Basic principles of chemotherapy. Penicillins, cephalosporins.

J. Mojžiš

The antiinfective drugs

- **Antiinfective agents are *drugs that are designed to act selectively on foreign organisms* that have invaded and infected the body.**

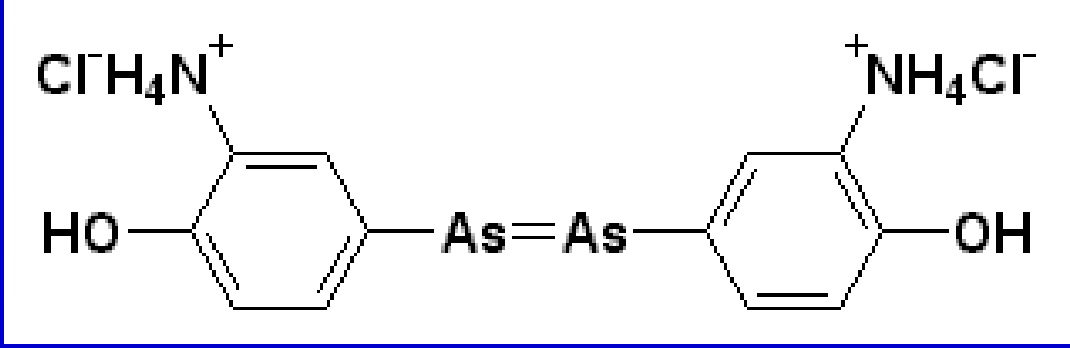
The antiinfective drugs

Antiinfective drugs - range from

- **Antibacterials**
- **Antifungals**
- **Antiprotozoals**
- **Antihelminthics**
- **Antivirals**
- **Antimycobacterial**

History of antibacterial therapy

- **1909 Paul Ehrlich**
  - **Search for magic bullet that would attack bacterial structures, not ours.**
  - **Developed salvarsan, arsenic derivative used against syphilis.**

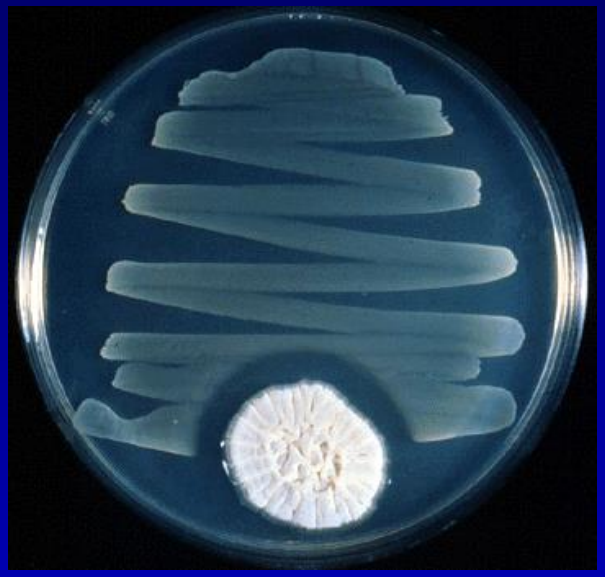


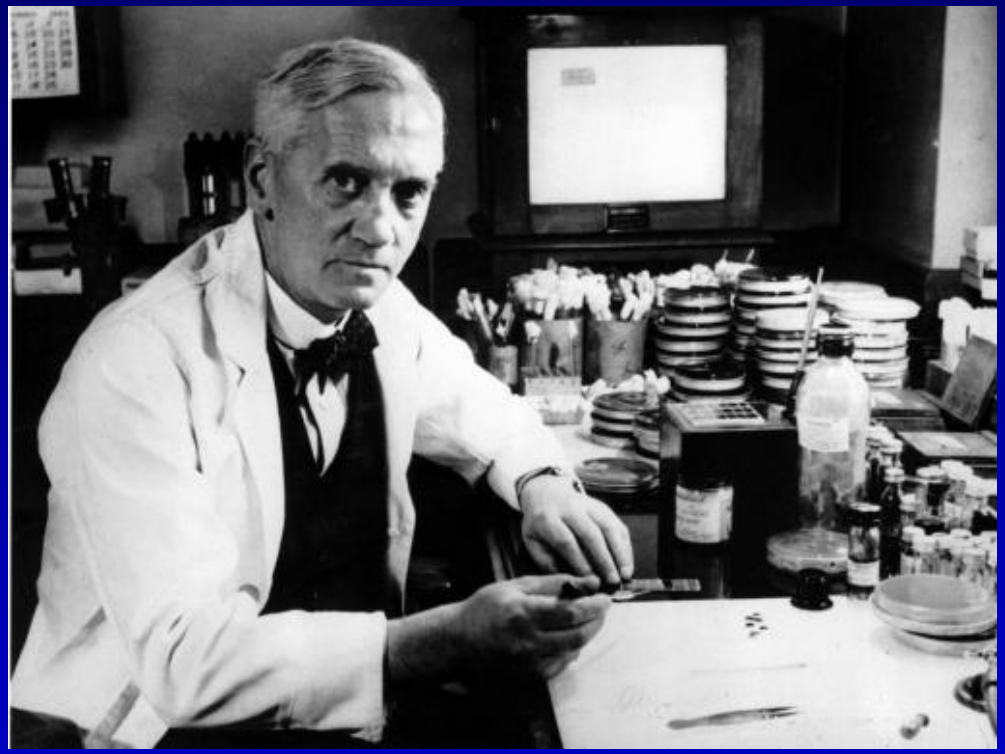
Ehrlich's Magic Bullets

Timeline

- **1929 Penicillin discovered by Alexander Fleming**
- **1932 Sulfa drugs discovered** (Domagk, prontosil)
- **1940 Florey and Chain mass produce penicillin for war time use, becomes available to the public.**
- **1943 Streptomycin discovered**
- **1949 Chloramphenicol was available**
- **1952 Erythromycin discovered**
- **1964 Cephalosporins introduced**

Fleming and Penicillin





"One sometimes finds what one is not looking for"

Sir Alexander Fleming

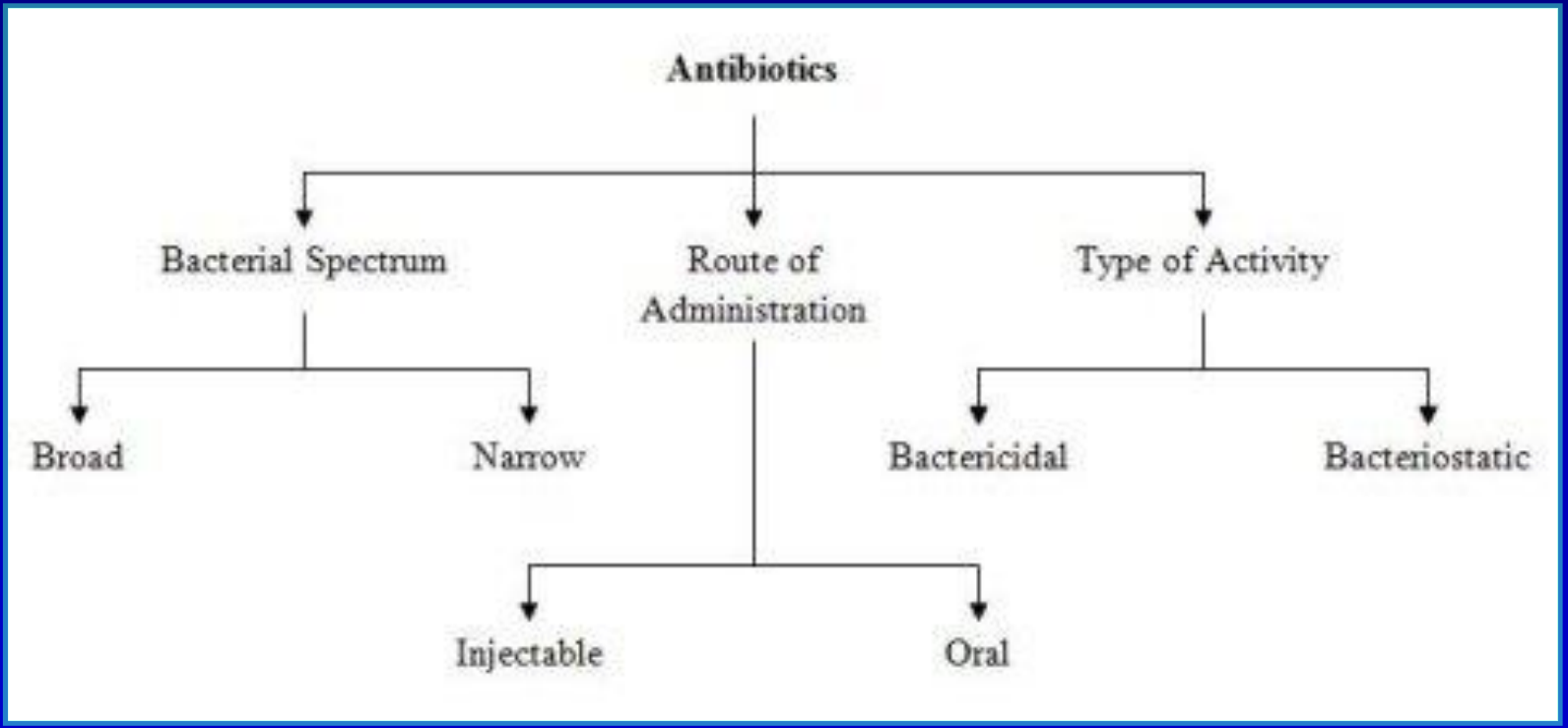
Historical distinctions

- **Antibiotics:** substances produced by organisms that have inhibitory effects on other organisms.
  - Penicillin, streptomycin
- **Synthetic drugs:** produced in a lab.
  - Salvarsan, sulfa drugs
- Nowadays, most antimicrobials are **semi-synthetic**
  - Chemically modified versions of natural products
  - Distinction between “antibiotics” and “synthetic drugs slowly being abandoned.

Basic criteria for ATB

- maximal microbial toxicity
- minimal organ toxicity

ATB classifications



Basic terminology

- antibacterial spectrum
- MIC
- resistance
- dysmicrobia
- superinfection
- bactericidal effect
- bacteriostatic effect

Spectrum of activity of antibacterials

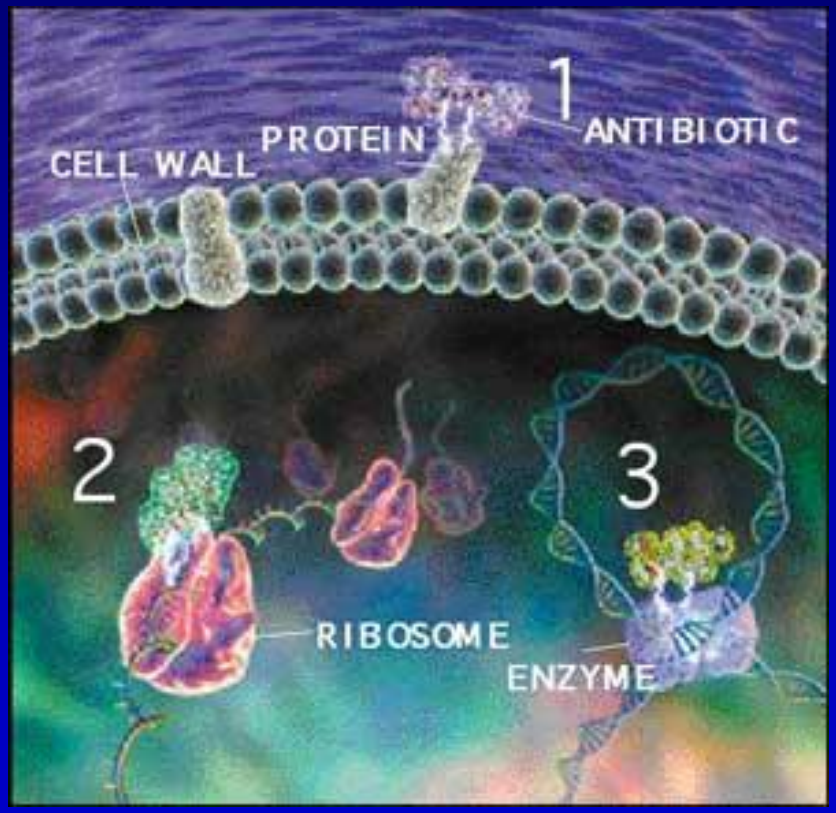
- **Antibacterials that interfere with the ability of the cell to reproduce/replicate without killing them are called BACTERIOSTATIC drugs.**
- **Tetracycline is an example.**

Spectrum of activity of antibacterials

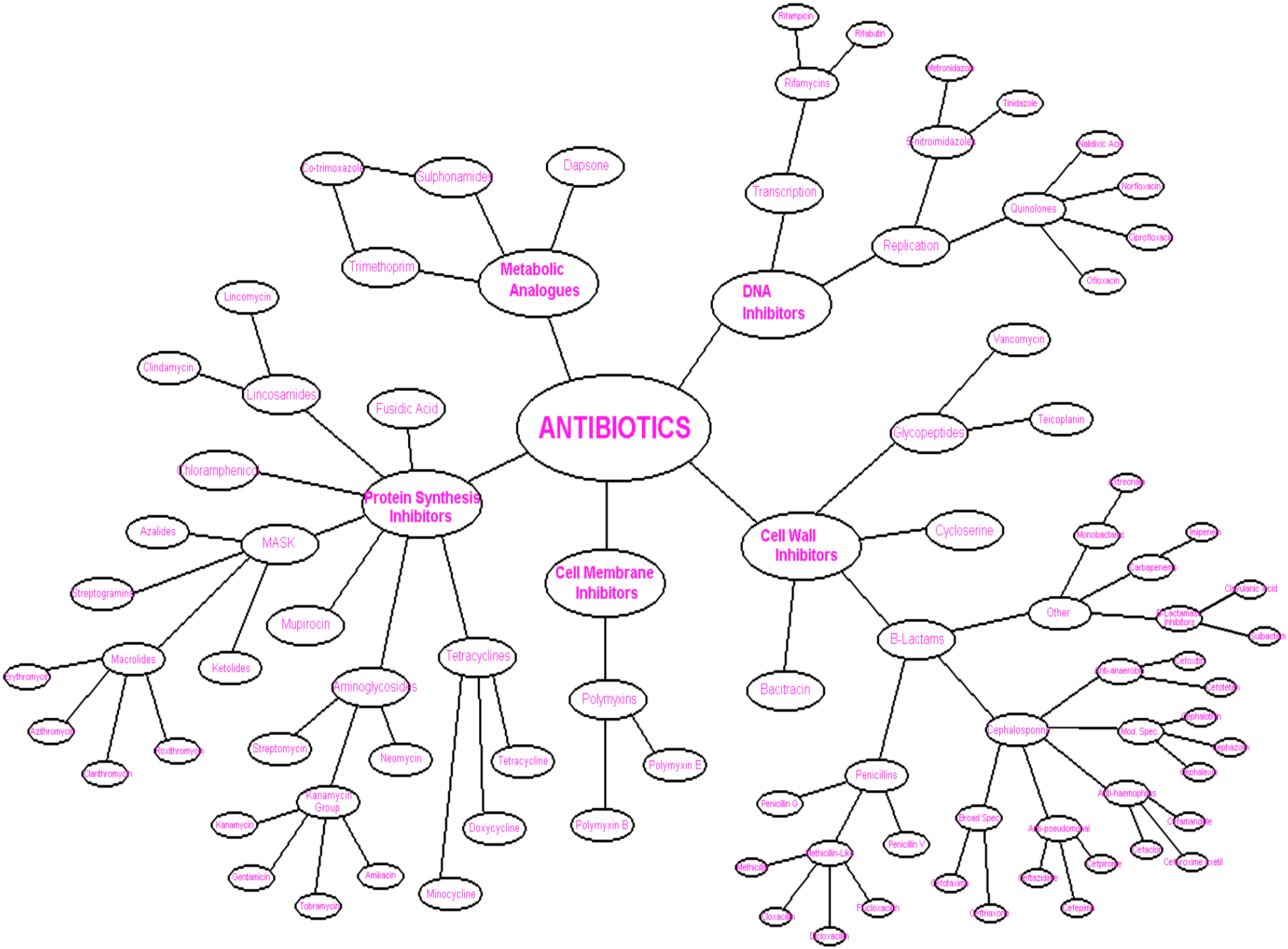
- Antibiotics that can aggressively cause bacterial death are called **BACTERICIDAL.**
- PNC is an an example

- These properties (-cidal and –static) can also depend on the ATB concentration in the blood.
- (e.g. Erythromycin and Clindamycin may be bactericidal at higher blood levels)

Mechanisms of action



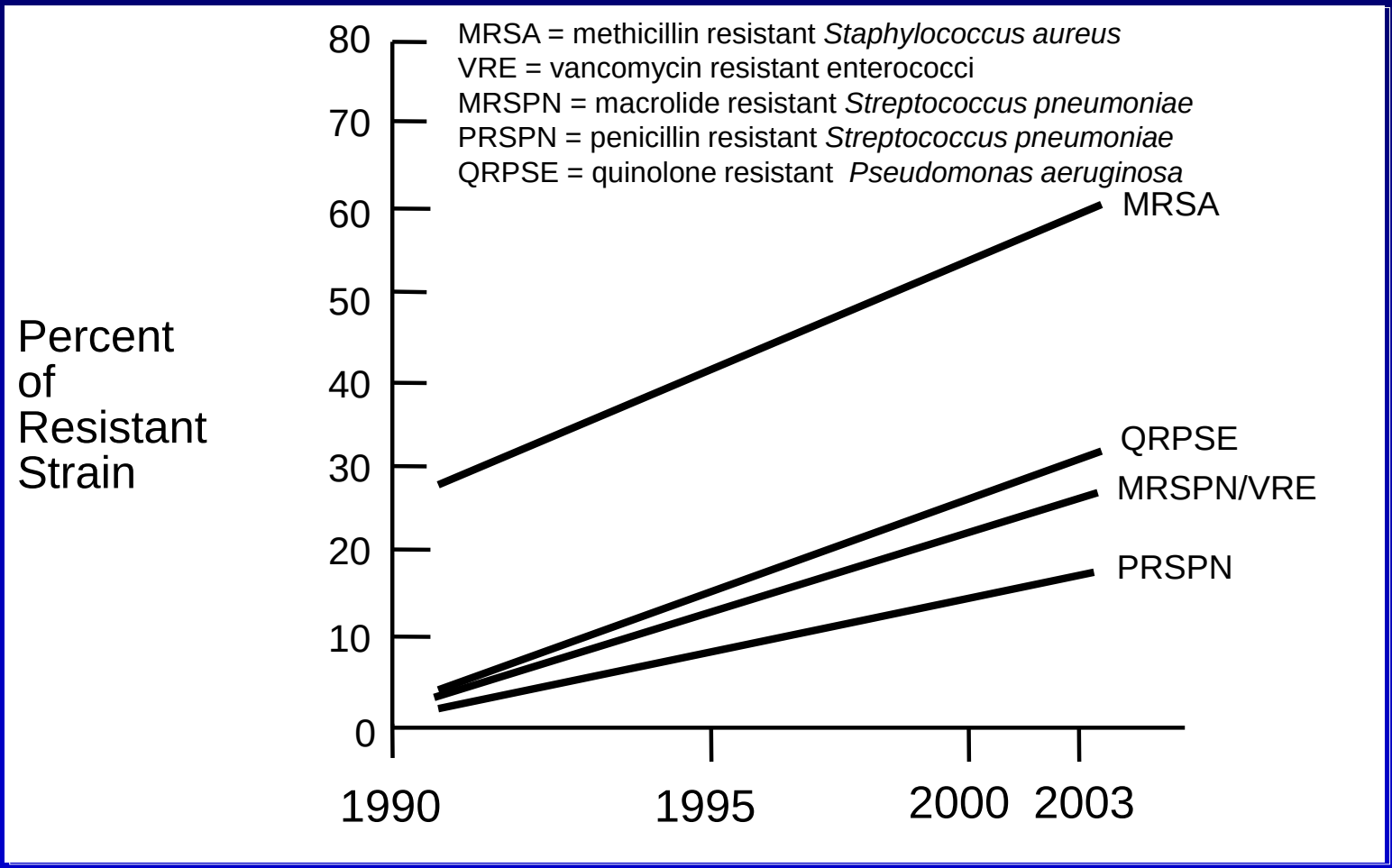
- **interference with cell wall synthesis**
  (β-lactams, vancomycin, cycloserin)
- **interference with protein synthesis**
  (CMP, TTC, AMG, macrolides)
- **influence of cell membrane**
  (polymyxines)
- **interference with nucleic acid metabolism**
  (rifampicin, quinolones)
- **interference with intermediary metabolism**
  (sulfonamides)


ANTIBIOTICS
Metabolic Analogues
Co-trimoxazole
Sulphonamides
Dapsone
Trimethoprim
DNA Inhibitors
Transcription
Rifampicin
Rifabutin
Rifamycins
Replication
5-nitroimidazoles
Metronidazole
Tinidazole
Quinolones
Nalidixic Acid
Norfloxacin
Ciprofloxacin
Ofloxacin
Protein Synthesis Inhibitors
Lincomycin
Clindamycin
Lincosamides
Fusidic Acid
Chloramphenicol
MASK
Azalides
Streptogramins
Macrolides
Erythromycin
Azithromycin
Clarithromycin
Roxithromycin
Ketolides
Mupirocin
Aminoglycosides
Streptomycin
Neomycin
Kanamycin Group
Kanamycin
Gentamicin
Tobramycin
Amikacin
Tetracyclines
Tetracycline
Doxycycline
Minocycline
Cell Membrane Inhibitors
Polymyxins
Polymyxin E
Polymyxin B
Cell Wall Inhibitors
Vancomycin
Glycopeptides
Teicoplanin
Cycloserine
Bacitracin
B-Lactams
Penicillins
Penicillin G
Penicillin V
Methicillin-Like
Methicillin
Flucloxacillin
Dicloxacillin
Oxacillin
Other
Aztreonam
Monobactams
Imipenem
Carbapenems
Clavulanic Acid
B-Lactamase Inhibitors
Sulbactam
Cephalosporins
Anti-anaerobic
Cefoxitin
Cefotetan
Mod. Spec.
Cephalothin
Cephazolin
Cephalexin
Anti-haemophilus
Cefamandole
Cefaclor
Cefuroxime axetil
Broad Spec.
Anti-pseudomonal
Cefpirome
Ceftazidime
Cefotaxime
Ceftriaxone
Cefepime

Mechanisms of resistance

- **enzymes**
- **change of cell wall permeability**
- **↑ synthesis of antagonist** (folic acid)
- **change of penicilin-binding protein** (PBP)

Antibiotic resistance is rising



Toxic effects of ATB

myelosuppresion *(CMP)*

hematotoxicity *(sulfonamides)*

hepatotoxicity *(macrolides)*

nephrotoxicity *(aminoglycosides)*

ototoxicity (*aminoglycosides)*

neurotoxicity *(anti-TBC)*

Other side effects (SE)

allergy *(β-lactams)*

dysmicrobia *(large spectrum ATB)*

superinfection *(large spectrum ATB)*

Jarisch-Herxheimer *(PNC)*

sy Hoigné (PNC-retard)

Combinations of ATB

Aims:

- **increase of therapeutic effect**
- **decrease in AR**
- **prophylaxis of resistance**

Bacteriostatic
+
bactericidal
↓
?

Principles of ATB therapy

- primary focus inf.
- possible inf. agent
- sensitivity
- variability of pacient´s response
- kinetics & penetration
- hospitalisation
- ATB SE
- effectiveness of elimination organs
- start therapy in right time
- regular dosing
- optimal ther. period
- don´t repeat therapy
- price of ATB

Conclusions

- **Past**

  Antibiotics have revolutionised medicine and have saved millions of lives

- **Present**

  Increasing bacterial resistance and falling antibiotic production is reducing the efficacy of antibiotics

- **Future**

  A continuous supply of new antibiotics is needed, with activity against non-multiplying bacteria

β - lactame ATB

Penicillins

- **basic PNC**
- **anti-staphyloccocal**
- **aminoPNC**
- **carboxyPNC**
- **acylureidoPNC**
- **β-lactamase inhib.**

Cephalosporins

- I. -
- II. -
- III. -
- IV. -
- V. -

- generation

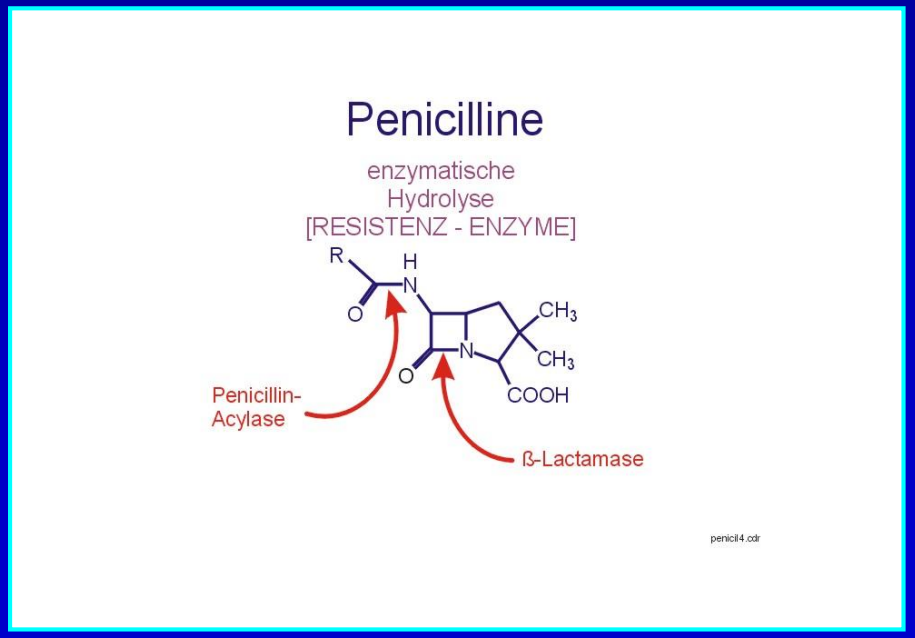
Carbapenems
Monobactams

Penicillins
(bactericidal)

- ***Penicillium notatum***

- 6-aminopenicillanic acid

penem



Mechanism of action

They act by inhibition of bacterial cell wall synthesis

The β-lactam binds to Penicillin Binding Protein (PBP)

PBP is unable to crosslink peptidoglycan chains

The bacteria is unable to synthesize a stable cell wall

This cause lysis of bacterial cell wall

These agents are **bactericidal**

Active against **multiplying** and not resting bacteria

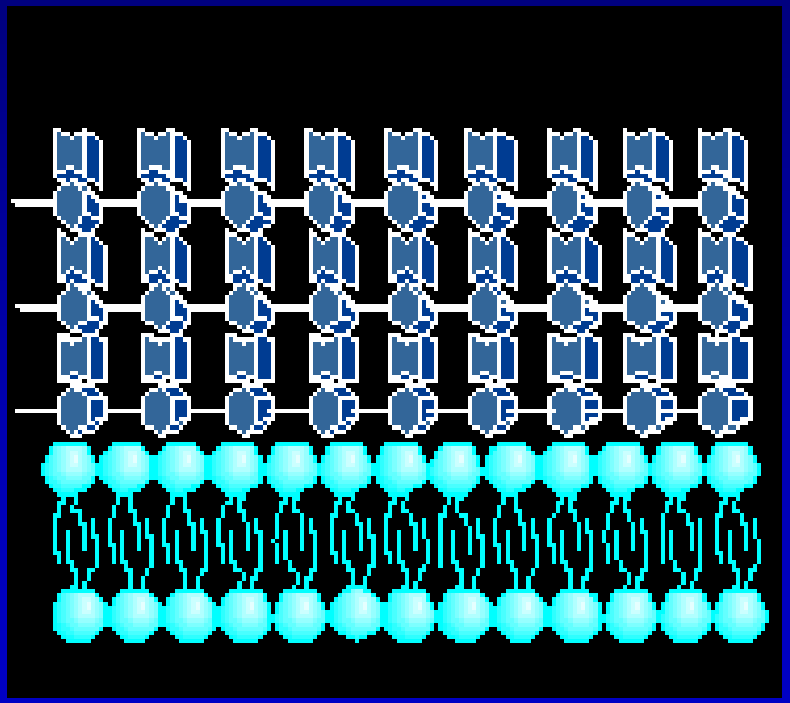
Inactive against mycobacteria, protozoa, fungi and viruses

Gram positive & Gram Negative

- **Gram positive bacteria have a thick cell wall**
  - **Peptidoglycan directly accessible from environment**

- **Gram negative bacteria have a different wall**
  - **Thin layer of peptidoglycan**
  - **Surrounded by an outer membrane (OM) composed of lipopolysaccharide, phospholipids, and proteins**
  - **OM is a barrier to diffusion of molecules including many antibiotics**
    - **Only some antibiotics are that hydrophobic**
    - **Porins allow passage of only some antibiotics**

Mechanism of action



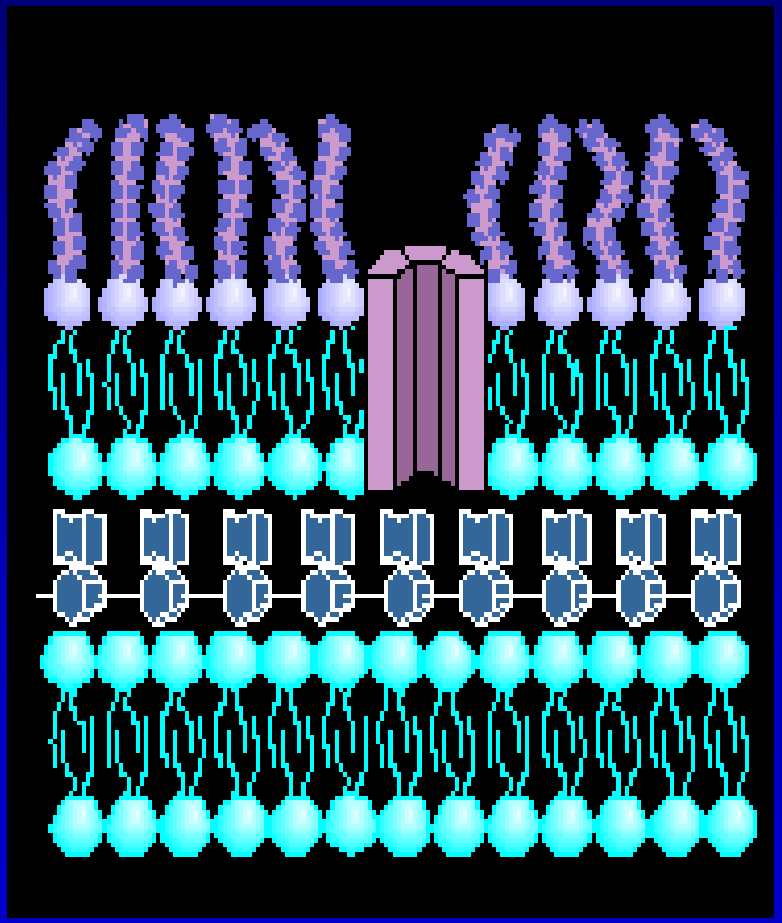
- Gram +

←peptidoglycane

← **PBP**

← lipidic bilayer

Mechanism of action



- Gram -

← LPS & lipids

← membrane & porines

←peptidoglycane

← **PBP**

← membrane

There is no molecule similar to peptidoglycan in humans, making drugs that target cell wall synthesis very selective in their toxicity against bacteria.

Basic PNC

- ***benzylpenicilline*** **(PNC G)**
- ***procain-benzyl-PNC***
- ***benzatine-PNC***
- ***phenoxymethyl-PNC*** **(PNC V)**
- ***penamecilline***

Pharmacokinetics

- **i.v.** ***benzylpenicilline – PNC G***
- **i.m.** ***Pc-PNC, benzatine-PNC***

- **extracellular distribution**
- **renal excretion of active substance**
  (probenecide)

- acidostabile
- incomplete absorption (60%)
- hydrolytic cleavage, activation, prolonged effect

  (penamecilline)

Antimicrobial spectrum

- **gram + cocci**
  (*St. pyogenes, St.viridans, St. pneumoniae*)
- ***staphylococci***
  (β-lactamase-negative)
- **gram + bacilly**
  (B. anthracis, Clostridium spp., L. monocytogenes,)

- **gram – bacilly**
  (*Pasteurella*)
- ***spirochetes***
  (*Treponema pallidum*)
- ***borelia, leptospira***

Side effects

- anaphylaxis
- Jarisch-Herxheimer
- sy Hoigné
- neurotoxicity

- allergy
- pregnancy & breast feeding are not contraindicted

Disadvantages of penicillin G

A. Destroyed by gastric HCl

B. Inactivated by penicillinase

C. Narrow spectrum of activity

Antistaphylococcal PNC
(penicillinase-resistant)

- ***meticilline*** (acidolabile)
- ***oxacilline***
- ***cloxacilline***
- ***dicloxacilline***

- acidostabile
- strong alb. binding
- good diffusion in parenchym. org.
- weak BBB passage

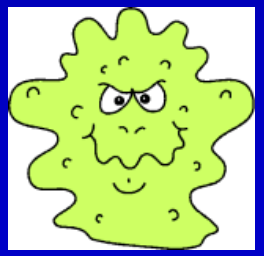
Antistaphylococcal PNC
(penicillinase-resistant)

Sensitivity:

- ***staphylococci***
  (β-lactamase-positive)

Resistance:

- ***enterococci***
- **gram - bacteries**



MRSA

- **Methicillin-Resistant *Staphylococcus aureus***
- **Most frequent nosocomial (hospital-acquired) pathogen**
- **Usually resistant to several other antibiotics**

Amino-PNC

(penicillinase-non-resistant)

- ***ampicilline***
- ***amoxicilline***
- combination with clavulanic acid

- acidostabile
- absorption variable
- low albumine binding
- good inflammatory tissue diffusion
- increased bile concentration
- mild nephrotoxicity

Amino-PNC

(penicillinase-non-resistant)

Sensitivity:

- G^+ cocci
- enterococci
- G^- cocci

(N.meningitis & gonorrhoeae)

- *H. influenzae*
- aerobic G^- bacilly

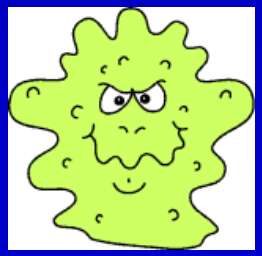
(E.coli, Salmonella,Shigella)

Resistance:

- *enterobacteriaceae*
- *staphylococci*

*(*β-lactamase-positive*)*

- *Pseudomonas sp.*
- *B. fragilis*



Uses

H. Influenza infections (otitis media, sinusitis, bronchitis, pneumonia)

E. coli infections (Urinary & biliary infections).

Samonella infections (typhoid fever)

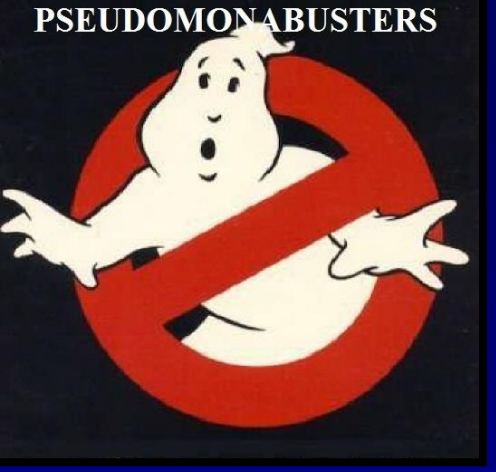
Shigella infections (ampicillin)

Gonococcal infections (alternative for penicillin in the treatment of gonorrhea)

Prophlaxis of infective endocarditis

Disadvantages

Amoxicillin & ampicillin alone are readily destroyed by Staph. penicillinase.



Carboxy-PNC
(antipseudomonas PNC)

- ***carbenicilline***
- ***ticarcilline***
- combination with clavulanic acid

- ***Pseudomonas***
- ***Proteus***
- **anaerobs**

- **severe infections**
- **septicemies**
- **meningitis**
- **endocarditis**
- **urogenital & respiratory infections**

Acylureido-PNC
(wider spectrum against gram – bacilly)

- ***piperacilline***
- ***azlocilline***
- combination with tazobactam

- ***gram + cocci***
- ***gram - bacteries***
- ***Pseudomonas***

- **severe infections**
- **septicemies**
- **meningitis**
- **endocarditis**
- **abdominal cavity inf.**
- **pneumonia**

Carbapenems
(β-lactams with the widest spectrum)

- ***imipenem***
- combination with cilastatin

- good tissue penetration
- good BBB difusion
- renal excretion-70% of active substance
- rest as metabolites

Cilastin: inhibitor of renal dehydropeptidase I - enzyme responsible for hydrolysis of imipenem to nephrotoxic metabolites with no antibacterial activity. Does not increase plasma levels of imipenem but does prevent nephrotoxicity and maintains urinary levels of the intact drug.

Carbapenems

- **G^+ cocci, *staphylococci***

(even producing penicillinase)

- ***Enterococcus faecalis, L. monocytogenes***
- **G^- aerobs**
- **enterobacteries**
- **anaerobic bacteries**

Monobactams

- ***aztreonam***

- **good tissue & body fluid penetration**
- **good BBB difusion**
- **good bone penetration**
- **renal elimination**

Monobactams

Sensitivity:

- **exclusively G^- aerobic bacteries**

(N.meningitis a gonorrhoeae, H. influenzae)

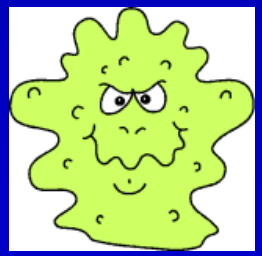
- **aerobic G^- bacilly**

(E.coli, Salmonella,Shigella)

- ***Pseudomonas aeruginosa***

Resistance:

- ***G^+ bacteries***
- ***anaerobs***



β-lactamase inhibitors

- *clavulanic acid*
- *sulbactam*
- *tazobactam*

- irreversible inhibition
- combination with β-lactame ATB
- similar kinetics & tissue penetration
- with no antibacterial activity

ADME

Oral absorption of most penicillins is poor

Exception: penicillin v

Amoxicillin

Food interfer with absorption

Distribution

- **Widely distributed**
- **Relatively insoluble in lipid**
- **Hence, have poor penetration into cells and BBB**
- **Inflammation (eg. meningitis) permits entrance into CSF**

ADME(cont.)

Protein binding differs

Ampicillin and penicillin G 20% bound

Nafcillin, oxacillin, 90% bound
cloxacillin , dicloxacillin

Metabolism and excretion

Not metabolized in human

Excreted mostly unchanged in urine(except. oxacillin, cloxacillin, dicloxacillin)

Probenecid blocks their secretion

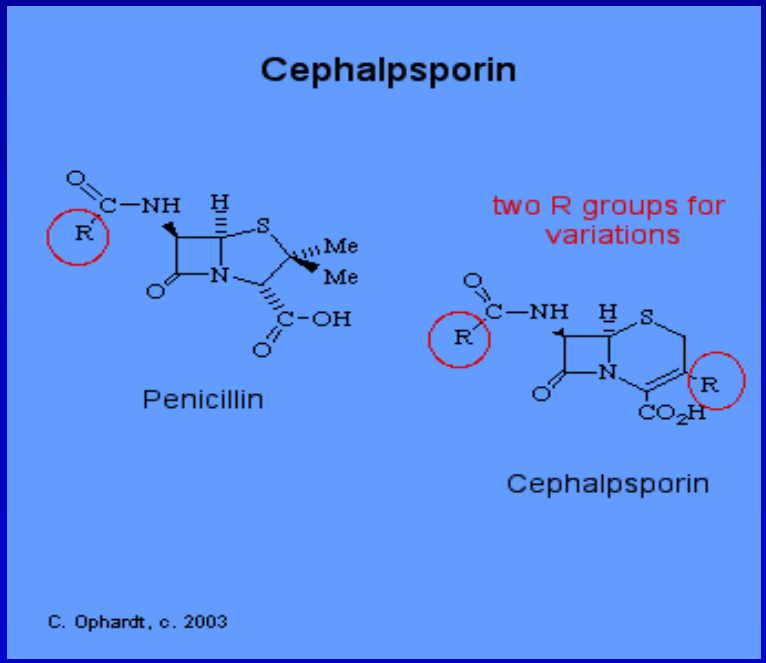
Half-life 30-60 min (increased in renal failure)

Cephalosporins
(bactericidal)

- ***Acremonium chrysogenum***

- 7- aminocephalosporanic acid

cefem



Cephalosporins

- First generation cephalosporins
- Second generation cephalosporins
- Third generation cephalosporins
- Fourth generation cephalosporins
- Fifth generation cephalosporins

Cephalosporins

- **First generation cephalosporins - are largely effective against the same gram-positive organisms affected by penicillin.**

- **Second generation cephalosporins - are effective against those strains as well as H. influenza, Entreobacter aerogenes and Nesseria sp. These drugs are less effective against gram positive bacteria**

Cephalosporins

- **Third generation cephlosporins- are relatively weak against gram-positive bacteria but more potent against gram-negative bacteria, to include Serratia marcescens.**

- **Fourth generation cephalosporins- are developed to fight against the resistant gram-negative bacteria (G+ are also sensitive). The first drug is cefepime.**

Cephalosporins

- **Fifth generation cephalosporins - broad-spectrum activity against G+ and G- organisms; against MDR G+ (e.g. MRSA, VRSA); ceftaroline**

Cephalosporins - I. generation

- *cephazolin*
- *cephalotin*

- *cephalexin*
- *cephadroxil*

- good GI absorption
- higher levels & activity (parent.)
- renal elimination of active substance
- allergies, flebitis, blood cell formation

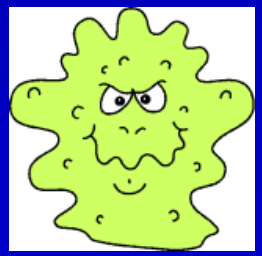
Cephalosporins - I. generation

Sensitivity:

- **high effectiveness G^+ *cocci***
- **resistance to β-lactamases of *staphylococci***

Resistance:

- ***G^- bacteries***
- **weak resistance to β-lactamases of *gram - bacteries***



Cephalosporins - II. generation

- ***cefuroxim***
- ***cephamandol***

- ***cefuroxim-axetil***
- ***cephaclor***

- **current G– infections with good sensitivity**
- **renal elimination 85-95% (50% in *cefuroxim-axetil*)**
- **risk of bleeding; disulfiram-like reactions *(cephamandol)***

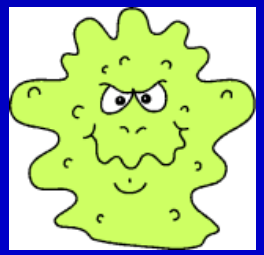
Cephalosporins - II. generation

Sensitivity:

- **high effectiveness G^+ *cocci***
- **good effectiveness some G^- *bacteries***

Resistance:

- ***Proteus vulgaris***
- ***Providencia spp.***
- ***Serratia spp.***



Cephalosporins - III. generation

- *cephotaxim*
- *cephtrizoxim*
- *cephtriaxom*
- *cephtazidine*

- *cephixim*
- *cephtibutem*
- *cephetamet-pivoxil*

- rare G^- infections
- mixed G^- & G^+
- G^- meningitis
- severe pseudomonas infections
- severe *Haemophilus inf.* infections
- renal elimination in dependence on substance
- pseudomembranous colitis, bleeding, allergy

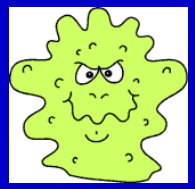
Cephalosporins - III. generation

Sensitivity:

- **lower effectiveness:**
  - **G^+ *cocci***
  - **the highest effectiveness G^- *bacteries***
  - **majority of *pseudomonas***

Resistance:

- ***Klebsiella pneumoniae*** **(produces cephotaximases)**
- **some *E.coli, Proteus mirabilis, Salmonella spp.* (chromosome encoding β-lactamases)**



Cephalosporins - IV. generation

- ***cefpirom***
- ***cefepim***

- **high effectiveness G+ & G-**

  bacteries
- ***Pseudomonas aer.***

- ***enterobacter spp. & citrobacter spp.*** **resist. to III. gen.**

Cephalosporins - V. generation

Ceftaroline - approved for the treatment of:

community-acquired pneumonia (CAP)

acute bacterial skin and skin structure infections caused by susceptible G- and G+ bacteria, including (MRSA).

It is the first “5th-generation cephalosporin” and has a broader G+ spectrum of activity than all other cephalosporins due to its activity against MRSA

Therapeutic uses of CFS

1. Upper respiratory tract infections and otitis media
   cefaclor , cefuroxime axetil
   cefixime , cefprozil

2. Septicaemia caused by G- bacteria (P.aeruginosae)

A cephalosporin(eg. ceftazidime) + AG

3. Urinary tract infections
   Cefuroxime, Cefixime

4. Prophlaxis in surgery
   Appendectomy (bowel anaerobes) eg. Cefoxitin
   Obstetrical &gynecological, urological, orthopedic procedures, etc
   (S. aureus & S. epidermidis) eg. Cefazoline

5. Meningitis- N. Meningitidis
   Ceftriaxone
   Cefotaxime(pref. in neonate)

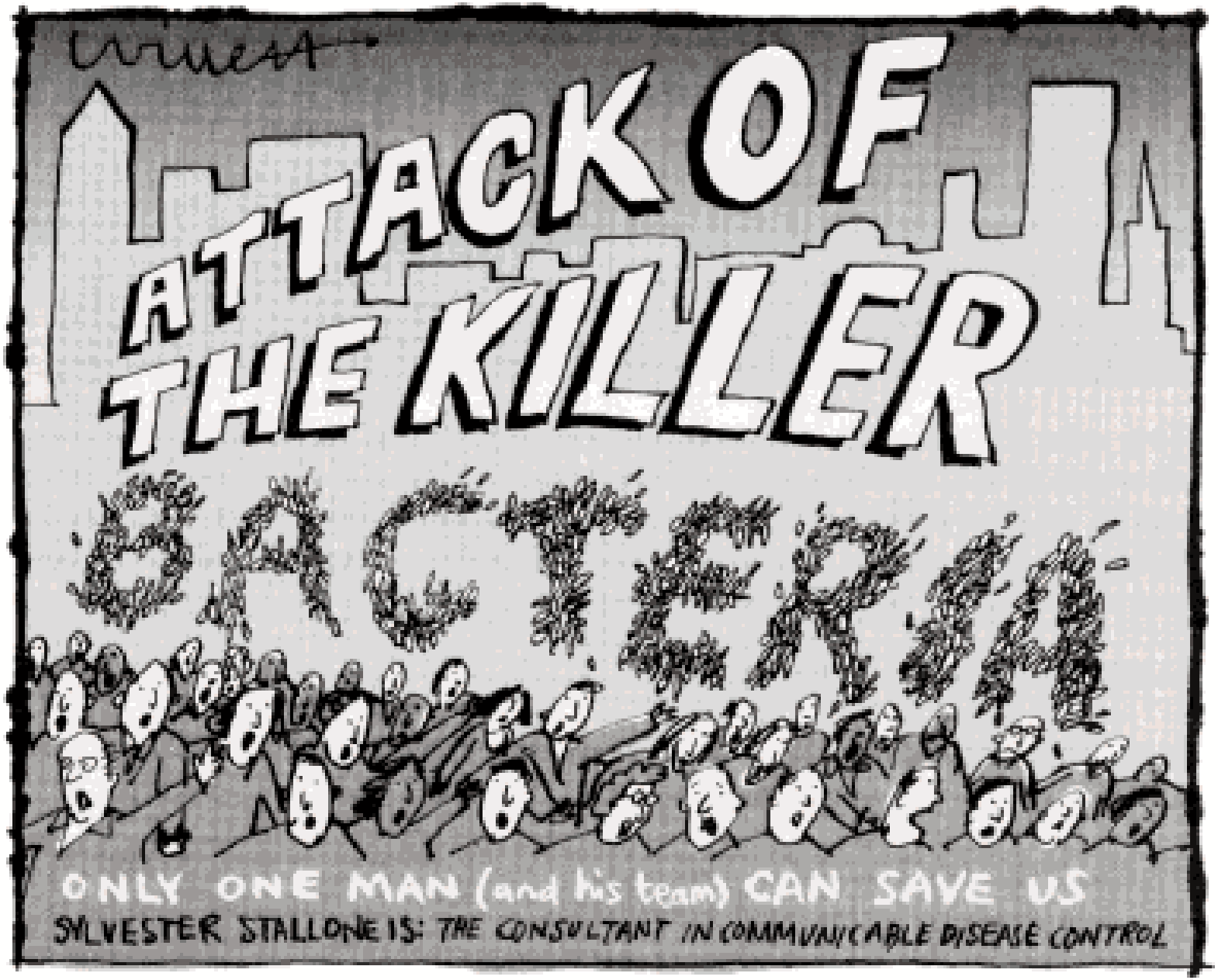
6. Gonococcal infections
   Ceftriaxone

Adverse effects

1. Hypersensitivity reactions- most common
   Anaphylaxis, bronchspasm, urticaria
   Maculopapular rash- more common
2. Nephrotoxicity ; esp. cephradine
3. Thrombophlebitis (i.v admin.)
4. Superinfections
5. Diarrhea-oral cephalosporins, cefoperazone, ceftriaxone & moxalactam.
6. cefamandole, moxalactam & cefoperazone may cause:
   a) bleeding disorders
   b) Flushing, tachycardia, vomiting with alcohol intake

CFS - bleeding

- The second-generation cephalosporins-cefamandole, cefotetan, and cefoperazone, contain an N-methylthiotetrazole (NMTT) side chain.
- NMTT group can:
  - dissociate from the parent antibiotic and competitively inhibit vitamin K action ⇨ prolongation of the prothrombin time and bleeding
  - NMTT is also associated with a disulfiram-like reaction to alcohol
  - clinical bleeding has been less frequently reported with cefotetan than with cefoperazone or cefamandole



Careers : Become a Microbiologist.