

Antibiotics

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- **Antibiotic:** Chemical produced by a microorganism that kills or inhibits the growth of another microorganism
- **Antimicrobial agent:** Chemical that kills or inhibits the growth of microorganisms

Microbial Sources of Antibiotics

TABLE 20.1

Representative Sources of Antibiotics

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

Antibiotics

Actions

- **Bactericidal**

- Kills bacteria, reduces bacterial load

- **Bacteriostatic**

- ✓ Inhibit growth and reproduction of bacteria

- All antibiotics require the immune system to work properly

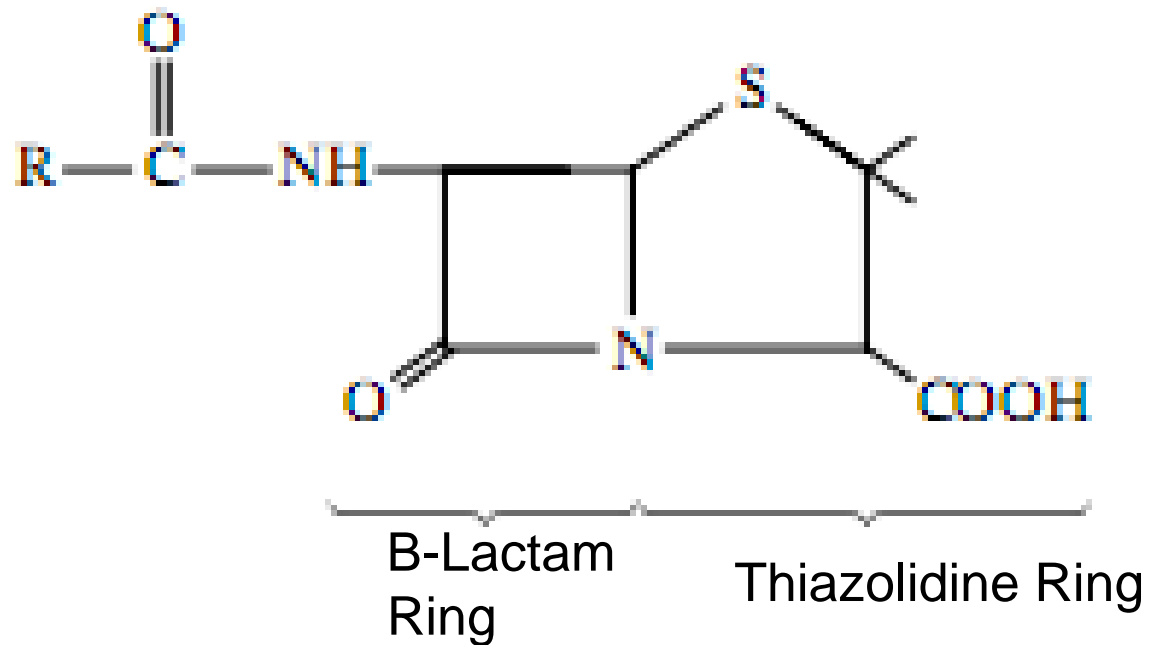
- Bactericidal appropriate in poor immunity

- Bacteriostatic require intact immune system

Mechanisms of Antimicrobial Action

- Inhibition Cell wall formation
- Inhibition Protein synthesis
- Inhibition DNA replication
- Inhibition RNA synthesis
- Inhibition Synthesis of essential metabolites
- Alteration of cell membrane synthesis

β -Lactams



β -Lactams

β -Lactams

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graph TD; A["beta-Lactams"] --> B["Cephalosporin"]; A --> C["Carbapenem"]; A --> D["Penicillin"]; B --- B1["•Cefalexin"]; B --- B2["•Cefuroxime"]; B --- B3["•Cefotaxime"]; B --- B4["•Ceftriaxone"]; C --- C1["•Meropenem"]; C --- C2["•Imipenem"]; C --- C3["•Doripenem"]; C --- C4["•Ertapenem"]; D --- D1["Narrow Spectrum"]; D --- D2["•Benzylpenicillin (Penicillin G)"]; D --- D3["•Phenoxymethylpenicillin (Pen V)"]; D --- D4["•Flucloxacillin"]; D --- D5["Broad Spectrum"]; D --- D6["•Amoxicillin/Co-amoxiclav"]; D --- D7["•Ampicillin"]; D --- D8["•Piperacillin with Tazobactam (Tazocin)"];
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Cephalosporin

- Cefalexin
- Cefuroxime
- Cefotaxime
- Ceftriaxone

Carbapenem

- Meropenem
- Imipenem
- Doripenem
- Ertapenem

Penicillin

Narrow Spectrum

- Benzylpenicillin (Penicillin G)
- Phenoxymethylpenicillin (Pen V)
- Flucloxacillin

Broad Spectrum

- Amoxicillin/Co-amoxiclav
- Ampicillin
- Piperacillin with Tazobactam (Tazocin)

Cephalosporins

- 1st generation of Cephalosporins (cefazolin, cephalotin).
- Cephalosporins are active primarily against G+ and G-cocci. (G-spectrum is limited).
- Pseudomonas resistant

- **2nd generation of Cephalosporins (cefamandol, cefuroxime)**
- **They are effective against G+ and G-cocci and anaerobes similar 1st generation.**
- **They have elevated activity against G-bacteria (E.coli, Proteus, Shigella, Salmonella)**
- **No active against P.aeruginosa.**

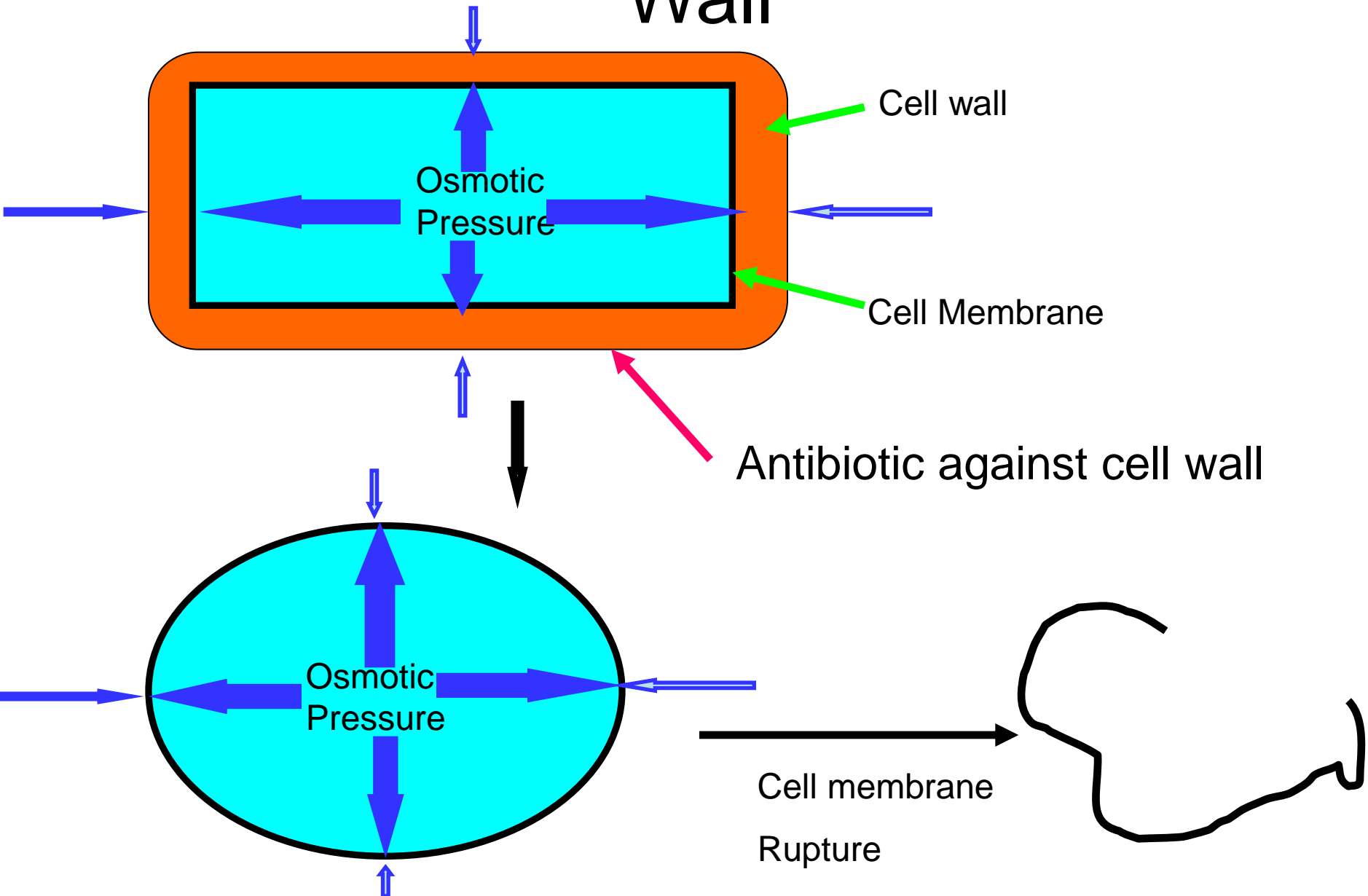
- **3rd Generation of Cephalosporins (Cefoperazone, Cefotaxime, Ceftriaxone).**
- **•They have elevated activity against G-bacteria (E.coli, Proteus, Shigella, Salmonella)**
- **•Variable activity against P.aeruginosa.**
- **•Variable activity against nonspor forming G-anaerobic bacteria (*Bacteroides fragilis*).**

- **4th generation of Cephalosporins**
- **(Cefpiron,Cefitim).**
- **•Abroad spectrum of activity.**
- **•Active against P.aeruginosa.**
- **•No active against enterococcus**

Mechanisms of Action

- **Anti Cell Wall Activity**
- **Bactericidal**

Beta Lactams Against Bacterial Cell Wall



Spectrum of Activity

- Very wide
- Gram positive and negative bacteria
- Anaerobes
- Spectrum of activity depends on the agent and/or its group

Adverse Effects

Penicillin hypersensitivity – 0.4% to 10 %

- Mild: rash
- Severe: anaphylaxis & death
- There is cross-reactivity among all Penicillins

Important Points

- Beta lactams need frequent dosing for successful therapeutic outcome
 - Missing doses will lead to treatment failure
- Beta lactams are the safest antibiotics in renal and hepatic failure

Summary

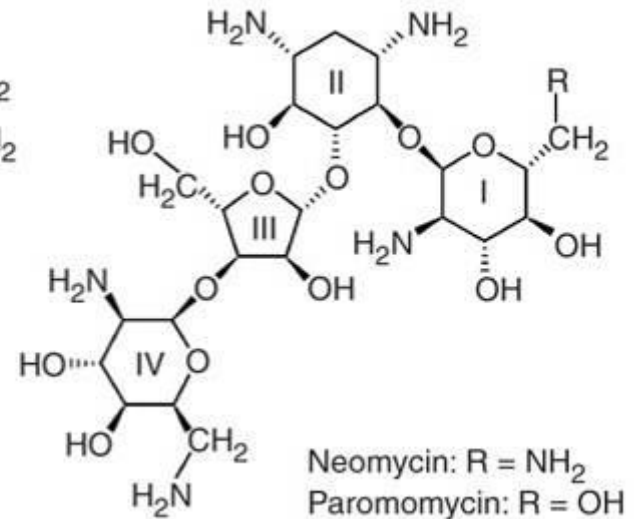
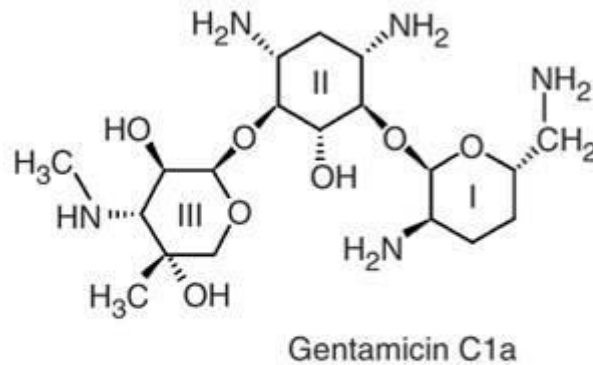
- Cell wall antibiotics
 - Bactericidal
- Wide spectrum of use
 - Antibiotics of choice in many infections
 - Limitations
 - Allergy
 - Resistance due to betalactamase
- Very safe in most cases
 - No monitoring required

Aminoglycosides

Inhibit bacterial protein synthesis by irreversibly binding to 30S ribosomal unit

• Naturally occurring:

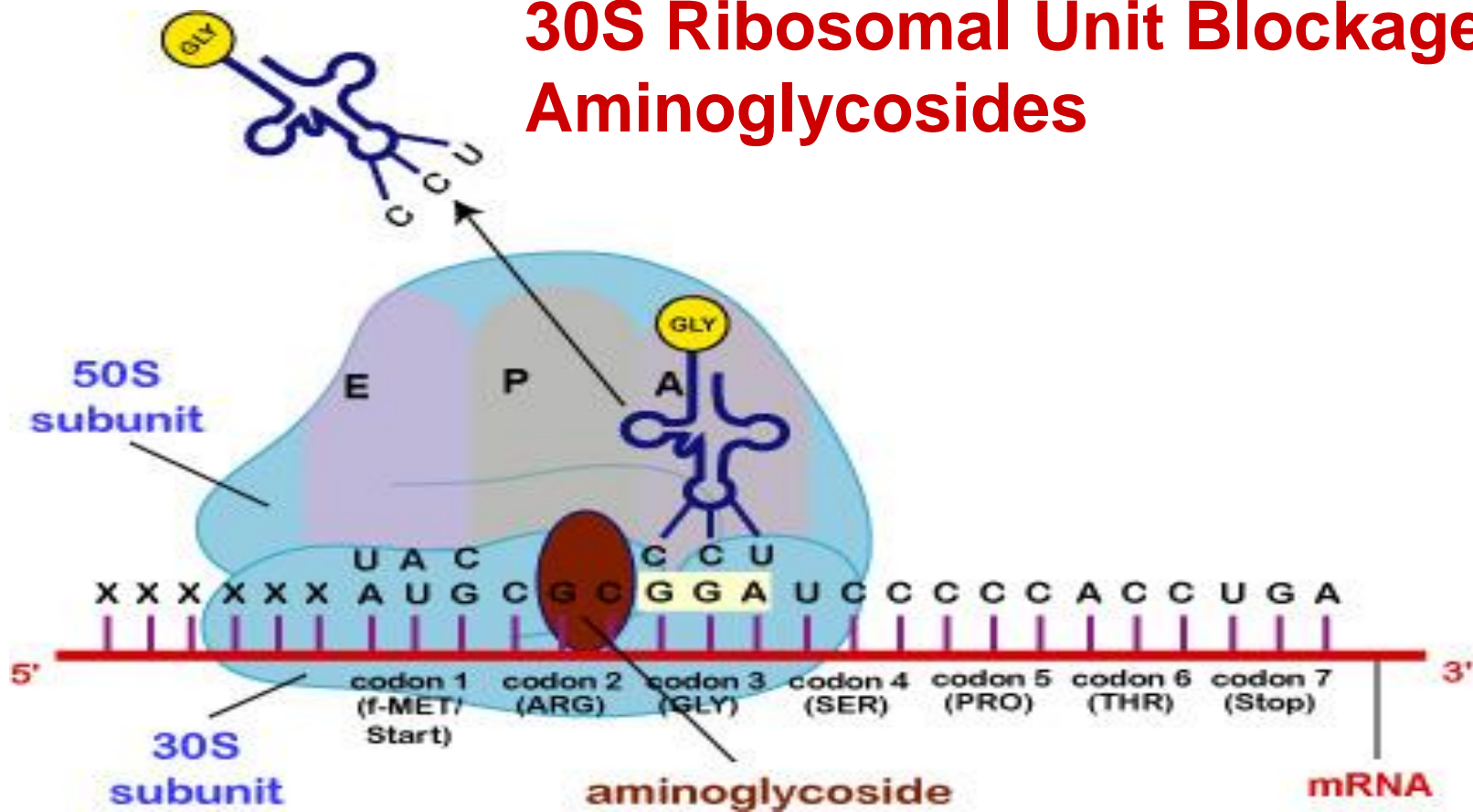
- Streptomycin
- Neomycin
- Kanamycin
- Tobramycin
- Gentamicin



• Semisynthetic derivatives:

- Amikacin (from Kanamycin)
- Netilmicin (from Sisomicin)

30S Ribosomal Unit Blockage by Aminoglycosides



- Causes mRNA decoding errors

Spectrum of Activity

- Gram-Negative **Aerobes**
 - *Enterobacteriaceae*;
E. coli, *Proteus sp.*, *Enterobacter sp.*
 - *Pseudomonas aeruginosa*
- Gram-Positive **Aerobes** (Usually in combination with β -lactams)
 - S. aureus* and coagulase-negative staphylococci
 - Viridans streptococci
 - Enterococcus sp.* (gentamicin)

Adverse Effects

- **Nephrotoxicity**

- Direct proximal tubular damage - reversible if caught early
- Risk factors: Prolonged duration of therapy, underlying renal dysfunction.

- **Ototoxicity**

- 8th cranial nerve damage – irreversible vestibular and auditory toxicity
 - Vestibular: dizziness, vertigo, ataxia
 - Auditory: decreased hearing
- Risk factors: as for nephrotoxicity

- **Neuromuscular paralysis**

- Can occur after rapid IV infusion especially with;
 - Myasthenia gravis (Muscle weakness).
 - Concurrent use of succinylcholine during anaesthesia

Prevention of Toxicity

- a) Levels need to be monitored to prevent toxicity due to high serum levels

- b) To be avoided where risk factors for renal damage exist
 - 1) Dehydration
 - 2) Renal toxic drugs

Important Points

- Aminoglycosides should be given as **a large single dose** for a successful therapeutic outcome
 - Multiple small doses will lead to treatment failure and likely to lead to renal toxicity
- Aminoglycosides are toxic drugs and require monitoring
 - Avoid use in renal failure but safe in liver failure
 - Avoid concomitant use with other renal toxic drugs
 - Check renal clearance, frequency according to renal function

Summary

- Restricted to aerobes
- Toxic, needs level monitoring
- Best used in Gram negative bloodstream infections
- Good for UTIs
- Limited or no penetration
 - Lungs
 - Joints and bone
 - CSF
 - Abscesses

Macrolides

Mechanism of Action

- Bacteriostatic- usually
- **Inhibit bacterial RNA-dependent protein synthesis**
 - Bind reversibly to the 23S ribosomal RNA of the 50S ribosomal subunits
 - Block translocation reaction of the polypeptide chain elongation

Spectrum of Activity

- **Gram-Positive Aerobes:**

- Activity: Clarithromycin>Erythromycin>Azithromycin
 - *Streptococcus pneumoniae*
 - Beta haemolytic streptococci and viridans streptococci

- **Gram-Negative Aerobes:**

- Activity: Azithromycin>Clarithromycin>Erythromycin
 - *Haemophilus influenzae, Moraxella catarrhalis, Neisseria sp.*
 - **NO activity** against *Enterobacteriaceae*

- Anaerobes: upper airway anaerobes

- Atypical Bacteria

Clinical Use

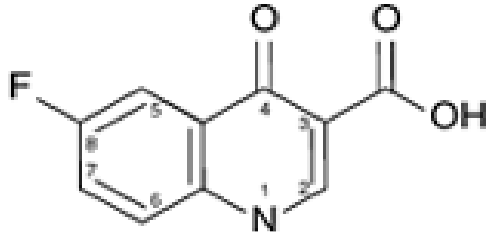
- Cellulitis/Skin and soft tissue
 - Beta haemolytic streptococci
 - Staphylococcus aureus
- Intra-cellular organisms
 - Chlamydia
 - Gonococcus

Summary

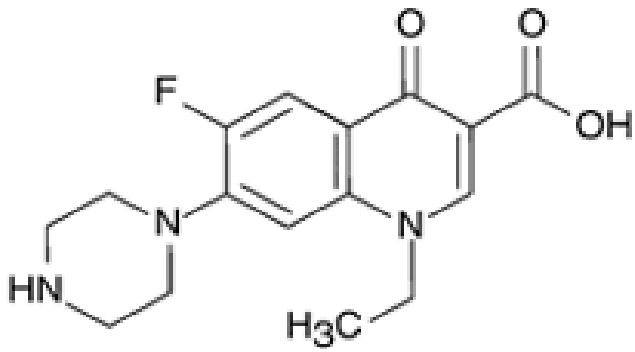
- Bacteriostatic
- ALL hepatic elimination
- Gastrointestinal Sideeffects (up to 33 %)
(especially Erythromycin)
 - Nausea
 - Vomiting
 - Diarrhoea
 - Dyspepsia (indigestion)
- Best used in atypical pneumonia
- Excellent tissue and cellular penetration
 - Very useful in susceptible intracellular infections

Fluoroquinolones

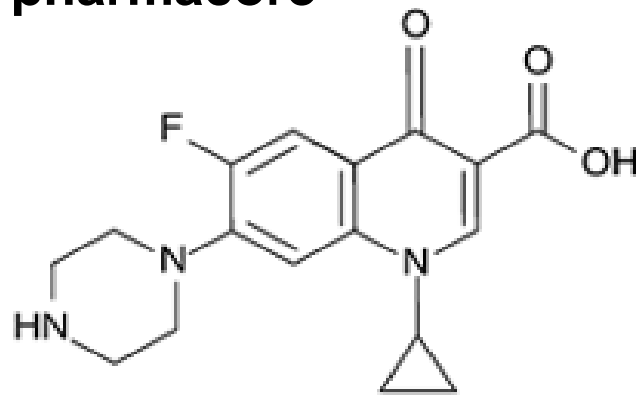
Fluoroquinolones



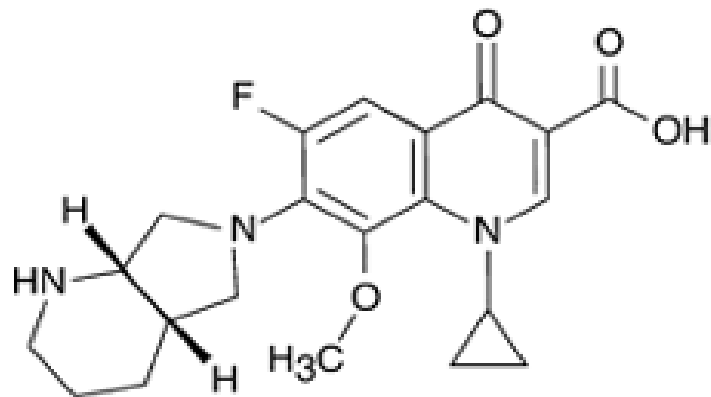
Quinolone pharmacore



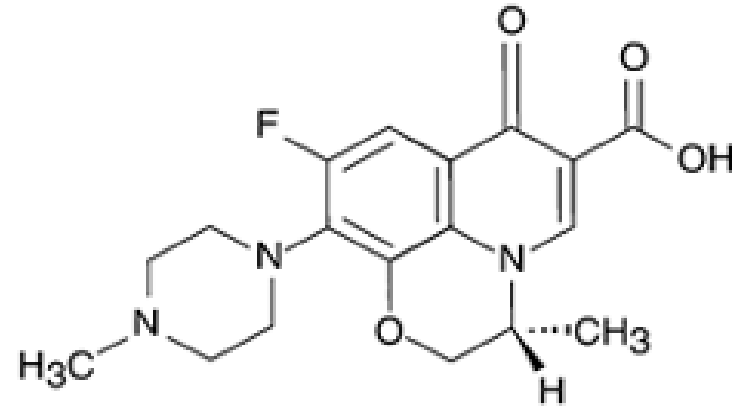
norfloxacin



ciprofloxacin



moxifloxacin



levofloxacin

Mechanism of Action

- Prevent:
 - Relaxation of supercoiled DNA before replication
 - DNA recombination
 - DNA repair

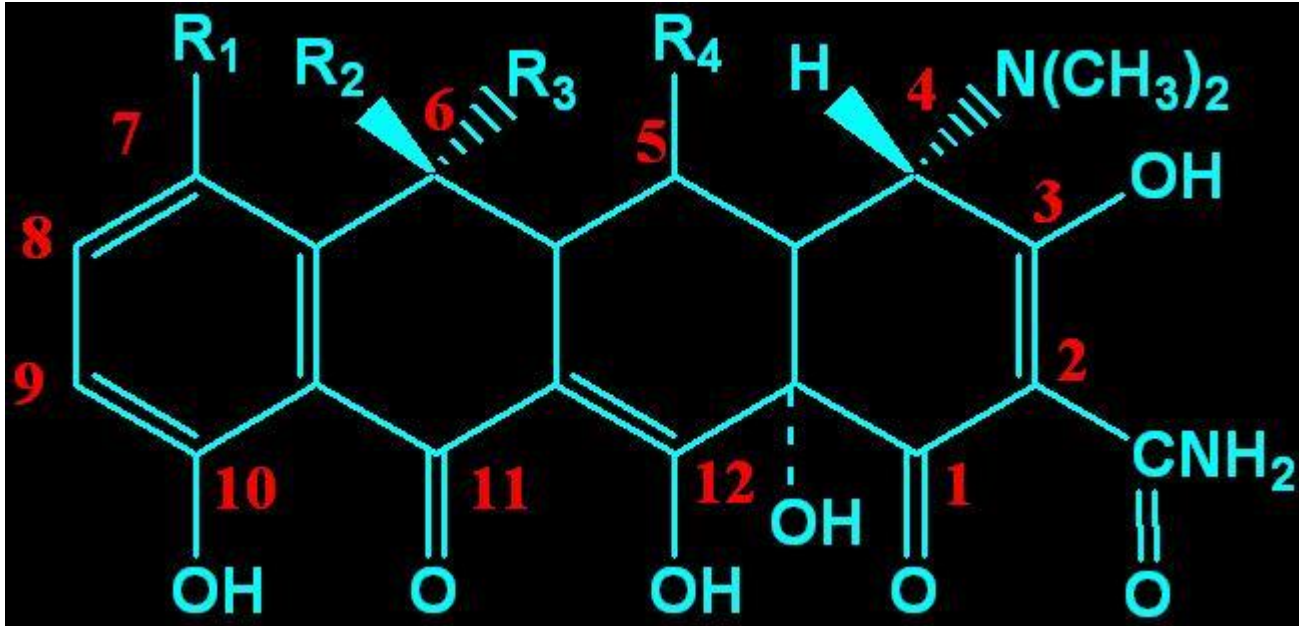
Spectrum of Activity

- Gram-positive
- Gram-Negative (*Enterobacteriaceae* *H. influenzae*, *Neisseria sp.* *Pseudomonas aeruginosa*)
 - Ciprofloxacin is most active
- Atypical bacteria: all have excellent activity

Summary

- Wide range of activity against Gram positive and negative bacteria.
- Sepsis from Intra-abdominal and Renal Sources
 - Coliforms (Gram negative bacilli)
- UTI
 - E. coli
- Very good tissue penetration
- Excellent oral bioavailability
- High risk for *Clostridioides difficile*

Tetracyclines



- Hydronaphthacene nucleus containing four fused rings

- Tetracycline**

- Short acting

- Doxycycline**

- Long acting

Mechanism of Action

- Inhibit protein synthesis
 - Bind reversibly to bacterial 30S ribosomal subunits
 - Prevents polypeptide synthesis
- Bacteriostatic

Spectrum of Activity

- All have similar activities
- Gram positives aerobic cocci and rods
 - Staphylococci
 - Streptococci
- Gram negative aerobic bacteria
- Atypical organisms
 - Mycoplasmas
 - [Chlamydiae](#)
 - Rickettsiae
 - Protozoa

Adverse Effects

- Oesophageal ulceration
- Photosensitivity reaction

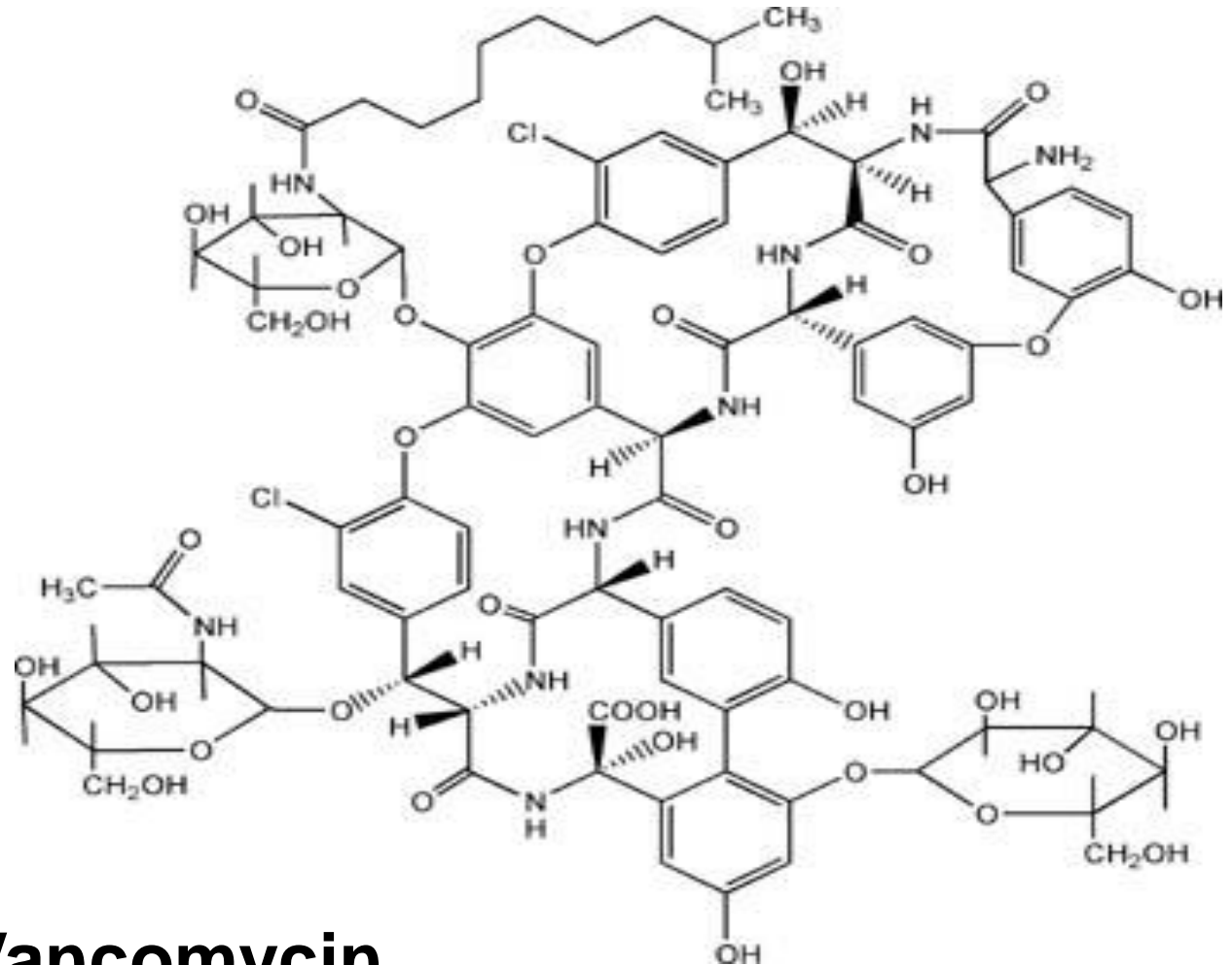
Avoid in pregnancy and newborn

Summary

- Very good tissue penetration
- Use usually limited to;
 - Skin and soft tissue infections
 - Chlamydia

Glycopeptides

- **Vancomycin**
- **Teicoplanin**



Vancomycin

Mechanism of Action

- **Inhibit peptidoglycan synthesis in the bacterial cell wall**
 - Prevents cross linkage of peptidoglycan chains

Summary

- Large molecule
- Only active against Gram positive bacteria
- Second choice in all its uses except;
 - MRSA (Methicillin-resistant *Staphylococcus aureus*)
 - *C.difficile*

Metronidazole

- Antibiotic
- Amoebicide
- Anti-protozoal
 - Trichomonas Vaginalis

Mechanisms of Action

- Molecular reduction
 - Nitroso intermediates
 - Sulfamides
- Metabolised
 - Bacterial DNA de-stabilised

Spectrum of Activity & Uses

- Anaerobes
 - Bacterial Vaginosis
 - Pelvic Inflammatory Disease
 - C. Difficile

Bio-Availability

- Oral
- Intra-venous
 - Expensive
- Rectal
 - Cheap

Summary

- Wide spectrum of activity
- Anaerobes
- In combination

Use of Pharmacokinetics in Treatment

Beta lactams

Good/variable (Dependant on individual antibiotic)

Soft tissue

Bone and joints

Lungs

CSF

Poor

Abscesses

Aminoglycosides

Good

Circulating organisms

Poor

Soft tissue

Bone and joints

Abscesses

Lungs

CSF

Examples of good Tissue Penetrators

Tetracyclines

Macrolides

Quinolones

Clindamycin

Key Message 2

- When selecting an antibiotic consider the following;
 - Where is the infection?
 - Which antibiotics will reach the site of infection
- Match the two and select your antibiotic

Key Message 3&4

- Aminoglycosides are toxic drugs and require monitoring
 - Avoid use in renal failure but safe in liver failure
 - Avoid concomitant use with other renal toxic drugs
 - Check renal clearance, frequency according to renal function
- Beta lactams are the safest antibiotics in renal and hepatic failure

THANKS