Infectious disease

BACTERIA

The most important step in medical microbiology for guiding treatment for a potential bacterial infection is <u>isolation and gram stain</u>

- Cell wall is made up of polymer
  - (positive) Thick peptidoglycan → sugars form the cross links for rigid walls to maintain the structure of bacteria and resist the external physical stress. Crystal violet dye will stain bacteria to purple.
  - (negative) Thin peptidoglycan with extra outer membrane above for additional protection (made up of lipopolysaccharides (LPS) → a combination of sugar and lipid). As a result, they are not good at resisting dryness and heat, therefore have to live in mucosal tissue. Counter stains will stain bacteria to pink.

2 ways of bacteria classification

<u>Phenetic (phenotypic)</u> → important for identification or pathogenicity

- Gram reaction and morphology
- Carbon sources, energy sources
- Electron acceptors (eg. aerobic and anaerobic)

<u>Phylogenetic (genotype)</u> → systematic approach

- Ribosomal RNA sequence
- Other DNA, RNA, protein sequence

GRAM NEGATIVE BACTERIA

Proteobacteria (Phylum)

Escherichia (Genus)

- Part of the family **enterobacteriaceae**
- Found in **gut of humans and animals**
- Facultative anaerobic (can survive w/wo oxygen)
- Heterotrophic (obtaining organic carbon sources)
- Rods shaped, motile by **peritrichous flage**
- Widely used in microbiology as a **model organism (E.Coli)**

- E. coli

- Most strains are **normal flora** and beneficial → K12 biosynthesis vitamin K
- Some are **pathogenic** → food or water borne pathogens
- O157- (sero bar for bacteria system by human immune system, O is stomach) infection by animal food
- Sx → diarrhoea and fever
- Virulence factors → **endotoxin** (from LPS; Very inflammatory hance human immune system can response with high immune response eventually damage our own body), **enterotoxin** (target the enterocytes, the epithelial lining of the gut eventually let body to loss lots of irons to lumen and loss lots of water through stools)

Salmonella (Genus)

- Part of the family **enterobacteriaceae**
- Facultative anaerobic (can survive w/wo oxygen)
- Heterotrophic (obtaining organic carbon sources)
- Rods shaped, motile by **peritrichous flage**
- **Normal flora** in animal gut,
- **Pathogenic** to humans
- Virulence factors → **endotoxin, enterotoxin,** cytotoxin

- S. enterica

- Food borne infection
- Self limiting diarrhoea → eradicate by hydration

- S. typhi

- Water borne infection
- Cause **Typhoid fever** (high and sustain fever)
- Potentially fatal

* identify **enterobacteriaceae**

Selective + differential agars for identifying **enterobacteriaceae**

Salmonella on XLD

- Lactose negative
- H_2S positive (black precipitate as a by product)

E.coli on XLD

- Lactose positive
- H_2S negative

Vibrio (Genus)

- Facultative anaerobic (can survive w/wo oxygen)
- Heterotrophic (obtaining organic carbon sources)
- Curved rods, motile by various flagella arrangement
- Habitat is primarily marine → normally do not associate with human, but can cause **gut infection**

- V. chloerae

- The most pathogenic Vibrio species
- Cause **Cholera**; Sx: severe diarrhea → transmission
- Transmission usually by faecal contamination of water
- V. cholerae is more rarely a food borne disease (seafood)
- Virulence factor: cholera toxin (exotoxin)
- Polar flagellum, bundles of pili and curved cell
- Common in sewage contamination

Pseudomonas (Genus)

- Aerobic
- Heterotrophic (obtaining organic carbon sources)
- Rods, motile by polar flagellum
- **Ubiquitous** in soil and water
- **Opportunistic pathogens**
- Large genome (6 Mb) → metabolically **versatile**, colonise diverse niches

- P. aeruginosa

- **Common**, but person-person transmission is **rare**
- **Nosocomial infection (hospital acquired) -** esp. Burns
- Virulence factors: innate antibiotic resistance (low membrane permeability, have thick and denser LPS compared to other gram negative bacteria), haemolysin, proteases

Neisseria (Genus)

- Aerobic
- Heterotrophic (obtaining organic carbon sources)
- **Diplococci**
- Habitat → mammalian **mucous membranes**
- Carrier → back of throat and nose
- Virulence factors: **capsules** (evasion of immune response), **fimbriae** (adhesion to tissues)

- N. gonorrhoeae

- Cause **Gonorrhoea** : a sexually transmitted disease (STD)
- Adherence of Neisseria cells to epithelial cells
- Diagnose by microscopic examination
- Safranin → epithelial cells and Nerisseria appear pink

- N. meningitidis

- Cause **Meningitidis** : inflammation of meninges (membrane around brain). Sx: fever, rash, headache, confusion, death
- Serious and **rapid progressing** disease - needs rapid diagnosis and treatment (antibiotics) within 48 hours.
- Adherence of N.meningitidis cells adhering to cilia in the respiratory tract
- Diagnose by microscopic examination of cerebrospinal fluid (CSF) from lumbar puncture, and use crystal violet stain to observe.

Riskettesia (Genus)

- Aerobic
- Heterotrophic (obtaining organic carbon sources)
- **Coccibacilli**
- Small **degenerate** genome (1Mb) → specialised lifestyle (adhere)
- Cannot be grown in vitro - only in tissue culture → **very dependent on host metabolism**
- **Intracellular parasites** of arthropods - Eg. fleas, lice, thicks (so human is the second host)

- Transmission to humans occurs via **bites** or **faeces of** arthropods → various fever diseases
- Zoonitic

- R. prowazekii

- **Epidemic typhus** (spread to lots of people)
- Overcrowded conditions → **transmitted by body louse**
- Sx: headache, fever, rash (up to 50% mortality)
- Virulence factors: adhesin, **phospholipase**

Bacteroidetes (Phylum)

Bacteroides (Genus)

- **Obligate anaerobe** (survive only wo oxygen)
- Heterotrophic (obtaining organic carbon sources)
- Robs
- **Normal flora,** but can be **opportunistic pathogens**
- The most abundant cells in human body
- Several beneficial species: digestion of carbohydrates, **exclude pathogens** by competitions (Salmonella)

- B. fragilis

- **Opportunistic pathogen**: cause infection if it escapes the gut. Eg. abscess, septicemia, appendicitis
- Virulence factors: capsule and **antibiotic resistance** (tetracycline resistance)

Spirochaetes (Phylum)

Treponema (Genus)

- Anaerobic
- Heterotrophic (obtaining organic carbon sources)
- **Spirochaetes**
- **Obligate parasites**, require animal cells for growth
- Use **axial filament** for structure and **corkscrew motility**
- Great to move thought viscous fluid

- T. pallidum

- Cause **Syphilis:** a sexually transmitted disease (STD)
- First degree: **chancres** (open lesion)
- Second degree: rash
- Tertiary degree: nervous system damage
- Cannot be grown in standard media '**degenerate'** small genome (1Mb)

Chlamydiae (Phylum)

Chlamydia (Genus)

- Aerobic
- Heterotrophic (obtaining organic carbon sources)
- Cocci
- **Obligate intracellular parasite** of humans and animals
- Cause **STD** and **eye infection**
- Cannot be grown on agar, **small genome** (1Mb) consistent with host dependence
- An energy parasite (has no mitochondria) → dependent on host cells for ATP and other metabolites
- Koala have high mortality rate and high infectious rate, can be asymptomatic but if its symptomatic → black bottom disease
- Virulence factors → **unusual cell wall** allows growth indie phagocytes and it has **no peptidoglycan** → intrinsic resistance to all antibiotic target PG (limited effects)

- C. trachomatis

- Cause **Urethritis** (STD) and **Trachoma** (eye infection)

GRAM POSITIVE BACTERIA

Firmicutes (Phylum) Low GC**, Acinobacteria (Phylum)** high GC

Facultative anaerobic rods or cocci, some make endospores	Aerobic rods or filaments, some make exospores for spreading

Firmicutes (Phylum)

Bacillus (Genus)

- Facultative anaerobic (can survive w/wo oxygen)
- Heterotrophic (obtaining organic carbon sources)
- **Ubiquitous** in the environment, esp. Soil
- Transient flora on skin (normally not adapted to human)
- older/ starving/ stressed cells make **endospores**

- B. anthracis

- Causes **Anthrax,** highly infectious and deadly disease
  - Cutaneous: common, ~20% mortality (eschar lesion)
  - Gastrointestinal: rare, ~50% mortality
  - Pulmonary: rare, ~80% mortality

  - all potentially treatable with antibiotics Eg. Ciprofloxacin
- Usually **zoonotic** (woolcutter's disease)**,** transmitted from animals (cattle, sheep)
- Possible **bioterrorism** agent due to stable endospores → can be aerosolised, breath in can cause pulmonary anthrax, lung necrosis
- Plasmid-encoded virulence factors: **exotoxin**
  1. Protective antigen heptamer → makes pore in target cell
  2. Edema factor (blister) and lethal factor (cell death) → enter cells, disrupt signalling pathway
     *anthrax exotoxin - three secreted proteins work together to kill cells

Clostridium (Genus)

- Anaerobic (survive wo oxygen)
- Heterotrophic (obtaining organic carbon sources)
- Rods
- Habitat: Deep soil, human and animal gut
- Some species are normal flora and some are pathogens

- C. tetani

- Cause **Tetanus**: muscle rigidity, death due to respiratory failure
- Caused by / requires deep wounds to multiply (anaerobic)
- **Common source** disease, not a contagious disease
- Source → soil. Manure, inoculated into puncture wound
- Virulence factor: **tetanospasmin (neurotoxin)**, exotoxin
  - Blocks transmission of 'relaxation' (inhibits the release of GABA and glycine → signal to muscle → body rigidity; locked jaws, contracted back muscles, lung contracts → death from respiratory paralysis)

- C. botulinum

- Cause **Botulism**, a dangerous type of food poisoning (common source disease)
- Lives in soil. Spores enter food chain, persist thru processing, **germinate** in food (anaerobic, neutral pH)
- Virulence factor: **botulinum toxin (BOTOX)** - the most deadly poison known, lethal dose ~ 1 microgram
- Very potent toxin and more localised
- Botulinum cause **flaccid** paralysis of muscle - opposite to tetanospasmin
- Despite extreme toxicity BOTOX is used in cosmetic medicine.

Lactobacillus (Genus)

- L. acidophilus

- Facultative anaerobic (can survive w/wo oxygen)
- Heterotrophic (obtaining organic carbon sources)
- **Non- sporing rod**
- **Normal flora -** non pathogenic of mouth, gut, vagina
- **Probiotic** effect..? Competition with pathogens in gut → produce **antimicrobial peptide** to kill other bacteria
- Cheese + yoghurt production : **lactic acid** fermentation

Staphylococcus (Genus)

- Facultative anaerobic (can survive w/wo oxygen)
- Heterotrophic (obtaining organic carbon sources)
- **Cocci - clumps**
- **Non-motile**
- Contain **both** normal flora and pathogenic species

- Habitat: **human-associated,** either as normal flora (**skin, nose**) or as pathogens (wound infection)
- A tough cell wall makes Staph. **Resistant to physical stress** (eg. desiccation) → long survival in environment
- **Resistant to salt** - trait needed to survive on skin and nose

- S. epidermidis

- On mannitol-salt ager; non mannitol fermentating (red)

- S. aureus (Golden Staph)

- On mannitol-salt ager; mannitol- fermenting (yellow) * able to metabolise sugar means they can use more source → more survival rate → also can be more pathogenic
- **Opportunistic pathogen** (skin, physical barrier protect us)
- Infection: wound infections, boils, impetigo, toxic shock (organ shuts down)
- **Nosocomial** spread - hospital strains antibiotic resistant *because to survive on human
- Virulence factors: **coagulase**, exotoxins
- Coagulase as a diagnostic text (use fibrinogin in the blood to from a clot around them, and let them to protect staph, which is a way to protect themself from human immune system)
- Resistance due to the plasmid (bla z) mediated beta lactamase and a chromosomal gene → alter PBP-2a decrease affinity for binding beta lactam

Streptococcus (Genus)

- Facultative anaerobic (can survive w/wo oxygen)
- Heterotrophic (obtaining organic carbon sources)
- **Cocci - chains**
- **Non-motile**
- Contain **both** normal flora and pathogenic species
- Habitat: **mouth and gut** of animals and humans

- S. thermophilus (beneficial streptococcus)

- In yoghurt + cheese production, normal flora

- S. pyogenes (harmful streptococcus)

- Cause **Scarlet fever** - contagious, mostly affects young children *colonise oropharyngeal regions particularly pathogenic
- Characteristic **beta - haemolysis reaction on blood agar** (clearing)

- S. pneumoniae (harmful streptococcus)

- Cause **Pneumonia** and **Meningitis**
- Characteristic **alpha - haemolysis reaction on blood agar** (greening)
- Virulence factors: **capsules, haemolysin**
  - Encapsulated strings are 100,00 times more virulent
  - Even macrophage and neutrophils engulfs the S.pneumoniae, capsules prevent them dying from enzymes

Acinobacteria (Phylum)

Streptomyces (Genus)

- **Aerobic**
- **Filaments (floppy,** powdery surface, diffusible pigments**)** or **rods**
- Can make exospores
- Makes antibiotics

Mycobacterium (Genus)

- **Aerobic**
- Heterotrophic (obtaining organic carbon sources)
- **Rods**
- Virulence factor: **mycolic acids** in cell wall → waxy layer → **acid fast** stain
- **Wax** protects against stresses, incl. Immune system

- M. leprae

- Cause **Leprosy**

- M. tuberculosis

- Cause **Tuberculosis (TB)**
- **Obligated pathogen** of humans - no environmental reservoir
- Usually live in the alveoli of the lungs
- One of the Big 3 killer disease of humanity
- **Chronic** infection of **lungs**: fever, coughing, weight loss
- Can be grown in vitro (lab setting), but slow growing and fastidious
- Virulence factors: **waxy cell wall** gives resistance to many stresses. Eg. antibiotic, macrophage

ANTIBACTERIAL

Antibacterial agent

- Bacteriostatic - inhibit cell growth, allowing the host's immune system to overcome the infection
- Bactericidal - kill bacterial cell

Antibiotics

- Chemical substances produced by micro-organisms that inhibit the growth (or even destroy) other micro-organism

Fungi

Penicillium chyrsogenum (penicillins)

Penicillin griseofulveum (grisofulvin)

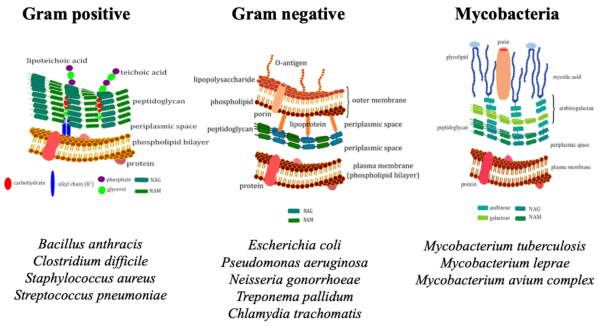
Cephalosporium (cephalosporins)

Bacteria

Streptomyces (streptomycin, chloramphenicol, macrolides, tetracyclines)

Nocardia (rifamycins)

Cell walls

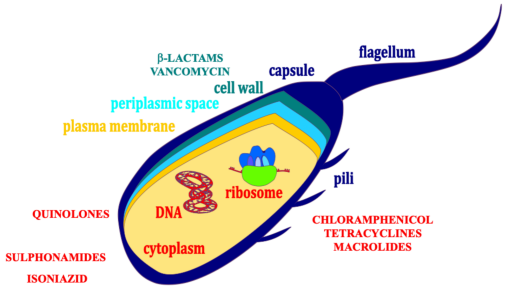


Bacillus anthracis
Clostridium difficile
Staphylococcus aureus
Streptococcus pneumoniae

Escherichia coli
Pseudomonas aeruginosa
Neisseria gonorrhoeae
Treponema pallidum
Chlamydia trachomatis

Mycobacterium tuberculosis
Mycobacterium leprae
Mycobacterium avium complex

The bacterial cell (prokaryotic)



Selectivity toxicity to the bacterial cell

The differences between prokaryotic and eukaryotic cells

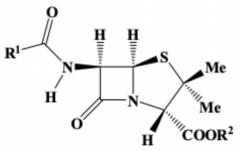
- Bacterial cell has a cell wall and plasma membrane (the cell wall protects the bacteria from differences in osmotic pressure and prevents swelling and bursting due to the flow of water into the cell)
- Bacterial cells do not have defined nuclei
- Bacterial cells are relatively simple, and do not contain organelles
- The biochemistry of bacterial cells is very different to that of eukaryotic cells

Inhibiting of bacterial cell wall synthesis
(β-lactams, Cycloserine, Vancomycin)

β-lactams - interfere with cell wall synthesis in growing bacteria resulting in a weakened cell wall, lysis and death

- Bactericidal; affect mature cell walls as affect the balance between **penicillin binding protein (PBP)**, which catalyse cell wall synthesis and **murein hydrolase**, which catalyse cell wall lysis
- Penicillins (piperacillin, amoxicillin)
- Cephalosporins (ceftriaxone, cefoxitin)
- Monobactams (aztreonam)
- Capbapenems (imipenem); normally is the last resource in treatment

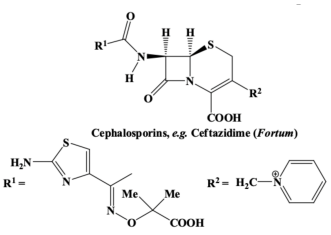
Penicillin



R2 - is normally Na (sodium)

- Since reaction in a weak acid with a strong base, makes the penicillin more soluble.
- Increase acid stability, making the drug allow oral absorption.
- If there is no acid stability, the drug would degrade by stomach acid and degrade β-lactam ring → inactive the drug

Cephalosporin



1st
po (**Cefalexin**),
iv (**Cefazolin**, **Cefalotin**)
- G+ (strep+Staph)
- Some G- (E.coil)
- Avoid use cefalexin in allergic to amoxicillin
- Cefazolin has no common side chain with other beta lactams; can use it for immediate non-severe allergy

2nd
po (**Cefaclor**, **Cefuroxime**)
- Avoid use cefaclor in allergic to amoxicillin

3rd
iv (**Ceftriaxone**, **Cefotaxime**, **Ceftazidime**)
- G+, G-
- Do NOT cover pseudomonas

4th
iv (**Cefepime**)

- Higher generation have increase G- coverage
- For non-immediate and non-severe penicillin allergy
- None of them cover enterococcus
- Active against *Salmonella typhi*
- 3rd/4th generations have a broad spectrum of activity

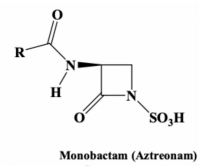
Beta lactam allergies → due to R1 side chain

- IgE mediated immediate hypersensitivity reaction → anaphylaxis
- Severe immediate hypersensitivity → avoid both PCN&CP
- Delayed reaction → T cell mediated (rashes after Tx)

Extended Spectrum Beta Lactamase producing organism

- Inactive all PCN&CP
- Found in G-, gene transfer

Monobactam



Has activity against
Gram negative organisms ONLY

Cabapenem **(Imipenem, Meropenem, Ertapenem)**

- Over G+ and G- and anaerobes
- Primarily reserved for ESBL

RESISTANCE

Methicillin Resistant Staphylococcus Aureus

- Resistant to all beta lactams

Carbapenem**ases**

- Increase in carbapenem resistance genes, (also carries resistance to macrolides, aminoglycosides, aminoglycosides, rifampicin, sulfamethoxazole, tigecycline and aztreonam)
- NDM-1 metallo-β-lactam**ase** (*bla*NDM-1 gene) → hydrolyse carbapenems
- Ser70 residue of the carbapenemases' active site target the β-lactam → form covalent bond on the active site → inactivate the β-lactam
- So Colistin (a polymyxin) and rifampicin in combination is effective but toxic and expansive

β-lactam**ase** inhibitor (BLIs)
Clavulanic acids (from streptomyces clavuligerus) and **Tazobactam** have a weak antibiotic action but suicide inhibitor of β-lactam**ases** (class A), add to penicillin to increase G- activity

- The combinations are not active against carbapenemases (amoxicillin + clavulanic acids, ampicillin +sulbactam, piperacillin + tazobactam)

Penicillin + Beta lactamase inhibitor → extended spectrum of action

- Covers aerobic G+ and - and anaerobes
- Ideal for infection from numerous types of organisms

po/iv (**Amoxicillin + Clavulanic acid**) → do NOT cover pseudomonas
iv **(Ticarcillin + Clavulanic acid)** → cover pseudomonas
iv (**Piperacillin + Tazobactam**) → cover pseudomonas

Non β-lactam- β-lactam**ase** inhibitor
They maintain the efficacy of the β-lactam drugs

- the combination are active against carbapenemases (avibactam + ceftazidime, vaborbactam + meropenem)

Currently no approved BLIs which inhibit metallo-β-lactamases such as NDM-1

Resistance in general
Microbiological resistance

- Intrinsic resistance - is expressed by bacteria, the natural resistance an organism has to an antibiotic
- Acquired resistance - due to chance mutation in genetic material (can happen in survival bacterium if was not enough concentration for treatment) or the acquisition of resistance genes via a plasmid

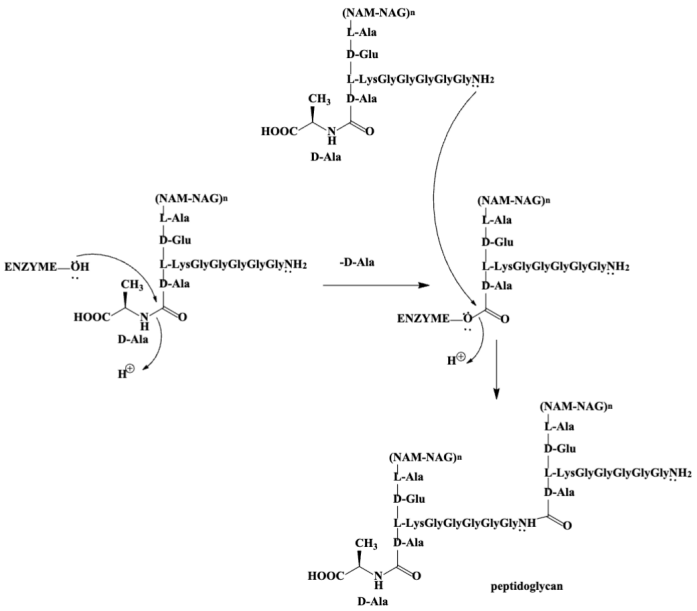
Clinical resistance

- The failure to achieve an antimicrobial concentration which inhibit the growth of an organism

Peptodoglycan

Consists of parapelle sugar backbones composed of alternating NAG (N-Acetylglucosamine) and NAM (N-Acetylmuramic acid)

- Peptide chains are then linked together to give extra strength to the cell wall through crosslink formation (by using carboxylic acid in NAM to form amide bond) , catalysed by peptidoglycan transpeptidase/ penicillin binding protein (PBP)
- Crosslinking of peptide chains inhibited by the β-lactams



PBP classified by size and are essential in the final stage of peptidoglycan synthesis and activities include D-alanine carboxypeptidase, removal of D-ala from peptidoglycan precursor, **peptidoglycan transpeptidase** and peptidoglycan endopeptidase

Penicillin

MOA

- β-lactams bind covalently to active site of enzyme, preventing access of peptidoglycan fragments and preventing attack of hydroxy group on D-ala residue

INTERETHNIC (beta lactam)

- Mainly renally cleared
- Higher AUC and longer half life in Asian and Hispanic compared to Caucasian for cefdinir, cephradine, cefotaxidine, flucloxacillin
- No significant PK difference after being adjusted for weight

TYPES

Natural - po (**Phenoxymethylpenicillin**), iv/im (**Benzylpenicillin**)

- Against cocci e.g. staphylococcus for pharyngitis and tonsillitis
- Produce penicillinases

Penicillinase resistant penicillines

Flucloxacillin or **Dicloxacillin**

- Against G+ cocci e.g. staphylococcus + streptococcus → skin infections such as cellulitis
- Available in po + iv

Aminopenicillines - po (**Amoxicillin**), iv (**Ampicillin**)

- Ideal for pneumonia
- Against some G+ cocci e.g. streptococcus
- Against few G- e.g. haemophilus influenza
- Breakdown by beta lactamases/penicillinases

D-Cycloserine (**DCS**);

Inhibit two bacterial enzymes which is alanine racemase and D-Ala-D-Ala ligase ← not used anymore

Vancomycin;

Glycopeptide antibiotic and prevents the release of the disaccharide from its lipid carrier

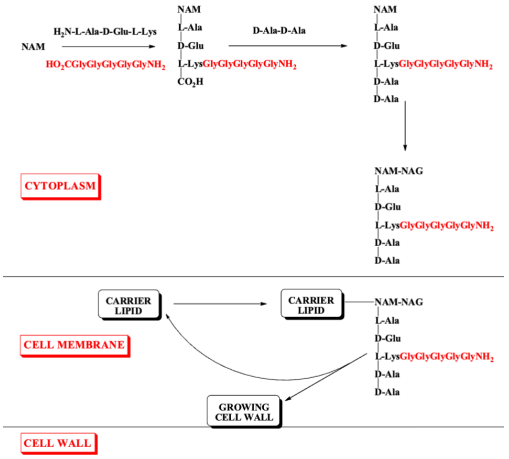
- Produced by *Streptomyces orientalis*
- It is the last resort in treatment of MRSA
- Not absorbed orally so usually given IV
- Can be toxic to ears and kidney
- Oral vancomycin can used in treatment of Clostridioides difficile (target in the gut, so does not have to be absorbed) associated disease

MOA

- It is hydrophilic and form hydrogen bonds to the terminal D-Ala-D-Ala sequence - preventing crosslink formation and blocking the release of disaccharide from the carrier lipid

RESISTANCE

- Vancomycin resistant enterococci (VRE) Van A phenotype produces a D-Ala-D-Lactate ligase which synthesis an easter (D-Ala-D-Lac) rather than (D-Ala-D-Ala) amide
- D-Ala-D-Lacate sequence has a 1000-fold reduction in affinity for vancomycin, BUT can still be added to L-Lys and act as precursor for crosslink formation. Such altered ligases are also produced by vancomycin producing micro-organisms



INTERETHNIC

- Vancomycin has narrow TDM and require loading dose
- Glycopeptides had similar physicochemical and PK properties with the aminoglycoside → large molecular size and larger Vd
- No interethnic difference in PK of (tecioplanin)
- No interethnic difference in PK of vancomycin

PHARMACOKINETIC

- Poor absorption, absorption increased in inflammatory GI conditions
- Renal excretion (glomerular) if absorbed → accumulation in renal impairment

ADVERSE EFFECTS

- GI disturbance
- Hypersensitivity
- Thrombocytopenia
- Nephrotoxicity: reduced dose intervals and or dose in renal impairment
- Ototoxicity: Dizziness, Vertigo, Tinnitus
- Nephrotoxicity& ototoxicity more likely increase with co administration with aminoglycoside → require concentration monitoring
- Infusion reaction "red man syndrome" caused by histamine, leukopenia → sx are fever, chills, erythema, itch, hypotension

po/iv -Vancomycin

- Give over at least 1 hour
- Monitoring is recommended for over 48 hours
  → Measure AUC or trough level
  → AUC/MIC ratio for efficacy (AUC is preferred, target 400 mg*hr/L, but requires two plasma concentrations, 30 mins after dosing and 6-14 hours after dosing)

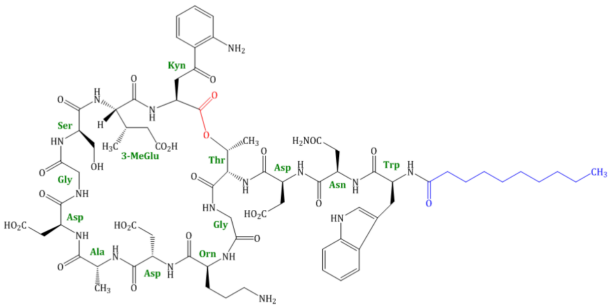
→ Use Aladdin or TCIWorks to adjust for variation in Vd & E
→ Reduce under dosing and prevent toxicity
- New dose = Old dose*Target AUC / measured AUC

iv - **Tecioplanin**

Daptomycine (Lipopeptide)

- Produced by *Streptomyces roseoporus*
- Treatment for complicated skin and skin structure infection (SSSI) caused by MRSA and right-sided endocarditis
- It binds strongly to pulmonary surfactant, so cannot be used in the treatment of pneumonia

STRUCTURE



- 10 of the 13 amino acids form a depsipeptide ring, with the other 3 attaches to this ring though a threonine residue

MOA

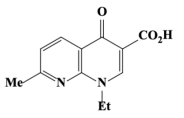
- Calcium ions are essential for the rapid bactericidal activity against Gram positive bacteria
- Involved the insertion of daptomycin into the lipid bilayer, facilitated by the lipid tail, promoting weak hydrophobic interactions with the phospholipid bilayer
- Interaction of daptomycin, calcium and phosphatidyl glycerol (its on the surface of the bilayer + interact with cyclic part) promotes mild disturbances in the lipid membrane and causes content leakage → SELECTIVE to prokaryotic cells because it recognise phosphatidylglycerol content of lipid bilayer
- Interaction with the cytoplasmic membrane alter permeability
- Daptomycin oligomerisation (which is promoted by binding to Ca^{2+}) creates a large pore in the membrane, allowing potassium efflux, membrane depolarisation → cell death

RESISTANCE

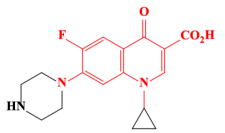
- Point mutations in mprF genes (influences the nature of the phospholipid content; it catalyses the addition of lysine to membrane phosphatidylglycerol)
- Point mutation in yycG genes (involved in cell permeability)
- *S. aureus* often associate with vancomycin-unresponsive strains (vancomycin resistance VRSA or vancomycin intermediate S. aureus VISA) have thickened cell walls and daptomycin resistance is due to is inability to diffuse through these thicker cell walls to its site of action at the lipid membrane
- But the resistance is still rare and established daptomycin surveillance programs

Inhibit bacterial DNA gyrase (topoisomerase II) and topoisomerase IV (Quinolone)

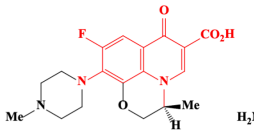
- Weak anti-bacterial (bactericidal) activity in a concentration dependent* manner
- Treat urinary treat urinary tract infections
- All quinolones well absorbed orally and usually highly serum-protein bound, giving long half-lives
- Used in high doses due to protein binding and weak activity
- Side effects include GI disturbance, rash, prolongation of the QT interval, fatigue, dizziness, visual disturbances, convulsions and spontaneous tendon ruptures
- Later generations have broader spectrum, mostly due to the introduction of a fluoring at the 6 position



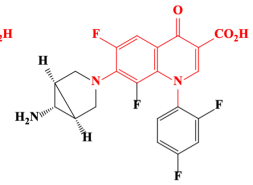
Nalidixic acid
(1st gen) active against Gram -ve



Ciprofloxacin (Cipro, Ciproxin)
(2nd gen) active against *P. aeruginosa*



Levofloxacin (Cravit, Levaquin)
(3rd gen) used in treatment of community-acquired pneumonia



Trovafloxacin (Trovan)
(4th gen) improved Gram +ve activity

DNA gyrase and topoisomerase IV relax bacterial DNA by cutting one of the strands, passing the other strand through the cut and then resealing the cut

MOA

- Quinolone bind to these enzymes preventing them from relaxing DNA helix and so preventing replication
- Quinolone target the DNA gyrase in Gram negative bacteria and the topoisomerase IV in Gram positive
- Fluoroquinolones → inhibit ligase activity (join the cut pieces back together) of topoisomerase II +IV → DNA with lots of cut / breaks with no ability to repair back together → cell death

SELECTIVELY

- Mammalian cells do not have DNA gyrase or topoisomerase IV (they do have topoisomerases I and II but quinolones do not bind to these enzymes)
- Inhibition of DNA gyrase and topoisomerase IV leads to cell death, especially if cell is also dealing with the other toxic effects of quinolones at the same time

RESISTANCE

- Alterations in the target enzymes (DNA gyrase occur via mutation in the quinolone- resistance determining region QRDR) of the gyrA gene which encodes the two A subunits of the tetrameric enzyme (gyrB encodes the two B subunits)
- Decreased uptake of the quinolones in cells due to the impermeability of the outer membrane to small hydrophobic molecules
  → giving this bacterium intrinsic resistance to the quinolones (P.aeruginosa)
  → one of the porin (OmpF) out of three decreased the number is associated with an increase in resistance to the quinolones (E.coil)
- Increased efflux, over expression of efflux pumps (P.aeruginosa and S.aureus)
- Similar mutations have been described in topoisomerase IV which decrease quinolone binding
- Resistance increases around the world (not good)

INTERETHNIC

- Ciprofloxacin is moderately lipophilic and undergoes hepatic metabolism, glomerular filtration and tubular secretion, PgP substrate
- No interethnic PK difference for levofloxacin, gatifloxacin and moxifloxacin

PHARMACOKINETIC for fluoquinolones/quinolone

- High bioavailability 80-95% (po)
- Absorption impaired by antacids, dairy (Ca2+, Mg2+ etc)
- Renal excretion - tubular / glomerular → adjust dose in renal impairment

ADVERSE EFFECTS for fluoquinolone/quinolone

- Neurotoxicity: Peripheral neuropathy
- Tendon damage (rapture of Achilles tendon)
- Dizziness, Faintness, increase Seizure risk
- Avoid in Myasthenia gravis (worsen muscle weakness)

Norfloxacin

- Cover G- incl. pseudomonas
- has low serum levels
- Mainly used for UTIs

Ciprofloxacin

- Cover G- incl. pseudomonas