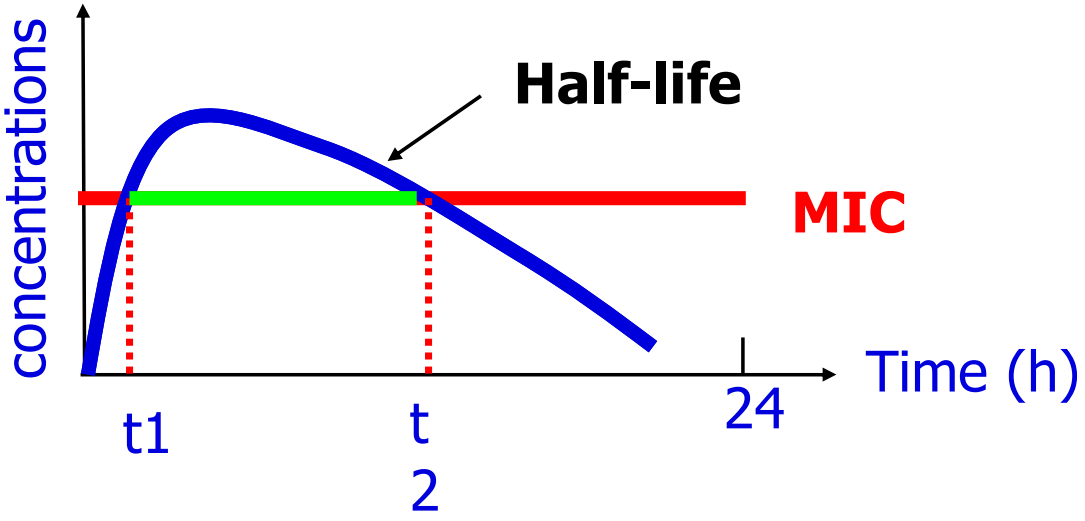
Time-dependent bactericidal effect

% T > MIC



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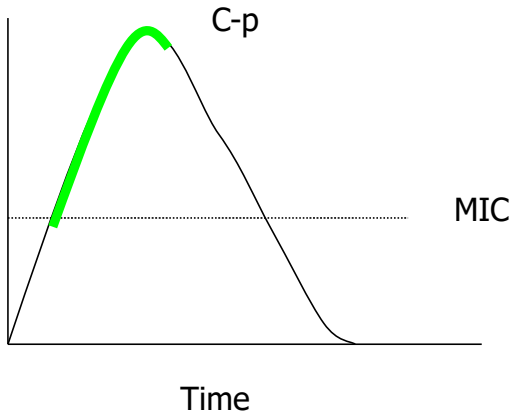
Concentration dependent effect

Cmax / MIC



PK

$$\frac{C\,\max}{MIC_{90}}$$

PD

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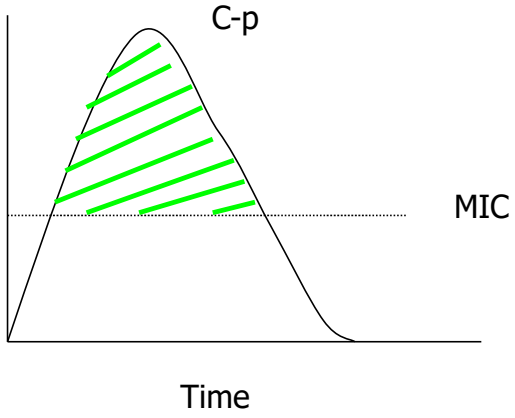
AUC dependent killing

AUC/MIC



PK

$$\frac{AUC}{MIC} = \frac{Dose / Clearance}{MIC_{90}}$$

PD

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CLASSIFICATION

1. Chemical structure

betalactams, glycopeptides, macrolides, amphenicols etc.

2. Microbial spectrum

wide spectrum
narrow spectrum

3. Extent of the effect

bacteriostatic
Bactericidal

4. Mode of the action

interfering with: cell wall
plasma membrane
inhibiting: proteosynthesis
synthesis and metabolism of nucleic acids

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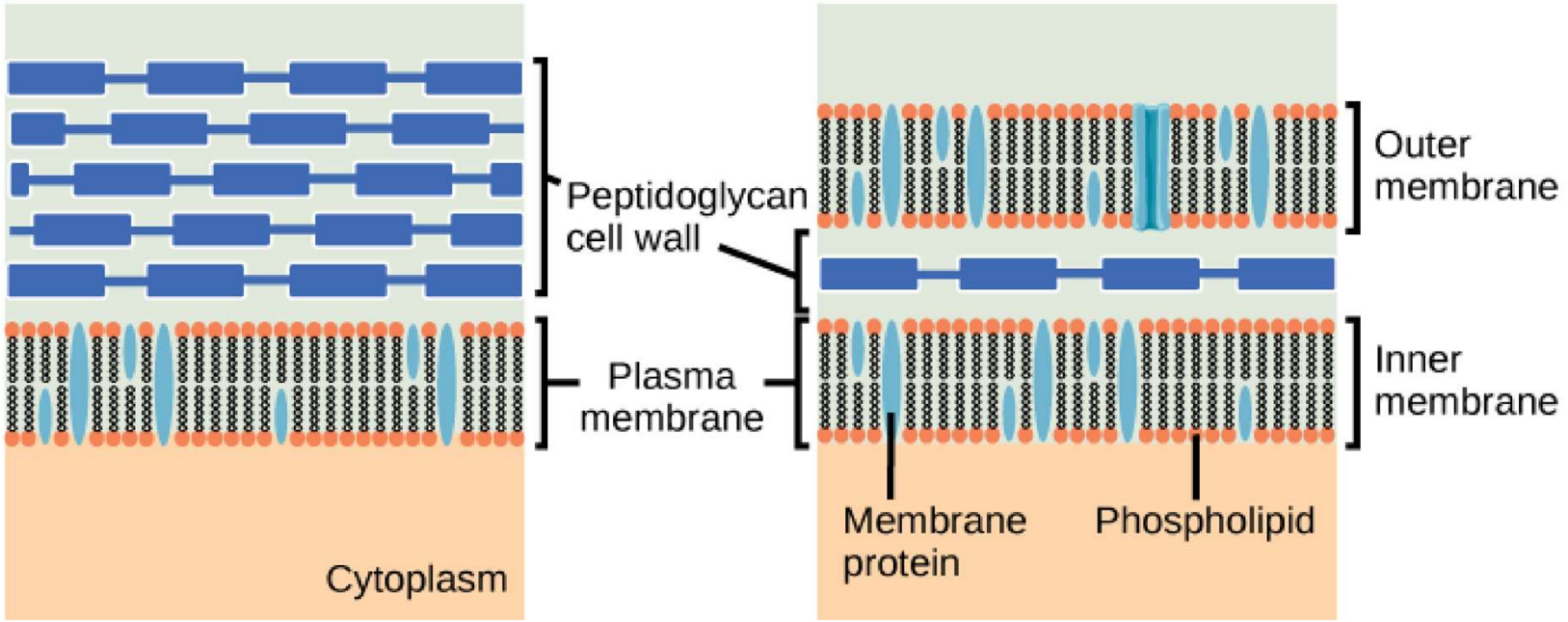
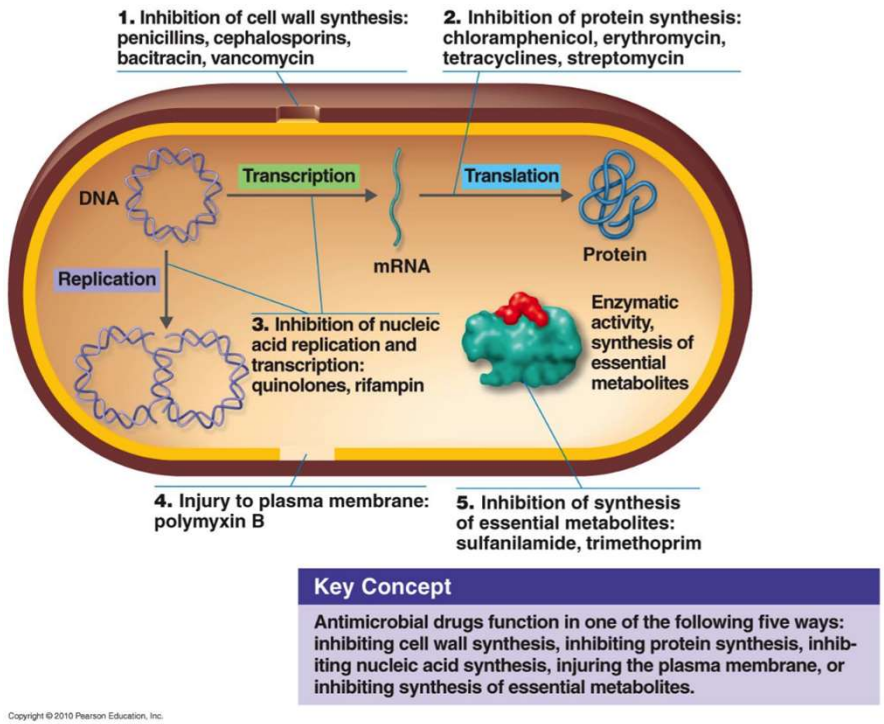


http://simbac.gatech.edu/wordpress/wp-content/uploads/2013/04/cellwall-1.png

Modes of the action

Target sites

1. Cell wall
   - G+
   - G-
2. Plasma membrane
3. Ribosomes
4. Nucleic acids
   a) bacterial topoisomerase inhibition
   b) nucleotide synthesis inhibition – folic acid



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Classification of antibacterial drugs

Antibiotics I

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

Antibiotics II (chemotherapeutics)

- sulphonamides
- pyrimidines
- quinolones
- nitroimidazoles
- nitrofurans

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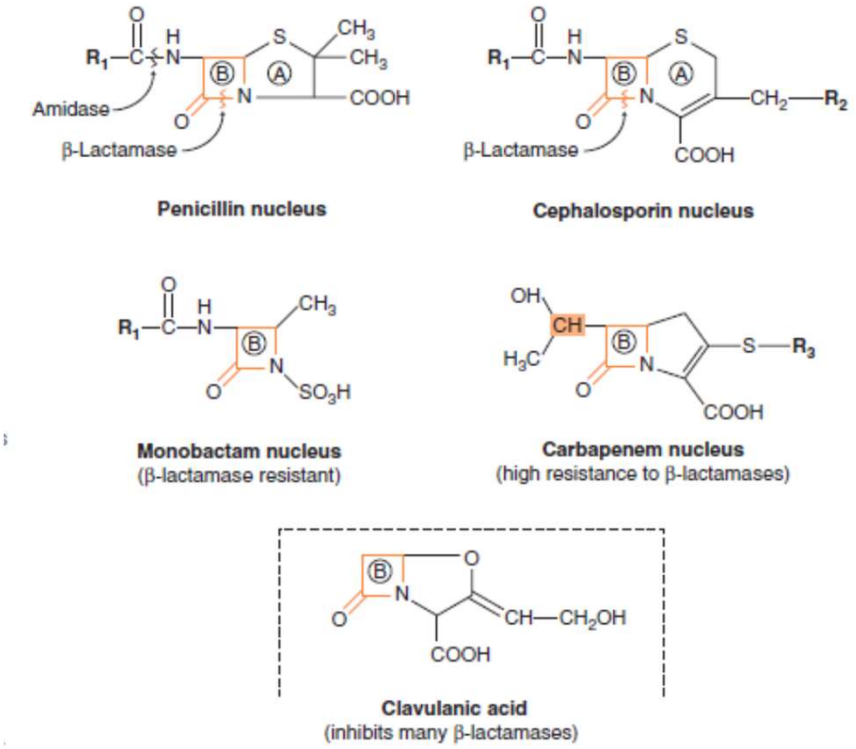
ATBs damaging the cell wall or membrane

β-LACTAMS

- penicillins
- cephalosporins
- monobactams
- carbapenems

- combination with beta lactamase inhibitors



Rang and Dale; 2012

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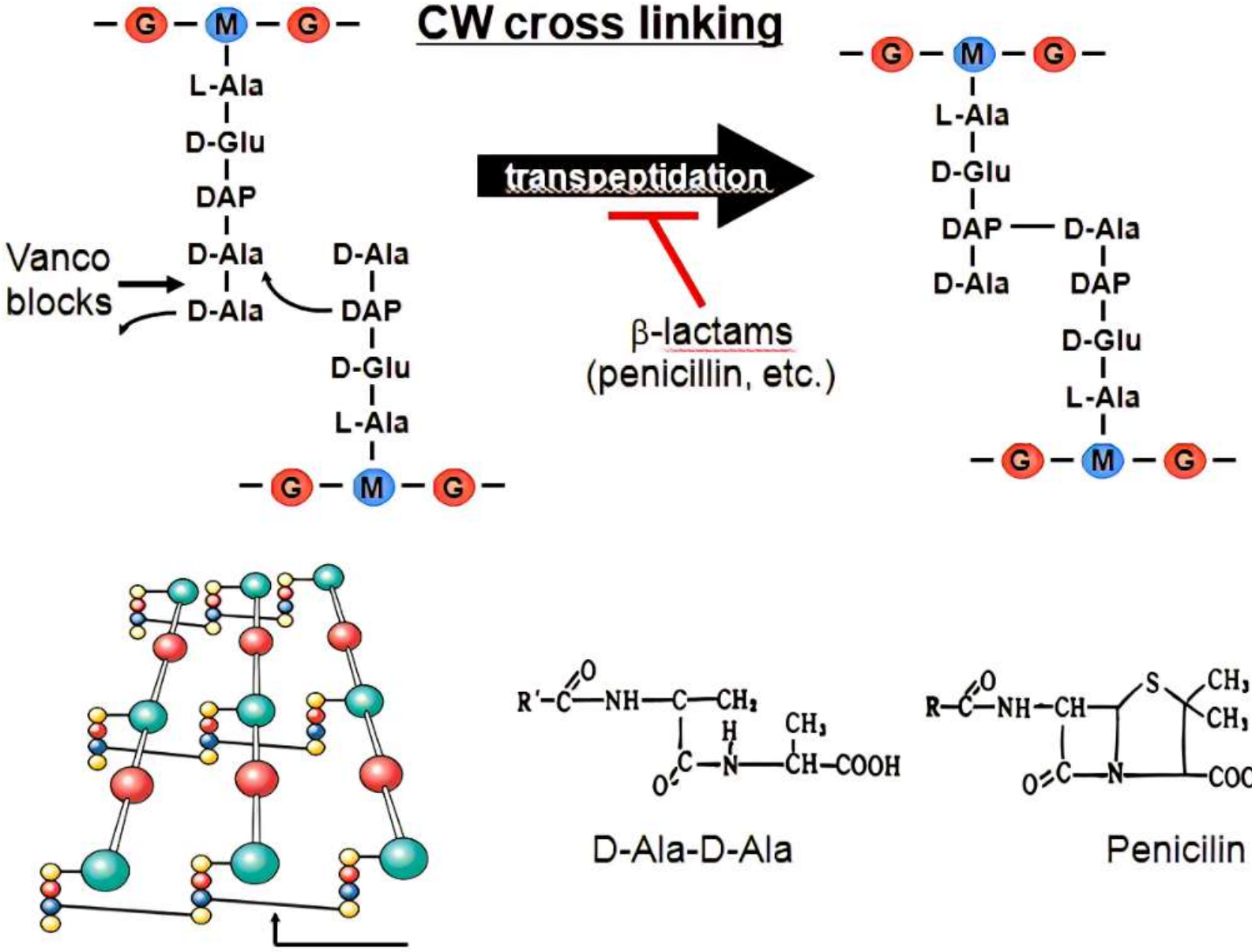
CW cross linking
G
M
G
L-Ala
D-Glu
DAP
D-Ala
D-Ala
Vanco blocks
D-Ala
DAP
D-Glu
L-Ala
transpeptidation
β-lactams
(penicillin, etc.)
D-Ala
DAP
D-Glu
L-Ala
D-Ala-D-Ala
Penicillin

β-lactams

MofA: destruction of cell wall, PBP, transpeptidases, autolysis
bactericidal effect
oral and parenteral administration

AE: low toxicity
well tolerated
allergic reactions

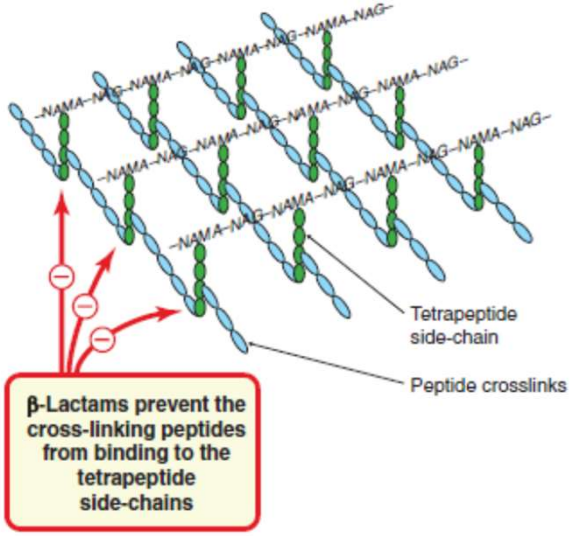

Fig. 49.2 Schematic diagram of a single layer of peptidoglycan from a bacterial cell (e.g. *Staphylococcus aureus*), showing the site of action of the β-lactam antibiotics. In *S. aureus*, the peptide crosslinks consist of five glycine residues. Gram-positive bacteria have several layers of peptidoglycan. (NAG, *N*-acetylglucosamine; NAMA, *N*-acetylmuramic acid; more detail in Fig. 49.3.)

Rang and Dale; 2012

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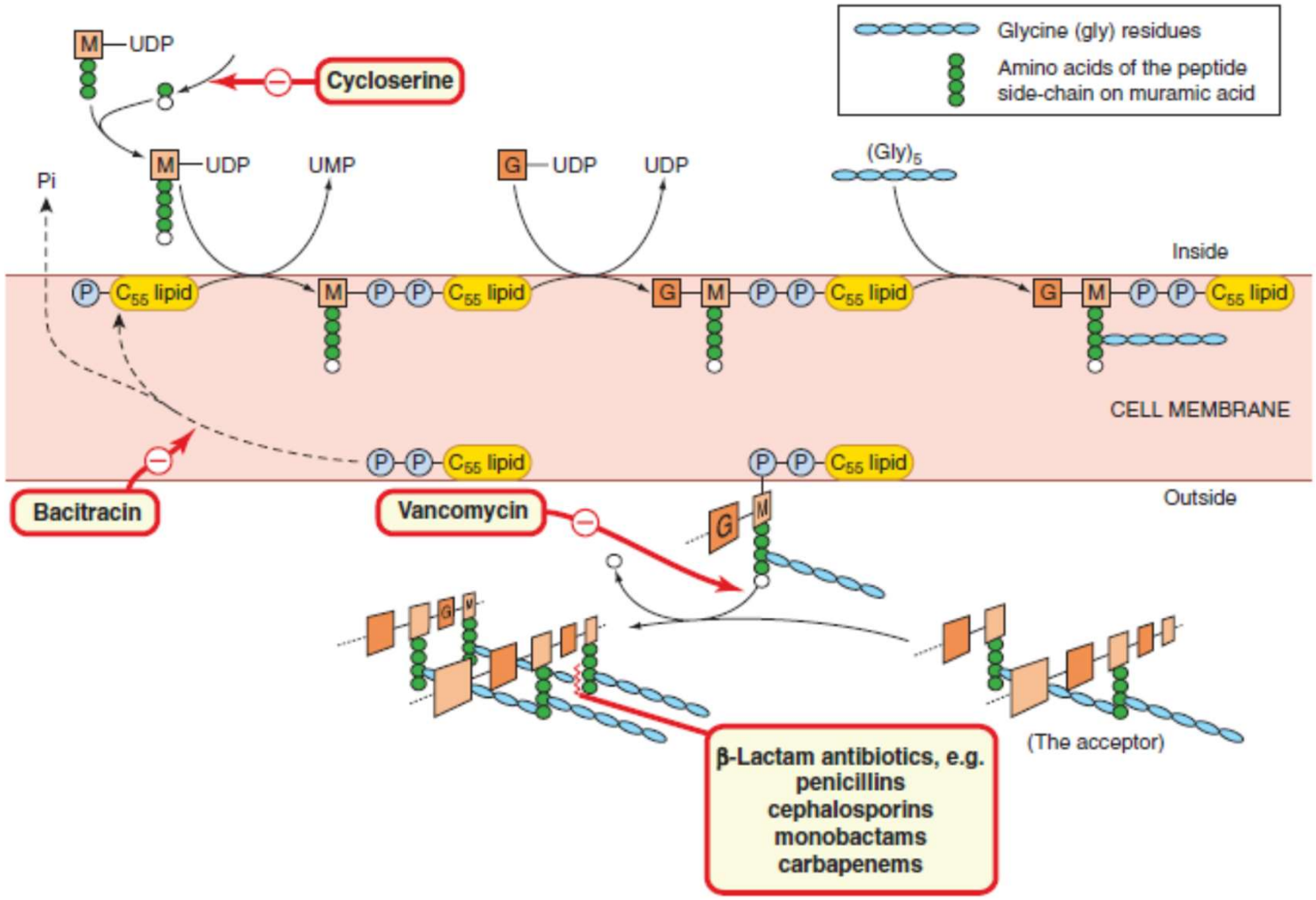

Fig. 49.3 Schematic diagram of the biosynthesis of peptidoglycan in a bacterial cell (e.g. *Staphylococcus aureus*), with the sites of action of various antibiotics. The hydrophilic disaccharide–pentapeptide is transferred across the lipid cell membrane attached to a large lipid (C_{55} lipid) by a pyrophosphate bridge (–P–P–). On the outside, it is enzymically attached to the 'acceptor' (the growing peptidoglycan layer). The final reaction is a transpeptidation, in which the loose end of the (Gly) 5 chain is attached to a peptide side-chain of an M in the acceptor and during which the terminal amino acid (alanine) is lost. The lipid is regenerated by loss of a phosphate group (Pi) before functioning again as a carrier. G, *N*-acetylglucosamine; M, *N*-acetylmuramic acid; UDP, uridine diphosphate; UMP, uridine monophosphate.

Rang and Dale; 2012

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PENICILLINS

natural or semisynthetic

Classification: narrow spectrum
anti-staphylococcus
wide spectrum

PK: i.v., i.m., p.o.

-well distributed to body fluids, passing into joints, bile, saliva, milk and across placenta

- lipid-insolubile, do not penetrate into cells

-short $t_{1/2}$, renal excretion

-T>MIC main pharmacodynamic driver of effectiveness

-dosing every 6-8h, SR drug forms

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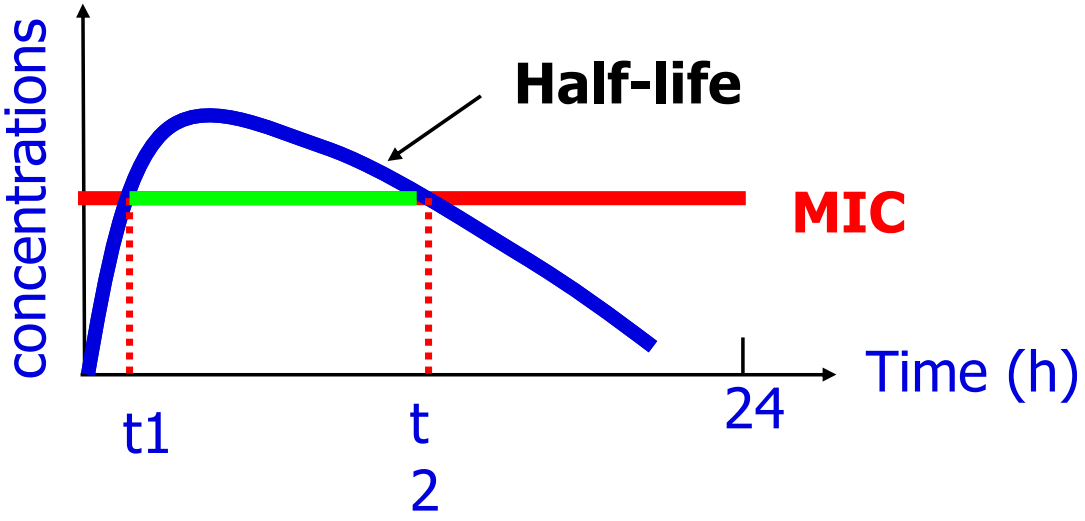
Time-dependent bactericidal effect

% T > MIC



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Penicillins

Narrow spectrum (basic) penicillins:

benzylpenicillin (PEN G)

- i.v. or i.m. (K+ salt)
- procainpenicillin (depot form)

phenoxymethylpenicillin (PEN V)

- for oral use (or benzathine-phenoxymethylpenicilin)

- respiratory tract infections, skin infections, meningitis (high doses), endocarditis and others evoked by G+ and G- cocci, streptococci, pneumococci,gonococci, meningococci, actinomycosis, anaerobic infections (gas gangrene), syphilis, borreliosis

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Penicillins

Anti-staphylococcus penicillins

- stable against β-lactamases
- *S. aureus* and streptococcal infections

methicillin

oxacillin

cloxacillin
dicloxacillin
flucloxacillin

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Penicillins

Wide spectrum penicillins
-wider spectrum againts G-: enterobacterias *(E.coli, Salmonela spp., Shigella spp., Proteus), Haemophilus spp., Enterococcus spp.*

Aminopenicillins
ampicillin
amoxicillin

respiratory infections, UTI,
otitis media, E.coli, Salmonella spp., Shigella spp., Pseudomonas, Haemophilus spp., Enterococcus spp., Proteus, H. pylori (amoxicilin)

With antipseudomonal activity

Acylureidopenicillins

- **piperacillin/tazobactam (i.v.)**

Carboxypenicillins

- tikarcillin
- temocillin

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Potentiated penicillins

Combination with β-lactamase inhibitors

clavulanic acid→ co-amoxicillin

sulbactam → i.e. sultamicillin (ampicillin + sulbactam)

tazobactam → i.e. co-piperacillin

avibactam (+ ceftazidim)

-protection against some types of β lactamases
-wider spectrum against G- (sulbactam)
-*E. coli*, *Proteus*, *Salmonella*, *Haemophilus, M. catarrhalis, Klebsiella, Neisseria, Enterobacter, Bacteroides*
-co-amoxicillin – drug of choice in otitis media and sinusitis
-ESBL production -) the need of new β-lactamase inhibitors

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CEPHALOSPORINS

- more stable against β-lactamases
- classified into 5 generations with regard to their spectrum: increasing G-, decreasing G+ sensitivity

PK: i.v., i.m., p.o.
widely distributed, some cross BBB (cefuroxime, cefotaxime, ceftriaxone)
renal excretion (ceftriaxone 40% biliary excretion)

AE: allergy often crossed with penicillins (up to 10%)
GIT dysmicrobia, changes in the blood counts
disulphiram reaction

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Cephalosporins

Ist generation
cefazolin
cefadroxil (p.o.)
G+ cocci (*staphylococci, streptococci) , E. coli, Proteus, Klebsiella, Neisserie*
other G- are usually resistant (e.g. haemophilus)
I: S. aureus infections, prophylaxis in surgery, tonsil pharyngitis, bronchitis, sinusitis, urinary infections

IInd generation
cefuroxime (cefuroxime axetil p.o.)
cefprozil

wider spectrum against *G+ i G- : H. influ., enterobacterias, Neisseria, Proteus, E. coli, Klebsiella, Moraxella catarrhalis, anaerobes* and *B. fragilis*.
I: tonsil pharyngitis, bronchitis, sinusitis, urinary infections, borreliosis

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Cephalosporins

IIIrd:

i.v.: ceftriaxon
cefotaxim
ceftazidim
cefoperazon (+ sulbaktam)

p.o.
cefixim

- *enterobacterias*, partially *pseudomonades*
- more stable against β-lactamases, higher efficacy (the best for G-)
- all i.v. agents cross BBB!!!!

I: meningitis, UTI, respiratory infections, infections of skin, bones, joints; septicemia

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Cephalosporins

IVth: cefepime, i.v.

- the widest spectrum
- *G+ and G- bacterias (no anaerobes)*
- high stability against β-lactamases, longer half life

I: pneumonia, septicemia, meningitis, intraabdominal infections, febrile neutropenia

Vth: ceftolozane, i.v. - MRSA

ceftaroline, i.v. - UTI, intaabdominal infections

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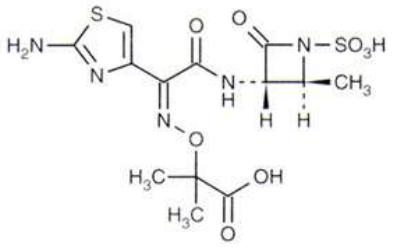
MONOBACTAMS



aztreonam (inh., inj.)
resistant against β-lactamases
narrow spectrum
aerobe G- bacilli (*Pseudomonas, Neisseria, Haemophilus*)

I: pseudomonas infections in patients with cystic fibrosis

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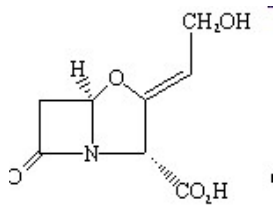
CARBAPENEMS



meropenem, i.v.
imipenem (+ cilastatin), i.v.
ertapenem , doripenem, i.v.

-reserved for the therapy of life-threatening infections caused by mixed or multiresistant flora

AE: allergy, GI intolerance, convulsions, headache

I: pneumonia, UTI, intraabdominal inf., skin and soft tissue inf., meningitis, febrile neutropenia

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GLYCOPEPTIDES

vancomycin, i.v.
teicoplanin, i.v.

MofA: cell wall synthesis inhibition – binding to pentapeptide precursor; bactericidal

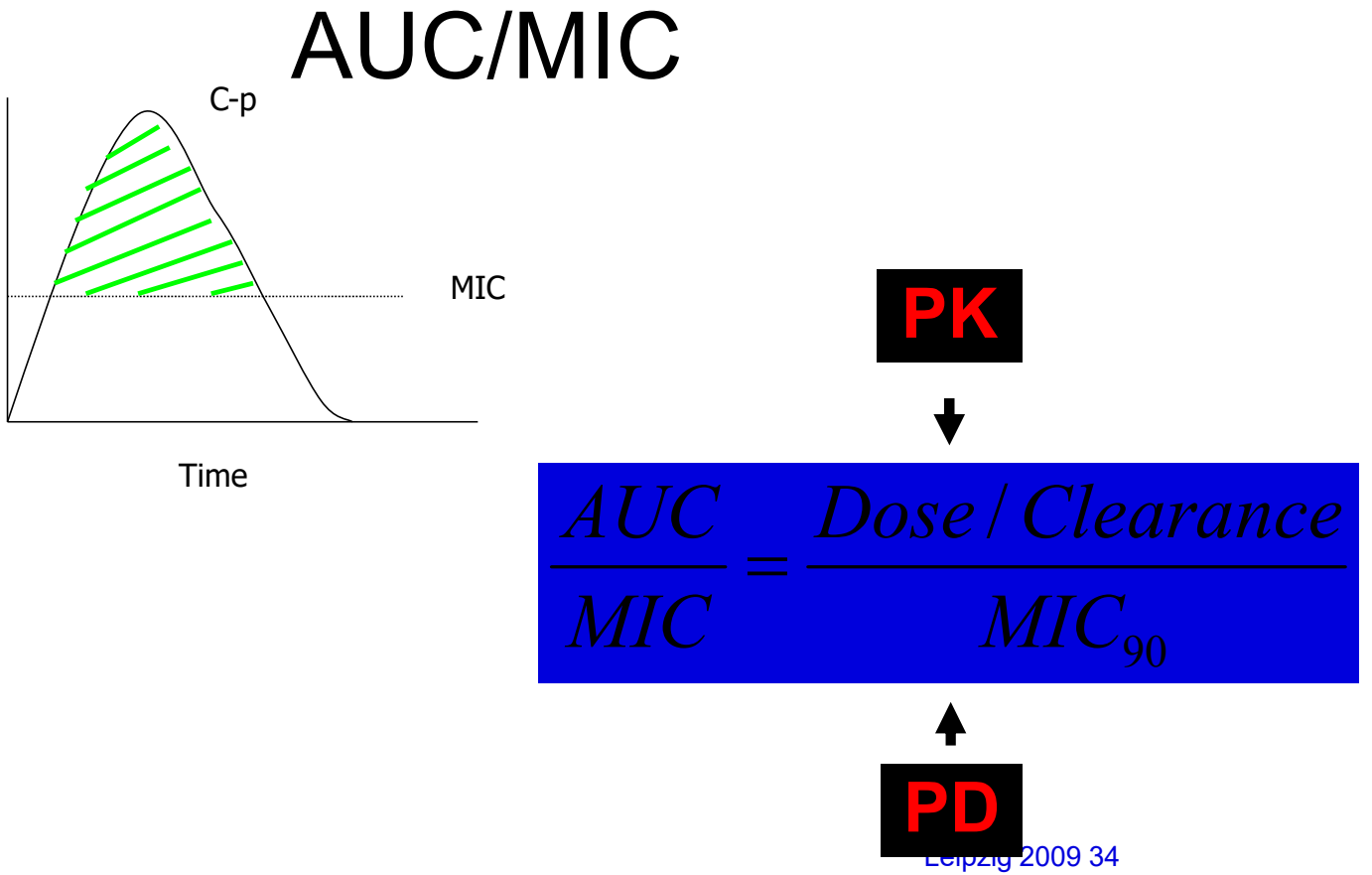
resistance, VRE; synergic effect with aminoglycosides
TDM - vancomycin

PK: i.v. infusion, min. mtb., renal excretion
I: reserve ATB for the serious, resistant G+ infections (MRSA) – endocarditis, osteomyelitis, pneumonia; local (p.o.) intestinal infections (not absorbed from gut)
AE: rashes (red man syndrome), ototoxicity, nephrotoxicity

LIPOPEPTIDES

daptomycin – only G+ (MRSA – skin, endocarditis); in combination therapy in G+-

AUC dependent killing



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LIPOGLYCOPEPTIDES

dalbavancin
telavancin
oritavancin

- similar antimicrobial spectrum with vancomycine, higher activity against G+
- dalbavancin - extremely long plasma half-life (14 days)
- perspective therapy (skin infections, OPAT regimen - Outpatient Parenteral Antimicrobial Therapy)

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POLYPEPTIDES

colistin (**colistimethate;** polymyxin E), i.v., inh.
polymyxin B

MofA: disrupts the plasma membrane by its detergent activity

I: aerobic, multiresistant G- (*Ps. aeruginosa, Haemophilus, Klebsiella)*
local application (oph., ORL, GYN, gut decontamination, cystic fibrosis) or infusion/injection

AE: nephrotoxicity, ototoxicity, neurotoxicity!
return to use of colistin in nosocomial infections

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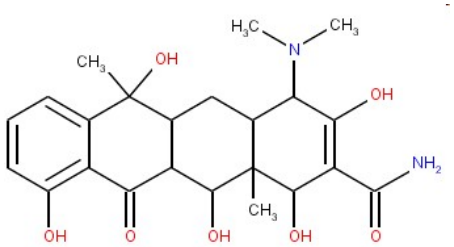
ATBs damaging proteosynthesis

TETRACYCLINES



doxycykline, p.o.
tigecycline (glycylcyclin), i.v. - *Clostridium difficile therapy!*
minocycline, tetracycline

MofA: proteosynthesis inhibition – reversible binding to 30S ribosomal subunit; bacteriostatic
primary resistant staph., strept. + pneumococci!

PK: doxycycline absorption p.o., (non-absorbable complexes with cations in GIT), lipophilic, widely distributed, high conc. in bile, enterohepatic recirculation

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

I: respiratory and urinary tract infections, ORL, therapy of biliary tract inf., borreliosis, syphilis, gonorrhea, ureaplasma, leptospirosis, chlamydiosis, mycoplasmosis, acne (minocycline)

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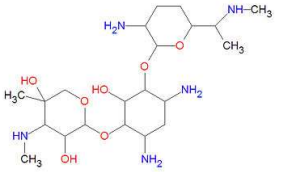
AMINOGLYCOSIDES



gentamicin, amikacin (i.v.)
isepamicin, netilmicin, tobramycin (inh.)
kanamycin (oph.), **neomycin** (oph., drm., vag.)

MofA: proteosynthesis inhibition, irreversible binding to 30S ribosomal subunit (bactericidal effect), not in anaerobic bact.
post antibiotic effect and concentration-dependent effect
PK: parent. (highly polar molecules), not cross BBB, $T_{1/2}$ 2-3hod, renal excretion (>50% unchanged)
AE: nephrotoxicity, ototoxicity, ↑↑ doses - neurotoxicity

I: sepsis, serious uroinfections (pyelonephritis), lower respiratory infections (in combination), orthopedic and surgical infections (postoperative)
syst. toxicity (TDM!) - not drugs of choice, comb. therapy (β-lactams)

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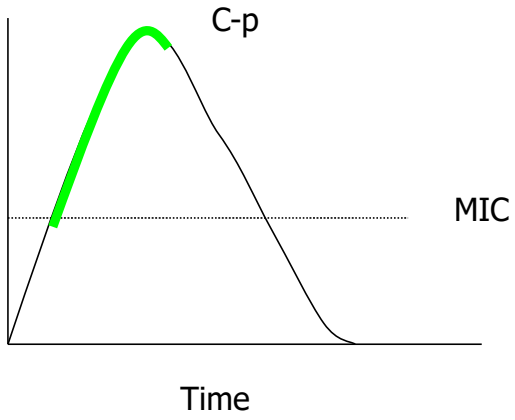
Concentration dependent effect

Cmax / MIC



PK

$$\frac{C\,\max}{MIC_{90}}$$

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Administration of aminoglycosides

- in combination therapy
- in one daily dose
- concentration dependent effect+ post antibiotic effect
- more daily doses
- synergic effect in comb. with β-lactams (exceptionally glycopeptides)
- in bacterial endocarditis caused G+ cocci (enterococci, staphylococci)

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AMPHENICOLS

chloramphenicol, i.v., oph., drm.

MofA: protein synthesis inhibition, binds to 50S ribosomal subunit, bacteriostatic, wide spectrum (incl. anaerobic bact.)

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

AE: myelosuppression: reversible vs. irreversible (aplastic anemia), grey baby syndrome, neurotoxicity, GIT intolerance, suprainfection

I: bacterial meningitis, typhus and paratyphus, serious pneumonia (abscessing forms), anaerobic and mixed flora infections, abdominal and serious invasive haemophilus infections, loc. conjunctivitis

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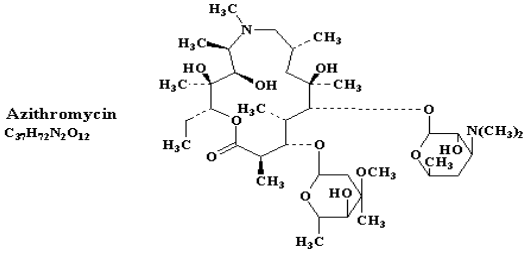
Macrolides



- **clarithromycin, azithromycin**
- **roxithromycin, spiramycin**
- erythromycin (drm.)

MofA: reversible binding to 50S ribosomal subunit, translocation block
PK: p.o. admin., CYP3A4 inhibitors (strongest erythromycin, clarithromycin), P-gp inhibitors,

Spectrum: G+ G- microbes (mycoplasmas, chlamydia, campylobacters, *Neisseria, Legionellla sp., Toxoplasma gondii, H. pylori*)

- increase in resistance in streptococci in the last years
- crossed resistance – MLSB (macrolide–lincosamide–streptogramin B) phenotype

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Macrolides

- **AE:**
  - GIT intolerance – diarrhea, anorexia, nausea, vomiting, cholestatic jaundice
  - allergies
  - suprainfections
  - prolong. QT int.

- **drug interactions**
  - CYP inhibitors
  - increase in blood levels of statins, antiepileptic drugs, BZD, antidepressants, monoclonal antibodies, , immunosuppressant drugs (cyclosporine, tacrolimus), warfarin
  - decrease in effects of clopidogrel, betalactams, lincosamides

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Macrolides

clarithromycin, i.v., p.o.

- both upper and lower respiratory infections, *Mycobacterium leprae, otitis media*, skin and soft tissues
- in combination therapy *Helicobacter pylori*
- not in pregnant women (interference with angiogenesis)
- prolongs QT interval
- high risk of drug interactions

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Macrolides

azithromycin, p.o.

- best penetration to most tissues
- less drug interactions
- **long $T_{1/2}$**
- **post-antibiotic effect**
- **DO NOT use in common infections, tonsillitis etc....**

roxithromycin, p.o.

- safe in pregnant women (with allergy to betalactams)

spiramycine, p.o.

- drug of choice in **congenital toxoplasmosis**
- safe in patients treated with theophylline

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ATB related to macrolides

Oxazolidinones

linezolid i.v, p.o.

- novel MofA (inhibition of proteosynthesis – blocks formation of 70S ribosome)
- G+ (MRSA, VRE, nosocomial/community pneumonia, *Cl. difficile*)
- non-selective MAO inhibitor – interactions
- serotonin syndrome

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ATB related to macrolides

Streptogramins

quinupristin
dalfopristin

} G+ (MRSA, VRE)

Ketolides

telithromycin

pneumonia, bronchitis, sinusitis, tonsillitis/pharyngitis in infections resistant to beta lactam and macrolide therapy

solithromycin – MRSA, gonococci

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LINCOSAMIDES

clindamycin, p.o., i.v., i.m., loc.

MofA: proteosynthesis inhibition – reversible binding to 50S ribosomal subunit
PK: p.o. and parent., well penetrates to teeth and bones, placenta, milk, not cross BBB
AE: allergy, pseudomembranous colitis
-crossed-resistance with macrolide

I: respiratory infections, skin and soft tissues infections, osteomyelitis, dental, intraabdominal, gyn., pneumonia, malaria, endocarditis prophylactic use, gynecologic infections (loc.), alternative treatment of beta lactams hypersensitivity

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Antibacterial drugs

Antibiotics - I

- β-lactams
- glycopeptides
- polypeptides
- amphenicols
- tetracyclines
- makrolides
- makrolides related ATBs
- lincosamided
- aminoglycosides
- ATBs for local treatment

Antibiotics – II (previously called chemotherapy)

- sulphonamides
- pyrimidines
- quinolones
- nitroimidazoles
- nitrofurans
- ansamycins

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Drugs damaging synthesis of NA

Sulphonamides

Wide-spectrum:
G+ and G- bacteria, streptococci, hemophilia, actinomycetes, nocardiosis, Pneumocystis jiroveci, chlamydia, Toxoplasma gondii, Neisseria meningitides

ineffective in Pseudomonas, Proteus - resistance !!!

Bacteriostatic, in combination – bactericidal

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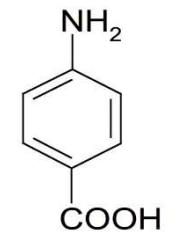
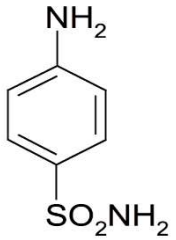
Sulphonamides – Mechanism of Action

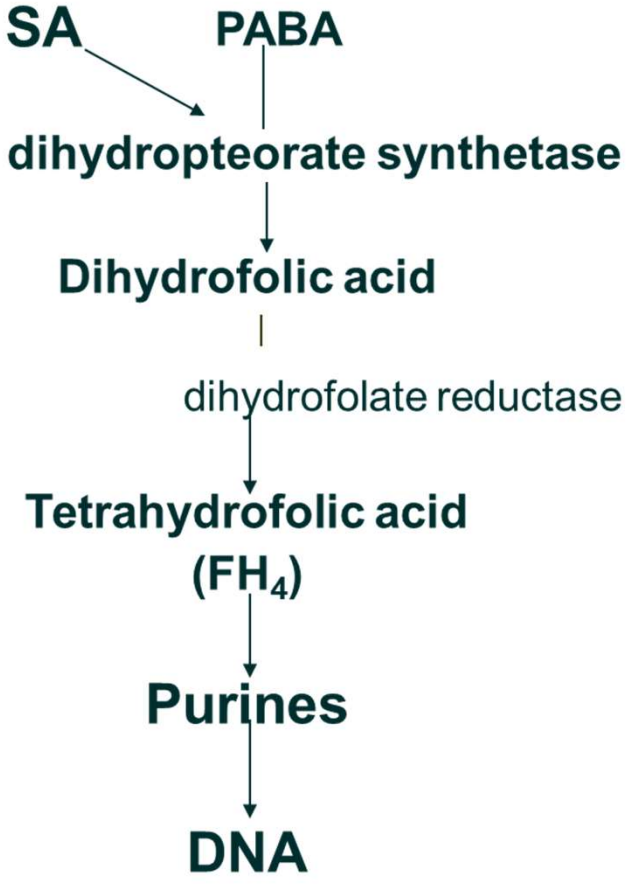
structural analogue of PABA
competitive inhibitor of the enzyme necessary for folic acid synthesis



PABA
(metabolit)



Sulfonamid
(antimetabolit)



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Sulphonamides

Long acting effect (8-10 hours)
sulphamethoxazole in combination with trimethoprim
(cotrimoxazol, SMZ-TMP)

Local use:
sulphasalazine
microflora metabolizes it to sulphapyridine (SA) and 5-aminosalicylic acid (anti-inflammatory) – inflammatory bowel disease
silver salt of sulfadiazine (local skin treatment)
sulphacetamide (oph.)

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Sulphonamides - Pharmacokinetics

- parenteral and p.o. administration, local use
- good absorption >70%
- great penetration into tissues and cells
- hepatic metabolism via acetylation and glucuronidation
- high binding to plasma proteins - displacement of other drugs and increase of their free fraction
- Drug interactions!!!
  - p.o. anticoagulants, methotrexate, sulphonylureas
- penetrate to the placenta and partly HEB
- renal excretion

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Sulphonamides - Adverse Effects

- **GIT disorders**
- **Allergic skin reactions** – rash (Stevens-Johnson´s and Lyell´s syndrome), **photosensitivity**, drug fever (5-10 days after initiation of treatment) even with topical application
- **Hematotoxicity** – hematopoietic disorders, bone marrow suppression, anemia, leucopenia, thrombocytopenia
- **Deficiency of folate -** megaloblastic anemia
- **Interstitial nephritis -** risk of precipitation in the urinary tract - acid pH of the urine (avoid of acidic foods, vitamin C, acetylsalicylic acid ...)

KI:

gravidity and breastfeeding

newborns (until 2 months) with immature enzymatic system (hyperbilirubinemia)

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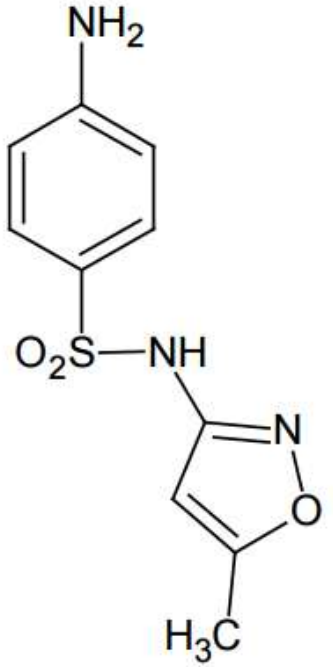
Sulphamethoxazole with trimethoprim

- fixed combination of sulphamethoxazole with trimethoprim (5:1) = **cotrimoxazol** (p.o., i.v.)
- synergistic effect of both substances in the inhibition of folic acid synthesis, reducing the risk of developing resistance, wide antimicrobial spectrum



Indications:

- Treatment of urinary tract infection
- Treatment of pneumonia caused by Pneumocystis jiroveci (prophylaxis + treatment)
- Treatment of exacerbation of chronic bronchitis
- Treatment of otitis media acuta
- Treatment of nocardiosis, toxoplasmosis

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Sulphasalazine

anti-inflammatory drug with an immunosuppressive effect

derivate of aminosalicylic acid

Indication:

Treatment of ulcerative colitis, Crohn's disease, rheumatoid arthritis (DMARDs)

after p.o. administration 30% of dose is absorbed

70% is degraded by intestinal bacteria in the colon:

sulphapyridine

inhibits the action of NK cells and transforms lymphocytes

AE - nausea, vomiting, abdominal pain, drowsiness, anuria, crystalluria and / or hematuria, convulsions

mesalasine (5-aminosalicylic salt)

inhibits cyclooxygenase and lipoxygenase in the intestinal wall, thereby preventing the formation of prostaglandins, leukotrienes and other inflammatory mediators

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Silver salt of sulphadiazine

Local use – cream, impregnated bandage

Indications:

- prophylaxis and treatment of infected skin lesions, wounds, abrasions and burns, leg ulcers and bed sores

CI:

- preterm infants and infants up to one month of age
- pregnant and nursing women

Sulphacetamide

Local use – eye drops

Indications:

- Treatment of eye infection and inflammation
- Prophylactically after injuries and burns of eye

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Sulphonamides - Indications

- UTI (SMZ-TMP)
- respiratory infection (Pneumocystis pneumonia) (SMZ-TMP)
- *otitis media acuta* (SMZ-TMP)
- malaria, nocardiosis (sulphadoxine)
- Local treatment of eye infection (sulphacetamide)
- Local treatment of skin – burns, dekubitus (silver salt of sulphadiazine)
- ulcerative colitis, Crohn´s disease (sulphasalazine s 5-aminosalicylic acid)

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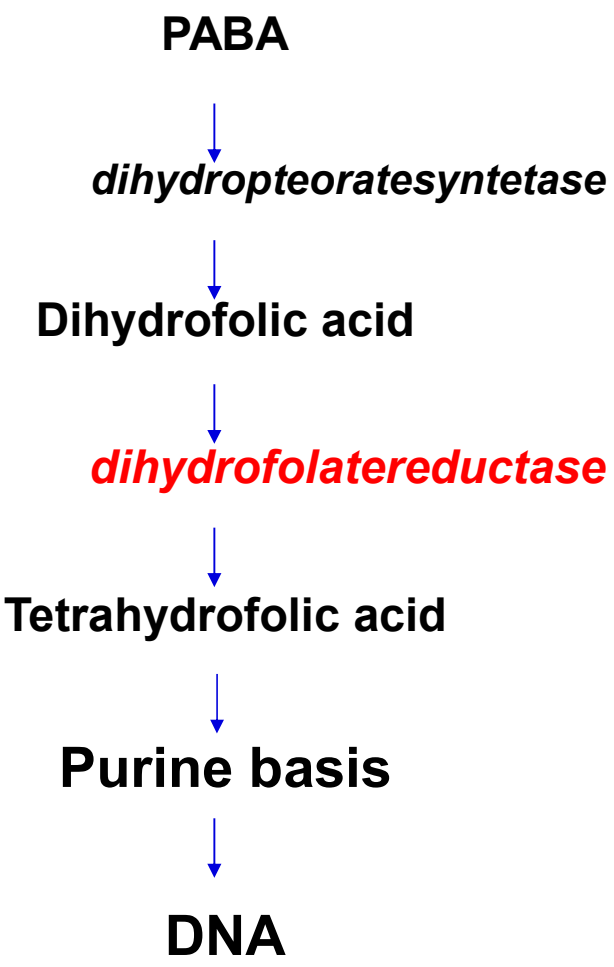
Trimethoprim

- bacteriostatic effect, spectrum similar to SA
- MA: inhibition of dihydrofolate reductase
- AE: nausea, vomiting, rash, megaloblastic anemia, leukopenia, thrombocytopenia –
- Leukemia deficiency in predisposed patients (alcoholics)
- Significant - combined treatment with SA

- **Cotrimoxazole** - sulphamethoxazole + trimethoprim (5: 1)
    - synergistic effect, bactericidal, decreased resistance



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Pyrimethamine

Indication

treatment and prophylaxis of protozoal infections - toxoplasmosis, malaria, nocardiosis
only p.o.

Adverse effects

GIT disorders - nausea, vomiting
hematopoietic disorders
exacerbation of the deficiency of folic acid in the body (in alcoholics)
convulsions
renal toxicity - crystalluria, hepatotoxicity

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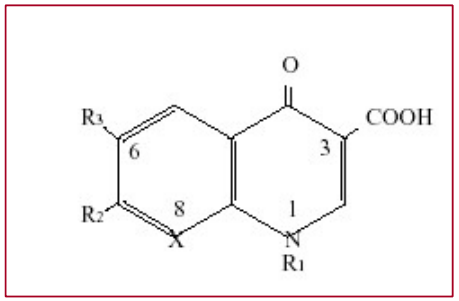
Quinolones



- bactericidal drugs
- divided into 4 generations according to their pharmacological characteristics and spectrum
- quinolons (not fluorinated) and **fluoroquinolons** (fluorinated derivates)

- newer generations - broader spectrum, better distribution in body
- parenteral and p.o. administration

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Quinolones - Pharmacokinetics

- administration p.o., i.v., oph.
- after p.o. administration – well absorbed
- decreased p.o. absorption after co-administration of antacids, Mg^{2+}, Al^{3+}, Fe^{3+}, Zn^{2+}, Ca^{2+}
- good penetration into tissues
- fluoroquinolones are excreted renal way
- the dosage should be adjusted in renal failure

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Quinolones – Mechanism of action

- selectively inhibit the synthesis of DNA, e.g. enzymatic activity of bacterial DNA gyrase:
  - topoisomerase II (for most G-bacteria)
  - topoisomerase IV (for most G+bacteria)
- inhibit DNA transcription that are required for replication, transcription, repair and recombination of bacterial DNA
- modern fluoroquinolones have a balanced activity on both enzymes - a broad-spectrum effect
- AUC dependent killing
- postantibiotic effect
- the risk of developing and increasing resistance during treatment

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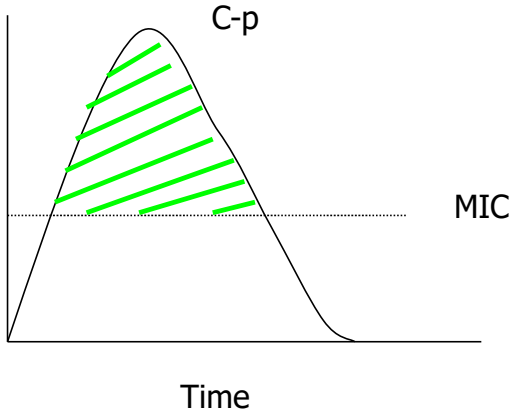
AUC dependent killing

AUC/MIC



PK

$$\frac{AUC}{MIC} = \frac{Dose / Clearance}{MIC_{90}}$$

PD

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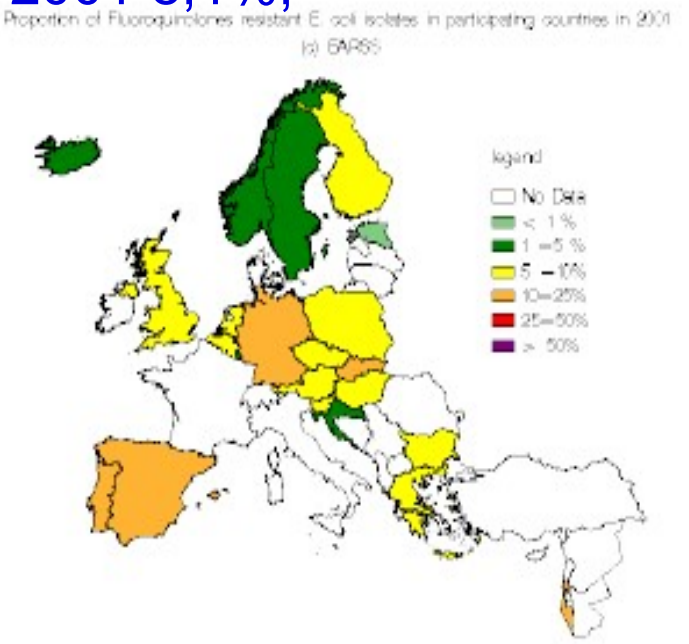
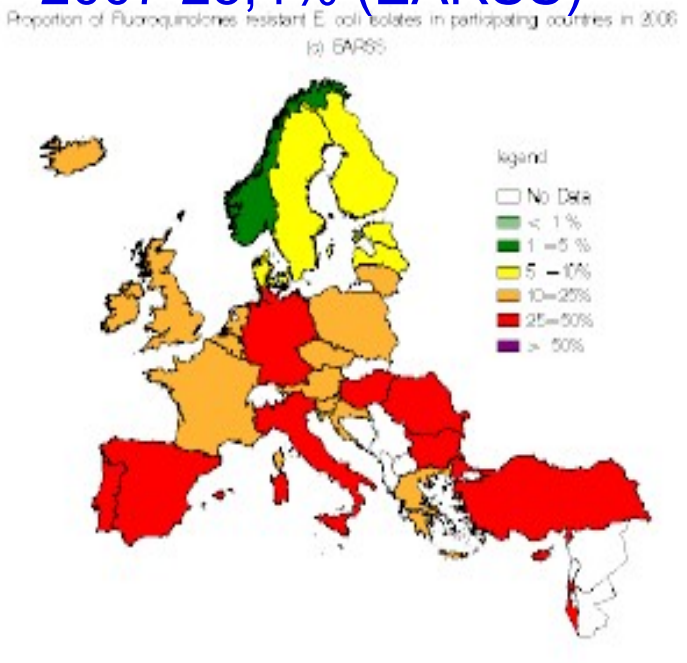
Escherichia coli and Fluoroquinolones

2001 8,1%,



2007 25,4% (EARSS)



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Quinolones – Indications in general

Treatment of infections urogenital system (UTI)
Treatment of respiratory infections
Treatment of infections skin, bones, joints, soft tissues, gonorrhoea

Fluoroquinolones are back-up drugs, indicated only in situations where other antibiotics are inactive in vitro or inappropriate for treatment because of toxicity or side effects.

Usually administered in combination with other ATBs

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Quinolones – Adverse Effects

- often, but mild (nausea, vomiting, neurotoxicity, cramps, vertigo, headache)
- GIT disorders (5 %) - nausea, vomiting
- CNS toxicity (1-4%) – headache, vertigo, **spasm, convulsion**, depression (elderly patients)
- **Prolongation of QT interval**, malignant arrhythmia
- allergy (1-2%), photo toxicity
- hepatotoxicity

IT – antacids, theophylline, caffeine, warfarin, cyclosporine
tendinitis/tendinopathy, rupture of Achilles tendon
arthropathy in animal models (in children with cartilage damage not shown except for arthralgia (1.3%) in patients with CF)

KI: newborns and children (inhibition of bone cartilage growth),
1. trimester of pregnancy, breastfeeding
epilepsy

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Quinolones - generations

Generation	Drug	Indication
I.	nalidixic acid, oxolinic acid	Drugs with limited effect on G- (urinary ATBs)
II.	**norfloxacine** **ofloxacine**	Treatment of UTI
	ciprofloxacine	Treatment of respiratory, UTI, GIT infections, bones, joints, soft tissue, skin infections enterobacteria, *P. aeruginosa*, neisseria, haemophilus, legionella, *Neisseria meningitidis,* Anthrax
	levofloxacine	Drugs with higher activity on G + (pneumococcus), respiratory ATB
III.	sparfloxacine, gatifloxacine, tosufloxacine, pazufloxacine	Drugs more effective against G+ (pneumococcus), respiratory ATBs
IV.	trovafloxacine, gemifloxacine, sitafloxacine, **moxifloxacine**	Drugs more effective against anaerobes, same spectrum as III. generation of cephalosporines

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Nitroimidazoles

primarily bactericidal effects on anaerobes and protozoa

Mechanism of action: inhibition of DNA replication

Indications:

- treatment of peptic ulcers - Helicobacter pylori eradication
- in combination with other antibiotics - peritonitis
- amoebic dysentery - intestinal disease
- trichomoniasis - caused by *Trichomonas vaginalis* - in women it is manifested by vaginal discharge, men show inflammation of the urethra, both partners should be treated simultaneously

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Nitroimidazoles

Pharmacokinetics:

- 80% absorption after p.o. administration
- good penetration into tissues and cerebrospinal fluid, through the placenta into breast milk (KI)
- renal excretion

AE:

- GIT disorders - nausea, vomiting, diarrhea
- CNS disorders (dizziness, insomnia, depression)
- dark colored urine
- long-term administration - neutropenia, leukopenia (blood count)

metronidazole (disulfiram effect)

- ornidazole
- tinidazole

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Ansamycines

- inhibit bacterial RNA polymerase, bactericidal effect

Indications:

- Treatment of pulmonary tuberculosis, G +, G-bacteria
- Mycobacterium sp.

easy resistance - always in combination!
drug interactions: inductors of CYP 450

AE:

- GIT disorders (nausea, vomiting, increase in liver enzymes, jaundice)
- Hematopoietic disorders (leukopenia, thrombocytopenia, anemia)
- arthralgia, myalgia

rifampicin
rifabutin (i.v., p.o., local use)
rifamixine (non-absorbable form) – p.o., local use

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Other MoA

Nitrofurans

bacteriostatic, at higher concentrations bactericidal ATBs
G + and G-bacteria, protozoa
Mechanism of action:

- non-specific inhibition of bacterial enzymes
- release of superoxides and other oxygen compound

Indications:
prophylaxis and treatment UTI
(**nitrofurantoin**, p.o.)
gynecological infections, including trichomoniasis
(**nifuratel**, p.o., topical treatment)
intestinal infection
(**nifuroxazid**, p.o.)

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Nitrofurans

AE:
- allergy
- GIT disorders
- hepatotoxicity
- hematopoietic disorders - megaloblastic and haemolytic anemia
- neurotoxicity
- pneumonia

KI:
- pregnant, breastfeeding
- children

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Topical antibiotics

mupirocin
MofA: proteosynthesis inhibition
I: impetigo, folliculitis, furunculosis

bacitracin + neomycin
oph, drm., nas.

fusidic acid
inhibits synthesis of proteins in cell wall
against G+ - staphylococci
I: impetigo, superficial folliculitis, skin wounds with infection; with betamethasone atopic dermatitis and contact dermatitis

retapamulin
(fusafungin)

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ATB combinations

Advantages:

1. Spectrum widening
2. Decrease of resistance development risk
3. Decrease of adverse reaction probability
4. Increase in ATB efficacy

Unsuitable combinations

drugs with similar AE (nephrotoxicity, hepatotoxicity, …)

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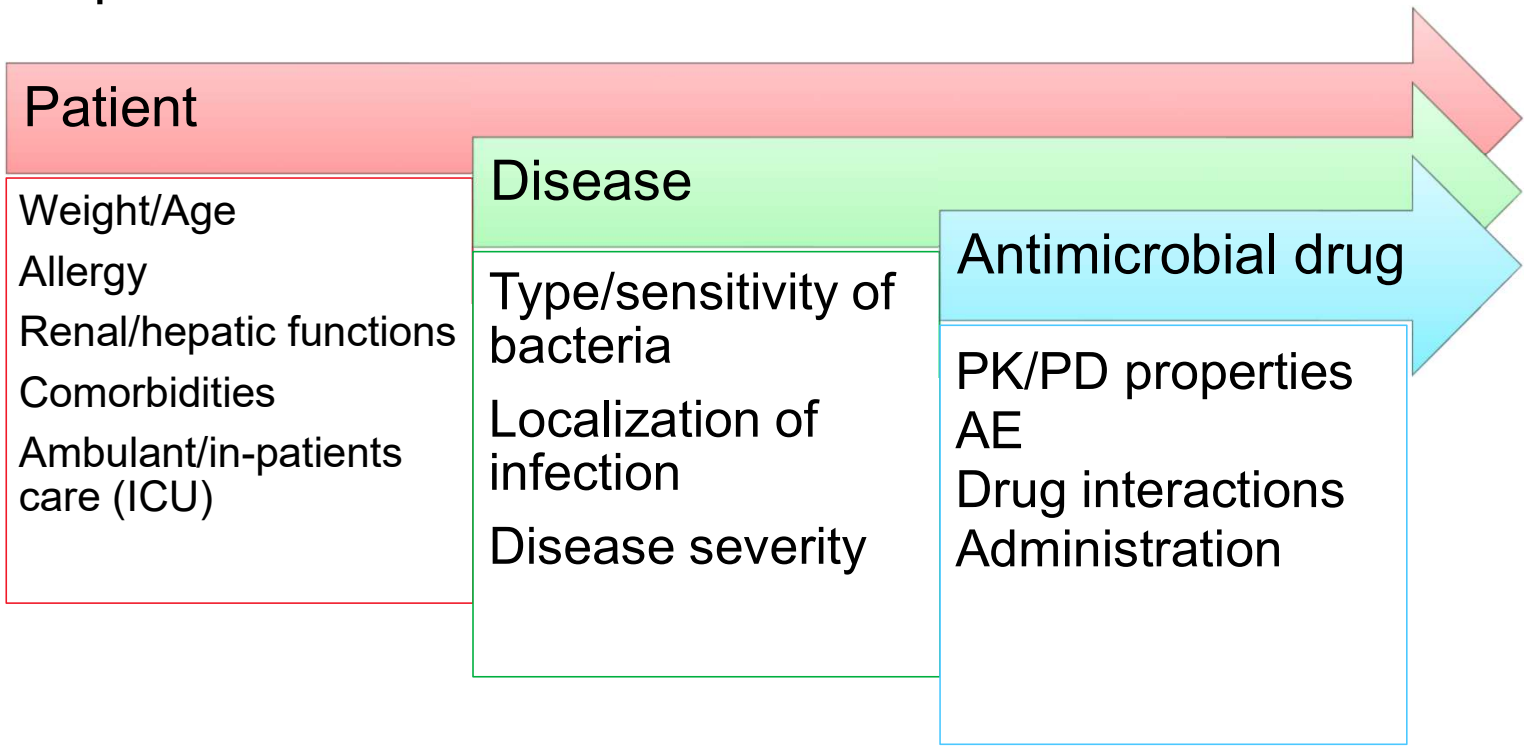
Selection of antibacterial drugs

Depends on:



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Selection of antibacterial drugs

ATB policy in Czechia
Antibiotic centers, free and bound ATB
National reference centre for healthcare associated infections (NRC-HAI)
EARS-NET

Antibiotic prophylaxis
single dose in perioperative period
during immunosuppression

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ATBs in dentistry

Use

- prevention – for risk patients (due to ADA)
    - artificial heart valves
    - a history of ineffective endocarditis
    - a cardiac transplant with developed valve problem
    - some of congenital heart conditions

- in some types of stomatosurgeries
    - for all dental procedures that involve manipulation of gingival tissue or the periapical region of the teeth, or perforation of the oral mucosa

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ATBs in dentistry

Drugs

- penicillin 1,5-3 mil. IU
- amoxicillin/clavulanic acid 1,2 g i.v. /1g p. o.
- ampicillin/sulbactam 2 g i.v./ 750 mg p.o.
- beta lactams allergic patients
  - clindamycin 600 mg p.o./i.m./i.v.
  - vancomycin 500 mg/i.v.

  - oral administration is recommended at least 1 hr before procedure and parenteral administration 15-30 mins before. In long lasting interventions can ATB be administered repeatedly after 4-6 hrs

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Local therapy in oropharyngeal cavity

Hexetidine (Stopangin)

- bacteriostatic, fungistatic effect

Chlorhexidine digluconate (Corsodyl)

- against G+,G-, Candida, viruses

Other antiseptics

- *Benzydamin hydrochlorid* - Tantum Verde
- *Oktenidin dihydrochlorid -* PHYTENEO Neocide gel
- *Benzalkonium chlorid* – Septolette
- *Benzoxonium chlorid* – Orofar
- *Cetylpyridinium chlorid* – Neo Septolette, Calgel (+lidokain)
- *Dichlorobenzenmethanol* – Neoangin, Strepsils (2-složˇ.)
- *Tridekanamin* - Septisan

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Antivirotics

MofA:

- block of viral penetration/uncoating
- inhibition of virus specific proteins/enzymes
  - reverse transcriptase inhibition
  - DNA polymerase inhibition
- inhibition of viral mRNA translation
- inhibition of neuraminidases

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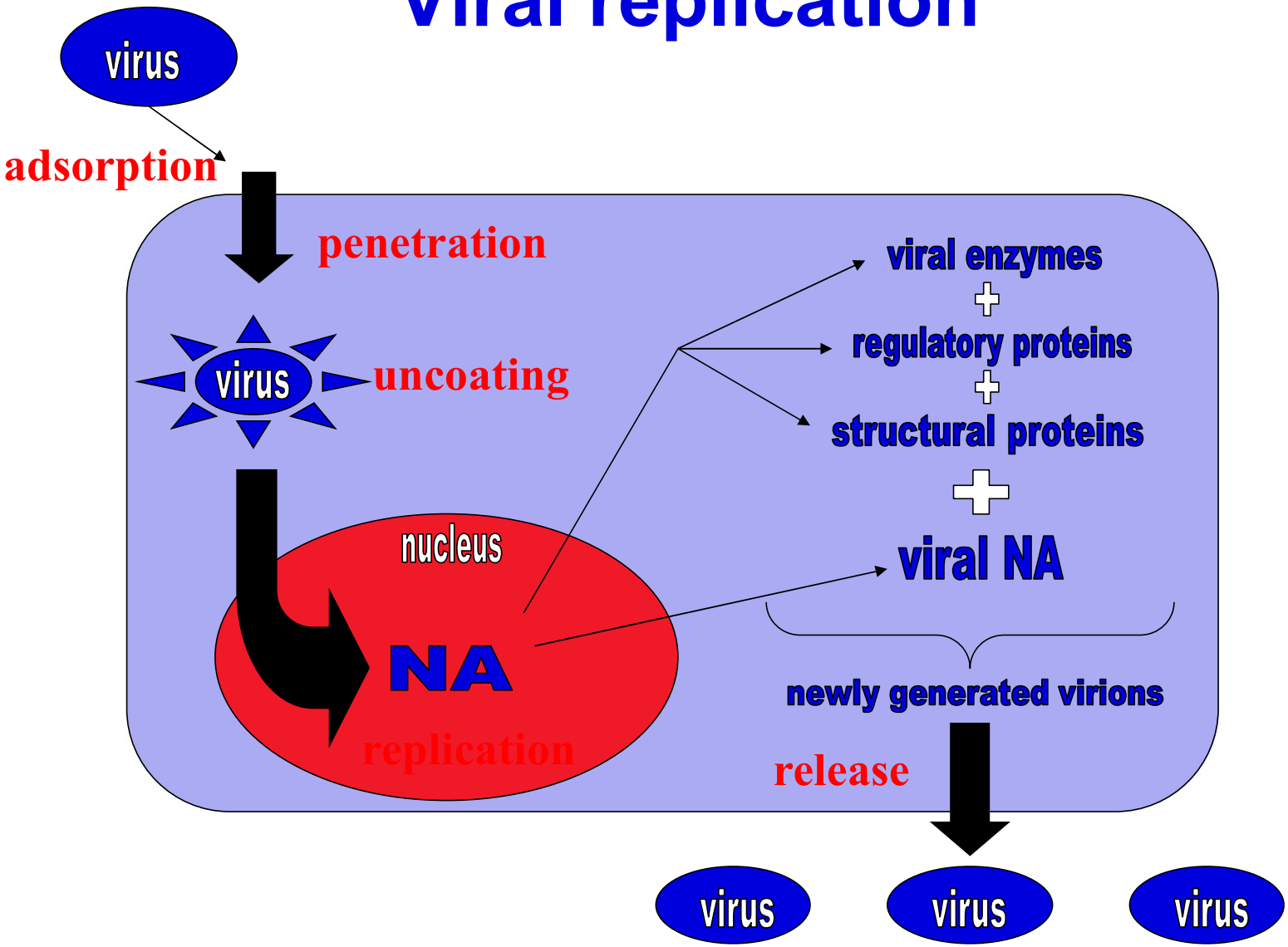
Viral replication



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Antivirotics

- anti-herpetics
- flu medicines
- antiretroviral drugs
- drugs of viral hepatitis and other antiviral drugs

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Therapy of herpetic infections

Aciclovir

MofA: DNA synthesis inhibition - DNA competitive polymerase inhibition

Efficacy: herpes labialis, herpes genitalis, varicella-zoster, less against cytomegalovirus and Epstein-Baar v.

AE: thromboflebitis after i.v.injections, neurologic symptoms (fuzziness, hallucination, depersonalisation) – more pronounced in renal failure

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Local antiviral drugs

- ***aciclovir***
- Herpesin®, Zovirax®
- ***penciclovir***
- Vectavir®
- ***docosanol***
- Erazaban
- ***tromantadin***
- Viru-Merz

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MYCOSES

- ↑incidence: immunodeficiency, DM, radiotherapy, chemotherapy, HIV

Classification:

  - pathogen: candodisis, aspergillosis, cryptococcosis, zygomycosis
- localization: systemic, organ, mucosal, skin

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ANTIMYCOTICS

Specific

- selective toxicity for mycotic cell
- targeted against mycotic cell specific structures

Nonspecific

- toxic for all organisms
- MofA – protein denaturation,
- cell membrane disruption etc.
- antiseptic and disinfectant agents

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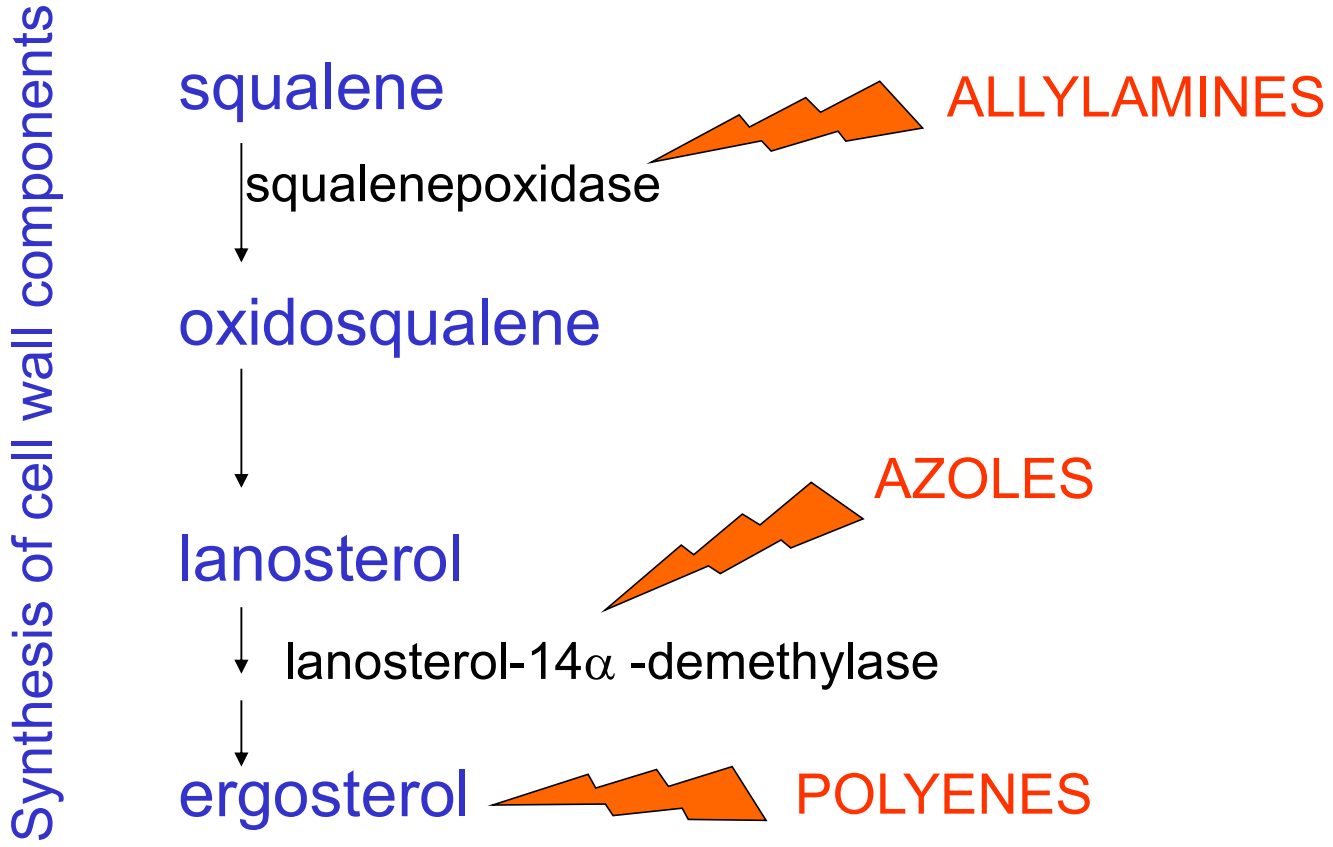
ANTIMYCOTICS



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AZOLES

MofA: inhibition of C-14-α-demethylase (CYP450)

Classification:

local x systemic

imidazoles x triazoles

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Antifungals in dentistry

Indications

- oral fungal infections due to
  - » immunosuppression
  - » inadequate oral hygiene
  - » wide spectrum antibiotics, glucocorticoids, chemotherapy

- most often candidosis

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Antifungals in dentistry

Drugs

- topically: nystatin, natamycine, clotrimazole, miconazole
- systemically: fluconazole, itraconazole, posaconazole

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