Antibiotics, Antifungals, Anthelmintics, Antiparasite agents

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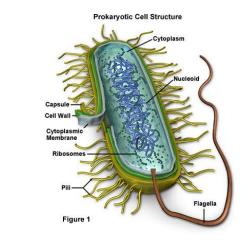
Department of Pharmacology and Pharmacotherapy

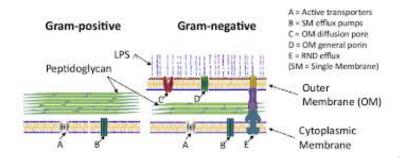
University of Debrecen

Antibiotics

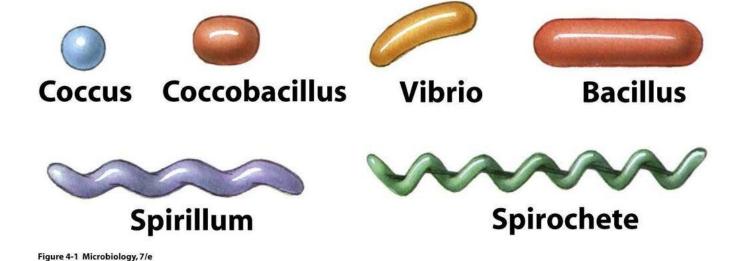
Structure of bacteria

- 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



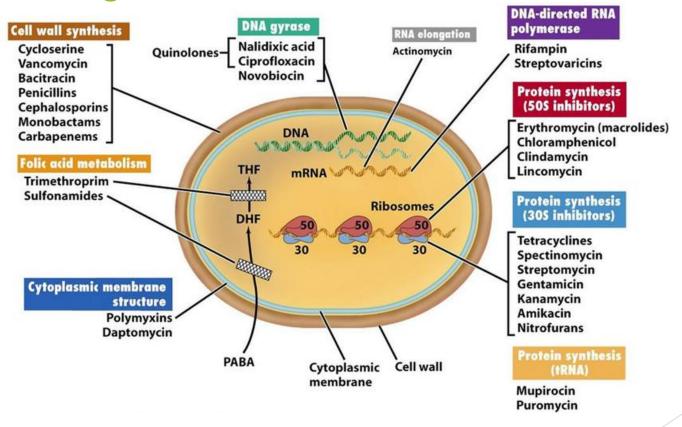


Morphology of bacteria



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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
- Common cold symptoms
- · Cough
- Diarrhea
- Hoarseness
- Inflammation of the oral mucosa
- · Rash

- · Abdominal pain
- · Abrupt onset of sore throat
- · Fever, headache
- · History of GAS pharyngitis exposure
- . Inflammation in the throat
- · Nausea, vomiting
- · Patchy exudates in the throat
- . Purple spots on the roof of the mouth
- · Scarlatiniform rash
- . Tender lymph nodes around throat

^{*}Age between 5 and 15 years and winterlearly spring presentation are epidemiologic features associated with GAS pharyngitis. GAS: group A streptococcus. Source: References 3, 7.

Key resistance mechanisms

- 1. Alternative proteins: B-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.
- Biofilm formation

Basic concepts

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

Classification of antibiotics:

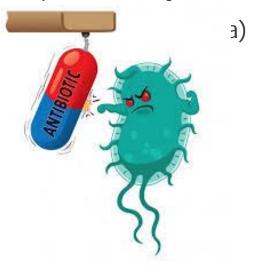
- Antibiotic use and efficacy
- ► MIC: minimum inhibitory concentration → based on this...
 - Cmax / MIC: the antimibrobial effect depends on how many times higher is the peak serum concentration is compared to the MIC - the effect is concentration dependent (eg aminoglycosides)
 - AUC / MIC: the bactericidal 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 B-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)

IN	IHIBIT		CLASIFI	ATION				ANT	IBIOTICS		
						Penicini	lase - S	ensible			
				Natural Penicilli	ns	Penicillin	G: Na, k	, Proca	inic, Benza	thine (IV, IM)	
				(narrow spectrum)	Penicillin					
				Aminopenicillin	S	Ampicillin					
				(broad spectrum)		Amoxicilli					
				Per	icini	Ilase – Res		erv narn	ow spectrum)	
			Penicillins	Nafcillin	, -,,,,,		acillin	.,		loxacillin	
				Tranciani	Ant			ended so		ionaeiiini	
					7	tipseudomonal (extended spectrum)					
Cell				Carboxipenicillin	15	Carbenici	lin				
					375	Piperacilli	_				
Wall				Ureidopenicillin		Azlocillin					
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y				1 Generation				Cepha		Cephalotin	
n	Beta			2° Generation		-	_	Cefama		Cefprozil	
t	Lactams					Cefuroxime				Cefmetazole	
h								Cefonicid Cefactor		Cermetazoie	
e			Cephalosporins		_			Cefactor		Ceftazidime	
s			cpiiuiospoiiiis	3° Generation				Ceftizo		Cefotaxime	
1				3 Generation		Cefpodox	ime	Ceftibu		Cefixime	
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			C 1	5° Generation	-		-				
			Carbapenems	Meropenem	Er	tapenem	Dorip	enem	Imipenen	n + Cylastatine	
	200	-	Monobactams	Aztreonam	_	-			et t		
		- manifel and	r-lactamase inhib.	Sulbactam	Lookes	Tazobac	tam		Bacitracin	anic Acid	
	1			Vancomycin							
	lactam			Teicopl	anın				Polymyxin		
		305	Amino-	Gentamycin		Neomycir			Stre	Streptomycin	
		303	glycosides	Amikacin		Tobramyo					
			Tetracyclins	Doxycycline	_	Demeclocylin *			* Minocycline		
p.	rotein	_		Tetracyclin		110	gecyclin				
	nthesis	8	Oxazolidonones	Linezolid	-						
Syl	itilesis	505	Streptogramins	Quinupristin/Dalfo	opris	tin					
		300	Cloramphenicol				1004.0				
		1 8	Macrolides	Erythromycin		Azithrom	cin			omycin	
			Lincosamides	Cline	iamy	-			Lincom	- Contract of the Contract of	
N 100	DNA	Fluoi	rquinolones	Ciprofloxacin	-	Norfloxaci			floxacin	Ofloxacin	
topois	omerases			Sparfloxacin		Moxifloxac	in	Gemi	floxacin	Enofloxacin	
		-	olones	Nalidixic Acid							
	ic Acid	Sulfo	onamides	Sulfamethoxaze	ole	Ag Sulfa	adiazine	Sult	fasalazine	Sulfisoxazole	
Syr	nthesis			(SMX)							
		-100	R inhibitors	Trimeth	ropr	im (TMP)			Pirymet	thamine	
_	(damage)		ronidazole								
	A synth.	Difa	mpim								

- 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)

Resistance mechanisms

- B-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



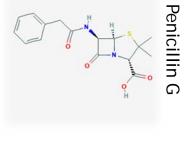
Penicillines

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





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 B-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

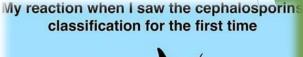
Penicillins in practice

- ► 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!



IN	IHIBIT		CLASIFIC	CATION				ANTI	BIOTICS		
						Penicini	llase – S	ensible			
				Natural Penicillin	ns	Penicillin	G: Na, K	, Procai	inic, Benza	thine (IV, IM)	
				(narrow spectrum))	Penicillin	V: VO	, , , , , , , , , , , , , , , , , , , ,			
				Aminopenicillin	s	Ampicillin					
				(broad spectrum) Amoxicillin							
				Per	icini	illase – Res	istant (v	ery narro	w spectrum)	
			Penicillins	Nafcillin		-	acillin	-	Dicloxacillin		
					Antipseudomonal (extended spectrum)						
Cell			Carboxipenicillins Carbenicillin								
Wall				Ureidopenicillin	Ureidopenicillins Azlocillin						
s						Mezlocilli	n				
y				1° Generation		Cefazolin		Cephal	exine	Cephapirin	
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ť	Lactams				- 5	Cefuroxin	ne	Cefama	ndole	Cefprozil	
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e			A COMPANION CARRY			Cefotetan		Cefaclor			
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ī				3° Generation		Cefpodox	ime	Ceftizo	xime	Cefotaxime	
s						Cefdinir	- 1	Ceftibu	ten	Cefixime	
-						Cefditore	n		201		
				4° Generation		Cefepime			Cefpiro	me *	
				5° Generation		Ceftarolin	e			***	
	· •		Carbapenems	Meropenem	Er	tapenem	Doripe	enem	Imipener	n + Cylastatine	
		- 1	Monobactams	Aztreonam				- 7			
	***	• Beta	-lactamase inhib.	Sulbactam		Tazobac	tam		Clavula	anic Acid	
	No	1	Glycopeptides	Vancom	ycin				Bacitracir	1	
	lactam			Teicopla	anin			1	Polymyxin	В	
			Amino-	Gentamycin		Neomycin		in S		eptomycin	
		305	glycosides	Amikacin		Tol	oramycir				
		3	Tetracyclins	Doxycycline		Dem	eclocylin	1 *	Mi	nocycline	
			The second second	Tetracyclin							
Pi	rotein		Oxazolidonones	Linezolid							
Syı	nthesis		Streptogramins	Quinupristin/Dalfo	opris	tin					
		505	Cloramphenicol	· · · · · · · · · · · · · · · · · · ·							
			Macrolides	Erythromycin	- 1	Azithrom	ycin		Clarith	omycin	
			Lincosamides	Clino	lamy	cin			Lincom	ycin	
	DNA	Fluo	rquinolones	Ciprofloxacin		Norfloxaci	n	Levol	loxacin	Ofloxacin	
3				Sparfloxacin		Moxifloxac	in	Gemi	floxacin	Enofloxacin	
	somerases	Quinolones		Nalidixic Acid			7.0				
	somerases	Quin	oiones		ole Ag Sulfa		Sulfadiazine Sulf		asalazine	Sulfisoxazol	
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topois Fol Syr	lic Acid	Sulfa	onamides	(SMX)			adiazine	Juli			

- 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 B-lactamase enzymes
- 5 generations: with increasing number of generations
 - Increased Gr activity
 - Decreased Gr + activity
 - Resistance to β-lactamases increases





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

- 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

- 4th generation
 - Cefepime: more balanced antibacterial spectrum than 3rd generation agents -> have a better effect on Staphylococci and greater βlactamase 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)

IN	HIBIT		CLASIFIC	CATION				ANTIE	IOTICS			
					35	Penicinil	lase – S	ensible				
				Natural Penicillii (narrow spectrum	100	Penicillin Penicillin		, Procain	ic, Benza	thine (IV, IM)		
				Aminopenicillin		Ampicillin						
				(broad spectrum) Amoxicillin Penicinillase – Resistant (very narrow spectrum)								
			Penicillins		nicinil			ery narrov				
			renicillins	Nafcillin			acillin			loxacillin		
					Anti	tipseudomonal (extended spectrum)						
Cell				Carboxipenicillir	ns	Ticarcillin Carbenicil	lin					
Wall				Ureidopenicillin	15	Piperacilli Azlocillin Mezlocillii						
S				1° Generation		Cefazolin		Cephale	xine	Cephapirin		
y	120000			2 02	Cefadroxil		_	Cephadr		Cephalotin		
n	Beta					Cefuroxim		Cefamar		Cefprozil		
t	Lactams			2° Generation	1	Cefoxitin		Cefonicid		Cefmetazole		
h					1	Cefotetan		Cefaclor		Cometacot		
e		(ephalosporins					Ceftriax		Ceftazidime		
s				3° Generation		Cefpodoxi	_	Ceftizoxi		Cefotaxime		
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				4° Generation		Cefepime			Cefpiro	me *		
				5° Generation	_	Ceftarolin	Р		ceipine			
			Carbapenems	Meropenem	Ert	apenem	Doripe	enem	Imipenen	n + Cylastatin		
		_	vionopactams	Aztreonam				7/3				
	***		-lactamase inhib.	Sulbactam		Tazobac	tam		Clavula	anic Acid		
	No		Glycopeptides	Vancomycin		n			Bacitracin	1		
	lactam			Teicopl	-			Polymy		200		
			Amino-	Gentamycin		Ne	omycin		Stre	eptomycin		
		305	glycosides	Amikacin		Tob	ramycir	i				
			Tetracyclins	Doxycycline		Deme	eclocylin	*	Mi	nocycline		
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Pr	otein		Oxazolidonones	Linezolid								
Syr	nthesis	1	Streptogramins	Quinupristin/Dalfo	oprist	in						
		505	Cloramphenicol		T.							
			Macrolides	Erythromycin		Azithromy	rcin		Clarithr	omycin		
			Lincosamides	Clino	lamy	in			Lincom	ycin		
ा	DNA	Fluo	rquinolones	Ciprofloxacin		Norfloxaci	n	Levofl	oxacin	Ofloxacin		
topois	omerases			Sparfloxacin	1	Moxifloxac	in	Gemifl	oxacin	Enofloxacir		
		Quin	olones	Nalidixic Acid								
Fol	ic Acid	Sulfo	namides	Sulfamethoxazo	ole	Ag Sulfa	diazine	Sulfa	salazine	Sulfisoxazol		
Syr	nthesis			(SMX)								
		DHF	R inhibitors	Trimeth	ropri	m (TMP)			Pirymet	thamine		
DNA (damage)	Meti	ronidazole									
	mRNA synth. Rifampim											

Carbapenems

- Imipenem (Tienam), meropenem (Meronem), ertapenem, doripenem
- For intravenous use
- They are also bound to PBP
- They are extremely resistant to β-lactamase
- These ABs have the broadest spectrum in the β-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

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



HIBIT		CLASIFIC	CATION				ANTIE	BIOTICS		
				- 35	Penicini	lase – Si	ensible			
			Natural Penicillin	15	Penicillin	G: Na, K,	Procair	nic, Benza	thine (IV, IM)	
			(narrow spectrum)		Penicillin'	V: VO				
			Aminopenicillins	5	Ampicillin					
			(broad spectrum) Amoxicillin							
			Pen	icinil	llase – Resi	stant (ve	ry narro	w spectrum)	1	
		Penicillins	Nafcillin		Dic	loxacillin				
				Anti						
			Carboxipenicillin	s	Ticarcillin Carbenicil	lin				
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Lactams							Cefonici	d	Cefmetazole	
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No			Vancomycin					Bacitracin	1	
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ic Acid	-	(EXEMPE)	Transmitte French	le	Ag Sulf	diazina	Sulfa	salazino	Sulfisoxazole	
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Synthesis					(TAAD)			Pirymet	L to -	
DHFR inhibitors										
(damage)		R inhibitors ronidazole	Trimeth	ropri	im (TIVIP)			Pirymei	namine	
	No lactam rotein nthesis DNA somerases ic Acid	Beta Lactams No lactam 30S Totein nthesis DNA Fluo iomerases Quin lic Acid Sulfa	Beta Lactams Cephalosporins Cephalosporins Monobactams Beta-lactamase inhib. No Glycopeptides Iactam Amino- glycosides Tetracyclins Coazolidonones Streptogramins Cloramphenicol Macrolides Lincosamides Pluorquinolones Quinolones Sulfonamides	Penicillins Penicillins Penicillins Penicillins Penicillins Carboxipenicillin (broad spectrum) Pen Nafcillin Ureidopenicillin: 1° Generation 2° Generation 4° Generation 5° Generation Meropenem Meropenem Aztreonam Sulbactam Vancom Glycopeptides Vancom Teicople Amino- Gentamycin Amikacin Tetracyclins Tetracyclins Oxazolidonones Streptogramins Oxazolidonones Lincosamides Cioramphenicol Macrolides Erythromycin Lincosamides Cioramplessicol Cloramphenicol Macrolides Erythromycin Lincosamides Cioralianic Acid Sulfamethoxazoi Quinolones Nalidixic Acid Sulfamethoxazoi	Natural Penicillins (narrow spectrum) Aminopenicillins (broad spectrum) Penicini Nafcillin Nafcillin Ant	Penicillin Natural Penicillins Penicillin Natural Penicillins Penicillins Penicillins Penicillins Penicillins Penicillins Penicillins Ampicillins Penicillins Penicinillase - Resi Nafcillin Ox Antipseudomo Ticarcillins Carboxipenicillins Carboxipenicillins Piperacilli Azlocillin Piperacilli Azlocillin Piperacillins Piperacillins Penicinillase - Resi Nafcillin Carboxipenicillins Penicinillase - Resi Nafcillin Carboxipenicillins Penicinillase - Resi Nafcillin Carboxipenicillins Carboxipenic	Penicillins Penicillins Penicillin G: Na, K, Penicillin G: Na, K, Penicillins Penicillin G: Na, K, Penicillins Penicillin G: Na, K, Penicillin S: VO	Natural Penicillins Penicillin G: Na, K, Procair Penicillin G: Na, K, Procair Penicillin G: Na, K, Procair Penicillin V: VO Aminopenicillins Penicillin V: VO Ampicillin Amoxicillin Penicillin Mamoxicillin Amoxicillin Penicillins Ampicillin Amoxicillin Amoxicillin Amoxicillin Amoxicillin Penicillins Amoxicillin Amoxicillin Piperacillin Azlocillin Azlocillin Azlocillin Azlocillin Azlocillin Azlocillin Piperacillin Azlocillin Azlocillin	Natural Penicillins Penicillin G: Na, K, Procainic, Benza Penicillin Meziculin G: Na, Filoropanic, Benza Penicillin Meziculin G: Na, Fi	

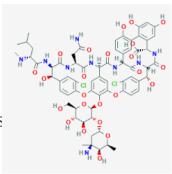
Monobactams

- 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.

IN	IHIBIT		CLASIFIC	CATION				ANTIE	BIOTICS		
					357	Penicini	llase – S	ensible			
				Natural Penicillin (narrow spectrum	0.00	Penicillin Penicillin		, Procair	nic, Benza	thine (IV, IM)	
				Aminopenicillin (broad spectrum)		Ampicillin Amoxicillin					
			Penicillins	Penicinillase – Resistant (very narrow spectrum) Nafcillin Oxacillin Dicloxacillin							
			rememms	Natcillin	Antipseudomonal (extended spectrum)						
					Anti	Ticarcillin	nai (exte	naea spe	ctrumj		
Cell				Carboxipenicillir	15	Carbenicil	lin				
Wall				Ureidopenicillin	s	Piperacilli Azlocillin Mezlocilli					
5				1° Generation		Cefazolin		Cephale	xine	Cephapirin	
y	0.200000					Cefadroxil		Cephadi		Cephalotin	
n	Beta					Cefuroxim		Cefamai		Cefprozil	
ţ.	Lactams			2° Generation		Cefoxitin		Cefonicid		Cefmetazole	
h					t	Cefotetan		Cefaclor		- Commercial Commercia	
e			ephalosporins			Cefoperazone		Ceftriaxone		Ceftazidime	
s				3° Generation		Cefpodox	-	Ceftizox		Cefotaxime	
s					-	Cefdinir	_	Ceftibut	en	Cefixime	
						Cefditore					
				4° Generation		Cefepime			Cefpiro	me *	
				5° Generation		Ceftarolin	e			424.2	
		1	Carbapenems	Meropenem	Ert	apenem	Doripe	enem	Imipenen	n + Cylastatine	
		- 1	Monobactams	Aztreonam				7/3			
	***	• Beta	-lactamase inhib.	Sulbactam		Tazobac	tam		Clavula	anic Acid	
	No	3	Glycopeptides	Vancomycin					Bacitracin		
	lactam			Teicoplanin		1		Polymyxin B			
			Amino-	Gentamycin		Ne	omycin		Stre	Streptomycin	
		305	glycosides	Amikacin		Tob	ramycir	1		27	
			Tetracyclins	Doxycycline		Dem	eclocylin	*	Mi	nocycline	
	cocarso			Tetracyclin		Tig	gecyclin				
	rotein		Oxazolidonones	Linezolid		y-					
Syı	nthesis		Streptogramins	Quinupristin/Dalfo	prist	in					
		505	Cloramphenicol								
			Macrolides	Erythromycin		Azithromy	cin		-	omycin	
			Lincosamides		amyo				Lincom		
100	DNA	Fluo	rquinolones	Ciprofloxacin		Norfloxaci			oxacin	Ofloxacin	
topois	omerases			Sparfloxacin	1	Moxifloxac	in	Gemif	loxacin	Enofloxacin	
		-	olones	Nalidixic Acid			-				
5.53	ic Acid nthesis	Sulfo	onamides	Sulfamethoxazo (SMX)	ole	Ag Sulfa	adiazine	Sulfa	salazine	Sulfisoxazol	
-	enomonación de la composition della composition	DHF	R inhibitors	Trimeth	ropri	m (TMP)			Pirymet	thamine	
-	(damage)	Meti	ronidazole	•							
DNA	nRNA synth. Rifampim										

Glycopeptides

- 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)



Vancomycin

Other agents which act on bacterial dell 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 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

IN	IHIBIT		CLASIFIC	CATION	1		ANTIBIO	TICS			
					Penicini	llase – Se	nsible				
				Natural Penicillins	Penicillin	G: Na, K,	Procainic,	Benza	thine (IV, IM)		
				(narrow spectrum)	Penicillin	V: VO					
				Aminopenicillins	Ampicillin	Ampicillin					
				(broad spectrum)	Amoxicilli	in					
				Penid	inillase – Res	istant (ve	ry narrow sp	ectrum,)		
			Penicillins	Nafcillin Oxacillin Dicloxacillin							
				,	Antipseudomo	tipseudomonal (extended spectrum)					
Cell				Carboxipenicillins	Ticarcillin Carbenici						
Wall				Ureidopenicillins	Piperacill Azlocillin	19 (27 (27 (27 (27 (27 (27 (27 (27 (27 (27					
					Mezlocilli	n					
S				1° Generation Cefazolin		lin Cephale		9	Cephapirin		
y	Beta				Cefadroxi	1 (ephadrine		Cephalotin		
n t	Lactams				Cefuroxin	ne C	efamando	le	Cefprozil		
h	Lactams	W- W		2" Generation	Cefoxitin	(efonicid		Cefmetazole		
n e				120 120 120 120 120 120 120 120 120 120	Cefotetar	1 (Cefaclor				
s		C	ephalosporins		Cefopera	Cefoperazone			Ceftazidime		
i				3° Generation	Cefpodox	ime (eftizoxime	100	Cefotaxime		
s					Cefdinir	- 0	eftibuten	- 1	Cefixime		
					Cefditore	n	.,.				
				4° Generation	Cefepime		C	efpiro	me *		
				5° Generation	Ceftarolin	ne	10.000				
			Carbapenems	Meropenem	Ertapenem	Doripe	nem Imi	pener	n + Cylastatine		
		- 1	Monobactams	Aztreonam			7/3				
	***	• Beta	-lactamase inhib.	Sulbactam	Tazobao	tam		Clavula	anic Acid		
	No	(Glycopeptides	Vancomy	cin		Bac	itracir	1		
	lactam			Teiconlar	in		Poly	muvin	R		
	-		Amino-	Gentamycin	Ne	eomycin	cin Strepto		eptomycin		
		305	glycosides	Amikacin	Tol	oramycin			24		
			Tetracyclins	Doxycycline	Dem	eclocylin		Mi	nocycline		
	-50-65000		The Part of English Control	Tetracyclin	Ti	gecyclin					
P	rotein		Oxazolidonones	Linezolid							
Sy	nthesis		Streptogramins	Quinupristin/Dalfop	ristin						
		505	Cloramphenicol	*****							
			Macrolides	Erythromycin	Azithrom	ycin	C	larith	omycin		
			Lincosamides	Clinda	mycin		L	incom	ycin		
		Fluor	quinolones	Ciprofloxacin	Norfloxac	in	Levofloxa	cin	Ofloxacin		
	DNA	riuorquinoiones		Sparfloxacin	Moxifloxac	in	Gemifloxa	cin	Enofloxacin		
	DNA somerases			- partionaem		HOAHOAGUI					
			olones	Nalidixic Acid		Moxifloxacin Gemi		Sulfasalazine Sulfisox			
Fo		Quin	olones namides		e Ag Sulf	adiazine	Sulfasala	azine	Sulfisoxazole		
Fo	somerases lic Acid	Quin	200000000000000000000000000000000000000	Nalidixic Acid Sulfamethoxazol (SMX)	Ag Sulf	adiazine			Sulfisoxazole thamine		
Foi Sy	somerases lic Acid	Quin Sulfo	namides	Nalidixic Acid Sulfamethoxazol (SMX)		adiazine					

Aminoglycosides

- pentamicin, 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 (eq 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 gonor<mark>rhea (← single dose, im.)</mark>



IN	IHIBIT		CLASIFIC	CATION					BIOTICS		
					Penicinillase – Sensible Natural Penicillins Penicillin G: Na, K, Procainic, Benzathine (I'						
				Natural Penicillin (narrow spectrum)		Penicillin Penicillin		, Procair	Procainic, Benzathine (IV, IM)		
				Aminopenicillina (broad spectrum)	s	Ampicillin Amoxicillin					
					icinil	lase – Resi		en narro	w enectrum	1	
			Penicillins	Nafcillin	TC/////		acillin	ery number		loxacillin	
				Halcillii	Anti			anded ene		OXACIIIII	
Cell				Antipseudomonal (extended spectrum) Ticarcillin Carboxipenicillins Carbenicillin							
Wall				Ureidopenicillin	s	Piperacilli Azlocillin Mezlocilli					
S				1° Generation				Conhalo	vino	Cephapirin	
y	049300000			1 Generation		Cefadroxil		Cephalexine Cephadrine		Cephalotin	
n	Beta					Cefuroxin				Cefprozil	
t	Lactams			2" Generation		Cefuroxime Cefoxitin		Cefamandole Cefonicid		Cefmetazole	
h				2 Generation	- 1	Cefotetan		Cefaclor		Cennetazore	
e		-	ephalosporins			Cefoperazone		Ceftriax		Ceftazidime	
5				3° Generation		Cefpodox	-	Ceftizox		Cefotaxime	
i				J Generation		Cefdinir		Ceftibut		Cefixime	
5						Cefditore		00111041		- CONTRACTOR	
				4° Generation		Cefepime			Cefpiro	me *	
				5° Generation	_	Ceftarolin					
		1	Carbapenems	Meropenem	Erta	apenem	Dorip	enem	Imipener	n + Cylastatine	
		- 1	Monobactams	Aztreonam		•		7/3	• • • • • • • • • • • • • • • • • • • •		
	***	* Beta	-lactamase inhib.	Sulbactam		Tazobac	tam		Clavula	anic Acid	
	No	Glycopeptides		Vancomycii		n			Bacitracir	1	
	lactam			Teicopla	nin			P	olymyxin	В	
	7	0.50000	Amino-	Gentamycin		Ne	omycin		Stre	eptomycin	
		305	glycosides	Amiliacia		Tok					
			Tetracyclins	Doxycycline			eclocyli		Mi	nocycline	
1023	39314			Tetracyclin Tigecyclin							
	rotein		Oxazolidonones	Linezolid							
Syl	nthesis	505	Streptogramins	Quinupristin/Dalfo	pristi	in					
		303	Cloramphenicol	Bright Constitution	_						
			Macrolides	Erythromycin	_	Azithromy	ycin		-	omycin	
-	DAIA	Cl.	Lincosamides		amyc			1 mon Pl	Lincom		
	DNA somerases	Fluo	rquinolones	Ciprofloxacin Sparfloxacin		Norfloxaci Moxifloxac			loxacin loxacin	Ofloxacin Enofloxacin	
opois	omerases	0	-1	Nalidixic Acid	P	vioxilioxac	III I	Gemii	ioxacin	Enonoxacin	
C-1	lic Acid		olones onamides	Nalidixic Acid Sulfamethoxazo	la	Ag Sulfa	diani-	C.,16.	salazine	Sulfisoxazole	
3.53	nthesis			(SMX)	200		autazine	Sulfa			
			R inhibitors	Trimeth	roprii	m (TMP)			Piryme	thamine	
DNA	(damage)	Meti	ronidazole								
	IA synth.	Dif.	npim								

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

IN	IHIBIT		CLASIFIC	CATION				ANTIE	BIOTICS			
					353	Penicinillase – Sensible						
				Natural Penicillin (narrow spectrum)	S 10	Penicillin Penicillin		, Procain	nic, Benza	thine (IV, IM)		
				Aminopenicillins (broad spectrum)	-	Ampicillin Amoxicillin						
				Penicinillase – Resistant (very narrow spectrum)								
			Penicillins	Nafcillin Oxacillin Dicloxacillin								
			rememms	Antipseudomonal (extended spectrum)								
						ACTOR DESCRIPTION OF THE PARTY OF	nai (exte	ended spe	ctrum)			
Cell				Carboxipenicillin		Ticarcillin Carbenicil	lin					
Wall				Ureidopenicillins	5	Piperacilli Azlocillin Mezlocilli						
S				1° Generation		Cefazolin		Cephale	xine	Cephapirin		
y	052755500					Cefadroxi	_	Cephadr		Cephalotin		
n	Beta				_	Cefuroxim		Cefamar		Cefprozil		
t	Lactams			2° Generation	-	Cefoxitin		Cefonici		Cefmetazole		
h						Cefotetan		Cefaclor		Committee		
e			ephalosporins					Ceftriax		Ceftazidime		
5				3° Generation		Cefpodox		Ceftizox	ime	Cefotaxime		
i						Cefdinir	-	Ceftibut	en	Cefixime		
3						Cefditore						
				4° Generation		Cefepime			Cefpiro	me *		
				5° Generation		Ceftarolin	e					
			Carbapenems	Meropenem	Erta	apenem	Doripe	enem	lmipenen	n + Cylastatine		
		- 1	Monobactams	Aztreonam			7	7/3				
	***	• Beta	-lactamase inhib.	Sulbactam		Tazobac	tam		Clavula	anic Acid		
	No	Glycopeptides		Vancomycir		n			Bacitracin			
	lactam			Teicoplanin		i.		Polymyxin B		В		
	7		Amino-	Gentamycin		Ne	omycin		Stre	eptomycin		
		305	glycosides	Amikacin		Tob	ramycir			27		
		8	Tetracyclins	Doxycycline		Dem	eclocylir	*	Mi	nocycline		
	5000000			Tetracyclin		Tig	gecyclin					
100	rotein		Oxazolidonones	Linezolid								
Syı	nthesis	505	Strentogramine	Quinunristin/Dalfo	nristi	in						
		303	Cloramphenicol									
			Macrolides	Erythromycin	_	Azithromy	cin		-	omycin		
			Lincosamides	Clinda	_				Lincom	- Contraction of the Contraction		
	DNA	Fluo	rquinolones	Ciprofloxacin		Norfloxaci		Levofl		Ofloxacin		
opois	omerases			Sparfloxacin	N	Moxifloxac	in	Gemifl	oxacin	Enofloxacin		
		-4-00	olones	Nalidixic Acid								
3153	ic Acid nthesis	Sulfo	namides	Sulfamethoxazo (SMX)	le	Ag Sulfa	adiazine	Sulfa	salazine	Sulfisoxazole		
	constitution.	DHF	R inhibitors	Trimethr	roprir	m (TMP)			Pirymet	thamine		
DNA	(damage)	Meti	onidazole					-				
	A synth.	Rifar	npim									

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)

IN	IHIBIT		CLASIFIC	CATION				ANTIE	BIOTICS		
					301	Penicini	llase – Se	nsible			
				Natural Penicilli	ns	Penicillin	G: Na, K,	Procair	nic, Benza	thine (IV, IM)	
				(narrow spectrum)	Penicillin	V: VO				
				Aminopenicillin	s	Ampicillin					
				(broad spectrum) Amoxicillin							
				Per	nicinill	ase – Res	istant (ve	ry narro	w spectrum)		
			Penicillins	Nafcillin		Ox	acillin		Dic	oxacillin	
					Antip	oseudomo	nal (exte	nded spe	ctrum)		
Cell				Carboxipenicilli		Ticarcillin Carbenici	llin				
Wall				Ureidopenicillins		Piperacillin Azlocillin					
				100000000000000000000000000000000000000		Mezlocillin					
S				1° Generation		Cefazolin	(ephale	xine	Cephapirin	
y	Beta					Cefadroxi		ephadi		Cephalotin	
n						Cefuroxime		efamai	ndole	Cefprozil	
t h	Lactams			2° Generation				Cefonicid		Cefmetazole	
								Cefaclor			
e		(ephalosporins			Cefoperazone		Ceftriaxone		Ceftazidime	
s				3° Generation	-	Cefpodox		eftizox		Cefotaxime	
s					100	Cefdinir		eftibut	en	Cefixime	
						Cefditore	n				
				4° Generation		Cefepime			Cefpiro	me *	
		Carbapenems		5° Generation		Ceftarolin	e				
				Meropenem	Erta	penem	Doripe	nem	Imipenen	n + Cylastatine	
		- 1	Monobactams	Aztreonam				7/8			
	***	• Beta	Beta-lactamase inhib.	Sulbactam Vancomycir		Tazobactam n		Clavulanic Acid Bacitracin		anic Acid	
	No	-	Glycopeptides								
	lactam			Teicoplanin		1		P	olymyxin	В	
			Amino-	Gentamycin		Neomyci		in S		treptomycin	
		305	glycosides	Amikacin		Tob	pramycin				
			Tetracyclins	Doxycycline		Dem	eclocylin	*	Mi	nocycline	
			The state of the s	Tetracyclin		Tip	gecyclin				
P	rotein		Oxazolidonones	Linezolid							
Sy	nthesis		Streptogramins	Quinupristin/Dalf	opristi	in					
		505	Cloramphenical	- *							
			Macrolides	Erythromycin		Azithrom	ycin		Clarith	omycin	
			Lincosamides	Cline	lamyc	in			Lincom	ycin	
3	DNA	Fluo	rquinolones	Ciprofloxacin	1	Norfloxaci	n	Levofl	oxacin	Ofloxacin	
topois	omerases		X1	Sparfloxacin	٨	/loxifloxac	in	Gemif	loxacin	Enofloxacin	
		Quin	olones	Nalidixic Acid	-						
3.03	ic Acid	Sulfa	onamides	Sulfamethoxaz (SMX)	ole	Ag Sulfa	adiazine	Sulfa	salazine	Sulfisoxazole	
	8000000000	DHF	R inhibitors		roprir	n (TMP)			Pirymet	hamine	
DNA	(damage)	Meti	ronidazole			A COUNTY			-450-#300TA		
	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



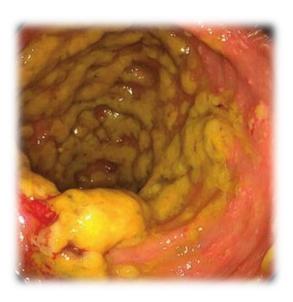


Ketolides

- 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
- Iong 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

IN	IHIBIT		CLASIFIC	CATION		ANTIBIOTICS																			
						Penicinii	lase - S	ensible																	
				Natural Penicillin (narrow spectrum)		Penicillin G: Na, K, Procainic, Ben Penicillin V: VO				thine (IV, IM)															
				Aminopenicillins (broad spectrum)		Ampicillin																			
						Amoxicilli																			
			Penicillins		icinill	ase – Resi		ry narrow	-																
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Cell				Carboxipenicillin		Ticarcillin Carbenicil	lin																		
Wall				Ureidopenicillin	s	Piperacilli Azlocillin Mezlocilli																			
S		-		1° Generation	_	Cefazolin		ephales	ino	Cephapirin															
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n	Beta							Cefaman		Cefprozil															
t	Lactams			2° Generation						Cefmetazole															
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e s		,	Cephalosporins	4	_			Cefaclor Ceftriaxone		Cofee-tillion															
		Septimiosporiito		3° Generation				Ceftizoxime		Ceftazidime															
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				4° Generation	_)		C-6-1																
				5° Generation	_	Cefepime			Cefpiro	me															
			c 1		_	Ceftarolin	-																		
			Carbapenems Monobactams	Meropenem Aztreonam	Erta	apenem	Doripe	nem	imipenen	n + Cylastatine															
			r-lactamase inhib.	Sulbactam		Tazobac	50 a.c. v	_	Cl. I	nic Acid															
	No	-		Vancomycin		Tazobac	tam																		
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															Tetracyclins	Doxycycline	-				IVII	nocycline			
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	nthesis			Quinupristin/Dalfopristin																					
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			Macrolides	Erythromycin	- 1	A -talt-		Class		1															
			Lincosamides		_		CIII																		
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mĸN	A synth.	Kijai	mpim																						

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

INHIBIT		CLASIFICATION				ANTIBIOTICS									
			Penicinillase – Sensible												
			Natural Penicillin	ns	Penicillin	G: Na, I	C, Proca	, Procainic, Benzathine (IV, IM)							
			(narrow spectrum)	Penicillin	V: VO									
			Aminopenicillin	s	Ampicillin										
			(broad spectrum)		Amoxicilli	n									
			Per	icini	llase – Res	istant (verv narn	ow spectrum)						
		Penicillins	Nafcillin			-			loxacillin						
				Ant	ipseudomo	nal (ex	ended so	ectrum)							
					Ticarcillin										
			Carboxipenicillin	15	Carbenici	llin									
				000	Diporacilli										
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			2" Generation						Cefmetazole						
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		Cephalosporins					The second second		Ceftazidime						
			3° Generation						Cefotaxime						
						ime			Cefixime						
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	Suife	onamiaes		ne	Ag Sulfa	adiazini	Sull	asalazine	Sulfisoxazole						
Lilesis	DHE	P inhibitors		ronr	im /TMP\			Dirumo	thamine						
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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)





Classification of antibiotics by mechanism of action

IN	IHIBIT		CLASIFIC	ATION ANTIBIOTICS															
-				Penicinillase – Sensible															
				Natural Penicillins Penicillin G: Na, K,			K. Proca	Procainic, Benzathine (IV, IM)											
				(narrow spectrum) Penicillin V: VO															
				Aminopenicillin	s	Ampicillin													
				(broad spectrum)		Amoxicilli	n												
				Pen	icini	Ilase – Resi	stant (very narr	ow spectrum)									
			Penicillins	Nafcillin			acillin	-		loxacillin									
					Ant	ipseudomo	nal (ex	tended so	ectrum)										
Cell				Carboxipenicillin	15	Ticarcillin Carbenici	llin												
Wall				Ureidopenicillin	ıs	Piperacilli Azlocillin Mezlocilli													
S						1110 210,0111	n												
y				1° Generation		Cefazolin		Cepha		Cephapirin									
n	Beta					Cefadroxil		Cepha		Cephalotin									
t	Lactams	Cephalosporins		2° Generation				Cefam		Cefprozil									
h						Cefoxitin		Cefonicid		Cefmetazole									
e						Cefotetan		Cefaclo		- 4 - 1									
s				3° Generation		Cefoperazone		Ceftriaxone		Ceftazidime									
1						Cefpodoxime		Ceftizoxime		Cefotaxime									
s						Cefdinir	- 3	Ceftibu	iten	Cefixime									
						Cefditore			-										
				4° Generation		Cefepime			Cefpiro	me *									
				5° Generation		Ceftaroline													
		Carbapenems		Meropenem	Er	tapenem	Dorip	enem	Imipener	n + Cylastatine									
		Monobactams		Aztreonam			1.												
			-lactamase inhib.	Sulbactam		Tazobac	tam			anic Acid									
	No	Glycopeptides		Vancomycin		i e		Bacitracin											
-	lactam			Teicoplanin					Polymyxin										
		200	Amino-	Gentamycin			Neomycin		Str	eptomycin									
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							8		8	8		8	8	Tetracyclins	Doxycycline			eclocyli	
	2000			Tetracyclin		Tigecyclin													
	rotein		Oxazolidonones	Linezolid															
Syl	nthesis	505	Streptogramins	Quinupristin/Dalfo	opris	tin													
		303	Cloramphenicol						1	TOTAL CO.									
		1 8	Macrolides	Erythromycin		Azithromycin				romycin									
			Lincosamides	Clind	lamy				Lincom										
700	DNA	Fluo	rquinolones	Ciprofloxacin		Norfloxaci			floxacin	Ofloxacin									
topois	poisomerases					Moxifloxac	in	Gem	ifloxacin	Enofloxacir									
			olones	Nalidixic Acid															
	ic Acid nthesis		namides	Sulfamethoxazo (SMX)	OWO CV	Ag Sulta	adiazini	e Sul		Sulfisoxazole									
		DHF	R inhibitors	Trimeth	ropi	im (TMP)			Piryme	thamine									
DNA	(damage)	Meti	ronidazole																
mRN	A synth.	Rifar	npim																

Fluoroquinolones

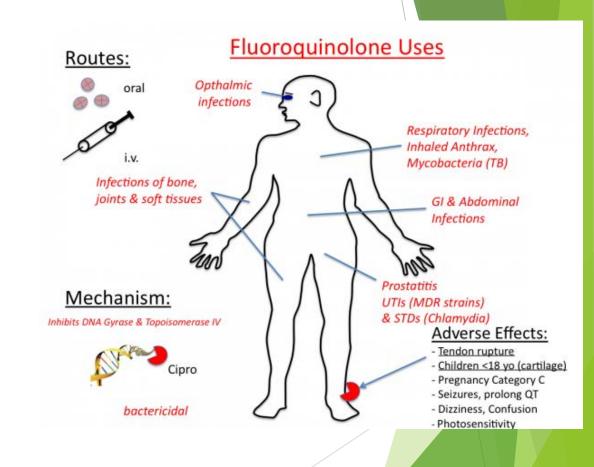
- Effect: Inhibition of DNA gyrase or topoisomerase IV enzyme
- Bactericidal agents
- They penetrate well into tissues (except CSF)
- Concentration and time dependent antibacterial effect (AUC / MIC)
- Long PAE
- Mechanisms of resistance (plasmid-encoded resistance is rare)
 - Efflux
 - Mutation in DNA gyrase or topoisomerase IV
 - Mutations in porins
- Generations: Gram + spectrum increases with growth
 - Oth. 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 widespread resistence
- Treatment of tuberculosis (cipro, levo and moxifloxacin)

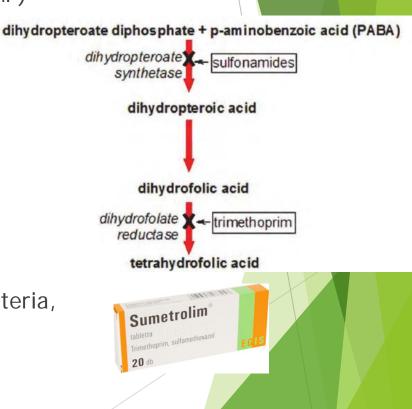


Classification of antibiotics by mechanism of action

IN	IHIBIT		CLASIFIC	ATION					BIOTICS										
				Penicinillase - Sensible															
				Natural Penicillir (narrow spectrum)	225	Penicillin Penicillin	Procain	Procainic, Benzathine (IV, IM)											
				Aminopenicillin (broad spectrum)	s	Ampicillin Amoxicillin													
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Wall				Ureidopenicillin	s	Piperacillin Azlocillin Mezlocillin													
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n	Beta				- 5	Cefuroxin		Cefamar		Cefprozil									
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e			ephalosporins		-	Cefoperazone		Ceftriaxone		Ceftazidime									
s				3° Generation		the state of the s		Ceftizoxime		Cefotaxime									
						Cefdinir		Ceftibute	2007-0-0	Cefixime									
s						Cefditore				COMMITTEE									
				4° Generation		Cefepime			Cefpiro	me *									
				5° Generation		Ceftarolin	e												
		Carbapenems		Meropenem	Ert	tapenem	Doripe	nem	Imipenen	n + Cylastatine									
		- 1	Monobactams	Aztreonam			7	7/8											
		• Beta	-lactamase inhib.	Sulbactam		Tazobac	tam		Clavula	nic Acid									
	No	Glycopeptides		Vancomycir				1	Bacitracin										
	lactam			Teicoplanin		1		Polymyxin B											
		305	Amino-	Gentamycin		Neomycin		St		reptomycin									
			glycosides	Amikacin	- 1	Tobramyci				27									
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Sy	nthesis	505	Streptogramins	Quinupristin/Dalfo	prist	tin													
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			Macrolides	Erythromycin	- 1	Azithromy	rcin		Clarithr										
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			olones	Nalidixic Acid															
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		DHF	R inhibitors	Trimethroprim (TMP)			Pirymethamine												
DNA	(damage)	Metr	ronidazole																
	A synth.	Dif.	npim																

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



Classification of antibiotics by mechanism of action

IN	HIBIT		CLASIFIC	CATION					BIOTICS		
						Penicini	-				
				Natural Penicillii (narrow spectrum		Penicillin Penicillin		K, Procai	Procainic, Benzathine (IV, IM)		
				Aminopenicillin (broad spectrum)		Ampicillin Amoxicilli					
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Wall				Ureidopenicillin	ıs	Piperacilli Azlocillin Mezlocilli					
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n	Beta			2° Generation		Cefuroxim		Cefama		Cefprozil	
ŧ.	Lactams					Cefoxitin		Cefonic		Cefmetazole	
h		Cephalosporins				Cefotetan		Cefaclo	-	Cometacore	
e						Cefoperazone		Ceftriax		Ceftazidime	
s				3° Generation		Cefpodox	-	Ceftizox		Cefotaxime	
s						Cefdinir		Ceftibuten		Cefixime	
3						Cefditore	1	001000		- CONTRACTOR	
				4° Generation		Cefepime			Cefpiro	me *	
				5° Generation		Ceftarolin	e				
		-	Carbapenems	Meropenem	Ert	rtapenem Doripenem Imipenem + Cylasta					
		Monobactams		Aztreonam				7/3			
		• Beta	-lactamase inhib.	Sulbactam		Tazobac	tam		Clavula	anic Acid	
	No	Glycopeptides		Vancomycin					Bacitracir	1	
	lactam			Teicoplanin				F	olymyxin	В	
			Amino-	Gentamycin Neo		omycin		Streptomycin			
		305	glycosides	Amikacin		Tob	ramyci	in			
			Tetracyclins	Doxycycline		Demeclocylin		lin *		Minocycline	
	50/03/100			Tetracyclin		Tig	ecyclir	1			
	otein		Oxazolidonones	Linezolid		000					
Syn	thesis	505	Streptogramins	Quinupristin/Dalfo	oprist	in					
		505	Cloramphenicol								
			Macrolides	Erythromycin		Azithromy	rcin			romycin	
			Lincosamides	Clindam					Lincom	-	
1000	DNA	Fluo	rquinolones	Ciprofloxacin		Norfloxaci			oxacin	Ofloxacin	
topois	omerases			Sparfloxacin		Moxifloxac	in	Gemif	loxacin	Enofloxacin	
-		-	olones	Nalidixic Acid							
5.000	ic Acid	Sulfa	onamides	Sulfamethoxaze	ole	Ag Sulfa	idiazini	e Sulfa	salazine	Sulfisoxazole	
Syn	thesis	DUC	R inhibitors	(SMX) Trimethroprim (TMP)				Dimm	the male a		
		- 1/40	R inhibitors ronidazole	Trimeth	ropri	m (HMP)			Piryme	thamine	

Rifamycins

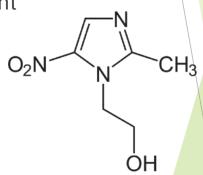
- Rifampicin, rifabutin, rifaximin
- Inhibition of RNA polymerase
- bactericides
- Good tissue penetration (thoracal and abdominal processes, bone, abscess)
- ▶ It reaches therapeutic concentrations in the cerebrospinal fluid
- Effective against:
 - Gr + bacteria: pl. S aureus, C. difficile
 - Gr- bacteria: 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)

Classification of antibiotics by mechanism of action

114	HIBIT		CLASIFIC	CATION				ANTIE	NTIBIOTICS ble			
						Penicinil	lase – S	ensible				
				Natural Penicillin (narrow spectrum	7.00	Penicillin G: Na, K, Procainic, Benzathine (IV, Penicillin V: VO						
				Aminopenicillin (broad spectrum)		Ampicillin						
						Amoxicilli						
			Penicillins	Nafcillin	icinii	llase – Resi		ery narrov		loxacillin		
			rememms	Natcillin			acillin			loxacillin		
					Anti	ipseudomo Ticarcillin	nai (exte	ended spe	ctrum)			
Cell				Carboxipenicillir	15	Carbenicil	lin					
Wall				Ureidopenicillin	s	Piperacillin Azlocillin Mezlocillin						
S		1		1° Generation		Cefazolin		Cephale	vine	Cephapirin		
y	012105000			a deneration		Cefadroxil	_	Cephadr		Cephalotin		
n	Beta					Cefuroxim		Cefamar		Cefprozil		
ţ.	Lactams	Cephalosporins		2° Generation		Cefoxitin		Cefonici		Cefmetazole		
h						Cefotetan		Cefaclor		Commetatore		
e						Cefoperazone		Ceftriaxone		Ceftazidime		
s				3° Generation		Cefpodoxi		Ceftizoxime		Cefotaxime		
s						Cefdinir		Ceftibuten		Cefixime		
s						Cefditorer				- CONTRACTOR OF THE CONTRACTOR		
				4° Generation		Cefepime			Cefpiro	me *		
				5° Generation		Ceftarolin	e					
			Carbapenems	Meropenem	Ert	tapenem	Doripe	enem	lmipenen	n + Cylastatine		
		- 1	Monobactams	Aztreonam				7/3				
		• Beta	-lactamase inhib.	Sulbactam		Tazobac	tam		Clavula	anic Acid		
	No lactam	Glycopeptides		Vancomycin					Bacitracin			
				Teicoplanin				P	olymyxin			
			Amino-	Gentamycin	ycin Neomy		omycin		Streptomycin			
		305	30S glycosides	Amikacin			ramycir					
			Tetracyclins		Doxycycline		Demeclocylin *			Minocycline		
1025	2023400			Tetracyclin		Tig						
			Oxazolidonones	Linezolid								
Syr	nthesis	505	Streptogramins	Quinupristin/Dalfo	prist	tin						
		303	Cloramphenicol				17/4.7		l service serv			
			Macrolides	Erythromycin		Azithromycin			-	omycin		
		Lincosamides			lamy			4	Lincom	and the same of th		
1000		Fluo	rquinolones	Ciprofloxacin		Norfloxaci		Levofl		Ofloxacin		
topois	omerases			Sparfloxacin Moxifloxac		ın	Gemifl	oxacın	Enofloxacin			
F - 1	Protein Synthesis DNA DPOisomerases		olones	Nalidixic Acid	1-	A - C. 11	diante	C. 15	- deale	C(C		
5.753	5.515 115.5574	Sulfo	namides	Sulfamethoxazole		Ag Sulfadiazine		Sulfa	salazine	Sulfisoxazole		
Syr	nthesis	DHFR inhibitors		(SMX) Trimethroprim (TMP)		im /TMP\			Dirumot	thamine		
	(damage)			rimeth	ropri	iiii (TIVIP)			rirymet	martine		
		Weti	onidazole									

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</p>
- Their cell wall consists of polysaccharides: chitin, αand β-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 Superficial Subcutaneous (Cutan mycosis) mycosis mycosis Malassezia furfur topical Trichophyton rubrum Mechanical Sporothrix shenkii | oral Microsporium canis removing, topical, Microsporium gypseum nystatin, natamycin oral Epidermophyton species itraconazole, fluconazole, Systemic mycosis ketoconazole topical terbinafine (Only in Dimorphic fungi Coccidioides immitis dermatomycosis) Lungs → oral Histoplasma capsulatum Meningitis → fluconazole · ketoconazole, fluconazole, Blastomyces dermatitis Disseminated → i.v.ampB itraconazole Oral Paracoccidioides brasiliensis Skin → topical • terbinafine (Only in dermatomycosis)

Opportunist mycosis

- Candida species (C.albicans, C.krusei, C.tropicalis, C.glabrata, C.parapsilosis)
- Aspergillus species (A.fumigatus, A.flavus, A.niger) outer → topical, oral; inner → oral, i.v.
- Absidia corynbifera
- Rhizomucor pusillus
- Rhizopus arrhizus
- Pneumocystis carinii Oral i.v. ampB

Sumetrolim (Trimethoprim + Sulfamethoxazol) Pentamidin (antiprotozoal agent)

Mucocutan > topical, oral

J Invasive → oral, i.v. ampB

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 Susceptibility 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 cellmembran 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
 - <u>Effectiveness:</u> fungistatic in lower doses, fungicidal in higher doses

Agents that damage the cellmembrane Polyenes II.

HO.

- 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

OH

OH

HO

- 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

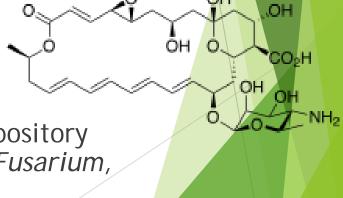
► characteristics like amph B, but systemically more toxic

► 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)



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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)
 - ► <u>Effectiveness:</u> they are fungistatic agents
- Azoles have two groups: imidazoles and triazoles

Agents that damage the cellmembrane Azoles II.

Imidazoles:

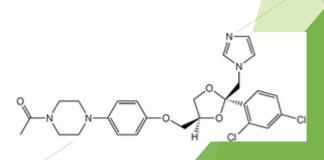
Miconazole, Econazole, Ketoconazole, Clotrimazole, Bifonazole, Clomidazole, Croconazole, Fenticonazole, Isoconazole, Neticonazole, Oxiconazole, Sertaconazole, Sulconazole, Tioconazole

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 cellmemorane 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
 - <u>Effectiveness:</u> fungicidal
 - <u>Terbinafine:</u>
 - 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

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-add 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
 - ► <u>Effectiveness:</u>
 - 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 **B-glucane synthase** enzyme ← B-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.

<u>In Hungary</u> roundworm and tapeworminfections are the most common.

Groups of helminths

Helminths

Nematoda (roundworms)

Intestinal occurrence: Enterobius vermicularis Trichuris trichiura Ascaris lumbricoides

- → Toxocara canis Ancylostoma duodenale Necator americanus Strongyloides stercolaris
- Trichinella spiralis

 Blood and Tissues occurrence:

 Wuchereria bancrofti

Loa Loa Oncocerca volvulus Dracunculus medinensis Platyhelminths (flatworms)

Cestoda (tapeworms)

Intestinal occurrence: Taenia saginata

- → Taenia solium
 - → Echinococcus granulosis
- → Echinococcus multilocularis Dipylidium caninum Diphyllobotrium latum Hymenolepis nana

Trematoda (flukes)

Intestinal occurrence:
Fasciola hepatica
Schistosoma mansoni
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



Nematoda (roundworms)

Intestinal occurrence:

Enterobius vermicularis - mebendazole

Trichuris trichiura - mebendazole

Ascaris lumbricoides - mebendazole, tiabendazole, levamisol

Toxocara canis - tiabendazole

Ancylostoma duodenale - mebendazole, tiabendazole, levamisol Echinococcus multilocularis - surgical, mebendazole, albendazole

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

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)

<u>Targets</u> 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

<u>Drug target:</u> 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

<u>Mechanism of effect:</u> 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

<u>Mechnism of effect:</u> 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 <u>mechanism of effect</u> 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 <u>mechanism of action</u> 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 <u>mechanism of action</u> is unknown, presumably it also inhibits the ATP-production

<u>Spectrum:</u> 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

<u>Mechanism of effect:</u> not thoroughly understood; presumably it increases the permeability of the membrane of the helminths to Ca²⁺ 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

<u>Mechanism of effect:</u> 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

<u>Arylsulphonate-derivative:</u>

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)





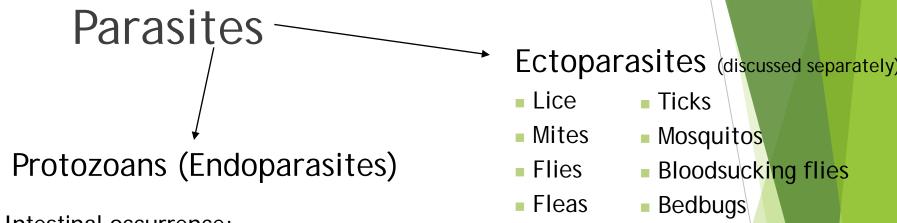


VERMOX tabletts (mebendazole) 6x (100mg)

Each against intestinal roundworm infections

Antiparasite agents ATC codes P01 and P03

Groups of parasites and medications against them



Intestinal occurrence:

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

emetine

paromomycin (aminoglycoside antibiotic agent)

iodoquinol

diloxanide-furoate

(tetracycline antibiotics)

Groups of parasites and medications against them (con

<u>Protozoans with intestinal occurrence (cont.):</u>

- 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)

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

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

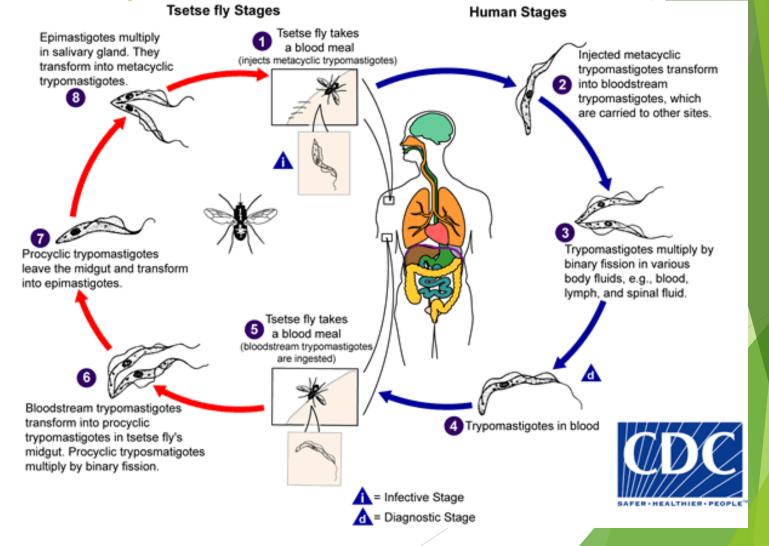
Agents against Entamoeba histolytica Luminal amebicides (cont.)

- Halogenised Hydroxyquinole-derivatives
 (lodoquinol, 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.

<u>Use:</u> 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)
- <u>Use:</u> 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 SHgroups of enzymes (e.g.:glycolytic phosphopyruvatekinase), 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.

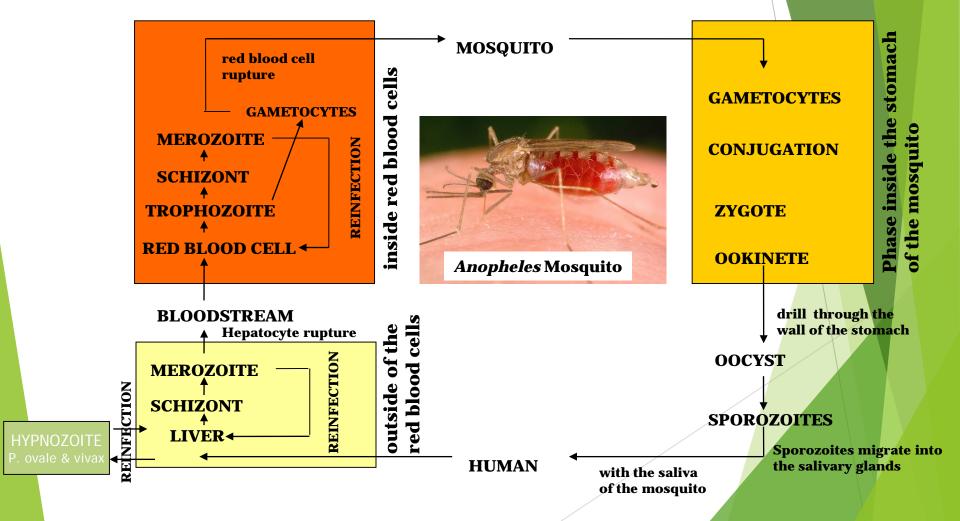
Agents against Trypanosoma brucei species sleeping sickness (cont.)

- 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
 - <u>Use:</u> 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
 - <u>Use:</u> 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 8aminoquinolines 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

- 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)
 - <u>Use:</u> blood-schizontocid; also used in giardiasis

- 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 Ca²⁺ 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

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)

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®

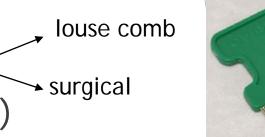
- Atovaquone (naftoquinon-derivative)
 - Mechanism of effect:
 - Ubiquinon-analogue, interferes with ubiquinon, thus, inhibits the terminal oxidation in the mytochondrium (thus energy production is inhibited) (as primaquine)
 - Use: very effective in the hepatic phase of the Plasmodium infection; against 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 ectoparasi es

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



- 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 Natchannels in the membrane of the neurons, thus, cause hyperexcitation
 - <u>Use:</u> first-choice agenst; against every ectoparazitosis
- They are toxic to fish and cats!

- Lindane (hexachlorcyclohexane)
 - ► Mechanism of effect: non-competitively inhibits 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!

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

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

- Crotamiton
 - ► <u>Mechanism of effect:</u> unknown
 - ► <u>Use:</u> as scabicidum in the form of solution;
- irritative to skin

- Benzyl-benzoate
 - Mechanism of effect: unknown
 - <u>Use:</u> 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



