Antibiotics, Antifungals, Anthelmintics, Antiparasite agents

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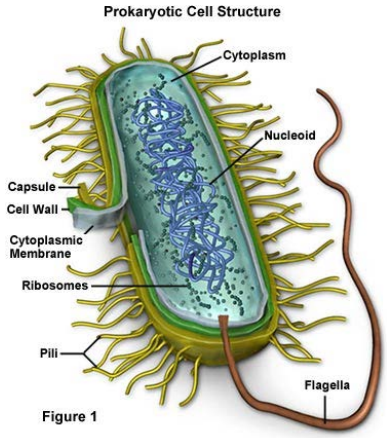
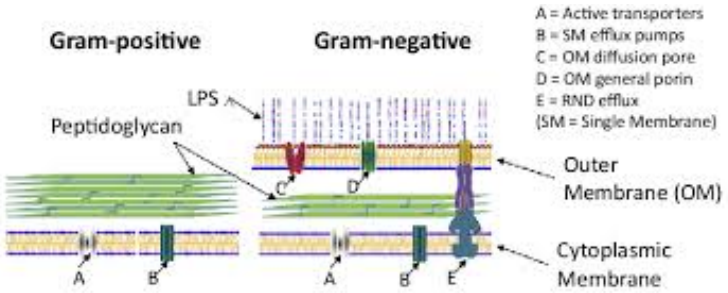
Antibiotics

Structure of bacteria

- Prokaryotes
- Essential components:
  - Core material
  - Cytoplasm
  - Ribosome (70 S, 50 S, 30 S)
  - Cell membrane
  - Cell wall (it detemines → Gram + or -)
- Not essential components:
  - Cilium
  - Pilus, fimbra
  - Capsule
  - Inclusion
  - Endospore





Morphology of bacteria

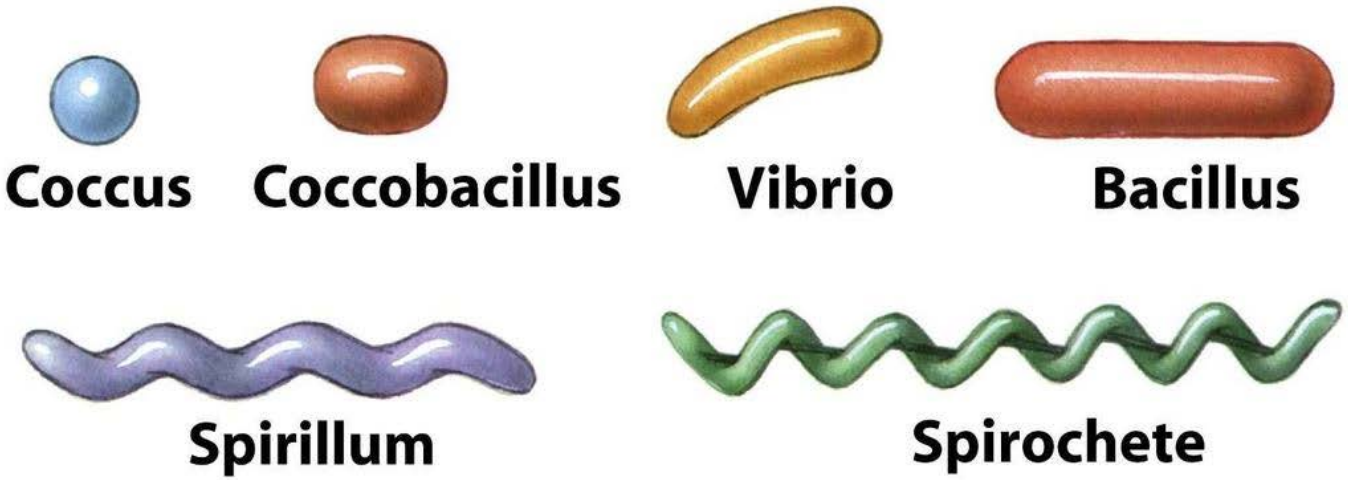
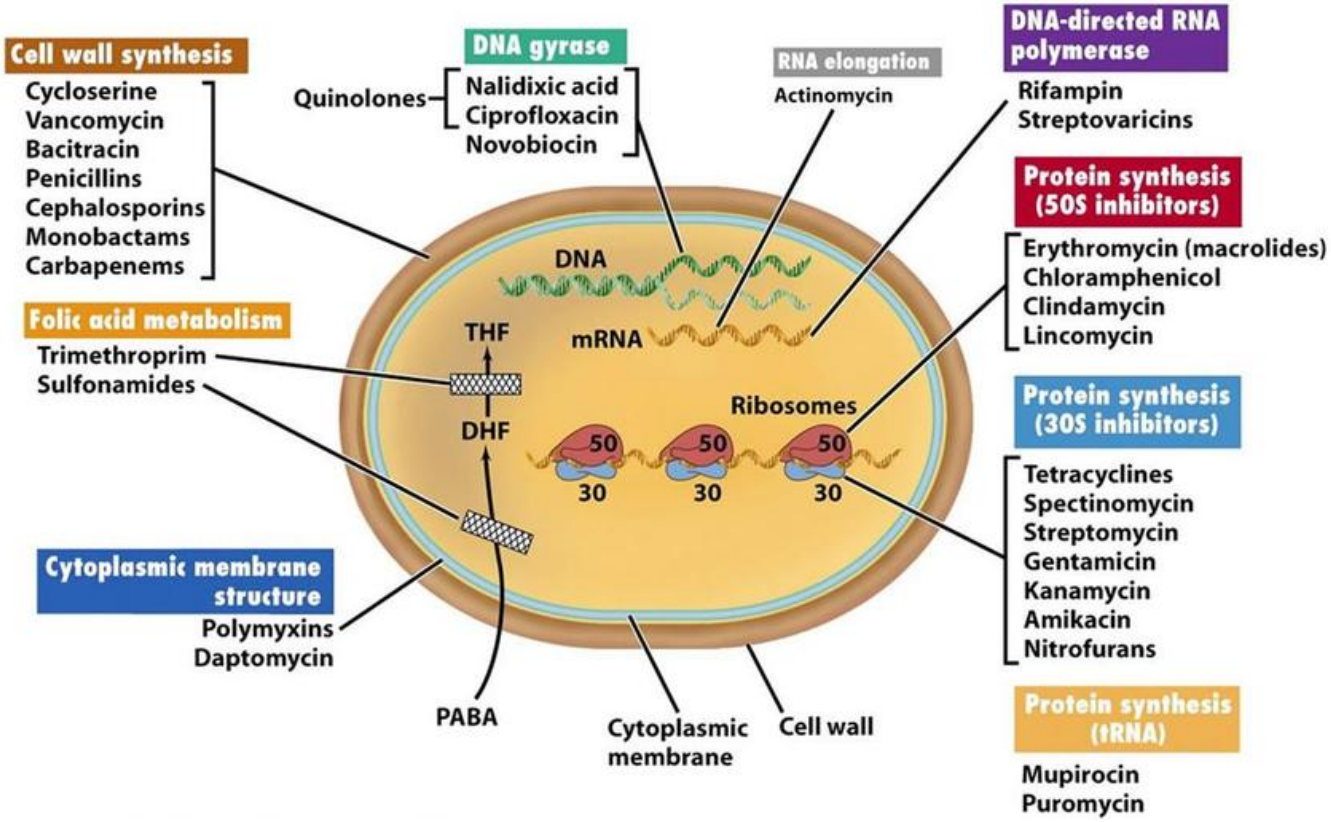


Figure 4-1 Microbiology, 7/e

Targets of the antibiotics



Antibiotics – The double-edged sword

- Penicillin – Alexander Fleming – 1928
  → After 1943, injured English soldiers were treated with it during World War II. There were many more amputated soldiers in Germany, Japan, and Italy where penicillin was not available.
- Based on 2019 data: more than 2.8 million antibiotic-resistant bacterial infections are identified each year in the U.S., and more than 35,000 people die as a result.
- It is important that the patient be given antibiotics only when indicated.

Table 2. Viral Versus GAS Pharyngitis

Symptoms Suggestive of Viral Pharyngitis	Symptoms Suggestive of GAS Pharyngitis[a]
• Conjunctivitis	• Abdominal pain
• Common cold symptoms	• Abrupt onset of sore throat
• Cough	• Fever, headache
• Diarrhea	• History of GAS pharyngitis exposure
• Hoarseness	• Inflammation in the throat
• Inflammation of the oral mucosa	• Nausea, vomiting
• Rash	• Patchy exudates in the throat
	• Purple spots on the roof of the mouth
	• Scarlatiniform rash
	• Tender lymph nodes around throat

[a] Age between 5 and 15 years and winter/early spring presentation are epidemiologic features associated with GAS pharyngitis. GAS: group A streptococcus. Source: References 3, 7.

Key resistance mechanisms

1. **Alternative proteins:** β-lactam antibiotics have no effect on mutant PBPs (penicillin binding protein). An example is the methicillin-resistant Staphylococcus aureus and its PBP2a protein.
2. **Inactiviting proteins:** The bacterium produces proteins, that neutralizes/destroys the antibiotic. Known examples are β-lactamases. These hydrolyze the β-lactam ring, so the antibiotic can no longer bind to the target protein.
3. **Target-mutation**: The target protein gets mutated, thus the antibiotic can no longer act on it.
4. **Modification after translation and transcription:** If an antibiotic binds to a particular region of the target protein, minor modifications after translation and transcription may result in weakening or even loss of binding.
5. **Decreased intake:** Due to the change in the cell wall, the antibiotic can no longer, or only to a reduced extent, can pass through the cell wall.
6. **Efflux-pumps:** Special transport proteins pump out the antibiotic that has entered, keeping the antibiotic concentration low.
7. **Overproduction:** The protein attacked by the antibiotic is overproduced, so if the antibiotic renders some of the molecules inoperable, there will still be enough functional molecules left, so the bacteria can survive.
8. **Alternative Metabolic Routes:** If an antibiotic blocks a metabolic pathway, it may be substitutable under certain conditions. The bacteria switches to another metabolic pathway, as a result, it no longer needs the blocked metabolite.
9. **Biofilm formation**

Basic concepts

- Forms of application
  - Antibiotic prophylaxis
  - Targeted therapy
  - Empiric therapy

Classification of antibiotics:

- Antibiotic use and efficacy
- MIC: minimum inhibitory concentration → based on this…
  - Cmax / MIC: the antimibrobial effect depends on how many times higher is the peak serum concentration is compared to the MIC - the effect is concentration dependent (eg aminoglycosides)
  - AUC / MIC: the bactericidal effect depends mainly on the peak concentration, but it is also important to maintain a persistent AB concentration above the MIC (eg fluoroquinolones)
  - T> MIC: the determinant of efficacy is that the AB concentration permanently exceeds the MIC, so the effect of AB is time-dependent (eg ß-lactams, glycopeptides, macrolides)
- The antibiotic effect can be…
  - Bactericidal (such an agent is chosen in an immunodeficient patient,or if the infection is severe, life-threatening, difficult to treat, or if it is difficult for AB to access)
  - Bacteriostatic
- Based on the spectrum of effects:
  - Narrow spectrum (eg. vancomycin)
  - Wide spectrum (eg. carbapenemes)

Classification of antibiotics by mechanism of action

INHIBIT		CLASIFICATION		ANTIBIOTICS			
Cell Wall Synthesis	Beta Lactams	Penicillins		***Penicinillase – Sensible***			
			Natural Penicillins (narrow spectrum)	Penicillin G: Na, K, Procainic, Benzathine (IV, IM) Penicillin V: VO			
			Aminopenicillins (broad spectrum)	Ampicillin Amoxicillin			
				Penicinillase – Resistant *(very narrow spectrum)*			
				Nafcillin	Oxacillin	Dicloxacillin	
				Antipseudomonal *(extended spectrum)*			
			Carboxipenicillins	Ticarcillin Carbenicillin			
			Ureidopenicillins	Piperacillin Azlocillin Mezlocillin			
		Cephalosporins	1° Generation	Cefazolin	Cephalexine	Cephapirin	
				Cefadroxil	Cephadrine	Cephalotin	
			2° Generation	Cefuroxime	Cefamandole	Cefprozil	
				Cefoxitin	Cefonicid	Cefmetazole	
				Cefotetan	Cefaclor		
			3° Generation	Cefoperazone	Ceftriaxone	Ceftazidime	
				Cefpodoxime	Ceftizoxime	Cefotaxime	
				Cefdinir	Ceftibuten	Cefixime	
				Cefditoren			
			4° Generation	Cefepime	Cefpirome *		
			5° Generation	Ceftaroline			
		Carbapenems		Meropenem	Ertapenem	Doripenem	Imipenem + Cylastatine
		Monobactams		Aztreonam			
		**** Beta-lactamase inhib.		Sulbactam	Tazobactam	Clavulanic Acid	
	No lactam	Glycopeptides		Vancomycin	Bacitracin		
				Teicoplanin	Polymyxin B		
Protein Synthesis		30S	Amino-glycosides	Gentamycin	Neomycin	Streptomycin	
				Amikacin	Tobramycin		
			Tetracyclins	Doxycycline	Demeclocylin *	Minocycline	
				Tetracyclin	Tigecyclin		
		50S	Oxazolidonones	Linezolid			
			Streptogramins	Quinupristin/Dalfopristin			
			Cloramphenicol				
			Macrolides	Erythromycin	Azithromycin	Clarithromycin	
			Lincosamides	Clindamycin		Lincomycin	
DNA topoisomerases		Fluorquinolones		Ciprofloxacin	Norfloxacin	Levofloxacin	Ofloxacin
				Sparfloxacin	Moxifloxacin	Gemifloxacin	Enofloxacin
		Quinolones		Nalidixic Acid			
Folic Acid Synthesis		Sulfonamides		Sulfamethoxazole (SMX)	Ag Sulfadiazine	Sulfasalazine	Sulfisoxazole
		DHFR inhibitors		Trimethroprim (TMP)		Pirymethamine	
DNA (damage)		Metronidazole					
mRNA synth.		Rifampim					

B-lactame antibiotics

- Groups in this class:
  - Penicillines
  - Cefalosporines
  - Carbapenemes
  - Monobactames
- Mode of action
  - Binding to PBP (penicillin binding protein)
  - Transpeptidase inhibition → cross-linking does not occur = inhibition of cell wall synthesis
  - Activation of autolysins → no new cell wall is formed
  - Bactericidal
  - They only affect pathogens in the logarithmic phase
  - It is given to the patient in 3 to 6 divided doses per day because they have a short half-life and a time-dependent bactericidal effect (the post-antibiotic effect is not significant).
  - Synergism with aminoglycosides
  - Poorly penetrate into the intracellular space → ineffective against intracellular pathogens
  - They are generally excreted by the kidneys (exeption: nafcillin)

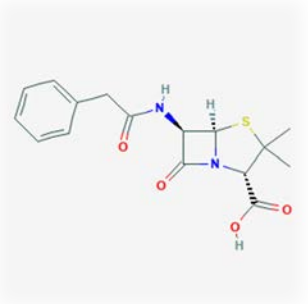
ß-lactame antibiotics

Resistance mechanisms

1. ß-lactamase production: eg S. aureus, E. coli, H. influenzae, P. aeruginosa
2. Binding protein change: e.g. MRSA
3. Decreased cell wall permeability
4. Efflux mechar ə)

ß-lactam antibiotics

Penicillines



Penicillin G

Classification:

- Basic Penicillins
  - Benzylpenicillin : Penicillin G (parenteral)
  - Phenoxy Penicillin : Penicillin V (oral)

They pass through BBB

  - Clinical application :
    - Group A Streptococcus: S. pyogenes: tonsillitis follicularis, erysipelas, cellulitis, endocarditis
    - Lues
    - Actinomycosis
    - Skin-soft tissue infections caused by anaerobic streptococci, clostridia (eg gas gangrene)

- ß-lactamase resistant penicillins
  - Izoxazolilpenicillines: Oxacillin, flucloxacillin, nafcillin
  - Today, they can only be used against Staphylococcus infection, they do not work against MRSA and MRSE strains

ß-lactam antibiotics

Penicillines

- Broad-spectrum penicillins
  - aminopenicillins: Ampicillin, amoxicillin
  - Effective: Streptococcus (pyogenes, pneumoniae), Enterococcus, E. coli, H. influenzae, Proteus mirabilis, salmonella, shigella, Listeria monocytogenes. H. pylori (in combination), Borellia burgdorferi
  - Amoxicillin is recommended for oral use (well absorbed from the intestine)
- Broad-spectrum anti-“pseudomonas” penicillins
  - Carboxipenicillins: Carbenicillin
  - Ureidopenicillinek: Piperacillin (gets into liquor) – today only this is used from the group
- Combined with a ß-lactamase inhibitor
  - aminopenicillins: Ampicillin + sulbactam (Unazyn), amoxicillin + clavulanic acid (Augmentin)
  - Ureidopenicillin: piperacillin + tazobactam (Tazocin) - polymicrobial infections, nosocomial infections
  - Moderate respiratory, urinary tract infections, cholecystitis, post-dental surgery prophylaxis

Β-lactam antibiotics

Penicillins in practice

- IMPORTANT: commonly used drugs, especially the combination of amoxicillin + clavulanic acid (Aktil Duo, Augmentin) - are often used incorrectly:
  - In children under 3 years, group A (haemolysing) Streptococcal follicular tonsillitis infection is not typical - almost always a viral infection! (the structure of the tonsils is different, it is more difficult to develop a bacterial infection) - often children are hospitalized as result of AB therapy! - Diarrhea (sometimes pseudomembranous colitis) → dehydration
  - If follicular tonsillitis is suspected, it is advisable to perform a culture - complications may appear after at least 2 weeks → if the culture is positive, there is time to start targeted AB therapy - amoxicillin! (usually Augementin or Aktil Duo is prescribed, although clavulanic acid is not needed because there is no β-lactamase production)
  - If EBV causes tonsillitis and penicillin treatment is given to the patient → amoxicillin rash
  - They are effective in treating N. meningitidis
  - N. gonorrhoeae: resistance is spreading
  - Treponema pallidum treatment (intramuscular).
  - Allergic reactions are quite common!

Classification of antibiotics by mechanism of action

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Cell Wall Synthesis	Beta Lactams	Penicillins		***Penicinillase – Sensible***			
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				Cefadroxil	Cephadrine	Cephalotin	
			2° Generation	Cefuroxime	Cefamandole	Cefprozil	
				Cefoxitin	Cefonicid	Cefmetazole	
				Cefotetan	Cefaclor		
			3° Generation	Cefoperazone	Ceftriaxone	Ceftazidime	
				Cefpodoxime	Ceftizoxime	Cefotaxime	
				Cefdinir	Ceftibuten	Cefixime	
				Cefditoren			
			4° Generation	Cefepime	Cefpirome *		
			5° Generation	Ceftaroline			
		Carbapenems		Meropenem	Ertapenem	Doripenem	Imipenem + Cylastatine
		Monobactams		Aztreonam			
		******* Beta-lactamase inhib.***		Sulbactam	Tazobactam	Clavulanic Acid	
	No lactam	***Glycopeptides***		Vancomycin	Bacitracin		
				Teicoplanin	Polymyxin B		
Protein Synthesis		30S	***Amino-glycosides***	Gentamycin	Neomycin	Streptomycin	
				Amikacin	Tobramycin		
			Tetracyclins	Doxycycline	Demeclocylin *	Minocycline	
				Tetracyclin	Tigecyclin		
		50S	***Oxazolidonones***	Linezolid			
			Streptogramins	Quinupristin/Dalfopristin			
			Cloramphenicol				
			Macrolides	Erythromycin	Azithromycin	Clarithromycin	
			Lincosamides	Clindamycin	Lincomycin		
DNA topoisomerases		***Fluorquinolones***		Ciprofloxacin	Norfloxacin	Levofloxacin	Ofloxacin
				Sparfloxacin	Moxifloxacin	Gemifloxacin	Enofloxacin
		Quinolones		Nalidixic Acid			
Folic Acid Synthesis		***Sulfonamides***		Sulfamethoxazole (SMX)	Ag Sulfadiazine	Sulfasalazine	Sulfisoxazole
		DHFR inhibitors		Trimethroprim (TMP)		Pirymethamine	
DNA (damage)		***Metronidazole***					
mRNA synth.		***Rifampim***					

ß-lactam antibiotics

Cephalosorins

- They are also bound to PDB
- Broad-spectrum antibiotics
- They cause allergic reaction rarer, but should not be given to people with penicillin allergies
- They are non-toxic
- They have advantageous pharmacokinetics
- They are resistant to most ß-lactamase enzymes
- 5 generations: with increasing number of generations
  - Increased Gr - activity
  - Decreased Gr + activity
  - Resistance to ß-lactamases increases

ß-lactam antibiotics

Cephalosorins

Generation	Usage	
	Parenteral	Oral
1. generation	cefalotin cefazolin	cefalexin cefadroxil
2. generation	cefamandol cefuroxim cefoxitin	cefaclor cefuroxim-axetil cefprozil
3. generation	cefotaxim ceftriaxon ceftizoxim cefoperazon ceftazidim	
4. generation	cefepim	
5. generation	Ceftobiprol Ceftarolin	
Cephalosporin – beta-lactamase combination	Ceftolozan – tazobactam Cefazidim - avibactam	

ß-lactam antibiotics

Cephalosorins

- 1st generation
  - Cefazolin, cefalexin, cefadroxil
  - Gram + cocci (eg Staphylococcus), some Gram - bacterias (eg E. coli)
  - They do not penetrate into the CSF
- 2nd generation
  - Cefaclor, Cefuroxime axetil (Zinnat - both iv and oral), Cefoxitin
  - They do not penetrate into the CSF
  - For upper and lower respiratory tract infections
  - Efficacy against some Gr – bacteria (H. influenzeae, Neisseria) is increasing
- 3rd generation
  - Cefixime (Suprax), Cebtibuten, Cefotaxime (Claforane), Ceftriaxone (Rocephine), Ceftazidime (Fortum), Cefoperazone
  - Cefotaxime and ceftriaxone are good for empiric therapy for meningitis! ->they get into the CSF (including ceftazidime)
  - Gram - spectrum increased
  - Ceftazidime is effective against P. aeruginosa

ß-lactam antibiotics

Cephalosorins

- 4th generation
  - Cefepime: more balanced antibacterial spectrum than 3rd generation agents -> have a better effect on Staphylococci and greater ß-lactamase stability
  - Pass through the BBB
  - Only for severe infections
  - It is good against P. aeruginosa!
- 5th generation
  - Ceftaroline, Ceftobiprole – iv.
  - Pass through the BBB
- New combination agents: Ceftolozan – tazobactam, Cefazidim – avibactam
  - Indication: complicated urinary tract infection, complicated intra-abdominal infections
- A significant problem is the spread of ESBL-producing intestinal bacteria (with a plasmid) - especially in the case of E. coli and Klebsiella pneumoniae - in which case the new combination agents are effective (also against multidrug-resistant P. aeruginosa)

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mRNA synth.		***Rifampim***					

B-lactam antibiotics

Carbapenems

- Imipenem (Tienam), meropenem (Meronem), ertapenem, doripenem
- For intravenous use
- They are also bound to PBP
- They are extremely resistant to ß-lactamase
- These ABs have the broadest spectrum in the ß-lactam group
- They are also effective against Gr + and - aerobes and anaerobes (also P. aeruginosa - except Ertapenem) + effective against Acinetobacter species
- Bactericidal effect
- There is generally no cross-resistance between cephalosporins and carbapenems
- Resistance Mechanisms :
  - Decreased bacterial wall permeability
  - Efflux mechanism
  - Carbapenemase enzyme production

B-lactam antibiotics

Carbapenems

- Meropenem
  - It penetrates well into the CNS and is suitable for the treatment of meningitis
- Imipenem
  - intravenously
  - In combination with cilastatin (a reversible inhibitor of renal dehydropeptidase) imipenem is stable
  - Important side effect: epileptiform seizures (13%)
- Therapeutic indications:
  - It should be the first choice in Acinetobacter infection
  - Multimicrobial infections
  - In septic states

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B-lactam antibiotics

Monobactams

- Aztreonam
- It only affects Gr - bacteria, not Gr + and anaerobes ▫ e.g. Gr - cocci (H. influenzae), Gr - intestinal bacteria, Pseudomonas + aminoglycoside resistant strains
- for intramuscular or intravenous use
- But an aerosol form is also available for the treatment of P. aeruginosa infection in cystic fibrosis (FDA 2010)
- Therapeutic indication: Gram - skin, soft tissue, abdominal, pelvic, postoperative infections
- Not avaliable in Hungary.

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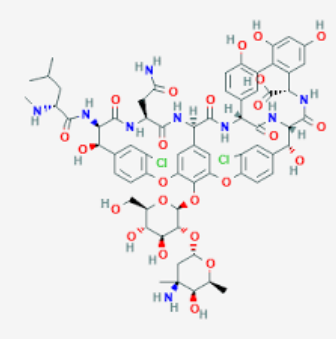
				Cefoxitin	Cefonicid	Cefmetazole	
				Cefotetan	Cefaclor		
			3° Generation	Cefoperazone	Ceftriaxone	Ceftazidime	
				Cefpodoxime	Ceftizoxime	Cefotaxime	
				Cefdinir	Ceftibuten	Cefixime	
				Cefditoren			
			4° Generation	Cefepime	Cefpirome *		
			5° Generation	Ceftaroline			
		Carbapenems		Meropenem	Ertapenem	Doripenem	Imipenem + Cylastatine
		Monobactams		Aztreonam			
		***** Beta-lactamase inhib.*		Sulbactam	Tazobactam	Clavulanic Acid	
	No lactam	*Glycopeptides*		Vancomycin	Bacitracin		
				Teicoplanin	Polymyxin B		
Protein Synthesis		*30S*	*Amino-glycosides*	Gentamycin	Neomycin	Streptomycin	
				Amikacin	Tobramycin		
			Tetracyclins	Doxycycline	Demeclocylin *	Minocycline	
				Tetracyclin	Tigecyclin		
		50S	*Oxazolidonones*	Linezolid			
			Streptogramins	Quinupristin/Dalfopristin			
			Cloramphenicol				
			Macrolides	Erythromycin	Azithromycin	Clarithromycin	
			Lincosamides	Clindamycin	Lincomycin		
DNA topoisomerases		*Fluorquinolones*		Ciprofloxacin	Norfloxacin	Levofloxacin	Ofloxacin
				Sparfloxacin	Moxifloxacin	Gemifloxacin	Enofloxacin
		Quinolones		Nalidixic Acid			
Folic Acid Synthesis		*Sulfonamides*		Sulfamethoxazole (SMX)	Ag Sulfadiazine	Sulfasalazine	Sulfisoxazole
		DHFR inhibitors		Trimethroprim (TMP)		Pirymethamine	
DNA (damage)		*Metronidazole*					
mRNA synth.		*Rifampim*					

Glycopeptides



Vancomycin

- Vancomycin, teicoplanin (dalbavancin, telavancin)
- Inhibit enzyme transglycosylase (glycopeptide synthesis
- Time-dependent antibacterial effect
- They NEVER act against Gr – bacterias
- Narrow spectrum
  - MRSA, penicillin-resistant Streptococcus pneumoniae, Clostridium difficile, Listeria monocytogenes, Bacillus anthracis
  - Generally iv. application, orally only in C. difficile infection (because they do not absorb from the bowel)
  - Synergism with aminoglycosides
  - Side effects (vancomycin)
    - They are nephro- and ototoxic
    - Red man syndrome: due to the direct histamine-releasing effect of vancomycin
  - Therapeutic use: severe infection caused by MRSA or MRSE, ampicillin-resistant Enterococcus infections, Str. pneumoniae meningitis, life-threatening pseudomembranous colitis (so not the first drug of choice for C. difficile infection)

Other agents which act on bacterial cell wall or cell membrane

- Lipopeptidek: daptomycin
  - Bactericide effect
  - It damages the bacterial cell membrane at several points (eg form pores on it)
  - Its spectrum of action is similar to that of vancomycin -> it acts against Gram +
  - Side effect: myopathy
  - Only iv., 1x daily
  - MRSA, Streptococci, vancomycin resistent Enterococci
- Fosfomycin (Monural)
  - Inhibition of cell wall synthesis
  - For the treatment of urinary tract infections in women (a single dose is enough!)
  - Also against Gr + and Gr - infections: e.g. E. coli, Klebsiella spp., Proteus mirabilis, S. aureus
  - It is well absorbed from the intestine and excreted in high concentrations in the urine where it reaches an antibacterial concentration for 48 hours after a single administration.
  - Do not use in patients with renal insufficiency
  - Indication: uncomplicated lower urinary tract infections

Other agents which act on bacterial cell wall or cell membrane

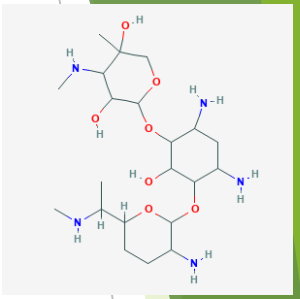
- Polymixins
  - basic peptides
  - polymixin B / polymixin E = colistin
  - cationic detergents - disrupt membranes
  - active only against Gram-
  - endotoxin (LPS) inactivation
  - Toxicity: nephro- and neurotoxic effects ➔ for treatment of bacteria resistant to other agents
  - clinical use
    - mainly topical BUT
    - with emergence of multiresistant pathogens
      - A. baumannii
      - P. aeruginosa
      - parenteral salvage therapy – usually in combination

Classification of antibiotics by mechanism of action

INHIBIT		CLASIFICATION		ANTIBIOTICS			
Cell Wall Synthesis	Beta Lactams	Penicillins		*Penicinillase – Sensible*			
			Natural Penicillins (narrow spectrum)	Penicillin G: Na, K, Procainic, Benzathine (IV, IM) Penicillin V: VO			
			Aminopenicillins (broad spectrum)	Ampicillin Amoxicillin			
			Penicinillase – Resistant (very narrow spectrum)				
			Nafcillin	Oxacillin	Dicloxacillin		
			Antipseudomonal (extended spectrum)				
			Carboxipenicillins	Ticarcillin Carbenicillin			
			Ureidopenicillins	Piperacillin Azlocillin Mezlocillin			
		Cephalosporins	1° Generation	Cefazolin	Cephalexine	Cephapirin	
				Cefadroxil	Cephadrine	Cephalotin	
			2° Generation	Cefuroxime	Cefamandole	Cefprozil	
				Cefoxitin	Cefonicid	Cefmetazole	
				Cefotetan	Cefaclor		
			3° Generation	Cefoperazone	Ceftriaxone	Ceftazidime	
				Cefpodoxime	Ceftizoxime	Cefotaxime	
				Cefdinir	Ceftibuten	Cefixime	
				Cefditoren			
			4° Generation	Cefepime	Cefpirome *		
			5° Generation	Ceftaroline			
		Carbapenems		Meropenem	Ertapenem	Doripenem	Imipenem + Cylastatine
		Monobactams		Aztreonam			
		**** Beta-lactamase inhib.		Sulbactam	Tazobactam	Clavulanic Acid	
	No lactam	Glycopeptides		Vancomycin		Bacitracin	
				Teicoplanin		Polymyxin B	
Protein Synthesis		30S	Amino-glycosides	Gentamycin	Neomycin	Streptomycin	
				Amikacin	Tobramycin		
			Tetracyclins	Doxycycline	Demeclocylin *	Minocycline	
				Tetracyclin	Tigecyclin		
		50S	Oxazolidonones	Linezolid			
			Streptogramins	Quinupristin/Dalfopristin			
			Cloramphenicol				
			Macrolides	Erythromycin	Azithromycin	Clarithromycin	
			Lincosamides	Clindamycin		Lincomycin	
DNA topoisomerases		Fluorquinolones		Ciprofloxacin	Norfloxacin	Levofloxacin	Ofloxacin
				Sparfloxacin	Moxifloxacin	Gemifloxacin	Enofloxacin
		Quinolones		Nalidixic Acid			
Folic Acid Synthesis		Sulfonamides		Sulfamethoxazole (SMX)	Ag Sulfadiazine	Sulfasalazine	Sulfisoxazole
		DHFR inhibitors		Trimethroprim (TMP)		Pirymethamine	
DNA (damage)		Metronidazole					
mRNA synth.		Rifampim					

Aminoglycosides

- gentamicin, tobramycin, neomycin, streptomycin, amikacin, netilmicin, kanamycin
- Effect on the 30S subunit -> cause misreading
- Bactericidal compounds
- Concentration dependent effect
- They also have a long post-antibiotic effect
- In combination with beta-lactams and glycopeptides
- iv. and im. can be administered and do not penetrate the CNS (large polar compounds)
- Irreversible ototoxicity, reversible nephrotoxicity
- Transport to cells requires ATP -> do not affect anaerobes (eg abscess)
  + ineffective against: enterococci, atypical pneumonia pathogens
- Mechanisms of resistance :
  - Conjugation (phosphorylation, adenylation, acetylation)
  - Change target (30S subunit)
  - Decreased permeability
- Indication: Gram - aerobic bacterias: E. coli, Klebsiella, Enterobacter, Acinetobacter, Pseudomonas, etc.
- Clinical use: nosocomial pneumonia, septic conditions of unknown origin, febrile episode of neutropenic patient, intra-abdominal infections (with metronidazole / clindamycin), pelvic infections,
  amikacin and streptomycin are also antituberculotic drugs
- Spectinomycin is similar to amidoglycosides - for penicillin allergy or penicillin-resistant gonorrhea (← single dose, im.)



Gentamicin

Classification of antibiotics by mechanism of action

INHIBIT		CLASIFICATION		ANTIBIOTICS			
Cell Wall Synthesis	Beta Lactams	Penicillins		***Penicinillase – Sensible***			
			Natural Penicillins (narrow spectrum)	Penicillin G: Na, K, Procainic, Benzathine (IV, IM) Penicillin V: VO			
			Aminopenicillins (broad spectrum)	Ampicillin Amoxicillin			
			Penicinillase – Resistant (very narrow spectrum)				
			Nafcillin	Oxacillin	Dicloxacillin		
			Antipseudomonal (extended spectrum)				
			Carboxipenicillins	Ticarcillin Carbenicillin			
			Ureidopenicillins	Piperacillin Azlocillin Mezlocillin			
		Cephalosporins	1° Generation	Cefazolin	Cephalexine	Cephapirin	
				Cefadroxil	Cephadrine	Cephalotin	
			2° Generation	Cefuroxime	Cefamandole	Cefprozil	
				Cefoxitin	Cefonicid	Cefmetazole	
				Cefotetan	Cefaclor		
			3° Generation	Cefoperazone	Ceftriaxone	Ceftazidime	
				Cefpodoxime	Ceftizoxime	Cefotaxime	
				Cefdinir	Ceftibuten	Cefixime	
				Cefditoren			
			4° Generation	Cefepime	Cefpirome *		
			5° Generation	Ceftaroline			
		Carbapenems		Meropenem	Ertapenem	Doripenem	Imipenem + Cylastatine
		Monobactams		Aztreonam			
	****	Beta-lactamase inhib.		Sulbactam	Tazobactam	Clavulanic Acid	
	No lactam	Glycopeptides		Vancomycin	Bacitracin		
				Teicoplanin	Polymyxin B		
Protein Synthesis	30S	Amino-glycosides		Gentamycin	Neomycin	Streptomycin	
		Tetracyclins		Doxycycline	Demeclocylin *	Minocycline	
				Tetracyclin	Tigecyclin		
	50S	Oxazolidonones		Linezolid			
		Streptogramins		Quinupristin/Dalfopristin			
		Cloramphenicol					
		Macrolides		Erythromycin	Azithromycin	Clarithromycin	
		Lincosamides		Clindamycin	Lincomycin		
DNA topoisomerases		Fluorquinolones		Ciprofloxacin	Norfloxacin	Levofloxacin	Ofloxacin
				Sparfloxacin	Moxifloxacin	Gemifloxacin	Enofloxacin
		Quinolones		Nalidixic Acid			
Folic Acid Synthesis		Sulfonamides		Sulfamethoxazole (SMX)	Ag Sulfadiazine	Sulfasalazine	Sulfisoxazole
		DHFR inhibitors		Trimethroprim (TMP)		Pirymethamine	
DNA (damage)		Metronidazole					
mRNA synth.		Rifampim					

Tetracyclines

- Tetracyclin, doxycyclin, domeclocycline, minocyclin, metacycline
- Effect: Inhibits tRNA binding to the ribosome - 30S subunit
- Bacteriostatic
- Wide spectrum but many secondary resistant pathogens
- Resistance mechanisms:
  - Decreased permeability
  - Active efflux
- They are effective against the pathogens of atypical pneumonia!
- Ineffective: Pseudomonas spp. And Proteus spp.
- Adverse effects: photosensitivity, GI disturbances, C. difficile inf., hepatotoxicity
- Contraindications: pregnancy, children under 8 years (discoloration of the teeth)
- Indications:
  - Acute exacerbation of chronic bronchitis
  - STD – Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis
  - Atypical pneumonia
  - H. pylori eradication (in combination)
  - Doxycycline: Borrelia burgdorferi - Lyme disease, malaria prophylaxis

Tetracyclines
Tigecyclin

- Tigecycline is effective against tetracycline-resistant strains
- Broad spectrum (including Gr + and - bacteria)
- Also effective against MRSA, vancomycin-resistant enterococci and ESBL-producing Gram-bacteria
- Bacteriostatic
- Has a post-antibiotic effect (PAE)
- AUC / MIC determines the antibacterial effect
- Parenteral only
- Side effects: nausea, vomiting, diarrhea, thrombocytopenia
- Indication:
  - Skin, soft tissue, intra-abdominal infections
  - Community-acquired pneumonia

Classification of antibiotics by mechanism of action

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			Penicinillase – Resistant (very narrow spectrum)				
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			Antipseudomonal (extended spectrum)				
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			Ureidopenicillins	Piperacillin Azlocillin Mezlocillin			
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				Cefadroxil	Cephadrine	Cephalotin	
			2° Generation	Cefuroxime	Cefamandole	Cefprozil	
				Cefoxitin	Cefonicid	Cefmetazole	
				Cefotetan	Cefaclor		
			3° Generation	Cefoperazone	Ceftriaxone	Ceftazidime	
				Cefpodoxime	Ceftizoxime	Cefotaxime	
				Cefdinir	Ceftibuten	Cefixime	
				Cefditoren			
			4° Generation	Cefepime	Cefpirome *		
			5° Generation	Ceftaroline			
		Carbapenems		Meropenem	Ertapenem	Doripenem	Imipenem + Cylastatine
		Monobactams		Aztreonam			
		**** ***Beta-lactamase inhib.***		Sulbactam	Tazobactam	Clavulanic Acid	
	No lactam	***Glycopeptides***		Vancomycin	Bacitracin		
				Teicoplanin	Polymyxin B		
Protein Synthesis		30S	***Amino-glycosides***	Gentamycin	Neomycin	Streptomycin	
				Amikacin	Tobramycin		
			Tetracyclins	Doxycycline	Demeclocylin *	Minocycline	
				Tetracyclin	Tigecyclin		
		50S	***Oxazolidonones***	Linezolid			
			Streptogramins	Quinupristin/Dalfopristin			
			Cloramphenicol				
			Macrolides	Erythromycin	Azithromycin	Clarithromycin	
			Lincosamides	Clindamycin		Lincomycin	
DNA topoisomerases		***Fluorquinolones***		Ciprofloxacin	Norfloxacin	Levofloxacin	Ofloxacin
				Sparfloxacin	Moxifloxacin	Gemifloxacin	Enofloxacin
		Quinolones		Nalidixic Acid			
Folic Acid Synthesis		***Sulfonamides***		Sulfamethoxazole (SMX)	Ag Sulfadiazine	Sulfasalazine	Sulfisoxazole
		DHFR inhibitors		Trimethroprim (TMP)		Pirymethamine	
DNA (damage)		***Metronidazole***					
mRNA synth.		***Rifampim***					

Chloramphenicol

- It is broad-spectrum but toxic and many bacteria has secondary resistance
- It binds to the 50 S subunit and inhibits protein synthesis
- Bacteriostatic effect
- Also against Gr + and - aerobic and anaerobic bacteria + spirochaetes, chlamydia
- Resistance mechanisms:
  - Decreased membrane permeability
  - Deacetylation (plasmid)
- It is well absorbed, penetrates into the brain and abscesses excellently
- Side effects:
  - Bone marrow toxicity
    - Dose-dependent bone marrow depression (reversible)
    - Non-dose-dependent: aplastic anemia (irreversible)
  - "gray baby" syndrome: due to insufficient glucuronide conjugation in neonates
- Indication: its use is reduced
  - Brain abscess (if metronidazole + cephalosporin does not work)
  - In meningitis in case of penicillin-cephalosporin allergy
  - Developing countries for Salmonella infections (because it is cheap)

Classification of antibiotics by mechanism of action

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			Antipseudomonal *(extended spectrum)*				
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		Cephalosporins	1° Generation	Cefazolin	Cephalexine	Cephapirin	
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			2° Generation	Cefuroxime	Cefamandole	Cefprozil	
				Cefoxitin	Cefonicid	Cefmetazole	
				Cefotetan	Cefaclor		
			3° Generation	Cefoperazone	Ceftriaxone	Ceftazidime	
				Cefpodoxime	Ceftizoxime	Cefotaxime	
				Cefdinir	Ceftibuten	Cefixime	
				Cefditoren			
			4° Generation	Cefepime	Cefpirome *		
			5° Generation	Ceftaroline			
		Carbapenems		Meropenem	Ertapenem	Doripenem	Imipenem + Cylastatine
		Monobactams		Aztreonam			
		**** ***Beta-lactamase inhib.***		Sulbactam	Tazobactam	Clavulanic Acid	
	No lactam	***Glycopeptides***		Vancomycin	Bacitracin		
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Protein Synthesis		30S	***Amino-glycosides***	Gentamycin	Neomycin	Streptomycin	
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			Cloramphenicol				
			Macrolides	Erythromycin	Azithromycin	Clarithromycin	
			Lincosamides	Clindamycin		Lincomycin	
DNA topoisomerases		***Fluorquinolones***		Ciprofloxacin	Norfloxacin	Levofloxacin	Ofloxacin
				Sparfloxacin	Moxifloxacin	Gemifloxacin	Enofloxacin
		Quinolones		Nalidixic Acid			
Folic Acid Synthesis		***Sulfonamides***		Sulfamethoxazole (SMX)	Ag Sulfadiazine	Sulfasalazine	Sulfisoxazole
		DHFR inhibitors		Trimethroprim (TMP)		Pirymethamine	
DNA (damage)		***Metronidazole***					
mRNA synth.		***Rifampim***					

Macrolides

- Erythromycin (Zineryt), roxithromycin, claritromycin (Klacid), spiramycin, azitromycin (Azi, Sumamed),
- Good oral bioavailability, do not penetrate into the CNS, they accumulate in the liver, azithromycin accumulates in the phagocytes
- Bacteriostatic agents, time-dependent antibacterial effect
- Effect: Inhibition of polypeptide chain translocation - 50S subunit
- Narrow spectrum: mainly against Gram +, +Campylobacter, pathogens of atypical pneumonia, atypical mycobacteria
- Resistance mechanisms:
  - Ribosome methylation
  - Active efflux
- Side effects: safe, non-toxic substances
  - Nausea, vomiting, diarrhea (especially with erythomycin - anhydrohemiketal metabolite)
  - Headache, dizziness
  - Cholestatic jaundice (mainly erythromycin)
  - Allergic skin phenomena, eosinophilia

Macrolides

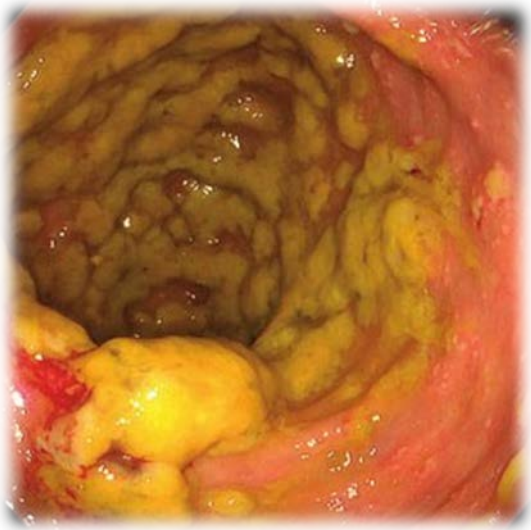
- Therapeutic indication:
  - An alternative drug for the treatment of follicular tonsillitis in people with penicillin allergies
  - Atypical pneumonia
  - Home-acquired upper and lower respiratory tract infections
  - Campylobacter jejuni infection (only if it cause
  - Spiramycin - gestational toxoplasmosis
  - Clarithromycin:
    - H. pylori,
    - H. influenzae,
    - Legionellosis
  - Azithromycin: Accumulates in i.c. space, 3 days of therapy is sufficient
    - H. inflenzae
    - 1 g given once in Chlamydia trachomatis infection is sufficient
    - In early stage of Lyme disease
    - Legionellosis

Ketolides

- Improved macrolides
- Telithromycin
- Effect: same as for macrolides - but much stronger binding to the 50 S subunit ->effective for macrolide-resistant strains
- Long PAE
- bactericidal
- Concentration Dependent effect
- For oral application
- Indication:
  - Upper respiratory tract infections
  - Home-acquired pneumonia
  - Acute exacerbation of chronic bronchitis

Macrocyclines

- Macrolide derivative
- Fidaxomicin
- Bactericidal
- Inhibits the RNA polymerase enzyme
- long PAE
- Selectively affects C. difficile infection (developed for this purpose) - does not damage the normal intestinal flora
- Not absorbed from the gut -> high intraluminal concentration + no systemic side effects
- Lower relapse rate than with metronidazole or vancomycin



Classification of antibiotics by mechanism of action

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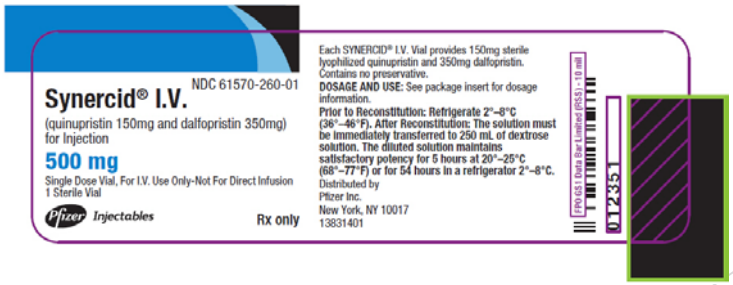
		Quinolones		Nalidixic Acid			
Folic Acid Synthesis		***Sulfonamides***		Sulfamethoxazole (SMX)	Ag Sulfadiazine	Sulfasalazine	Sulfisoxazole
		DHFR inhibitors		Trimethroprim (TMP)		Pirymethamine	
DNA (damage)		***Metronidazole***					
mRNA synth.		***Rifampim***					

Streptogramins

- Fixed combination of quinopristin + dalfopristin (Synercid)
- Intravenously only
- Bactericidal
- It inhibits protein synthesis on the 50 S subunit
- Spectrum of action: vancomycin-resistant Enterococcus faecium, MSSA, MRSA, penicillin-resistant Streptococcus pneumoniae
- Does not penetrate into CNS
- Side effects: phlebitis, arthralgia
- Indication: severe infection with multidrug-resistant Gram + bacteria



Classification of antibiotics by mechanism of action

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			4° Generation	Cefepime	Cefpirome *		
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		DHFR inhibitors		Trimethroprim (TMP)		Pirymethamine	
DNA (damage)		***Metronidazole***					
mRNA synth.		***Rifampim***					

Lincosamides

- Clindamycin (oral use)
- Bacteriostatic
- Effect: inhibition of protein synthesis on the 50S subunit + enhances opsonization of bacteria + inhibition of toxin production (Staphyloc., Streptoc., Clostridium)
- They act similarly to macrolides
- Narrow spectrum (Gr + aerobes and Gr + and - anaerobes)
- Does not get into the CNS
- Side effects:
  - Morbilliform rash, erythema multiforme
  - Neutropenia, agranulocytosis
  - Pseudomembranosus colitits

- Indication
  - Chronic lower and upper respiratory tract infections (aspiration pneumonia, pulmonary abscess)
  - Polimicrobial abdominal infections
  - Bacterial vaginosis
  - Odontogenic infections
  - Osteomyelitis
  - Skin and soft tissue infections (eg diabetic foot, gangrene, fasciitis) (Gr - in combination with AB affecting bacic)

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DNA (damage)		***Metronidazole***					
mRNA synth.		***Rifampim***					

Fluoroquinolones

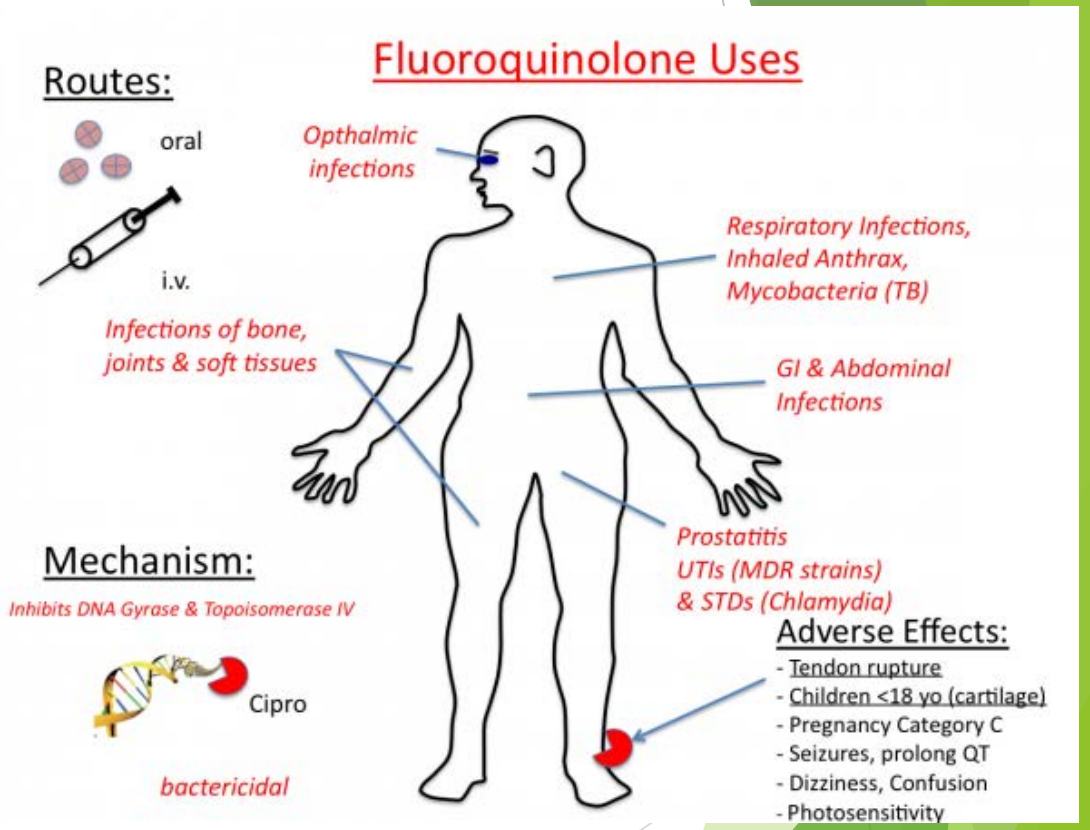
- Effect: Inhibition of DNA gyrase or topoisomerase IV enzyme
- Bactericidal agents
- They penetrate well into tissues (except CSF)
- Concentration and time dependent antibacterial effect (AUC / MIC)
- Long PAE
- Mechanisms of resistance (plasmid-encoded resistance is rare)
  - Efflux
  - Mutation in DNA gyrase or topoisomerase IV
  - Mutations in porins
- Generations: Gram + spectrum increases with growth
  - 0th. generation: nalidixic acid, oxolinic acid (no F atom yet)
  - 1st. generation: norfloxacin
  - 2nd. generation: perfloxacin, ofloxacin, ciprofloxacin
  - 3rd. generation: levofloxacin
  - 4th. generation: moxifloxacin

Fluoroquinolones

- Therapeutic indication:
  - o. generation: nalidixic acid, oxolinic acid (no F atom yet) - only for urinary tract infections
  - 1. generation: norfloxacin
    - also for lower urinary tract infections
    - for the treatment of enteritis (Salmonellosis, traveler diarrhea)
  - 2. generation: perfloxacin, ofloxacin, ciprofloxacin
    - Wide spectrum, especially against Gr - bacteria
    - Urinary tract infections
    - Intestinal infections caused by Shigella, Salmonella, E.coli, Campylobacter
    - Ciprofloxacin: anthrax prophylaxis and treatment
    - Osteomyelitis
  - 3. generation: levofloxacin (Tavanic)
    - Similar to 2nd generation but better Gram + spectrum -> Str. pneumoniae, S aureus
    - Against atypical respiratory pathogens
    - Urinary tract and soft tissue infections
  - 4. generation: moxifloxacin (Avelox)
    - Like 3rd generation, but also good against anaerobes
    - They are effective against penicillin-resistant pneumococcus
    - Upper respiratory tract infections, home-acquired and nosocomial pneumonia, acute exacerbation of chronic bronchitis

Fluoroquinolones

- Side effects:
  - headache, nausea, dizziness
  - phototoxicity
  - Seizures, psychotic reactions, loss of consciousness (rare)
- Drug interaction :
  - Followings reduce absorption: antacids, mixtures containing iron
  - They inhibit the breakdown of theophylline
- Administration to children and pregnant women is not recommended
- For the treatment of uncomplicated urinary tract infections, fosfomycin should be considered (due to spreading fluoroquinolone resistance).
- They are not recommended anymore for the treatment of gonorrhea because of the wide-spread resistence
- Treatment of tuberculosis (cipro, levo and moxifloxacin)



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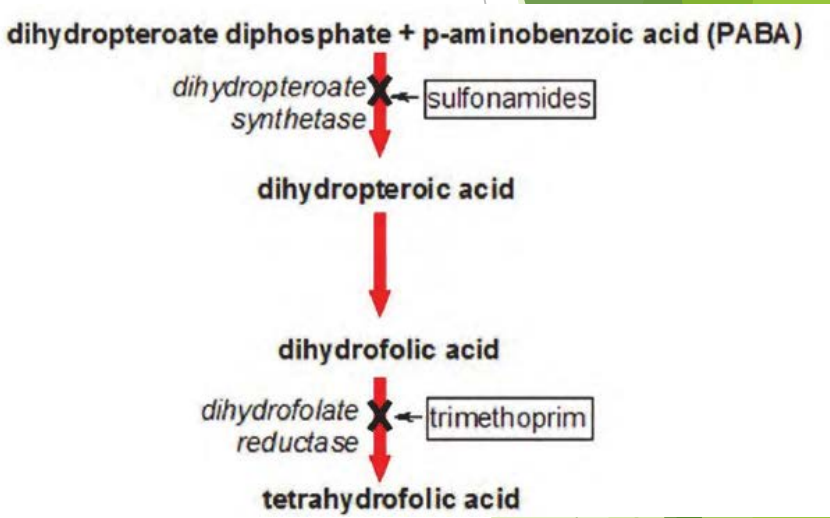
DNA (damage)		Metronidazole					
mRNA synth.		Rifampim					

Sulfonamides and trimethoprim

- Sulfasalazin: RA, IBD
- Sulfamethoxazole (SMX) + trimethoprim (TMP)
- Inhibition of two different steps of folic acid synthesis
  - Sulfonamide: inhibits the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid
  - Trimethoprim: inhibition of dihydrofolate reductase (no FH4 is formed)
- Synergistic effect:
  SMX: TMP 5: 1 combination: Sumetrolim
- Selective toxicity
- It is also effective against Gram + and - bacteria, but has a lot of secondary resistance



Sulfonamides and trimethoprim

- Side effects:
  - Gastro Intestinal symptoms
  - Allergic skin symptoms, rarely exfoliative dermatitis
  - Haematological abnormalities: neutropenia, thrombocytopenia, haemolytic anemia
  - Enhances the effect of coumarins
- Indication:
  - Home-acquired sinusitis, otitis
  - Uncomplicated urinary tract infections
  - Acute exacerbation of chronic bronchitis
  - Selective decontamination of a patient with neutropenia
  - Treatment of Pneumocystis carinii pneumonia in an AIDS patient

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DNA (damage)		***Metronidazole***					
mRNA synth.		***Rifampim***					

Rifamycins

- Rifampicin, rifabutin, rifaximin
- Inhibition of RNA polymerase
- bactericides
- Good tissue penetration (thoracal and abdominal processes, bone, abscess)
- It reaches therapeutic concentrations in the cerebrospinal fluid
- Effective against:
  - Gr + bacteria: pl. S aureus, C. difficile
  - Gr- bacteria: Neisserias, H inflenzae
- Strong enzyme inducers -> increase the metabolism of other drugs (or it's own)
- Side effects:
  - Urine, saliva, tears turn red-orange
  - Abdominal pain, hepatitis
- Therapeutic indication:
  - Rifampicin, rifabutin: they are preferred in combination because they damage the biofilm, so the other agent can work better - Staphylococcus, Pseudomonas infection
    + For prophylaxis: against N. megingitidis and H. influenzae B.
    + As part of combination therapy: Against Mycobacteria
  - Rifaximin: no absorbtion from the bowel → it reaches high intraluminal conc. → for the treatment of GI infections (Acinetobacter, Bacteroides fragilis)

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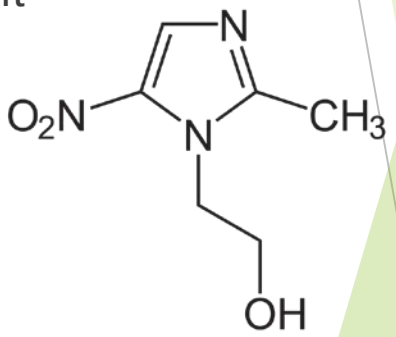
Metronidazole

- a nitroimidazole (tinidazole is related)
- Effect: damage of the nucleic acids
- oral absorption / permeation with simple diffusion / liver metabolism
- The resistence is rare
- active against anaerobic and microaerophilic pathogens
  - extraluminal amebiasis – together with a luminal agent
  - giardiasis – lower dose
  - trichomoniasis
  - various anaerobic bacteria
- adverse effects
  - nausea
  - metallic taste in the mouth
  - dark urine
  - disulfiram like effect
  - teratogenic in some animals / mutagenic in bacteria



Antifungal drugs
ATC codes D01 and J02

Fungi (=fungus plural)

- Eukaryotic organisms (= they have real nucleus)
- According to modern taxonomy:
  - In the „domain” of eukaryota they constitute a separate kingdom, as the animals and plants
- They spread with spores
- More than 100 000 species are known, (more than 1M exist), although only <1000 are human-pathogen
- Their cell wall consists of polysaccharides: chitin, α- and ß-glucans
- Main component of their cell membrane: ergosterol

Fungal infections

- In otherwise healthy people, fungal infections are mainly benign, generally associated with skin or mucous membrane.
- However in case of compromised immune-system, facultative pathogen fungi may cause „opportunist infections”, which can be fatal.

Fungal infections II.

- Superficial fungal infections
  - External infections on the surface of skin, mucous membrane, hairy skin, generally do not cause inflammation
    - E.g.: pityriasis versicolor, tinea nigra
  - If the infection spreads into epidermis,or into mucous membrane, hairy skin, fingernail, hair, ➔ inflammation
    - Trichophyton-infections, candida-infections
- Subcutaneous mycosis
  - Dermis, muscle or fascia is affected ➔ systemic agents
    - E.g. usually caused by low-virulence soil fungi e.g. after traumatic injury
- Systemic mycosis
  - Usually lungs are affected (inhalative infections),
  - but fungal-sepsis also exists
    - E.g.: caused by yeasts or yeast-like fungi, or molds

Important! In case of sepsis, „blind" use of wide-spectrum antibiotics may facilitate the spread of a fungal infection. ← or in case of mycotic sepsis, upon use of antibiotics, the process progrediates ← cause: physiological bacteria&fungi are in balance

Groups of fungi and the therapy

Dermatomycosis

Dermatophytosis (Cutan mycosis)

- Trichophyton rubrum
- Microsporium canis
- Microsporium gypseum
- Epidermophyton species

} Mechanical removing, topical, oral

Superficial mycosis

- Malassezia furfur } topical

Subcutaneous mycosis

- Sporothrix shenkii } oral

topical
- nystatin, natamycin
- itraconazole, fluconazole, ketoconazole
- terbinafine (Only in dermatomycosis)

Oral
- ketoconazole, fluconazole, itraconazole
- terbinafine (Only in dermatomycosis)

Systemic mycosis

Dimorphic fungi
- Coccidioides immitis
- Histoplasma capsulatum
- Blastomyces dermatitis
- Paracoccidioides brasiliensis

} Lungs ➔ oral
Meningitis ➔ fluconazole
Disseminated ➔ i.v.ampB
Skin ➔ topical

Opportunist mycosis

- Candida species (C.albicans, C.krusei, C.tropicalis, C.glabrata, C.parapsilosis) } Mucocutan ➔ topical, oral; Invasive ➔ oral, i.v. ampB
- Cryptococcus neoformans } Dissem. ➔ i.v. ampB; meningitis ➔ fluconazole
- Aspergillus species (A.fumigatus, A.flavus, A.niger) } outer ➔ topical, oral; inner ➔ oral, i.v.
- Absidia corynbifera
- Rhizomucor pusillus
- Rhizopus arrhizus

} Oral i.v. ampB

- Pneumocystis carinii } Sumetrolim (Trimethoprim + Sulfamethoxazol) Pentamidin (antiprotozoal agent)

Problems with antifungal therapy

- Few appropriate agent
- Toxicity:
  - Similarity to human cells ➔ some agents can only be used superficially
- Tissue distribution of agent
  - Does it accumulate in keratin-rich tissue? ➔ some per os agent only for mucocutaneous or only for hair/nail or only for gastrointestinal use
- Interactions
  - CYP-inhibitors:
    - CYP2D6: terbinafin, CYP2C9: fluconazole, CYP3A4: ketoconazole, myconazole, itraconazole
- Resistance
  - Constantly follows and publishes: EUCAST-SAS: European Cimmittee on Antimicrobial Susceptibiliy Testing – Subcommittee on Antifungal Susceptibility

Groups of antifungals

One classification:

- Systemically used
  - For systemic fungal infections
  - For local fungal infections
- Locally used

Another classification:

- Based on mechanism of action
  - Subdivision based on chemical structure

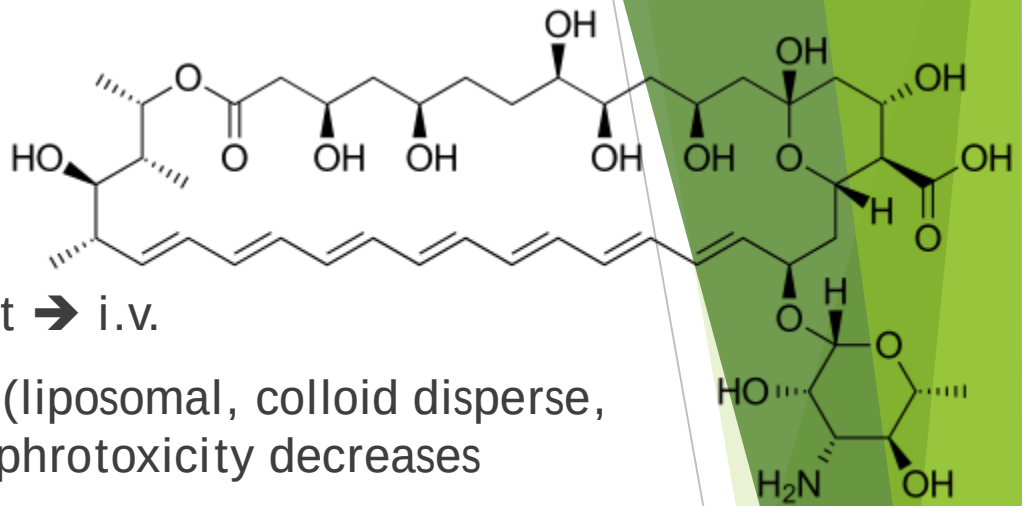
Agents that damage the cellmembrane

- Polyene macrolides („Polyenes”)
- Azoles
  - imidazoles and
  - triazoles
- Allylamines
- Morpholines

Agents that damage the cellmembrane Polyenes I.

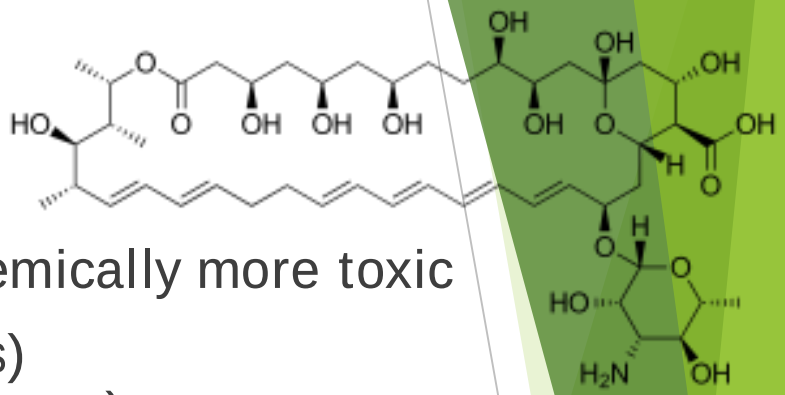
- Polyene macrolides („Polyenes”)
  - Produced by *Streptomyces* species ~150 polyene exists: macrocyclic lactone ring with diff. numbers of conjugated double bonds
  - Mechanism of effect: they bind the ergosterol in the membrane and form a **pore** leading to a disfunction in the ion-exchanging mechanisms and eventually the energy production (ATP synthesis)
  - They bind to other sterols (cholesterol) ➔ many are toxic (lipidassociated variants exist, that are less toxic) ➔ not all can be used sytemically
  - Effectiveness: fungistatic in lower doses, fungicidal in higher doses

Agents that damage the cellmembrane – Polyenes II.

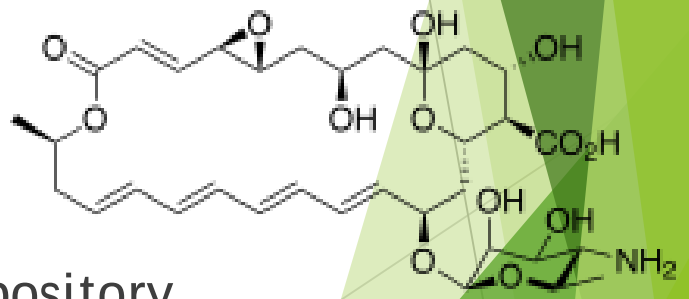


- Agents:
  - Amphotericin B
    - Poorly absorbed from GI tract ➔ i.v.
    - Can be combined with lipids (liposomal, colloid disperse, phospholipid complex) ➔ nephrotoxicity decreases
    - Long term exposure: nephrotoxicity, liver and hematopoietic toxicity
    - mainly for systemic therapy (i.v.), in severe systemic fungal infections
    - rarely for oral therapy of GI *Candida*
    - in combinative treatments: catastrophe-mix
      amph B + flucytosin
      amph B + fluconazol
      amph B + echinocandins
      echinocandins + triazoles
    - contraindications: other nephrotoxic agents (aminoglycosides, cyclosporin); pregnancy (gets through placenta)

Agents that damage the cellmembrane - Polyenes III.



- Nystatin
  - characteristics like amph B, but systemically more toxic
  - for topical therapy of GI tract (per os) (*Cryptococcus, Histoplasma, Blastomyces*)
  - for vaginal fungal infections (*Candida*)



- Natamycin
  - merely penetrates
  - for topical therapy in ointment or in suppository (*Candida, Aspergillus, Cephalosporium, Fusarium, Penicillium*)

Agents that damage the cellmembrane – Azoles I.

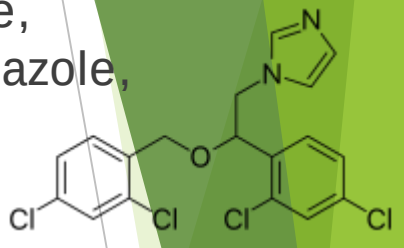
- Azole-derivatives
  - broad spectrum effect: not only antifungal but against some Gram-positive bacterias as well
  - Mechanism of effect:
    - they inhibit the **lanosterol-14α-demethylase** enzyme ➔ the biosynthesis of ergosterol is inhibited
      - (the ergosterol is crucial for the cellmembrane of the fungi) (like cholesterol in the animal, required for proper permeability and fluidity)
  - Effectiveness: they are fungistatic agents
- Azoles have two groups: imidazoles and triazoles

Agents that damage the cellmembrane – Azoles II.

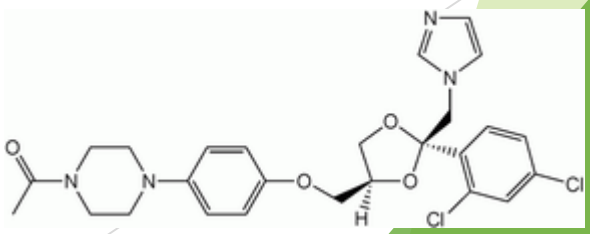
- Imidazoles:

  Miconazole, Econazole, Ketoconazole, Clotrimazole, Bifonazole, Clomidazole, Croconazole, Fenticonazole, Isoconazole, Neticonazole, Oxiconazole, Sertaconazole, Sulconazole, Tioconazole

  - Use:
    - mainly topical: fungal infection of
      - Skin (duration: 4-6 weeks)
      - Vagina (duration: 1-2 weeks)
    - rarely for systemic use as well (ketoconazole)
    - they have a broad spectrum
  - Ketoconazole:
    - first (and only) per os imidazole-derivative
    - well absorbed
    - excretion: bile, intestines
    - adverse effects: even severe hepatitis
    - CYP3A4 enzyme-inhibitor



Miconazole
WHO essential medicine



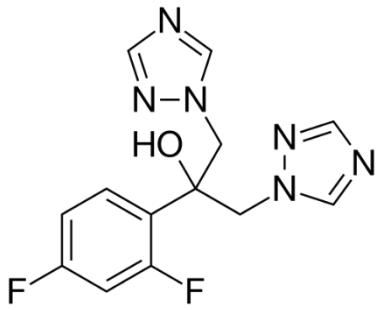
Agents that damage the cellmembrane – Azoles III.

- triazoles:

I.gen.: Fluconazole, Fosfluconazole, Itraconazole,

II.gen.: Posaconazole, Voriconazole

  - Use:
    - mainly systemically (for local use imidazoles are preferred)
    - they have a broad spectrum
  - Fluconazole:
    - both per os or i.v.
    - relatively few adverse effects
    - also in catastrophe-mix
    - not metabolised
    - CYP2C9 enzyme-inhibitor (coumarins!)
  - Itraconazole:
    - mainly per os
    - highly protein bound (99,8%)
    - binds keratin ➔ accumulates in hair, skin, nail
  - Posaconazole:
    - mainly in per os suspension for systemic mycosis
  - Voriconazole:
    - similar to fluconazole but
    - metabolised (by CYPs)

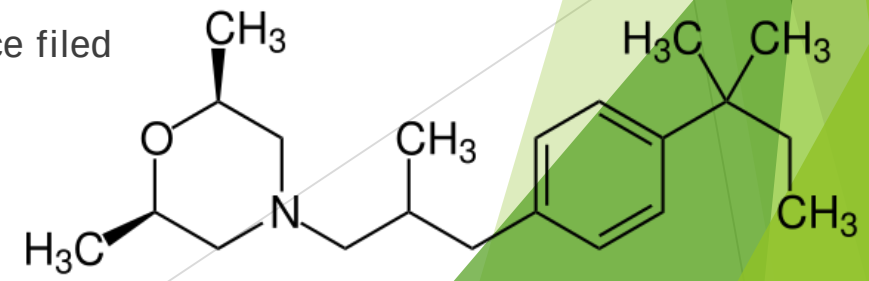


Agents that damage the cellmembrane – Allylamines

- Allylamines: Terbinafine, Naftifine (Butenafine)
  - Mechanism of effect: they inhibit the **squalene epoxydase** enzyme
    ➔ biosynthesis of ergosterol is inhibited
    ➔ squalenes accumulate in fungus, which is toxic for them
  - Effectiveness: fungicidal
  - Terbinafine:
    - both locally and systemic (per os)
    - Absorbed in 70-80%
    - Metabolised in liver
    - Excreted through urine (80%) and fecally (20%)
    - Against dermatomycosis, onychomycosis, tinea pedis/corporis
  - Naftifine, butenafine:
    - only topically
    - they are effective mainly against filamentous fungi – in dermatomycosis

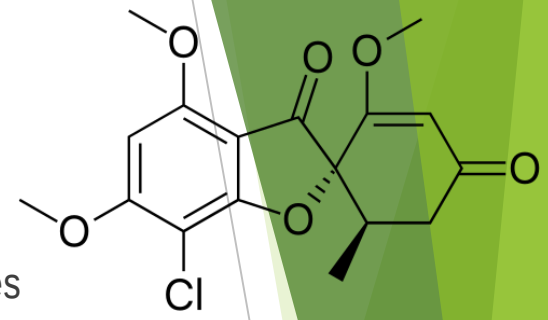
Agents that damage the cellmembrane - Other

- Amorolfine
  - Morpholine-structure (N and O in the same ring)
  - Mechanism of effect:
    - it inhibits enzymes that function in the biosynthesis of ergosterol (e.g. **D14-reductase** and **D7-D8-isomerase**)
      - thus it inhibits the ergosterol-synthesis
      - intermediates accumulate in fungal membrane
  - Effectiveness:
    - fungicidal
  - Use:
    - topically, mainly on nail as a nail lacquer
    - Nail should be softened, or the surface filed



Agents that inhibit the microtubules

- Griseofulvin
  - Benzofuran-derivative, insoluble in water
  - Mechanism of effect:
    - it **binds to tubulin** ➔ inhibits microtubular processes e.g. mitosis
    - Accumulates in keratin precursor cells ➔ newly formed nail/hair will be protected against fungal invasion ➔ old infected nail/hair is to be cut off
    - Absorbed by fungus through energy dependent transport ➔ decreased in resistant fungi
  - Effectiveness:
    - fungistatic
  - Use:
    - Per os ➔ used in ultra-microsized particles (due to insolubility)
    - greasy food increases absorption
    - against dermatophytes - Epidermophyton, Microsporum and Trichophyton species;
      for topical therapy



Agents that inhibit the nucleic-acid synthesis

- 5-fluorocytosine/flucytosine
  - Fluoropirimidine
  - Mechanism of effect:
    - Inside cell transforms into **5-fluoro-uracyl** (⇔ few in mammalian cells ➔ selectivity)
    - nucleotide analogue ➔ it inhibits the RNA and DNA synthesis of the fungi
  - Effectiveness:
    - fungistatic
  - Use:
    - Per os/i.v. (systemic Candida/Cryptococcus)
    - Topical (ointment)
    - synergistic with amph B (better absorbed due to amph B)

Agents that inhibit cell wall synthesis

- Echinocandines: Caspofungin, Micafungin, Anidulafungin
  - Mechanism of effect:
    - they inhibit the **ß-glucane synthase** enzyme ← ß-glucane is a crucial component of the cell wall of the fungi
  - Effectiveness:
    - against yeastlike fungi e.g. Candida it is fungicidal
    - against filamentous fungi e.g. Aspergillus it is fungistatic
  - Use:
    - mainly against Candida and Aspergillus;
      mainly sytemically
    - In catastrophe mixes

Summary

- Systemically used antifungals for systemic infections
  - Polyenes – Amph B
  - 5-Fluorocytosine
  - Azoles
    - Imidazoles – Ketoconazole
    - Triazoles – Itraconazole, Fluconazole, Voriconazole, Posaconazole
  - Echinocandins – Caspofungin, Micafungin, Anidulafungin
- Systemically used antifungals for mucocutaneous infections
  - Allylamines – terbinafine
  - Griseofulvin
- Topically used antifungals
  - Polienes – Nystatin, Natamycin, Candicin
  - Allylamines – Terbinafine, Naftifine
  - Amorolfine
  - Azoles
    - Imidazoles – Miconazole, Econazole, Clotrimazole etc.

Summary

- Agents used most most frequently against fungi:
  - Amphotericin B (*i.v.*)
  - Itraconazole (or Fluconazole) (*per os*)
  - Ketokonazol (*topical)*

Anthelmintics

ATC code P02

Introduction

Helminthiasis: Disease caused by parasitic worms (helminths) living inside the human or animal gastrointestinal tract or tissues.

Worldwide, helminthiasis is very prevalent, it occurs in great numbers in the economically underdeveloped countries.

In Hungary roundworm and tapeworm-infections are the most common.

Groups of helminths

Helminths

Nematoda (roundworms)

Intestinal occurrence:
- Enterobius vermicularis
- Trichuris trichiura
- Ascaris lumbricoides
- S → Toxocara canis
- Ancylostoma duodenale
- Necator americanus
- Strongyloides stercolaris
- S → Trichinella spiralis

Blood and Tissues occurrence:
- S → Wuchereria bancrofti
- S → Loa Loa
- S → Oncocerca volvulus
- S → Dracunculus medinensis

Platyhelminths (flatworms)

Cestoda (tapeworms)

Intestinal occurrence:
- Taenia saginata
- S → Taenia solium
- S → Echinococcus granulosis
- S → Echinococcus multilocularis
- Dipylidium caninum
- Diphyllobotrium latum
- Hymenolepis nana

Trematoda (flukes)

Intestinal occurrence:
- Fasciola hepatica
- Schistosoma mansoni
- S → Schistosoma japonicum
- Scistosoma haematobium
- Paragonismus westermani

S = sexual reproduction can occur in human ➔ can occcur in human tissues

Groups of helminths and drugs against them

Helminths

Nematoda (roundworms)

Intestinal occurrence:
Enterobius vermicularis – mebendazole
Trichuris trichiura – mebendazole
Ascaris lumbricoides – mebendazole, tiabendazole, levamisol
Toxocara canis – tiabendazole
Ancylostoma duodenale – mebendazole,tiabendazole,levamisol
Necator americanus – mebendazole, tiabendazole, levamisol
Strongyloides stercolaris – tiabendazole
Trichinella spiralis – tiabendazole

Blood and Tissues occurrence:
Wuchereria bancrofti – dietilkarbamazin, ivermektin
Loa Loa – dietilkarbamazin, ivermektin
Oncocerca volvulus – dietilkarbamazin, ivermektin
Dracunculus medinensis – surgical

Platyhelminth (flatworms)

Cestoda (tapeworms)

Intestinal occurrence:
Taenia saginata – niklozamid, prazikvantel
Taenia solium – niklozamid, prazikvantel
Echinococcus granulosis – surgical, mebendazole, albendazole
Echinococcus multilocularis – surgical, mebendazole, albendazole
Dipylidium caninum – niklozamid, prazikvantel
Diphyllobotrium latum – niklozamid, prazikvantel
Hymenolepis nana – niklozamid, prazikvantel

Trematoda (flukes)

Intestinal occurrence:
Fasciola hepatica – bithionol
Schistosoma mansoni – prazikvantel
Schistosoma japonicum – prazikvantel

Scistosoma haematobium – prazikvantel

Paragonismus westermani – prazikvantel

Anthelmintics

Anthelmintics: drugs, that are – applied alone or with other therapeutical interventions – able to kill the helminths (vermicide) or able to decrease their number in human or animal host organism (deworming)

Targets of these drugs are usually found in the developed helminth:

- Neuromuscular coordination of the helminths' motion
- Carbohydrate-metabolism, as the energysource of the helminth (glucose is the primary substrate)
- Integration of the microtubules, that is important in laying eggs, hatching, development of the larva, glucose-transport, enzyme-activity, and secretion

Diagnostics

The difficulty in the anthelmintic therapy is, that the biochemical and physiological properties of the parasite and host organism are very similar, thus, most of the drugs used against the helminths have toxic adverse effects toward the host organism.

Therefore it is expedient – before the beginning of the therapy – to detect and define the parasite, then on this basis the adequate medicine to choose.

The detection of the various developmental stages of the helminths (egg, larva, developed form) can be carried out from faeces, urine, blood, sputum and tissues.

Benzimidazoles

Mebendazole, albendazole, tiabendazole, triclabendazole

Drug target: microtubular system of the helminths (b-tubulin)

Mechanism of effect:

they bind to b-tubulin
↓
they inhibit the polimerisation of the microtubules
↓
the helminth will be immobilised,
then it will slowly die and be excreted from the organism

The reason for selective toxicity is, that benzimidazoles bind with higher affinity to the b-tubulin of the parasite than that of the mammalian cell.

Spectrum: they are effective against almost every helminth, but mostly against the roundworms occurring in the intestines

roundworms	Mebendazole	Trichuris, Enterobius, Ancylostoma
	Tiabendazole	Toxocara, Strongyloides, larva migrans (Necator, Ancylostoma)
tapeworms	Albendazole	Echinococcus, cysticercus (Taenia)
flukes	Triclabendazole	Fasciola hepatica

Agents acting on the nervous system Parasympathomimetics

Mechanism of effect: they act on acetylcholinergic synapses and they paralyse the muscles of the helminths in a contracted state (spastic paralyses – depolarising neuromuscular inhibition)

Agents stimulating cholinergic synapses:

- Imidazolothiazoles
  - Levamisole – against Ascaris, Necator, Ancylostoma (so against intestinal roundworms), it has immunmodulator effect as well
- Tetrahydropyrimidines (mainly in veterinary practice):
  - Pyrantel – against Ancylostoma, Necator, Enterobius, Trichinella (so against intestinal roundworms)
  - Oxantel – Trichuris (intestinal roundworms)
- Benzylammonium-derivatives
  - Bephenium – against Ascaris, Necator, Ancylostoma (so against intestinal roundworms)

Cholinesterase inhibitors:

- Phosphonic acid-derivatives (irreversible organophosphates)
  - Metrifonate – against Schistosoma haematobium (fluke) (otherwise it is an antiAlzheimer drug as well)

Agents acting on the nervous system
Agents acting on receptors

Mechnism of effect: they act on synapses (Glutamatergic/GABAergic) and they paralyse the muscles of the helminths in flaccid state (flaccid paralysis – non-depolarising neuromuscular inhibitions)

Agents acting on Glutamatergic receptors:

- Macrolide-derivatives
  - Ivermectin – against roundworms, e.g.: Strongyloides; its relative-compund the avermectin is an anti-arthropod agent

Agents acting on GABAergic synapses:

- Piperazine-derivatives
  - Piperazine – against Ascaris, Enterobius (so against intetinal roundworms)
  - Diethylcarbamazine – against Dracunculus, Ascaris (so against intetinal roundworms)

    Latter has another hypothetical mechanism of effect as well: it may inhibit the arachidonic acid metabolism, thus, the outer membrane of the helminth will be altered, in other words, it reveals helminth-antigens and makes the helminths more sensitive against the immunsystem of the host organism

Agents acting on the metabolism of the helminths

Salicylanilide-derivatives:

- Niclosamide

  The exact mechanism of action is unknown, it presumably uncouples the enzymes of the oxidative phosphorylation, thus, inhibiting the ATP-synthesis.

  Spectrum: against every tapeworms (cestoda)

Sulphanylphenol-derivatives:

- Bithionol

  The exact mechanism of action is unknown, presumably it also inhibits the ATP-production

  Spectrum: against Fasciola, Paragonismus (flukes)

Quinolin-derivative:

- Pyrvinium

  Mechanism of effect: it inhibits the carbohydrate- (glucose) uptake of the helminths

  Spectrum: effective against most roundworms (nematoda)

Agents with other mechanism of effect

Quinolin-derivatives:

- Praziquantel

  Mechanism of effect: not thoroughly understood; presumably it increases the permeability of the membrane of the helminths to Ca^{2+} ions, thus, the helminth is paralysed with contracted musculature;
  another mechanism may be, that it inhibits the adenosin uptake of the helminth (and the helminths can not synthetise purins *de novo*)

  Spectrum: against flukes (e.g. Schistosoma, Paragonismus), and tapeworms

- Oxamniquin

  Mechanism of effect: presumably it binds to the DNA of the helminth, and damages it; also the helminth will be paralysed with contracted muscles;
  an anticholinerg effect-route is also supposed

  Spectrum: effective against Schistosoma mansoni

Other agents / Agents with mixed spectrum

Naphtalenesulphonate-derivatives:

- Suramin

  Mechanism of effect: Presumably it exerts its effect through the enzymes of the DNA-RNA metabolism, e.g. in onchocerciasis the grown up female helminth will be sterilised, then killed; it is also an antiprotozoon agent (see there)

  Spectrum: against Onchocerca volvulus, as well as antiprotozoon agent (see there)

Aminoacridin-derivatives:

- Quinacrine

  antiprotozoon (see there), anthelmint, and also antiprion (=anti-Creutzfeldt-Jakob disease) agent
  Mechanism of effect is uncertain

Butyrophenon-derivative:

- Desapidin

  the mechnism of action is unknown, against tapeworms

Chlorophenol-derivative:

- Dichlorophen

  the mechnism of action is unknown, against tapeworms

Thiazole-derivative:

- Niridazole

  the mechnism of action is unknown, against flukes

Arylsulphonate-derivative:

- Stibophen

  the mechnism of action is unknown, against flukes

Summary

- Intestinal helminths
  - Against roundworms ➔ mebendazole/tiabendazole
  - Against tapeworms ➔ niclosamid/praziquantel
  - Against flukes ➔ praziquantel
- Blood infecting helminths (roundworms)
  - ➔ diethylcarbamazine/ivermectin

Beside these some agents of greater importance:

levamisol ➔ against intestinal roundworms

metriphonate ➔ against flukes

bithionol ➔ against flukes

Agents on the market of Hungary

- DECARIS 150 mg tabletts (levamisol) 1x

- DECARIS 50 mg tabletts (levamisol) 2x (for children)

- VERMOX tabletts (mebendazole) 6x (100mg)

Each against intestinal roundworm infections

Antiparasite agents

ATC codes P01 and P03

Groups of parasites and medications against them

Parasites

Protozoans (Endoparasites)

Ectoparasites (discussed separately)

- Lice
- Mites
- Flies
- Fleas
- Ticks
- Mosquitos
- Bloodsucking flies
- Bedbugs

Intestinal occurrence:

- Amoeboids
  - Entamoeba histolytica – metronidazole, tinidazole (=nitroimidazoles)

    emetine

    paromomycin (aminoglycoside antibiotic agent)

    iodoquinol

    diloxanide-furoate

    (tetracycline antibiotics)

New agents are typed **bold**. Other agents have already been discussed in other presentations (e.g. antibacterial, antifungal, anthelmint therapy) look for them there!

Groups of parasites and medications against them (cont.)

Protozoans with intestinal occurrence (cont.):

- Flagellates
  - Dientamoeba fragilis (not an amoeba!) – metronidazole
  - Giardia lamblia – metronidazole, nitrofurantoin (latter is a nitrofuran antibiotic agent)
  - Trichomonas vaginalis – metronidazole, nitrofurantoin (sexual partner must be treated as well!)
- Ciliates
  - Balantidium coli – metronidazole, tetracyclines
- Sporozoans
  - Isospora hominis – co-trimoxazol (=trimethoprim + sulphametoxazol)
  - Cryptosporidium parvum – (only AIDS-patients need therapy) spiramycine (macrolide antibioticum with 16 membered ring)

New agents are typed **bold**. Other agents have already been discussed in other presentations (e.g. antibacterial, antifungal, anthelmint therapy) look for them there!

Groups of parasites and medications against them (cont.)

Protozoans living in blood and tissues:

- Amoeboids
  - Naegleria – amphotericin B (=ampB) + miconazole + rifampicin
    (antifungal poliene) (antifungal azole) (anza-macrolide antibioticum)
  - Acanthamoeba – miconazole (topically) or ampB + miconazole + rifampicin
- Flagellates
  - Trypanosoma brucei gambiense – **suramin**, **pentamidin**; **melarsoprol**, **eflornitin**
    (Sleeping sickness) (in hemolimphatic stage) (after appearance of CNS-smptoms)
  - Trypanosoma brucei rhodesiense – **suramin** ; **melarsoprol**
  - Trypanosoma cruzi (Chagas-disease) – benznidazole (nitroimidazole antibioticum), nifurtimox (nitrofuran antibioticum)
  - Leishmania species – **Sodium stibogluconate**, IFN-γ (universal immunstimulant), **pentamidin**, ampB, azoles, paromomycine
- Sporozoans
  - Plasmodium falciparum, P. vivax, P. ovale, P. malariae – **all agents** *Discussed separately*
  - Toxoplasma gondii – Fansidar® (sulphadoxine+Pyrimethamine), spiramycin, **atovaquone**

New agents are typed **bold**. Other agents have already been discussed in other presentations (e.g. antibacterial, antifungal, anthelmint therapy) look for them there!

Agents against Entamoeba histolytica - Luminal amebicides

- Emetine/Dehydroemetine
  (latter has fewer adverse effects)
  - Mechanism of action: unknown; it inhibits translocation *in vitro*
- Dichloroacetamide-derivatives (Diloxanide-furoate, Clefamide, Etofamide, Teclozan)
  - Mechanism of action: unknown; also effective against cysts

Agents against Entamoeba histolytica - Luminal amebicides (cont.)

- Halogenised Hydroxyquinole-derivatives

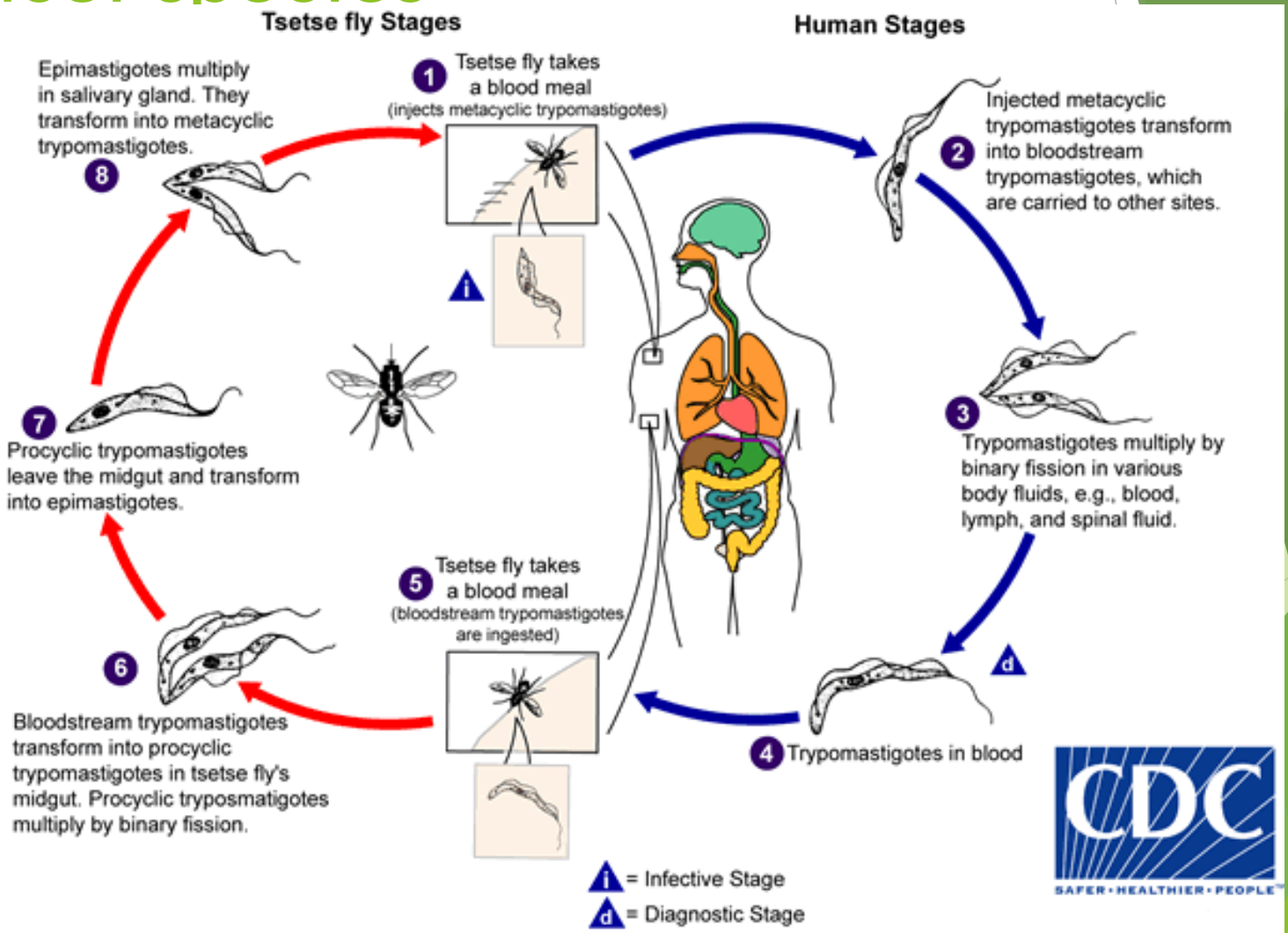
  (Iodoquinol, Chlorquinaldol, Tilbrokinol, Broxyquinoline, Clioquinol, Chiniofon)

  - Mechanism of effect: not thoroughly understood,
    - presumably it inactivates crucial enzymes of the protozoan,
    - as well as halogenisating its proteins;

    thus, it inhibits the proliferation of the parasite

- Chronic use may result in blindness!

Life cycle of Trypanosoma brucei species



Agents against Trypanosoma brucei species – sleeping sickness

Suramin

- Mechanism of effect:
  it inhibits many enzymes e.g.:
  - glycolytic enzymes found in the special glycosomes of the protozoans (α-glycerinphosphate oxydase (this enzyme can be found only in protozoans), glycerin-3-phosphate dehydrogenase, phosphofructokinase, aldolase and pyruvate kinase),
  - RNa polimerase, succinate dehydrogenase,
  - enzymes of the pirimidin-synthesis (timidylate synthase, dihydrofolate reductase)
  - protein-kinase of the parasite

  Thus, the ATP-synthesis of the parasite is inhibited, and also the RNA- and DNA-metabolism, and also the protein-synthesis.
- Use: very effective in early gambiense infection,
  lesser in rhodesiense trypanosomiasis;
  does not penetrate into CNS, thus can be used only in hemolimphatic stage, before appearing of the CNS-symptoms.

  (Also effective against Onchocerca volvulus and Wuchereria bancrofti (roundworms))

Agents against Trypanosoma brucei species – sleeping sickness (cont.)

- Pentamidin
  - Mechanism of effect: not thoroughly understood;
    - presumably it binds to DNA of the kinetoplast (kDNS), thus, inhibiting the replication and functioning of the kinetoplast,
    - also may cause the kinetoplast to disintegrate;
    - beside these it may have effect on succinate-dehydrogenase (thus, on cell respiration) and
    - it may have effect on S-adenozyl-methyonin (thus on the process of biological metilation)
  - Use: treatment of early stage of african trypanosomiasis; as well as in leishmaniasis, if stibogluconate is not effective; rarely in pneumonia caused by Pneumocystis carinii

Agents against Trypanosoma brucei species – sleeping sickness (cont.)

- **Melarsoprol** (trivalent arsenic-derivative)
  - Mechanism of effect: covalently binds to essential SH-groups of enzymes (e.g.:glycolytic phosphopyruvate-kinase), thus the proliferation is inhibited
  - Use: Against Trypanosoma brucei gambiense and also rhodesiense; penetrates into CNS, thus, can be used in later stages of the infection

- Other, pentavalent arsenic-derivatives also exist (Tryparsamide, Glycobiarsone, Difetarsone), but these are much more toxic, thus were withdrawn from market.

Agents against Trypanosoma brucei species – sleeping sickness (cont.)

- Eflornithine/α-Difluoromethylornithine (DFMO)
  - Mechanism of effect: ornithine-analogue agent ➔ irreversibly inhibits the ornithine-decarboxylase, thus, the cell proliferation and cell differentation of the protozoan is inhibited, thus, the growth of protozoan
  - Use: against sleeping sickness (Trypanosomiasis), and also in pneumocystis (fungus) and cryptosporidium (protozoan) infections;

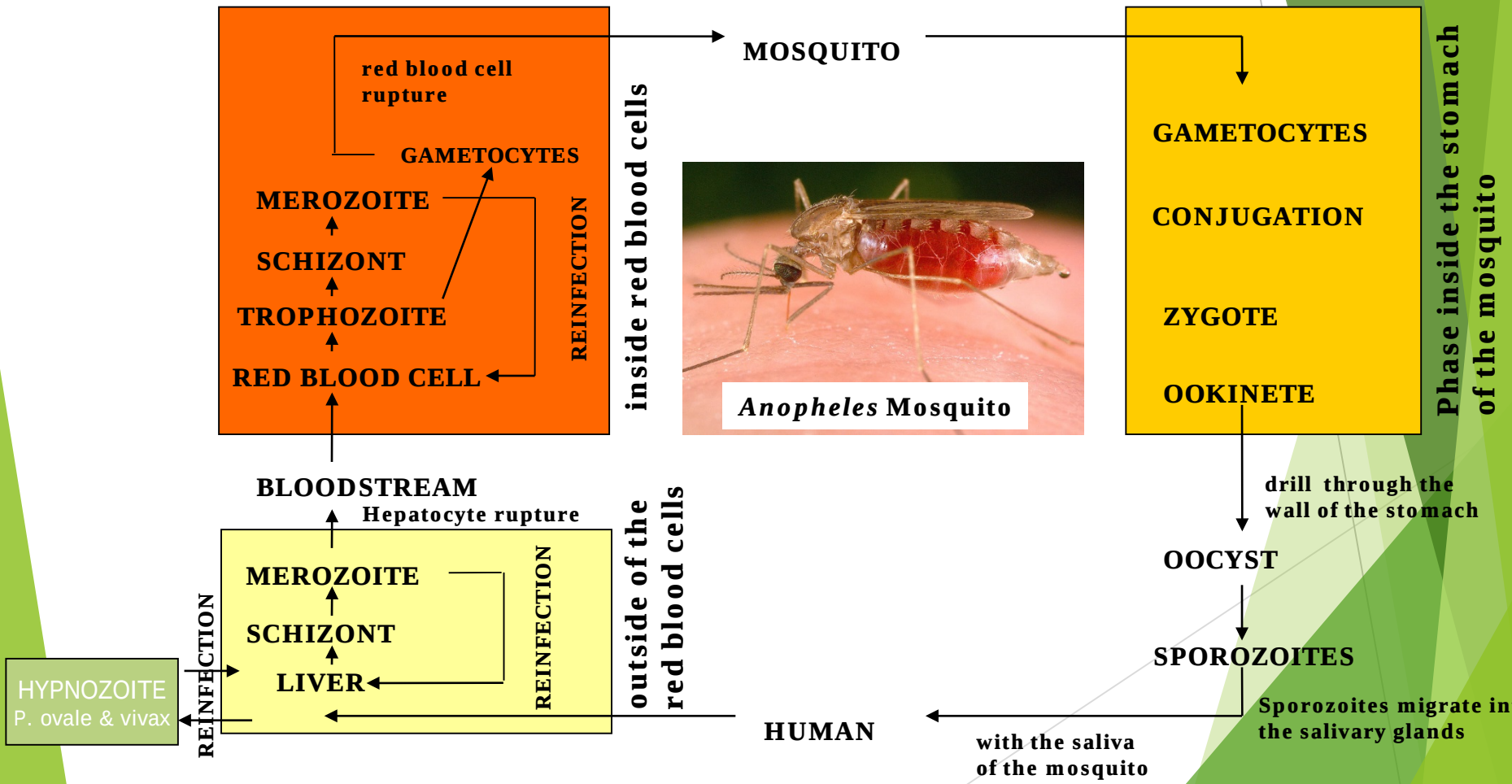
    As it is able to penetrate into CNS, it can be administered in trypanosomiasis to patients in the later, hemolimphatic stage of the disease (with CNS symptoms).

Agents against Leishmaniasis

- Pentavalent antimony-derivatives (Meglumine antimoniate, Sodium stibogluconate)
  - Mechanism of effect: they inhibit the phosphofructokinase enzyme of the parasites, thus, glycolysis – the main energysource – of the parasites is inhibited;
    another Mechanism of effect: inhibiting the enzymes of the β-oxidation of the fatty acids

- Trivalent antimonials also exist (e.g. antimony-sodium-tartarate), but these are much more toxic, thus were withdrawn from market.

Malaria – the lifecycle of Plasmodium species



Agents against Malaria – Summary

- Blood-schizontocid agents = against merozoites
  - Agents with Quinolin structures
    - Aminoquinolines
      - 4-aminoquinolines (Amodiaquine, Chloroquine, Hydroxychloroquine)
      - 8-aminoquinolines (Primaquine, Pamaquine) (NOT Blood-schizontocids!!)
    - Methanolquinolines
      - Cinchona-alkaloids (Quinine, Quinidine)
      - Mefloquine
  - Halofantrin (Phenanthrene derivative)
  - Quinacrine (Amino-acridine derivative)
  - Artemisinin-derivatives (Sesquiterpene lactones)

Agents against Malaria – Summary (cont.)

- Folate-metabolism-inhibitors

  (Blood schizontocid and gametocytocid)

  - DHPS-inhibitors
    - Sulphonamides (e.g. sulphadoxine)
    - Sulphones (e.g. Dapson)
  - DHFR-inhibitors
    - Biguanides (e.g. Proguanil, Chlor-proguanil)
    - Diaminopyrimidines (pl. Pyrimethamine, Trimethoprim)
- Atovaquone (naftoquinon-derivative)
- Tetracyclines
- Clindamycin

} Effective against Bacterial ribosomes ➔ in protozoans on the mytochondrial DNA-synthesis

Agents against Malaria

- 4-aminoquinolines (Amodiaquine, Chloroquine, Hydroxychloroquine)
- Cinchona-alkaloids (Quinine, Quinidine)
- Mefloquine
  - Mechanism of effect:
    - They bind to the free hem and to the so called hemozoin in the hemoglobin-metabolising vacuolum, thus, inhibit the further polimerisation and detoxification;
      Digesting of hemoglobin results in free heme, that is toxic to the parasite, thus, parasites transform it into hemozoin, a non-toxic polimer;
    - May also integrate into DNA, inhibiting the DNA, RNA synthesis
    - May interfere with some fatty acids, that are needed for the protozoan to break out from red blood cells
  - Use: in P. vivax, P. ovale, P. malariae & P. falciparum infection; only effective against blood-schizonts, no other forms; chloroquine is the first-choice agent in malaria!

Agents against Malaria (cont.)

- 8-aminoquinolines (Primaquine, Pamaquine) (NOT blood-schizontocides!!)
  - Mechanism of effect:
    - Its metabolite interferes with ubiquinone, thus, inhibits the terminal oxidation in mytochondrium (thus the energyproduction is inhibited)
    - May inhibit pirimidin-synthesis as well
    - May intercalate into DNA, thus inhibiting the DNA, RNA and protein synthesis
  - Use: These are NOT blood-schizontocid agents!, they have no effect on the erythrocyter-phase!, But they are effective against P. ovale and vivax *hypnozoites* and hepato-schizonts, and also have gametocytocid effect;
    - In glucose-6-phosphate-dehidrogenase deficiency the 8-aminoquinolines must not be adminitered: they may cause lifethreathening hemolysis!

Agents against Malaria (cont.)

- Halofantrin (Phenanthrene derivative)
  - Mechanism of effect: exact mechanism of effect is unknown; presumably has mefloquine-like activity still its not a quinolin (inhibition of hemozoin-formation; DNA intercalation)
  - Use: QT elongation, causes arrhythmia, thus, cannot be administered to heart patients; absorption increases with fatty food, thus, it must be taken before first meal

Agents against Malaria (cont.)

- Quinacrine (Aminoacridine derivative)
  - Mechanism of effect: unknown;
    - presumably damages the membrane of the protozoan;
    - may act as phospholipase A2 inhibitor as well;
    - others suppose a chloroquine like mechanism of effect (inhibition of hemozoin-formation; DNA intercalation)
  - Use: blood-schizontocid; also used in giardiasis

Agents against Malaria (cont.)

- Artemisinin-derivatives
  (Artemether, Artesunate, Artenimol, Arteether/Artemotil)
  - these are the active components of a chinese antimalarial herb (*Artemisia annua*)
  - Mechanism of effect:
    - hem in the parasite activates the molecule ➔ forming of free radicals
    - inhibits a SER Ca^{2+} ATPase pump; the mutation of this may prove as a resistance for the protozoan against these agents
  - Use: very fast acting blood-schizontocid agents, against every form, except hypnozoits;
    synergist with mefloquine, primaquine, tetracyclines

Agents against Malaria (cont.)

- Sulphonamides and sulphones

  (Sulphadoxine) (Dapson)

  - Mechanism of effect: dihydropteroate-synthase (DHPS) inhibitors: they competitively displace the p-aminobenzoic acid from the enzyme, thus, folic acid (B10) synthesis is inhibited (thus, the synthesis of purin bases will be inhibited)
  - Use:
    - wide spectrum bacteriostatic antibiotics;
    - dapson – against lepra
    - sulphadoxine,dapson – against malaria,
    - sulphadoxine – against Toxoplasmosis
  - sulphadoxine belongs to the family of ultra long time of action sulphonamids.
  - sulphadoxine is sinergist with Pyrimethamine (latter is a diaminopyrimidine)

Agents against Malaria (cont.)

- Biguanides and diaminopyrimidines

(proguanil, chlorproguanil) (pyrimethamin, trimethoprim)

  - Mechanism of effect: dihydrofolate reductase (DHFR) inhibitors: inhibit the transforming of dihydrofolic acid into tetrahydrofolic acid, thus, inhibit the folic acid (B10) synthesis (thus they inhibit the synthesis of the purin bases).
  - Use:
    - wide spectrum baktericid antibiotics
    - Pyrimethamine,(chlor)proguanil – against malaria
- Synergists (combinations):
  - sulphamethoxazole + Trimethoprim = Sumetrolim®
  - sulphadoxine + Pyrimethamine = Fansidar®
  - Atovaquone + Proguanil = Malarone®

Agents against Malaria (cont.)

- Atovaquone (naftoquinon-derivative)
  - Mechanism of effect:
    - Ubiquinon-analogue, interferes with ubiquinon, thus, inhibits the terminal oxidation in the mytochondrium (thus energy production is inhibited) (as primaquine)
  - Use: very effective in the hepatic phase of the Plasmodium infection; against *Leishmania donovani*, *Toxoplasma gondii* and *Pneumocystis carinii* as well;

    synergist with proguanil (latter is a biguanide) (Malarone®)

Agents against ectoparasites ATC code P03

Therapies against ectoparasites

- Mechanical removing
  - louse comb
  - surgical
- Chemotherapy (=medications)
  - pyrethroides
    - pyrethrin, [cy]permethrin, phenothrin, deltamethrin
  - lindane
  - organophosphates (e.g. malathion)
  - ivermectin
  - crotamiton,
  - benzyl-benzoate,
  - sulphamethoxazole + trimethoprim

Agents against ectoparasites

- Pyrethroides: Pyrethrin I,II , permethrin, cypermethrin, phenothrin, deltamethrin, bifenthrin
  - Mechanism of effect: in small amounts they are repellents, in large amounts they are neurotoxic against insects; they elongate the open-time of the Na^+ channels in the membrane of the neurons, thus, cause hyperexcitation
  - Use: first-choice agenst; against every ectoparazitosis
- They are toxic to fish and cats!

Agents against ectoparasites

- Lindane (hexachlorcyclohexane)
  - Mechanism of effect: non-competitively inhibtis the $GABA_A$ receptor-chloride-ion-channels on the picrotoxin binding-place = neurotoxic, causes hyperexcitation
  - Use: most often in the form of shampoo and solution;
    it is also toxic to human, thus, were withdrawn from market in many countries;
    requires further attetion in epileptic patients;
    avoid overdosing, and patients should always keep the doctor's instructions!

Agents against ectoparasites

- Organophosphates (malathion)
  - Mechanism of effect: irreversible acetylcholinesterase inhibitors, thus the metabolism of acetylcholine is decreased ➔ overexcitation in acetylcholinergic synapses
  - Use: against every ectoparasite; also effective against humans (=thus some of them are war-gases as well)

Agents against ectoparasites

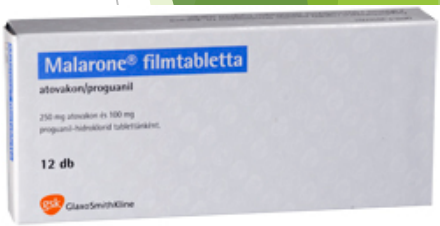
- Ivermectin and avermectin (makrolid-derivatives)
  - Mechanism of effect: they bind to glutamate mediated chloride ion channels on neurons and muscle cells and activate them;
  - Use: avermectin mostly against ants; ivermectin is mostly as anthelmintic agent (against roundworms), but also effective against ectoparasites

Agents against ectoparasites

- Crotamiton
  - Mechanism of effect: unknown
  - Use: as scabicidum in the form of solution;
- irritative to skin

- Benzyl-benzoate
  - Mechanism of effect: unknown
  - Use: colourless scabicid liquid; for topical use

Market of Hungary



AGAINST PROTOZOANS

- DELAGIL tabletts (30x) Chloroquine
  For therapy of malaria, and amoebiasis and also for therapy of some arthropathies, connective tissue and skin diseases
- KLION tabletts (20x) Metronidazol
- LARIAM "ROCHE" 250 mg tabletts (8x) Mefloquine against malaria
- MALARONE filmtabletts (12x) Atovaquone + Proguanil against malaria
- SUPPLIN 250 mg filmtabletts (20x) Metronidazol
- SUPPLIN 500 mg filmtabletts (20x) Metronidazol
- TINIDAZOL-POL 500 mg filmtabletts (4x) Tinidazol

AGAINST ECTOPARASITES

- JACUTIN emulsion (100 ml) Lindane (scabicidum)
- JACUTIN gel (50 g) Lindane (scabicidum, and also against head louse and crab louse
- NOVASCABIN emulsion (70 g) Dimethyl-ftalate and Benzyl-benzoate