UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Subject: Microbiology (1)
Topic: Antimicrobials

Academic Year 2023/2024

Faculty: Medicine
Field of study: Medicine
Level of study (unif. Master's):
Form of study (full time, part-time):
Year of study: II, III

Academic title/professional title: prof. dr hab.
Name, last name of the lecturer: Beata Sobieszczańska
Position of person conducting classes: professor
Wroclaw Medical University

Glossary

- **MIC** - minimal inhibitory concentration
- **MBC** - minimal bactericidal concentration
- **BLIs** - β-lactamase inhibitors
- **β-lactamases** (e.g., penicillinases) – bacterial enzymes degrading β-lactam antibiotics
- **Empirical treatment** – use of antibiotic/antibiotics active against the most probable etiology (pathogen unknown) of infection based on documented clinical experience
- **Targeted treatment** – selection of antibiotic based on drug sensitivity pattern (known pathogen – isolated from the patient)
- **Combined** - simultaneous use of 2 or more antibiotics (effective treatment and reducing the risk of resistance development): tuberculosis, mixed infections: aerobic + anaerobic, H. pylori, use of drug synergism (TMP-SMX) - reduction of doses of individual drugs
- **Prophylaxis** - the use of antibiotics in a healthy person who has contact with sick people to prevent the development of the disease

Antimicrobials

Bactericidal

β-lactams
Glycopeptides
Bacitracin
Fosfomycin
Aminoglycosides
Polymyxins
Daptomycin

Bacteriostatic

Tetracyclines
Macrolides
Lincosamides
Streptogramins
Ketolides
Mupirocin
Oxazolidinones
Fusidic acid

Narrow spectrum

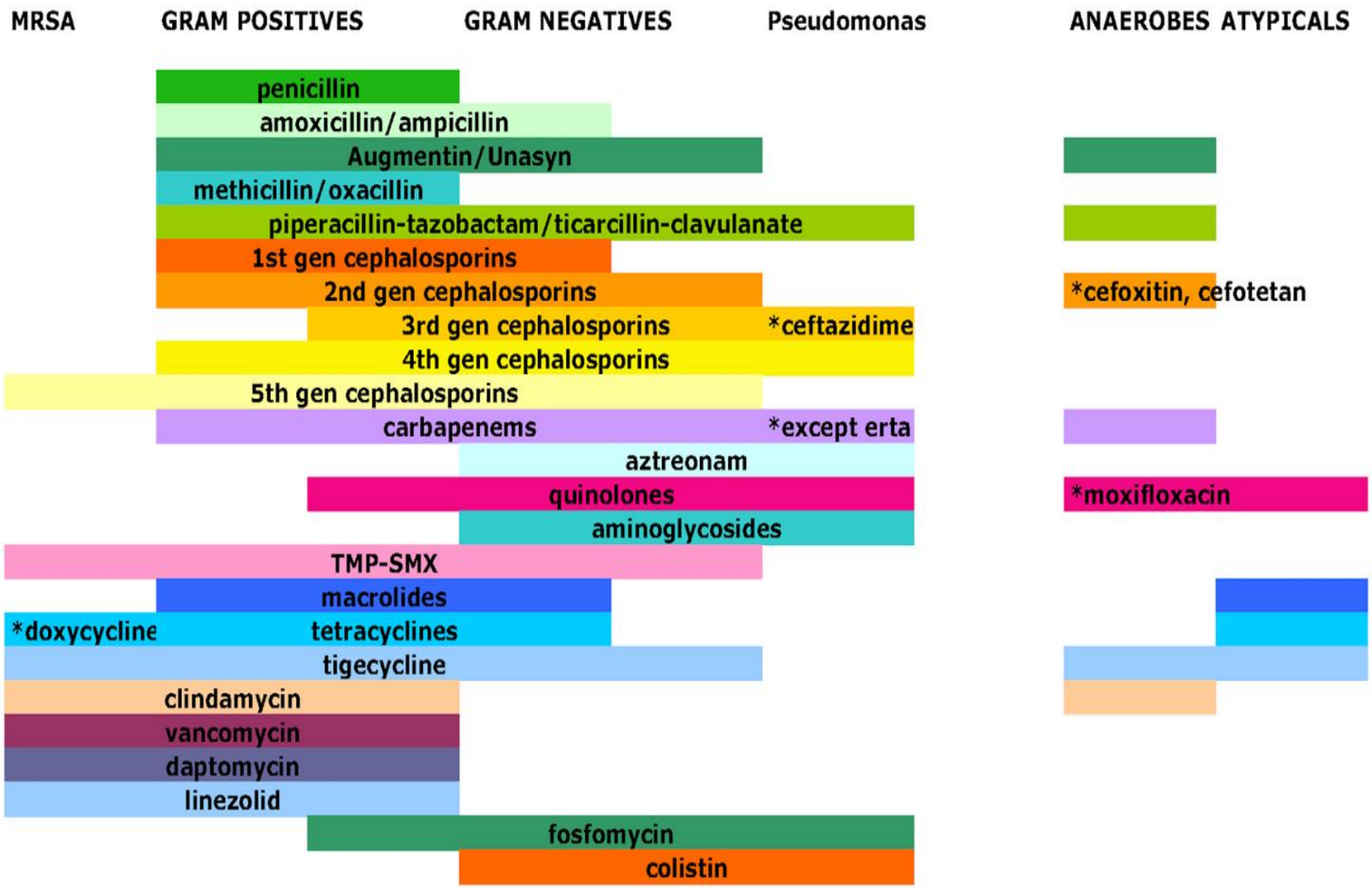
One bacterial group
GP or GN

Glycopeptides - GP
Fidaxomicin - C. difficile

Wide spectrum

GP, GN bacteria,
anaerobes

β-lactams
Aminoglycosides
Tetracyclines
Macrolides



Mechanisms of action of antibiotics on bacteria

- **Inhibition of bacterial cell wall (peptidoglycan) synthesis** (β-lactam antibiotics, glycopeptides, fosfomycin, bacitracin)
- **Disruption of the cytoplasmic membrane** (daptomycin, polymyxins)
- **Inhibition of protein biosynthesis** (tetracyclines, aminoglycosides, macrolides, lincosamides, oxazolidinones)
- **Inhibition of nucleic acid synthesis** (quinolones, rifamycins, TMP-SMX, fidaxomicin)

Mode of action of antibiotics

Cell wall synthesis inhibitors

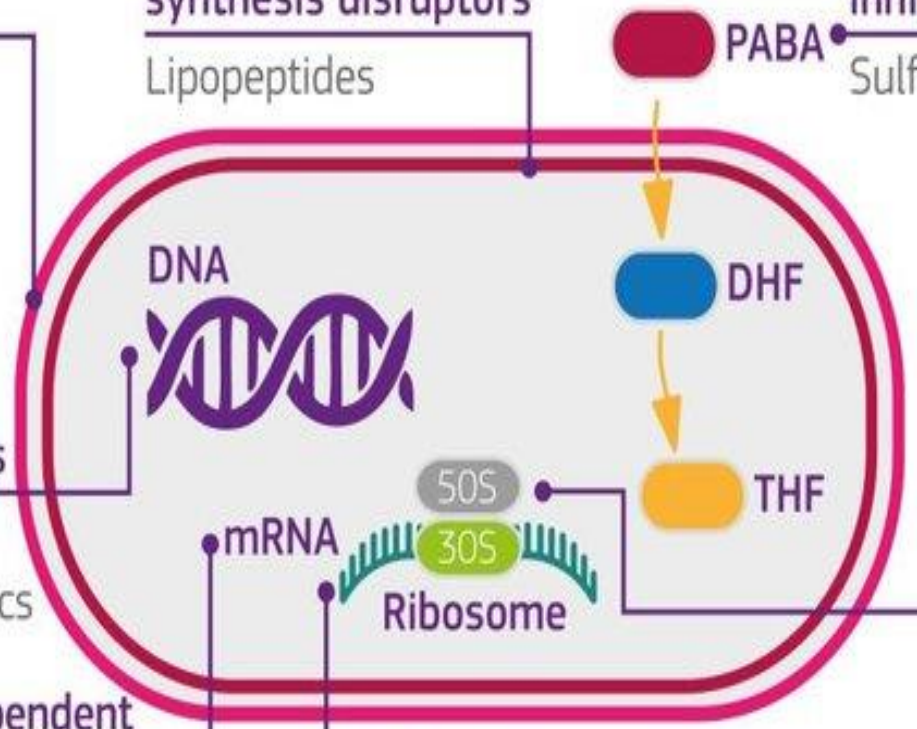
β-lactams
Glycopeptides
Fosfomycin
Bacitracin
Alafosfalin

Cell membrane synthesis disruptors

Lipopeptides

Folate synthesis inhibitors

Sulfonamides



DNA gyrase inhibitors

Quinolones
Coumermycin antibiotics

Protein synthesis (30S and 50S inhibitors)

Tetracyclines
Aminoglycosides
Macrolides
Lincosamides
Amphenicols
Pleuromutilins
Oxazolidinones

Inhibition of DNA-dependent RNA polymerase

Rifampicin

RNA synthesis inhibitors

Ansamycines

PBP = Penicillin-Binding Proteins (enzymes - transpeptidases)

β-lactam antibiotics

- Penicillins – natural and semisynthetic
- Cephalosporins
- Monobactams
- Carbapenems

β-lactamase Inhibitors (BLIs)

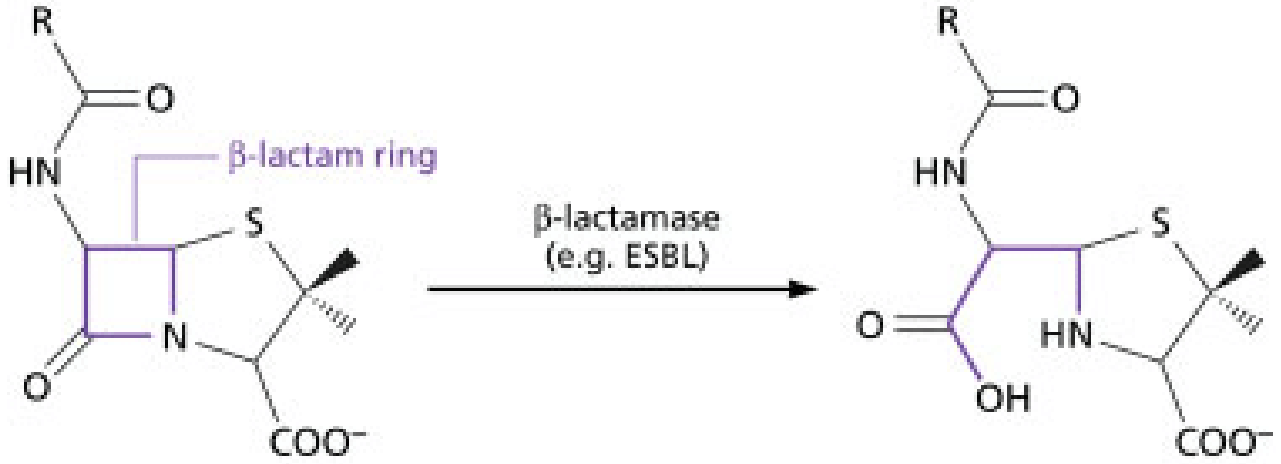
BLIs – β-lactamase inhibitors

I generation (old):
Clavulanic acid
Sulbactam
Tazobactam
II generation (new):
Avibactam
Vaborbactam
Relebactam

BLIs – lack or weak antibacterial activity
Bind irreversibly with bacterial b-lactamases
= structurally, they resemble β-lactams

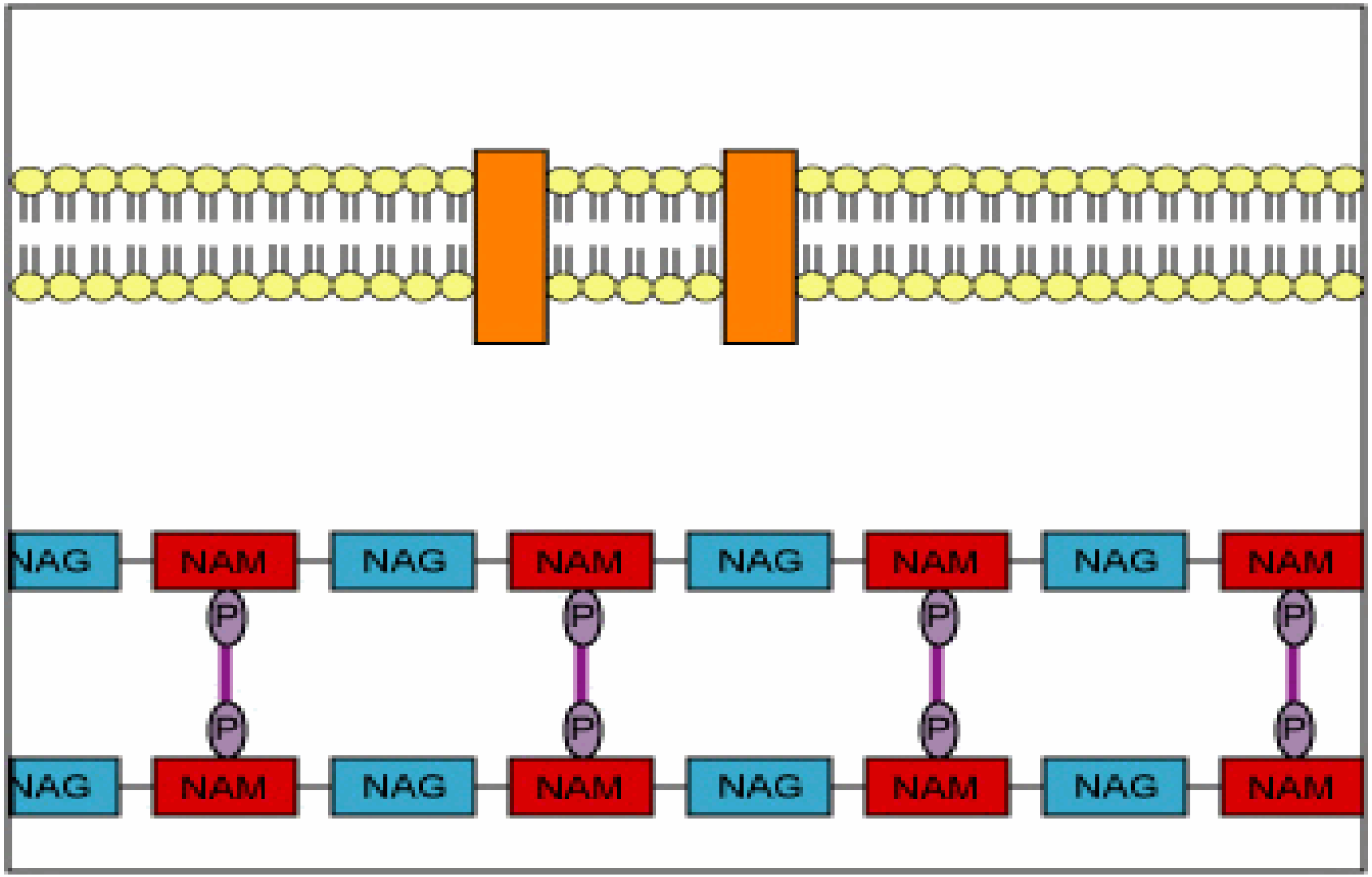
Bacterial β-lactamases = enzymes that degrade β-lactam antibiotics

Examples:
Amoxicillin + clavulanic acid
Ampicillin + sulbactam
Piperacillin + tazobactam
Ceftazidime + avibactam
Aztreonam + avibactam
Meropenem + vaborbactam
Aztreonam + avibactam
Imipenem + relebactam



Penicillin **Penicilloic acid**

β-lactams block the enzyme transpeptidase responsible for assembling peptide cross-links in peptidoglycan



Antibiotics that inhibit cell wall synthesis

PENICILLINS

Natural

Benzyl, benzathine, procaine penicillin (parenteral)
Phenoxymethyl (oral)

Semisynthetic

Anti-staphylococcal (isoxazolyl)
- Cloxacillin
- Flucloxacillin
- Nafcillin
- Oxacillin

Aminopenicillins
- Ampicillin
- Amoxycillin

Anti-Pseudomonal

Ureidopenicillins
- Azlocillin
- Mezlocillin
- Piperacillin

Carboxypenicillins
- Ticarcillin
- Carbenicillin
- Carfecillin

Penicillins are not effective in the treatment of infections caused by intracellular bacteria

MRSA = resistant to β-lactams Staphylococcus aureus
PRP = resistant to penicillins Streptococcus pneumoniae
ESBL - β-lactamases of extended spectrum of activity

Penicillins - spectrum

Penicillinase-sensitive: natural penicillins

GP bacteria: streptococci, pneumococci, staphylococci, enterococci, Actinomyces, Corynebacterium
Spiral: Treponema, Borrelia, Leptospira
Some GN: Pasteurella, Neisseria
Anaerobic GP: Streptococcus, Clostridium

Penicillinase-resistant: isoxazolyl

GP cocci + penicillinase-producing staphylococci, but NOT MRSA and MRSE !!!
Weak activity against streptococci, anaerobic GP cocci
Enterococci resistant !!!

Aminopenicillins
Susceptible to penicillinases

GP bacteria: streptococci, staphylococci, enterococci, Listeria
GN bacteria: Haemophilus, E. coli, Proteus mirabilis, Salmonella, Shigella, Bordetella pertu

In combination with BLIs, they are active against bacteria producing β-lactamases

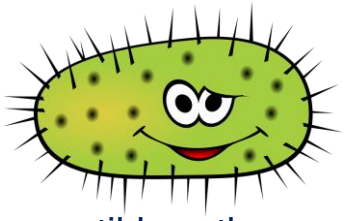
Ureidopenicillins & carboxypenicillins:
Susceptible to penicillinases

GP: streptococci, pneumococci, staphylococci, T. pallidum, Borrelia, Actinomyces
GN: Haemophilus, E. coli, Proteus mirabilis, Pseudomonas

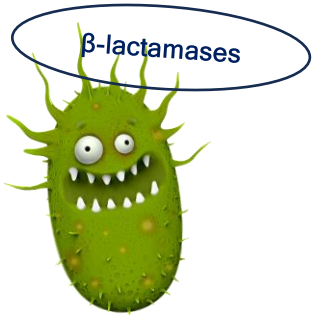
Treatment: respiratory tract infections (strep pharyngitis, pneumonia), urinary tract infections, bile tract infections, otitis media, endocarditis, meningitis, osteomyelitis, arthritis, skin & soft tissue infections, bacteremia, sepsis, sexually transmitted diseases, listeriosis, tetanus, borreliosis, etc.

Cephalosporins are more resistant to β-lactamases

Ambulatory patient – susceptible pathogens



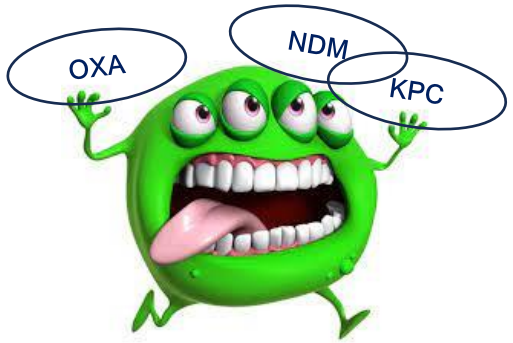
Susceptible pathogens



Less susceptible pathogens

Hospitalized patients – resistant pathogens

Resistant bugs



Highly resistant nasty bags

Cephalosporins I gen.

Cephalosporins II gen.

Cephalosporins III gen.

Cephalosporins IV & V gen.

Cephalosporins are more resistant to β-lactamases

I generation:
Cefalexin, cefadroxil
cefazoline

GP cocci (streptococci, staphylococci, BUT NOT resistant strains: PRP, MRSA)
Some GN rods (E. coli, Klebsiella, Proteus mirabilis);
preoperative prophylaxis, outpatient treatment

II generation:
Cefuroxime, cefaclor
cefamandole

GP cocci (streptococci, staphylococci), GN rods (Haemophilus, Moraxella - including β-lactamase-producing strains, E. coli, Klebsiella pneumoniae, Proteus mirabilis)
outpatient treatment (e.g., bacteria resistant to aminopenicillins)

III generation:
Cefixime
Cefotaxime, ceftriaxone, ceftazidime, cefoperazone

GP cocci (streptococci, staphylococci, but NOT resistant strains MRSA, MRSE !!!)
Better activity against GN bacteria - especially Pseudomonas (Neisseria, Haemophilus, Intestinal rods, but NOT ESBL+ strains
used only in hospital treatment
Most active against P. aeruginosa - **ceftazidime** (inactive against GP cocci) and **cefoperazone**

IV generation:
Cefepime

Resemble III gen. GN and GP; greater stability against β-lactamases
P. aeruginosa, Acinetobacter, intestinal rods (including AmpC-producing strains)
Reserved for the treatment of serious hospital infections, including resistant strains

V generation:
Ceftaroline, ceftobiprole, ceftozolane

GP cocci, including resistant strains: MRSA, PRP, pneumococci resistant to ceftriaxone, Enterococcus faecalis (but **NOT** E. faecium), Listeria; limited activity against anaerobes
GN rods (but **NOT** ESBL+), Pseudomonas and Acinetobacter RESISTANT !!!

Siderophore cephalosporin
Cefiderocol - active against resistant GN rods (but inactive against GP bacteria and anaerobes)

Enterococci are resistant to all cephalosporins (except E. faecalis to ceftaroline), intracellular bacteria, and ESBL+

Monobactams

Aztreonam

Aerobic GN bacteria: Enterobacterales, Pseudomonas, Neisseria, Haemophilus, Neisseria (except strains producing ESBL and AmpC β-lactamases)

Intrinsically resistant are Stenotrophomonas maltophilia, Alcaligenes, Burkholderia cepacia, GP bacteria and anaerobes

Safe for people allergic to penicillins

Carbapenems

GP↑ Imipenem/cilastatin
GN↑ Meropenem
GN↑ Doripenem

Ertapenem

With new BLI:
Imipenem/relebactam
Meropenem/vaborbactam

Broad spectrum: GP bacteria (streptococci, staphylococci **except MRSA!!!** enterococci, Listeria, Nocardia etc.),
GN bacteria (intestinal rods, Pseudomonas, Acinetobacter, Neisseria, etc.)
Anaerobes (Clostridium **except C. difficile**, Prevotella, Bacteroides etc.)
Ertapenem INACTIVE against P. aeruginosa and Acinetobacter and Enterococcus
Reserved for the treatment of nosocomial severe infections caused by resistant strains of bacteria (hospital lung infections - cystic fibrosis, ventilation, complicated urinary tract infections, skin and soft tissue infections, endocarditis, etc.)
Except for ertapenem - used in the outpatient treatment of lung and intra-abdominal infections and prophylactically in surgical procedures on the large intestine

Stenotrophomonas maltophilia, Burkholderia cepacia, Enterococcus faecium and intracellular bacteria (Chlamydia, Mycoplasma) are **intrinsically resistant to carbapenems**

In the treatment of pseudomonas infections often used with aminoglycosides

Antibiotics that inhibit cell wall synthesis

Glycopeptides

Vancomycin
Teicoplanin

Lipoglycopeptides

Telavancin
Oritavancin
Dalbavancin

Ramoplanin (resemble vancomycin) – inhibits peptidoglycan synthesis; active against aerobic and anaerobic GP bacteria

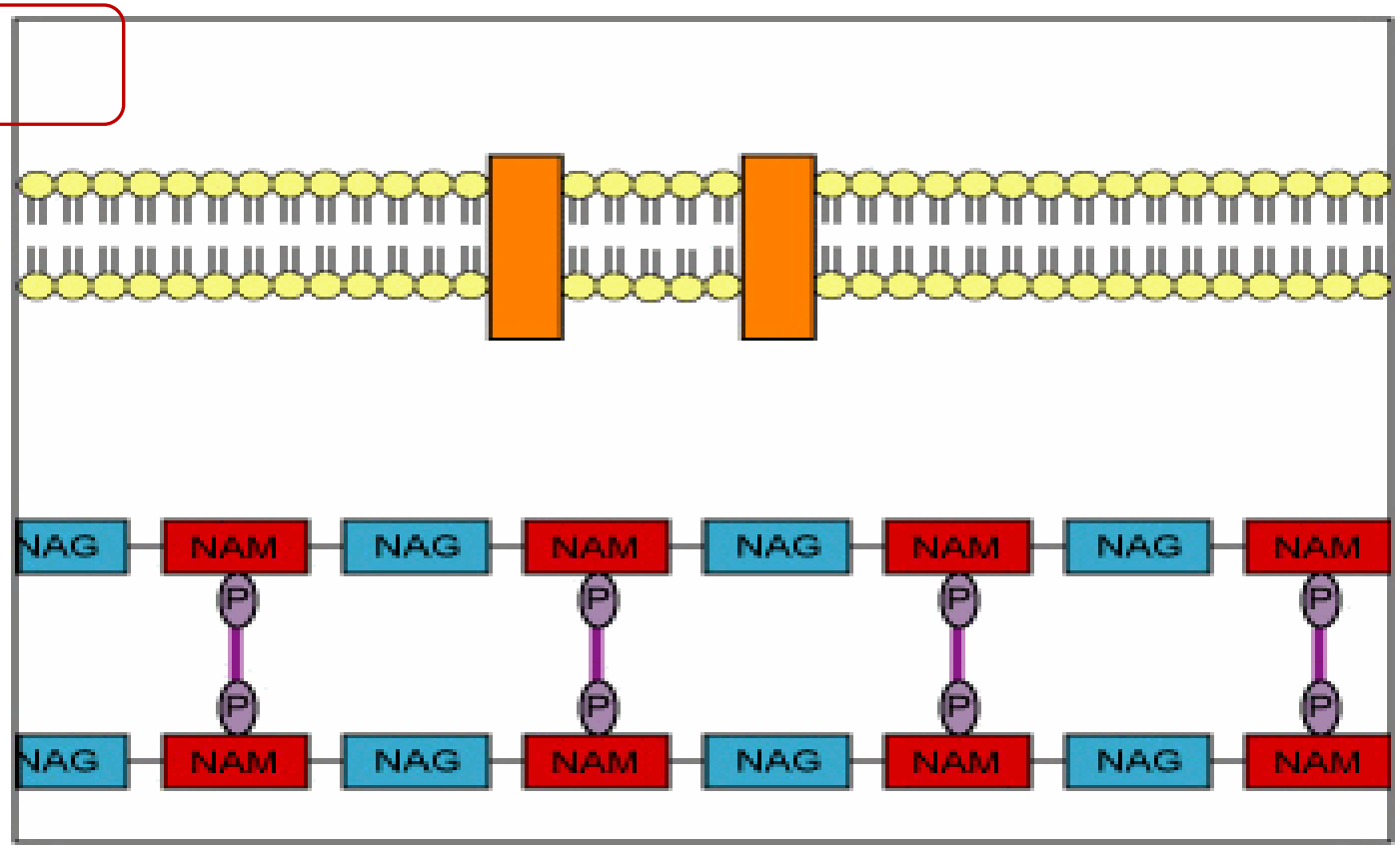
Bactericidal – inhibit cell wall synthesis in bacteria
Spectrum: **GP bacteria ONLY**, including resistant strains (e.g., MRSA)

Treatment of blood, endocardial, and soft tissue infections

Treatment of soft tissue infections

Active against: streptococci, enterococci, staphylococci, C. difficile, Corynebacterium jejkeium, Listeria

Lipoglycopeptides: S. aureus/(MRSA), Enterococcus/VRE, S. pyogenes, S. agalactiae



Antibiotics that inhibit cell wall synthesis

Fosfomycin

Bactericidal

Broad spectrum: GP bacteria (Staphylococcus – including resistant strains: MRSA, Enterococcus - including resistant strains: VRE, Neisseria gonorrhoeae, Listeria) and GN bacteria (intestinal rods: Salmonella, Shigella, Proteus, Enterobacter, Citrobacter)

Non-fermenting rods are intrinsically resistant

Used orally in urinary tract infections (UTI) or parenterally in serious infections (e.g., endocarditis, complicated urinary tract infection, intra-abdominal infections)

Bacytracyna

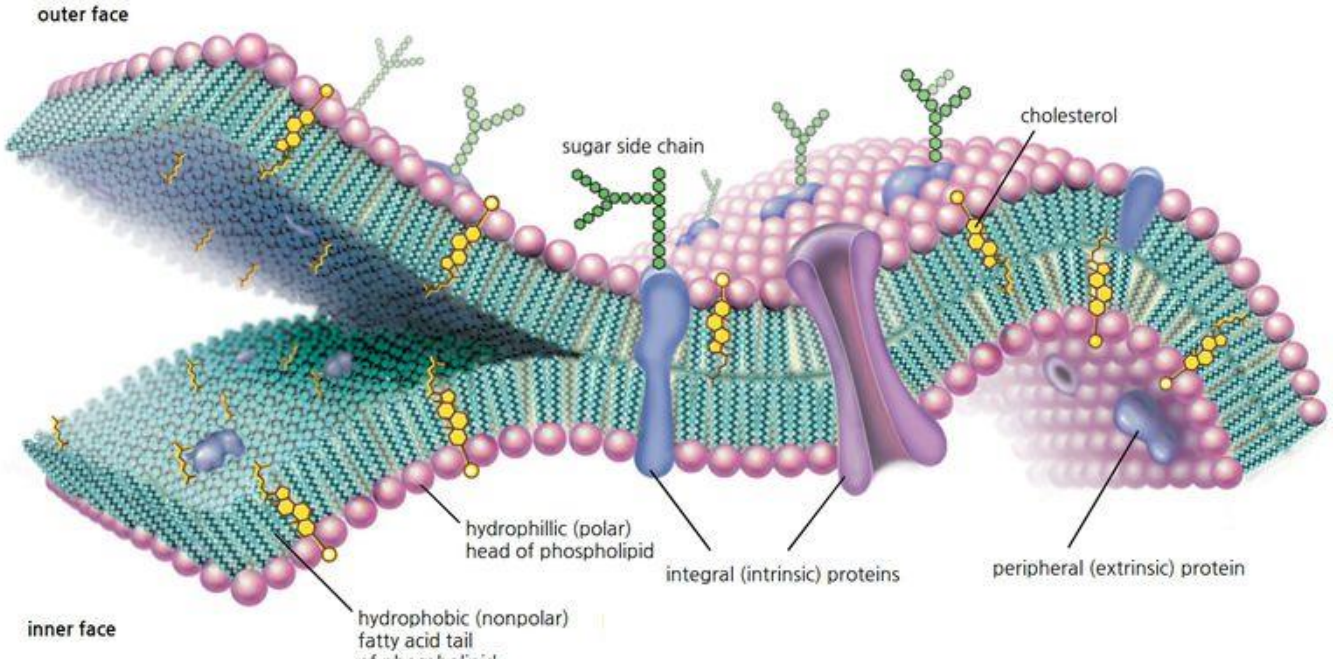
Bactericidal

Narrow spectrum: GP bacteria (Staphylococcus, Streptococcus, Corynebacterium, Clostridium)

Applied topically (ointments), often with neomycin and/or polymyxin B (toxic !)

Polymyxins: polymyxin B i polymyxin E (colistin)

Bactericidal polypeptide antibiotic
surfactant (neutralizes LPS)
Narrow spectrum: GN bacteria ONLY
(fermenting and non-fermenting rods)
Intrinsically resistant are: Proteus, Burkholderia, Neisseria, Brucella, Morganella, Providencia, Legionella



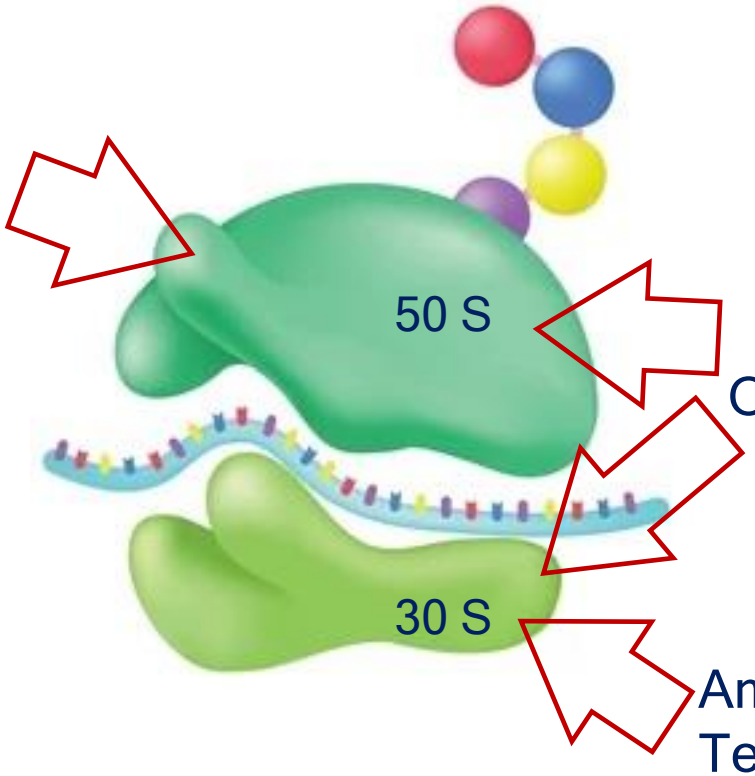
Daptomycin

Bactericidal lipopeptide antibiotic (depolarize membranes)
Narrow spectrum: GP bacteria ONLY, including resistant (MRSA, VRE, etc.)
Pulmonary surfactant inactivates daptomycin - DO NOT use it to treat pneumonia!
Active in soft tissue infections (diabetic foot), bone and joint infections, staphylococcal bacteremia
Contraindicated in children

Antibiotics that inhibit bacterial protein biosynthesis

Bacteriostatic except aminoglycosides, nitrofurans

Macrolides
Lincosamides
Ketolides
Streptogramins
Chloramphenicol



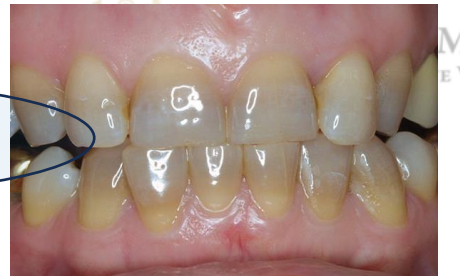
Oxazolidynones

Aminoglycosides
Tetracyclines
Glicylcyclines (tigecycline)

Antibiotics that inhibit bacterial protein biosynthesis

Tetracyclines: doxycycline, tetracycline, chlortetracycline, eravacycline

Contraindicated in children



Bacteriostatic

Broad spectrum: **GP and GN bacteria, atypical, spiral, and anaerobes** (good penetration into host cells)

It must not be used in streptococcal pharyngitis - it does not prevent rheumatic fever (no eradication)

Bacteria often resistant: staphylococci, streptococci, pneumococci, intestinal rods, Bacteroides fragilis, M. genitalium

NO activity against Legionella pneumophila, Pseudomonas aeruginosa, Proteus, Serratia

Treatment – infections caused by atypical and spiral bacteria: borreliosis, atypical pneumonia, skin anthrax, plaque, leptospirosis, cholera

Eravacycline – active against GP cocci (MRSA, VRE), GN rods (ESBL, KPC)

Glicylcyclines: tigecycline (parenteral)

Bacteriostatic

Broad spectrum: **GP cocci** (including resistant strains: MRSA, VRE),

GN bacteria (including resistant intestinal rods: ESBL-, KPC-, and AmpC – producing Acinetobacter baumannii, Klebsiella pneumoniae

Anaerobes (Cutibacterium, Peptostreptococcus, Clostridium)

Atypical bacteria (Mycoplasma, Chlamydia, Legionella), and Mycobacterium

BUT weak activity against Pseudomonas aeruginosa, Proteus mirabilis, Burkholderia cepacia, Morganella, Providencia

Antibiotics that inhibit bacterial protein biosynthesis

C15 C16

Macrolides: erythromycin, clarithromycin, roxithromycin, azithromycin, spiramycin

C14

Bacteriostatic

Broad spectrum: GP and GN bacteria, atypical and spiral bacteria, anaerobes, mycobacteria (penetrate into tissues)

GN rods (Bordetella, Haemophilus, Pasteurella) - clarithromycin, azithromycin

Treatment - infections caused by atypical bacteria

Immunomodulatory, inhibit bacterial adherence and biofilm production

Ketolides: telithromycin, solithromycin

Bacteriostatic

Broad spectrum resembling macrolides: GP and GN bacteria

Solithromycin - active against S. pneumoniae MLS, S. aureus VISA, Enterococcus VRE

Lincosamides: clindamycin

Bacteriostatic

penetrate well into tissues, including bones, leukocytes, and macrophages

Narrow spectrum: GP bacteria (cocci, GP anaerobes (Fusobacterium), Actinomyces)

Inactive against GN rods and cocci

Oxazolidinones: Linezolid, tedizolid

Bacteriostatic against staphylococci and enterococci but bactericidal against streptococci

Narrow spectrum: GP cocci (Staphylococcus/MRSA, VISA, VRSA, Streptococcus pneumoniae/PRP, Enterococcus/VRE and Corynebacterium, Mycobacterium

An alternative to glycopeptides, daptomycin, tigecycline

Antibiotics that inhibit bacterial protein biosynthesis

Aminoglycosides: streptomycin, gentamycin, tobramycin, netilmicin, amikacin

Bactericidal

Broad spectrum: **aerobic GN bacteria** (fermenting and non-fermenting rods), Mycobacterium tuberculosis

Active against GP bacteria ONLY in combination with β-lactams (e.g., treatment of streptococcal and enterococcal endocarditis)

NOT active against Stenotrophomonas maltophilia and Burkholderia cepacia

Chloramphenicol (toxic ! = limited usage)

Bacteriostatic, but bactericidal against: Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae

Broad spectrum: **GP and GN bacteria, atypical, spiral**

Inactive against GN rods: Pseudomonas aeruginosa, Acinetobacter, Proteus mirabilis, Enterobacter cloaceae, Citrobacter freundii

Nitrofurans: furazidine (furagin), nitrofurantoin, nifuroxazide, furazolidone

Bactericidal (inhibits protein synthesis and damages DNA)

Broad spectrum: **GP cocci** (Staphylococcus, Streptococcus, Enterococcus) **and GN rods** (intestinal - except Proteus, Serratia, Morganella)

Inactive against Pseudomonas aeruginosa and Acinetobacter

Urinary tract infections

Streptogramins: quinupristin + dalfopristin (Synercid)

Bacteriostatic, but at higher concentrations bactericidal
Broad spectrum: GP cocci (staphylococci, streptococci – including resistant strains)
Atypical bacteria (Mycoplasma, Legionella, Chlamydia), anaerobes

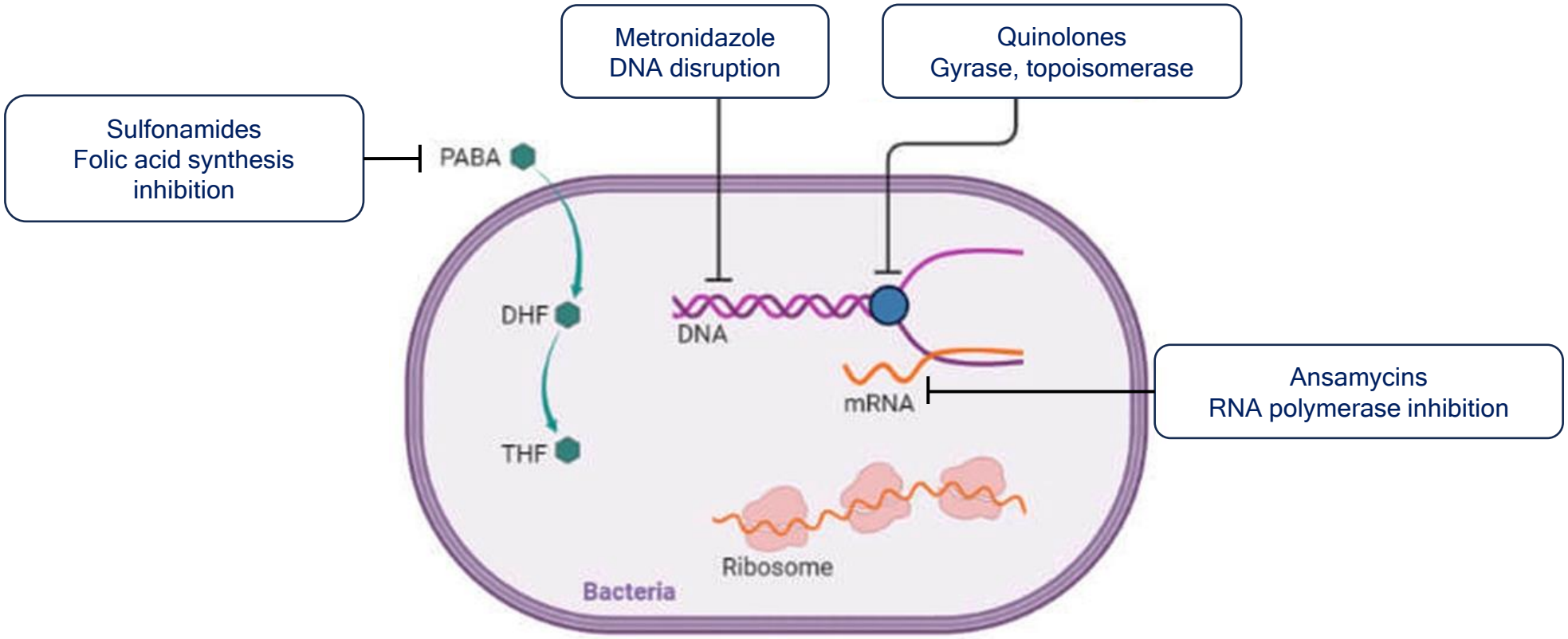
Mupirocin

Bacteriostatic or bactericidal – depending on the concentration
Narrow spectrum: Staphylococcus (including MRSA), streptococci
Creams and ointments for topical treatment of minor skin infections and combating the carriage of Staphylococcus aureus

Fusidic acid

Bacteriostatic, but at higher concentrations bactericidal
Spectrum: GP cocci (staphylococci/MRSA) and GN bacteria (meningococci, gonococci, Moraxella, Bordetella, Corynebacterium
Staphylococcal resistance is rapidly increasing - combined treatment with cloxacillin, rifampicin, clindamycin, vancomycin

Antibiotics that disturb the biosynthesis of nucleic acids in bacteria - bactericidal



Antibiotics that disturb the biosynthesis of nucleic acids in bacteria - bactericidal

Quinolones and fluroquinolones

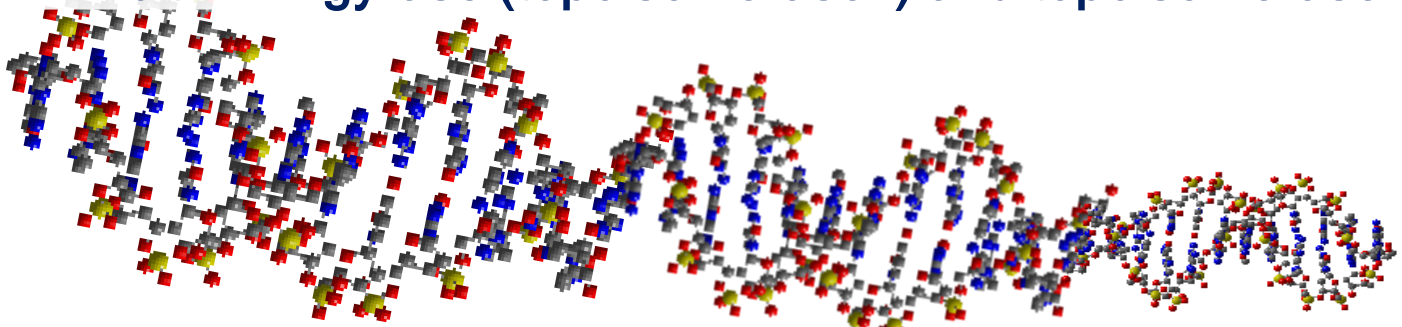
I generation QUINOLONES	II generation Fluoroquinolones	III & IV generations Respiratory fluoroquinolones
Nalidixic acid	Norfloxacin Pefloxacin Ciprofloxacin	Levofloxacin Moxifloxacin Gatifloxacin

Narrow spectrum: ONLY GP bacteria
Urinary tract infections (+ norfloxacin)

Broad spectrum: aerobic GN rods, some GP bacteria, atypical bacteria, Mycobacterium tuberculosis & MOTT
Ciprofloxacin – Pseudomonas aeruginosa

Broad spectrum:
GP cocci (resistant pneumococci/PRP, staphylococci, streptococci, enterococci
GN rods (intestinal, some non-fermenting)
GN small rods (Haemophilus, Bordetella
Spiral bacteria (Helicobacter, Campylobacter
GN cocci (Neisseria, Moraxella,
Atypical bacteria
Mycobacterium tuberculosis and M. fortuitum (atypical)

Inhibit DNA gyrase (topoisomerase I) and topoisomerase IV



Antibiotics that disturb the biosynthesis of nucleic acids in bacteria - bactericidal

Nitroimidazoles: metronidazole

Disrupts DNA via intermediate metabolites, active only in anaerobic conditions
Treatment of infections caused by anaerobes and mixed ones (aerobes + anaerobes)
Active against: anaerobic non-spore-forming GN rods (Bacteroides, Prevotella, Porphyromonas)
GP spore-forming bacilli (Clostridium, including C. difficile)
Helicobacter pylori (although currently often resistant)
Intrinsically resistant are other anaerobes: Actinomyces, Lactobacillus, Cutibacterium

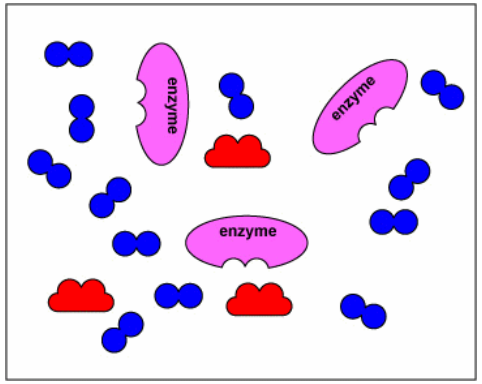
Ansamycins:

rifampin, rifaxmin (for treatment of gastrointestinal tract infections)
(rifapentine, rifabutin - tuberculosis treatment)

Block bacterial RNA polymerase
Spectrum: **rifampin = first-line drug in the treatment of tuberculosis (always in combination);**
Active against: GP cocci (staphylococci/MRSA, streptococci), atypical bacteria (Chlamydia, Legionella),
Some GN bacteria (Haemophilus, Neisseria meningitidis)
Low activity against intestinal GN rods

Cotrimoxazole (sulfamethoxazole trimethoprim, TMP-SMX)

Inhibit folic acid synthesis – bacterial cell growth inhibited; indirectly DNA synthesis inhibition
Sulfamethoxazole – sulfonamide, PABA analogue (para-aminobenzoic acid)
component of the folic acid molecule
Trimethoprim – blocks dihydrofolic acid reductase



Sulfamethoxazole + trimethoprim = synergy

Broad spectrum: **GP and GN bacteria**
GP cocci: staphylococci/MRSA, but **NOT enterococci !**
Other GP bacteria: Actinomyces, Nocardia, **Pneumocystis jirovecii**
GN intestinal rods (E. coli, Salmonella, Shigella, Yersinia), Haemophilus, Moraxella, gonococci, Bordetella, Legionella, Brucella, Vibrio, Listeria
and **Burkholderia cepacia & Stenotrophomonas maltophilia**

Fidaxomicin

Blocks bacterial RNA polymerase
Active against: GP bacteria, especially **Clostridium difficile** (next to metronidazole, vancomycin the drug of choice to treat post-antibiotic diarrhea)
Not absorbed from the intestines

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