Mechanisms of Action
Definitions

- **Bacteriostatic**: slow or stop bacterial growth
  - Needs a competent immune system to eliminate the microbe

- **Bactericidal**: results in bacterial death

- **Concentration-dependent killing**: concentration of the drug must reach a threshold before it is efficacious
  - Leads to post-antibiotic effects

- **Time-dependent killing**: requires microbes to be exposed to the drug for a period of time before it is efficacious
Mechanisms of Resistance

- Potential methods of developing antibiotic resistance include:
  - Decreased cell permeability
  - Enzymatic inactivation of the drug
  - Alteration of the target binding site
  - Active transport out of the cell (efflux pump)
β-Lactams

- Bacterial cell wall synthesis inhibitors
- Bactericidal
- Only kills cells that are actively developing
- Classes include:
  - Penicillins
  - Cephalosporins
Penicillins

- All have a β-lactam ring that binds to D-ala-D-ala of a Penicillin-binding protein
  - Interferes with transpeptidation of the bacterial cell wall
  - This process is unique to bacteria
- Results in cell lysis, however only in cells actively dividing
- Mechanisms of resistance include;
  - Formation of β-lactamases
  - Modification of target binding site
  - Development of efflux pump
Classification

- Penicillins (e.g. Benzylpenicillin)
  - Greatest activity against Gram-positive, Gram-negative cocci and non-β-lactamase producing anaerobes
  - Susceptible to hydrolysis by β-lactamases
- Anti-Staphylococcal Penicillins (Methicillins e.g. Flucloxacillin/Dicloxacillin)
  - Resistant to staphylococcal β-lactamases
  - Active against staphylococci and streptococci, but ineffective against Gram-negative and anaerobic bacteria (narrow-spectrum)
- Extended-Spectrum Penicillins (Aminopenicillins e.g. Ampicillin/Amoxicillin; Carboxypenicillins e.g. Ticarcillin)
  - Improved activity against Gram-negative organisms, but susceptible to β-lactamases
Pharmacokinetics

- A: differs greatly for different penicillins
  - Dicloxacillin, Ampicillin and Amoxicillin are acid stable and well absorbed
  - Absorption of most oral penicillins are impaired by food
- D: widely distributed in body fluids and tissues
  - Concentration in most tissues is equal to serum with poor penetration into the eye, central nervous system
    - With active meningeal infections, the BBB is disrupted
- M: mostly excreted in tact, some inactivation facilitated by the liver
- E: rapid renal clearance (generally requires frequent dosing)
Indications

- Penicillins: streptococcal, meningococcal, enterococcal, staphylococcal
- Methicillins: Gram-positive infections with β-lactamase activity
- Aminopenicillins and Carboxypenicillins: greater activity against Gram-negative bacteria
Adverse Effects

- Generally non-toxic
- Most serious reaction is hypersensitivity
  - All are cross-sensitising and cross reacting
  - <1% of people who have had a penicillin in the past develop a new allergy
  - Anaphylaxis occurs in 0.05%
- Serum sickness reactions can occur
- High doses (especially in renal failure) can precipitate seizures
- Desensitisation processes can be used if necessary
Cephalosporins

- Similar to Penicillins, but are more stable to β-lactamase activity
- Generally have a broader spectrum of action
- Not effective against enterococci or listeria species
- Currently, there are four generations
Adverse Effects

- Allergic reactions
  - 5-10% cross reactivity with Penicillins
  - Do NOT give if anaphylaxis with Penicillins
- Local irritation and pain after intramuscular and intravenous injection
- Renal toxicity with acute interstitial nephritis and acute tubular necrosis
First-Generation Cephalosporins

- Mostly Gram-positive activity, with little Gram-negative activity
- No CSF bioavailability
- Inactivated by β-lactamases
- Includes Cefalothin, Cephazolin
Pharmacokinetics

- **Oral (e.g. Cephalexin)**
  - A: absorbed in the gut to varying degrees
  - D: varying tissue penetration
  - M: little hepatic metabolism (10%)
  - E: urinary excretion via tubules of unchanged drug (90%)
    - Probenecid blocks tubular secretion and may increase serum levels

- **Parenteral (e.g. Cephazolin)**
  - A: 100% bioavailability
  - D: low Vd
  - M: minimal
  - E: urinary excretion of unchanged drug
Indications

- Urinary tract infections
- Cellulitis with Staphylococcal and Streptococcal species
- Surgical prophylaxis
Second-Generation Cephalosporins

- Active against organisms resistant to first-generation cephalosporins
- Extended Gram-negative coverage, including Haemophilus and Proteus species
- No activity against Pseudomonas
- No CSF bioavailability
- Inactivated by β-lactamases
- Includes: Cefaclor
Pharmacokinetics

- Cefaclor
  - A: well absorbed orally (90%), has sustained release preparations
  - D: unknown
  - M: no metabolism
  - E: renally excreted
Indications

- Effective against β-lactamase producing Haemophilus influenzae or Moraxella catarrhalis
- Primarily used to treat sinusitis, otitis media or lower respiratory tract infections
Third-Generation Cephalosporins

- Reversed spectrum - covers Gram-negative organisms, including Pseudomonas species
- Have CSF bioavailability
- Resistant to $\beta$-lactamases
- Includes: Ceftriaxone, Cefotaxime
Pharmacokinetics

- **Ceftriaxone**
  - A: intravenous administration
  - D: large Vd, penetrate body tissues well, all penetrate to the CSF
  - M: moderate hepatic metabolism into inactive form
  - E: metabolites excreted into the bile, proportion also excreted via urine as unchanged (33-67%) – does not require renal adjustment
    - Other Third-Generations are more dependent on renal excretion - require adjustment
Indications

- Ceftriaxone and Cefotaxime are used for meningitis
- Fever of unknown origin in immunocompetent hosts
Fourth-Generation Cephalosporins

- Similar spectrum to Third-Generation Cephalosporins
- Has CSF bioavailability
- More resistant to β-lactamases compared to Third-Generation
- Includes: Cefepime
Pharmacokinetics

- **Cefepime**
  - **A**: intravenous administration
  - **D**: high Vd, penetrates into CSF well
  - **M**: little
  - **E**: predominantly excreted unchanged in the urine (85%)
Monobactams

- Synthetic monocyclic β-lactam
- Well tolerated in penicillin allergic individuals
- Relatively resistant to β-lactamases
- Active against Gram-negative rods
- Includes: Aztreonam
Pharmacokinetics

- Aztreonam
  - A: intravenous infusion or intramuscular injection
  - D: moderate Vd (12.6L approx. equivalent to ECV)
  - M: little hepatic metabolism
  - E: urinary excretion of predominantly unchanged drug
β-Lactamase Inhibitors

- Inhibitors of many, but not all bacterial β-lactamases
  - Can protect Penicillins that would otherwise be hydrolysed from these enzymes
- Activity against staphylococcal, haemophilus, neisseria, gonorrhoea, salmonella, shigella, echerichia, klebsiella species
- Includes: Clavulanate, Sulbactam, Tazobactam
Carbapenems

- Structurally related to β-lactam antibiotics
- Prevents bacterial cell wall synthesis by binding to and inhibiting cell wall transpeptidases
- Bactericidal
- Includes: Meropenem, Ertapenem
Pharmacokinetics

- **Meropenem**
  - **A**: intravenous administration
  - **D**: high Vd, penetrates tissues well including CSF
  - **M**: small hepatic metabolism
  - **D**: predominantly excreted unchanged in the urine (70%)
Indications

- Enterobacter infections
- Extended-Spectrum β-Lactamase producing Gram-positive, Gram-negative and anaerobic organisms
Adverse Effects

- Nausea and vomiting
- Diarrhoea
- Rash
Glycopeptides

- Inhibits cell wall synthesis by binding to the D-Ala-D-Ala terminus of newly formed peptidoglycans
- Exclusive Gram-positive activity
- Bactericidal
- Slower killing effect compared to β-lactam antibiotics as only works on new peptidoglycans
- Includes: Vancomycin
Pharmacokinetics

- **Vancomycin**
  - **A:** poor oral absorption
    - Intravenous administration for systemic effects
    - Oral administration for *Clostridium difficile* infections
  - **D:** low Vd, moderate protein binding (55%), CSF levels are approx. 30% of serum levels
  - **M:** none
  - **E:** renal excretion as unchanged drug
Indications

- Infections caused by Gram-positive bacteria resistant to Methicillins, including:
  - Sepsis
  - Endocarditis
  - Meningitis
- Clostridium difficile infections
Adverse Effects

- Red man syndrome – flushing of the upper body, may be followed by hypotension, angioedema and pruritis
- Nephrotoxicity is rare
  - More common when used with aminoglycosides
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome can develop – potentially life threatening
  - Severe drug eruption, erythematous rash, inflammation of internal organs
Aminoglycosides

- Reversible inhibitors of protein synthesis
- Initially passively diffuses into bacterial cells via porin channels, then is actively transported
  - Transport is enhanced by cell wall synthesis inhibitors, including penicillins, vancomycin
- Binds to the 30S ribosomal subunits, which inhibits protein synthesis by:
  - Interfering with peptide formation
  - Misreading mRNA, which causes incorporation of incorrect amino acids
  - Formation of non-functional monosomes
- Concentration-dependent killing
- Includes: Gentamicin, Streptomycin, Amikacin
Aminoglycosides

- Resistance occurs via three mechanisms:
  - 1. Inactivation by phosphorylation of the aminoglycoside
  - 2. Impaired intracellular transport
  - 3. Receptor on 30S subunit may be deleted
Pharmacokinetics

- Gentamicin
  - A: poor oral absorption
  - D: small Vd, highly polar compound that does not readily enter cells; in presence of inflammation, have higher rate of CSF bioavailability
  - M: not metabolised
  - E: renal clearance
Indications

- Sepsis caused by aerobic Gram-negative bacteria
- Synergistic activity in endocarditis caused by streptococci, staphylococci and enterococci
Adverse Effects

- Most likely to occur when dosing is continued for 5 days
  - Toxicity is both concentration- and time-dependent
- Nephrotoxicity (reversible)
- Ototoxicity (irreversible)
  - Results in tinnitus and high frequency hearing loss
  - Vestibular damage can result in vertigo and ataxia
- Neuromuscular blockade may occur in very high doses
Tetracyclines

- Inhibitors of the 30S ribosomal subunit
- Broad spectrum - covers Gram-positive, Gram-negative, protozoa
- Bacteriostatic
- Resistance occurs via:
  - Impaired influx or increased efflux
  - Production of proteins that interfere with ribosomal binding
  - Enzymatic inactivation
Pharmacokinetics

- **Doxycycline**
  - A: well-absorbed orally, although varies between different types
    - Portion remains intraluminal and alters gut flora
  - D: distributes widely into tissues, except CSF; able to cross the placenta
  - M: susceptible to enzyme induction when also taking anticonvulsants, and chronic alcohol consumption leading to a shortened half-life
  - E: mixed clearance - bile and urine
    - Doxycycline in particular has non-renal mechanisms of elimination
Indications

- Infections caused by mycoplasma, chlamydiae, rickettsiae, some spirochetes
- Malaria
- Helicobacter pylori
- Acne
Adverse Effects

- Photosensitivity
- Gastrointestinal upset
- Hepatotoxicity
- Deposition in bone and teeth, particularly during foetal development
Macrolides

- Inhibitors of the 50S ribosomal subunit
  - Activity is enhanced by alkaline pH
- Bacteriostatic
- Effective against Gram-positive (pneumococci, streptococci, staphylococci) and Gram-negative (neisseria, bordetella, treponema)
Pharmacokinetics

- Erythromycin
  - A: IV, oral - enteric coated as gastric acid interferes with absorption
  - D: widely distributed, except the CNS
  - M: half-life of 1.5h, metabolised by liver
  - E: excreted in biliary system

- Azithromycin has a higher Vd thus has once daily dosing
Indications

- Community acquired pneumonia
  - Penicillin substitute in allergic patients
- Drug of choice in Coryneabacterium
Adverse Effects

- Nausea, vomiting, diarrhoea
- Cholestatic hepatitis
- Interacts with anticoagulants, theophylline, cyclosporin, methylprednisolone
Lincosamide

- Binds to ribosomal 50S subunits to interfere with protein synthesis
- Effective against Streptococci, Staphylococci and Pneumococci
  - Enterococci and Gram-negative organisms are resistant
- Includes: Clindamycin
Pharmacokinetics

- **Clindamycin**
  - A: well absorbed orally
  - D: well-distributed except CNS
    - Penetrates well into abscesses
  - M: metabolised by liver, half-life of 2-2.5h
  - E: cleared by liver
Indications

- Skin and soft tissue infections
- Anaerobic infections
Adverse Effects

- GI upset
- Impaired LFTs
- Clostridium difficile colitis
Folate Antagonists

- Synergistic combination of folate antagonists blocks purine production and nucleic acid synthesis
  - Interferes with folate production and therefore DNA synthesis
    - Mammalian cells use exogenous folate
  - Active against Gram-positive, Gram-negative, nocardia, chlamydia and some protozoa
- Includes:
  - Trimethoprim which inhibits dihydrofolate reductase
  - Sulphonamides antagonise dihydropteroate synthase as a PABA analogue
- Trimethoprim + Sulphonamides in combination are bactericidal
  - In isolation, they are each bacteriostatic
  - Synergistic as trimethoprim acts on the sequential step of folate synthesis
Folate Antagonists

- **p-Aminobenzoic acid**
  - **Sulfonamides** (compete with PABA)

- **Dihydrofolate synthase**
- **Dihydrofolate reductase**
  - **Trimethoprim**

- **Tetrahydrofolate acid**
- **Purines**
- **DNA**
Pharmacokinetics

- Trimethoprim + Sulfamethoxazole
  - A: oral, IV
  - D: reasonable distribution
  - M: little metabolism
  - E: renal clearance
Indications

- Urinary tract infections
- Pneumocystis jiroveci pneumonia
- Toxoplasmosis
- Nocardiosis
Adverse Effects

- Bone marrow suppression
- Hyperkalaemia
- Rash
- Fever
Chloramphenicol

- Prevents bacterial protein synthesis by binding to the 50S ribosomal subunit
- Bacteriostatic against susceptible bacteria
- Broad spectrum antibiotic
Pharmacokinetics

- A: rapidly absorbed orally
- D: widely distributed to virtually all tissues, including CSF
- M: mostly inactivated by conjugation in the liver
- E: metabolites renally excreted
Indications

- Rarely used in the developed world due to serious toxicities
- Can be used against *Haemophilus influenzae*, *Neisseria meningiditis*, and bactericides
Adverse Effects

- Red cell suppression
- Aplastic anaemia
- Grey-Baby syndrome
- Nausea/vomiting/diarrhoea
- Interacts with phenytoin and warfarin to increase serum concentrations
Quinolones

- Inhibits DNA replication by binding to DNA gyrase and topoisomerase IV
- Bactericidal activity against susceptible bacteria
- Active against Gram-positive, Gram-negative and pseudomonas
- Includes: Ciprofloxacin, Moxifloxacin
Pharmacokinetics

- **Ciprofloxacin**
  - **A:** oral bioavailability 80-95%
  - **D:** large Vd
  - **M:** some hepatic metabolism
  - **E:** mixed clearance, predominantly renally excreted
Indications

- Urinary tract infections
- Gastroenteritis
- Osteomyelitis
- Anthrax
Adverse Effects

- Gastrointestinal upset
- Neurotoxicity
- QT prolongation
- Tendonitis
Nitroimidazole

- Disrupts electron chain transport
- Bactericidal
- Activity against anaerobic bacteria and protozoa
- Includes: Metronidazole, Tinidazole
Pharmacokinetics

- Metronidazole
  - A: oral or IV administration
  - D: widely distributed
  - M: some hepatic metabolism
  - E: excreted in urine both unchanged and as metabolites
Indications

- Anaerobic infections
- Vaginitis
- Clostridium difficile colitis
Adverse Effects

- Gastrointestinal upset
- Metallic taste
- Neuropathy
- Seizures
- Interacts with alcohol resulting in a disulfiram-like reaction
Anti-Malarials (Chloroquine)

- Various anti-malarial drugs with differing mechanisms of action
- Chloroquine is thought to be a rapidly acting schizonticide with some gametocytocidal activity
  - Increases intravacuolar pH and affects the parasite’s ability to metabolism haemoglobin
  - Interferes with DNA or RNA synthesis
  - Also has anti-inflammatory activity and may also have immunosuppressive effects
Pharmacokinetics

- Chloroquine
  - A: rapid and complete
  - D: large Vd
  - M: unknown
  - E: urinary excretion
Indications

- Considered in non-falciparum malaria
- Considered in sensitive falciparum cases
Adverse Effects

- Generally well tolerated
- Haemolysis in those with G6PD deficiency
- Pruritis
- Gastrointestinal symptoms
Antivirals

- Viral replication occurs via several steps:
  - Attachment and entry through cell membrane
  - Uncaging of nucleic acid
  - Synthesis of regulatory proteins
  - Synthesis of late proteins
  - Assembly of viral particles
  - Release

- Antivirals interfere with these steps
Antivirals
Aciclovir is a guanine analogue (produg) that is phosphorylated by viral and cellular enzymes.

- Conversion to its active form is limited in normal cells.
- Inhibits viral DNA polymerase and DNA synthesis.
Pharmacokinetics

- A: IV, oral (low oral bioavailability)
- D: low protein binding
- M: partial metabolism by liver
- E: urine (60% unchanged)
Indications

- Treatment and prevention of HSV, shingles
- Acute varicella zoster in immunocompromised patients
- HSV encephalitis
Adverse Effects

- Gastrointestinal upset
- Diarrhoea
- Headache
- Encephalopathy
- Neurotoxicity
- Seizures
Neuraminidase Inhibitors

- Oseltamivir is a produg that is activated by hepatic esterases
  - Inhibits the viral surface enzyme neuraminidase
- Prevents release of new virus from infected cells
Pharmacokinetics

- A: oral (75% oral bioavailability)
- D: low protein binding, moderate Vd
- M: liver activates produg
- E: urinary excretion of active metabolite (99%)
Indications

- Treatment and prevention of influenza A and B
Adverse Effects

- Gastrointestinal upset
- Headache
- Gastrointestinal bleeding
- Hepatitis