Antimicrobials 2

Interference with Protein Synthesis

PHRM 203

Allison Beale
5 fundamental sites of action for antibiotics

- **Cell Wall Synthesis**
  - Penicillins, cephalosporins, glycopeptides, monobactams, Carbapenems, Isoniazid

- **Protein Synthesis**
  - Aminoglycosides, Macrolides, Ketolides, Tetracyclines, Chloramphenicol, Lincosamides, Oxazolidinones, Streptogramins, Rifampin

- **Modifies a membrane**
  - Paracelsin, Calcimycin, Gramicidin

- **Interrupts DNA Synthesis**
  - Fluoroquinolones, Nalidixic acid

- **Interferes with an enzyme**
  - Sulfonamides, Trimethoprim, Dapsone

Today
Patient Counseling

for any & all antibiotics

• Take ALL the medication
  – Do not skip doses
  – Do not stop taking the medication early

• Use the medication ONLY to treat bacterial infections, not viruses etc.
  – Do not give your medicine to someone else

• Report any DIARRHEA
Antibiotics Issues

1. Superinfections
   1. *Clostridium difficile* - *CDAD*; *pseudomembranous colitis*
   2. *Candida albicans*

2. Drug-induced kidney failure
   1. Aminoglycosides/amphotericin B
   2. β-lactams
   3. NSAIDs
   4. ACE-I or ARBs + Diuretic(s)

3. Allergy

4. Antibiotics DO NOT treat viruses

5. Drug-induced liver failure

6. Often have CNS, skin &/or blood tissue effects
Prokaryotic Protein Synthesis: Initiation

mRNA

rRNA

Aminoacyl-tRNA

See handout
Prokaryotic Protein Synthesis: Elongation
Antibiotics Interfering with Protein Synthesis (classes in black, specific drugs in blue)

• Aminoglycosides
• **Chloramphenicol**
• Lincosamides
• Macrolides
• **Nitrofurantoin** (many mechanisms)
• **Rifampin** (covered with antimycobacterials)
• Tetracyclines
• Streptogamins
Means of interfering with protein synthesis

• 30S Ribosome sites
  • Aminoglycosides
    • Irreversibly bind 30S ribosomal proteins
  • Tetracyclines
    • Block tRNA binding to 30S ribosome-mRNA complex

• 50 S Ribosome sites
  • Chloramphenicol, Clindamycin, Streptogramin A
    • Binds peptidyl transferase component of 50S ribosome, which blocks peptide elongation
  • Macrolides, Lincosamides, Streptogramin B
    • Blocks peptide elongation by binding to 50S ribosome

• Interfere with transcription (block mRNA synthesis)
  • Rifampin
    • Blocks DNA dependent RNA polymerase
Bacterial rRNA

Rifampin blocks transcription of mRNA

Aminoglycosides

Streptogramin A & chloramphenicol

Macrolides, Lincosamides, Streptogramin B

Svedberg units are not additive
# Aminoglycosides

Mostly SERIOUS Gram $\ominus$ aerobic bacilli - all aminoglycosides bind to 30S & 16S rRNA and block protein synthesis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Neurotoxic to 8th CN!</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Deafness</td>
<td>SERIOUS Gram $\ominus$ infections</td>
</tr>
<tr>
<td><strong>Gentamicin</strong> (Garamycin) <strong>C</strong></td>
<td>Balance</td>
<td><strong>SERIOUS Pseudomonas, Staphylococcus &amp; Gram$\Theta$ infections.</strong> <strong>Topical (ophthalmic ointments &amp; solutions), IM or IV TID for 7-10 days</strong>  $t_{1/2} \sim 2-3\text{ hrs}$</td>
</tr>
<tr>
<td>Neomycin</td>
<td><strong>Very nephrotoxic</strong></td>
<td>Hepatic coma &amp; ↓ GI flora preop, skin inf. OTC <strong>TOPICAL ONLY, Rx PO</strong></td>
</tr>
<tr>
<td><strong>Streptomycin</strong> <strong>D</strong></td>
<td>Balance &amp; deafness</td>
<td>TB &amp; other serious infections. <strong>IM only, no more than 120 grams over course of treatment, usually BID for 2 weeks.</strong> <strong>Contains sodium metabisulfite.</strong> $t_{1/2} \sim 5-6\text{ hrs}$</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Deafness</td>
<td>Serious infections; Cystic Fibrosis inhaler</td>
</tr>
</tbody>
</table>

Note: TB isn’t G$\oplus$$\ominus$, they are “acid fast” & Ziehl-Neelsen staining results in bright pink MTB on contrasting buff/bluish background.
Bacterial cell

Aminoglycosides alter confirmation of 30 S subunit leading to the misreading of mRNA

They don’t work well in low pH or anaerobic conditions – e.g., abscesses, because $O_2$ required for uptake

http://faculty.ircc.edu/faculty/tfischer/micro%20resources.htm
Mechanisms for resistance to: Aminoglycosides

Resistance is common

- Enzyme modification is the most common form of resistance
- Altered ribosome binding sites
- Not important
Aminoglycosides

• Kinetic/dynamic considerations
  – Poorly absorbed PO, some not at all
  – Dosage based on **LEAN BODY MASS**
  – Excreted **unchanged** in urine
  – Toxic to kidney

• Contraindications and warnings
  – Allergy to any aminoglycosides
  – Kidney or liver disease
  – Pre-existing hearing loss
  – Herpes or mycobacterial infection
  – Myasthenia gravis or Parkinson’s disease (curare-like effect)
  – Pregnancy and lactation (permanent hearing loss in baby)

Gentamicin and Streptomycin are NOT used PO

While aminoglycosides are often co-administered with Penicillins, they must not be mixed in the same solution - Penicillin inactivates aminoglycosides. Same for Cephalosporins, Heparin & Amphotericin B
Aminoglycosides: Boxed Warnings

1. CNS/PNS
   - **Ototoxicity** (*8th cranial nerve damage*)
     - All aminoglycosides are toxic to sensory cells in the ears, but vary in relative effects on hearing vs balance
       - Hearing loss (cochlear toxicity)
       - Vestibular paralysis.
       - Tinnitus
     - Loop diuretics increase ototoxicity risk
   - Confusion, depression, disorientation, numbness/tingling
   - Injections may cause **neuromuscular blockade** (*curare-like effect*) and respiratory arrest

2. Renal
   - Size of drug damages glomerulus → kidney failure
   - Inhibition of protein synthesis in renal cells → tubular cell death
     → **kidney failure**
Aminoglycosides: 

Less serious ADRs

- **Liver**
  - Co-administration of cephalosporins increase hepatotoxicity risk

- **GI**
  - Nausea, vomiting, diarrhea

- **CV**
  - Palpitations, hypotension and hypertension

- **Hypersensitivity rxns**
  - Purpura (*bruising*), rash, urticaria (*hives*), exfoliative dermatitis

- **Drug-drug interactions**
  - No diuretics
  - Anesthetics should be avoided, and the class shouldn’t be used immediately after anesthesia (due to neuromuscular blocking)
Chloramphenicol (Chloromycetin)  
Broad Spectrum Antibiotic

- **Formulations:**
  - IV, Ophthalmic ointments, Otic solutions

- **Kinetics/dynamics**
  - $t_{1/2} = 1.5-4$ hours
  - *Chloramphenicol inhibits eukaryotic mitochondrial protein synthesis*

- **Indications**
  - *Life threatening infections: meningitis, rickettsia for which other drugs can not be used*

- **Contraindications**
  - Allergy
  - Trivial infections, viral infections, prophylaxis of bact. Inf.

**Bacteriostatic**

**P450↓**

**Narrow therapeutic margin, monitor plasma levels**
Chloramphenicol *(Chloromycetin)*

- **ADRs**
  - LOTS of drug interactions
  - Boxed warning
    - Serious and potentially fatal blood dyscrasias
    - Bone marrow fails to produce RBC (Aplastic anemia), etc.
  - Allergic reactions
  - GI
    - Diarrhea to fatal colitis
  - Gray baby syndrome
    - Neonates (insufficient liver function)
    - 2-9 days after IV dose
      - Hypotension, hypothermia, cardiovascular collapse
      - Cyanosis
  - Resistance is common
    - Resistance is probably on the plasmid and appears to be for multiple drugs
  - Pseudomembranous colitis usually due to *Clostridium difficile*. May be treated with Metronidazole (Flagyl)
## Macrolide Antibiotics

**Gram +, mycoplasma, Legionella**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication (all G + are resistant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin (Zithromax)</td>
<td>Mild to moderate RTI and UTI (best selling of the macrolides)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Various RTI, skin, sinus, maxillary infections and mycobacteria</td>
</tr>
<tr>
<td>Dirithromycin</td>
<td>RTI and skin</td>
</tr>
<tr>
<td>Erythromycin (E-Mycin)</td>
<td>Used in people allergic to penicillin, to treat various G + &amp; G −, mycobacterial and protozoal (Entamoeba) diseases, including <em>Corynebacterium diphtheriae</em>, syphilis, pertussis, and <em>chlamydial</em> infections; Legionnaire’s disease, <em>ureaplasma</em> species and <em>mycoplasma</em> pneumonias. Lots of indications primarily for mild to moderate RTIs. Acne vulgaris &amp; UTIs too.</td>
</tr>
</tbody>
</table>

*Macrolides and penicillins have a very similar spectrum of activity, but different mechanisms; macrolides ⊗ protein synthesis, penicillins ⊗ cell wall synthesis*

---

A Beale

PHRM 203: Micro 2

19
Macrolides: Azithromycin

- **IV Indications**
  - Specific bacteria that cause community-acquired (CA) pneumonia and pelvic inflammatory disease

- **PO indications**
  - Mycobacterial infections, CA pneumonia, pharyngitis, tonsillitis, uncomplicated skin infections, urethritis, cervicitis, acute otis media and chancroid (in men)

- **SID 2-5 days**

- **Okay with or without food**
  - Don’t take with Al\(^{++}\) or Mg\(^{++}\) antacids

- **t\(_{1/2}\) ~ 68 hours!**
  - Long \(t_{1/2}\), means allergy symptoms may occur long after therapy ends
Azithromycin (Zithromax)

- **NOT** for use in patients with:
  - Cystic fibrosis, nosocomial infections, bacteremia, immunodeficiency, syphilis, hospitalized patients or the elderly or debilitated - etc.

- **ADRs**
  - Serious allergic rxns including SJS & angioedema

  *May worsen or trigger Myasthenia Gravis*

  *Resistance is common*

  *Bacteriostatic*
Macrolides: Erythromycin

• Kinetic/dynamic considerations
  – 20-80% bioavailable PO, t½ ~5-6 hours
    • Food in stomach ↓ absorption
    • Strongly prokinetic for GIT
• Contraindications and warnings
  – Allergy to any macrolide
  – Viral, fungal, mycobacterial infection of eyes
  – Liver/kidney disease
  – Pregnancy/lactation
    – Erythromycin is contraindicated in patients taking pimozide (an antipsychotic DA antagonist) and cisapride (GI motility stimulant via 5-HT receptor stimulation). It should be used with caution in patients on statins.

Do not crush tablets

Usually given PO, IM painful. Available IV and topical (ophthalmic).

Clindamycin antagonizes erythromycin
Erythromycin
EryPed, Ery-Tab, Erythrocin, Eryzole

• ADRs
  – LOTS of Drug interactions related to inhibition of CYP3A
  – Hepatic dysfunction: cholestatic hepatitis
  – GI
    • Cramps, anorexia, vomiting, diarrhea, pseudomembranous colitis
  – CV
    • Ventricular arrhythmias including tachycardia and torsade de pointes
  – CNS
    • Confusion, uncontrolled emotions, hearing loss at high doses, ↓seizure threshold, anxiety, nightmares
  – Hypersensitivity
    • Rash, anaphylaxis, superinfections

P450↓

Symptoms of cholestatic hepatitis: dark urine, fatigue, hives, itching, yellowing of skin or eyes, skin rash, persistent nausea, persistent or worsening flu-like symptoms, shortness of breath, right upper belly pain

Symptoms of superinfection by Candida sp.: Black furry tongue, foul-smelling stools, vaginal itching or discharge, white patches in mouth.

Resistance is common

Bacteriostatic

Resistance is common

Bacteriostatic
Lincosamide Antibiotics

SERIOUS anaerobic and aerobic bacterial infections

Also used off label to treat toxoplasmosis in HIV-AIDS patients

Clindamycin • B (Clindamax, Cleocin)

- LOTS of parenteral and enteral formulations including topicals (gels and lotions for acne and cremes for vaginosis), vaginal suppositories, IM and IV injections. PO up to 90% bioavailable

Indications

- SEVERE respiratory, skin and soft tissue infections when other antibiotics can not be used.

- Examples of severe infections:
  - In the Lung – empyema (pus in a natural body cavity), anaerobic pneumonitis, abscess
  - In skin/soft tissue - septicemia, peritonitis, intra-abdominal abscess, endometritis, etc
Lincosamides: Clindamycin

- **Kinetic/dynamic considerations**
  - PO - 90% bioavailable, liver metabolism, excretion in urine/feces
    - Take with lots of water to avoid irritation
  - $t_{1/2}$ 2-3 h (up to 5 hr)
  - Adults – QID, kids – TID/QID

- **ADRs**
  - Severe GI
    - Boxed warning about CDAD
  - GI, joint Pain
  - Skin infections
  - Bone marrow depression

**Shoud be reserved for penicillin allergic patients**

**Don’t take with caffeine (coffee)**

**Clindamycin antagonizes erythromycin**

**Resistance is common**

**Bacteriostatic**

**Yeast superinfections a problem side effect with clindamycin**
Lincosamides: Clindamycin

• Contraindications
  – Allergy to clindamycin or lincomycin
  – History of ulcerative colitis, antibiotic associated colitis, or regional enteritis

• Warnings
  – May enhance NMJ blockers
  – Incompatible with aminophylline, ampicillin, barbiturates, phenytoin, calcium gluconate, magnesium sulfate
  – Tartrazine sensitivity (see tetracyclines)
  – IV Solution contains benzyl alcohol which may cause fatal “Gasping Syndrome” in neonates
  – Boxed warning about CDAD
Oxazolidinones: Linezolid (Zyvox®)

- Only oxazolidinone on market
- Used for serious $G^+$ infections
  - Against all clinically significant $G^+$ bacteria, including vancomycin-resistant strains and multi-drug resistant *Staphylococcus aureus* strains (MRSA)
  - Skin, soft tissues, lung
- ADRs
  - Weak MAO-I
    - Serotonin syndrome reported
    - Avoid tyramine-rich foods and OTC decongestants – may cause HTN
  - Optic & peripheral neuropathies
  - Myelosuppression, thrombocytopenia
  - Lactic acidosis
- Resistance is rare and 1° affects Enterococci
- Bacteriostatic
- $t_{1/2}$ ~ 5-7 hrs

PO, IV
Streptogramins

**Synercid** (quinupristin + dalfopristin)

- Dalfopristin binds to 23S
  - Conformation change \( \uparrow \) affinity for quinupristin which prevents elongation
    - Bacteriostatic alone, bactericidal together
  - Only for specific, serious, life-threatening infections

- Bacteriostatic alone, bactericidal together

- Only for specific, serious, life-threatening infections

- Resistance is rapidly increasing

- P450 ↓

- Slow IV infusion
# Tetracycline Antibiotics

Broad spectrum antibiotics with effects against **G⁺ & G⁻** bacteria, rickettsia, and protozoans (*Plasmodium* sp. and some amoeba)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demeclocycline</td>
<td>Penicillin resistant infections</td>
</tr>
<tr>
<td><strong>Doxycycline (Adoxa, Vibramycin, Oracea)</strong></td>
<td>Lots of <strong>G⁺ &amp; G⁻</strong> infections including traveler’s diarrhea, STDs, acne and periodontal disease; <em>(Used to treat infections caused by protozoa (amoeba, plasmodia), rickettsia, and spirochete bacteria (Lyme disease &amp; Leptospirosis). JUST NOT Staph infections.</em></td>
</tr>
<tr>
<td></td>
<td>• $t_{1/2} \sim 18-22$ hrs – may be given chronically</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Meningococcal carriers, UTI/pelvic infections</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>Penicillin resistant or contra-indicated infections, amebiasis</td>
</tr>
<tr>
<td><strong>Tetracycline (Sumycin)</strong> <strong>D</strong></td>
<td>Lots of <strong>G⁺ &amp; G⁻</strong> infections including skin (acne, rosacea), eye and STDs, malaria prophylaxis, other protozoa and rickettsial diseases.</td>
</tr>
<tr>
<td></td>
<td>• $t_{1/2} \sim 6-11$ hrs – may be given chronically</td>
</tr>
</tbody>
</table>
Tetracyclines

- **Kinetics/dynamics**
  - Up to 100% PO bioavailability affected by food, Ca++ or other drugs in GI
    - Don’t take with milk (except doxycycline)
  - Concentrated in liver, excreted unchanged in urine & bile

- **Contraindications and warnings**
  - Allergy to tetracycline or tartrazine
  - Pregnancy or lactation
  - Damage to bones/teeth
  - Don’t use in eye if have viral, fungal or mycobacterial infections
  - Superinfections possible

**SC & IM available for Vets, not for human use**

**Usually given PO; IM very painful, IV causes irritation, phlebitis**

**Tartrazine is a commonly used yellow azo dye. It is very inexpensive, used globally, and colors lots of different foods, medicines and cosmetics. It is implicated in allergic reactions such as hives.**

**Outdated tetracyclines are toxic to kidneys!!**
Tetracyclines

• ADRs
  – Tinnitus
  – **PHOTOSENSITIVITY!**
  – Superinfection
  – May stain teeth (permanent *dyscoloration*)
  – ↓ plasma prothrombin activity (inhibits clotting)
  – ↓ oral contraceptive efficacy
  – Bulging fontanels in infants and benign intracranial hypertension in adults
  – Drug interactions
    • + Ca++, Al++, Fe++, Zn++, OTC heartburn and antacid medications → all may inactivate tetracyclines (except doxycycline)
    • + methotrexate → ↑ competition for PPB sites
    • + methoxyflurane → fatal renal toxicity

Doxycycline is drug of choice for renal failure patients
Mechanisms for resistance to: **Tetracyclines**

- ATP-dependent efflux pumps are synthesized
- Enzyme inactivation is rare
- Altered ribosome binding sites are common

**Resistance is common**

**Bacteriostatic**

- Uptake is not very important
- Bacteria have an uptake mechanism for tetracyclines