ANTIBIOTICS I.

Introduction

Inhibitors of cell wall synthesis

Pathogens

Any agent causing disease.
Usually a living microorganism.
Capable of producing infection.
Poisons like Arsenic would be excluded

VIRUSES

Multi-celled but can only reproduce inside a plant, animal, or person.

Hepatitis	SARS
Herpes, Mono	AIDS,HIV
Warts	Influenza
Chicken Pox	Cold Sores
Small Pox	Cold Germs
Bird Flu H5N1	Measles
Norovirus	Tetanus
Yellow Fever	Typhoid
Ebola Hemmorhagic Fever	

BACTERIA

Tiny one-celled creatures
Can live inside or outside the body.

Tuberculosis	Pheumonia
Anthrax	Urinary Tract Infection
Staph	Peritonitis
E.Coli	Strep Throat
Typhoid	Stomach Ulcers
Salmonella	Tularemia
Morgellons ?	Lyme Disease

FUNGI

Multi-celled but plant-like similar to tree fungus.
Takes nutrition from a plant, tree, or animal.

Ringworm	Yeast Infection
Adv Pneumonia	Histoplasmosis
Candidiasis	Cryptococcosis

PROTOZOA

One-celled creatures.
Usually spread through water.

Malaria	Giardiasis
Chagas Disease	Cryptosporidiosis

PARASITES

Actual complex living organism.
Can live in intestinal tract or blood stream.

Round Worm	Tape Worm
Morgellons ?	Triginosis

PROTEIN

Multi-celled but can only reproduce inside a plant, animal, or person.

BSE Mad Cow Disease
vCJD Disease

Incomplete list gathered from various medical books.

Chemotherapy

- The use of drugs to treat a disease
- **Selective toxicity**: A drug that kills harmful microbes without damaging the host

Antibiotic/Antimicrobial

- **Antibiotics -** agents produced by a microorganism that kills or inhibits the growth of another microorganism

- **Antimicrobial agents** – mostly synthetic that kill or inhibit the growth of microorganisms

Microbial Sources of Antibiotics

[redacted]

Representative Sources of Antibiotics

Microorganism	Antibiotic
Gram-Positive Rods	
Bacillus subtilis	Bacitracin
Bacillus polymyxa	Polymyxin
Actinomycetes	
Streptomyces nodosus	Amphotericin B
Streptomyces venezuelae	Chloramphenicol
Streptomyces aureofaciens	Chlortetracycline and tetracycline
Streptomyces erythraeus	Erythromycin
Streptomyces fradiae	Neomycin
Streptomyces griseus	Streptomycin
Micromonospora purpureae	Gentamicin
Fungi	
Cephalosporium spp.	Cephalothin
Penicillium griseofulvum	Griseofulvin
Penicillium notatum	Penicillin

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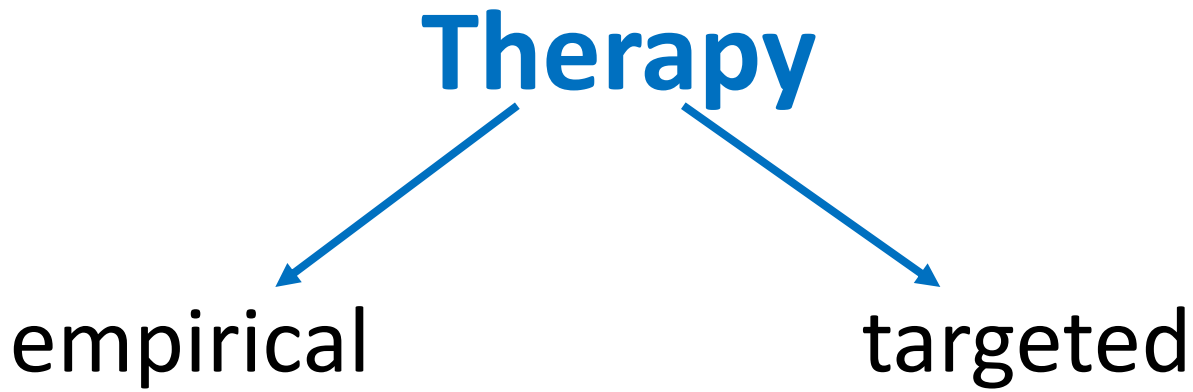
Treatment with ATB

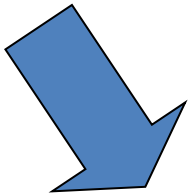


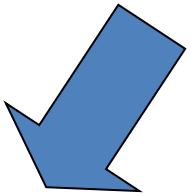
Prophylaxis

Nature of infection

Bacterial infection

High risk of infection





prophylaxis

Antibiotic therapy

Features of antibiotics

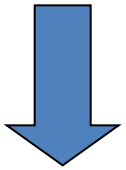
- Spectrum of activity
- Efficacy against suspected organism
- Mode of administration
- Dosing regimens
- Interrelated pharmacokinetic parameters
- Safety and tolerability
- Toxicity

Classes of antibiotics with different antimicrobial spectra

Antibiotic class	Gram +	Gram -	Anaerobes	Atypicals
Penicillins	++	+/-	+/-	-
1st generation cephalosporins	++	+	-	-
2nd generation cephalosporins	++	++	+/-	-
3rd generation cephalosporins	+	+++	-	-
4th generation cephalosporins	+	+++	-	-
Monobactams	+	+++	-	-
Carbapenems	-	+++	+	-
Beta-lactam/beta-lactamase inhibitor combinations	+++	+++	+++	-
Fluoro-quinolones	+++	++	+/-	+
Macrolides	+++	+/-	+/-	+++
Aminoglycosides	+/-	+++	+/-	-
Tetracyclines	+	++	+	+++

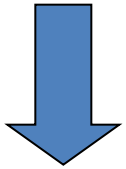
Spectrum of activity

narrow



When identity of infecting organism is known

broad



Initially when pathogen is known

Principles of ATB treatment

- indicated case – bacterial infections
- the earliest therapy
- **optimal dose**, effective level
- **optimal time interval**
- **optimal duration** of the treatment
- pharmacokinetics
- patient - contraindications

Duration of ATB treatment

- **one-shot** - uncomplicated gonorrhoea, ulcus molle, colpitis - Candida
- **5 -7-10 days** - common infection (airways)
- **long-lasting** - TBC, sepsis, endocarditis….

Why to combine ATB?

- to enlarge spectrum of effectivity
- to reduce toxicity
- to prevent resistance
- to increase activity
    - synergic or additive effect

ATB classification - antimicrobial effect

- **Antibacterial**
- **Antituberculotics**
- **Antimycotics**
- **Antiprotozoics**
- **Antivirotics**

ATB Classification – spectrum

narrow

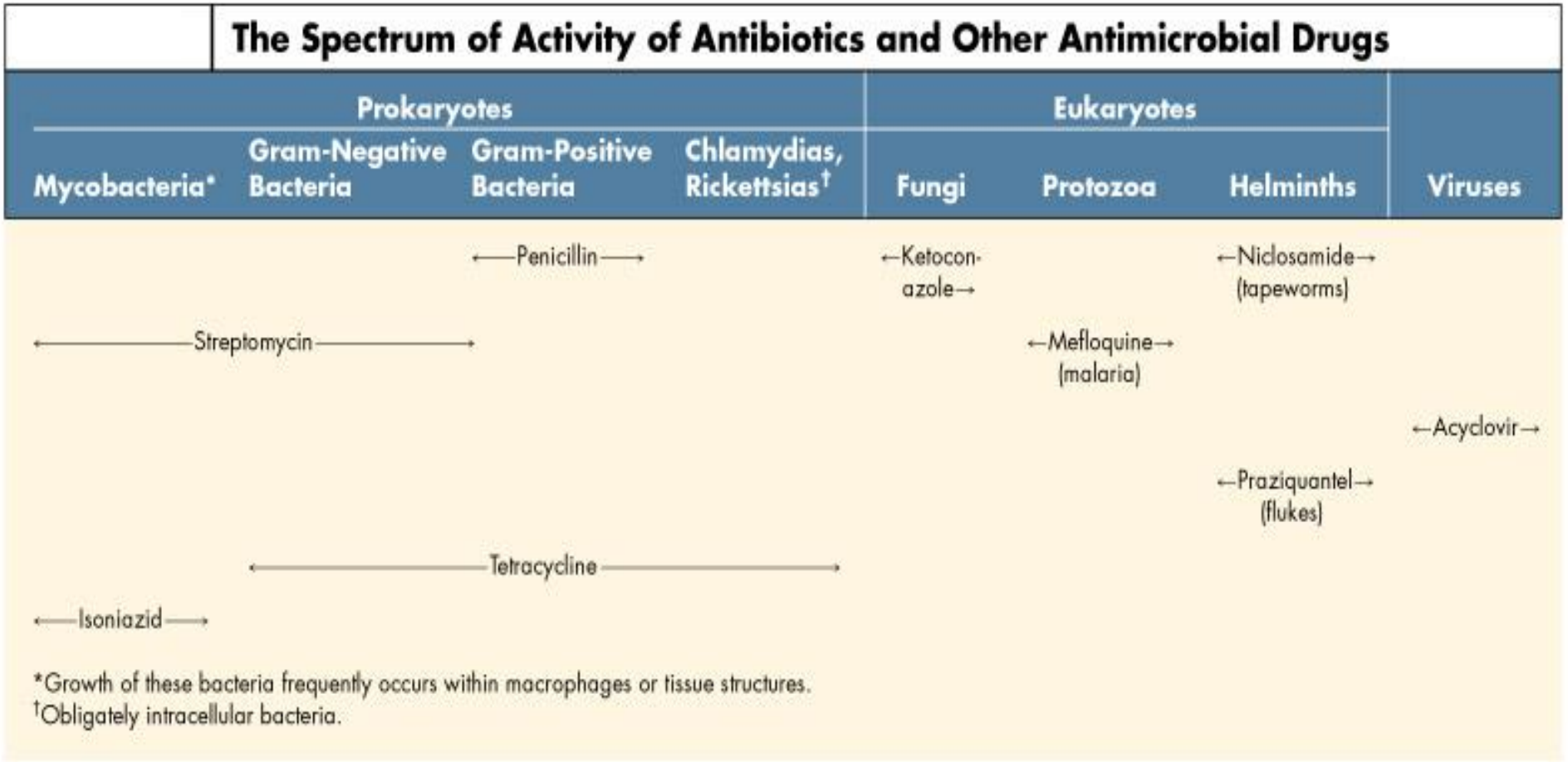
- for targeted therapy

- TBC (viomycin)

broad

- aminoglycosides
- ampicillin
- chloramphenicol
- tetracyclines
- cotrimoxazol

Spectrum of Activity



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ATB Classification – type of effect

bactericidal

- penicillines
- cephalosporines
- streptomycin
- polymyxines...

bacteriostatic

- chloramphenicol
- tetracyclines
- macrolides
- sulphonamides
- nitrofuranes...

Bacteriostatic	Bactericidal
Macrolides	Beta-lactams
Tetracyclines	Penicillins, Cephalosporins
Chloramphenicol	Monobactams, Carbapenems
Sulphonamides	Aminoglycosides
Trimethoprim	Bacitracin
Lincomycin, clindamycin	Isoniazid
Ethambutol	Metronidazol
Nitrofurantoin	Polymyxines
	Pyrazinamid
	Quinolons, Rifampicin
	Vancomycin, teicoplanin

Bactericidal

I. Active in the resting phase

- aminoglycosides, polypeptides…

II. Active in the growth phase

- PNCs, cefalo-…

Bacteriostatic

III. With rapid onset

- TTC, macrolides, chloramphenicol...

IV. With slow onset

- sulphonamides, cycloserin....

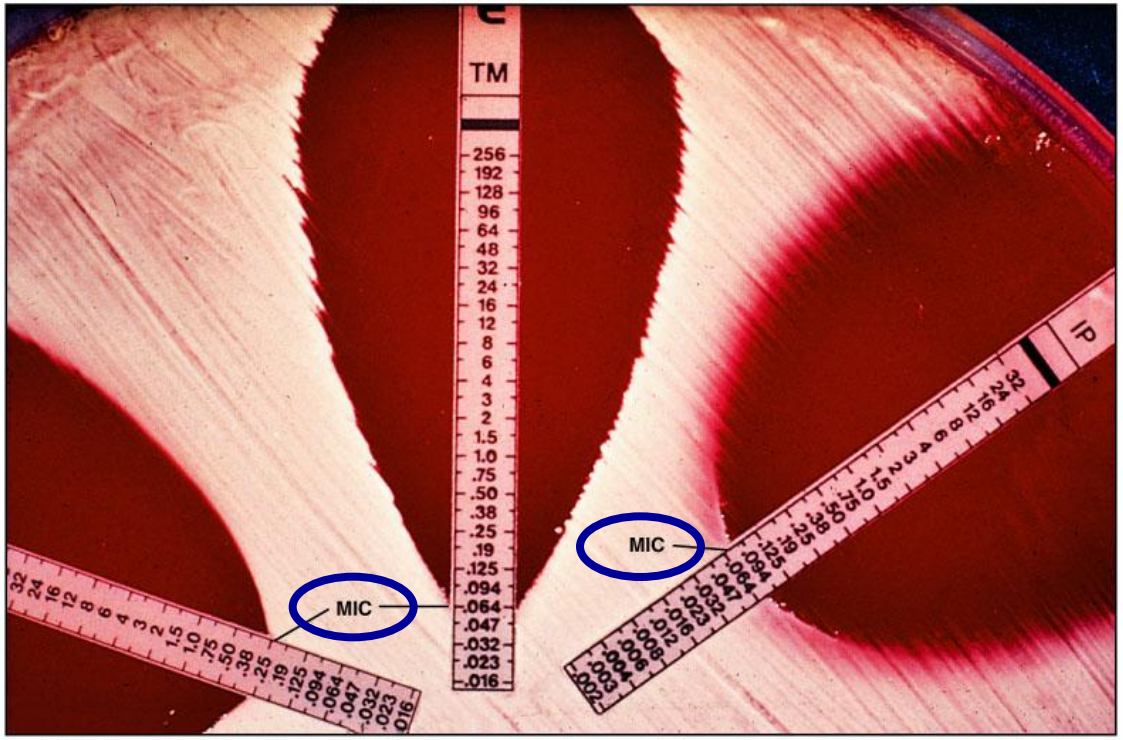
Don't combine groups II. and III.

Minimal inhibitory concentration (MIC)

- the lowest **concentration** of an **antimicrobial** that will **inhibit** the visible **growth** of a **microorganism**
  - activity of agent against an organism
  - resistance
  - monitoring of the activity of new agents

Measuring Antimicrobial Sensitivity

- **Minimal inhibitory concentration**



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Minimal Bactericidal Concentration (MBC)

- the **lowest** concentration of antibiotic required to **kill** an organism
- antimicrobials are usually regarded as bactericidal, if the MBC is no more than four times the MIC

Postantibiotic effect (PAE)

- the **persistent suppression** of bacterial growth after short antimicrobial exposure
  - shows the capacity of an antimicrobial drug to inhibit the growth of bacteria after **removal** of the drug from the culture
  - serum concentrations - below MIC
  - aminoglycosides, fluoroquinolones, tetracyclines, clindamycin, ketolides, rifampicin, azithromycin

ATB - pharmacodynamic characteristic

Concentration-dependent effect	Concentration-non-dependent effect
Antibiotics	
• aminoglycosides • fluoroquinolones metronidazol	• penicillines • cephalosporines • macrolides
Target of the treatment	
• to maximize the ATB concentration	• to maximize time of ATB exposure
Clinical effectivity	
• AUC/MIC • 10 - 12 x MIC • ↑dose 1 x daily	• time above MIC • time above MIC > 40-60 % • continual infusion

Burgess, 1999

Mechanisms of ATB action

- Cell wall formation
- Plasma membrane
- Protein synthesis
- DNA replication and RNA synthesis
- Synthesis of essential metabolites

Modes of ATB Action

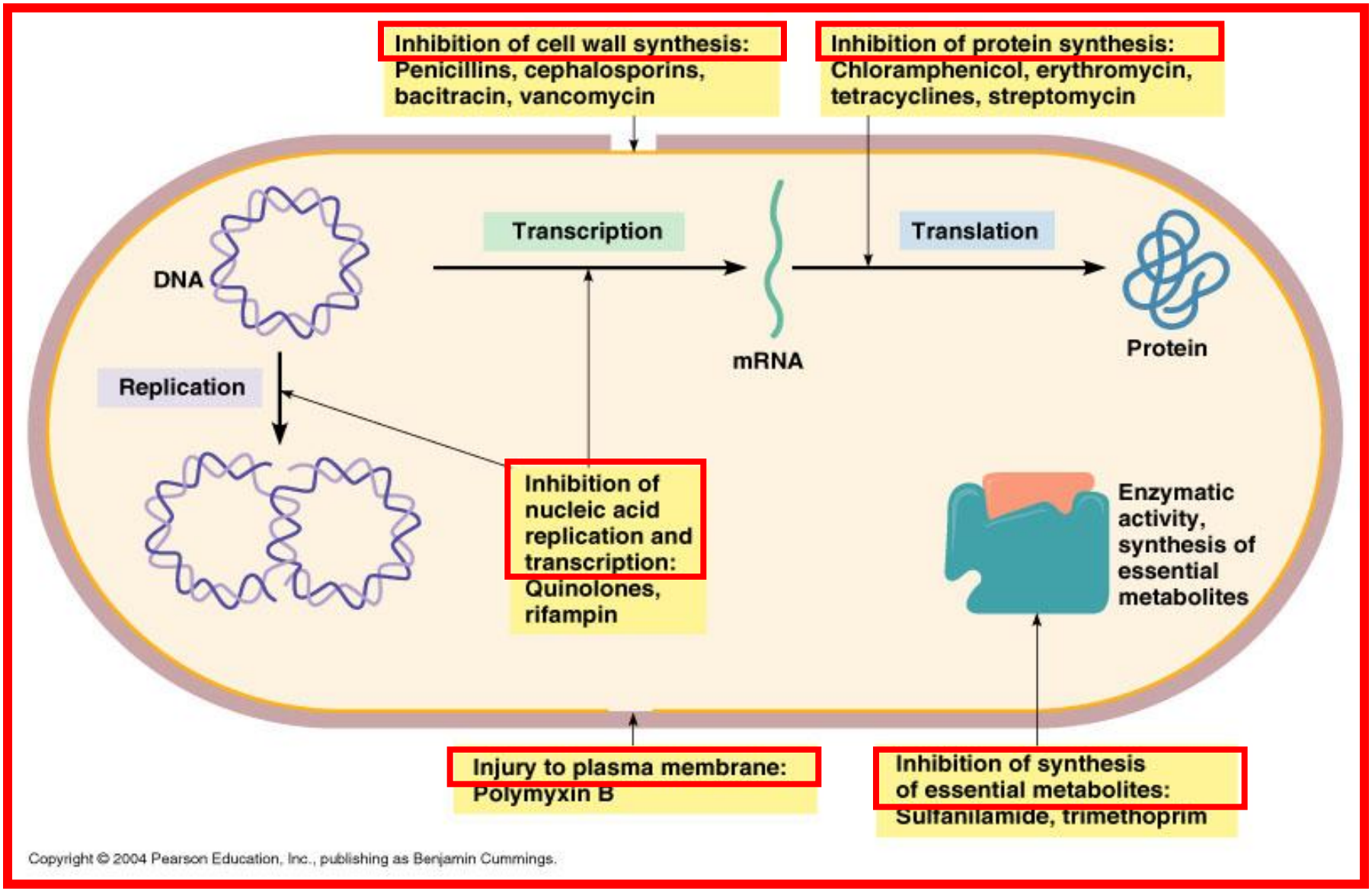

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TABLE 11-1 Mechanisms of Action of Antimicrobial Agents

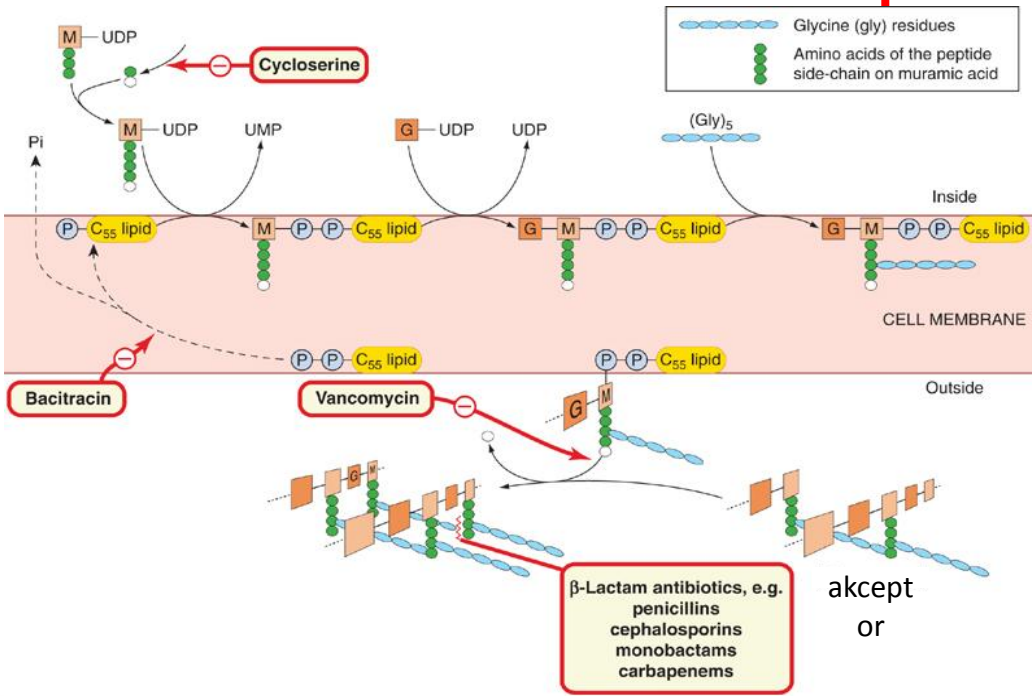
Inhibitors of Bacterial Cell Wall Synthesis
- Drugs that inhibit biosynthetic enzymes
  - Fosfomycin
  - Cycloserine
- Drugs that combine with carrier molecules
  - Bacitracin
- Drugs that combine with cell wall substrates
  - Vancomycin
- Drugs that inhibit polymerization and attachment of new pepidoglycan to cell wall
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Monobactams

Inhibitors of Cytoplasmic Membranes
- Drugs that disorganize the cytoplasmic membrane
  - Tyrocidins
  - Polymyxins
- Drugs that produce pores in membranes
  - Gramicidins
- Drugs that alter structure of fungi
  - Polyenes (amphotericin)
  - Imidazoles (ketoconazole, fluconazole)

Inhibitors of Nucleic Acid Synthesis
- Inhibitors of nucleotide metabolism
  - Adenosine arabinoside (viruses)
  - Acyclovir (viruses)
  - Flucytosine (fungi)
- Agents that impair DNA template function
  - Intercalating agents
  - Chloroquine (parasites)
- Inhibitors of DNA replication
  - Quinolones
  - Nitroimidazoles
- Inhibitors of RNA polymerase
  - Rifampin

Inhibitors of Ribosome Function
- Inhibitors of 30S units
  - Streptomycin
  - Kanamycin, gentamicin, amikacin
  - Spectinomycin
  - Tetracyclines
- Inhibitors of 50S units
  - Chloramphenicol
  - Clindamycin
  - Erythromycin
  - Fusidic acid

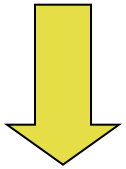
Inhibitors of Folate Metabolism
- Inhibitor of pteroic acid synthetase
  - Sulfonamides
- Inhibitor of dihydrofolate reductase
  - Trimephoprim



akceptor

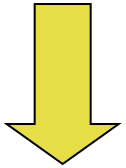
Mechanisms of ATB Action

- Cell wall
- Membrane



- bactericidal
- irreversible
- effect within 48 h

- Protein
- DNA, RNA
- Metabolites



- bacteriostatic
- reversible
- effect within 3-4 days

ATB – adverse effects

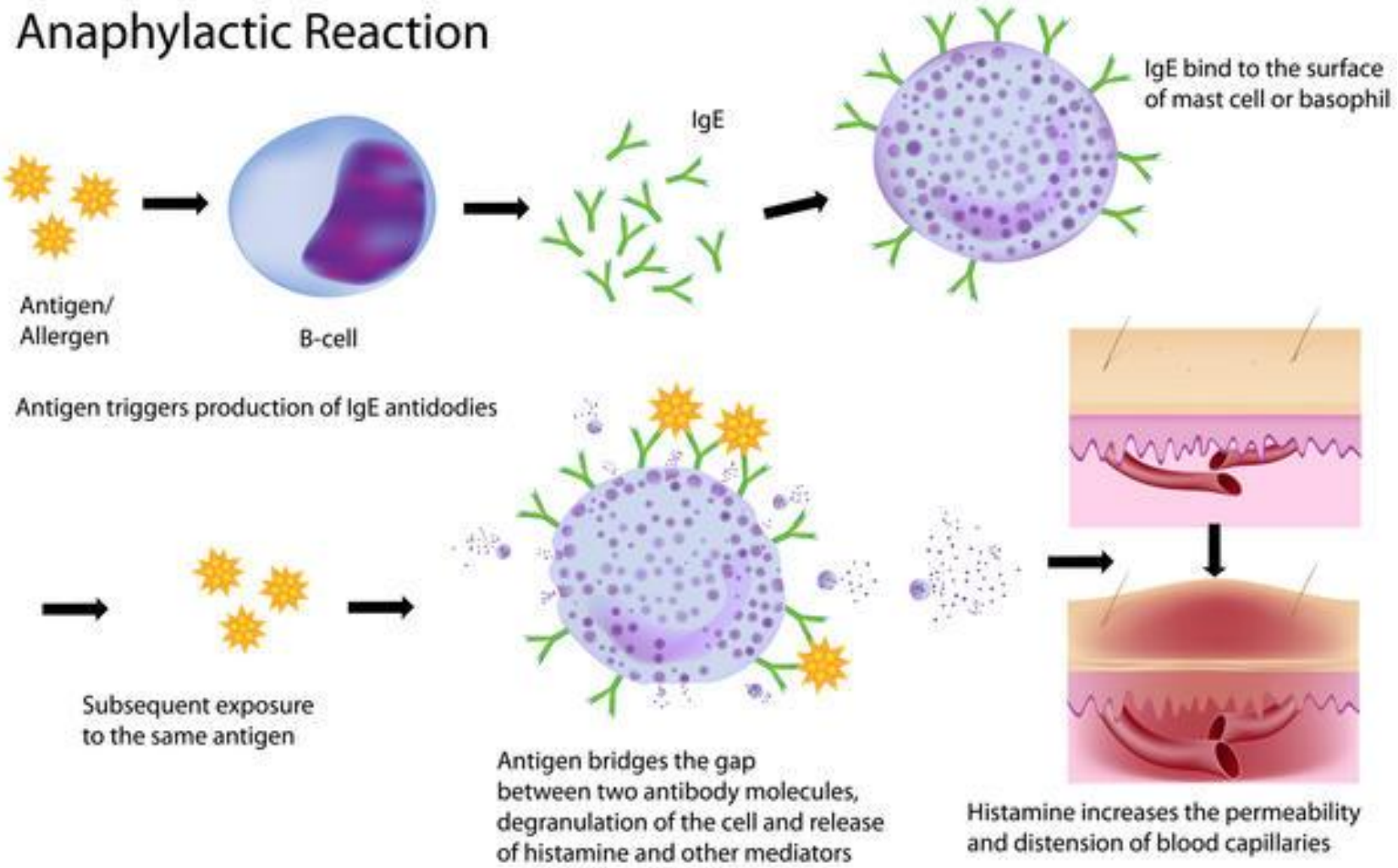
- **Toxicity**
  - neuro- sulph, antiTBC...
  - nefro- AGs, amfoterB...
  - hepato- rifam,ketokonazol...
  - hemo- chloramph, sulph...
  - oto- AGs
  - GIT- TTC, sulph, erythr...
  - CNS- antiTBC, polymyx...
  - electrolytes viomycine

ATB – adverse effects

- **Allergic** - local
  - systemic

- **Biological** - resistance
  - superinfection
  - dysmicrobia
  - Jarisch-Herxheimer reaction

Anaphylactic Reaction



www.healthtap.com

ATB and Allergy

PNCs, cephalosporins, sulphonamides, nitrofurantoin, vankomycin....

- **Immediate:** (2 min-2 h) - anaphylactic shock, angioneurotic edema, asthma attack, urticaria

- **Accelerated:** (2-24 h) - urticaria, pruritus, respiratory problems

- **Delayed:** (24h- 26 days) - fever, urticaria, pain and edema of joints, organic lesions, haemolytic anaemia...

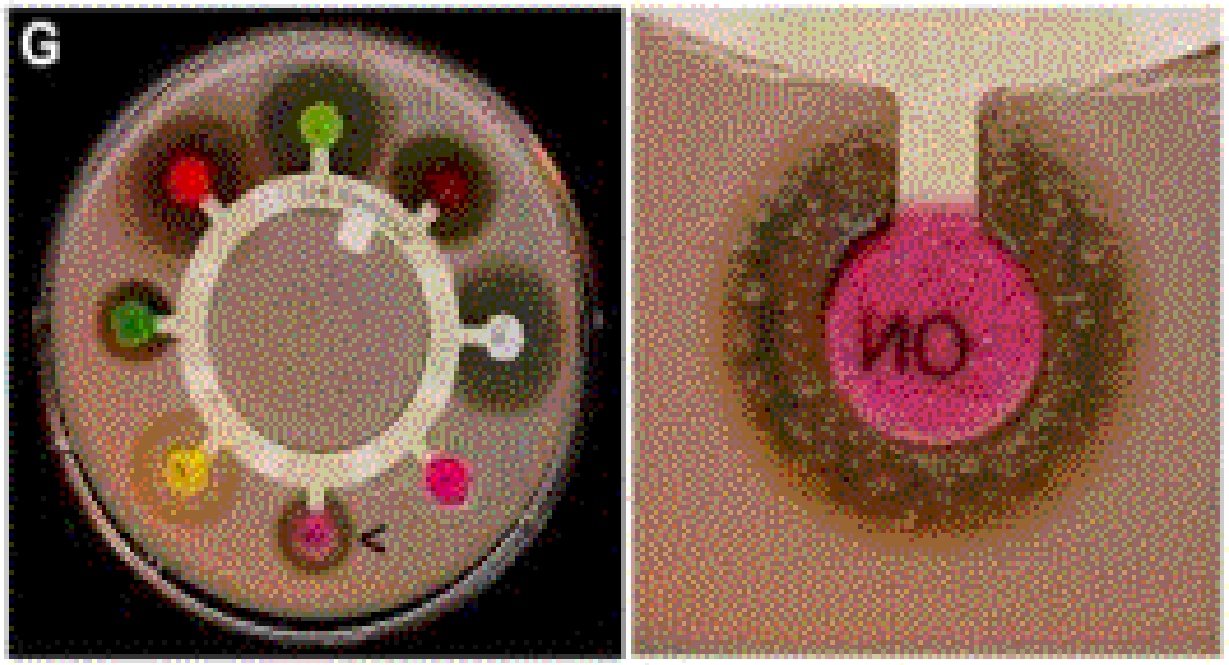
Antimicrobial Resistance

- Relative or complete lack of effect of antimicrobial against previously susceptible microbe
- Increase in MIC

ATB – resistance

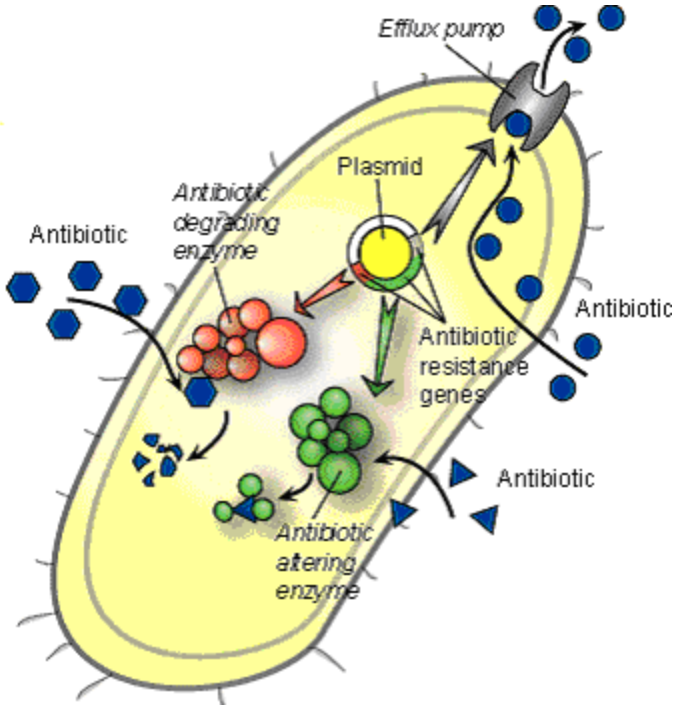
- **Primary** - genetically conditioned
  - without reference to previous contact with ATB
- **Secondary** - during the ATB treatment or after previous contact with ATB

Measuring Antimicrobial Sensitivity: Disk Diffusion



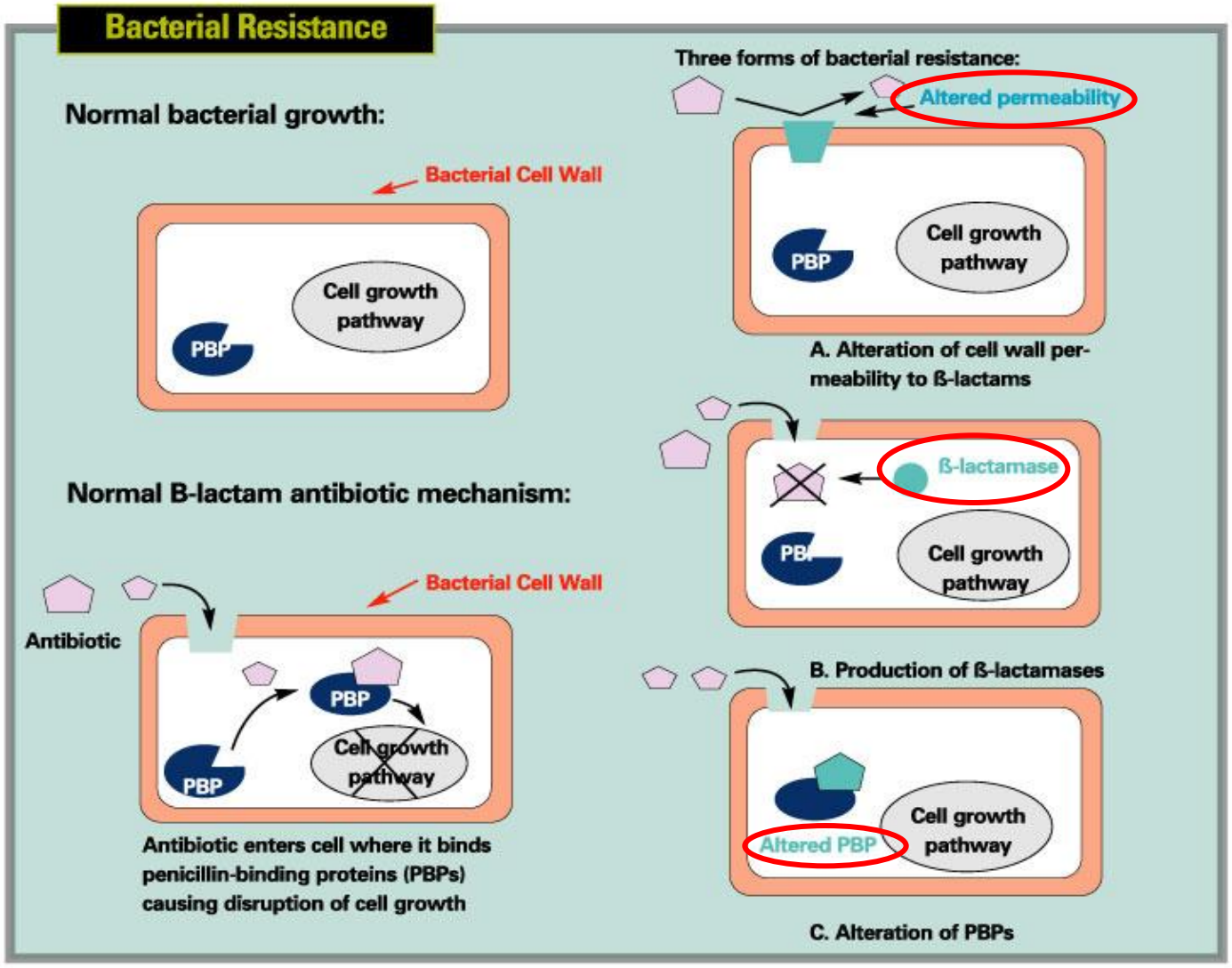
Antibiotic resistance testing in the lab.

Mechanisms of Antibiotic Resistance



www.scidev.net

- Prevention of penetration of drug
- Enzymatic destruction of drug
- Alteration of drug's target site
- Rapid ejection/efflux of the drug


Bacterial Resistance
Normal bacterial growth:
Bacterial Cell Wall
Cell growth pathway
PBP
Normal B-lactam antibiotic mechanism:
Antibiotic
Bacterial Cell Wall
PBP
Cell growth pathway
PBP
Antibiotic enters cell where it binds penicillin-binding proteins (PBPs) causing disruption of cell growth
Three forms of bacterial resistance:
Altered permeability
PBP
Cell growth pathway
A. Alteration of cell wall permeability to ß-lactams
ß-lactamase
PBP
Cell growth pathway
B. Production of ß-lactamases
Altered PBP
Cell growth pathway
C. Alteration of PBPs

Multiple drug resistant organisms

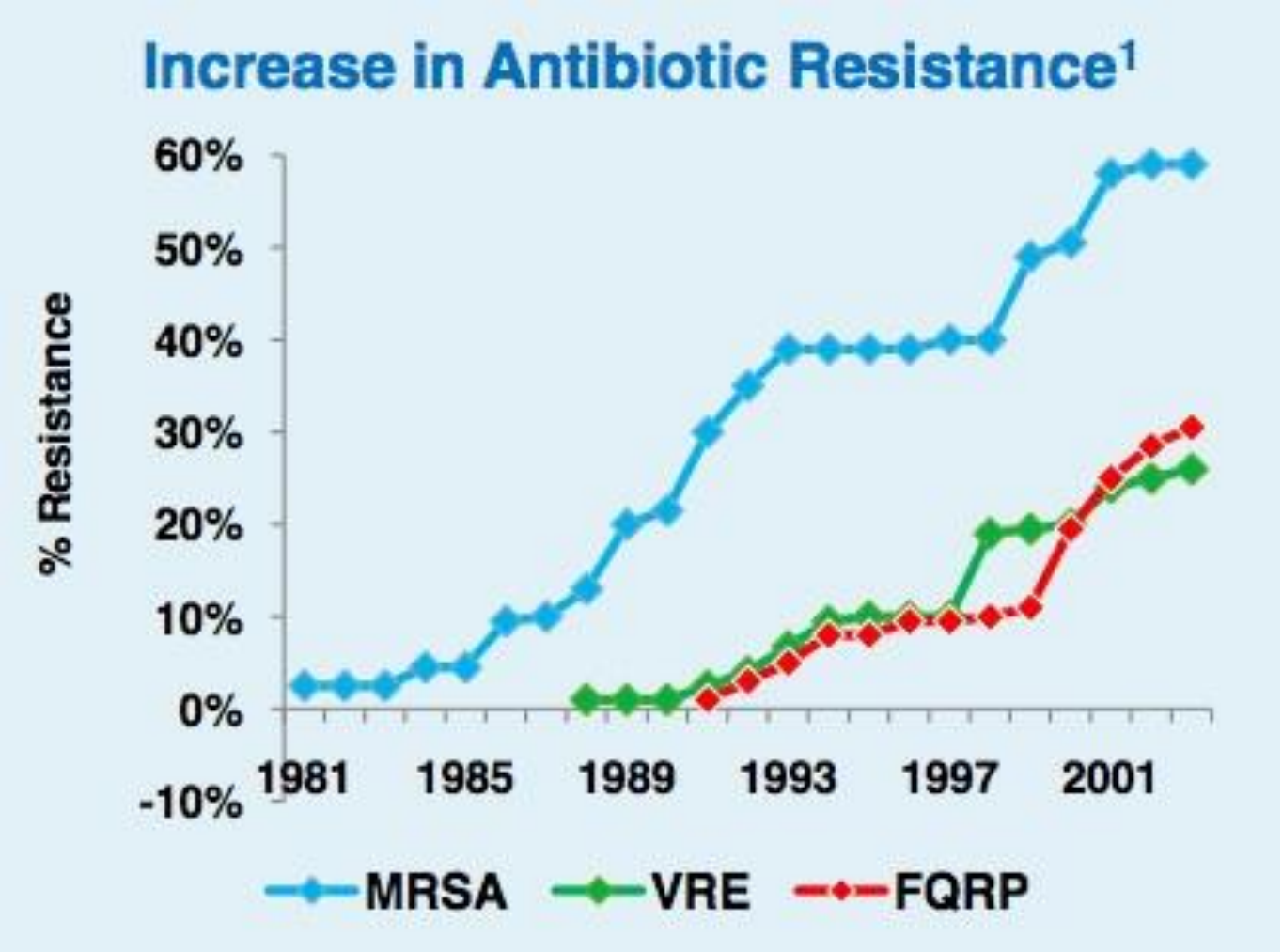
MRSA - methicillin/oxacillin-resistant *Staphylococcus aureus*

- most frequent nosocomial pathogen resistant to several other antibiotics

VRE - vancomycin-resistant enterococci

ESBLs - extended-spectrum beta-lactamases (which are resistant to cephalosporins and monobactams)

PRSP - penicillin-resistant *Streptococcus pneumoniae*



http://scienceinthetriangle.org/2011/03/rtp-panels-address-rogues-gallery-of-multidrug-resistant-bacteria/

Factors promoting antimicrobial resistance

- Exposure to sub-optimal levels of antimicrobial
- Exposure to microbes carrying resistance genes

Inappropriate Antimicrobial Use

- Prescribed drug not taken correctly
- Antibiotics for viral infections
- Antibiotics sold without medical supervision (OTC)
- Spread of resistant microbes in hospitals due to lack of hygiene
- Lack of quality control in manufacture antimicrobial
- Inadequate surveillance or defective susceptibility assays
- Poverty or war
- Use of antibiotics in animals/foods

Antimicrobial agents affecting cell wall synthesis

Beta-lactam antibiotics

- **Penicillins**
- **Cephalosporins and Cephamycins**
- **Monobactams**
- **Carbapenems**

  - Beta-lactam ring
  - Interfere with the construction of the cell wall

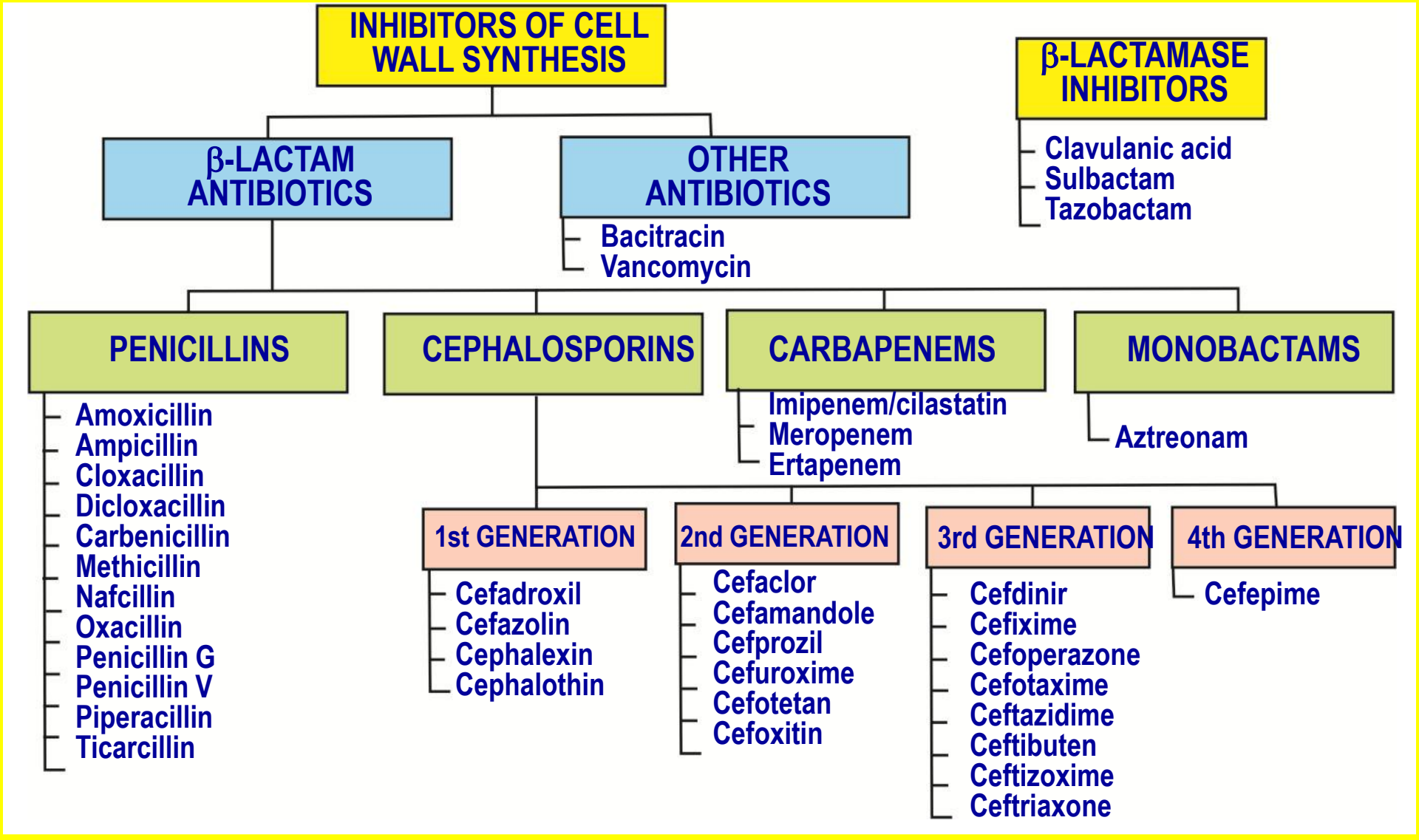
Glycopeptide antibiotics

- **Vancomycin**
- **Teicoplanin**
- **Dalbavancin**
- **Telavancin**

Other cell wall- or membrane-active agents

- **Daptomycin**
- **Fosfomycin**
- **Bacitracin**
- **Cycloserine**

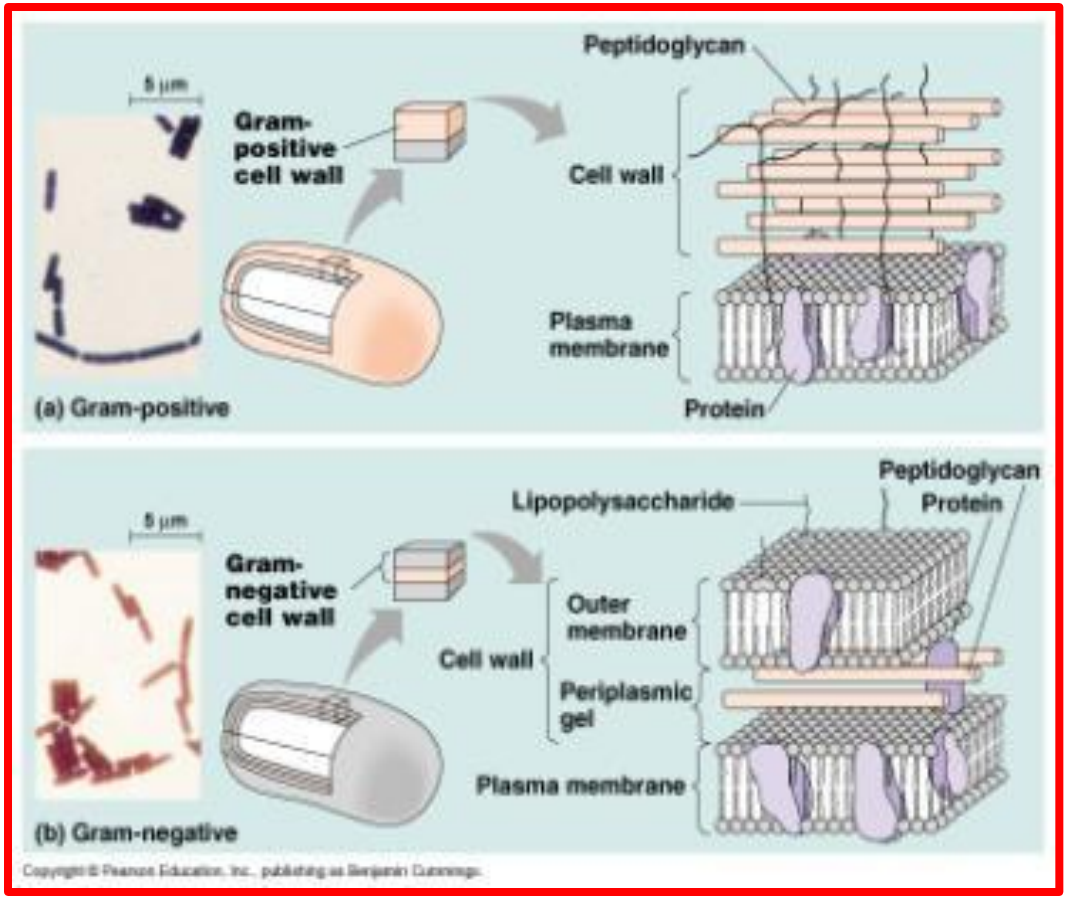
Antimicrobial agents affecting cell wall synthesis

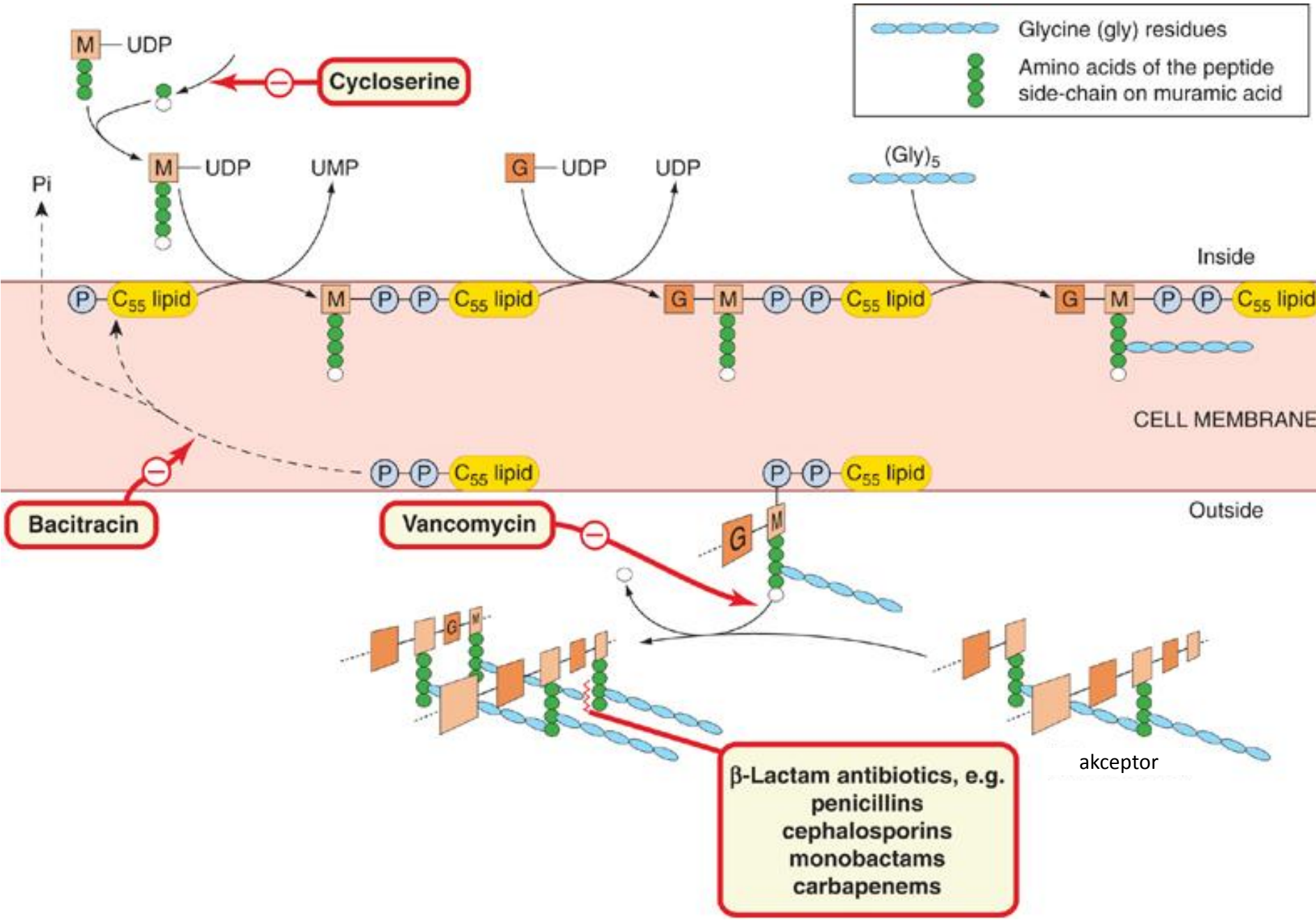


(according to Lippincott´s Pharmacology, 2006)

Beta-lactams

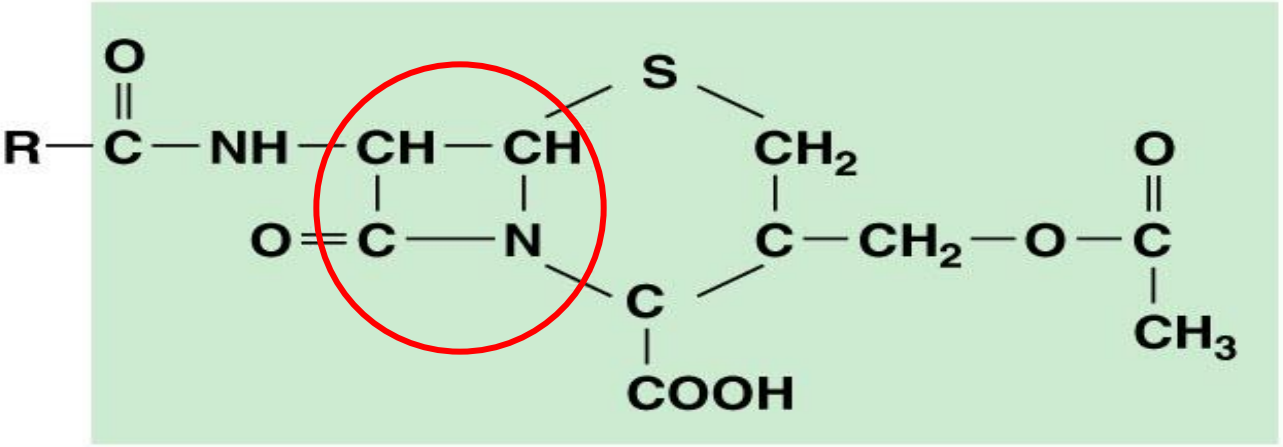
- Beta-lactams inhibit transpeptidase
- Only effective against rapidly growing organisms that synthesize peptidoglycan



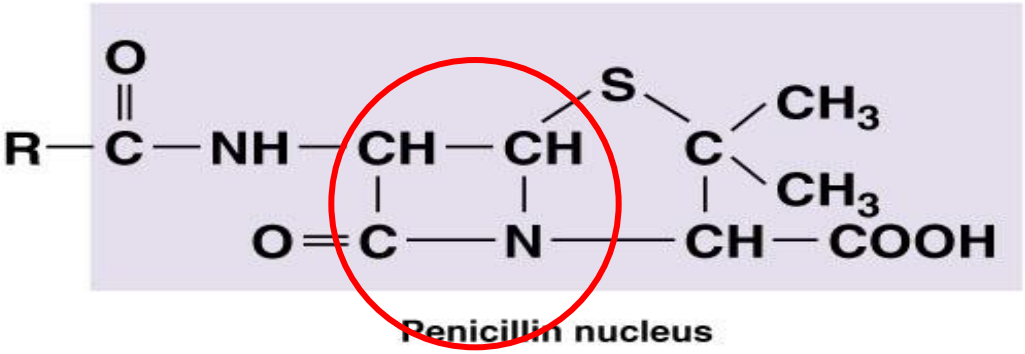


Rang et al.: Rang and Dale's Pharmacology, 2012

Beta-lactams

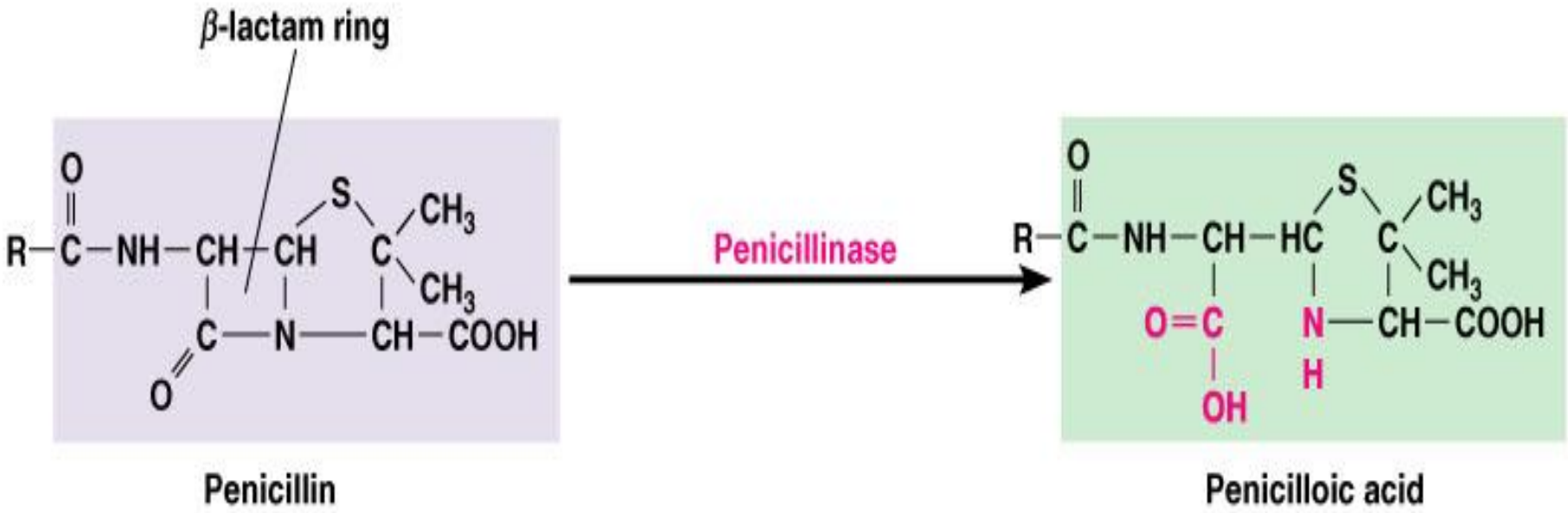


Cephalosporin nucleus



Penicillin nucleus

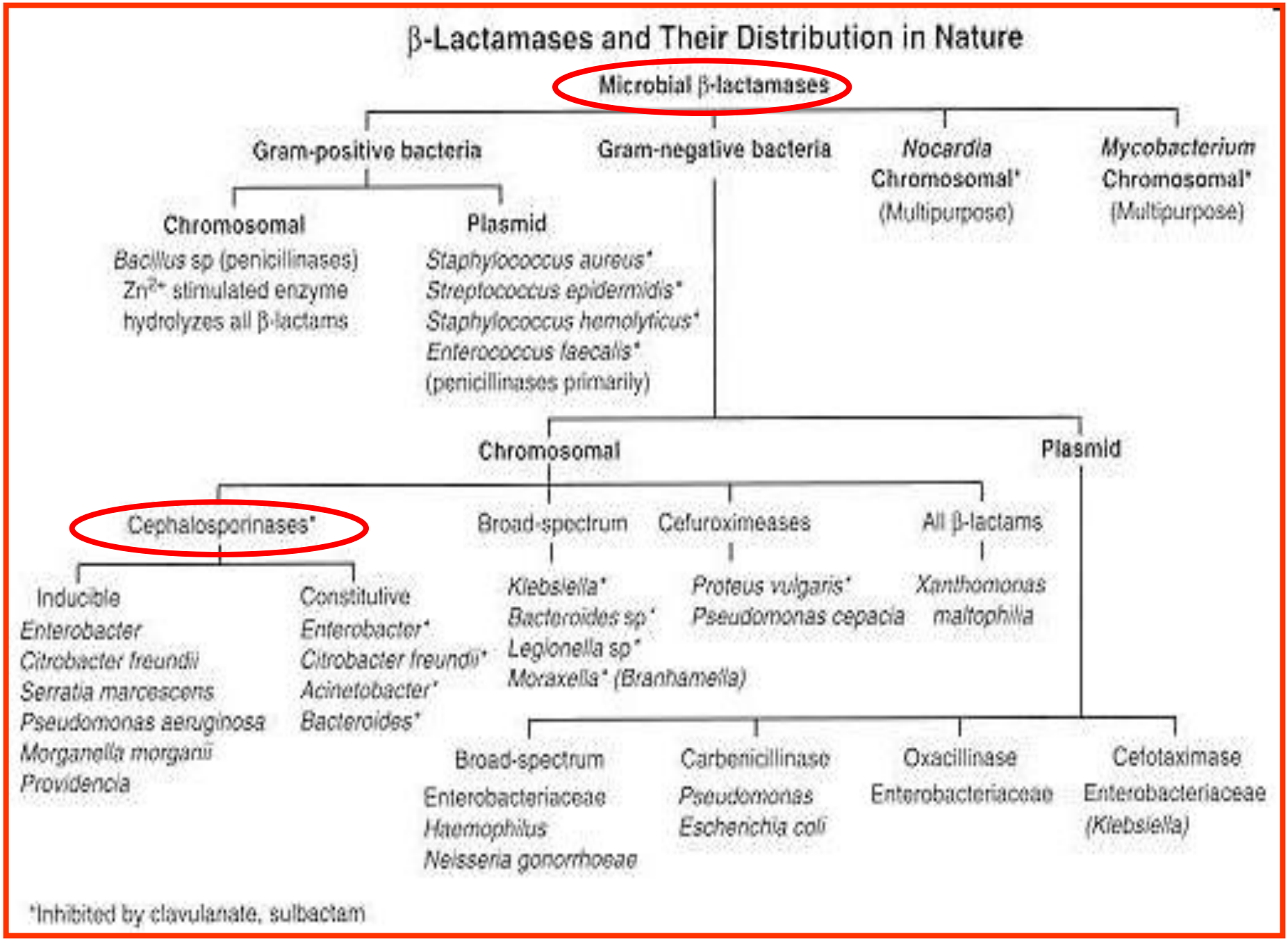
Penicillinase (β-lactamase)



β-lactamases

Cephalosporinases non-inhibited by clavulanic acid	**Chromosomes Ps.aeruginosa,** Ent.cloacae
Penicillinases, cephalosporinases inhibited by clavulanic acid	**plasmids, chromosomes Klebsiela spp., staphylococcus enzymes**
metaloenzymes	**hydrolyzing imipenem**
Penicillinases non-inhibited by clavulanic acid	**Chromosomes**

β-Lactamases and Their Distribution in Nature



*Inhibited by clavulanate, sulbactam

β-lactamases inhibitors

- G- - periplasmatic space
- G+ - released ouside
  - **clavulanic acid**
  - **sulbactam**
  - **tazobactam**

↑ binding to β-lactamases

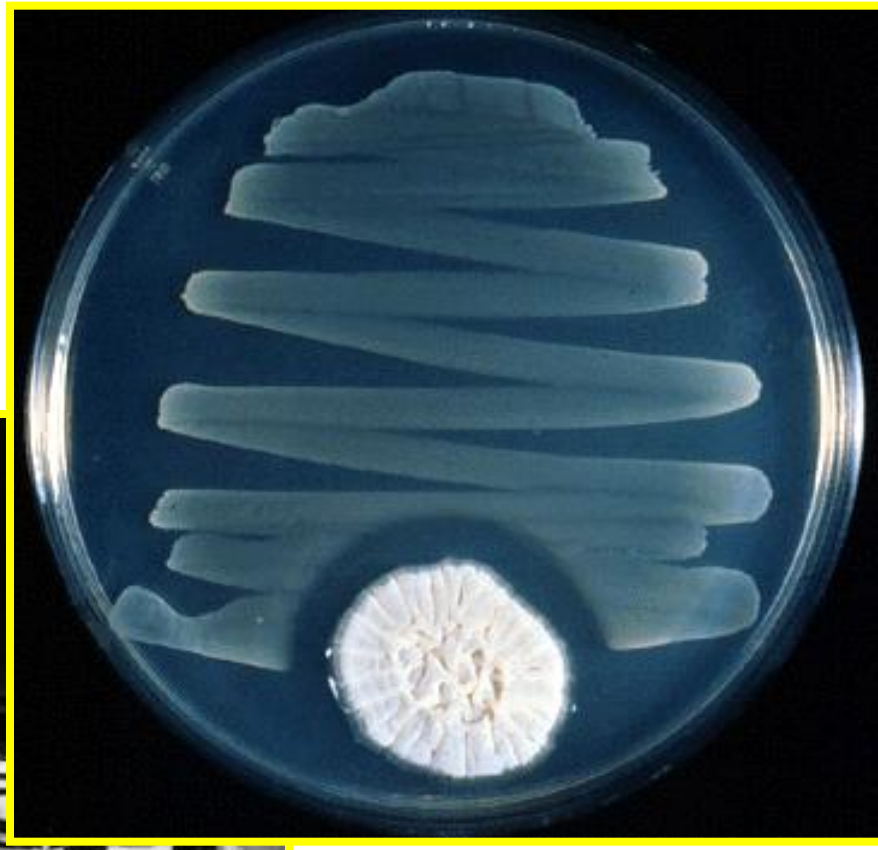
↓

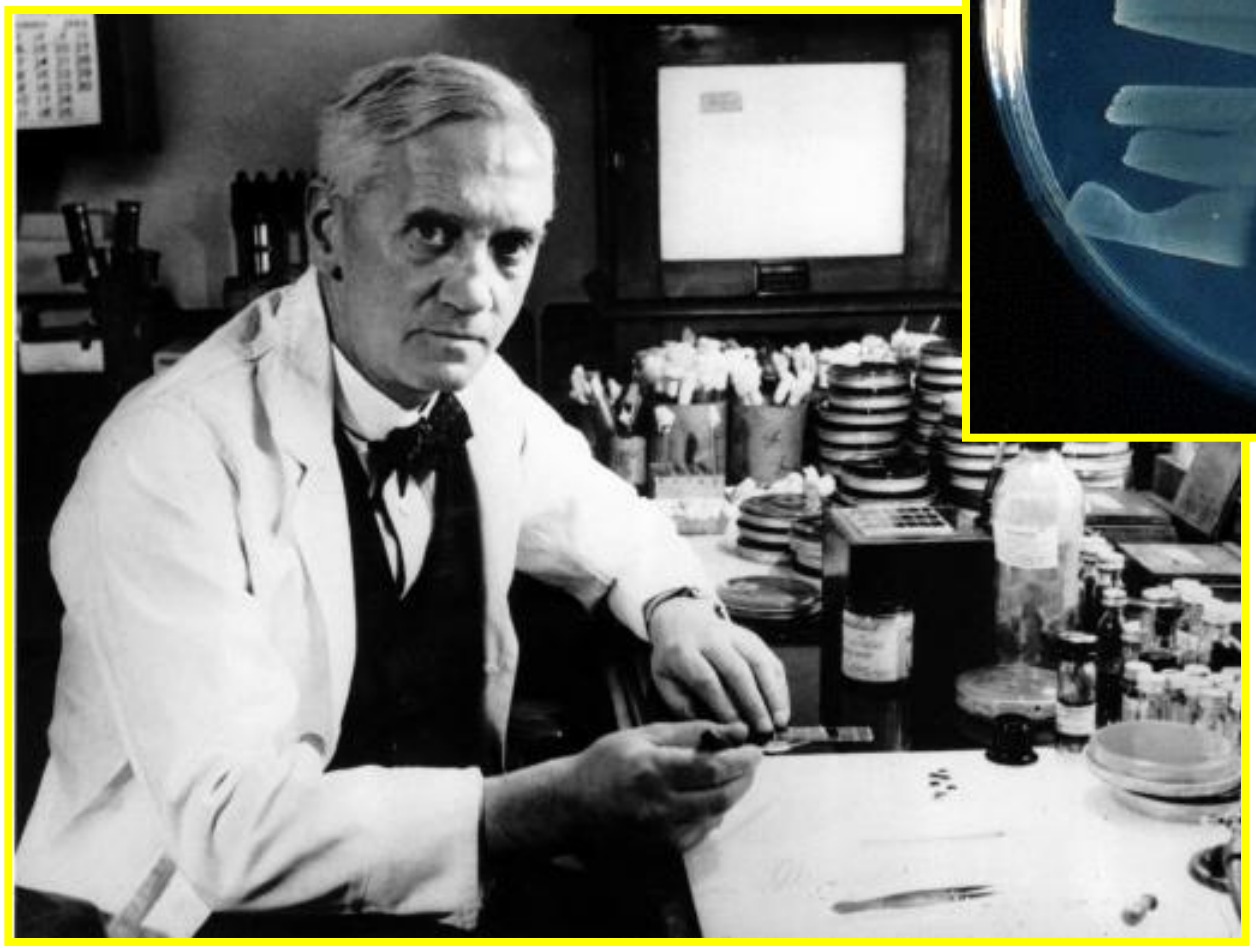
irreversible inactivation

↓

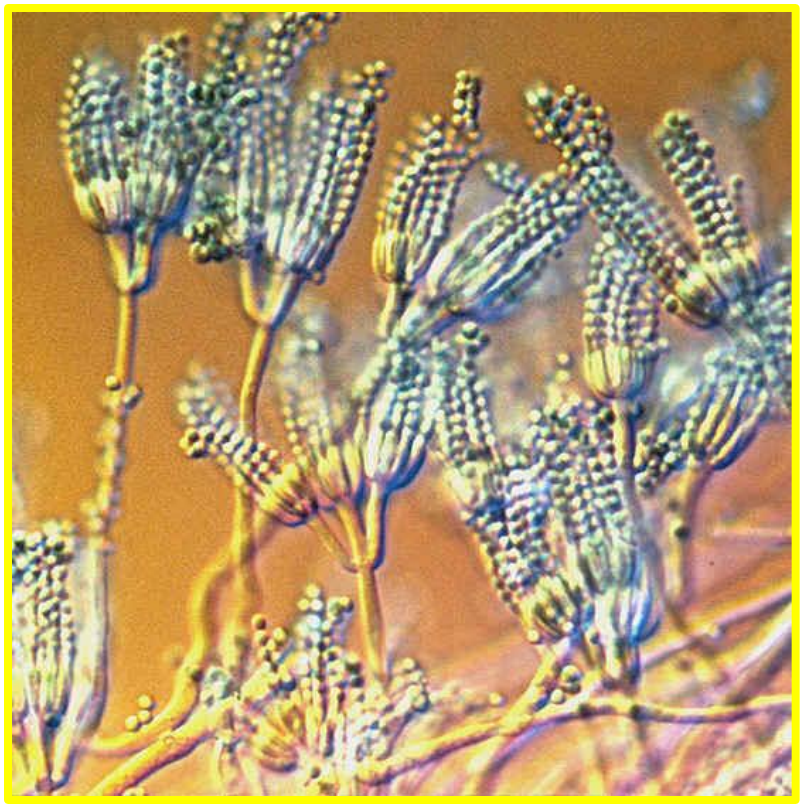
larger spectrum

Fleming and PNC



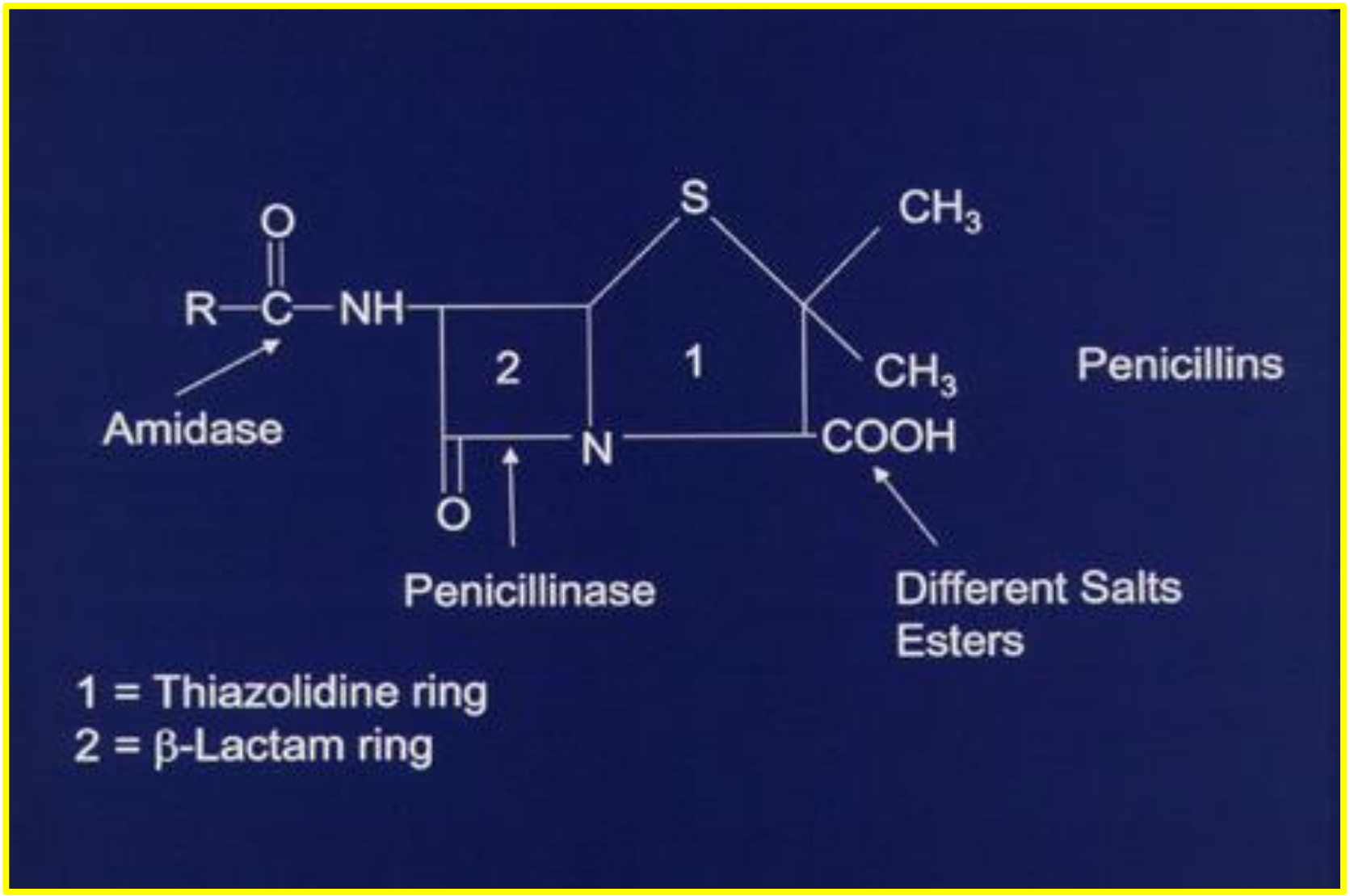


Penicillium



The name *Penicillium* comes from **penicillus = brush**, and this is based on the brush-like appearance of the fruiting structures

Penicillins



Penicillins

Penicillin sub-class	**Leading examples**	**Main activity against**
Natural penicillins	**Penicillin G, penicillin V**	Aerobic Gram-positive cocci (incl. pneumococci and enterococci), *Neisseria* spp and some anaerobes
Penicillinase-resistant	**Methicillin, oxacillin, cloxacillin**	Penicillinase-producing strains of *Staphylococcus aureus*
Aminopenicillins	**Ampicillin, amoxicillin**	Broad spectrum of Gram-positive and Gram-negative pathogens, but not *Pseudomonas*
Extended-spectrum	**Ticarcillin, carbenicillin, ureidopenicillins (e.g., piperacillin)**	Increased Gram-negative spectrum, including *Pseudomonas*

Classification of penicillins

- Basic penicillins (e.g. penicillin G)
- Antistaphylococcal penicillins (resistant to staphylococcal beta-lactamases)
- Extended-spectrum penicillins
  - Ampicilin
  - Antipseudomonal penicillins

Penicillin

- **Penicillin G (Penicillin G crystalline salt)**
  - streptococci, meningococci, enterococci, pneumococci (!), staphylococci (!), Treponema pallidum, clostridium sp., actinomyces
  - 4-24 million IU/day, divided in 4-6 doses
  - **i.v.**, infusion

- **Penicillin V (V- PENICILLIN, OSPEN , V PNC 1,0 MEGA, V PNC 250)**
  - minor infections, poor bioavailability
  - marrow spectrum, **p.o.** every 6 hours (4 times/day) (0.25-0.5 g)
  - alternative – penamecillin – p.o. every 8 hours

- **Benzathine (PENDEPON) and procaine penicillin G (PROCAIN PENICILIN)**
  - **i.m.** administration, prolonged activity
  - 1.2 million IU – Th of str. pharyngitis; every 3-4 weeks – prevention of reinfection
  - 2.4 million IU once a week for 1-3 weeks – Th of syphylis

Penicillins resistant to staphylococcal beta lactamases

- **methicillin, nafcillin, isoxazolyl penicillins** (oxacillin PROSTAPHLIN, cloxacillin AMPICLOX, dicloxacillin)
- Semisynthetic penicillins
- Infections by **beta-lactamase-producing staphylococci** (streptococci and pneumococci)
- **Resistant strains** – listeria, enterococci, methicillin-resistant strains
- **Isoxazolyl penicilins**
  - Administration p.o., 1 hour before or after meal, 0.25 – 0.5 g/every 4-6 hours (15-25 mg/kg/d)
- **Systemic staphylococcal infections** – i.v. administration of oxacillin or nafcillin, 8-12 g/d (infusions every 4-6 hours with 1-2 g)

Extended-spectrum penicilins

- **Aminopenicillins, carboxypenicillins, ureidopenicillins**
- Penetration through the gram-negative outer membrane – broader spectrum
- Inactivated by many beta-lactamases
- **Aminopenicillines** – **ampicillin** (AMPICILIN, PENSTABIL, 250-500 mg/4xd), **amoxicillin** (AMOCLEN, DUOMOX 250-500 mg/3xd)
  - UTI, sinusitis, otitis, LRTI, active against penicillin-resistant pneumococci, shigellosis (ampicillin)
  - Active against anaerobes, enterococci, Listeria monocytogenes, beta-lactamase-negative strains (*E.coli*, salmonella, haemophillus
  - Resistant strains – klebsiella, enterobacter, *Pseudomonas aeruginosa*, citrobacter, serratia, proteus...
- Ampicillin/sulbactam (UNASYN inj, p.o.)
- Amoxicillin/clavulanate (AUGMENTIN, AMOKSIKLAV)

Extended-spectrum penicilins

- **Carboxypenicillins** – carbenicillin (obsolete) – first antipseudomonadal, ticarcilin – p.o. (6 g divided in 4-6 doses) - UTI
- **Ureidopenicillins** – piperacillin (3-4 g divided in 4-6 doses), mezlocillin, azlocillin – active againt selected G- bacilli (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*) – UTI
- Often used in combination with **beta-lactamase inhibitors**
- Piperacillin/tazobactam (ZOSYN; IV)
- Ticarcillin/clavulanate (TIMENTIN; IV)

Units and formulations

- Activity defined in units (IU, UI)
- **Penicillin G** – crystallin sodium – 1,600 IU in 1 mg
  - 1 IU = 0.6 mcg
  - 1,000,000 IU = 0.6 g (600 mg)
- Semisynthetic penicillins – by weight (in mg)
- Sodium or potassium salts
  - Potassium penicillin G – 2.8 mEq/g of K^+ (1.7 mEq/1,000,000 IU)

- Procaine (PROCAIN PENICILIN) and benzathine (PENDEPON, RETARPEN) salts
- Longer stability in dry form

Mechanism of action

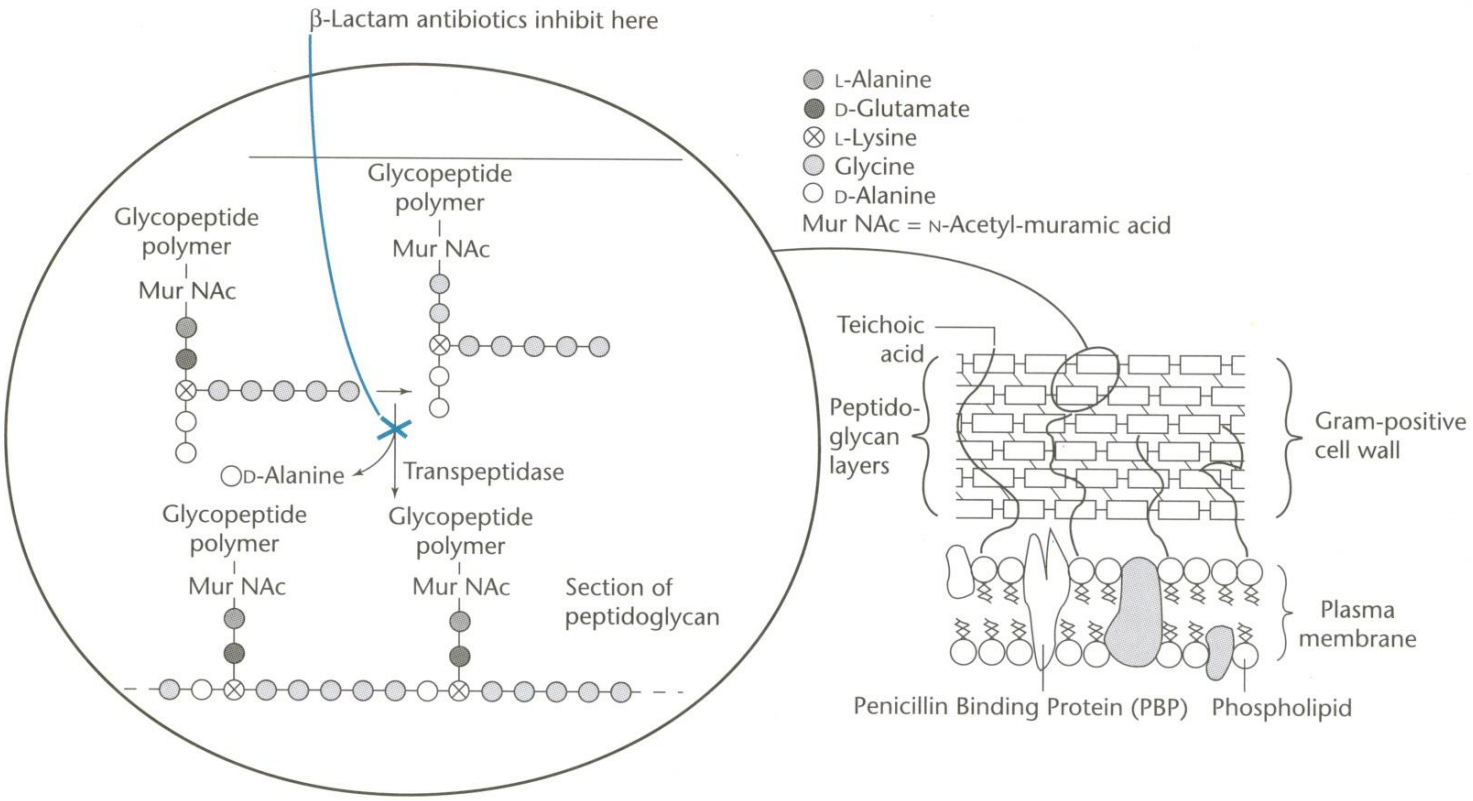
- Inhibition of bacterial growth – interferring with **transpeptidation reaction** in cell wall synthesis
- Structural analogue of **D-Ala-D-Ala substrate** binds covalently to active site of **PBP** responsible for removing the terminal alanin

- **Bactericidal activity** only during the growth of bacterias and synthetization of cell wall

Mechanism of PNCs action

- bind to the specific structure PBP
- inhibit transpeptidase
- interfere with cross linkage
- inhibit synthesis of peptidoglycan
- stimulate autolysin, lysis of the bacteria

Mechanism of action of beta-lactams

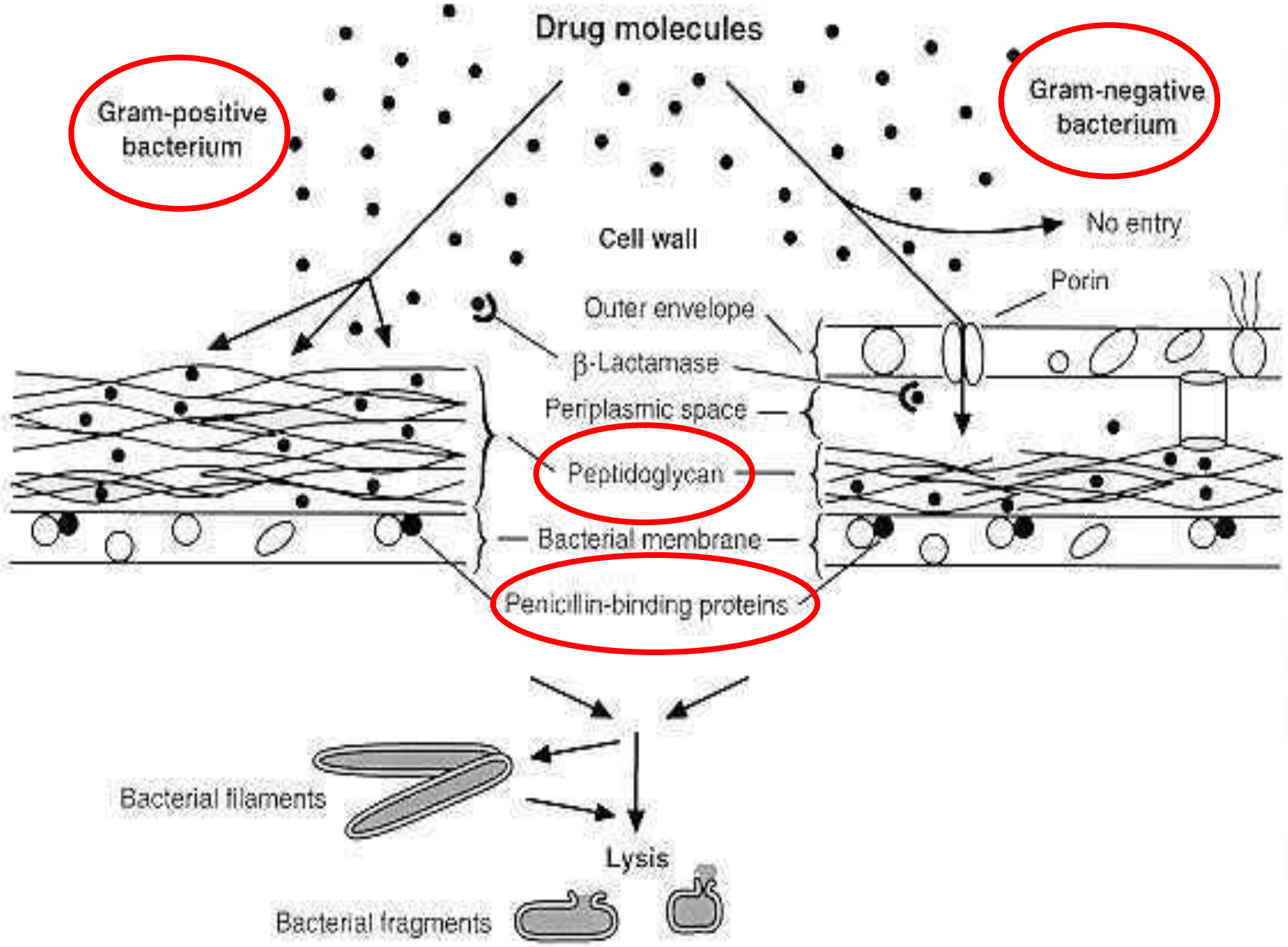


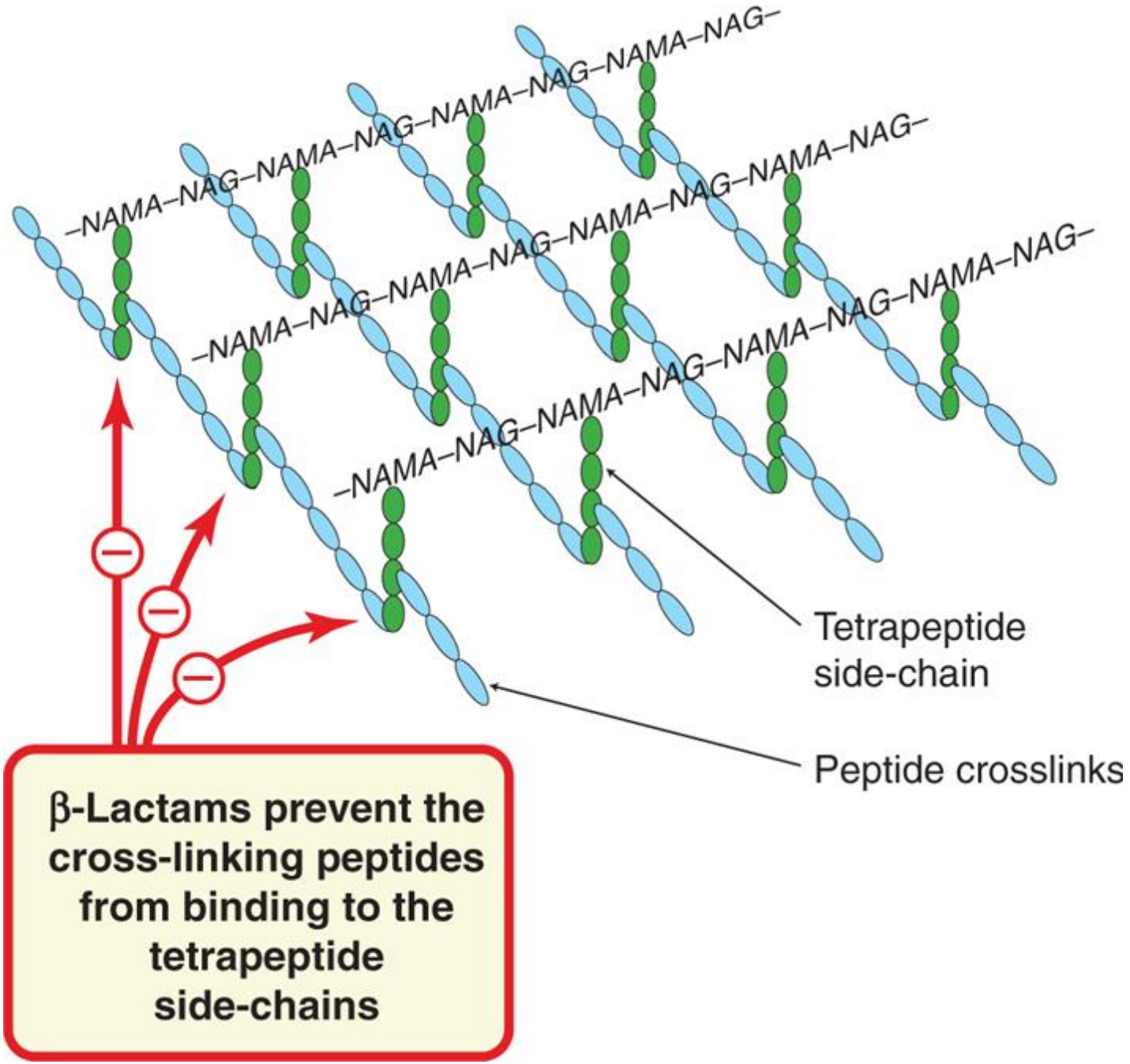
Penicillin-binding proteins (PBPs)

- involved in the synthesis of **peptidoglycan** - major component of bacterial cell walls
- inhibition of PBPs - irregularities in cell wall structure

  - cell death and **lysis**

- PBPs bind β-lactams - similar in chemical structure to pieces that form the peptidoglycan
- bind to penicillin – changes in the character of the bond - irreversible reaction and inactivates the enzyme


Drug molecules
Gram-positive bacterium
Gram-negative bacterium
No entry
Cell wall
Porin
Outer envelope
β-Lactamase
Periplasmic space
Peptidoglycan
Bacterial membrane
Penicillin-binding proteins
Bacterial filaments
Lysis
Bacterial fragments



Rang et al.: Rang and Dale's Pharmacology, 2012

Phamacokinetics

- **Peroral administration** – acid stability of dicloxacillin, ampicillin, amoxicillin
  - (4-8 mcg/ml after 500 mg dose)
  - Food interations (except of amoxicillin) – 1-2 hours before meal

- **Parenteral** – intravenously or intramuscularly – fast increase of serum levels (20-50 mcg/ml after 1g/1,600,000 IU of **penicillin G** i.v.), good general distribution, binding to proteins, polar molecules
- **Benzathine penicillin** – delayed absorption, 1,200,000 IU i.m. – 0.02 mcg/ml for 10 days, 0.003 mcg/ml after 21 days
- **Procaine penicillin** – 600,000 IU i.m. – 1-2 mcg/ml – up to 24 h

Pharmacokinetics

- Excretion to sputum and milk (3-15% of serum levels)
- Poor penetration into eye, prostate, CNS
  - Except of bacterial meningitis (pneumococci, meningococci) – 18-24 million IU daily p.o. – 1-5 mcg/ml

- **Excretion by kidneys** (GF 10%, tubular excretion 90%)

- **Halflife** – normal - 30 min; in renal failure – up to 10 hours
  - Creatinine clearance <10 ml/min – 1/3 or 1/4 of the dose

- **Nafcillin** - biliary excretion
- **Oxacillin, dicloxacillin, cloxaciline** - both

Administration

- 1-2 hours before or after meal (except of amoxicillin) – binding to food proteins, acid inactivation

- Co-administration of **probenecid** (0.5 g/6 hours) – increased blood levels

Penicillins - adverse effects

- **Hypersensitivity** – cross-sensitization, cross-reactivity
  - degradation products of PNC (e.g. penicilloic acid) – antigens
  - less than 1% of patient with previous intake of PNC
  - Anaphylactic shock, serum sickness-typ reaction – rare (urticaria, fever, joint swelling, angioneurotic edema, pruritus), skin rashes
    - Alternative drugs – e.g. erythromycin, klindamycin
    - Desensitization (enterococcal andocarditis, neurosyphilis)
- Minimal direct toxicity

Penicillins – adverse effects

- Pain & inflammation at injection site;
- **Gastrointestinal disturbances** (up to pseudomembranous collitis)
- **Secondary infections** (candidiasis)
- Seizures in renal impairement
- **Nafcillin** – neutropenia; **Oxacillin** – hepatitis; **Methicillin** – interstitial nephritis
- Non-allergic skin rashes – ampicillin and amoxicillin prescribed for viral infections
- ampicillin - rash in 50-100% of patients with **mononucleosis !!!**
- **Hoigné, Nicolau**

PNC - Adverse Effects

- **Hoigné** syndrome - pseudo-anaphylactic reaction induced by **i.m**. procaine penicillin with acute psychological and neurological manifestations – embolisation after i.v. admin.
- **Nicolau** syndrome - complication of i.m. benzathine penicillin inj. - severe pain, skin discoloration - marbled, tissue necrosis, atrophic ulcers – embolisation after i.a. admin.

Resistance

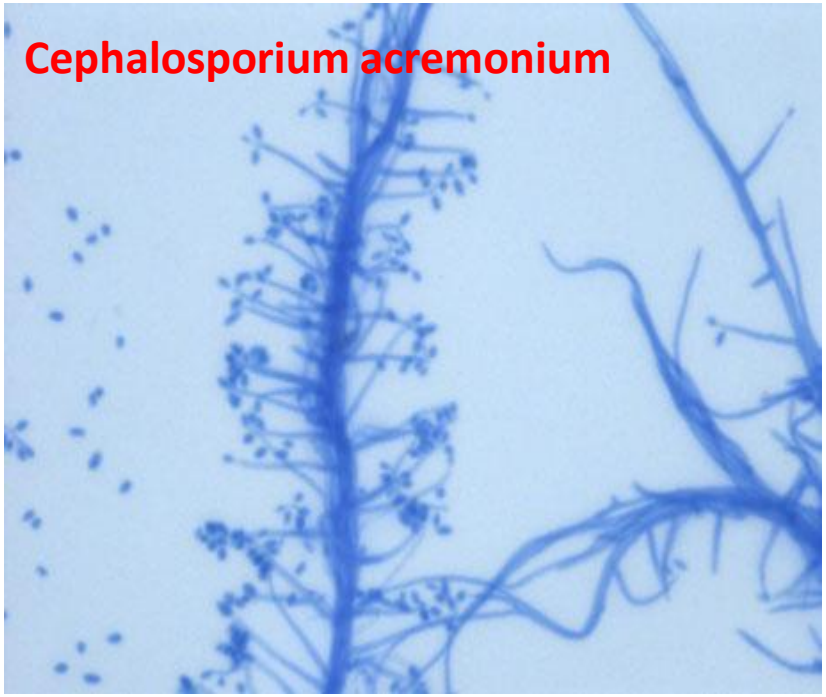
- **Four different mechanisms:**
  - Inactivation of antibiotic by beta-lactamase
  - Modification of target PBPs
  - Impaired penetration of drug to target PBPs
  - Efflux of the drug

- narrow specificity beta-lactamases – *St. aureus, Haemophilus sp., E.coli*
- extended spectrum (ESBL) – *Pseudomonas aeruginosa, Enterobacter sp.* – both PNC and Cephalosporins
- Carbapenemas – carbapenems
- Methicillin resistance – based on altered target PBPs (staphylococci, pneumococci, enterococci) – low affinity
- Impaired penetration and efflux – only in gram-negatives (porins)

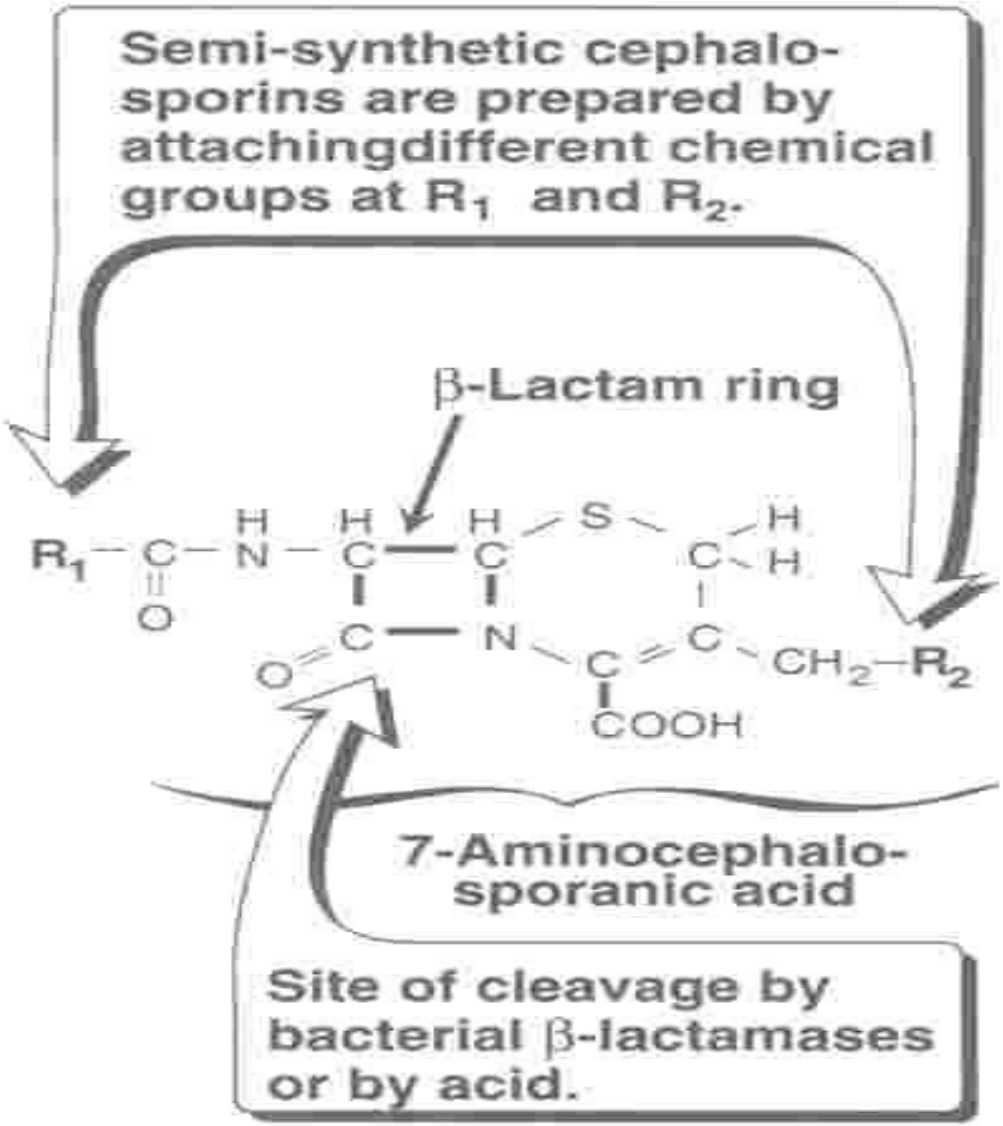
Penicillins - principal features

	Advantages and uses	Disadvantages
Natural penicillins	Inexpensive	▪Narrow spectrum ▪Resistance
Penicillinase-resistant	▪Active against penicillinase-producing *S. aureus* ▪Majority are oral	▪Narrow spectrum ▪MRSA strains resistant
Aminopenicillins	▪Wide use ▪Oral dosing	Resistance
Extended-spectrum	Active against *Pseudomonas*	Resistance

Cephalosporins



Cephalosporium acremonium was discovered in a Sardinian swamp by the Italian scientist **Giuseppe Brotzu**



Structural features of cephalosporins.

Cephalosporins

- Beta-lactam antibiotics (similar to PNC)
- Broad spectrum
- Act by inhibition of cell wall synthesis
- Bactericidal
- Inactive against: enterococci, MRSA, legionella, mycoplasma, chlamydia spp.
- Widely used
- 5 generations

Pharmacokinetics

- cephalosporins - parenterally and orally
- binding to plasma protein – different
  - Cefazolin is 80% protein bound (long t1/2)
  - Cephalexin is 10-15% protein bound
- absorption – ZINNAT – with food 50-60%
  without food 30-40%
- relatively lipid insoluble (like penicillins)
- do not penetrate cells or the CNS except for 3rd generation
- mostly excreted unchanged by the kidneys

Therapeutic uses

- URTI and otitis media
- Septicaemia caused by G- (Pseudomonas)
- UTI
- Meningitis - N. meningitidis
- Gonococcal infections
- Prophylaxis in surgery
  - gynecological,urological, orthopedic procedures, etc.

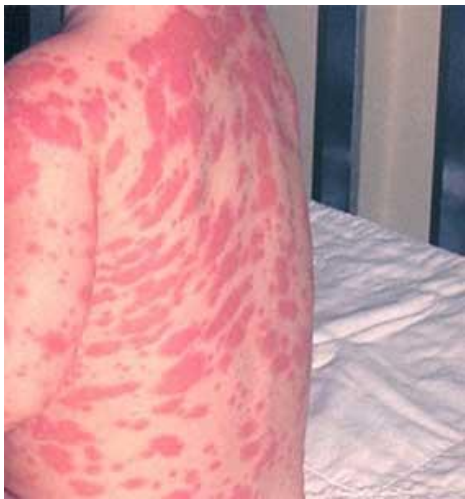
Therapeutic use of cephalosporins

Cephalosporin	URTIs	LRTIs	SSTIs	UTIs	STDs
1st generation	✓	✓	✓	✓	-
2nd generation	✓	✓	✓	✓	✓
3rd generation	✓	✓	✓	✓	✓
4th generation	-	✓	✓	✓	-

UTRIs–upper airways, LRTI–lower, SSTI–skin, soft tiss., UTI-urinary, STD-sex. dis.

Adverse effects

- hypersensitivity reactions- most common
    - anaphylaxis, bronchspasm, urticaria
    - maculopapular rash - more common
- 5-10% cross-sensitivity with PNC allergic patients
- 1-2% hypersensitivity reactions in non-PNC allergic patients
- nephrotoxicity - esp. cephradine
- thrombophlebitis (i.v.)



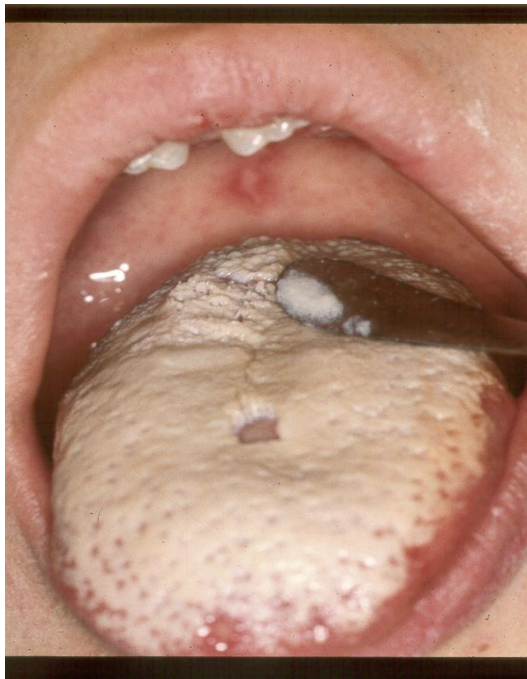
Adverse effects

- superinfections (candidiasis, colitis)
- diarrhea - oral cephalosporins
- cefamandole, ceftazidine, cefoperazone may cause:

    a) bleeding disorders

    b) flushing, tachycardia,

    c) vomiting with alcohol



1st generation

- Narrow spectrum
- Active against **G+ cocci**
  (except. enterococci & MRSA):
  Str.pneumoniae, Str.pyogenes, St. aureus,
  St. epidermidis)
- Modest activity against G- bacteria
  (E.coli, Klebsiela, Proteus)
- Ineffective against other G-
- Resistant against staphyl. penicilinase
- Weak resistant against β-lactamase of G-

1st generation

Cephalexin - KEFLEX, CEFACLEN, ORACEF - p.o. (0.25-0,5 g/4xday)

Cefadroxil - DURACEF - p.o. (0.5-1 g/2xday)

Cefazolin - KEFZOL, VULMIZOLIN, CEFAMEZIN - inj. (0.5 – 2 g /3xday)

Cefalothin - CEFALOTIN, KEFLIN - inj.

Cefapirin - CEFATREXYL - inj.

Cephradine - p.o.

2nd generation

- intermediate spectrum
- mainly and more effective against **G-** bacteria
- enlarged spectrum against G-
- modest activity against G+ bacteria
- higher resistance against β-lactamase of G-
- resistant against staphylococcal penicillinase
- are used primarily for acute ORL, respiratory disorders

2nd generation

Cefuroxime - ZINACEF - p.o., inj.

Cef. axetil - ZINNAT - p.o.

Cefaclor - CECLOR - p.o.

Cefprozil - CEFZIL - p.o.

Cefamandol - MANDOL - inj.

Cefoxitin - MEFOXIN - inj.

Loracarbef, p.o., Cefmetazol inj.

- p.o.
  - Adults 10-15 mg/kg/d in 2-4 doses
  - Children 20-40 mg/kg/d (max 1g/d)
- i.v.
  - 1-2 g /2-4 x day

3rd generation

- broad spectrum
- **enhanced G-** activity
- enhanced resistance against β-lactamases
- lower activity against staphylococcus
- good activity against streptococcus
- ↑ excretion into bile
- **antipseudomonas** – ceftazidime
  cefoperazone

3rd generation

Inj.

Ceftriaxone - ROCEPHIN
Cefotaxime - CLAFORAN
Ceftazidime - FORTUM, FORTAZ
Cefoperazone - CEFOBID
Ceftizoxime - CEFIZOX

P.o.

Cefixime - SUPRAX
Ceftibutene - CEDAX
Cefpodoxime - ORELOX
Cefdinir - OMNICEF
Cefditoren - SPECTRACEF

4th generation

- enhanced G- G+ activity
- active against G+ bacteria
- active against P. aeruginosa
- resistant against β-lactamases
- ↑ affinity to PBP
- **reserved** only for severe infections

Cefepime - MAXIPIME inj
Cefpirome – CEFROM inj

5th generation

- reserve antibiotics for MRSA, PRSP, pseudomonas, enterococci
- Intravenously
- Well tolerated – diarrhea, nausea, rash
- SSTI, LRTI
  - **ceftobiprole** (ZEFTERA)
  - **ceftaroline** (TEFLARO)

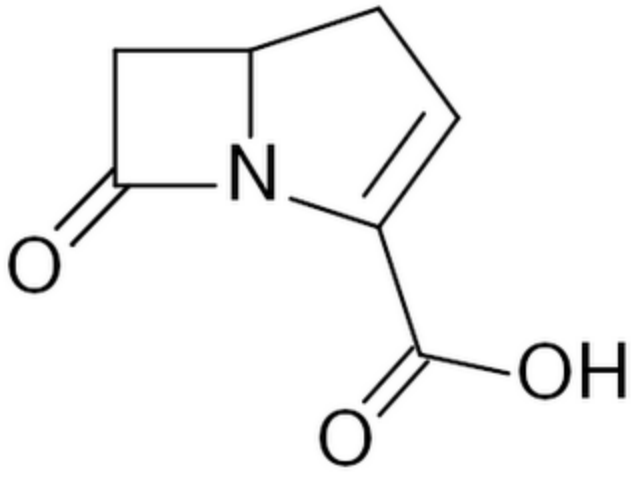
Cephalosporin – characteristics

	Advantages	Disadvantages
1st generation	• p.o. • cheap	• narrow spectrum • resistance
2nd generation	• p.o. • broad spectrum • active against B. fragilis	• resistance
3rd generation	• broader spectrum • active in nosocomial infections, meningitis	• resistance • i.v. mainly
4th generation	• against resistant microorganisms • serious infections	• resistance • i.v.
5th generation	• against resitant strains • serious infections	• i.v. • reserve ATB

Cephamycins

- very similar to cephalosporins
- are sometimes classified as CEPH
- originally produced by Streptomyces but synthetic are produced as well
- Cephamycins include: **Cefoxitin**
  Cefotetan
  Cefmetazole
  Flomocef

Carbapenems



Imipenem

Imipenem/Cilastin (PRIMAXIN; IV)

- **Cilastin** - selective dehydropeptidase inhibitor
  - inhibits degradation of imipenem into a nephrotoxic metabolite
- 0.25-0.5 g every 6-8 h i.v.
- broadest spectrum B-lactam
  - Staph (not MRSA), Strep,
    Neisseria, Haemophilus,
    Proteus, Pseudomonas,
    Klebsiella, Bacteroides, anaerobes

Meropenem

Meropenem (MERONEM inj., MERREM)

- 0.5-1 g every 8 h i.v.
- resistant to dehydropeptidase
  – without inhibitor
- ↑ activity against Enterobacteriace,
  Pseudomonas,
  Haemophilus

Doripenem

- **DORIBAX**
- **0.5 g in 4h infusion every 8h**
- high activity against a wide range of pathogens, (*P aeruginosa)*
- complicated intra-abdominal and urinary tract infections - by susceptible strains of *E coli*,*K pneumoniae*, *P aeruginosa*, *B caccae*, *B fragilis*, *B uniformis*, *B vulgatus*, *S intermedius*, *P micros;*
- does not need an administration with cilastatin

Ertapenem

- **INVANZ** - once-daily i.v., i.m. (1 g)
- moderate to severe infections –aerobic and anaerobic bacteria
- limited activity – Enterococus, Pseudom.
- in community-acquired pneumonia,

  intra-abdominal, skin, urinary tract,

  kidney and post-surgical

  gynecological infections

Carbapenems

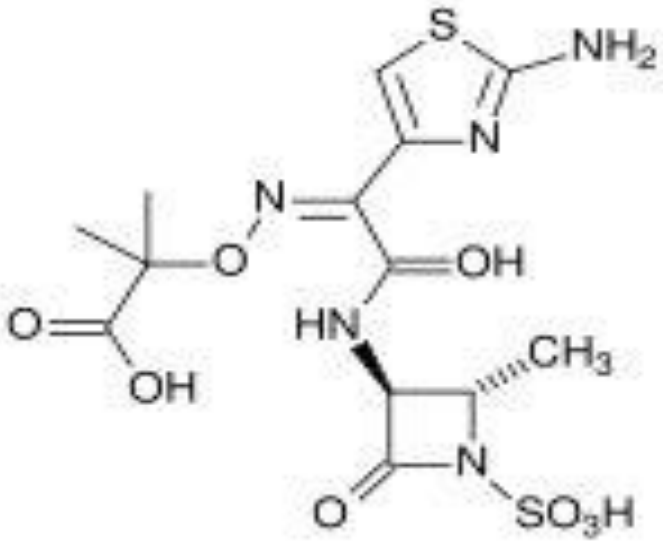
Adverse effects

- PCN allergy cross reactivity
- seizures, leucopenia, eosinophilia

Therapeutic use

- serious infections
- anaerobic infections
- mixed infection

Monobactams



Aztreonam

- **Aztreonam** (AZACTAM; IM/IV – 1-2 g every 8 h)
- beta-lactamase resistant
- not – nefrotoxicity
- penetrate to CNS, bone and other tissue
- very little cross-allergenicity - low immunogenic potential
- a safe alternative for PNC allergic patients

Adverse reactions

  - G+ superinfection (20-30%)

Aztreonam

- Narrow antibacterial spectrum
  - Aerobic Gram - (*H. flu, N. gonorrhea* (penicillinase producers), *E. coli, Klebsiella, Proteus, Pseudomonas*).
  - Ineffective against G+ and anaerobic organisms
    - inability to bind to PBP
  - Antipseudomonal activity is greater than TIMENTIN and ZOSYN but less than the carbapenems

Other Inhibitors of Cell Wall Synthesis

Polypeptide antibiotics

Bacitracin

- Topical application
- Against gram-positives

Vancomycin (VANCOCIN, VANCOLED)

- Glycopeptide
- Important "last line" against antibiotic resistant *S. aureus*

Vancomycin

- prevents cross-linking of peptidoglycans at an earlier step than beta-lactams
- active against G+ bacteria
- highly resistant *Strep. pneumo, Clostridia, Enterococcus, Staph. epi* and MRSA
- synergy with aminoglycosides
- used in treatment of MRSA and highly resistant *Strep.* species
- i.v., 30 mg/kg/d in 2-3 doses

Vancomycin

- Resistance - changes in permeability
  - decreased binding affinity
- **Adverse effects**
  - fever, chills, phlebitis, red man syndrom
  - slow injection, prophyl. antihistamines
  - ototoxic – potentiate ototoxic agents
  - nephrotoxicity

Teicoplanin - TARGOCID

- similar spectrum to vancomycin
- used in the prophylaxix and treatment of serious infections(G-, MRSA, enterococcus faecalis)
- effective in the treatment of pseudomembranous colitis and *Clostridium difficile*

  associated diarrhoea
- long half-life - 1 daily i.m., i.v.

Bacitracin

- produced by *Bacillus subtillis*
- inhibits peptidoglycan synthesis
- active against G+ G-
- topical use only

  (nephrotoxicity)

Bacitracin

- **Adverse effects**
  - Contact dermatitis – top 10 allergen
  - Reports of anaphylaxis
- Combinations:
  - **NEOSPORIN**
    - neomycin+polymyxin B+bacitracin
  - **POLYSPORIN**
    - polymyxin B+bacitracin
  - **FRAMYKOIN, PAMYCON**
    - neomycin+bacitracin

Polymyxin

- disrupts the phospholipid layer in cell membranes
- **polymyxins B** and E (as **colistin**)
- neurotoxic, nephrotoxic
- are not absorbed from GIT - i.v. administration
- limited spectrum
  - decreased G+
  - active against Pseudomonas, Proteus, Serratia, *E. coli*, Klebsiella, Enterobacter
- cross reaction with bacitracin

Daptomycin - CUBICIN

- cyclic lipopeptide
- disrupts cell membrane function
- similar to vancomycin
- for complicated skin and soft tissue infect.
- not used for pneumonia – antagonizes a pulmonary surfactnat

Adverse effects

– reversible myopathy

Fosfomycin - MONUROL

- is an antimetabolite
  - enzyme's irreversible inactivation
- enters the bacterial cell through the transporter
- is indicated in the treatment of UTIs (women)
- administered as a single oralmegadose 3 g
- safe in pregnancy

Lysostaphin

- antibacterial enzyme
- Staphylococcus simulans
- cleaves pentaglycine cross-links unique to S. aureus cell wall
- potent anti-staphylococcal agent
- is bactericidal
- synergistic effect with B-lactams

Dalbavancin, Telavancin

- **Dalbavancin**
  - Semisynthetic lipoglycopeptide from teicoplanin
  - Including MRSA and vancomycin-intermediate SA
  - Long half-life
- **Telavancin**
  - Semisynthetic lipoglycopeptide from vancomycic
  - Exept of inhibition of cell wall synthesis causes disruption of membrane potential and increases membrane permeability
  - once daily