Antibacterial chemotherapy

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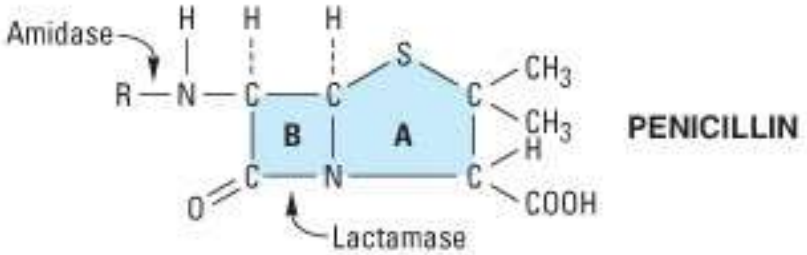
β-lactam antibiotics and other cell wall synthesis inhibitors

- Bacterial cell wall synthesis inhibitors
  - β-lactams
    - **penicillins**
    - **cephalosporins**
    - **carbapenems**
    - monobactams
  - glycopeptides
    - **vancomycin** / telavancin; teicoplanin / dalbavancin / oritavancin
  - other cell wall synthesis inhibitors
    - fosfomycin
    - bacitracin
    - cycloserine
- Cell membrane active antibiotics
  - daptomycin
  - polymixins

Penicillins

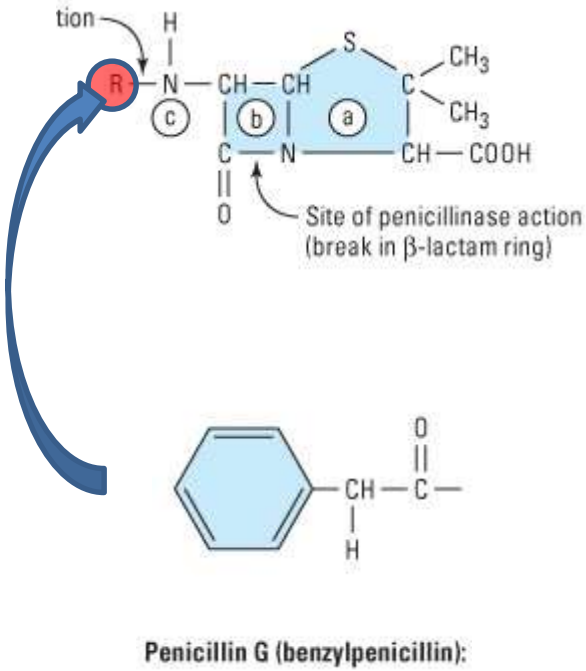
- base penicillins
- antistaphylococcal penicillins
- extended spectrum penicillins



Substituted 6-aminopenicillanic acid

Base penicillins

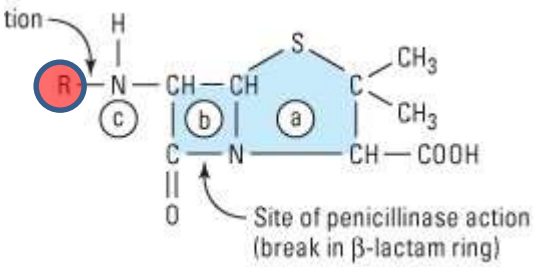
- parenteral
  - **penicillin G** (benzylpenicillin)
  - benzathine penicillin
  - procaine penicillin G
- oral
  - penicillin V
  - penamecillin

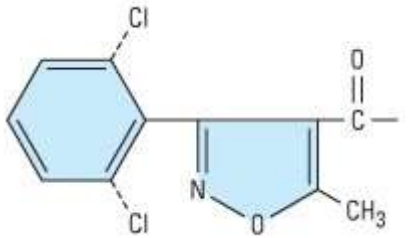


Penicillin G (benzylpenicillin):

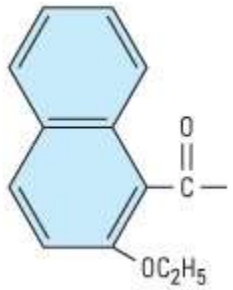
Antistaphylococcal penicillins

- *methicillin*
- **nafcillin (i.v.)**
- isoxazolyl penicillins
  - – parenteral
    - **oxacillin**
  - – oral
    - cloxacillin / dicloxacillin





isoxazolyl penicillins

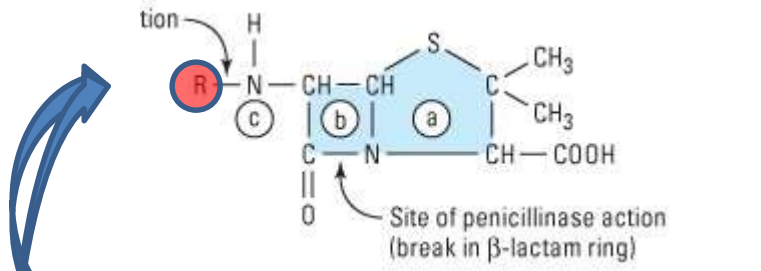


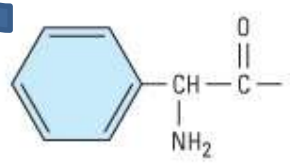
nafcillin

Extended spectrum penicillins

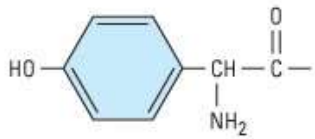
- aminopenicillins
  - **ampicillin**
  - **amoxicillin**
- carboxypenicillins
  - *carbenicillin*
  - ticarcillin
- ureidopenicillins
  - **piperacillin**
  - mezlocillin
  - azlocillin

antipseudomonal penicillins

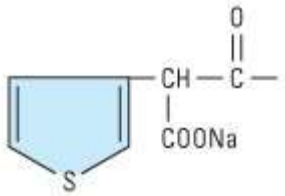




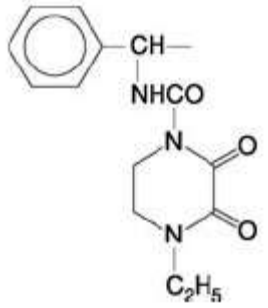
ampicillin



amoxicillin



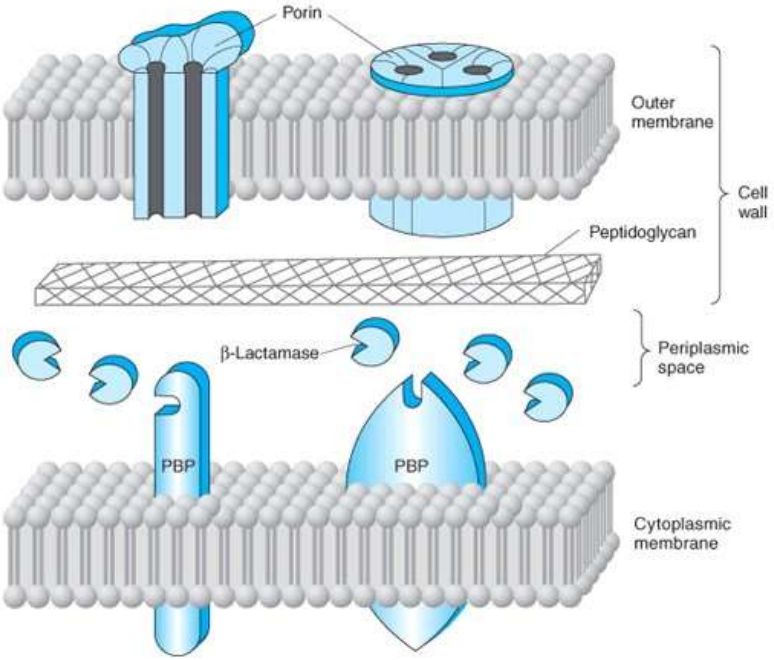
ticarcillin

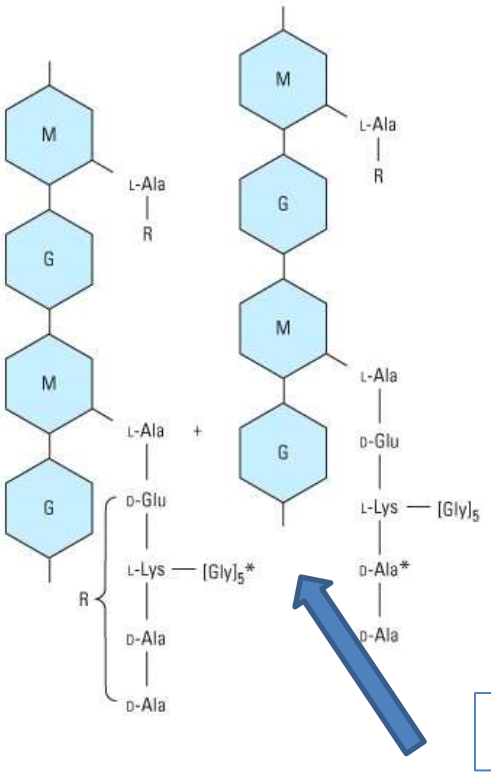


piperacillin

Mechanism of action

- cell wall peptidoglycan
- transpeptidation (structural analogs)
- **common for all β-lactams**





transpeptidase (PBP) – cross link

Resistance

- **β-lactamases** – inactivation
  - narrow spectrum – only penicillins
    - *S. aureus*, *Haemophilus spp.*, *E. coli*
  - ESBLs / AmpC – both penicillins and cephalosporins
    - *P. aeruginosa*, *Enterobacter spp.*
  - metallo-β lactamases / carbapenemases – carbapenems too
- **PBP modification**
  - methicillin resistant *S. aureus* (MRSA)
  - penicillin resistant *S. pneumoniae* / *Enterococci*
- impaired penetration
  - only in G- / porin absence
- efflux
  - in G-

Absorption

- oral – 1-2 hours before or after meal (except amoxicillin)
  - penicillin V
  - ampicillin / amoxicillin
    - amoxicillin: better absorption
  - dicloxacillin
- parenteral – i.v. preferred
  - penicillin G – acid-labile
  - benzathine / procaine penicillin
    - i.m. delayed absorption
      - single 1.2 M IU benzathine penicillin – > 0.02 µg/ml for 10 days

Distribution

- high protein binding
  - nafcillin (90%) / isoxazolyl penicllins (95-98%)
- lower protein binding
  - penicillin G (60%) / ampicillin
- good distribution to most tissues (but no intracellular)
  - **exceptions: CNS / eye / prostate**
  - BUT for active meningitis 18-24 M IU/day is OK

Elimination

- excreted by the kidneys
  - glomerular filtration (~10%)
  - tubular secretion (~90%)
    - **see probenecid**
- $t_{1/2}$ – 30 min to 1 hour
- biliary excretion
  - **nafcillin** / oxacillin / cloxacillin / dicloxacillin

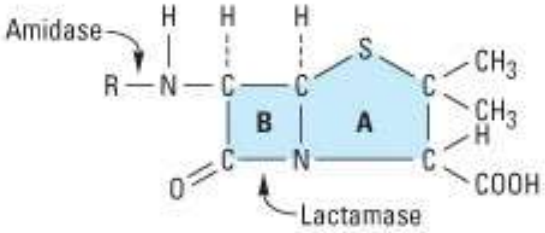
Antibacterial spectrum

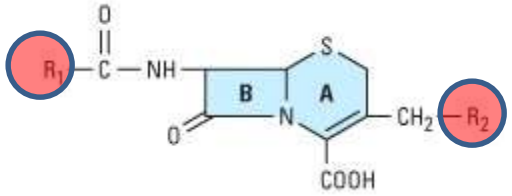
- base penicillins
  - G+ / G- cocci / anaerobs
  - only non β-lactamase producing strains
  - *T. pallidum*
  - resistance frequent in: *N. gonorrheae* (and *S. pneumoniae* in some areas)
- antistaphyloccocal penicillins
  - narrow spectrum
  - **staphylococci** (β-lactamase producing but not MRSA!) / streptococci
- extended spectrum penicillins
  - penicillin plus improved G-
  - only non β-lactamase producing strains
    - but see β-lactamase inhibitors
  - antipseudomonal penicillins
    - *P. aeruginosa / Klebsiella spp.*
    - sometimes in combination with an aminoglycoside or fluoroquinolone
      - might decrease *P. aeruginosa* resistance development / only in non-UTI

Adverse effects

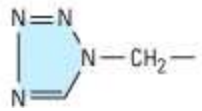
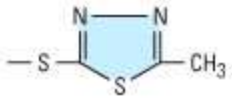
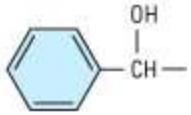
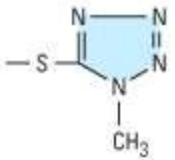
- **hypersensitivity**
  - frequency 0.7-4%
    - anaphylactic shock 4-40:100000 / lethal ~ 1:100000 (300 deaths per year worldwide)
  - risk is similar for all agents in the group
  - may occur at any age / previous known exposure is not necessary
  - cross sensitivity with other beta lactams (not complete)
  - frequency of manifestations in approximate decreasing order
    - maculopapular rash
    - urticarial rash
    - fever
    - bronchospasm
    - vasculitis
    - serum sickness (IgG mediated, 7-12 days after exposure)
    - exfoliative dermatitis
    - Stevens-Johnson syndrome
    - *anaphylaxis - fatal anaphylaxis happened after very small doses! , variable clinical picture*
  - history (and confirmation) is not reliable but use other antibiotic if possible
    - densensitization (only in ICU / dangerous and its efficacy is unproven)
- interstitial nephritis - methicillin
- neutropenia - nafcillin
- pseudomembranous colitis - ampicillin
- non-allergic skin rash - aminopenicillins

Cephalosporins





7-amino-cephalosporanic acid

	R_1		R_2
1st generation		Cefazolin	
2nd generation		Cefamandole	

Classification and antibacterial activity of cephalosporins

generation	examples	Gram +	Gram -	B. fragilis	P. aeruginosa
1st	cefazolin cephalexin	good	modest	resistant	resistant
2nd	cefuroxime cefoxitin	< 1st	> 1st/< 3rd	cefoxitin	resistant
3rd	cefotaxime ceftriaxone	close to 1st	good but no ESBL	resistant	resistant
antipseudomonal	ceftazidime ceftazidime/avibactam ceftolozane/tazobactam cefepime (4th gen)	poor poor poor ≈cefotax	no ESBL +MDR +ESBL ≈3rd	resistant	good
anti MRSA	ceftaroline ceftobiprole	≈3rd+MRSA	≈cefotax. ≈cefepime	resistant	resistant good

No activity against:

- *Enterococci*
- ESBL producing Gram- (except new lactamase inhib. combinations)
- methicillin-resistant *S. aureus* (except anti MRSA)
- penicillin-resistant *S. pneumoniae* (except ceftriaxone)

Pharmacokinetics of cephalosporins

generation	oral	parenteral
1st	cephalexin	cefazolin
2nd	cefuroxime axetil cefaclor	cefuroxime cefoxitin
3rd	cefixime	cefotaxime ceftriaxone
antipseudomonal	-	ceftazidime cefepime
anti MRSA	-	ceftaroline ceftobiprole

- Excretion: kidney – except: cefoperazone / ceftriaxone (biliary)
- Half life: 1-2 hours – except: ceftriaxone (8 hours)
- CNS penetration: good for ceftriaxone / cefotaxime / cefepime
- No metabolism – except: cefotaxime

Clinical use of cephalosporins

- 1st generation
  - oral – UTI
  - cefazolin (iv.) – surgical prophylaxis
- 2nd generation
  - oral – sinusitis, otitis
  - cefoxitin – peritonitis, diverticulitis
- 3rd generation
  - **serious infections**
  - ceftriaxon / cefotaxime – **meningitis** (CSF cc ↑)
  - penicillin resistant *S. pneumoniae*
    - ceftriaxone / cefotaxime
  - **febrile neutropenia** (post cytotoxic chemotherapy)
- antipseudomonal
  - nosocomial infections with Pseudomonas / other resistant Gram- bacilli
  - cefepime – meningitis
- anti MRSA

New cephalosporine lactamase inhibitor combinations 1.

- **ceftazidime/avibactam** (Avycaz® / Zavicefta®)
  - enhanced activity
    - MDR Enterobacteriaceae (ESBL- and KPC-producing)
    - AmpC β-lactamase-overexpressing *Pseudomonas*
  - EMA approval (2016)
    - complicated **UTI**
    - complicated **intra-abdominal** inf.
    - hospital-acquired pneumonia
    - Gram- infections with limited other treatment options

New cephalosporine lactamase inhibitor combinations 2.

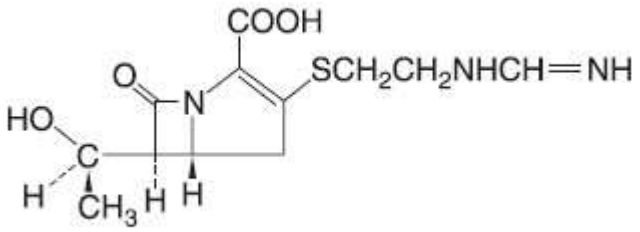
- **ceftolozane/tazobactam** (Zerbaxa®)
  - structural analogue of ceftazidime
    - modified side-chain → ↑ anti-*Pseudomonas* activity
  - tazobactam extends its activity
    - to most ESBL producing Enterobacteriaceae
  - EMA approval (2015)
    - complicated intraabdominal infections
    - complicated urinary tract infections

Adverse effects

- **hypersensitivity**
  - cross allergenicity with penicillins: ~5-10%
  - **anaphylaxis to penicillins – NO cephalosporins**
- local irritation
  - pain (i.m.)
  - thrombophlebitis (i.v.)
- cefamandole / cefotetan / **cefoperazone** (methylthiotetrazole)
  - hypoprothrombinemia
  - **disulfiram-like reactions**

Carbapenems

- imipenem/ meropenem/ ertapenem/ doripenem
- wide spectrum
  - G+, G- (*P. aeruginosa* too except ertapenem), anaerobes
  - choice for: *Enterobacter spp.,* ESBL producing G-
  - resistant: *E. faecium*, MRSA, *C. difficile*



IMIPENEM

Pharmacokinetics of carbapenems

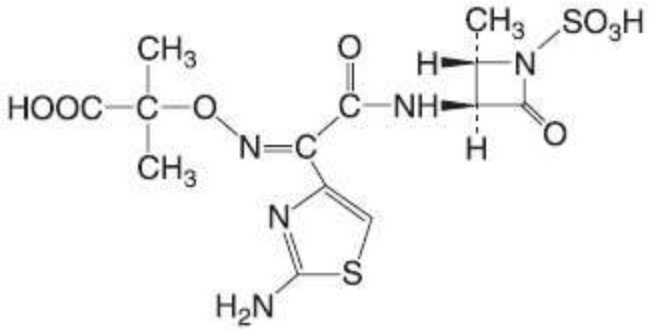
- A: parenteral (iv.) administration
- D: good CNS penetration (except ertapenem)
- M: renal tubular dehydropeptidase
  - **imipenem only**
  - combined with **cilastatin**
    - inhibitor of renal dehydropeptidase and
    - NOT a β lactamase inhibitor
- E: renal excretion
  - three times daily dosing
    - imipenem / meropenem / doripenem
  - longest $t_{1/2}$: ertapenem (4 hours)
    - once daily dosing

Adverse effects of carbapenems

- common (more with imipenem)
  - nausea, vomiting, diarrhea
  - skin rash
  - infusion site reactions
- severe
  - seizures (more with imipenem)
- hypersensitivity
  - cross reactivity with penicillins is possible (~1%)

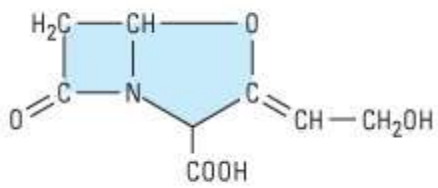
Monobactams

- only G- rods (e.g. *Pseudomonas*)
  - e.g. chronic suppression of *P. aeruginosa* in cystic fibrosis in an aerosol formulation (FDA 2010)
- no cross allergenicity with penicillin
- no major toxicity (hepatotoxicity in infants?)

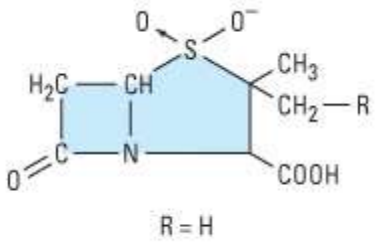


AZTREONAM

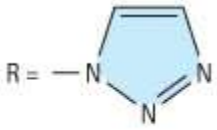
β-lactamase inhibitors



Clavulanic acid



Sulbactam

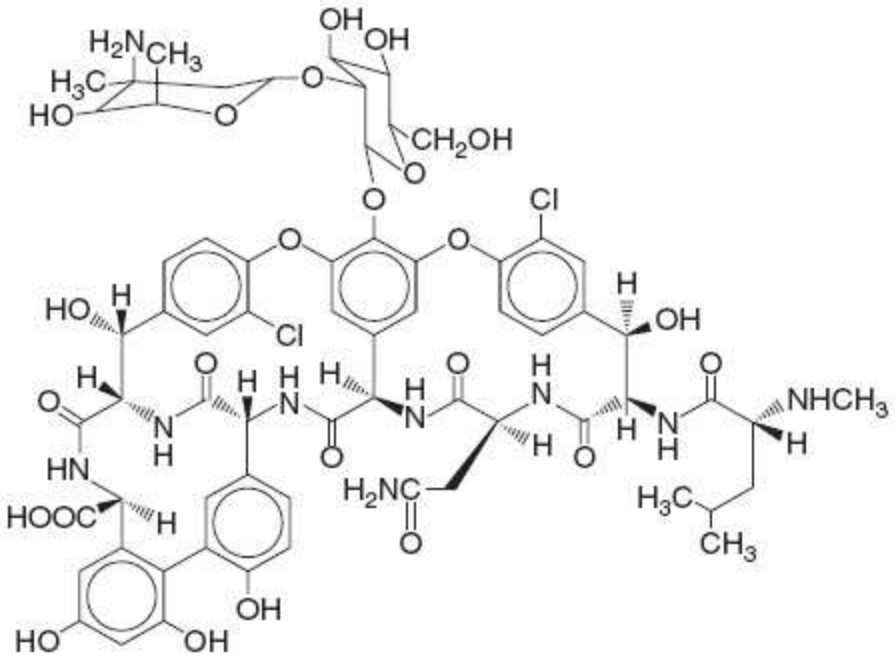


Tazobactam

- weak/no antibacterial action
- not all β-lactamases are inhibited
  - primarily inhibit plasmid-encoded β-lactamases
  - inactive against AmpC / carbapenemases (KPC/metallo)
  - **avibactam**: newer with broader spectrum (ESBL/AmpC/KPC)
- fixed combinations
  - amoxicillin + clavulanic acid
  - ampicillin + sulbactam
  - piperacillin + tazobactam / ceftolozane + tazobactam
  - ceftazidime + avibactam

Glycopeptides

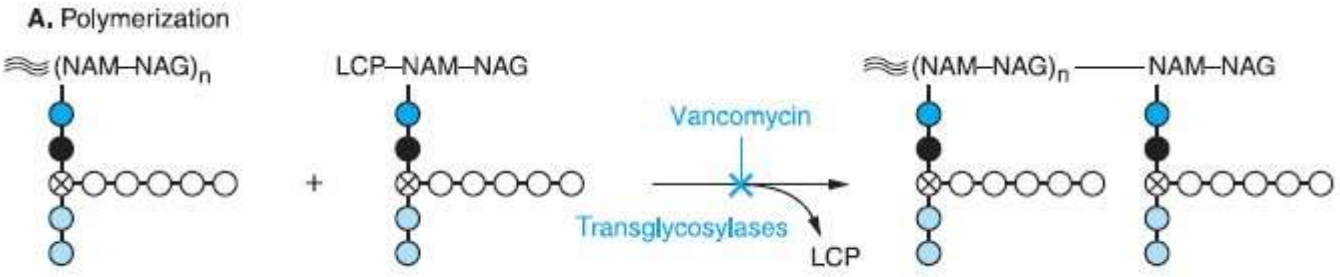
- **vancomycin** - telavancin
- teicoplanin - dalbavancin / oritavancin



VANCOMYCIN

Mechanism of action

- inhibits the polymerization (transglycosylase) reaction
- strong binding to the D-Ala-D-Ala terminus



Pharmacokinetics of vancomycin

- poor absorption from GI tract
  - i.v. administration
  - except for *C. difficile* (but NOT the first choice)
- in meningitis - CSF levels: 7-30% of serum
- glomerular filtration in kidney
  - dosage adjustment in renal impairment
  - drug concentration should be monitored
  - dose-related nephrotoxicity! – vicious circle

Spectrum / clinical use

- Gram+ aerobic / anaerobic (*C. difficile*), **MRSA** too
  - *in vitro* synergism with gentamicin / streptomycin
    - *E. faecium* / *E. faecalis*
- MRSA sepsis / endocarditis (not for MSSA!)
- enterococcal endocarditis
  - vancomycin + gentamicin (see risk of nephrotoxicity)
- penicillin resistant *S. pneumoniae* meningitis
  - only in comb. with ceftriaxon or cefotaxim or rifampin
- oral – pseudomembranous colitis (*C. difficile*)

Adverse effects

- phlebitis
- fever
- “red man” syndrome
  - histamine release (direct effect on mast cells)
  - prevented by prolonged infusion / antihistamines
  - true hypersensitivity (e.g. skin rash, anaphylaxis) is rare
- nephrotoxicity – espec. in combination
- ototoxicity – if plasma cc is high

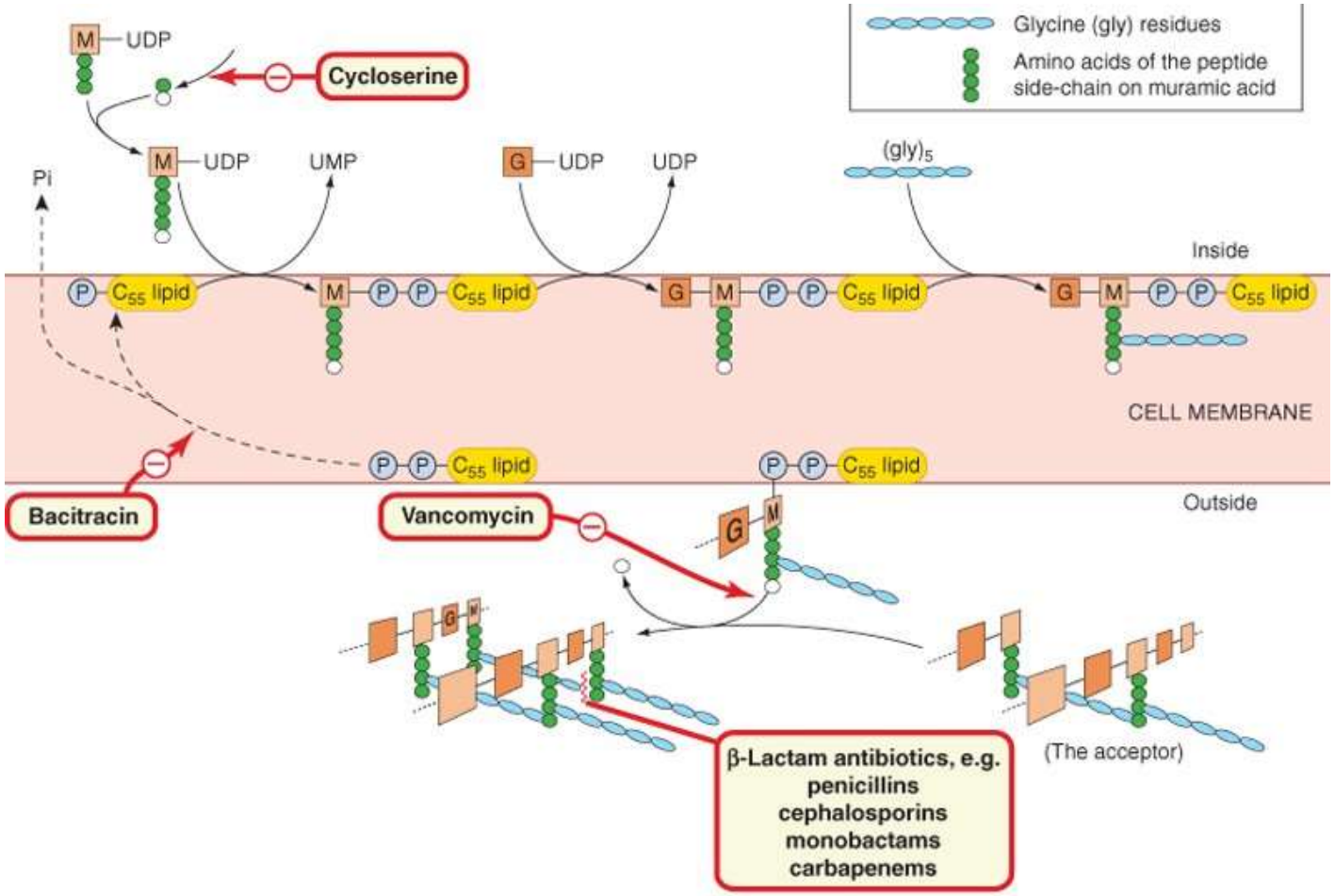
Other glycopeptides

- teicoplanin
  - can be given im. (not only iv.)
  - long $t_{1/2}$ – once daily
- telavancin; dalbavancin / oritavancin
  - semisynthetic lipoglycopeptides
  - effect in reduced vancomycin susceptibility
    - VRE: oritavancin (clinical ?)
  - dalbavancin/oritavancin: extremely long $t_{1/2}$ - **once weekly**
  - telavancin, oritavancin
    - additional mechanism – disrupt membrane
  - telavancin
    - nephrotoxicity maybe ↑ than vancomycin

Other cell wall synthesis inhibitors 1.

- **Fosfomycin**
  - phosphoenolpyruvate analog
    - blocks N-acetylmuramic acid synthesis
    - no cross resistance
  - resistance might occur after prolonged use
    - decreased transport
  - spectrum
    - excellent activity vs. *E. coli, Proteus, Enterococcus*
    - some (variable) activity vs. *Klebsiella, Enterobacter*
  - **oral, single dose** (3 grams)
    - indication: uncomplicated **UTI in women**
    - safe in pregnancy

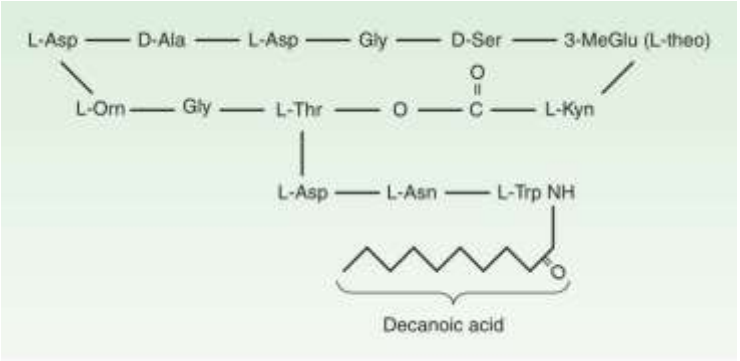
Inhibitors of cell wall synthesis



Other cell wall synthesis inhibitors 2.

- **Bacitracin**
  - cyclic peptide
  - Gram+ spectrum
  - interfere with lipid carrier dephosphorylation
  - **only topical** administration
    - because of serious nephrotoxicity after iv.
- **Cycloserine**
  - D-alanine analog – blocks incorporation
  - broad spectrum BUT mainly used as
  - **second line drug against *M. tuberculosis***
  - **oral** administration
  - dose related **CNS toxicity** (up to 50% - “psych-serine”)
    - headache, tremor, acute psychosis, convulsions
    - dose should be < 0.75 g/day

Cell membrane active antibiotics 1.



- **Daptomycin**
  - cyclic lipopeptide
  - Gram+ spectrum
  - active in vancomycin resistance (VRE, VRSA)
  - pore formation in cytoplasmic membrane ?
  - only i.v. administration
  - **myopathy** (↑CK)
  - should **NOT** be used **in pneumonia** – inactivated by surfactant

Cell membrane active antibiotics 2.

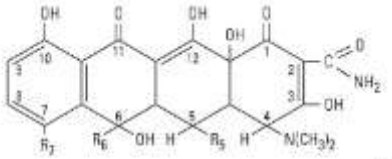
- **Polymixins**
  - basic peptides
    - polymixin B / polymixin E = **colistin**
  - active **only** against **Gram-**
  - **cationic detergents** – disrupt membranes
  - endotoxin (LPS) inactivation
  - clinical use
    - mainly topical BUT
    - with emergence of multiresistant
      - A. baumannii
      - P. aeruginosa
        - » **parenteral salvage therapy**

Protein synthesis inhibitors

- **basis of selectivity**
  - mammalian cytosolic ribosomes ≠ bacterial ribosomes
  - BUT less difference for mammalian mitochondrial ribosomes → unwanted effects in humans

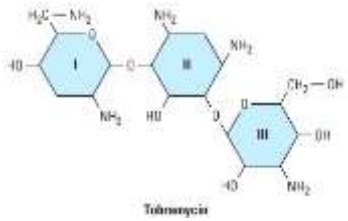
- **reversible → bacteriostatic**
  - chloramphenicol
  - tetracyclines: e.g. **doxycycline**, minocycline, (**tigecycline**)
  - macrolides: **erythromycin, clarithromycin, azithromycin**, telithromycin
  - **clindamycin**
  - streptogramins
  - linezolid
- **irreversible → bactericidal**
  - aminoglycosides: **streptomycin**, **amikacin, gentamicin, tobramycin**

Protein synthesis 1.

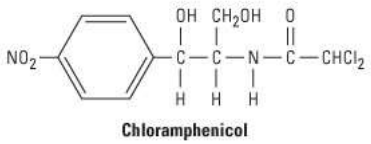


	R_7	R_6	R_5	Renal Clearance (mL/min)
Chlortetracycline	—Cl	—CH_3	—H	35
Oxytetracycline	—H	—CH_3	—OH	90
Tetracycline	—H	—CHG	—H	65
Demeclocycline	—Cl	—H	—H	35
Methacycline	—H	=CH_2*	—OH	31
Doxycycline	—H	—CH_3*	—OH	15
Minocycline	—$N(CH_3)_2$	—H	—H	10

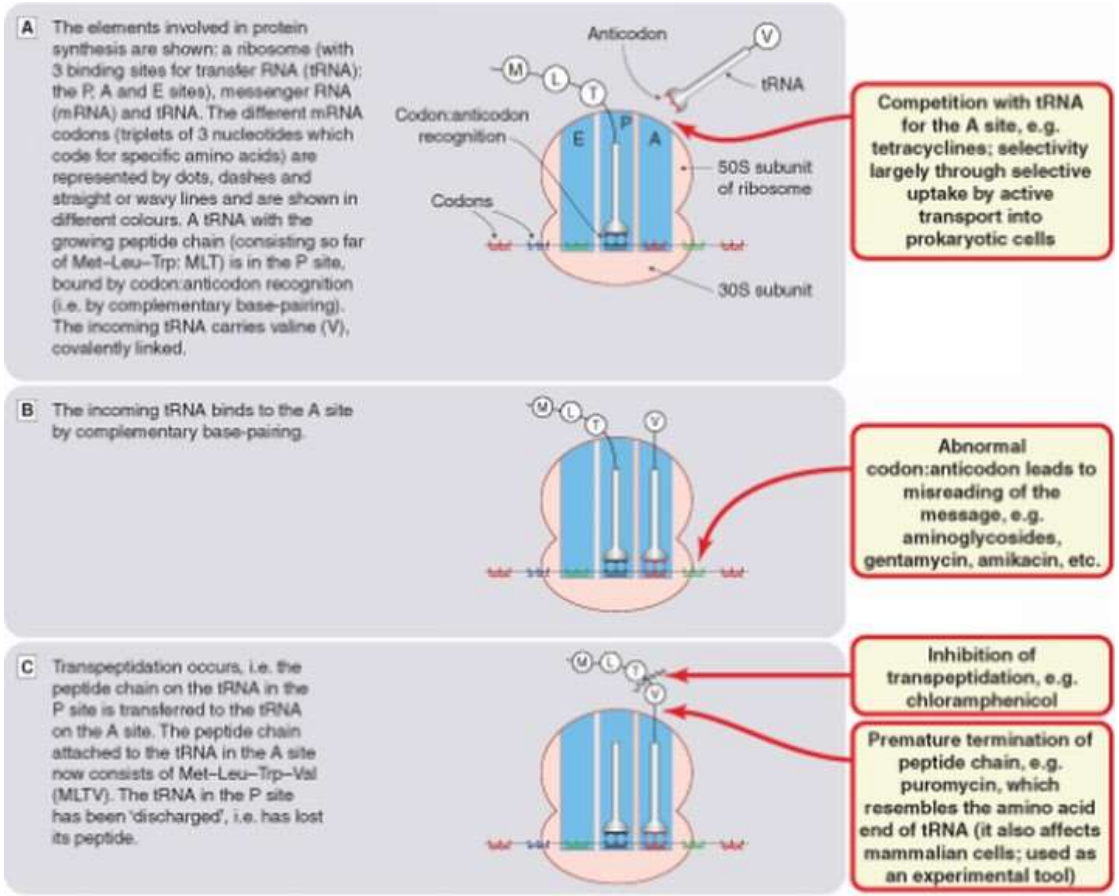
*There is no —OH at position 6 on methacycline and doxycycline.



Tobramycin



Chloramphenicol

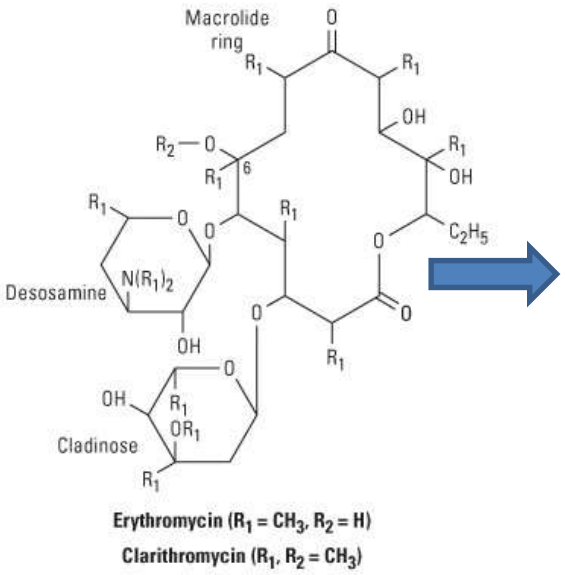


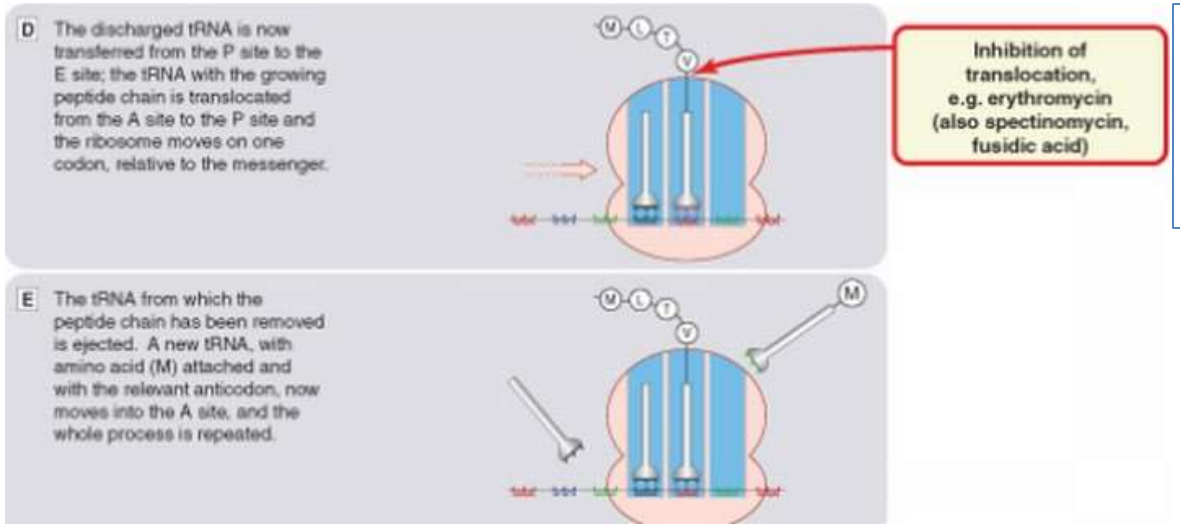
TC – 30S

AG – 30S

CL – 50S

Protein synthesis 2.



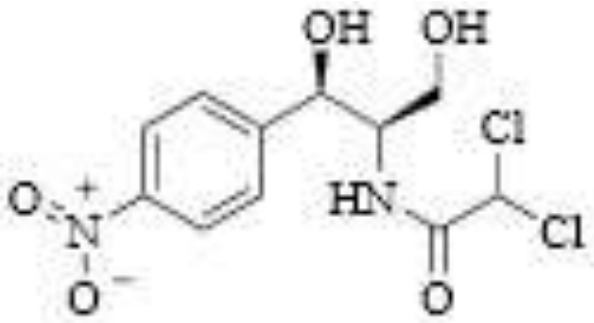


chloramphenicol / erythromycin / clindamycin – binding site close – no concurrent use

quinupristin/dalfopristin – also 50S, like macrolides

linezolid – 50S / prevents formation of a complex that initiates protein synthesis

CHLORAMPHENICOL



Chemistry

- unique structure
- lipophilic

Pharmacokinetics

Absorption, route of administration

- Oral: complete absorption
- IV

Distribution to tissues → good, incl. CSF and the fetus

Elimination

- Liver: glucuronidation
- Kidney: excretion of the glucuronide

Mechanism

50S ribosomal subunit
inhibition of peptidyl-transferase

CHLORAMPHENICOL 2.

Wide-spectrum, including anaerobes

Resistance

- Impaired permeability → multidrug-resistance
- Acetylation by bacterial acetyl-transferase

Adverse reactions

- Hematopoiesis
  - Hemolytic anemia (in G6P-dehydrogenase-deficient patients)
  - Dose-dependent, transient depression of the bone marrow
  - Aplastic anemia, agranulocytosis → rare but high lethality
- Gray-baby syndrome in neonates
- Superinfection (*Candida*)
- Other GI-disturbances

Clinical use

- Restricted to life-threatening infections for which no other agent is available (e.g. some severe *Salmonella*-infections)

•serious rickettsial infections

•meningococcal meningitis (in hypersensitivity to penicillin)

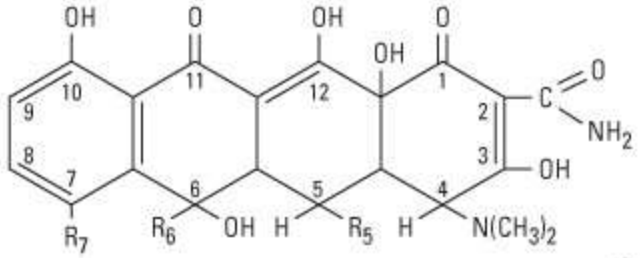
•topical in eye infections (but ineffective for chlamydia)

TETRACYCLINES

Chemistry

Substitutions → pharmacokinetic properties, dose-schedule

- Oxytetracycline
- Doxycycline
- Minocycline



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Demeclocycline	—Cl	—H	—H	35
Methacycline	—H	$=CH_2$*	—OH	31
Doxycycline	—H	$—CH_3$*	—OH	16
Minocycline	$—N(CH_3)_2$	—H	—H	10

*There is no — OH at position 6 on methacycline and doxycycline.

+ **tigecycline** (a glycylcycline, derivative of minocycline

TETRACYCLINES 2.

PHARMACOKINETICS

Absorption:

Oral bioavailability

good for doxycycline and minocycline

impaired by Ca, milk, diary-products, Mg, antacids, iron

Parenteral: doxycycline

Distribution

- Liver, kidney, spleen, skin
- Bone and teeth
- Body fluids
  - In CSF: only minocycline reaches therapeutic concentrations (even without inflammation)
- Fetus
- Entry to bacterial cells
  - passive diffusion
  - active, energy-dependent transport

Elimination

Liver → conjugation with glucuronic acid → excretion in the bile

Enterohepatic circulation

Excretion in the kidney (negligible for doxycycline)

Long half-life for doxycycline →once-daily dosing

TETRACYCLINES 3.

Mechanism

Bind to the 30S subunit of the ribosomes →
prevent the binding of aminoacyl-tRNA to the ribosome

Antibacterial spectrum

Broad
- Gram + and gram- bacteria
- Chlamydia
- Mycoplasms
- *Borellia burgdorferi* (Lyme-disease)
- *Vibrio cholerae*
- *Rickettsia*
- *Treponema pallidum*

Resistance
- Mechanism: active efflux, plasmid-mediated $_{TetA}$
- Wide-spread now, includes penicillinase-producing *Staphylococci*
- Cross-resistance among all tetracyclines

Adverse reactions
- Gastric discomfort, nausea, diarrhea
- Superinfection e.g. with *Candida*, resistant *staphylococci* or *Clostridium difficile*
- Deposition in bones and teeth
- Sensibilisation to UV rays → photosensitivity
- hepatotoxicity

Tigecycline 1.

- glycylcycline
  - derivative of minocycline
- broad spectrum
  - active against many tetracycline-resistant strains
    - MRSA / VISA / VRSA / VRE*
    - enterobacteriaceae / MDR *A. baumannii**
    - anaerobes
    - Chlamydia / Legionella / Rickettsiae
  - not active
    - *Proteus* / *Pseudomonas* / *Providencia*

*comparative clinical efficacy in MDR infections is not well established

Tigecycline 2.

- pharmacokinetics (PK)
  - A: iv only
  - D: excellent
    - all tissues and intracellular / bone, teeth / CSF
    - large V_d / low serum concentration*
  - E: mostly unchanged in bile*
    - dose adjustment in **renal** insufficiency: **NO**
    - dose adjustment in **hepatic** insufficiency: **YES**
    - long half life (≈ 40 hours)

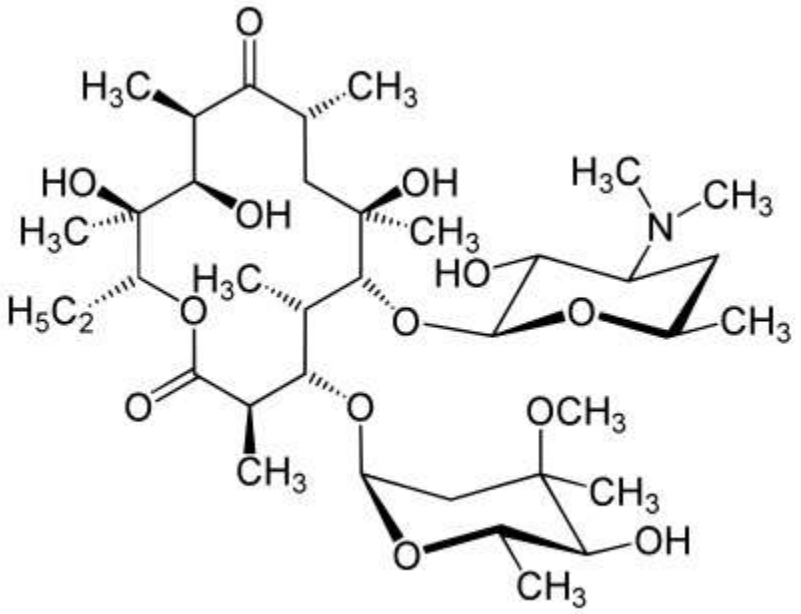
*may not be effective for urinary tract infections or primary bacteremia

Tigecycline 3.

- clinical indications
  - skin & soft tissue infections
  - abdominal infections
  - community acquired pneumonia
- adverse effects
  - nausea & vomiting (+class effects)
  - FDA: ↑ **risk of death** compared with other ABs
    - **reserved where no alternative**

MACROLIDES

- erythromycin
- roxithromycin
- clarithromycin
- azithromycin
- telithromycin (a ketolide)



Chemistry

Macrocyclic lactone + deoxysugars

Pharmacokinetics

Absorption

- oral
  - erythromycin is acid-labile → esters or enteric-coated tablets/granules
  - others: good oral bioavailability
- IV: azithromycin

Distribution

- widely to tissues but not to the CSF
- accumulation in the liver
- azithromycin: concentrated in phagocytes→large V_d, long half-life

MACROLIDES 2.

Elimination

- metabolism
  - erythromycin and telithromycin, CYP→drug interactions
  - clarithromycin→active metabolite (14-OH-derivative)
- excretion
  - erythromycin→mostly in the bile (active)
  - clarithromycin and its metabolites, azithromycine→bile and urine
- Half-life
  - Shorter→erythromycin→administration at 6 hours intervals
  - Longer→the others→administration twice daily
  - Even longer→azithromycin (2-4 days)→once daily, even single-high-dose
  - Telithromycin: once-daily dosing

Mechanism

- Bind to the 50S subunit
- Inhibit translocation and transpeptidation
- Bacteriostatic, but bactericidal at higher concentrations

MACROLIDES 3.

Spectrum

erythromycin: similar to penicillin-G

clarithromycin

- similar, but includes *Haemophilus influenzae*
- better activity against
- intracellular pathogens
    - *Chlamydia*
    - *Legionella*
    - *Moraxella*
- Helicobacter pylori

azithromycin → accumulation in phagocytes

- less active against streptococci and staphylococci
- better for respiratory-tract pathogens
    - H. influenzae
    - Moraxella catarrhalis
- preferred for *Chlamydia* infections

telithromycin

- similar to azithromycin but active against some macrolide-resistant bacteria

MACROLIDES 4.

Resistance: wide-spread

- lower concentration in the bacterial cell
  - efflux↑ or impaired penetration
  - esterase, plasmid-mediated
- decreased affinity of the target (complete cross resistance, MLS-B)

Adverse reactions

GI distress (erythromycin – motilin receptors)
Cholestatic jaundice (erythromycin, mainly for its estolate-derivative)
Ototoxicity (erythromycin)

Clindamycin 1.

- source
  - semisynthetic derivative of lincomycin
  - from *Streptomyces lincolnensis* (**a lincosamide**)
- pharmacokinetics (PK)
  - A: **oral and iv.** administration (3-4 times daily)
  - D: **no CNS** penetration, but well into abscesses
  - M: liver
    - active metabolites
  - E: urine and bile
    - parent and metabolites

Clindamycin 2.

- mechanism of action / resistance
  - **binding site identical with erythromycin** (50S)
    - cross resistance
    - e.g. MLS-type B (constitutive methylase production)
  - initiation complex / aminoacyl translocation
- antibacterial spectrum
  - **anaerobic**
  - Gram+ cocci **except Enterococci**
  - **NO Gram- aerobic**
- clinical use
  - **anaerobic infections**
  - skin and soft-tissue infections (streptococci and staphylococci, MRSA+)
  - endocarditis prophylaxis
    - e.g. in dentistry: valvular heart disease + penicillin allergy
- adverse effects
  - diarrhea (risk of pseudomembranous colitis)
  - skin rash

Streptogramins 1.

- source
  - quinupristin/dalfopristin (30:70)
  - semisynthetic derivatives of pristinamycins (from *Streptomyces pristinaespiralis)*
- pharmacokinetics (PK)
  - A: **only iv. infusion** (3 times daily)
  - D: $V_d \approx 1$ l/kg (short half life)
  - M: liver (phase II conjugation)
    - inhibitor of CYP3A4 → **interactions**
  - E: dominantly **biliary** (≈80%)

Streptogramins 2.

- mechanism of action / resistance
  - **quinupristin binding site is identical with erythromycin** (50S)
    - cross resistance
    - e.g. MLS-type B (constitutive methylase production)
  - initiation complex / aminoacyl translocation
  - dalfopristin enhances quinupristin binding → synergism → bactericidal
- antibacterial spectrum
  - **Gram+ cocci**
    - including: **multidrug resistant** streptococci, PRSP, MSSA, MRSA, *E. faecium* (but NOT *E. faecalis*)
  - generally no Gram- activity
- clinical use
  - **should be reserved for serious multi-drug ressitant Gram+ infections**
  - vancomycinR *E. faecium* caused infections
  - complicated skin infections
  - MRSA infections (e.g. nosocomial pneumonia)
- adverse effects
  - pain and phlebitis at the infusion site
  - arthralgia / myalgia

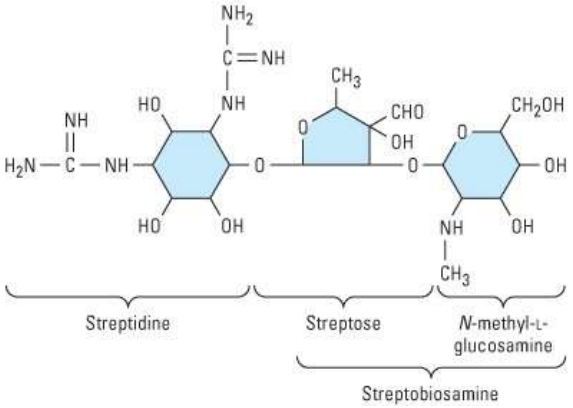
Linezolid 1.

- source
  - synthetic oxazolidinone
- pharmacokinetics (PK)
  - A: **oral** (100% bioavailability), twice daily
  - D: good
  - M: nonenzymatic oxidation
    - MAO inhibitor → risk of **serotonin syndrome** with SSRI
  - E: **renal** (≈80%) (30% active / 50% metabolites)
    - dose adjustment in renal insuff. is currently NOT recomm.

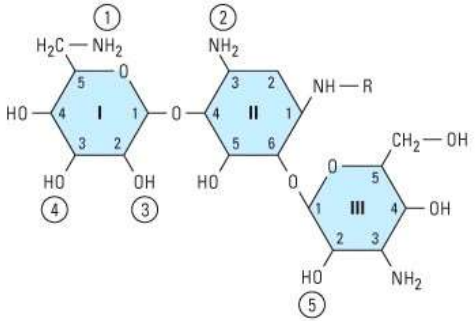
Linezolid 2.

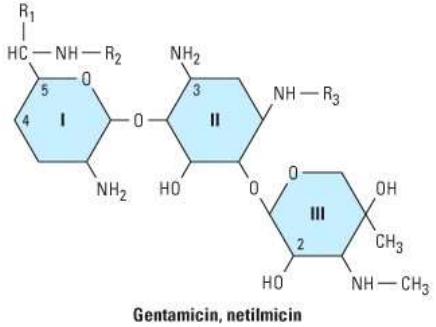
- mechanism of action / resistance
  - **unique binding site** (50S) → no cross resistance
  - prevents formation of the ribosome complex that initiates protein synthesis
  - resistance: mutation of binding site
- antibacterial spectrum
  - **Gram+ bacteriostatic** (except: streptocci bactericidal)
    - including: Gram+ rods (*L. monocytogenes*. *Corynebacterium spp.*)
  - *M. tuberculosis*
  - generally no Gram- activity
- clinical use
  - **should be reserved for serious multi-drug resistant Gram+ infections**
  - vancomycinR *E. faecium* caused infections
  - complicated skin infections
  - MRSA infections (e.g. nosocomial pneumonia)
- adverse effects
  - reversible thrombocytopenia (3%), myelosuppression
  - rare: neuropathy, lactic acidosis
    - perhaps related to inhibition of mitochondrial protein synthesis

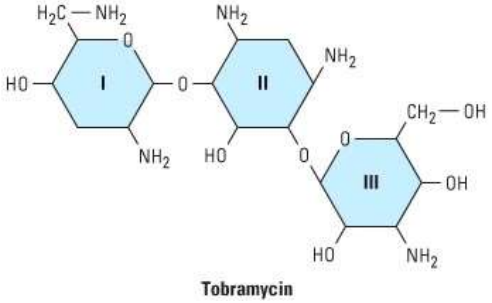
Aminoglycosides 1.



streptomycin







	Ring I			Ring II
	R_1	R_2	C4–C5 bond	R_3
Gentamicin C_1	CH_3	CH_3	Single	H
Gentamicin C_2	CH_3	H	Single	H
Gentamicin C_{1a}	H	H	Single	H
Netilmicin	H	H	Double	C_2H_5

Aminoglycosides 2.

- Pharmacokinetics
  - large polar compounds
    - no oral absorption
    - limited distribution
    - glomerular filtration
      - dose reduction in renal insufficiency
- Mechanism of action
  - bactericidal
    - 30S ribosomal subunit
    - block initiation complex
    - misreading
  - oxygen dependent active transport
  - synergism with cell wall synthesis inhibitors

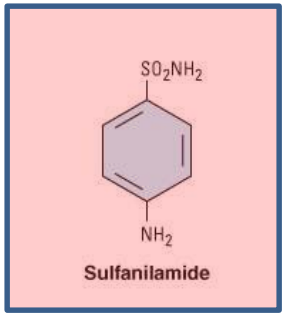
Aminoglycosides 3.

- Resistance
  - decreased penetration (e.g. streptococci, enterococci)
  - inactivating enzymes
    - acetylase / adenylase / phophorylase
    - different susceptibilities –> least: netilmicin
- Clinical uses
  - serious infections by aerobic G- rods
  - combination with β-lactams
  - streptomycin/amikacin: *M tuberculosis*
  - neomycin/kanamycin: topical or oral
  - netilmicin: in case of resistance
  - spectinomycin: single i.m. injection in gonorrhea
    - in β-lactam hypersensitivity

Aminoglycosides 4.

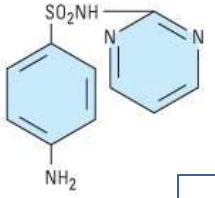
- Adverse effects
  - **ototoxicity**
    - may be irreversible
    - progressive destruction of sensory cells
    - loop diuretics may potentiate
    - monitoring
  - **nephrotoxicity**
    - neomycin, gentamicin, tobramycin
    - reversible
    - accumulation in the proximal tubular cells
    - time dependent
    - other nephrotoxic drugs may potentiate
  - neuromuscular blockade
    - calcium gluconate infusion may reverse
  - skin reactions – allergy / contact dermatitis (neomycin)

Sulfonamides & trimethoprim



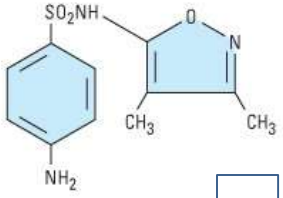
Sulfanilamide

p-Aminobenzoic acid (PABA)



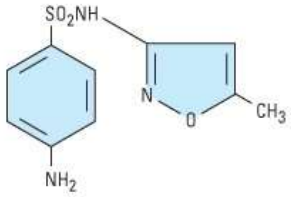
Sulfadiazine

I



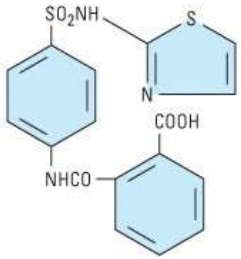
Sulfisoxazole

S



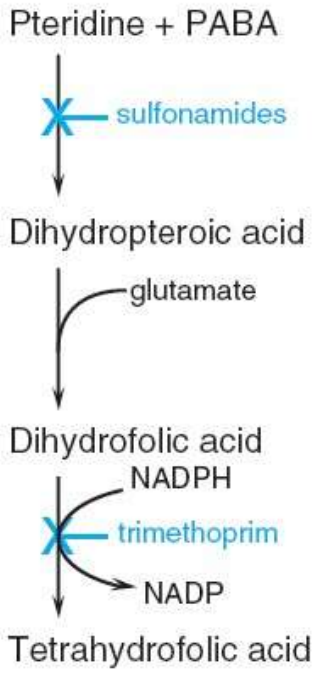
Sulfamethoxazole

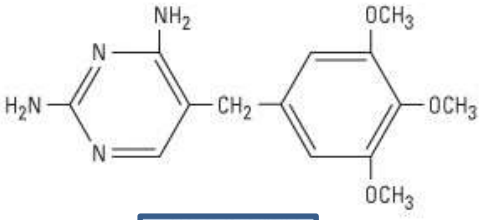
I



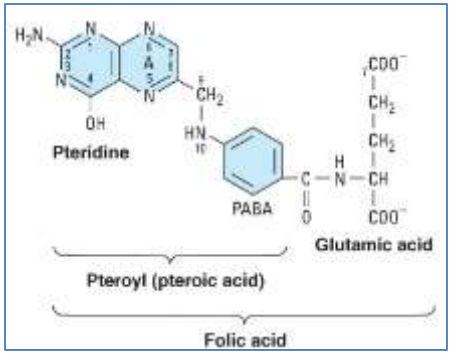
Sulfathalidine
(phthalylsulfathiazole)

+ sulfadoxine - L





Trimethoprim



sequential blockade

higher solubility at alkaline pH

topical: sulfacetamide, silver sulfadiazine

Sulfonamides & trimethoprim

Pharmacokinetics

- sulfonamides
  - for most: rapid and good GI absorption (but see sulfasalazine)
  - significant protein binding (albumin)
  - good distribution (CSF and placenta too)
  - liver metabolism
    - acetylation (not active but toxic)
  - mainly renal excretion
    - low solubility in acidic urine -> **crystalluria**
  - various duration of actions ($t_{1/2}$)
    - sulfisoxazole-5 h < sulfamethoxazole-11 h < sulfadoxine-7 d
- trimethoprim
  - weak base -> trapped in acidic environment
  - $t_{1/2}$: trimethoprim ≈ sulfamethoxazole

Sulfonamides & trimethoprim

- **Resistance**
  - common to sulfonamides and increasing for the combination
    - decreased intracellular accumulation
    - increased PABA production
    - lower affinity by the target enzyme
- **Clinical uses**
  - sulfonamides
    - simple UTI (frequent resistance, not recommended)
    - **topical**
      - ocular – *sulfacetamide*
      - prevention of burn infection – *silver sulfadiazine*
    - IBD – oral sulfasalazine
  - TMP-SMX (co-trimoxazole)
    - **UTI** (see prostatitis)
    - respiratory tract infections
    - *Pneumocystis jiroveci* pneumonia
    - has been used for MRSA infections
  - other combinations
    - **toxoplasmosis** (pyrimethamine + sulfadiazine)
    - **malaria** (pyrimethamine + sulfadoxine = Fansidar®)

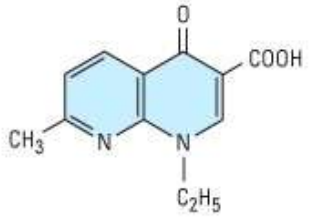
Sulfonamides & trimethoprim

Adverse effects

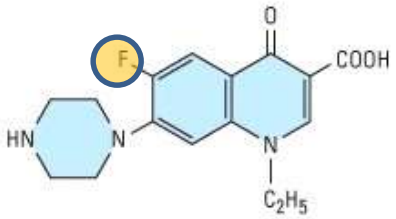
- hypersensitivity
  - common
  - skin rashes / exfoliative dermatitis / photosensitivity / fever
  - cross-allergenicity (oral antidiabetics / thiazides)
- gastrointestinal effects
- hematotoxicity
  - acute hemolytic anemia – G-6-PDH deficiency
  - rarely: agranulocytosis / aplastic anemia
    - usually spontaneous recovery with supportive care
- urinary tract disturbances
  - crystalluria / hematuria
- drug interactions
  - displace from plasma protein binding
    - warfarin / methotrexate / bilirubin (see kernicterus)

Quinolones, fluoroquinolones 1.

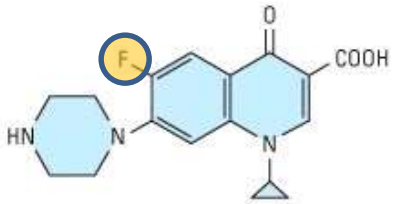
- 1st generation
  - norfloxacin
- 2nd generation
  - ciprofloxacin (G-)
  - ofloxacin
  - levofloxacin (G+)
  - pefloxacin
- 3rd generation (G+)
  - **moxifloxacin**
  - gemifloxacin



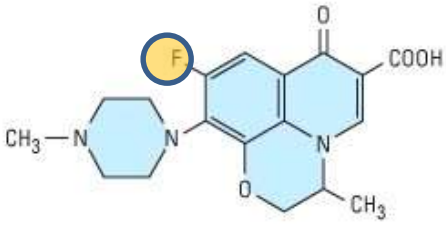
Nalidixic acid



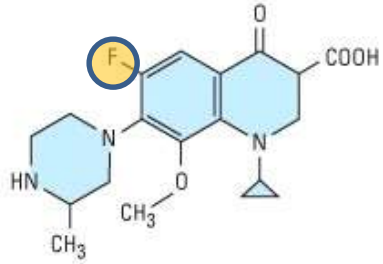
Norfloxacin



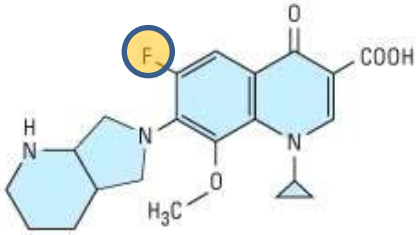
Ciprofloxacin



Levofloxacin



Gatifloxacin



Moxifloxacin

Quinolones, fluoroquinolones 2.

- **Pharmacokinetics**
  - good oral absorption (F ≈ 0.85-0.9)
    - impaired by di- and trivalent cations (e.g. antacids)
    - i.v.: ciprofloxacin / levofloxacin / moxifloxacin
  - wide distribution
    - BUT norfloxacin only urine
  - $t_{1/2}$: 3-10 hours (twice daily)
    - BUT once daily: levofloxacin, moxifloxacin
  - renal excretion for most
    - in part by tubular secretion – can be blocked by probenecid
    - exception: moxifloxacin
- **Mechanism of action**
  - DNA gyrase (topoisomerase II) and topoisomerase IV
    - topo II: relaxation of supercoiled DNA – Gram-
    - topo IV: separation of replicated chromosomal DNA – Gram+
  - bactericidal / AUC dependent killing (AUC/MIC)
  - postantibiotic effect

Quinolones, fluoroquinolones 3.

- **Antibacterial activity**
  - originally G- aerobic / but newer: improved G+ cocci
  - 2nd gen.: excellent G- / moderate G+
    - *E. coli / Enterobacter / Neisseria* (gonococcus too)
    - ciprofloxacin (*P. aeruginosa*)
  - 3rd gen.: significantly improved G+ / less G-
    - *Streptococci*: levofloxacin, moxifloxacin (PRSP too, "respiratory")
  - intracellular/atypical pathogens
    - *Chlamydia / Mycoplasma / Legionella / Mycobacterium*
- **Resistance**
  - increasing + generally cross resistance in the group
    - *Pseudomonas / Staphylococci / N gonorrhoeae / S pneumoniae*
  - decreased intracellular accumulation
    - decreased permeability
    - efflux: *M tuberculosis, S aureus, S pneumoniae*
  - **changes in target enzymes** (e.g. *gyrA* mutation in gonococci)
  - plasmid mediated
    - Qnr proteins – protect DNA gyrase
    - variant of aminoglycoside acetyltransferase – ciprofloxacin

Quinolones, fluoroquinolones 4.

- **Clinical uses**
  - urinary tract infections
    - BUT NOT moxifloxacin
  - bacterial diarrhea
    - *Shigella* / *Salmonella* / toxigenic *E. coli* / *Campylobacter*
  - osteomyelitis
    - in combination with rifampin - ↓ resistance development
  - anthrax - ciprofloxacin
  - respiratory tract infections
    - levo- and moxifloxacin
  - *N. gonorrhoea* now commonly resistant
    - cipro/levofloxacin is NOT recommended
    - BUT they active in chlamydial urethritis or cervicitis
  - tuberculosis / atypical mycobacterial infections
    - cipro- / levo-/ **moxifloxacin**
  - meningococci carrier eradication / prophylaxis

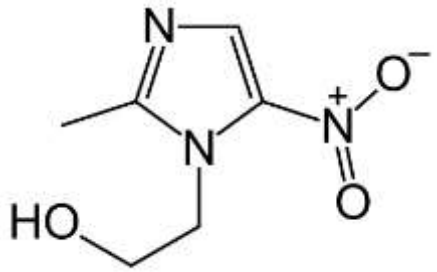
Quinolones, fluoroquinolones 5.

- **Adverse effects** – **overall they are well tolerated**
  - GI upset (most common)
    - nausea / vomiting / diarrhea
  - CNS
    - headache / dizziness / insomnia
  - skin
    - rash / photosensitivity
  - potential QT prolongation
    - levo- / gemi- / moxifloxacin
    - use with caution together with amiodarone
  - **damage to growing cartilage** -> arthropathy
    - NOT recommended under age of 18 / pregnancy
  - **tendinitis**
    - rare – can lead to tendon rupture

Other (primarily) antibacterial agents

- **metronidazole**
- urinary antiseptics
  - **nitrofurantoin**
  - methenamine mandelate / hippurate

Metronidazole



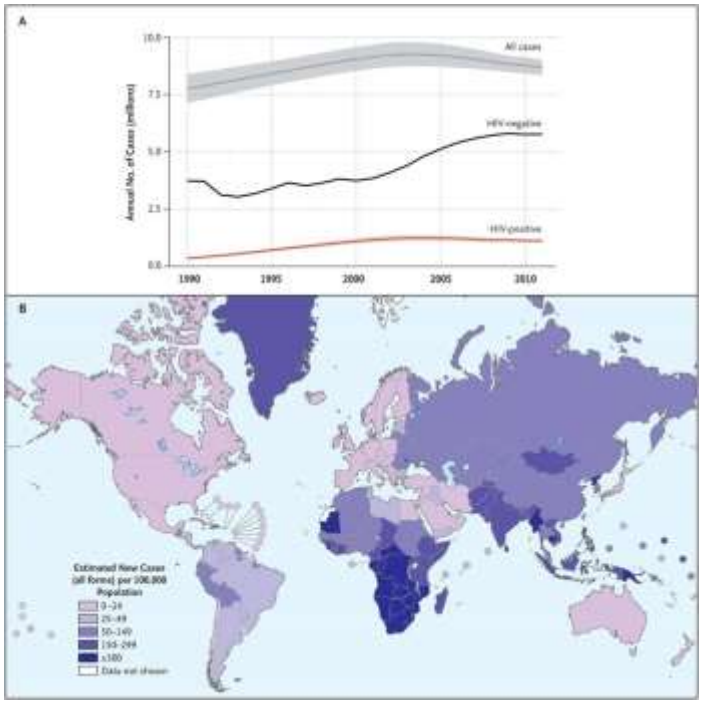
- a nitroimidazole (tinidazole is related)
- oral absorption / permeation with simple diffusion / liver metabolism
- active against **anaerobic** or microaerophilic pathogens
  - extraluminal amebiasis – together with a luminal agent
  - giardiasis – lower dose
  - trichomoniasis
  - various **anaerobic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

Nitrofurantoin

- **an important alternative oral agent for uncomplicated UTI**
- acts **only in urine** (only for cystitis, and NOT pyelonephritis)
- antibacterial effect is greater in **acidic urine**
- Proteus/Pseudomonas: NOT active
- reduced → reactive metabolites → DNA damage
- selectivity: reduction in bacteria is faster
- at lower concentration bacteriostatic / higher cc. bactericidal
- macrocristal form has longer half life – twice daily
- adverse effects – in case of ↓ renal function and long term admin.
  - **nausea, vomiting, diarrhea**
  - hypersensitivity: fever, leukopenia, cholestasis
  - liver damage
  - acute pneumonitis / subacute interstitial pulmonary fibrosis
  - neurological disturbances: polyneuropathies (most severe)

Antimycobacterial drugs 1.

- worldwide new active TB cases in 2011: 8.7 million
- “common” antibiotics are not active
  - slow growth
  - intracellular
  - low penetration ← special cell wall
- drug combinations
  - two, three (or four) drugs
    - → adverse effects and interactions
- long term treatment
  - month / years
- resistance is increasing
  - multi-drug resistance
  - initially four drug combinations



Antimycobacterial drugs 2.

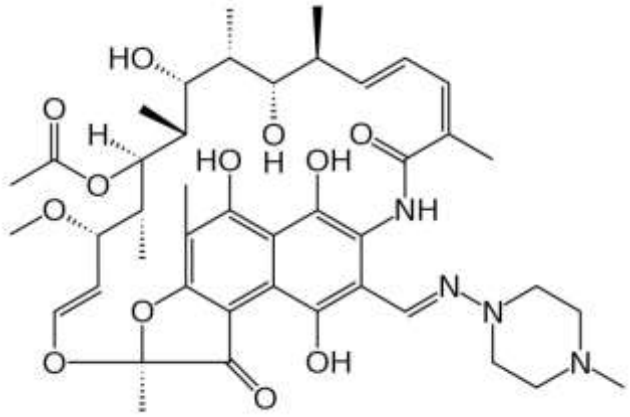
- **First line drugs**
  - **isoniazid (INH)**
  - **rifampin**
  - **pyrazinamide**
  - ethambutol

- *Alternative drugs*
  - ethionamide
  - capreomycin
  - aminoglycosides
    - streptomycin, amikacin
  - **fluoroquinolones**
    - moxifloxacin, levofloxacin
  - oxazolidinones
    - linezolid, tedizolid, sutezolid
  - cycloserine
  - aminosalicylic acid (PAS)
  - rifabutin / rifapentine

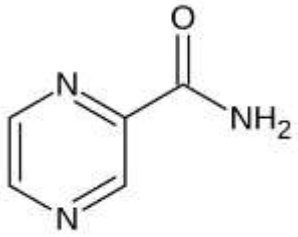
- **combinations**
- **long term therapy**
  - isoniazid + rifampin (for 9 months)
  - isoniazid + rifampin + pyrazinamide (for 6 months)

Antimycobacterial drugs 3.

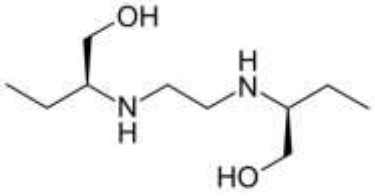
isoniazid



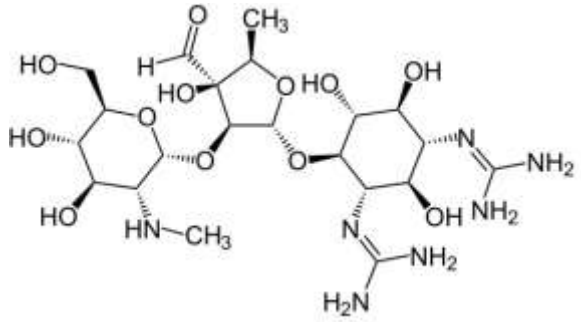
rifampin



pyrazinamide



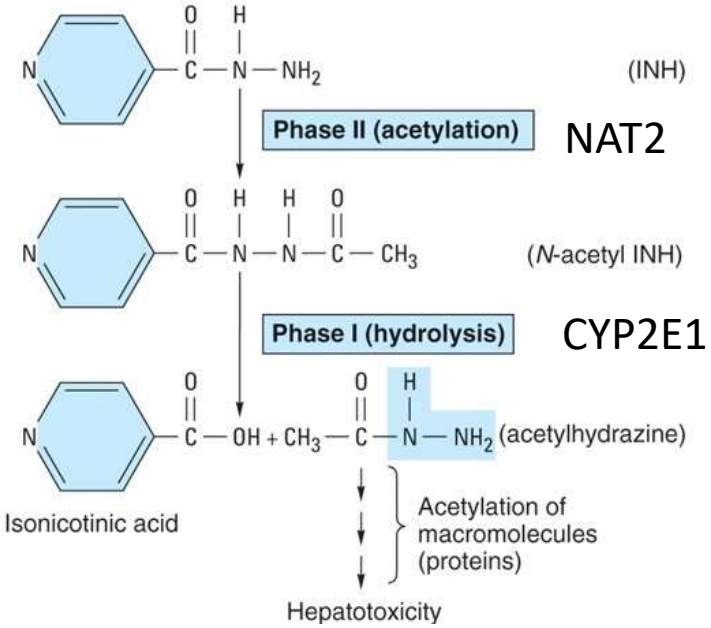
ethambutol



streptomycin

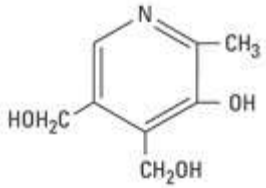
Isoniazid (INH)

- most active
- small moluecule – similar to pyridoxine
- prodrug – activated by mycobacterial catalase-peroxidase
- inhibits mycolic acid synthesis
- **oral**, iv.
- metabolism in liver
  - N-acetyltransferase ⟶ hydrolysis
  - genetic polymorphism (slow and fast acetylators)



NAT2 can detoxify acetylhydrazine

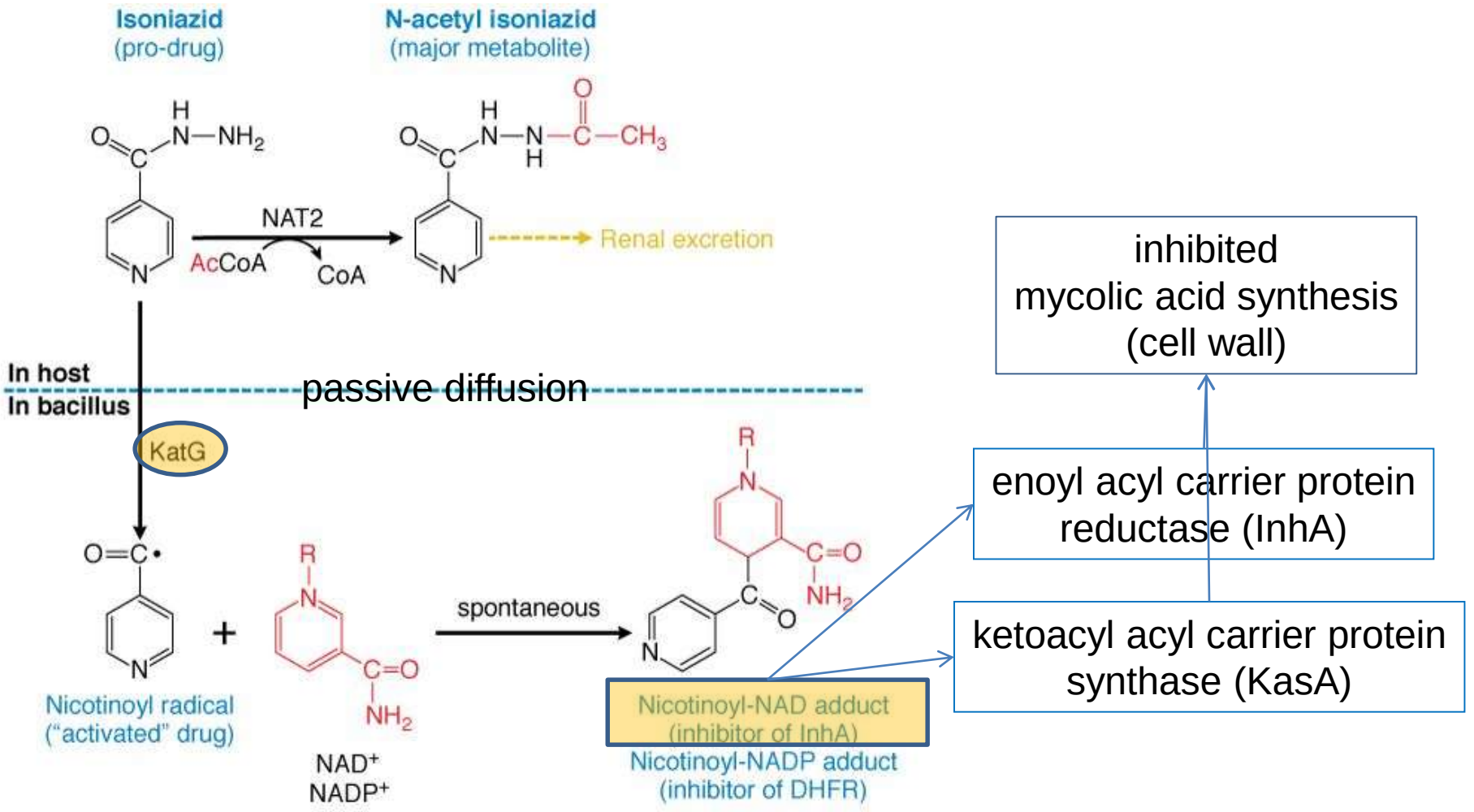
Isoniazid



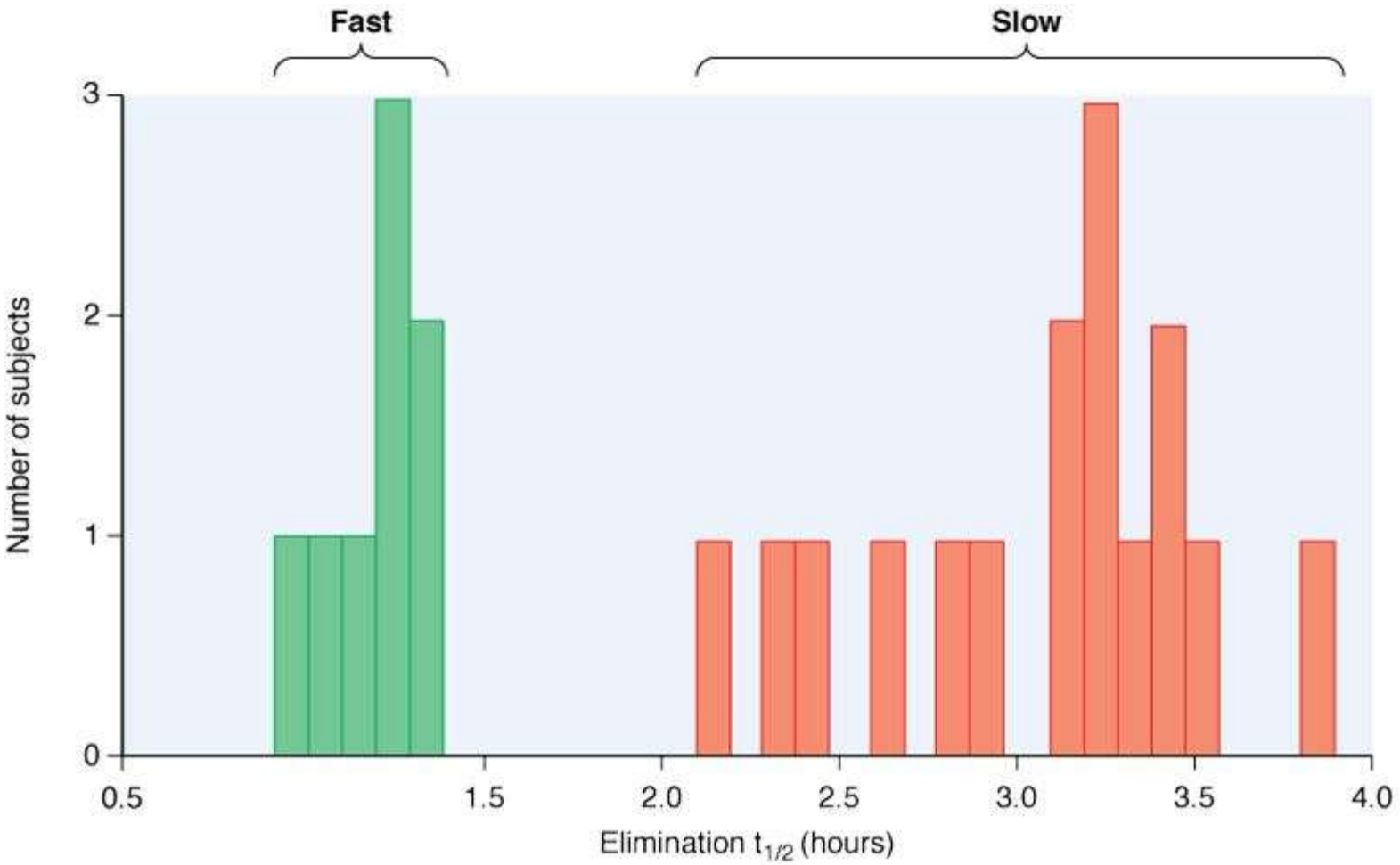
Pyridoxine

- **hepatitis** (~1%)
  - loss of appetite / jaundice / pain
  - age dependent (↑)
- **peripheral neuropathy** (slow acetyl.)
- CNS toxicity (memory loss, psychosis)
- fever / skin rash / SLE

Mechanism of action of isoniazid (INH)



Genetic polymorphism in NAT2



in slow acetylators: higher risk of neuropathy / hepatitis (esp. if CYP2E1 is induced)

Rifampin

- **inhibits** DNA dependent **RNA polymerase**
- acceptable **oral** absorption / distribution
  - intracellular too, but no CNS
- biliary excretion → enterohepatic circulation
- adverse effects
  - **orange colored metabolites** / rash / nausea
  - hepatitis / cholestasis
  - flu-like syndrome (with rare intermittent dosing)
  - thrombocytopenia / light-chain proteinuria
  - nephritis / acute tubular necrosis
- strong **liver enzyme inducer** (compare with rifabutin)
- no cross resistance with other classes
- indicated in:
  - tuberculosis
  - meningococcal carrier state (but see ciprofloxacin)

Pyrazinamide

- important **oral** first line drug in comb. with INH and rifampin
  - used during first 2 months (duration decreased from 9 to 6 months)
- **mechanism unknown**
  - active **only at acidic pH** (at the edges of necrotic TB cavities ?)
  - **requires activation** by pyrazinamidase (inside mycobacteria to pyrazinoic acid)
- pharmacokinetics
  - **oral** absorption (fast and slow absorbers)
  - concentrated 20-fold in lung epithelial lining fluid
  - **significant individual variation** of CL and V_d
    - increased with patient mass; V_d is larger in males
  - **renal excretion** of metabolites
    - decrease dose in renal insuff.
- adverse effects
  - **hepatotoxicity** (dose related, assess hepatic function)
  - hyperuricemia / nausea, vomiting / drug fever

Ethambutol

- first line **oral** agent
- **blocks arabinosyl transferase**s
  - arabinoglycan polym. block → **cell wall synthesis** block
- PK
  - special in children
    - unreliable absorption and increased CL and V_d
  - primarily **renal excretion** (≈80% in unchanged form)
- adverse effects
  - dose dependent retrobulbar neuritis
    - → **visual disturbances** (visual acuity, color blindness)
    - **periodic testing of visual acuity** and red-green discrimination is needed
  - increased urate cc. in blood

Streptomycin

- the protoype aminoglycoside
- used mainly in tuberculosis but only in combination
  - for other bacteria: frequent resistance
  - but in *Enterococci* sometimes no cross resistance with gentamicin
- **im. or iv.** administration
- toxicity is significant
  - dose related irreversible **vestibular toxicity** (deafness in newborns)
  - **nephrotoxicity**

Mechanism of action of first line drugs

drug	mechanism of action
isoniazid	inhibits **mycolic acid synthesis** (cell wall)
rifampin	inhibits DNA dependent **RNA polymerase**
ethambutol	blocks **arabinosyl transferase**s (cell wall)
pyrazinamide	unclear
(streptomycin)	inhibits protein synthesis (30S, misreading)

Severe or common toxicities of first line drugs

drug	adverse effect
isoniazid	• *hepatotoxicity* risk increases with age (~2% with age > 50y), liver disease, other hepatotoxic drugs • *rash* (2%) • peripheral neuropathy
rifampin	• *rash* • nausea, vomiting • ↑risk of *hepatotoxicity* with INH • flu-like syndrome if given < twice weekly
ethambutol	• retrobulbar neuritis (<1%) • hyperuricemia
pyrazinamide	• *hepatotoxicity* • hyperuricemia • *rash*
(streptomycin)	• ototoxicity • nephrotoxicity

Alternative drugs 1.

- are used
  - in case of **resistance**
  - in case of **failure of clinical response**
  - in case of **serious adverse effects**
  - and only when expert guidance is available
    - **to deal with the toxic effects**

Alternative drugs 2.

- **ethionamide**
  - **oral / related to INH**
    - inhibits mycolic acid synthesis (same enzyme)
    - activated by a mycobacterial monooxygenase (EthaA)
  - low-level cross resistance with INH
    - target mutations (inhA)
  - adverse effects
    - dose related GI upset / also **hepatotoxic**
    - neurologic symptoms
- **capreomycin**
  - cyclic peptide protein synthesis inhibitor
  - **intramuscular** for multidrug resistant TB
  - nephrotoxic and **ototoxic**

Alternative drugs 3.

- **amikacin**
  - an aminoglycoside
  - no cross resistance with streptomycin
  - used in **multidrug-resistant tuberculosis**
  - administered in iv. infusion
- **fluoroquinolones**
  - levofloxacin and moxifloxacin
  - also active against atypical mycobacteria
  - *important drugs in case of resistance*
  - used only in combination
  - under investigation as first line (moxifloxacin)

Alternative drugs 4.

- **bedaquiline**
  - mechanism: new
    - inhibits ATP synthase in mycobacteria
    - bactericidal / no cross-resistance
  - PK
    - oral absorption is increased by fatty food
    - CYP3A4 metabolism → interactions
    - large V_d, poor CNS, **very long half life** (5 months)
  - clinical use
    - in case of INH and rifampin resistance (MDR-TB)
    - combined with other three active drugs
  - adverse effects
    - GI: nausea, diarrhea
    - arthralgia
    - **cardiac toxicity** (QTc interval prolongation) / **death** ?

Alternative drugs 5.

- **linezolid**
  - a synthetic oxazolidinone inhibitor of protein synthesis
  - in combination in **multidrug-resistant tuberculosis**
  - prolonged courses → **adverse effects** → lower dose
    - *bone marrow suppression*
    - *neuropathy*
  - risk of *serotonin syndrome*
- **rifabutin** and **rifapentin**
  - rifampin analogs
  - antituberculotic activity similar, cross resistance
  - **rifabutin is less potent inducer** of cP450 → used in HIV-infected patients → complex interactions
  - rifabutin in AIDS patients for prevention too
  - **rifapentin** – $t_{1/2}$≈13h**, once weekly** after 2 months (in continuation phase)
    - since 2016 not recommended

Alternative drugs 6.

- **cycloserine**
  - **orally used cell wall** synthesis inhibitor (analog of D-alanine)
  - frequent CNS adverse effects (**“psycho-serine”**)
  - peripheral neuropathy
  - **pyridoxine** co-administration is useful
- aminosalicylic acid (PAS)
  - similar to PABA and sulfonamides
  - antagonize folate synthesis
  - used rarely **orally** in high dose (8-12 g/day)
  - other drugs are better tolerated
  - crystalluria, GI adv. effects, **ulcer** / **hypersensitivity**

Drug development against tuberculosis

CANDIDATE TUBERCULOSIS DRUGS IN CLINICAL TRIALS

CLASS	DRUG	TRIAL PHASE	DEVELOPER	MECHANISM OF ACTION	COMMENTS
Fluoroquinolone	Moxifloxacin	3	Bayer/GATB	-Inhibition of Topoisomerase IV and DNA gyrase	- Q-T interval prolongation: avoid use with long Q-T syndrome and caution when using with other drugs prolonging Q-T - Optimal doses not established - Gatifloxacin: More frequent dysglycemia; Not commercially available at present - Phase III trials to reduce treatment to 4 months: - Gatifloxacin (Oflotub III trial)– results available mid-2013 - Moxifloxacin – REMox trial to be completed late 2014
	Gatifloxacin	3	WHO		
	Levofloxacin	2	Janssen; generics now available		
Nitroimidazole	Delamanid (OPC-67683)	3	Otsuka	-For replicating *M.tb* bacilli - inhibition of mycolic acid synthesis -For non-replicating *M.tb* bacilli - generation of highly reactive nitrogen radicals	- Q-T interval prolongation - Mild antagonism with bedaquiline, probably has no substantial effect on sterilizing activity of combination use - Delamanid - NDA for accelerated approval has been filed with EMA; Phase III trial initiated - Phase IIB trial of PA-824 in combination with Pza and Mfx initiated
	PA-824	2	GATB		
Diarylquinoline	Bedaquiline (TMC-207)	2	Janssen	-Inhibition of ATP synthase	- Q-T interval prolongation - Metabolized by CYP3A4: with rifampin, AUC decreases by at least 50% - Excellent sterilizing activity and remarkable synergy with PZA - Prolonged tissue concentrations - Accelerated approval granted recently by the US Food and Drug Administration (FDA) for the treatment of multi-drug resistant tuberculosis. Phase III trial to begin mid-2013
Oxazolidinone*	Sutezolid (PNU 100480)	2	Pfizer	-Inhibition of translation by binding at the "A" site of peptidyl transferase center	- Whether hematologic and neurologic toxicity will be decreased vs. Linezolid is unknown - Appear to have good sterilizing activity - High barrier to development of resistance - Sutezolid Phase IIA (EBA) trial completed - AZD Phase IIA (EBA) trial now underway
	AZD 5847	2	Astra Zeneca		
Ethylenediamine	SQ109	2	Sequella	-Inhibition of MmpL3 transporter of trehalose mycolate across cell membrane for incorporation into cell wall	- Phase 2b MAMS trial will evaluate four new treatment regimens including SQ109, an increased dose of Rif, and Mfx, in early 2013 - Appears to have high barrier to development of resistance

* Two other oxazoldinones now in late clinical trials for other indications have substantial activity against *Mycobacterium tuberculosis*: Tedazolid (Trius) and Radezolid (Rib-X)

EBA = Early bactericidal activity. GATB = The Global Alliance for Tuberculosis Drug Development

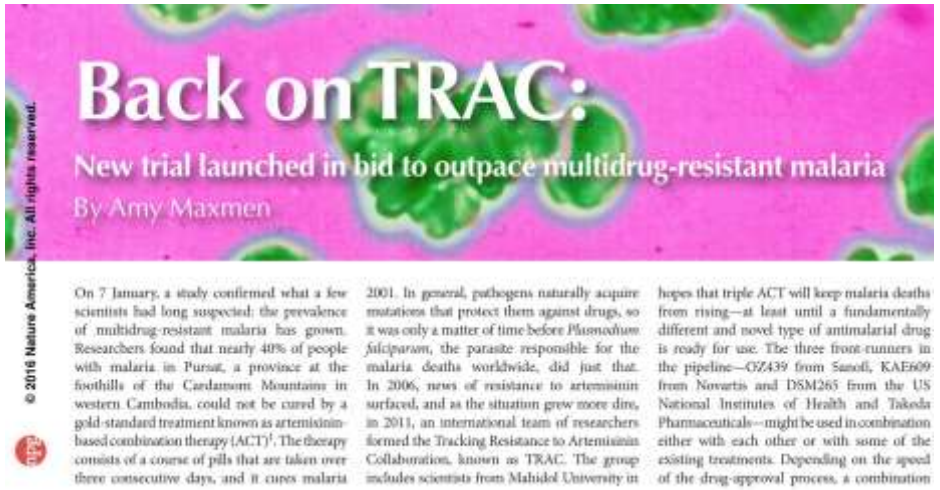
Singnificance of resistance (2016)

Comment

Colistin resistance: a major breach in our last line of defence

In hospital practice, clinicians have been buoyed by the recent development of new antibiotics active against multidrug resistant Gram-negative bacilli. However, recently approved antibiotics like ceftazidime-avibactam or ceftolozane-tazobactam do not provide activity against all Gram-negative bacilli, with notable gaps in their coverage, including the notorious New Delhi metallo-β-lactamase 1-producing organisms and many strains of carbapenem resistant *Acinetobacter baumannii*. For this reason, the polymyxins (colistin and polymyxin B) remain the last line of defence against many Gram-negative bacilli. Colistin-resistant and even pan-drug-resistant Gram-negative bacilli have already been reported.[1,2] Typically, colistin resistance is due to chromosomally mediated modulation

Liu and colleagues[3] present data from China showing that *E coli* from pigs at slaughter and from retail chicken and pork have high rates of plasmid-mediated colistin resistance. The same mechanism was found in *E coli* and *K pneumoniae* isolates from Chinese patients in hospital. These findings suggest that the links between agricultural use of colistin, colistin resistance in slaughtered animals, colistin resistance in food, and colistin resistance in human beings are now complete. One of the few solutions to uncoupling these connections is limitation or cessation of colistin use in agriculture. This will require substantial political will and we call upon Chinese leaders to act rapidly and decisively. Failure to do so will create a public health problem of major dimensions.



Back on TRAC:

New trial launched in bid to outpace multidrug-resistant malaria

By Amy Maxmen

On 7 January, a study confirmed what a few scientists had long suspected: the prevalence of multidrug-resistant malaria has grown. Researchers found that nearly 40% of people with malaria in Pursat, a province at the foothills of the Cardamom Mountains in western Cambodia, could not be cured by a gold-standard treatment known as artemisinin-based combination therapy (ACT)[1]. The therapy consists of a course of pills that are taken over three consecutive days, and it cures malaria

2001. In general, pathogens naturally acquire mutations that protect them against drugs, so it was only a matter of time before *Plasmodium falciparum*, the parasite responsible for the malaria deaths worldwide, did just that. In 2006, news of resistance to artemisinin surfaced, and as the situation grew more dire, in 2011, an international team of researchers formed the Tracking Resistance to Artemisinin Collaboration, known as TRAC. The group includes scientists from Mahidol University in

hopes that triple ACT will keep malaria deaths from rising—at least until a fundamentally different and novel type of antimalarial drug is ready for use. The three front-runners in the pipeline—OZ439 from Sanofi, KAE609 from Novartis and DSM265 from the US National Institutes of Health and Takeda Pharmaceuticals—might be used in combination either with each other or with some of the existing treatments. Depending on the speed of the drug-approval process, a combination

"**plasmid-mediated colistin resistance** for the first time"
"**readily passed** between Escherichia coli strains"
"the plasmid could be passed to *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* strains"

"It therefore seems inevitable that plasmid-mediated transfer of colistin resistance **will seriously limit the lifespan of the polymyxins** as the backbone of regimens against multiply resistant Gram-negative bacilli."

"On 7 January, a study confirmed what a few scientists had long suspected: the prevalence of **multidrug-resistant malaria** has grown. Researchers found that nearly **40% of people with malaria** in Pursat, a province at the foothills of the Cardamom Mountains in western Cambodia, **could not be cured by a gold-standard treatment** known as artemisinin-based combination therapy."

Potential new antibiotics

- β-lactamase inhibitors
  - ESBL, KPC, AmpC
    - imipenem/cilastatin-relebactam
    - meropenem-vaborbactam
    - see also ceftazidime/avibactam, ceftolozane/tazobactam
- eravacycline
  - tigecycline analog / maybe better
- cefiderocol
  - siderophore cephalosporine
    - binds Fe^{3+} → active transport via Fe^{3+} transporter
    - active against carbapenemase producing strains