Overview of antibiotics

- What am I treating?
  - Viral, bacterial, fungal, mycobacterial, etc.

- Who am I treating?
  - Host factors: age, genetic factors, co-morbidities (renal and liver failure), location of infection (ex. skin, CNS, etc), history of allergies, pregnancy

- Which antibiotic should I use?
  - Risk-benefit, best drug?, side effects, cost

- How do I administer the medicine?
Overview of antibiotics

- **3 basic mechanisms**
  - Cell wall inhibitors
  - Protein synthesis inhibitors
  - Nucleic acid synthesis inhibitors

- **Bactericidal vs bacteriostatic**

- **Minimum inhibitory concentration (MIC)**
  - Bacteria are killed at 4x MIC of at least 50-60% of the dosing interval

- **Antibiotic pharmacokinetics**
  - Absorption, distribution, excretion

- **Rational use of antibiotics**
# Overview of antibiotics

<table>
<thead>
<tr>
<th>Bactericidal</th>
<th>Bacteriostatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactams</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Macrolides (at higher concentrations)</td>
<td>Macrolides</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Spectinomycin</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Both = sulfonamides-trimethoprim</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
</tr>
</tbody>
</table>

**Bacteria-killing (bactericidal) antibiotics**

- Beta-lactams (e.g., penicillin, ampicillin)
- Macrolides (at higher concentrations)
- Vancomycin
- Fluoroquinolones (e.g., ciprofloxacin, levofloxacin)
- Spectinomycin
- Metronidazole
- Aminoglycosides (e.g., gentamicin, amikacin)

**Bacteria-growth-inhibiting (bacteriostatic) antibiotics**

- Chloramphenicol
- Macrolides
- Tetracyclines
- Spectinomycin
- Both = sulfonamides-trimethoprim
Overview of antibiotics

- Antibiotic pharmacokinetics
  - Drug absorption
    - Oral administration = will food affect intestinal absorption?
    - Better parenteral?
Overview of antibiotics

- Influence of food intake on drug absorption

<table>
<thead>
<tr>
<th>↓Bioavailability</th>
<th>↑Bioavailability</th>
<th>No change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Nitrofurantoin</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Cephaclor</td>
<td>Griseofulvin</td>
<td>Cefixime</td>
</tr>
<tr>
<td>Oxacillin</td>
<td></td>
<td>Cefuroxime</td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Tetracycline</td>
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<td>Azithromycin</td>
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<tr>
<td></td>
<td></td>
<td>Clarithromycin</td>
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<td></td>
<td></td>
<td>Doxycycline</td>
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<td></td>
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<td>Cotrimoxazole</td>
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<td></td>
<td></td>
<td>Clindamycin</td>
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<tr>
<td></td>
<td></td>
<td>Fluoroquinolone</td>
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<tr>
<td></td>
<td></td>
<td>Metronidazole</td>
</tr>
</tbody>
</table>
## Overview of antibiotics

- **Distribution and blood brain barrier penetration**

<table>
<thead>
<tr>
<th>Excellent, with or w/o inflammation</th>
<th>Good only with inflammation</th>
<th>Minimal even with inflammation</th>
<th>No passage at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonamides</td>
<td>Penicillins</td>
<td>Aminoglycosides</td>
<td>1\textsuperscript{st} and 2\textsuperscript{nd} gen cephalosporins</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>3\textsuperscript{rd} and 4\textsuperscript{th} gen cephalosporins (except cefoperazone)</td>
<td>Tetracyclines</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Carbapenems</td>
<td>Lincosamides</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Aztreonam</td>
<td>Macrolides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
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<td></td>
</tr>
</tbody>
</table>
Overview of antibiotics

- **Major elimination pathways**

<table>
<thead>
<tr>
<th>Hepatobiliary</th>
<th>Renal and Biliary</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td>Ampicillin</td>
<td>Penicillin G</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>Oxacillin</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Ceftriaxone</td>
<td>Cephalosporins (in general)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Tetracyclines (in general)</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
<td>Vancomycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ciprofloxacin</td>
</tr>
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</table>
Overview of antibiotics

- Rationale for combination therapy
  - Provide broad spectrum empiric therapy in severe life-threatening infections (ex. sepsis)
  - Treat polymicrobial infections (ex. abdominal abscess)
  - Prevent emergence of resistance (ex. PTB)
  - Decrease dose-related toxicity (ex. aminoglycosides + vancomycin)
  - Obtain enhanced killing (ex. synergism)
Beta lactam antibiotics

- Discovered by Alexander Fleming, a mold inhibited growth of bacteria around it.

- Penicillins
- Cephalosporins
- Monobactams
- Carbapenems
Beta lactam antibiotics

- Basic chemical structure: beta lactam ring, which can be inactivated by beta-lactamase.
Beta lactam antibiotics

- Penicillins: 3 groups
  - Penicillins
    - Ex. Penicillin G and penicillin V
    - Mostly for Gram + only
  - Antistaphylococcal penicillins
    - Ex. Cloxacillin, Oxacillin
    - Resistant to beta-lactamases
  - Extended spectrum penicillins
    - Ex. ampicillin, amoxicillin, piperacillin
    - Wider spectrum of antibacterial effect (Gram +/-)
Beta lactam antibiotics

- MOA: Inhibit bacterial cell wall synthesis (peptidoglycan layer)
  - Unique to bacteria only = humans are not affected
  - Bacterial cell wall is produced by combining proteins via an enzyme called penicillin binding protein (PBP)
  - Penicillins bind with PBP, inactivating it, thus a cell wall is not produced, thus killing the bacteria
  - Effective only for actively growing or dividing bacteria
    - Bacteriostatic
Beta lactam antibiotics

- Resistance to beta lactams
  - Inactivation of antibiotic by beta lactamase
    - Ex. staph aureus produces beta lactamases
  - Modification of target PBP
    - Ex. pneumococci produce different PBP which will not bind with penicillins
  - Impaired penetration of drug to target PBP
    - Ex. gram negative bacteria have an outer well that is relatively impermeable to penicillins, except thru channels called porins
  - Efflux
    - Ex. gram neg bacteria may have channels which pump out the antibiotic
Beta lactam antibiotics

- Pharmacokinetics
  - Well absorbed, but usually impaired by food (except amoxicillin) – take antibiotics 1hr before or 2hrs after a meal
  - Well distributed in the body, even in sputum and milk
  - Does not enter the prostate or brain easily, except during times of inflammation
  - Rapidly excreted by the kidneys
    - Dose adjustment for renal impairment
    - Body concentration of penicillin if given with probenecid (impairs renal secretion)
  - Other drugs are eliminated by both kidneys and liver.
Beta lactam antibiotics

- **Indications**
  - **Penicillins**
    - Gram + organisms (streptococci, meningococci, pneumococci, treponema, clostridium)
    - Some gram –
  - Penicillins resistant to beta lactamase
    - Staphylococci (except MRSA), streptococci
  - **Extended spectrum**
    - Gram + (listeria)
    - Gram – (escherichia coli, salmonella)
    - Shigella – only by ampicillin
    - Piperacillin – gram – (klebsiella and pseudomonas)
Beta lactam antibiotics

- Clinical indications
  - URTI
  - LRTI
  - UTI
  - Skin infections
Beta lactam antibiotics

- Combination with beta lactamase inhibitors

  - Beta lactamase inhibitors = very weak antibacterial activity
    - Activity is still determined by the penicillin group
    - Increases resistance to beta lactamase producing bacteria = increasing spectrum of activity
  - Amoxicillin + Clavulanic acid (co-amoxycylav)
  - Ampicillin + sulbactam
  - Piperacillin + Tazobactam
Beta lactam antibiotics

- Adverse drug reactions (ADR)
  - Hypersensitivity
    - All penicillins are cross-sensitizing and cross reacting
  - GI upset = vomiting or diarrhea
  - Ampicillin = pseudomembranous colitis
  - At extremely high doses = can cause seizures
Cephalosporins

- Similar to penicillins and less susceptible to beta lactamases
- 4 Groups = depending on spectrum of activity
  - 1st generation = more gram positive
    - Cefazolin, cephalexin, etc.
  - 2nd generation
    - Cefoxitin, cefaclor, cefuroxime, cefotetan
  - 3rd generation = more gram negative
    - Cefotaxime, ceftriaxone, ceftazidime, cefixime
  - 4th generation = both
    - Cefepime
- Most are resistant to Listeria
Cephalosporins

- 1st Generation
  - Gram + (pneumococci, streptococci, staphylococci)
  - Gram – (E. coli, klebsiella, proteus)
  - Anaerobes (peptococci, peptostreptococci)
  - Well absorbed orally
  - Excreted renally
    - Probenecid may increase blood concentrations
  - Clinical indications
    - UTI, soft tissue infections
    - Surgical prophylaxis
Cephalosporins

- 2nd Generation
  - Similar gram + with 1st gen plus more gram – coverage and some anaerobic coverage
  - Gram – (Klebsiella, Moraxella)
  - Cefuroxime – active against H. influenzae
  - Cefoxitin – active against Bacillus fragilis
  - NO activity against pseudomonas
  - Renal clearance

- Indications
  - URTI, LRTI, UTI
  - Peritonitis, diverticulitis, pelvic inflammatory disease
  - Meningitis – only for cefuroxime
Cephalosporins

- 3rd generation
  - Gram – (citrobacter, serratia, haemophilus, neisseria)
  - Gram + (resistant pneumococci)
  - Ceftazidime – good for pseudomonas
  - Most given by IV.
  - Oral agents = cefixime
  - All enter the CNS except cefoperazone and cefixime
  - Excreted by the kidneys (except ceftriaxone = liver)
- Indications
  - Meningitis, other brain infections
  - UTI, STD (gonorrhea, esp. ceftriaxone and cefixime)
  - Sepsis and febrile neutropenia (ceftazidime)
Cephalosporins

- 4\textsuperscript{th} Generation
  - Most resistant to beta-lactamases
  - Good activity against pseudomonas, enterobacteriacea, staph a., strep pneumo, neisseria
  - Penetrates into CNS well
  - Cleared by the kidneys
Cephalosporins

- ADR
  - Hypersensitivity
    - Some cross-reactivity to penicillins
  - Renal toxicity
  - Certain drugs (cefamandole, cefotetan, cefoperazone) may cause disulfiram-like reactions
Monobactams

- Aztreonam
  - Limited to aerobic gram neg rods only (ex. pseudomonas)
  - No activity against gram +, or anaerobes
  - Penetrates into CNS well
  - Almost no cross-reactivity to penicillins or cephalosporins
Carbapenems

- Imipenem, meropenem, ertapenem
  - Widest spectrum penicillins
  - Gram + and – (ex. pseudomonas, and anaerobes)
    - Except ertapenem for pseudomonas
  - Imipenem is inactivated by dihydropeptidases in the kidney
    - Combined with cilastatin (inhibitor of dihydropeptidase)
  - Enters the CNS
  - Renally cleared
  - Indications
    - Treatment for mixed infections (Gram +/- and aerobic/anaerobic)
Carbapenems

- ADR
  - GI irritation (nausea, vomiting, diarrhea)
  - Hypersensitivity and skin rash
  - Seizure at high doses
  - Cross reactivity with penicillins
Glycopeptide antibiotics

- Vancomycin
  - Produced by Streptococcus orientalis and Amycolatopsis orientalis
  - Active only against Gram + bacteria
  - MOA: cell wall inhibitor
    - Binds with D-Ala-D-Ala terminal ends of cell wall peptides, inhibiting cell wall formation (different from PBP binding by beta lactam antibiotics)
    - Bactericidal for gram +
  - Well distributed in the body and CNS
Glycopeptide antibiotics

- Renally excreted = adjust dose for renal failure and during hemodialysis
  - May need to check serum concentrations for prolonged use
  - Indication: MRSA

- ADR
  - Phlebitis (irritating to tissues)
  - Ototoxicity and nephrotoxicity, especially when combining with aminoglycosides
  - Red man or red neck syndrome
    - An allergic reaction during rapid infusion
    - Give anti-histamine and slow down infusion rate
BREAK
Protein synthesis inhibitors

- Tetracyclines
- Macrolides
- Lincosamides
- Chloramphenicol
- Aminoglycosides
- Spectinomycin
Tetracyclines

- Ex. Tetracycline, Doxycycline, minocycline

- MOA: inhibit protein synthesis
  - Bacteriostatic
  - Bind reversibly to the 30S subunit of the bacterial ribosome, blocking the binding of tRNA to the receptor on the mRNA. This prevents addition of amino acids to the growing peptide.
Tetracyclines

- Generally well absorbed in the intestines
  - Food, milk and alkaline pH decreases absorption
  - A portion remains in the intestines and is excreted with feces
    - Can alter normal intestinal flora

- ADR
  - Not for pregnant people and children <8 y/o
    - Binds with calcium in bone = brownish discoloration, enamel dysplasia and growth inhibition
  - Nausea, vomiting, diarrhea
  - Can cause alteration in gut flora = Clostridium difficile associated colitis
Tetracyclines

- Indications
  - Rickettsia and cholera (tetracycline)
  - Leptospirosis (doxycycline)
  - Mycoplasma, Chlamydia
  - H. pylori
  - Some CAP, URTI and UTI
  - Emergence of multiple resistances
Macrolides

- Erythromycin, clarithromycin, azithromycin
- MOA: protein synthesis inhibitor
  - Bactericidal
  - Binds to the 50S subunit of the rRNA and prevents peptide chain elongation
    - Erythromycin also inhibits formation of 50S subunit
- Complete cross-resistance with other macrolides and lincosamides
- Food interferes with absorption
- Excreted by the liver into the bile
- Azithromycin, very long half-life and is slowly released from tissues
  - Allows once daily dosing and shorter duration of treatment
Tetracyclines
Macrolides

- Indications
  - Diptheria
  - URTI, LRTI, CAP
  - Atypical pneumonia (esp. for clarithromycin and azithromycin)
    - Chlamydia and mycoplasma pneumonia
  - UTI
  - Substitute for patients with penicillin allergy
Macrolides

- **ADR**
  - Anorexia, nausea, vomiting, diarrhea
    - Erythromycin stimulates motilin, a hormone that increases peristalsis
  - Acute cholestatic hepatitis (fever, jaundice, impaired liver function)
    - Due to an allergic reaction to erythromycin
  - Inhibits cytochrome p450 enzyme in the liver
    - Affects metabolism of other drugs
Lincosamides

- Clindamycin
- MOA: inhibits protein synthesis
  - Binds with the 50S subunit of the rRNA and prevents peptide chain elongation (same with macrolides)
- Resistance = cross resistance with macrolides
- Minimal brain penetration
- Metabolized in the liver
Lincosamides

- Indications
  - Gram + aerobes and anaerobes
  - Gram – anaerobes
  - Gram – aerobes are resistant
  - Soft and skin tissue infections
  - MRSA
  - Anaerobic (gingival, oral, abdominal, pelvic, abscesses)

- ADR
  - Diarrhea, nausea, skin rash
  - Impaired liver function, pseudomembranous colitis
Chloramphenicol

- Chloramphenicol

- MOA:
  - Reversibly binds to 50S subunit of rRNA and inhibits peptide bond formation
  - Bacteriostatic

- Well absorbed and easily enters the brain

- Oral route produces a better drug concentration than IV route
  - Oral prodrug is metabolized in the intestines to yield the active drug, while IV prodrug is only partially hydrolyzed in the blood to yield the active drug.
Chloramphenicol

- Metabolized in the liver
- Indications
  - Gram +/- aerobes and anaerobes
  - Only for serious infections
  - Not a drug of choice for many infections due to many side effects
Chloramphenicol

- ADR
  - GI disturbances
  - Candidiasis
  - Aplastic anemia (due to suppression of RBC production)
  - Gray baby syndrome (newborns are unable to metabolize chloram to inactive metabolites = thus accumulation may occur)
    - Vomiting, flaccidity, hypothermia, gray color, shock and vascular collapse
  - Inhibits hepatic enzymes = drug metabolism interaction
Clinical question

- Can we combine bactericidal with bacteriostatic antibiotics?
  - Ex. penicillin + erythromycin
  - Avoid if possible
    - Bactericidal = needs actively growing or dividing cells
    - Bacteriostatic = will stop growth or division of cells
    - Antagonistic effect.