Micro 3

Inhibiting Cell Wall Synthesis

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Mechanisms

• Inhibition of cell wall synthesis
  – β-Lactams
  – Vancomycin (a glycoprotein)
  – Isoniazid

• Inhibition of nucleic acid synthesis or antimetabolic activity
  – Sulfonamides (e.g., sulfamethoxazole)
  – Dapsone

• Inhibition of transcription (DNA to mRNA)
  – Rifampin
β – Lactams

By far the most extensively used class of antibiotics

- Penicillins
- β – Lactamase inhibitors
- Cephalosporins
- Monobactams
- Carbapenems

Drug Resistant Organism Acronyms

- MDRO
  - Multi drug-resistant organism
- MRSA
  - Methicillin-resistant *Staphylococcus aureus*
- MDRSP
  - Multidrug-resistant *Streptococcus pneumoniae*
- CRKP
  - Carbapenem-resistant *Klebsiella pneumonia*
- CRE
  - Carbapenem-resistant Enterobacteria
- VREF
  - Vancomycin-resistant *Enterococcus faecium*
**β-Lactams**

**NOTES**

- Penicillins have some activity as $\text{GABA}_A$ antagonists so may cause seizures.
- Imipenem = broadest spectrum of β-lactams, but kidney metabolite is toxic.

**Probenecid (Benuryl)**

*Indicated to decrease the renal tubular secretion of ampicillin, methacillin, oxacillin, cloxacillin, and nafcillin. It is used off label for many other drugs.*

*May cause psychic disturbances.*

*It should not be given with salicylates (aspirin, for instance), because salicylates antagonize the activity of probenecid.*

*Penicillin “core”*
Penicillin

Types

1. Standard Penicillin
   a. Mostly Gram +

2. Extended Spectrum
   a. Semisynthetic, β-lactamase resistant
   b. Gram + and Gram −

3. Combo of Penicillin + Beta-lactamase inhibitor

Kinetics/Dynamics

• Good PO absorption
• Sensitive to acid, take on empty stomach
• Excreted unchanged in urine
  – Probenecid slows tubular secretion
  – Increases plasma levels 2-4X
  – May cause psychic disturbances
• Injection site pain common
• Hypersensitivity ~10%
• Drug interactions:
  – ↓ by tetracycline
  – Inactivates aminoglycosides
  – Efficacy of oral BC pills lost

BACTERICIDAL
Standard Penicillin

- Generally used for severe Gram + infections, examples:
  - Penicillin G benzathine
  - Penicillin G potassium
  - Penicillin V
    - Number 63 by units (2007)

**NOTE:** almost all Gram Θ bacteria produce β-lactamases (plasmid encoded), and there are many forms. The β-lactamases are mostly specific for different penicillins. They destroy the antibiotic by cleaving the β-lactam ring. In the combo products, Clavulanic acid inhibits some β-lactamases, others are inhibited by Sulbactam or Tazobactam.

Penicillin G Procaine

- Indications include moderately severe G+ infections
- ADRs
  - Procaine Reaction
    - Allergy to PABA
    - Lasts 15-30 min in 1/500 patients
    - Confusion, anxiety, hallucinations, “Fear of impending Death”
  - IV causes severe neurovascular damage leading to paralysis, necrosis and amputation

*Supplied as: 1ml syringe of 600K Units or 2ml syringe of 1.5M Units*
Semisynthetic Penicillin

Extended Spectrum

• Amoxicillin (Amoxil) *
• Ampicillin
• Carbenicillin
• Methicillin*
• Nafcillin*
• Oxacillin*
• Ticarcillin
• Zillions of others…

* β-lactamase resistant

Amoxicillin (Amoxil)

• PO BID or TID - t ½ ~ 1 hour
• Indicated for an array of mild/moderate & severe G+ and G θ infections of the ear/nose/throat, lower RTI, skin/skin structure, GIT and STDs
• Drug interactions
  – Probenecid ↓ tubular secretion
  – Amoxicillin (like other antibiotics) ↓ estrogen GI reabsorption and therefore may ↓ oral BC efficacy
  – High urine concentrations may cause some false + urine glucose tests (CLINITEST, Benedict’s or Fehling’s)
Penicillin & β-Lactamase inhibitor Combos

• Augmentin PO
  – Amoxicillin + Clavulanic acid
    • May turn teeth brown
    • Cholestatic hepatitis

• Unasyn IM or IV infusion
  – Ampicillin + Sulbactam

• Zosyn IV infusion
  – Piperacillin + Tazobactam

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Cholestatic hepatitis

Bile cannot be properly secreted from liver.

Causes include drug-, pregnancy-, and viral-induced forms, congenital abnormalities, trauma, cancer, gallstones, and autoimmune dysfunction.

Symptoms include pruritus, Jaundice, pale stools/dark urine.
Cephalosporins

Kinetics/Dynamics

- Moderate to Broad spectrum
- Some well absorbed PO
  - Most PO forms are taken with food
- Penicillin allergy X-RXN
- Lower dose/monitor, if:
  - Kidney failure or disease
  - Liver disease

ADRs

- False + direct Coomb’s & urine glucose tests
- Phlebitis/infection at injection sites
- Acute kidney failure
- Anemia/pancytopenia/hemorrhage
- Drug interactions:
  - +Aminoglycosides (↑ kidney risk)
  - +Oral BC (↑Prothrombin Time)
  - +Alcohol (disulfiram-like rxn)
  - +Probenecid (longer t ½)

BACTERICIDAL
1\textsuperscript{st} Generation Cephalosporins

\textbf{Cephalexin (Keflex)}

- PO w/o regard to meals
- t $\frac{1}{2}$ is 1 – 1.5 hours
- Excreted unchanged through kidneys
- Nausea & diarrhea common
- \textit{Indicated for RTI, skin, bone and GI infections}

\textbf{Others}

- Cefadroxil
- Cefazolin
- Cephardine

1\textsuperscript{st} generation are best used against G+ aerobic bacteria. They have little effect on G$\Theta$. 
2\textsuperscript{nd} Generation Cephalosporins

Cefaclor (Ceclor)

- PO, preferably fasted
- t $\frac{1}{2}$ is 30 – 45 minutes
- Excreted unchanged through kidneys
- \textit{Indicated for RTI, skin, UTI, otitis media, typhoid, anthrax.}

Others

- Cefmetazole
- Cefoxitin
- Cefprozil
- Cefuroxime
- Loracarbef

2\textsuperscript{nd} generation cephalosporins have improved G$\Theta$ coverage and anti-\textit{Haemophilus} activity. They are useful against G+/G$\Theta$ aerobes and some G+ anaerobes.
4th generation Cephalosporins

**Cefepime (Maxipime)**

- IM or IV BID 7-10 days
- $t\frac{1}{2}$ is about 2 hours
- *Indicated for facultative and aerobic G+/G− bacteria causing moderate to severe skin, UTI or RTI*

- ADRs
  - Rash (51%)
  - False + Coombs & urine glucose tests
  - ↑ Prothrombin time
  - Steven-Johnson Syndrome

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**It’s a GAS!**

*Group A streptococci (GAS) are Streptococcus pyogenes, the most common cause of acute pharyngitis and skin infections (e.g., non-bullous impetigo).*

*About 10% of kids are asymptomatic GAS carriers.*
Monobactams

**Aztreonam (Azactam, Cayston)**

- Wide Gram aerobic spectrum
- IV/IM or inhaled
  - ↓ dose in elderly and kidney patients
  - Doesn’t induce β-lactamase
- **Indications for Gram enterobacterial infections, UTIs, skin and pelvic infections** – often as an alternative to penicillin

**Cystic fibrosis**

CF = genetic disorder resulting in thick, sticky mucous. The mucous clogs the lungs, causing chronic RTIs, and clogs the pancreas, resulting in a loss of both endocrine (insulin and glucagon) and exocrine (digestive enzymes) pancreatic function.

*Cayston indicated to treat the #1 cause of death in CF, *Pseudomonas aeruginosa* pneumonias.*

Administer using Altera® nebulizer

*BACTERICIDAL*
Carbapenems

Ertapenem (Invanz)

- IV/IM
- Restricted use – NOT for MRSA
- Indicated for CA-pneumonias, and severe skin, abdominal, UTI/pelvic infections.
- Resistance
  - Carbapenemase producing enterobacteria
  - Carbapenem-resistant *Klebsiella pneumoniae*

Others

- Doripenem
- Faropenem
- Imipenem
- Meropenem

*Klebsiella pneumoniae*

- COMMON G Θ bacteria
- Known hospital- and community-acquired pathogen, causing:
  - UTI, nosocomial pneumonia, intra-abdominal infections (wound/surgical site infections) and meningitis
  - Dramatic onset, fever, hemoptysis (current jelly sputum)
Vancomycin (Vancocin, Covane)

- Antibiotic of last resort for severe G+ infections
  - CDAD and MRSA
  - Commonly given with an aminoglycoside
    - 8th cranial nerve toxicity a problem
    - Acute kidney failure risk
  - IV only (slow IV infusion) t½ of between 4-6 hours
    - RED MAN SYNDROME
      - Mast cell degranulation 4-10 minutes post infusion causes itching and flushing in upper part of body

- Resistance
  - VREF = Vancomycin-resistant *Enterococcus faecium*
    - Treat with Linezolid or Synercid
## Antimycobacterials

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<th>Indication</th>
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<td>Ethionamide</td>
<td>Inhibits cell wall synthesis</td>
<td>1\text{st} line TB</td>
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<tr>
<td>Isoniazid (INH, Nydrazid)</td>
<td>Inhibits transcription of mRNA from DNA</td>
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<td><em>isonicotinic acid hydrazide</em></td>
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<tr>
<td>Rifampin (Mycostat)</td>
<td>Inhibits transcription of mRNA from DNA</td>
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<tr>
<td>Dapsone (Aczone)</td>
<td>Inhibits folic acid metabolism</td>
<td>Leprosy, pneumonia in AIDS, acne, dermatitis herpetiformis*</td>
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*Dematitis herpetiformis is an extremely itchy IgA-mediated allergic reaction to gluten.*
Isoniazid (INH)

Kinetics/Dynamics

• PO/IM
  – Never used alone (resistance is common)
  – Bactericidal/Bacteriostatic
    • TB goes through slow-fast growth cycles
    • INH kills actively growing bacteria
  – Several forms available
    • IM, syrup, pills
      – PO ↓ by Al\textsuperscript{++} antacids
• P450 inhibitor & MAOI

INH Metabolism Issue

• INH metabolized by Phase 2 acetylation
• 50\% of blacks & whites are “slow” acetylators
  – \( t \frac{1}{2} \) is between 2-5 hours
  – > risk for toxicity
• 80\% of Asians & Eskimos are “fast” acetylators
  – \( t \frac{1}{2} \) is between 30-90 minutes
  – Fast acetylators more likely to experience treatment failure
Isoniazid (INH)

- ADRs
  - **Peripheral neuropathy** (most common serious ADR)
    - ↑ risk in slow acetylators, malnourished, alcoholics, diabetics
    - Dose related (*protect against neuropathy with Vitamin B₆*)
    - Typically preceded by paresthesias of hands and feet
  - **Boxed Warning: Fatal hepatitis**
    - Check liver function after 2 weeks (*and possibly thereafter*)
    - Age, Alcohol & Hepatitis B infection ↑ risk of fatal hepatitis
  - **Seizures** (*status epilepticus* possible), encephalitis, psychosis
  - Blood dyscrasias
    - Agranulocytosis, aplastic anemia, thrombocytopenia
  - **Hyperglycemia**
  - Hypertensive crisis (*due to MAOI activity*)
Isoniazid (INH)

- Toxicity often manifested by:
  - CNS effects
    - Visual hallucinations
      - Bright colors, strange patterns
    - Dizziness
    - Slurred speech
    - Seizures
    - Respiratory depression, coma
  - Severe metabolic acidosis
    - Nausea, vomiting
Rifampin (Cavidin, Mycostat) 

Kinetics/Dynamics

• PO/IV infusion
  – Wide spectrum, and bactericidal, but only used as 1st line TB in combo therapy due to resistance

• P450 inducer

• Mechanism
  – Inhibits transcription of DNA into mRNA by blocking DNA-dependent RNA polymerase
  – End result is to inhibit protein synthesis

Rifampin causes secretions (tears, sweat, saliva, urine, vaginal secretions…) to turn bright orange or an orangey-red color. It’s harmless, but can cause PERMANENT staining, even of contact lenses!

BACTERICIDAL
Dapsone (Aczone)

Kinetics/Dynamics

- PO, topical
  - Long $t\frac{1}{2}$ of about 30 hours
  - Resistance is common
  - Don’t take with grapefruit juice
  - Use caution with G6PD
- Indicated for leprosy, pneumonia in HIV-AIDs, acne and dermatitis herptiformes
- Mechanism is like sulfonamides, it interferes with folate metabolism
  - Leprostatic