CLINICAL PHARMACOLOGY OF ANTIBIOTICS AND ANTIMICROBIEN CHEMOTHERAPEUTIC DRUGS WITH DIVERS CHEMICAL STRUCTURE

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WHY IS THIS IMPORTANT?

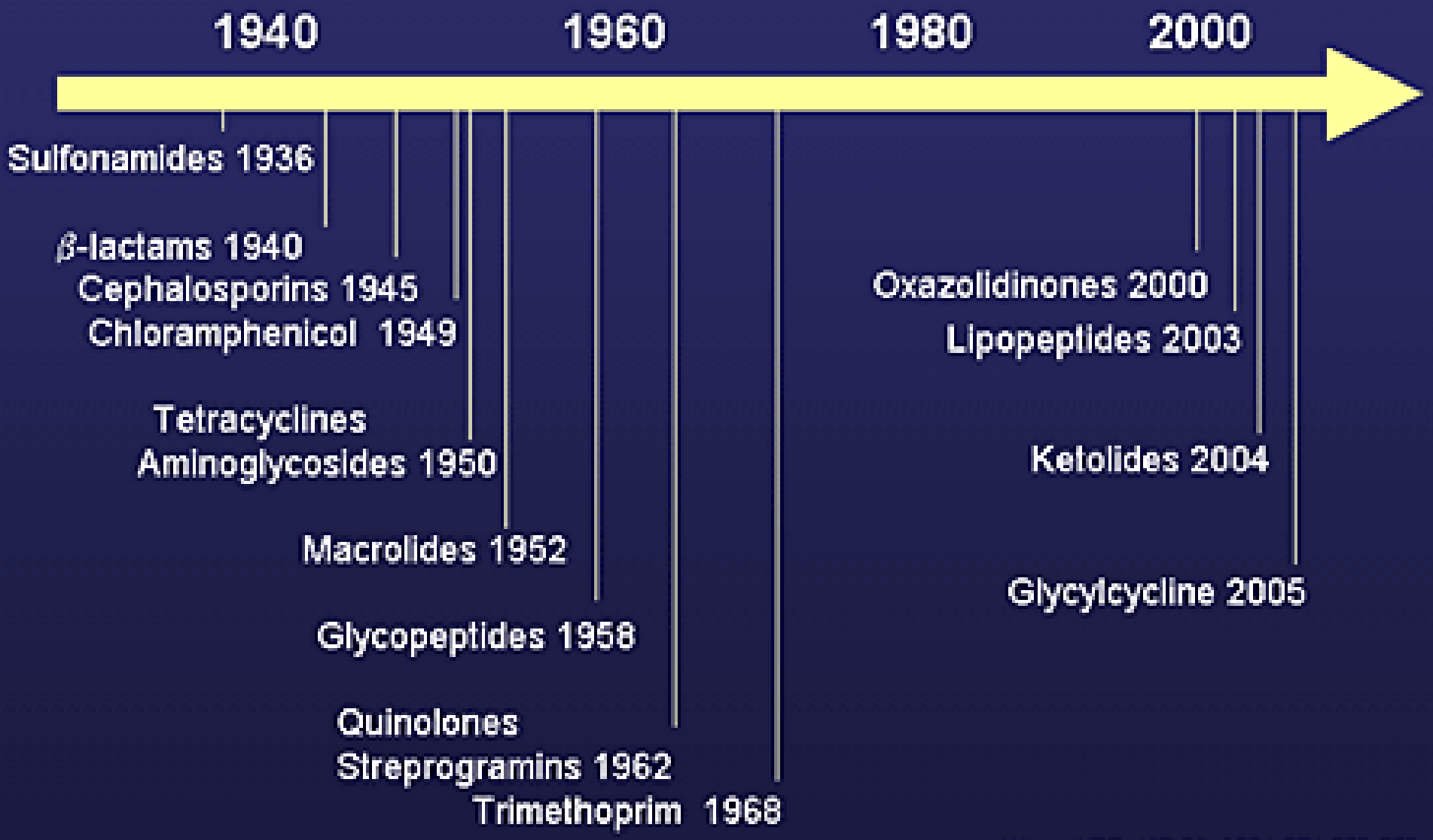
- Antibiotics have drastically reduced the number of deaths due to infection.
- They have changed the face of health care.

HISTORICAL PERSPECTIVES

- The German chemist Paul Ehrlich developed the idea of selective toxicity: that certain chemicals that would be toxic to some organisms, e.g., infectious bacteria, would be harmless to other organisms, e.g., humans.
- In 1928, Sir Alexander Fleming, a Scottish biologist, observed that *Penicillium notatum,* a common mold, had destroyed staphylococcus bacteria in culture.

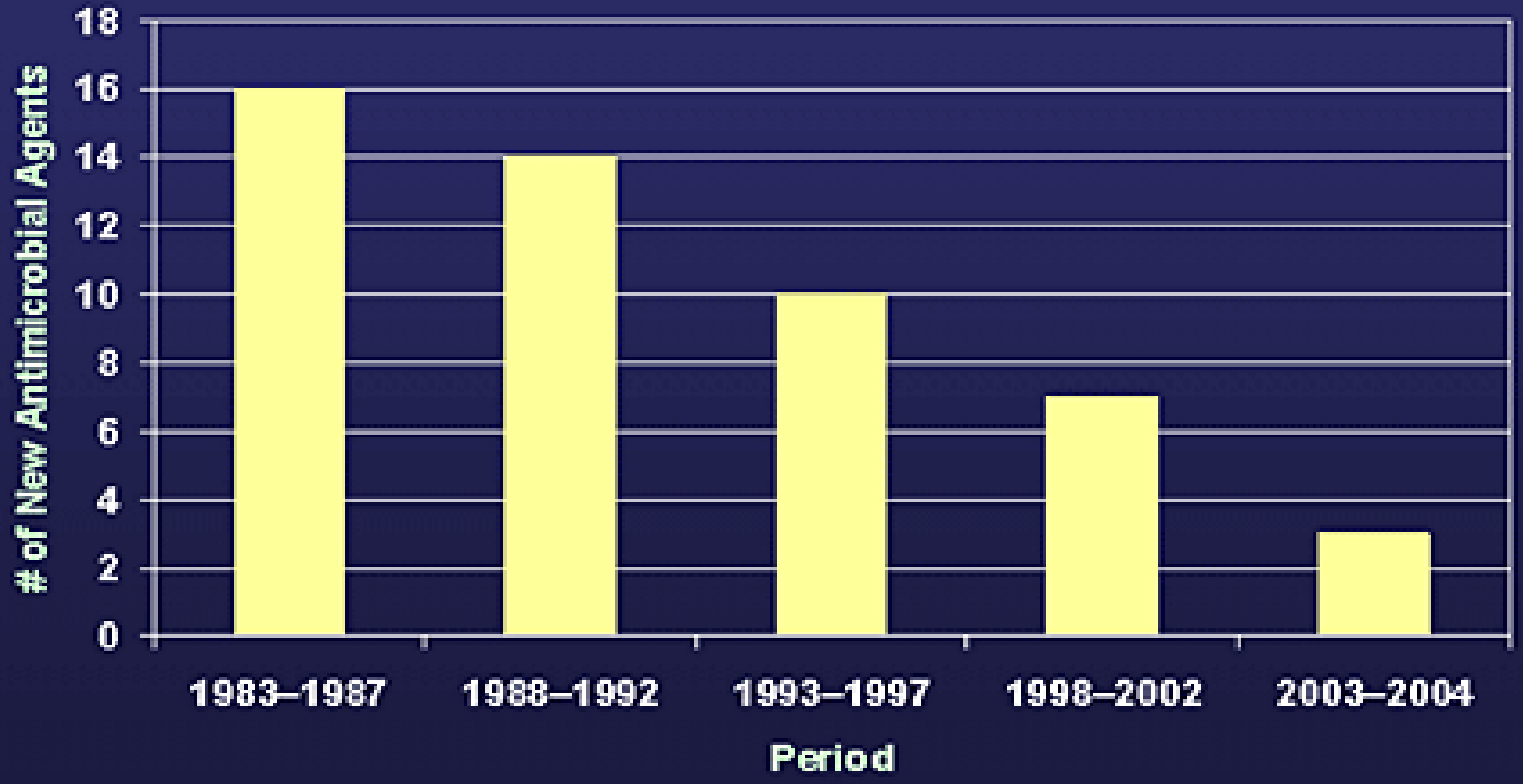
Sir Alexander Fleming

Introduction of New Classes of Antimicrobials

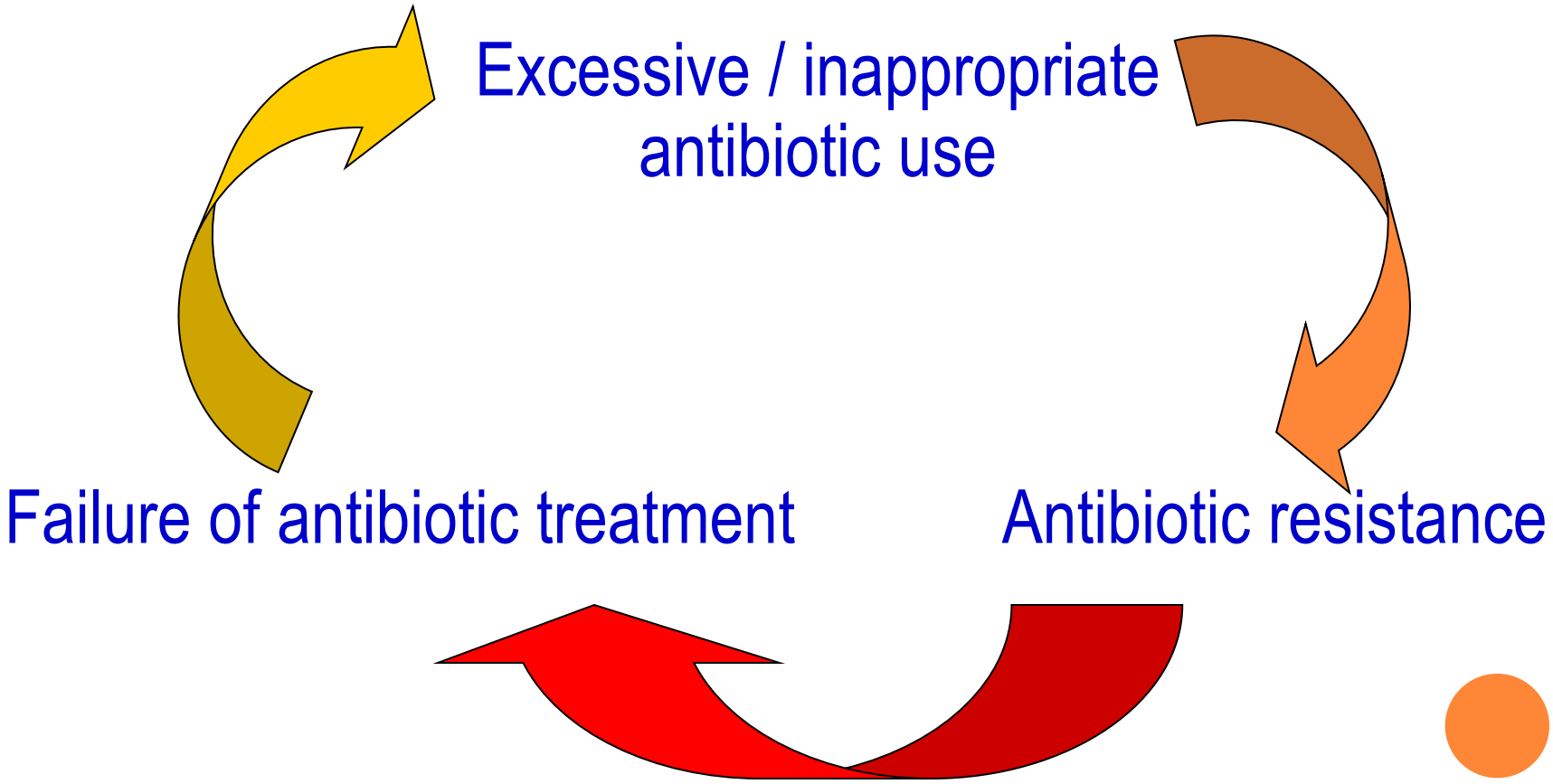


Wenzel RP. *NEJM*. 2004;351:523-526.

New Antimicrobial Agents



Spellberg B, et al. *CID*. 2004;38:1279–1286 (modified).


Excessive / inappropriate antibiotic use
Antibiotic resistance
Failure of antibiotic treatment

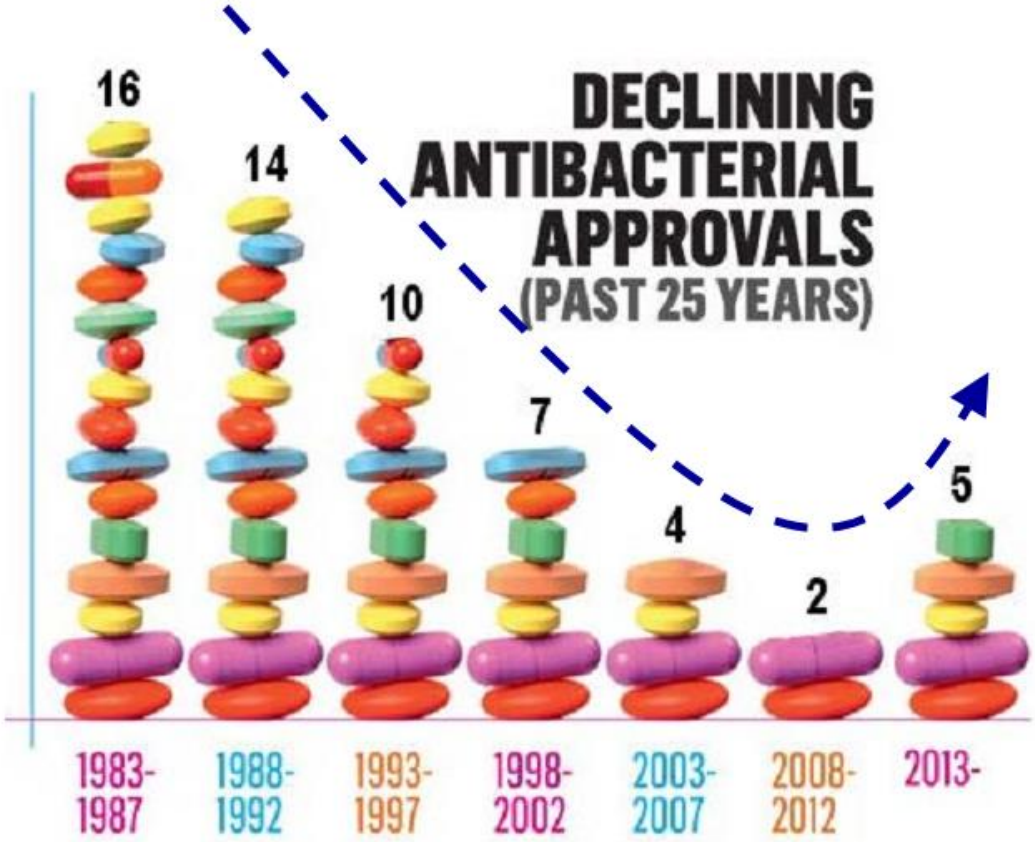
PROBLEMS

- Antimicrobial resistance.
- Adverse drug reactions and medication errors.
- Lost resources.
- Eroded patient confidence.

…HISTORICAL PERSPECTIVES

- No major discoveries of natural antibiotic substances have occurred for several years.
  - Efforts have now shifted to modifying existing antibiotics.
  - Searching in new places for potential antibiotics has also gained in prominence.
- Many antibiotics are produced by microorganisms as part of their survival mechanism.
  - They keep other organisms away.
  - They protect the supply of nutrients and oxygen.

Approvals by FDA/EMA – systemic antibiotics



- dalbavancin
- oritavancin
- tedizolid
- ceftazidime/avibactam
- ceftolozane/tazobactam

- telavancin
- ceftaroline

Classification of antibiotics

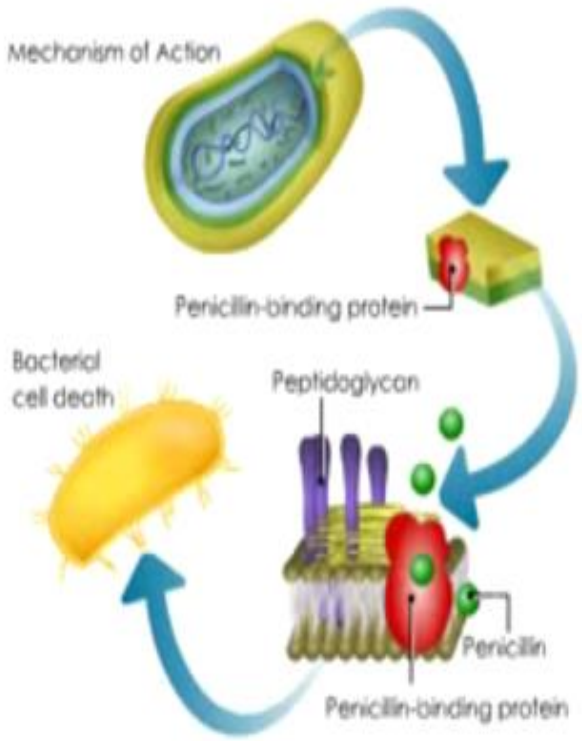
Based on their mechanism of action, antibiotics can be divided into the following classes:

- Inhibitors of Cell Wall synthesis
- Inhibitors of Protein synthesis
- Inhibitors of Nucleic Acid synthesis
- Affecting the permeability of the cell membrane.

Inhibitors of Cell Wall Synthesis

This class includes:

- Penicillins
- Cephalosporins
- Carbapenems
- Monobactams
- Vancomycin
- Beta lactamase inhibitors



Beta Lactams

- **Penicillins:**

a. Narrow spectrum (natural) : benzylpenicillin, phenoxymethylpenicillin
b. Antistaphylococcal: Cloxacillin, flucloxacillin
c. Broad spectrum: Ampicillin, amoxicillin
d. Mecillinam: pivmecillinam
e. Monobactam: Aztreonam
f. Antipseudomonal: Piperacillin, ticarcillin
g. Carbapenems: Meropenem, Imipenem-cilastatin
h. Penicillin-beta lactamase inhibitor combinations: co-amoxiclav, piperacillin-tazobactam

Cephalosporinele

Class	Examples	Routes of administration
First generation	Cefalexin Cefazolin	Oral i.v.
Second generation	Cefuroxime Cefoxitin	Oral/ i.v.
Third generation	Cefixime Ceftriaxone Ceftazidime	Oral i.v. i.v.
Fourth generation	Cefipime	i.v.

Cephalosporine generația a V-a

Ceftobiprol
Ceftarolin fosamil
Cefditoren

Inhibitors of Protein synthesis

This class includes:

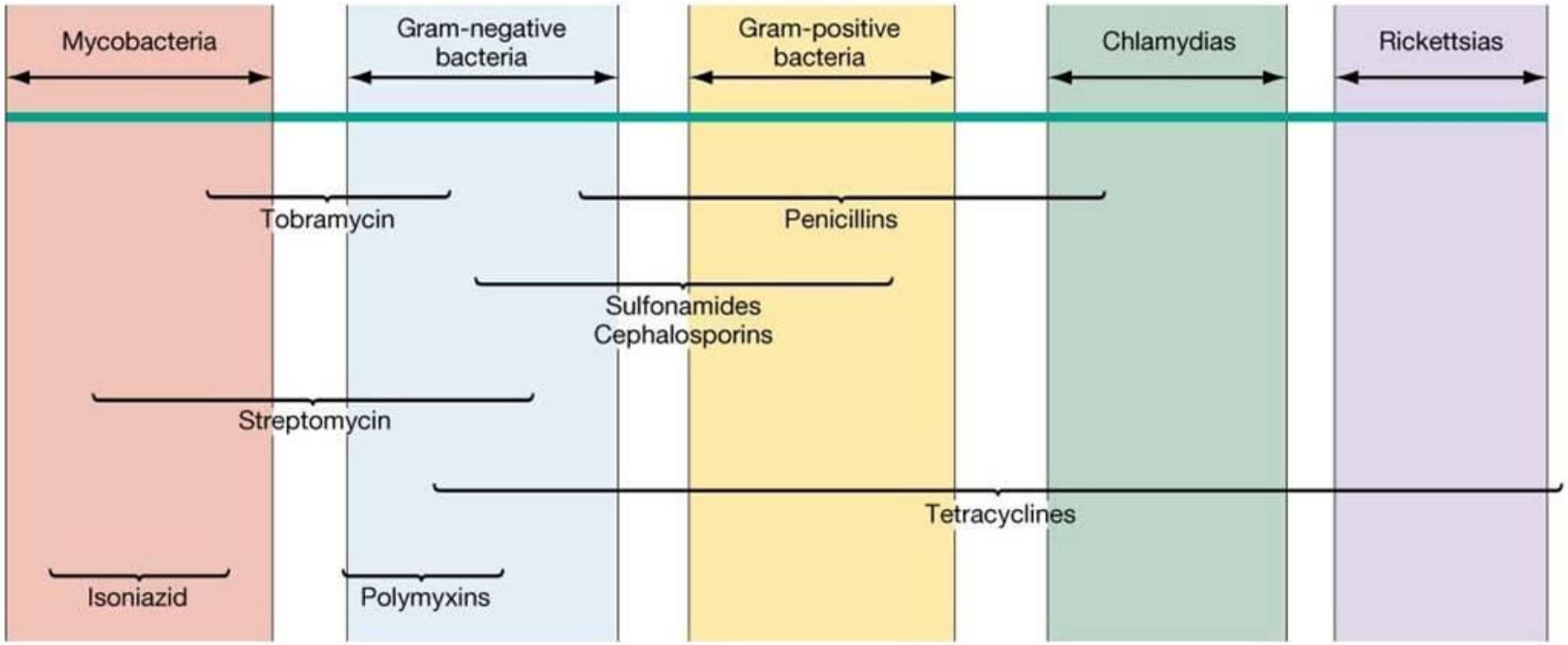
- **Macrolides-** erythromycin, clarithromycin, azithromycin
- **Lincosamides-** clindamycin
- **Aminoglycosides-** gentamicin, tobramycin, amikacin, netilmicin,neomycin, streptomycin,spectinomycin
- **Tetracyclines-** tetracycline, doxycycline,minocycline
- **Chloramphenicol**

Inhibitors of Nucleic Acid synthesis

This group includes:

- Sulphonamides: Sulfamethoxazole, sulfadoxine
- Trimethoprim
- Quinolones: Ciprofloxacin, levofloxacin, pefloxacin, ofloxacin, norfloxacin, gatifloxacin, moxifloxacin, sparfloxacin
- Rifampicin
- Azoles: This group includes-
- Antibacterial- Metronidazole, secnidazole, tinidazole,
- Antifungal- Ketoconazole, fluconazole, Isoconazole, Itraconazole, Clotrimazole
- Antihelminth- Albendazole, Mebendazole, thiabendazole

Spectrum of action of AB



With a predominant influence on the gram-positive flora

- Penicilinele biosintetice; - izoxazolilpenicilinele;
- macrolidele; - azalidele; - lincosamidele;
- glicopeptidele; - fuzidina; - cefalosporinele I gen.;

Cocii gram+: stafilococi; streptococi; enterococi; peptostreptococi; peptococi.

Cocii gram-: neiseria (gonococi; meningococi)

Bacilii gram+: bac.antracis; Clostridium perfrigens, Clostridum tetani; Clostridum dificile; Corinebacterium diphtheriae; Listeria monocytogenes; Erysipelotrix;

Spirochete : treponema palidum; leptospira

Actinomicete : actinomyces israeli

Atipici (Micoplasma, legionele, chlamidia)- macrolide, azalide

With a predominant influence on the gram-negative flora

- **polimixinele; aminoglicozidele; amino-şi carboxipenicilinele; cefalosporinele** II gen.

Spectrul: Bacilii gram-; cocii gram-; cocii gram+;

<u>Aminoglicozidele:</u>

- **Brucella;**
- **Yersinia pestis;**
- **Francisella tularensis;**
- **Micobacterium tuberculosis**
- **Micobacterium avum**

With a broad spectrum of action

- **tetraciclinele; - cloramfenicolul;**
- **ansamicinele.**

Spectrul:

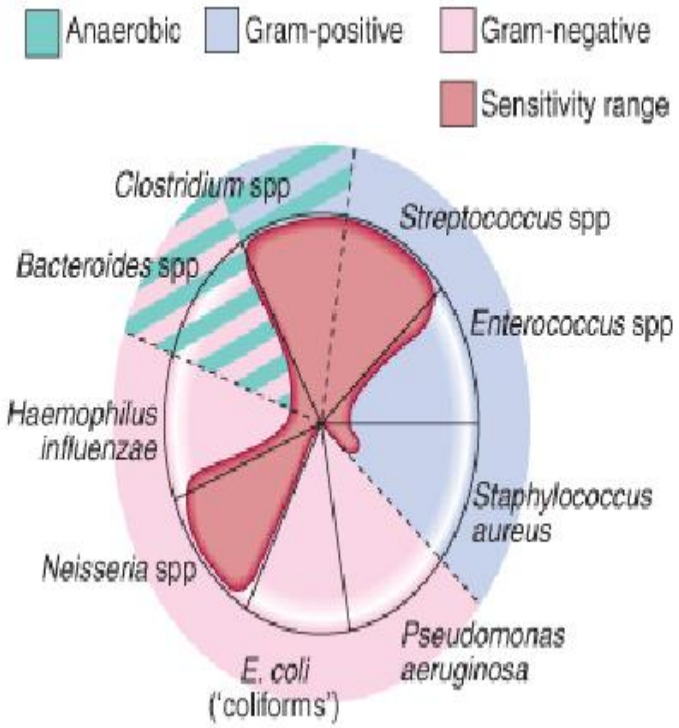
- cocii gram+; cocii gram-;
- Bacilii gram+; bacilii gram-;
- rlketsiile; chlamidiile; ureaplasma;
- vibrionii; micoplasma; protozoare;

With a "ultrabroad" spectrum of action

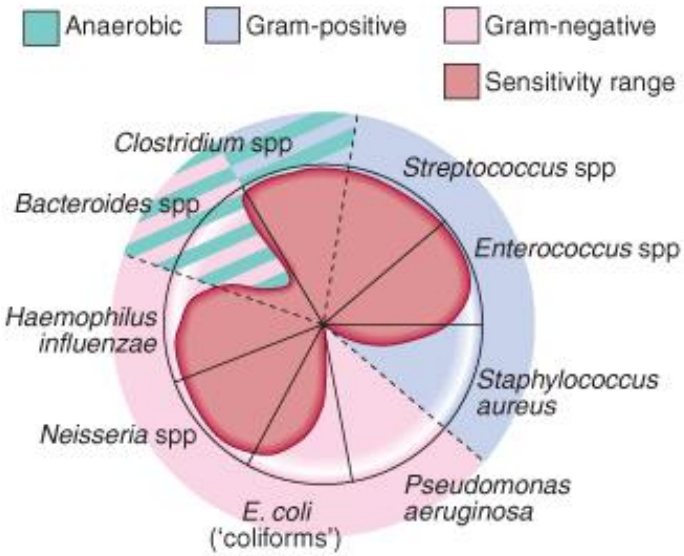
- ureidopenicilinele;
- monobactamii;
- cefalosporinele gen. III şi IV;
- carbapenemii;
- asocieri beta-lactamine+inhibitori beta-lactamaze
- agenți cu polirezistență;
- agenți intraspitaliceşti (nozocomiali)

Spectrum of action of Penicillins

- Natural Penicillin (narrow spectrum)

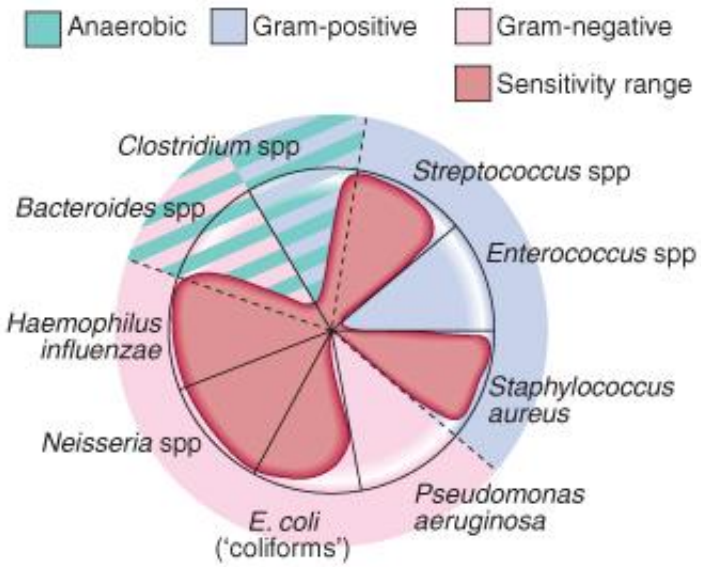


- Amoxicillin (broad spectrum)

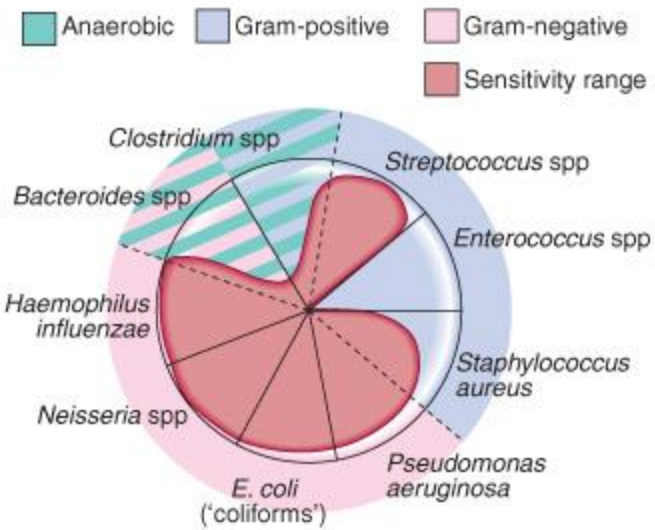


Spectrum of action of Cephalosporins

- Cefuroxime (2nd generation)



- Ceftazidime (3rd generation)



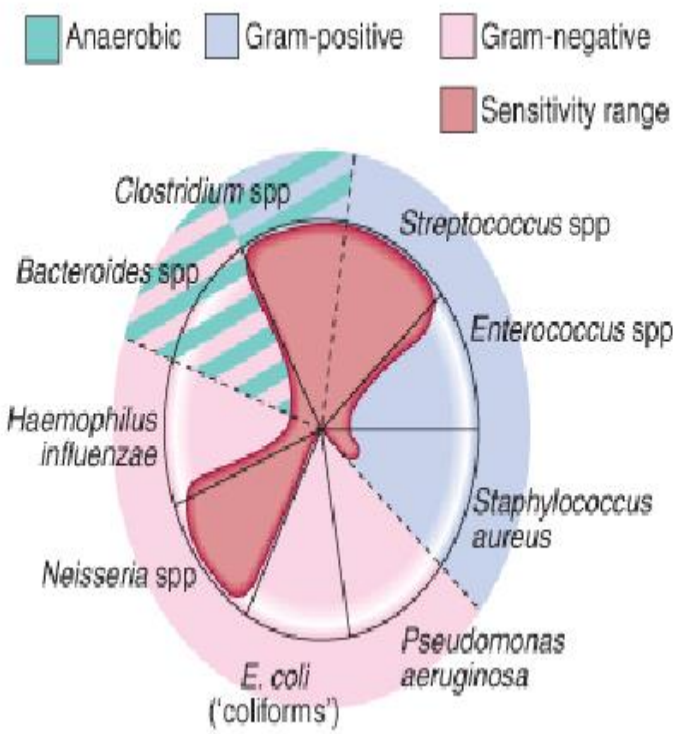
Pharmacokinetics and Adverse Effects of Beta lactams

- **Pharmacokinetics**:
  - Not inhibited by abscess environment (low pH,PMNs)
  - Low CSF levels except in presence of inflammation
  - **Safe in pregnancy**
  - **Dosage needs to be reduced in cases of impaired renal function**
  - Delayed excretion with concurrent administration of probenecid
  - Synergistic effect with aminoglycosides

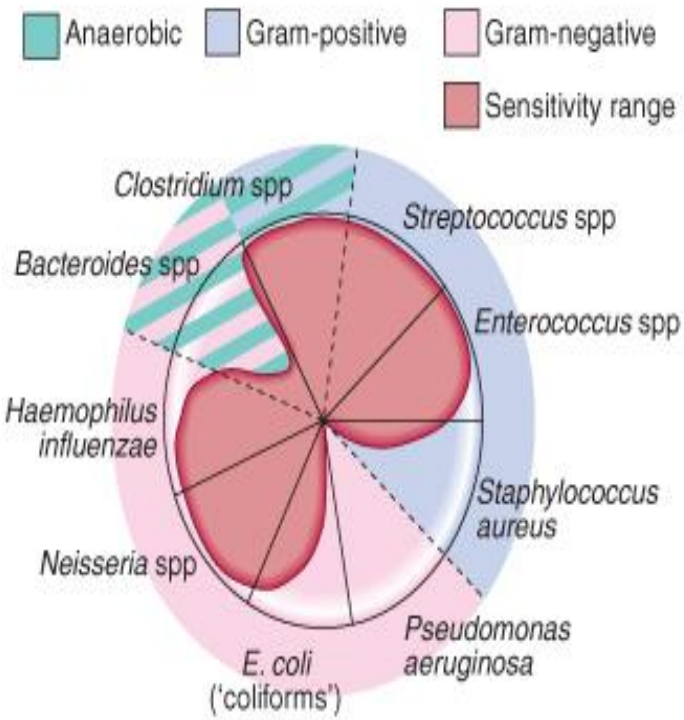
- **Adverse Effects:**
  - Allergic reactions: itch, rash, fever, angioedema, rarely anaphylactic reaction
  - GI upset and diarrhoea
  - Direct intrathecal (puncție lombară sau intraventricular) injection of a beta lactam is contra-indicated (very high doses cause seizures and encepha-lopathy)
  - Interstitial nephritis and increased renal damage in combination with aminoglycosides

Spectrum of action of Penicillins

- Natural Penicillin (narrow spectrum)

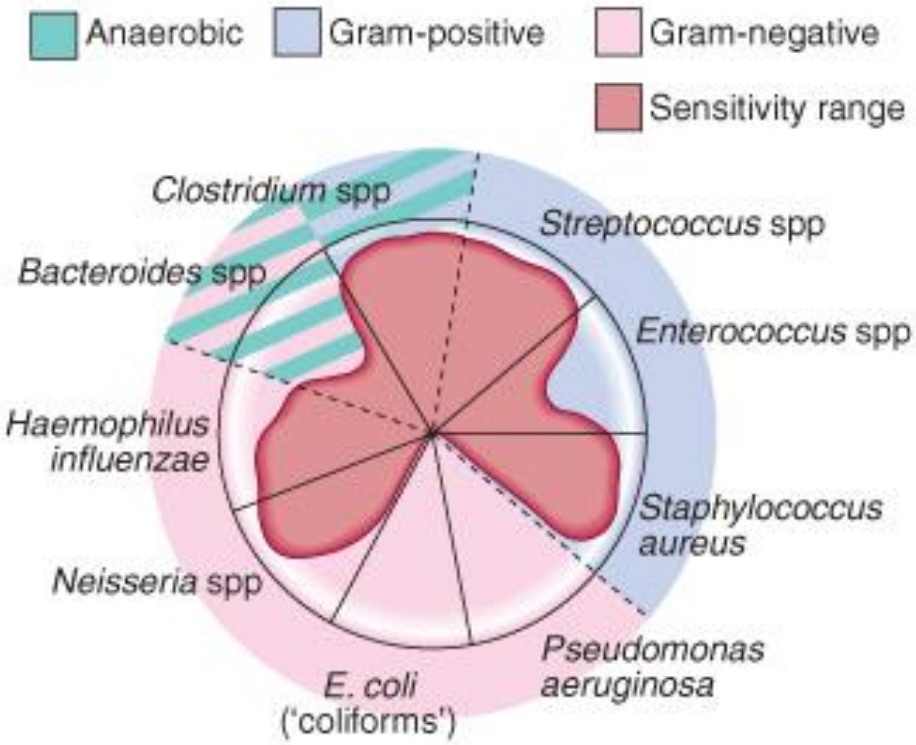


- Amoxicillin (broad spectrum)



Mechanism and Spectrum of Action of Macrolides

- It binds to the 50S subunit of ribosome and blocks the translocation and formation of initiation complex, thereby inhibiting protein synthesis.



Pharmacokinetics and Adverse Effects of Macrolides

- **Pharmacokinetics:**

  - Poorly absorbed orally
  - Short half life (except azithromycin)
  - Bacteriostatic
  - Good CSF penetration (erythromycin)
  - **Dose adjustment for renal failure is not necessary**

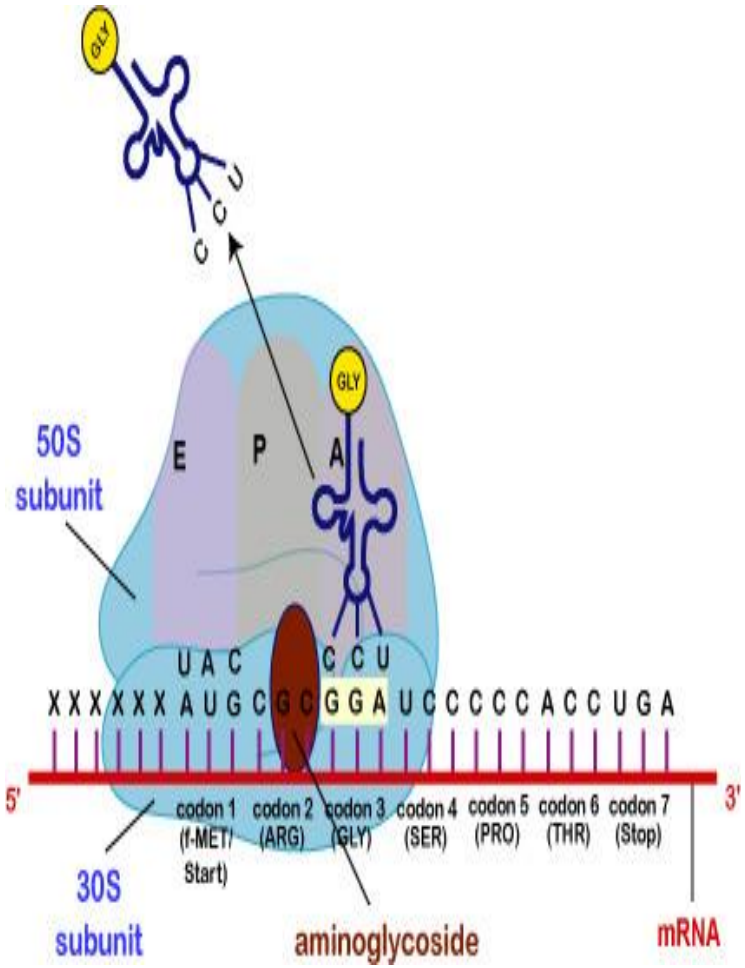
- **Adverse Effects**

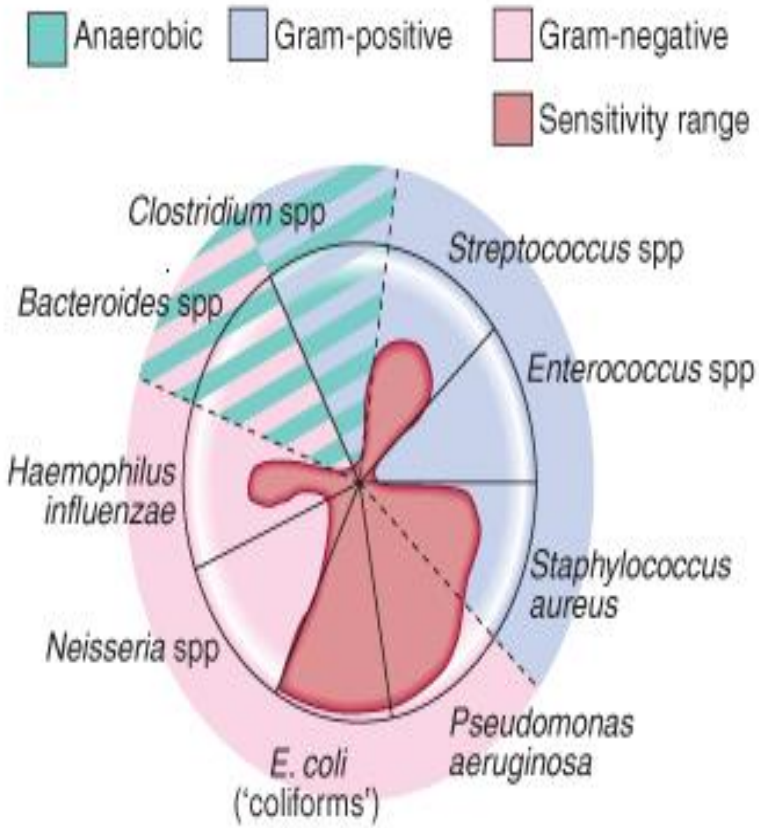
  - GI upset
  - Cholestatic jaundice
  - Prolongation of QT interval (erythromycin)
  - Diarrhoea related to *Cl. Difficile*
  - Theophylline, oral anticoagulants cannot be administered simultaneously

Mechanism and Spectrum of action of Aminoglycosides

- **Mode of action** - The aminoglycosides irreversibly bind to the 16S ribosomal RNA and freeze the 30S initiation complex (30S-mRNA-tRNA) so that no further initiation can occur. They also slow down protein synthesis that has already initiated and induce misreading of the mRNA. By binding to the 16 S r-RNA the aminoglycosides increase the affinity of the A site for t-RNA regardless of the anticodon specificity. May also destabilize bacterial membranes.
- **Spectrum of Activity** -Many gram-negative and some gram-positive bacteria
- **Resistance** - Common
- **Synergy** - The aminoglycosides synergize with ß-lactam antibiotics. The ß-lactams inhibit cell wall synthesis and thereby increase the permeability of the aminoglycosides.

Mechanism and Spectrum of action of Aminoglycosides





Efficacy vs. Safety

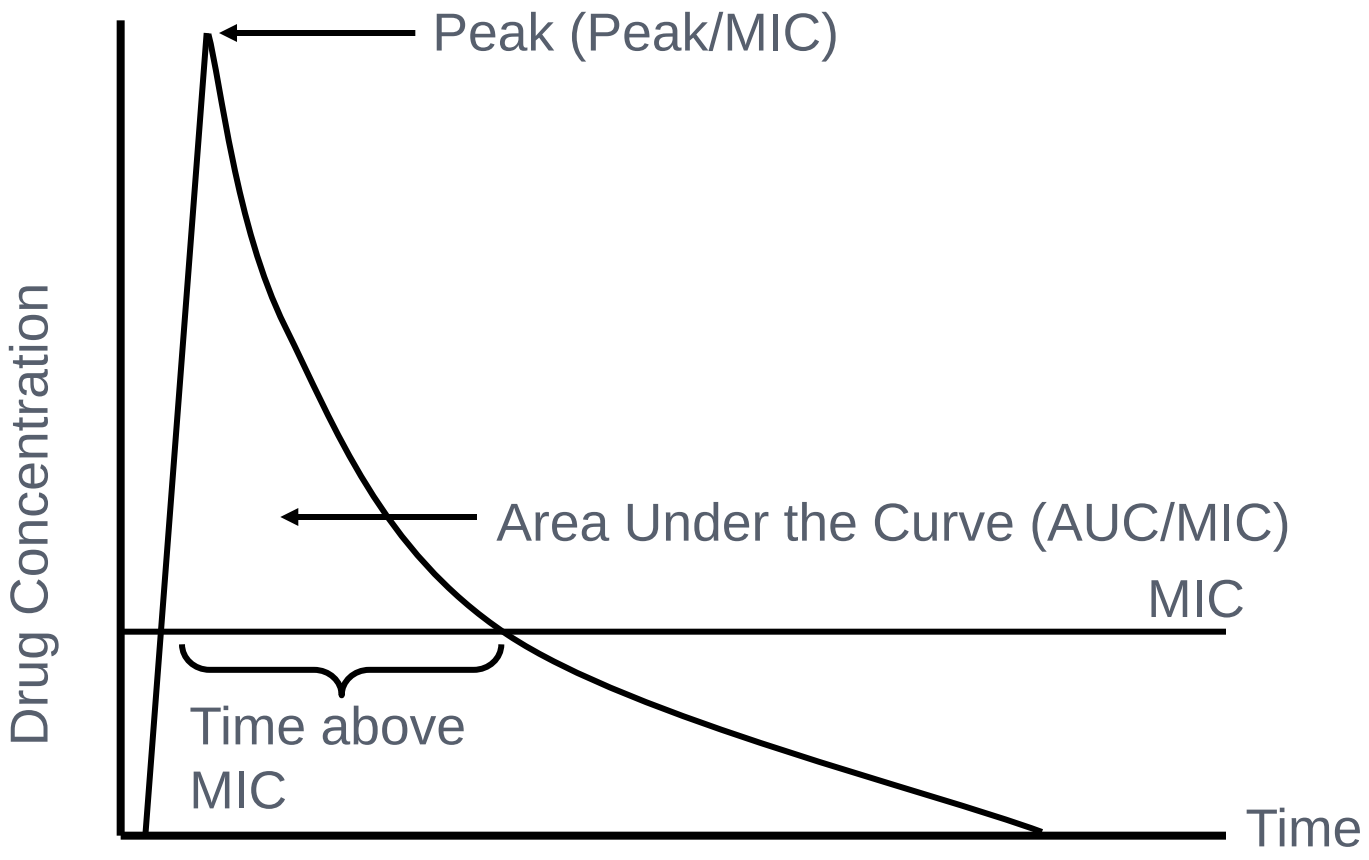
- Although effective, aminoglycosides are toxic, and this is plasma concentration related.
- It is essential to *monitor plasma concentrations* (shortly before and after administration of a dose) to ensure adequate concentrations for bactericidal effects, while minimising adverse effects, every 2-3 days.

Pharmacokinetics and Adverse Effects of Aminoglycosides

- **Pharmacokinetics**
  - Negligible oral absorption
  - Negligible CSF (**cerebrospinal fluid**)
  - and corneal penetration
  - **Dose adjustment is critical in renal impairment**
  - Post antibiotic effect allows daily once dosing

- **Adverse Effects**
  - **Ototoxic (permanent)**
  - **Nephrotoxic (reversible): not to be given with loop diuretics, vancomycin, amphotericin**
  - Neuromuscular blockade after rapid i.v. infusion

Antimicrobial activity



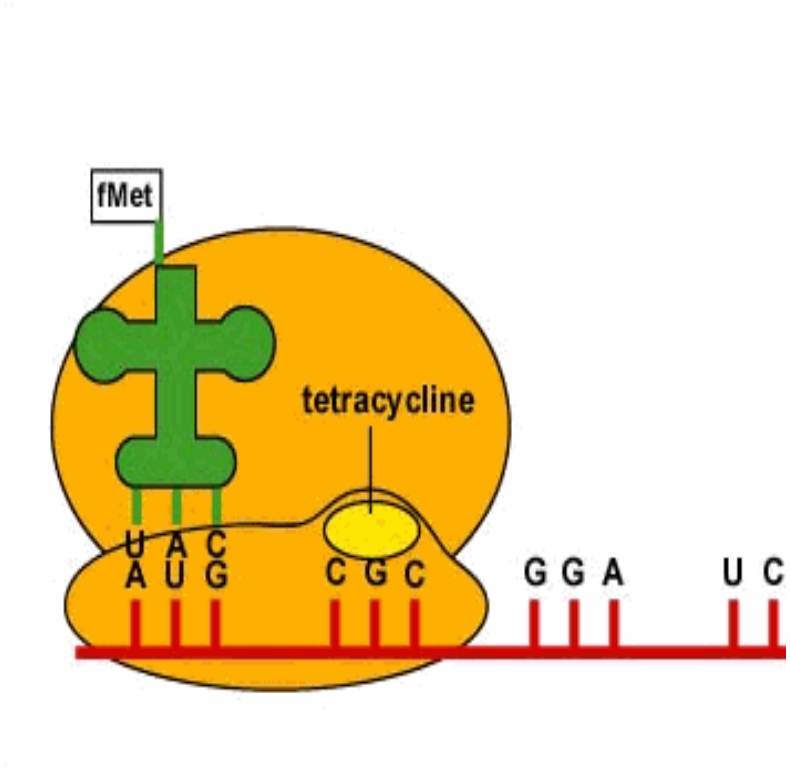
Pharmacodynamic properties of antibiotics

Type of bactericidal profile	Important parameter	Dosage optimization
Dose-dependent *Aminoglycosides, quinolones*	Cmax / MIC Prolonged PAE	Single daily dose
Time-dependent *Penicillin, cephalosporins*	T > MIC No PAE	Multiple DD or continuous infusion
Cumulative-dose dependent *Clarithromycin, clindamycin*	AUC / MIC Prolonged PAE	Total dose and duration

PAE: Post-Antibiotic Activity

Mechanism and Spectrum of action of Tetracyclines /Efect Bacteriostatic

- **Mechanism of Action:**



- **Spectrum of Action of Tetracyclines:**

  Tetracyclines have a broad spectrum of activity; mostly used against *Mycoplasma*, *Chlamydia* and *Rickettsia*, plus *Borrelia* and other spirochaetes.

Mechanis of action of T

- **Inhibitori ai sintezei proteice:**

Mode of action - The tetracyclines reversibly bind to the 30S ribosome and inhibit binding of aminoacyl-t-RNA to the acceptor site on the 70S ribosome.

- **Spectrum of activity** - Broad spectrum; Useful against intracellular bacteria

- **Resistance** - Common
- **Adverse effects** - Destruction of normal intestinal flora resulting in increased secondary infections; staining and impairment of the structure of bone and teeth (colorare şi afectarea țesutului osos şi dinților).

Pharmacokinetics and Adverse Effects of Tetracyclines

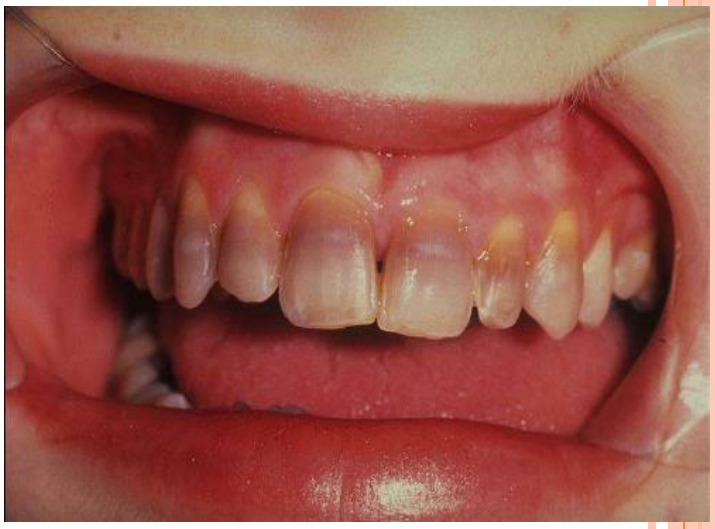
- **Pharmacokinetics**

  - Bacteriostatic
  - Best oral absorption in fasting state
  - CSF level increases in chronic inflammation

- **Adverse Effects**

  - **Contraindicated in renal failure (except doxycycline and minocycline)**
  - Nausea, diarrhoea
  - Binds to metallic ions in bones and teeth **(to be avoided in children and in pregnancy**)
  - Phototoxic skin reactions
  - Hypernatremia

DARs



- Gastrointestinal disorders
- The brown coloring of the teeth
- Superinfection -C. difficult S.aureus
- hepatotoxicity
- nephrotoxicity
- It is not used in children and pregnant women

Inhibitors of Nucleic Acid synthesis

This group includes:

- Sulphonamides: Sulfamethoxazole, sulfadoxine
- Trimethoprim
- Quinolones: Ciprofloxacin, levofloxacin, pefloxacin, ofloxacin, norfloxacin, gatifloxacin, moxifloxacin, sparfloxacin
- Rifampicin
- Azoles: This group includes-
- Antibacterial- Metronidazole, secnidazole, tinidazole,
- Antifungal- Ketoconazole, fluconazole, Isoconazole, Itraconazole, Clotrimazole
- Antihelminth- Albendazole, Mebendazole, thiabendazole

New Antimicrobien Drugs

I. new antibacterial groups:

cyclic lipopeptides (daptomycin);

glycyclines (der. tetracyclines - tigecycline);

pleuromutilins (lefamulin, retapamulin);

streptogramins (quinopristine / dalfopristine);

oxazolidinones (linesolid, tedizolid, eperezolid, sutezolid, etc.).

II. new antibiotics from already known groups:

4th generation cephalosporins (cefepim (maxipin), cefpirom (keiten), cefclidin, cefquinom, cefozopran, cefluprenam, cefoselis),

cephalosporin V generation (ceftobiprol, ceftaroline, ceftolozan, cefditoren);

carbapenems (ertapenem, biapenem, razupenem, faropenem, doripenem, panipenem, tebipenem, tonopenem);

monobactami (tigemonam);

beta-lactamine + beta-lactamase inhibitors (cefoperazone + sulbactam; piperacillin + tazobactam; ceftazidim + avibactam; ceftolozan + tazobactam; ceftaroline + avibactam; meropenem + vaborbactam);

macrolides (macrocyclics (fidaxomycin), ketolides (ketromycin), fluorocerolides (solithromycin), bicyclolides);

aminoglycosides (isepamycin, arbecacin, plazomycin);

tetracyclines (fluorciclines (eravacycline); aminomethylcyclines (omadacycline), pentacyclines, azatetracyclines);

glycopeptide (lipoglycopeptide (dalbavancin, oritavancin, telavancin)

company	drug	class	indications	MRSA	MDRSP	VRE
Theravance	Telavancin	lipoglyco-peptide	cSSSI / HABP/VABP	✓	✓	VanB only
Durata Ther.	Dalbavancin	lipoglyco-peptide	ABSSSI	✓	✓	VanB only
The MedCo	Oritavancin	lipoglyco-peptide	ABSSSI	✓	✓	✓
MSD	Tedizolid	oxazolidinone	ABSSSI	✓	✓	✓
Forrest Astra-Zeneca	Ceftaroline	β-lactam	ABSSSI / CABP	✓	✓	✓
Basilea	Ceftobiprole*	β-lactam	CAP / HAP	✓	✓	✓

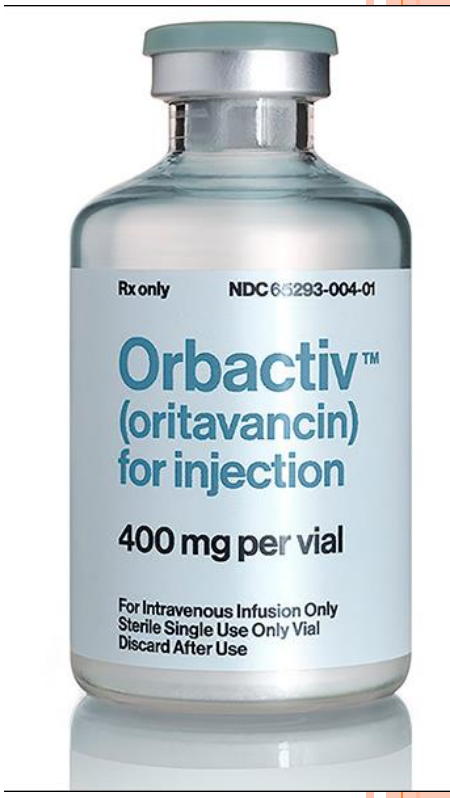
* licensed in 13 countries: AT, BE, CH, DE, DK, ES, FI, FR, IT, LU, NO, SE, UK; reimbursement and pricing authorization ongoing in most of them

Dalbavancin (Dalvance , Xydalba) was approved in May 2014 by FDA and has been recommended for approval by the European Medicines Agency (EMA)

- This drug has a long unsteady development history. Based on chemical modifications of the teicoplanin scaffold, it was first described in 1987 by researchers at Lepetit Research Center, which became Biosearch Italy and later merged with Versicor to become Vicuron, acquired by Pfizer
- Dalbavancin showed non-inferiority in 2 large clinical trials in patients with ABSTI compared with vancomycin. Due to the long half-life of 150-250 hours (protein binding >90%), a dosage regimen of 2 doses one week apart was chosen. Patients were treated for two weeks with either a two-dose regimen of Dalbavancin iv (1 g followed one week later by 500 mg) or vancomycin iv (1 g or 15 mg/kg every 12 hours, with the option to switch to oral linezolid after 3 days). In the clinical context of treatment options for Methicillin-resistant S. aureus (MRSA) infections, the long half live is the major differentiation to vancomycin. As the MRSA rate declined in most countries, this new glycopeptide should only be considered when MRSA is confirmed or strongly suggested. Dalbavancin is not active against vancomycin-resistant S. aureus. Future development efforts will focus on a single-dose regimen and additional indications, such as hospitalized community-acquired pneumonia (CAP) due to MRSA and pediatric osteomyelitis.

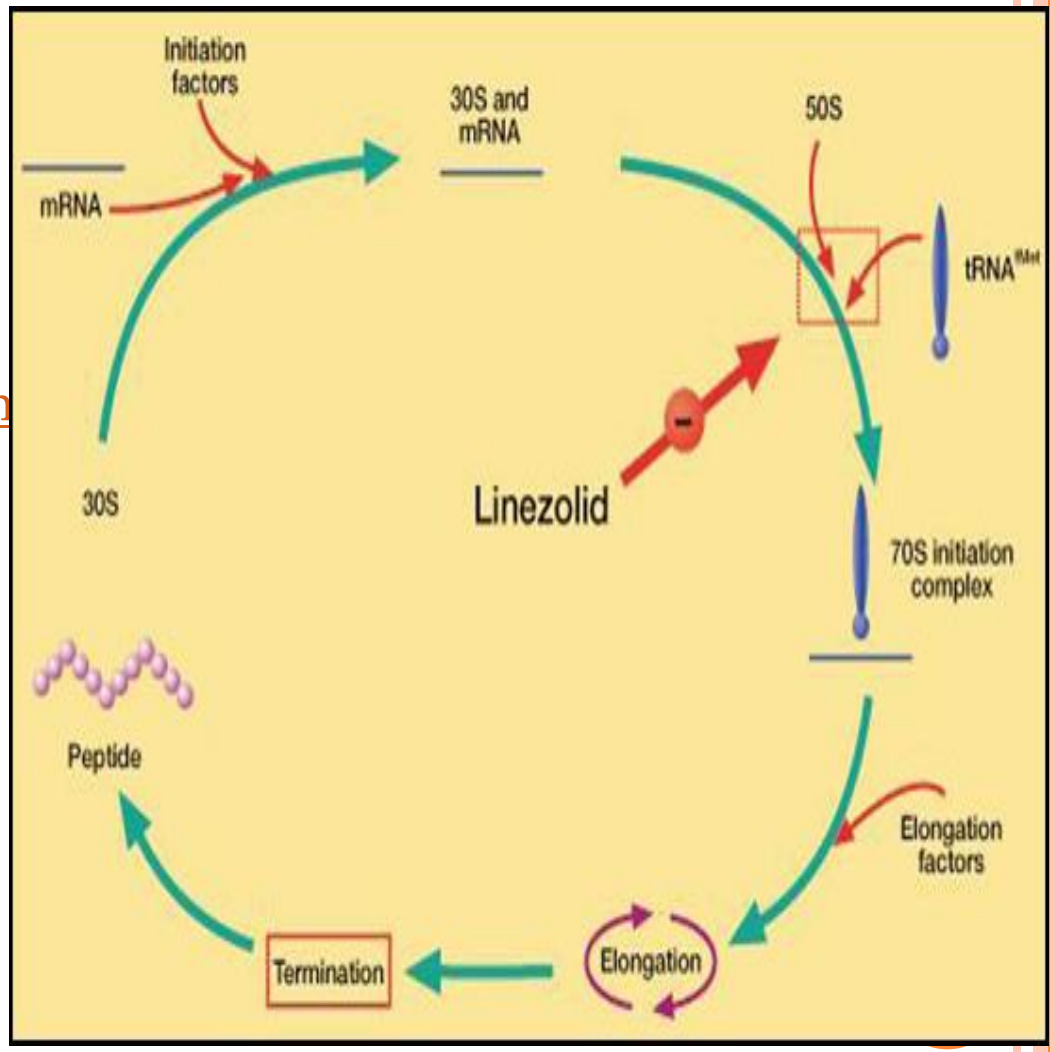
Oritavancin (Orbactive) was approved in August 2014 by the FDA

- Oritavancin is a vancomycin derivate originally discovered and developed by EliLilly . The first development was discontinued, and the drug was acquired by Targanta, which completed Phase 3 trials but failed to achieve approval. The Medicine Company then acquired the drug and successfully repeated the Phase 3 program in an appropriate patient population. Due to its long half-life of about 250 hours (about 90% protein binding), a single dose regimen was developed and approved to treat ABSTI in comparison to vancomycin



Oxazolidinone

- Linezolid
- is active against most Gram-positive bacteria that cause disease, including streptococci, vancomycin-resistant enterococci (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA).[
- MofA subunitatea ribozomală 50 S



INDICATIONS

- The main indications of linezolid are infections of the skin and soft tissues and pneumonia (particularly hospital-acquired pneumonia), although off-label use for a variety of other infections is becoming popular. Linezolid is marketed by Pfizer under the trade names **Zyvox** (in the United States, United Kingdom, Australia, and several other countries), **Zyvoxid**(in Europe), and **Zyvoxam** (in Canada and Mexico). Generics are also available, such as **Linospan** (in India, by Cipla)

Common adverse effects

of short-term use include headache, diarrhea, and nausea.

Long-term use, however, has been associated with serious adverse effects: linezolid can cause bone marrow suppression and low platelet counts, particularly when used for more than two weeks. If used for longer periods still, it may cause peripheral neuropathy (which can be irreversible), optic nerve damage, and lactic acidosis (a buildup of lactic acid in the body), all most likely due to mitochondrial toxicity.

FE COST-EFFECTIVE

- Linezolid is very expensive, costing approximately US$100 per pill in the United States.] Nonetheless, it appears to be more cost-effective than comparable antibiotics, such as vancomycin, mostly because of the possibility of switching from intravenous to oral administration as soon as patients are stable enough, without the need for dose adjustments.

Tedizolid (Sivextro)

- Approved by the FDA for ABSTI in 2014 (Merck)
- Oral și intravenos
- Comparativ cu linezolidul:
  - Afinitate de legare mai mare cu prot. plasm.
  - T ½ mai lung
    - Doze mai mici (200 mg/zi/6 zile)

Ceftazidime-avibactam (Avycaz)

- comercializat de Actavis si AstraZeneca
- aprobat de FDA in februarie 2015 pentru tratamentul:
  - infecțiilor complicate intra-abdominale (cIAI), in asociere cu metronidazol
- infecțiilor tractului urinar.
- Avibactam - extinde activitatea la tulpini producătoare de ESBL și AmpC precum, și de unele carbapenemaze.
- Metalo-beta-lactamazele nu sunt inhibate de avibactam.
- Administrarea – perfuzie i/v (2 ore).

Ceftolozană-tazobactam (Zerbaxa)

- Has been approved by FDA in December 2014
- Îmbunătățire importantă în activitatea împotriva P. aeruginosa
- Ceftolozana nu este stabilă față de beta-lactamazele clasa A, B, D (în principal ESBL sau carbapenemaze).
- Combinația cu tazobactamul crește activitatea sa împotriva enterobacteriilor ESBL-producătoare.

Ceftolozane is a new anti-Pseudomonas cephalosporin based on the ceftazidime

- This has been achieved by retaining activity against Pseudomonas strains with hyperexpression of efflux pumps, AmpC derepression and/or loss of porin OprD. Despite important improvement in the activity against P . aeruginosa resistance due to a combination of resistance mechanisms including a variety of beta-lactamases is not uncommon. Ceftolozane is not stable against class A, B, D beta-lactamases (mainly ESBLs or carbapenemases). The combination with tazobactam increases its benefit against enterobacteriaceae with ESBL production.
- Ceftolozane-tazobactam is approved in a dosage of 1 g/0.5 g administered every 8 hours by intravenous infusion over 1 hour for the treatment of cIAI in combination with metronidazole and cUTI. This drug was evaluated in Phase 3 non-inferiority clinical trials versus levofloxacin 750 mg daily in cUTI or meropenem 1 g q 8 hours in cIAI. A phase 3 clinical trial of ceftolozane-tazobactam in HAP/ V AP is planned. There are no head-to-head comparisons with Ceftazidime-avibactam. Both combinations may perform similarly with some minor differences in responding to the wide spectrum of resistance mechanisms in Pseudomonas. In enterobacteriaceae mainly carbapenemases of class A (e.g. KPC) are better covered with avibactam as the beta-lactamase inhibitor combination partner . Clinical decisions based on MIC determinations will be essential to make best use of a specific beta-lactam/beta-lactamase inhibitor combination in individual patients.

Renal dosing of commonly used antibiotics

Antibiotics	Usual dosage	Renal dosage
amoxicillin po	250-500mg 8-12h	>30:no change 10-30:12h <10:24h
amoxicillin/ clavulanate po	250/125 to 500/125 8h	>30:no change 10-30:12h <10:24h
ceftriaxone iv	1-2g 24h	no adjustment
cefuroxime po	250-500mg 12h	>30:no change 10-29: 12-24h <10: 250mg 24h
erythromycin po	250-500mg 6-12h	>/=10:no change <10: 50-75%of dose at same interval

Renal dosing of commonly used antibiotics

Antibiotics	Usual dosage	Renal dosage
clarithromycin po	250-500mg 12h	>/=30:no change <30:500 mgx1, then 250mg 12-24h
azithromycin po	500mg x1, then 250mg daily x4days	no adjustment
Tetracycline po ** Avoid if possible due to risk of liver toxicity	250-500 6h	>/= 50: no change 10-50: q12-24h <10: q24h
doxycycline	100mg 12h	no renal adjustment
ciprofloxacin po	250-750mg 12h	>/=30:no change <30: 24h

Renal dosing of commonly used antibiotics

Antibiotic	Usual dosage	Renal dosage
Ciprofloxacin iv	200-400mg 12h	>/=30:no change <30:24h
levofloxacin po/iv	500mg 12h	>/= 50: no change 20-49: 500mg x1, then 250mg 24h 10-19: 500mg x 1, then 250m 48h
metronidazole po/iv adjust for hepatic failure	500mg 6-8h	>/= 10: no change <10: 500mg 8-12h
isoniazid	300mg po daily	no renal adjustment
rifampicin po/iv	600mg 24h	>/=10:no change <10: may give half usual dose

Renal dosing of commonly used antibiotics

Antibiotic	Usual dosage	Renal dosage
ethambutol	15-25mg/kg 24h	>/=10:no change <10:48h
acyclovir iv	5-10mg/kg 8h	>50: no change 30-50: 5-10mg/kg 12h 10-30: 5-10mg/kg 24h <10: 2.5-5mg/kg 24h
fluconazole po/iv	100-400mg 24h	>50: no change 20-50: 1/2 usual dose 24h <20: 1/4 dose 24h, or 1/2 48h

Pharmacodynamic properties of antibiotics

Type of bactericidal profile	Important parameter	Dosage optimization
Dose-dependent *Aminoglycosides, quinolones*	Cmax / MIC Prolonged PAE	Single daily dose
Time-dependent *Penicillin, cephalosporins*	T > MIC No PAE	Multiple DD or continuous infusion
Cumulative-dose dependent *Clarithromycin, clindamycin*	AUC / MIC Prolonged PAE	Total dose and duration

PAE: Post-Antibiotic Activity

CHEMOTHERAPY ASSOCIATIONS

Bactericide numai în faza de multiplicare
Penicilinele, Cefalosporinele, Glicopeptide,

1

bactericide în orice fază
aminoglicozidele, polimixinele

2

3

8

Bacteriostatice
Tetracicline, cloramfenicol

5

6

4

bacteriostatice
macrolidele, azalidele, lincosamidele

7

bactriostatice sau bacterice
fluorchinolonele, co-trimoxazolul

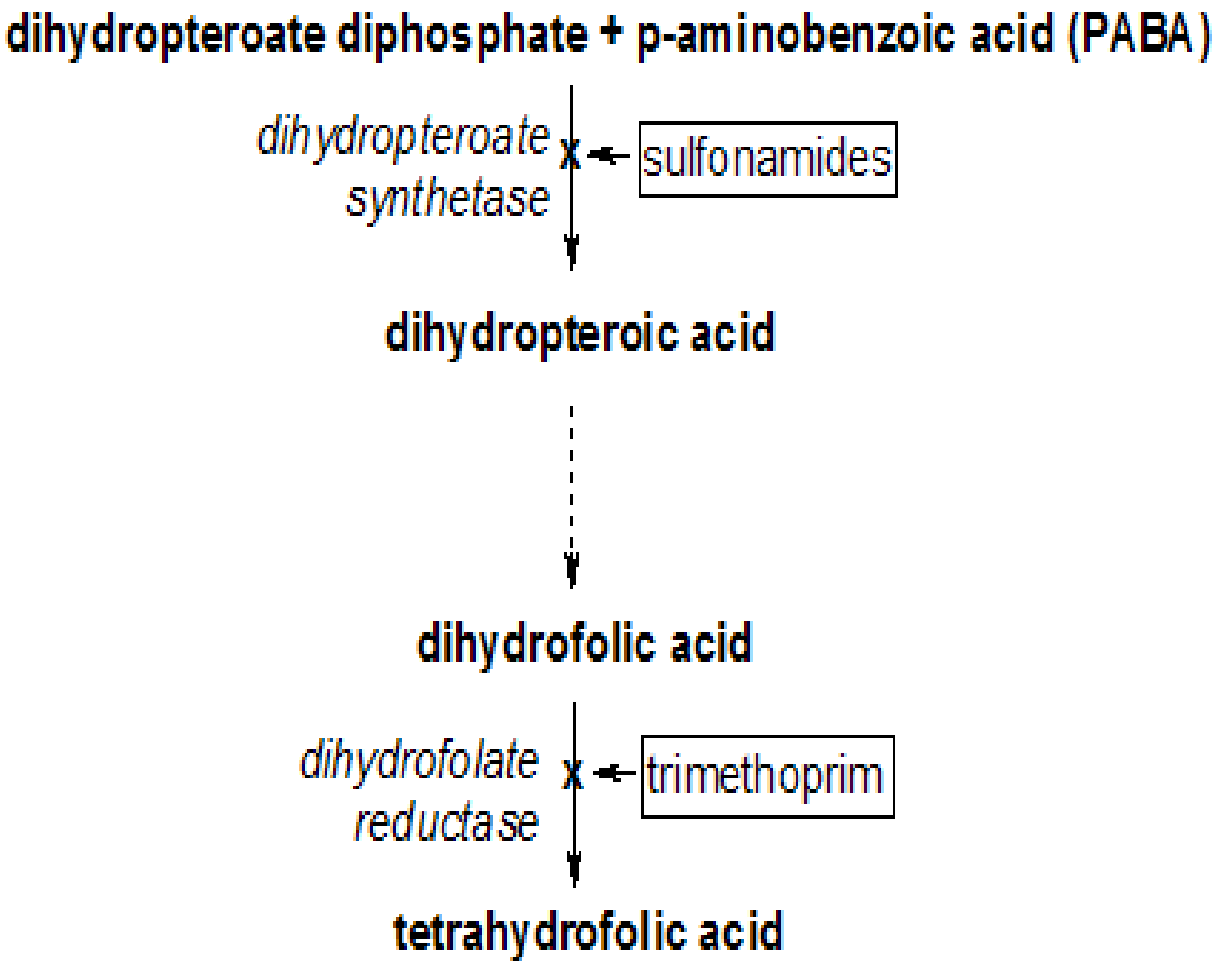
Inhibitors of Nucleic Acid synthesis

This group includes:

- Sulphonamides: Sulfamethoxazole, sulfadoxine
- Trimethoprim
- Quinolones: Ciprofloxacin, levofloxacin, pefloxacin, ofloxacin, norfloxacin, gatifloxacin, moxifloxacin, sparfloxacin
- Rifampicin
- Azoles: This group includes-
- Antibacterial- Metronidazole, secnidazole, tinidazole,
- Antifungal- Ketoconazole, fluconazole, Isoconazole, Itraconazole, Clotrimazole
- Antihelminth- Albendazole, Mebendazole, thiabendazole

- Nalidixic acid and other Quinolone Derivatives (Pipemidic acid, oxolinic acid) and Fluoroquinolones (ciprofloxacine)
- Nitrofuran Derivatives (Nitrofurantoin, Nitrofural, Furasidine)
- Nitroimidazol Derivatives (Metronidazol, Tinidazol)
- 8-oxiquinoline Derivatives (Chlorquinaldole, Nitroxoline)
- Quinoxalin Derivatives (Quinoxidin, Dioxidin)
- Oxazolidinone Derivatives (Linesolide)
- Tiosemicarbazone Derivatives (Ambazona)

Mechanism of action of Sulphonamides and Trimethoprim



Sulfonamides, Sulfones (bacteriostatic)

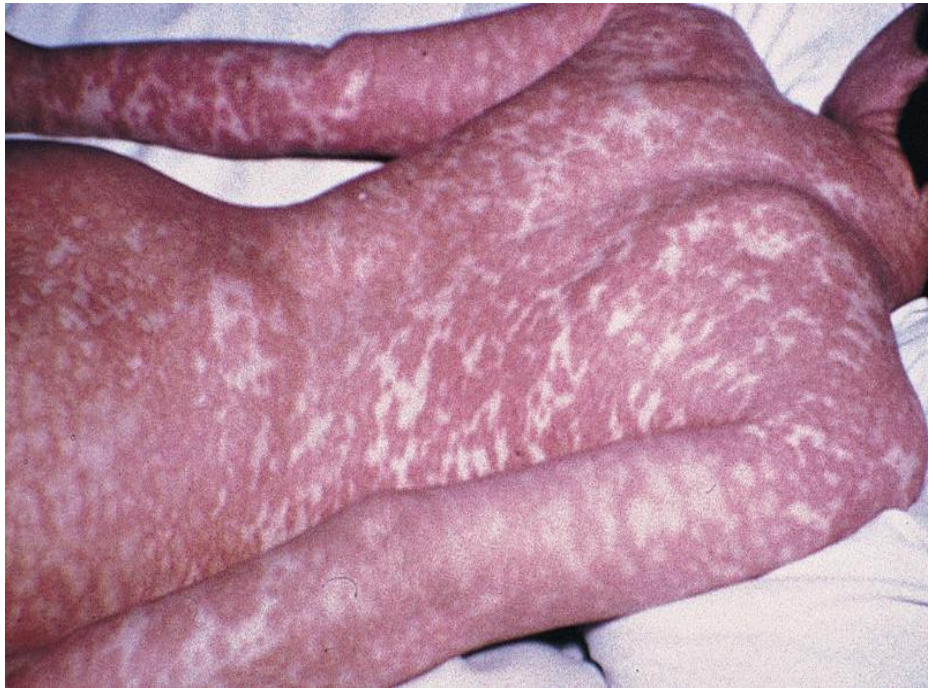
- **Mode of action** - These antimicrobials are analogues of para-aminobenzoic acid and competitively inhibit formation of dihydropteroic acid.
- **Spectrum of activity** - Broad range activity against gram-positive and gram-negative bacteria; used primarily in urinary tract and *Nocardia* infections.
- **Resistance** – Common
- **Combination therapy** - The sulfonamides are used in combination with trimethoprim; this combination blocks two distinct steps in folic acid metabolism and prevents the emergence of resistant strains.

Pharmacokinetics and Adverse Effects of Sulphonamides and Trimethoprim

- **Pharmacokinetics**
  - Well absorbed orally with good bioavailability
  - Sulphonamides are well distributed in ECF -extracellular fluid
  - Trimethoprim is lipophilic with high tissue concentrations
  - **Dose reduction necessary in renal failure**

- **Adverse Effects**
  - Fatal marrow dysplasia and haemolysis in G6PD deficiency
  - Skin and mucocutaneous reactions: Stevens-Johnson syndrome
  - **Contraindicated in pregnancy**

Rash



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MECHANISM OF ACTION

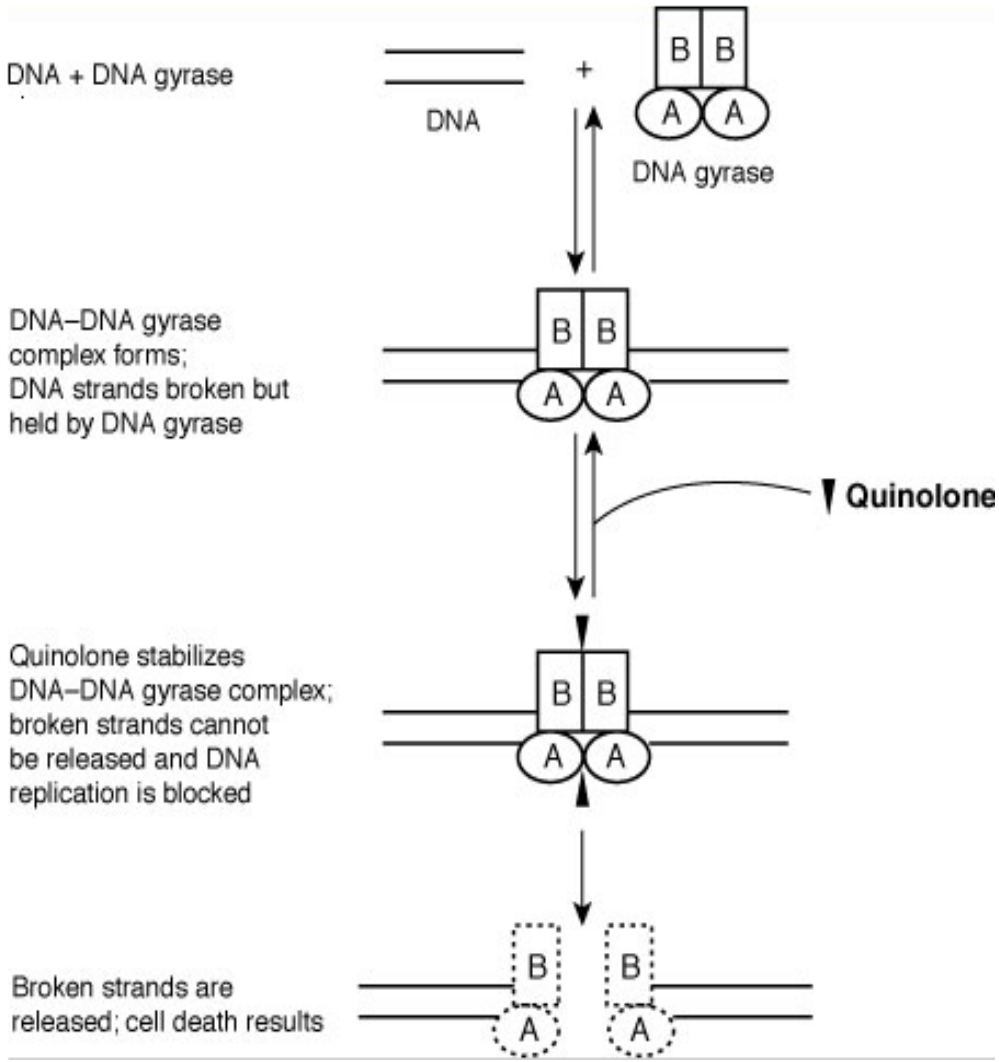
Inhibit DNA (Deoxyribonucleic Acid) gyrase, a bacterial Topoisomerase which controls the topology of supercoiled DNA.

These agents thereby interfere with a number of nucleic acid synthesis processes including replication, transcription and repair.

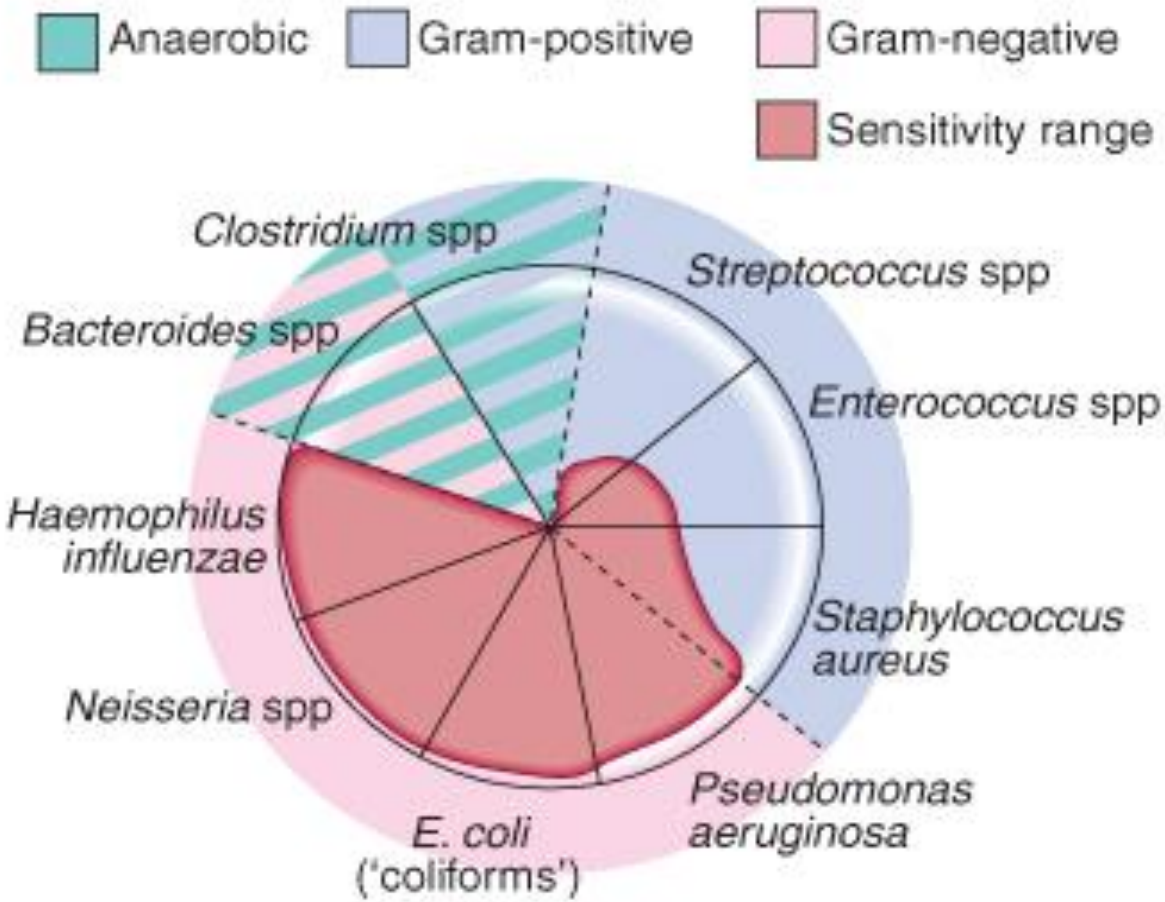
SELECTIVE TOXICITY

The mammalian Topoisomerase is much less sensitive to inhibition by these drugs.

Mechanism of Action of Quinolones



Spectrum of Action of Quinolones



Derivatives of Quinolones and Fluoroquinolones:

1. quinolones derivates:

I generation: nalidixic acid

II generation: oxolynic acid, pypemidinic acid

2. fluoroquinolones:

A. Monofluoroquinolones

Ciprofloxocin, ofloxacin, norfloxacin, pefloxacin, enoxacin

B. Difluoroquinolones

Lomefloxacin, difloxacin, sparfloxacin, amfloxacin

C. Trifluoroquinolones

Fleroxacin, tosufloxacin, temafloxacin

QUINOLONES

The earliest prototype drug, Nalidixic acid, was previously used in a limited capacity for Gram- urinary tract infections.

More recently developed fluoroquinolones (Ciprofloxacin, Norfloxacin,e.g.) have a much broader spectrum of action. Their full therapeutic potential is still being realized.

Pharmacokinetics and Adverse Effects of Quinolones

- **Pharmacokinetics**

  - Well absorbed after oral administration but delayed by food, antacids, ferrous sulphate and multivitamins.
  - Wide volume of distribution.
  - **Dose adjustment required in renal impairment (except moxifloxacin and trovafloxacin)**
  - **These two drugs are contraindicated in hepatic failure**

- **Adverse Effects**

  - GI side effects
  - CNS effects such as confusion and seizures in the elderly
  - Rare skin reactions

Fluoroquinolones

Contraindications

- Growing children (below 18 years), as fluoroquinolones may damage cartilage and cause an arthropathy.
- Pregnancy and lactating mothers.

Nitrofurans derivatives

A. **resorbtive action**

Nitrofurantoin
Nitrofural (furacilina)
Furazidine
Nifuratel
Nifurtoinol;

B. intestinale action

nifuroxazide
furazolidon;

C. local action

nitrofural
furazidine.

Spectrum of action

1. Bactera Gram "+" & Gram "–"
stafilococci, streptococci, enterococci, pneumococci, meningococi, colibacilul, salmonela, sighela, klebsiela, aerobacter, bacilul antrax, protei, v. holerae, anaerobi;

2. Protozoa: *trichomonadis, lambliosis*

3. Fungal agents: - *candida*

Mechanism of action

- The drug works by damaging bacterial DNA, since its reduced form is highly reactive. This is made possible by the rapid reduction of nitrofurantoin inside the bacterial cell by flavoproteins to multiple reactive intermediates that attack ribosomal proteins, DNA, respiration, pyruvate metabolism and other macromolecules within the cell. It is not known which of the actions of nitrofurantoin is primarily responsible for its bactericidal activity

Contraindications

- *renal insufficiency ;*
- *children under 1 y;*
- *deficiency of de glucozo-6 phosphatdehydrogenaze;*
- *pregnancy;*
– *allergy;*

Side effects

- *digestive: dispeptic disorders;*
- *allergic: eruption etc.*
- *CNS: nistagmus, ataxia, headache,*
- *Blood: haemolitic anemia.*

NITROIMIDAZOLES DERIVATIVES:

- **monocomponent drugs**
- **A. <u>Sistemic action</u>**
- ***metronidazol (trihopol, flagic, metrogil, etc.),***
- ***nimorazol (naxodjin),***
- ***tinidazol (fasigin, tinimed, tiniba etc.),***
- ***ornidazol (tiberal)***

- **B. <u>Local action</u>**
- ***Aminitrozol - metronidazol***

- **Combinative drugs**
- **Helicocine** (metronidazol + amoxicylline);
- **ginalgine** (metronidazol + clorchinaldol);
- **clion-D** (metronidazol + miconazol);

Mechanism of action

- Nitroimidazoles such as metronidazole inhibit anaerobic bacteria and protozoa.
- The drugs nitro group is reduced by an electron transport protein in anaerobic bacteria.
- The reduced drug causes strand breaks in the DNA.
- Mammalian cells are unharmed because they lack enzymes to reduce the nitro group of these agents.

Spectrum of action

- **Protozoa**:
- - *Entamoeba hystolitica,*
- - *Trichomonas vaginalis,*
- - *Giardia intestinalis,*
- - *Balantidium coli,*
- - *Blastocystis hominis,*

- **Anaerobes**:
- *Bacteroides (B.fragiles),*
- *Clostridium,*
- *Fusobacterium,*
- *H. Pylori, (campilobacter pylori),*
- - *Peptococcus*
- - *Peptostreptococcus*

Indications

1. Anaerobic infections
2. Trichomoniasis
3. Giardiosis
4. Disenteria
5. Balantidiasis.

Contraindications

- Hypersensitivity to drug
- First-trimester pregnancy in patients with trichomoniasis;

Precautions

Use cautiously in:

- severe hepatic impairment
- history of blood dyscrasias, seizures, or other neurologic problems
- breastfeeding patients
- children.

Adverse reactions

- **CNS:** dizziness, headache, ataxia, vertigo,
- **RS:** rhinitis, sinusitis, pharyngitis
- **GI:** nausea, vomiting, diarrhea, abdominal pain,
- **Renal:** dysuria, dark urine, incontinence
- **Hematologic: leukopenia**
- **Skin:** rash, urticaria, burning, mild skin dryness, skin irritation,
- **Other:** unpleasant or metallic taste, superinfection, phlebitis at I.V. site

8-OXOQUINOLINES DERIVATIVES:

- **Intestinal action:** clorchinaldol, cliochinol, diiodoxochinolin.
- - bacilli gram - ; protozoa, ameba, fungi
- **B. Resorbtive action:**- nitroxoline.
- gram „+” (coci, bacili) & gram „–”; micobacteria tuberculoses, trichomonasis, fungi.
- **C. Local action: -** clorchinaldol.
- gram „+” şi gram „–” ameba, fungi.

Antiprotozoal Agents

Classification

- **Drugs used for treatment and prophylaxis of malaria**
  - Chloroquine (chingaminum) — Primaquine
  - Pyrimethamine (chloridinum) — Quinine
  - Sulfonamides and sulfones — Mefloquine
- **Drugs used for the treatment of amebiasis**
  - Metronidazole — Tetracyclines
  - Chloroquine (chingaminum) — Chiniofone
  - Emetine
- **Drugs used for the treatment of lambliosis (giardiasis)**
  - Metronidazole — Furazolidone
  - Mepacrine (acrichinum)

- **Drugs used for the treatment of trichomoniasis**
  - Metronidazole — Trichomonacid
  - Tinidazole — Furazolidone
- **Drugs used for the treatment of toxoplasmosis**
  - Pyrimethamine (chloridinum)
  - Sulfadimidine (sulfadimezinum)
- **Drugs used for the treatment of balantidiasis**
  - Tetracyclines — Monomycinum
  - Chiniofone
- **Drugs used for the treatment of leishmaniasis**
  - Solusurminum — Stibogluconate
  - Metronidazole
- **Drugs used for the treatment of trypanosomiasis**
  - Melarsoprol — Pentamidine — Suramin
  - Primaquine — Puromycin

CHEMOTHERAPY ASSOCIATIONS

The most effective and recommended:

beta-lactamines + aminoglycosides;

Permissions (for spectrum broadening):

Beta-lactamine + macrolide, lincosamide;

Aminoglycosides + fluorquinolones, co-trimoxazole;

Macrolides, lincosamide + fluorquinolone, co-trimoxazole;

Tetracyclines, chloramphenicol + macrolides, lincosamide;

Tetracyclines, chloramphenicol + fluorquinolones, co-trimoxazole;

Aminoglycosides + tetracyclines, chloramphenicol;

Beta-lactamine + fluorquinolone;

Between beta-lactamines.

CHEMOTHERAPY ASSOCIATIONS

Antagonistic associations, not recommended:

Beta-lactamines + tetracyclines, chloramphenicol;

Prohibited associations:

Aminoglycosides + polymyxins;

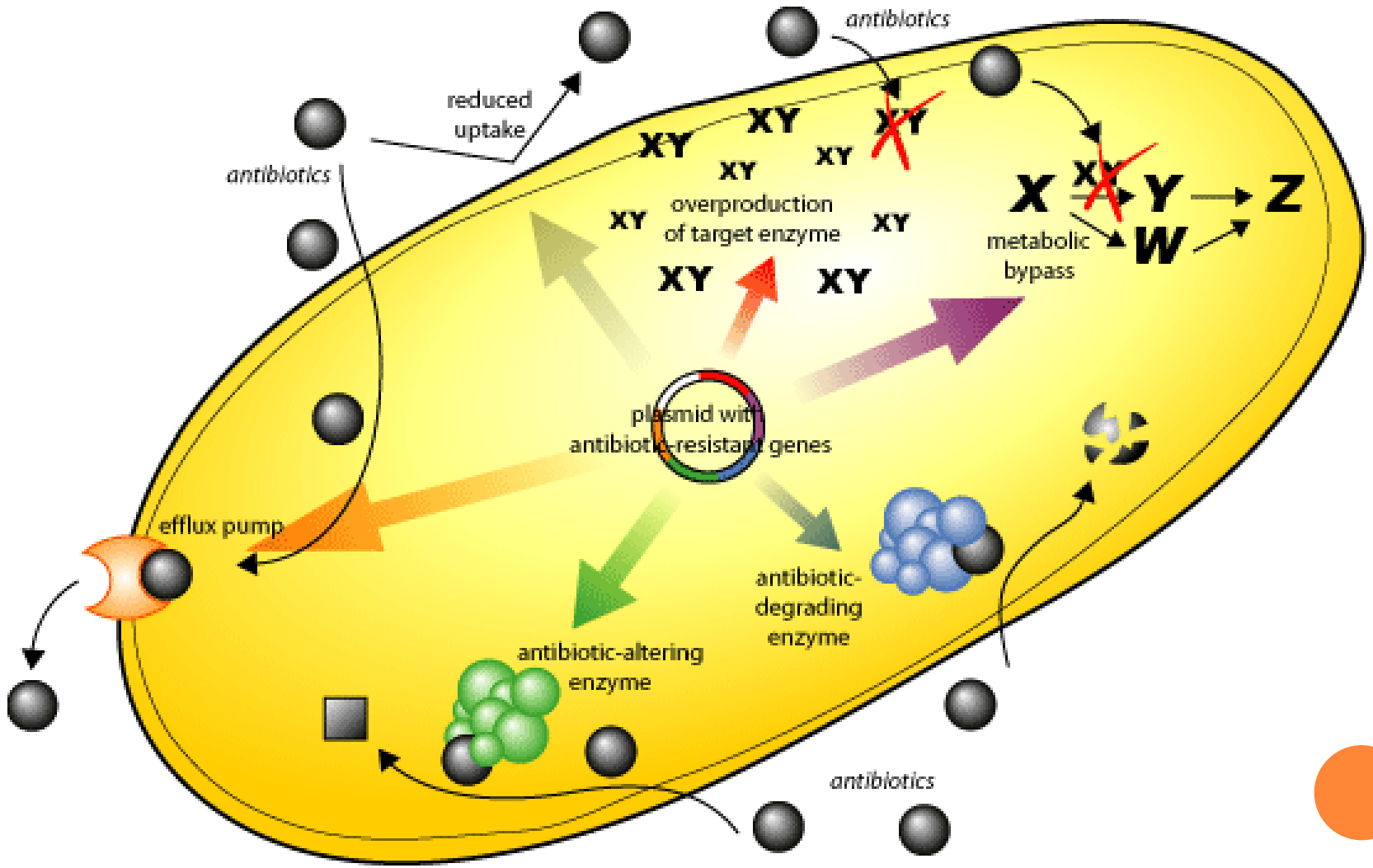
Tetracycline + chloramphenicol;

Macrolide + lincosamide;

Bacterial resistance to antibiotics mechanisms

- modification of bacterial permeability
- modification of antibiotic transport in bacteria
- target modification
- Antibiotic inactivation enzymes
- Activation of efflux pumps
- Combinations of these mechanisms.

Bacterial resistance to antibiotics



Pharmacoeconomy:

- Not just the unit cost of the antibiotic
- Materials for administration of drug
- Labour costs
- Expected duration of stay in hospital
- Cost of monitoring drug levels
- Expected compliance

Administration

- Oral vs parenteral
  - Traditional view
    - « serious = parenteral »
    - Previous lack of broad spectrum oral antibiotics with reliable bioavailability
  - Improved oral agents
    - Higher and more persistent serum and tissue levels
    - For certain infections as good as parenteral

WHO Classifiation of pathogens with dangerous resistance

- I gr. - with a very high degree of resistance
- Acinetobacter baumannii - resistant to carbapenems
- Pseudomonas aeruginosa - resistant to carbapenems
- Enterobacteriaceae - resistant to carbapenems, which produce broad-spectrum beta-lactamases
- II gr.- with a high degree of resistance
- Enterococcus faecium- resistant to vancomycin
- Staphylococcus aureus - methicillin resistant, moderately vancomycin resistant
- Helicobacter pylori - resistant to clarithromycin
- Campylobacter spp.- resistant to fluorchinolone
- Salmonellae - resistant to fluorquinolone
- Neisseria gonorrhoeae, - resistant to cephalosporins, fluorquinolones
- III gr. - with a moderate degree of resistance
- Streptococcus pneumoniae - insensitive to penicillin
- Haemophilus influenzae - resistant to ampicillin
- Shigella spp. - resistant to fluorquinolone

The 2019 WHO AWaRe (Access, Watch or Reserve) Classification: I category Access

Beta-lactams

- Benzylpenicillin Phenoxymethylpenicillin Benzatin benzylpenicillin Procain benzylpenicillin
- Cloxacillin Ampicillin Amoxicillin
- Cefazoline Cefalexin
- Cefotaxim * Ceftriaxon * Cefixim * Meropenem *
- amoxicillin + clavulanic acid

Antibiotics from other groups

- Amikacin Gentamicin Spectinomycina
- Azithromycin Clarithromycin * Clindamycin *
- Chloramphenicol Doxycycline
- Vancomycin, oral * Vancomycin, parenteral *

Synthetic chemotherapies

- Metronidazole Nitrofurantoin Ciprofloxacin *
- Sulfamethoxazole + trimethoprim

- * - antibiotics that are used in concrete diseases or in the case of specific agents

The 2019 WHO AWaRe (Access, Watch or Reserve) Classification: **II category WATCH**

- **Antibiotics**
- Antipseudomonadic penicillin with beta-lactamase inhibitors - piperacillin + tazobactam
- Cephalosporins III generation (without or with beta-lactamase inhibitors) - cefixim, ceftriaxon, cefotaxim, ceftazidim
- Macrolides - azithromycin, clarithromycin, erythromycin
- Glycopeptides - teicoplanin, vancomycin
- Carbapenems - meropenem, imipenem + cilastatin, faropenem etc.

Synthetic chemotherapies - fluorquinolones

- ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin

The 2019 WHO AWaRe (Access, Watch or Reserve) Classification: **III category RESERVE**

- **Monobactami - aztreonam, tigemonam**
- **4th generation cephalosporins - cefepim, cefpirom**
- **Cephalosporin V generation - ceftaroline, ceftobiprol**
- **Polymixin- polymyxin B, colistin, phosphomycin (I/V)**
- **Oxazolidindinone - linezolid, sutezolid, tadezolid**
- **Glycyclic - tigecycline,**
- **Daptomycin**

FDA Pregnancy Categories

- **Category A**
- Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)
- Example drugs: **levothyroxine**, **folic acid**, **liothyronine**.

FDA Pregnancy Categories

- **Category B**
- Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Example drugs: B-lactams(**amoxicillin) and** B-lactams Inhibitosr, carbapeneme, monobactam (aztreonam), macrolides, lincozamide, glicopeptide, polypeptide, ATB (rifabutina, etambutol), nitroimidazol and nitrofuran derive(Met and Nitrofurantoin), etc)

(**pantoprazole, metformin**, **hydrochlorothiazide**, **etc)**

FDA Pregnancy Categories

- **Category C**
- Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Example drugs:

Carbapenemi (imipenem+cilastatina), macrolide (clarotromicina), AG, Amfenicole, Fluorchinolons, ATB (Rif, Iz, Etionamide, Pz), Oxaz (linezolide), Nitrof (furazolidon), SA

- **Ex-tramadol**, **gabapentin**, **amlodipine**, **trazodone**

FDA Pregnancy Categories

- **Category D**
- There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Example drugs:
- AG (St ,Can),Tetracicllins)
- **lisinopril**, **alprazolam**, **losartan**, **clonazepam**, **lorazepam**

FDA Pregnancy Categories

- **Category X**
- Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits. Example drugs: **atorvastatin**, **simvastatin**, **warfarin**, **methotrexate**, **finasteride**

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- Clinical Pharmacology, P.N.Bennet, M.J.Brown, 9th Ed
- Basic and Clinical Pharmacology, Katzung, 11th Ed
- http://www.globalrph.com/renaldosing2.htm

Coronavirus disease 2019 (COVID-19)

- Is a respiratory tract infection caused by a newly emergent coronavirus, SARS-CoV-2, that was first recognized in Wuhan, China, in December 2019. Genetic sequencing of the virus suggests that SARS-CoV-2 is a betacoronavirus closely linked to the SARS virus (1).

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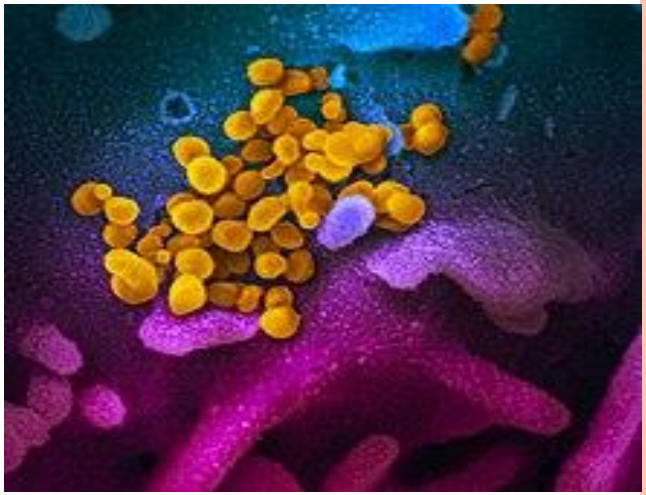


Coronavirus disease 2019 (COVID-19)

- While most people with COVID-19 develop mild or uncomplicated illness, approximately 14% develop severe disease requiring hospitalization and oxygen support and 5% require admission to an intensive care unit (1). In severe cases, COVID-19 can be complicated by acute respiratory disease syndrome (ARDS), sepsis and septic shock, multiorgan failure, including acute kidney injury and cardiac injury (2). Older age and co-morbid disease have been reported as risk factors for death, and recent multivariable analysis confirmed older age, higher SOFA score and d-dimer > 1 μg/L on admission were associated with higher mortality. This study also observed median duration of viral RNA detection was 20.0 days (IQR 17.0–24.0) in survivors, but SARS-CoV-2 virus was detectable until death in non-survivors. The longest observed duration of viral shedding in survivors was 37 days (3, 4).

Prepartatele recomandate pentru tratamentul infecției cu coronavirus

Preparat	Mecanismul de acțiune	Forma de livrare	Scheme de utilizare
Lopinavir+ ritonavir	Lopinavir inhibitor al proteazei virale HIV (HIV-1și 2) Ritonavir – inhibitor al aspartilproteazei HIV-1, HIV-2	Tab/suspensie	Tab.400 mg lopinavir/100 mg ritonavir fiecare 12 ore timp de 14 zile. Suspensia 400 mg lopinavir/100 mg ritonavir 5ml fiecare 12 ore timp de 14 zile prin sondă nazogastrală
Interferon recombinat beta-1b	crește activitatea supresoare a celulelor mononucleare din sângele periferic și reduce rezistența limfocitelor T la apoptoză, declanșează expresia unui număr de proteine cu efecte antivirale, antiproliferative și antiinflamatorii, schimbă echilibrul citokinelor în favoarea citokinelor antiinflamatorii, inhibă proliferarea leucocitelor și prezentarea autoanticorpilor reduce migrarea leucocitelor prin BHE prin reducerea expresiei metaloproteazelor care cresc permeabilitatea BHE, ↓capacitatea de cuplare și exprimare a receptorilor pentru interferon-gamma, antagonizează IFN-gamma	s/c	0.25 mg/ml (8 mln UI) s/c timp de 14 zile (7 injecții)
Ribavirina	Penetrează rapid în celulele infectate. Inhibă replicarea virionilor noi cu ↓ încărcăturii virale, inhibă selectiv sinteza ARN viral și nu influențează sinteza ARN în celulele normale	Tab., capsule.	2000 mg – doza de atac, apoi 4 zile câte 1200 mg fiecare 8 ore, 4-6 zile câte 600 mg fiecare 8 ore.

Preparate ce pot fi utilizate în coronavirus COVID-19

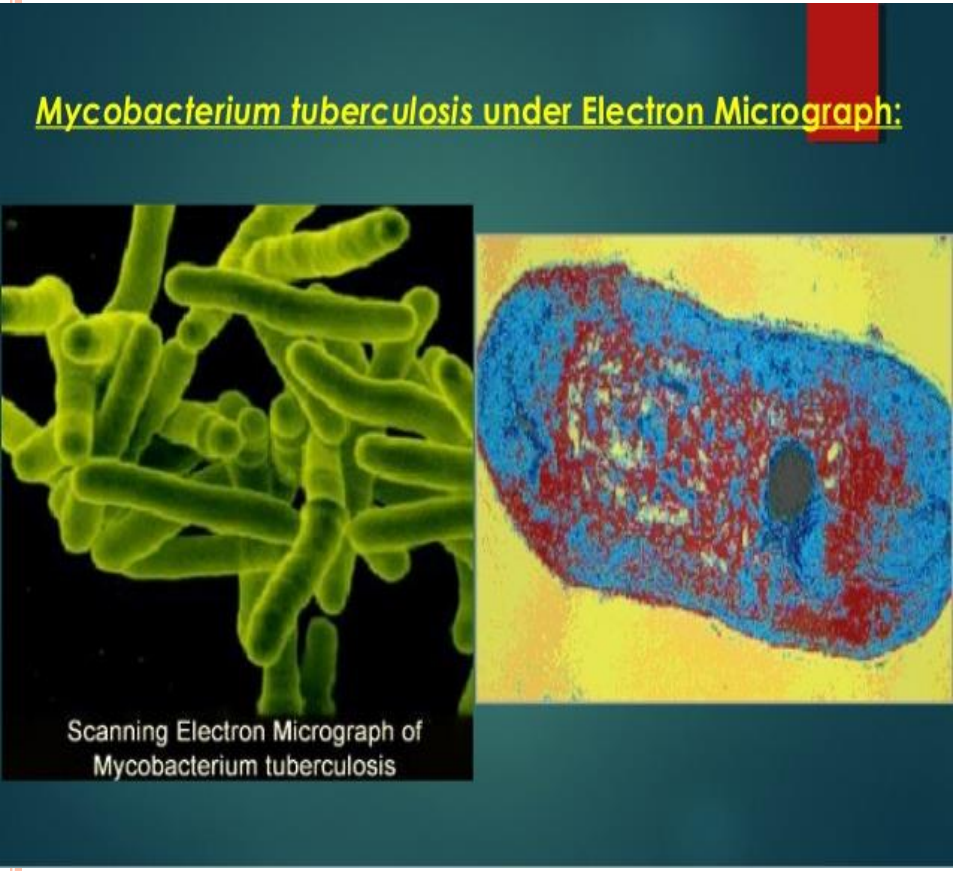
Agenți antivirali

- Studii clinice cu diverși agenți antivirali sunt în desfășurare, inclusiv oseltamivir, lopinavir și ritonavir, ganciclovir, favipiravir, baloxavir marboxil, umifenovir, interferon alfa și alții. Până în prezent, nu există dovezi care să susțină astfel de terapii.
- Remdesivir este eficient împotriva virusului *in vitro* și este utilizat în tratamentul COVID-19 în China. A fost, de asemenea, utilizat în tratamentul primului pacient din Statele Unite.

Preparate antimalarice (imunodepresive minore)

- Cloroquina și hidroxiclorochina
- Studiile clinice ale preparatelor antimalarice ale clorochininei și hidroxiclorochinelor sunt, de asemenea, în desfășurare, dar, până în prezent nu există dovezi care să susțină aceste terapii. Clorochina se dovedește a fi eficientă împotriva virusului in vitro și este probabil să fie adăugată la ghidurile clinice chineze. Există un mesaj din China potrivit căruia clorochina s-a dovedit a fi destul de sigură.
- **Plasma pacienților însănătoșiți și imunoglobulinele**
- **Tratament simptomatic**

ANTI-TB DRUGS



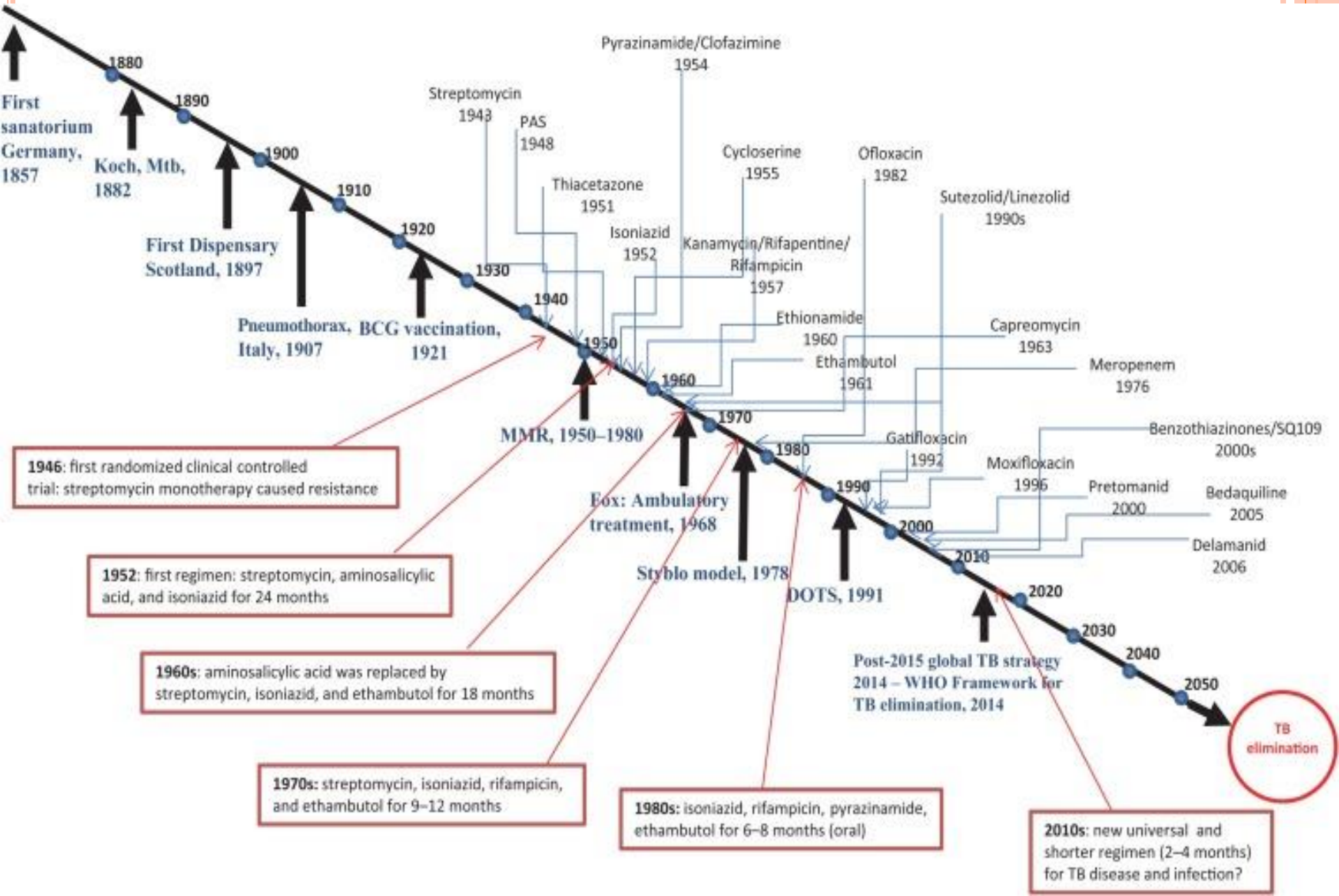
Clasificare științifică	
Regn:	***Bacteria***
Încrengătură:	***Actinobacteria***
Clasă:	***Actinobacteria***
Ordin:	***Actinomycetales***
Subordin:	***Corynebacterineae***
Familie:	***Mycobacteriaceae***
Gen:	***Mycobacterium***
Specie:	***M. tuberculosis***

The actuality

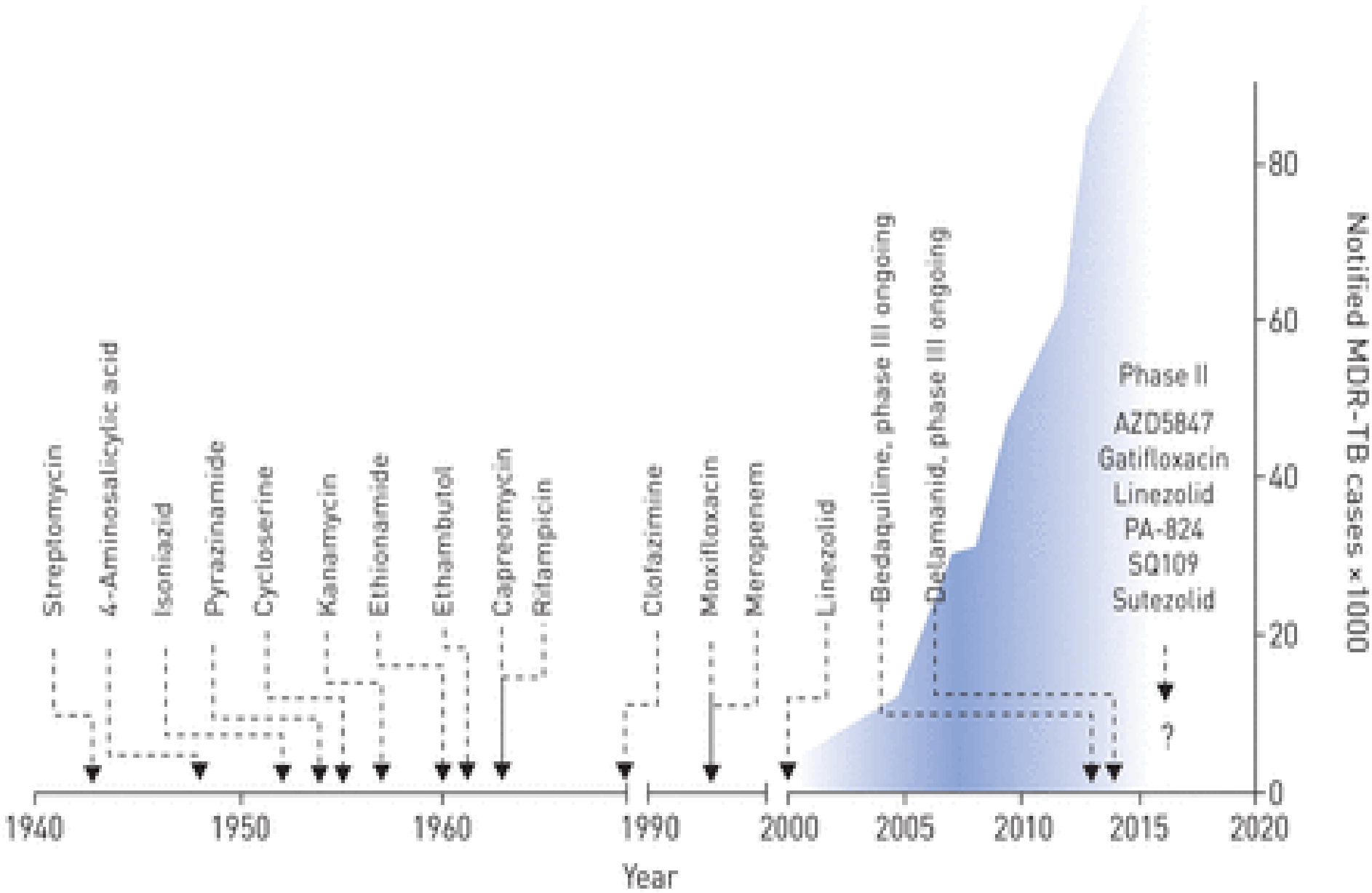
- **Tuberculosis (TB) remains a major worldwide public health problem, being the leading cause of death caused by a single infectious agent (only giving in to HIV / AIDS).**
- **World Health Organization (WHO) - the number of new cases and deaths from TB constituted respectively:**
- **- In 2013 - 9 million and 1.5 million,**
- **- in 2014 - 9.6 million and 1.5 million,**
- **- in 2015 - 10.4 million and 1.8-2 million,**
- **- in 2016 - 10.4 million and 1.3 million,**
- **- in 2017 10 mln and 1.3 mln**
- **There was a concomitant increase of the stems with polyresistence and extended resistance of about 480000-558000 cases.**
- **About 1.7 billion people, 23% of the world's population, are estimated to have an asymptomatic latent TB infection and are therefore at risk of developing active disease in their lifetime.**

(D'Ambrosio L.et al. , 2015; Hoagland D. et al., 2016; Podany A.T., Swindells S., 2016; Yong-Soo Kwon, 2017; Reiche MA.et al., 2017; **Rihwa Choi, M.D.et al. 2017;** Machado D.et al., 2018; WHO, 2018).

History of anti-TB drugs (Schito M.et al. 2015)



ANTI-TB DRUGS E (OLARU ID ET AL. 2014)



WHO 2011 CLASSIFICATION

Group 1 **I linie**
- Isoniazida
- Rifampicina
- Ethambutol
- Pirazinamida

Group 2 **Injectabile**
- Streptomicina
- Kanamicina
- Amikacina
- Capreomicina

Group 3 **Fluoroquinolonele**
- Levofloxacina
- Moxifloxacina
- Gatifloxacina
- Ofloxacina

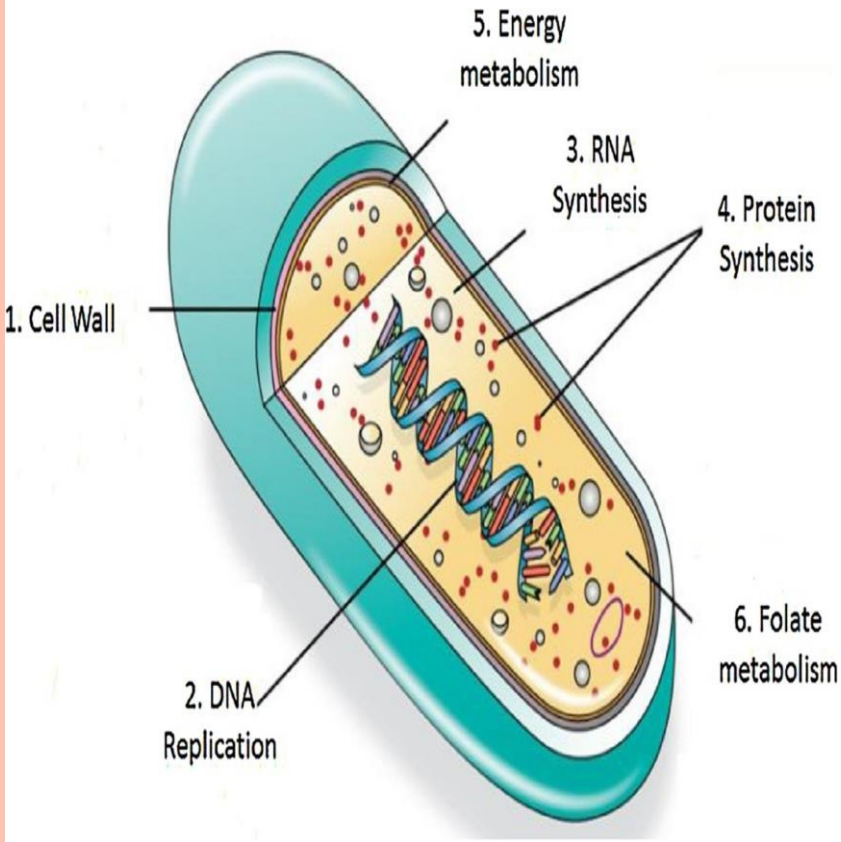
Group 4 **Orale bacteriostatice II linie**
- Ethionamida/protionamida
- Cicloserina/terizidon
- acid aminosalicilic

Gr 5 **preparate cu date limitate de E & I**
- Linezolid
- Clofazimina
- Amoxicillina/clavulanat
- Imipenem/cilastatina
- Meropenem
- dose mari isoniazidă
- Tioacetazonă
- Clarithromicină

(2) WHO 2016 classification			**(3) Possible future developments**	
Group A Fluoroquinolonele		• Levofloxacina • Moxifloxacina • Gatifloxacina	*Group A* Fluoroquino-lone	• Levofloxacina • Moxifloxacina • Gatifloxacina
Group B II linie injectabile		• Amikacina • Capreomicina • Kanamicina (Streptomicina)	*Group B* Alte II linie	• Bedaquilina • Delamanida • Ethionamid/prothionamida • Cycloserine/terizidone • Linezolid • Clofazimina
Group C Alte II linie		• Ethionamida/protionamida • Cicloserina/terizidon • Linezolid • Clofazimina	*Group C* Injectabile II linie	• Amikacina • Capreomicina • Kanamicina • Meropenem/clavulanat
Group D Add-on agents (not core MDR-TB Regimen components)	D1	• Pirazinamida • Ethambutol • doze mari isoniazidă	*Group D* Add-on agents (not core MDR TB regimen components)	• Pirazinamida • Ethambutol • doze mari isoniazidă • acid aminosalicilic • Amoxicillina–clavulanat • Rifabutina
	D2	• Bedaquilina • Delamanida		
	D3	• acid aminosalicilic • Imipenem–cilastatina • Meropenem • Amoxicillina–clavulanat • Tioacetazonă		

Tiberi S.et al.2017

Targets of anti-tuberculosis druds



Cell Wall

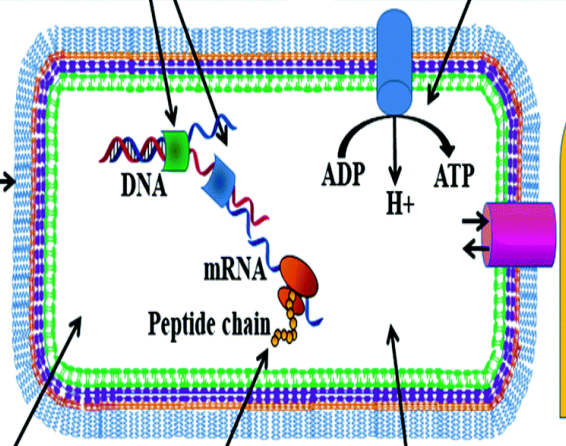
Arabinogalactan
•DprE1, IspD, RmlC, EmbB

Mycolic acid
•Antigen 85 complex, Fad32, Pks13, PimA, PcaA,, MmpL3, InhA, AccD6, Cyclopropane synthase

Peptidoglycan
•IspD, D,D-transpeptidase, L,D transpeptidase, MurA to G, MurX, GlmU

Replication and Transcription
DNA Gyrase, RNA polymerase

Energy Production
• QcrB, Isocitrate lyase , Malate synthase (GlcB), ATP synthase, Lipoamide dehydrogenase, Glutamine synthatase, Fumarate hydratase



Membrane transport
• SecA cytoplasmic ATPase, MmpL3

Regulatory Process
•PknB, PknG, DevR, DevS, Tyrosine phosphatase

Protein Synthesis
30S ribosomal subunit, Peptide Deformylase, AspS, LeuRS

Other targets
• FtsZ – Cell division
• ClpP – Degradation of damaged proteins
• 20S Proteasome - Degradation of damaged proteins
• MenA to G – Vitamin K2 synthesis

North EJ et al.2014; Zumla AI.et al.2014, Yuan T et al.2018; Hoagland D.et al., 2016, Machado D.et al. 2018; Abrahams K.A.et al, 2018; Bhat ZS et al., 2018 Khustro A.et al.2018; Pushkaran AC,.et al. 2019; Catalão MJ.et al,2019;

Classification of anti-TB drugs by M of A

A. Cell wall synthesis inhibitors:

Mycolic acid synthesis inhibitors: isoniazid, ethionamide, pretionamide, delamanide, pyrazinamide, thioacetazone;

Inhibitors of arabinogalactan synthesis: ethambutol,

Peptidoglycan synthesis inhibitors: meropenem, imipenem, amoxicillin / clavulanate, cycloserine, capuramycin.

B. Inhibitors of protein synthesis:

Aminoglycosides: streptomycin, kanamycin, amicacin;

Macrolides: clarithromycin, etc.

Oxazolidindones: linezolid, sutezolid, delpazolid, countzolid, etc .;

Pyrazinamide analogues - pyrazinamide;

C. Inhibitors of RNA and DNA synthesis:

DNA-gyrase and topoisomerase inhibitors:

Fluorquinolones: levofloxacin, gatifloxacin, moxifloxacin;

RNA polymerase inhibitors: ansamycins: rifampicin, rifapentin, rifabutin, etc.

DNA synthesis inhibitors: riminophenazine: clofazimine,

Folate inhibitors, nucleic acid predecessors: Paraaminosalicylic acid

D. Inhibitors of energy metabolism:

ATP-synthase inhibitors: Diarylquinoline - bedacvilin,

It inhibits energy metabolism: pyrazinamide

E. Other targets: auranofine, metformin, artemisine, chlorpromazine, verapamil,

New groups of anti-tuberculosis DRUGs (in clinical trials phase I-III)

- Fluorquinolone: ofloxacin, levofloxacin, gatifloxacin, moxifloxacin;
- Oxazolidinones: linesolid, sutezolid, delpazolid, tedizolid, AZD5847 etc .;
- Ansamicine: Rifapentin, Rifabutin
- Beta-lactamines: Amoxicil + clavulanate;
- Meropenem + clavulanate; faropenem
- Nitroimidazoles - delamanide, pretonamide; OPC-67683, TBA-354,
- Diarilquinoline - bedacvilin, TBAJ-587
- Ethylenediamines - SQ109;

New groups of anti-tuberculosis DRUGs (preclinical studies)

- **Macrolide:** claritromicina;
- **Spectinamide**: spectinamicina, Pb1599
- **Capuramicine:** capuramicina, SQ641;
- **Griselmicine:** griselmicina
- **Piridomicinele - piridomicina**
- **Amide Imidazopiridine** -Q-203
- **Benzotiazone** - BTZ-043; PBTZ-169
- **Adamantil ureici** - AU-1235,
- **Analogii pirazinamidei** – pirazinamida,
- **Riminofenazine** – clofazimina, TBI-166
- **Peptide antimicrobiene** – defensine, catelicidine de origine entomologică

Lead Optimisation

- Lipiarmycin
- Rotenone
- Thiolactomycin
- Aminopyridines
- Indoles
- Macrolides
- Pyrazinamide Analogues
- Antimicrobial Peptides
- Imidazoles
- Riminophenazines

Early-stage Development

- TBI-166
- CP-ZEN-45
- SQ609
- SQ641
- 1599
- DC-159a
- Q201
- SPR-10199

GLP Toxicity

- BTZ-043
- TBA-7371
- TBA-354
- GSK-070

Phase I

- Q203
- PBTZ169

Phase II

- Sutezolid
- Linezolid EBA
- High Dose Rifapentine for DS-TB
- Bedaquiline/Pretomanid/Pyrazinamide
- Levofloxacin with OBR for MDR-TB

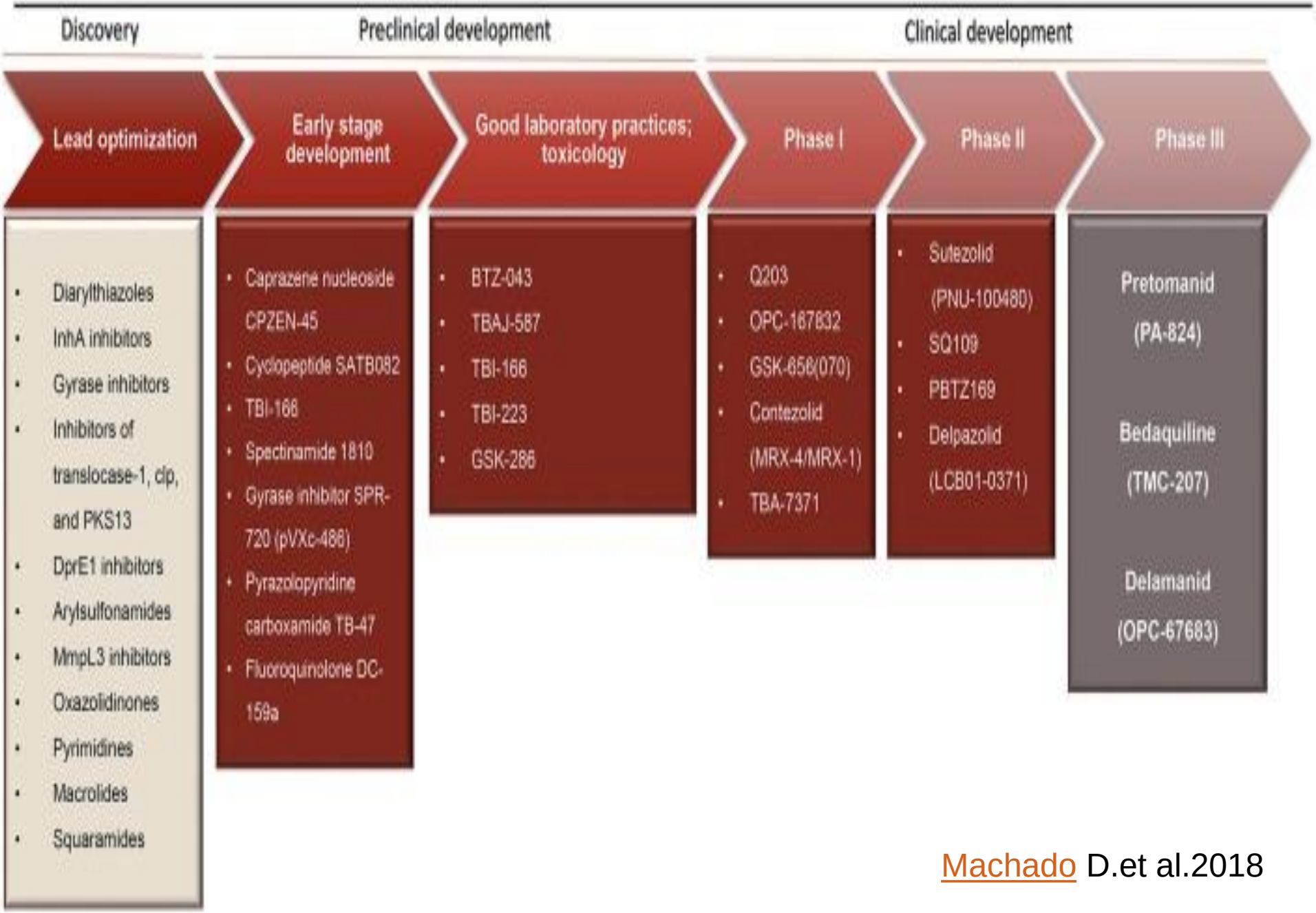
Phase III

- Rifapentine/Moxifloxacin for DS-TB
- Delamanid with OBR for MDR-TB
- Pretomanid/Moxifloxacin/Pyrazinamide
- Bedaquiline/Pyrazinamide/Linezolid
- Bedaquiline/STREAM with OBR
- Bedaquiline/Linezolid with OBR for MDR-TB

Chemical Class:

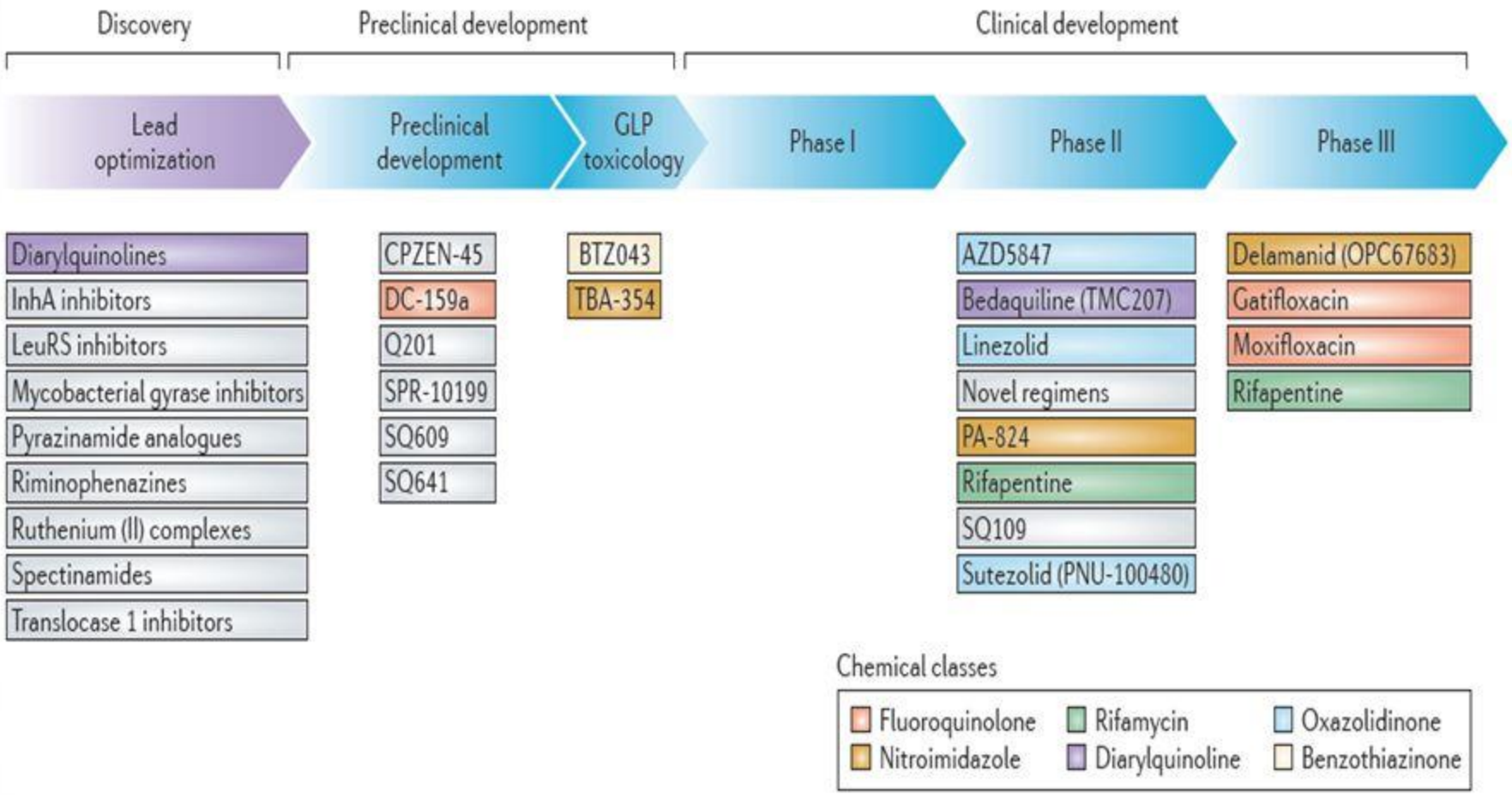
Quinolones	Imidazoles	Oxaborole
Phenazines	Indoles	Oxazolidinones
Mycins	Macrolides	Antimicrobial Peptides
Piperidines	Nicotinamide	Rotenoids

Global tuberculosis drug discovery pipeline



Machado D.et al.2018

Promising TB Drug pipeline



Combining these new drugs with existing TB drugs offers hopes for regimens – better tolerated, shorter duration with few drug-interactions

THANK YOU !