The ABCs of Antibiotics

Approach to Antibiotics

Mechanism of Action

Cell Wall
- β-Lactams: Penicillin Superclass
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Monobactams
- Glycopeptides: Vancomycin

Protein Synthesis
- 30S ribosome
  - Aminoglycosides
  - Tetracyclines
- 50S ribosome
  - Chloramphenicol
  - Macrolides
  - Ketolides
  - Lincosamides
  - Oxazolidinones
  - Streptogramins

Other
- Fusidic acid
- Mupirocin

Cellular metabolism
- Folate Metabolism: Sulfonamides

DNA replication
- Quinolones
- Rifamycins
- Nitrofurans/Nitroimidazoles (via radicals)

Membrane disruption
- Cyclic polypeptides: Polymixins
- Lipopeptides: daptomycin

Unknown or Other
Antimicrobial Spectrum

The World of Germs
This list is not complete; Genera are shown as examples.

Aerobic Gram positive [Cocci]

- *Staphylococcus*
  - *Staphylococcus aureus* is the major pathogen
  - Other *Staphylococci* are relative resistant and compose a small number of cases.

- *Streptococcus*
  - β− hemolytic Streptococci (Groups A-G)
  - *Streptococcus pneumoniae*
  - Other *Streptococci*
  - *Enterococcus*

Gram positive rods are variable in sensitivity, and generally follow *Streptococci*

Aerobic Gram negative [Rods]

- Community acquired
  - *Escherichia coli*
  - *Klebsiella spp.*
  - *Proteus*
  - *Hemophilus*

- Healthcare acquired
  - *Pseudomonas aeruginosa*
  - *Stenotrophomonas*
  - *Acinetobacter*
  - *Serratia marcescens*

Anaerobes

- Above the diaphragm: many Gram positive anaerobes, less resistant
  - *Peptostreptococcus*
  - *Fusobacterium*

- Below the diaphragm: many Gram negative and Gram positive
  - *Bacteroides fragilis*

Other

- *Spirochetes*
- *Mycoplama*
- *Rickettsia*
- *Chlamydia*
- *Mycobacteria*
- *Legionella*

Drug Delivery

- Route of administration
- Absorption and half-life
- Distribution
- Pharmacokinetic
  - Minimum inhibitory and bacteriocidal concentration
  - Time dependent killing or Concentration dependent killing

Toxicity

- Allergic
  - Related to mechanism of action
  - *C. difficile* colitis
  - Increased PT
  - Overgrowth and candidiasis
- Chemical adverse effects
Drug interactions

Cost

Gram negative
- Community Associated
- Resistant
- Above

Gram positive
- Enterococcus
- Streptococcus
- Staphylococcus

Anaerobes

Other
Specific Antibiotic Classes

β-Lactams

Mechanism
• Bind to penicillin binding proteins, Inhibit cell wall cross-linking
• Resistance patterns
  • breaking open the β-lactam ring
  • changing the target binding protein
  • limiting the access to active sites
Penicillins

Penicillin & Aminopenicillins

Examples
Penicillin G, V, Ampicillin, Amoxicillin

Pharmacokinetics
- Available P.O. or IV or IM depo
- Short half-life. Both renal and hepatic excretion
- Oral form is partially absorbed: levels much lower PO than IV
  penicillin G vs. V, amoxicillin vs. ampicillin
- Distributed outside cells.
- Crosses inflamed blood brain barrier, much lower otherwise.

Toxicity
- Well tolerated. Long(est) track record.
- Allergic reactions (0.7-4%).
- Anaphylaxis (0.004-0.015%)
- Skin rash.
- Renal toxicity (interstitial nephritis)
- Seizures at high doses

Cost: inexpensive

Spectrum of penicillins

Gram negative

Gram positive

Ampicillin
Spirochetes
Anaerobes
Other
• Penicillinase-resistant Penicillins

• Examples:
  - Nafcillin (IV)
  - Dicloxacillin (PO)
  - Methicillin (no longer used), Oxacillin

• Pharmacokinetics

- Toxicity
  - Interstitial nephritis may be higher
- Cost: Moderate
Extended-spectrum Penicillins

- Examples
  - Piperacillin, Mezlocillin, Ticarcillin
- Pharmacokinetics
  - IV only
- Spectrum

- Gram negative
- Gram positive
- Anaerobes
- Other

similar to penicillin PLUS
Gram negatives
includes most gram negatives including pseudomonas aeruginosa
losing ground against E. coli!
**Beta-Lactamase inhibitors**

- **Examples**
  - Ampicillin/Sulbactam (IV) [Unasyn]
  - Amoxicillin/Clavulanate (PO) [Augmentin]
  - Piperacillin/Tazobactam (IV) [Zosyn]
  - Ticarcillin/Clavulanate (IV) [Timentin]

- **Pharmacokinetics**
  - similar to cephalosporins & penicillins
  - how the mixture varies at different sites is not clear

- **Spectrum**
  
  **Ampicillin/Sulbactam**

  
<table>
<thead>
<tr>
<th>Gram negative</th>
<th>Gram positive</th>
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<tr>
<td>Anaerobes</td>
<td>Other</td>
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Piperacillin/Tazobactam (Zosyn)

**Gram negative**
- Extends gram-positive activity to most oxacillin sensitive *Staphylococcus aureus*
- Gram negatives
  - Extends activity to some *E. coli, Klebsiella*, and *Hemophilus* spp.
  - No activity against usual hospital acquired gram negatives (*Pseudomonas*) beyond β-lactam alone.

**Anaerobes**
- Anaerobic spectrum excellent
- Cost: moderate to high
- Role
  - mixed, community acquired infection
    - i.e. mouth infections, aspiration pneumonia (not hospital- or community-acquired pneumonia.)
  - not for UTI, urosepsis
- Lost art: removing the β-lactamase inhibitor and treating with piperacillin or ampicillin alone.
1st Generation Cephalosporins

- Examples:
  - Cephalexin (Keflex) (PO)
  - Cefazolin (Ancef, Kefzol) (IV)
- Pharmacokinetics
  - Variable, less reliable oral absorption
  - Do not penetrate the blood brain barrier
- Spectrum
  - ***** NO enterococcus in any cephalosporin *****

- Cost: Moderate
2nd Generation Cephalosporins

- **Examples**
  - Cefoxitin (IV)
  - Cefotetan (IV)
  - Cefuroxime (IV, PO)
  - Cefaclor (PO)

- **Pharmacokinetics**
  - Very short half lives
  - Do not reliably cross the blood-brain barrier

- **Spectrum**
  - **Gram negative**
    - Cefoxitin and Cefotetan
    - Only
  - **Gram positive**
  - **Anaerobes**
  - **Atypical Mycobacteria**
  - **Other**

Gram positive
- Less active against Staphylococcus
- Reasonable streptococcal activity
- Remember: NO enterococcus activity

Gram negative
- Expands spectrum to many *Hemophilus influenzae*
- Community acquired gram negatives
- Anaerobes
  - Substantial anaerobic capacity in cefoxitin and cefotetan

**Cost**
- Oral: high. Don’t use Cefaclor.
- Parenteral: Moderate
3rd Generation Cephalosporins

- Examples
  - Cefotaxime (IV) (Claforan)
  - Ceftriaxone (IV) (Rocephin)
  - Ceftazidime (IV) (Fortaz)
  - Cefepime (IV) (Maxipime)
  - Cefpodoxime proxitin (PO) (Vantin)
- Pharmacokinetics
  - Cross inflamed blood-brain barrier
- Spectrum
  - Gram negative
  - Gram positive
  - Cefepime & Ceftazidime
  - Spirochetes
  - Actinomycetales
  - Anaerobes
  - Other

- Ceftazidime covers *Pseudomonas*, but loses gram positive activity.
* Cefepime covers *Pseudomonas* and gram positives. (Cefepime = Ceftriaxone + ceftazidime)
* Other cephalosporins relatively weak against hospital-acquired gram negatives.

Cost: Moderate to High
Carbapenem

- Imipenem with cilastin (IV, IM) (Primaxin)
  Meropenem (Merrem)
  Ertapenem (Invanz)
- Pharmacokinetics
  * All IV
  * Similar to cephalosporins
- Toxicity
  * Central nervous system side effects are frequent (Seizures)
    10%+ cross reactive with PCN (more than cephalosporins)
- Spectrum

Gram negative

Gram positive

Anaerobes

Other

- Cost: High
- Role
  - Imipenem: drug of last resort; too broad for general use
  * Ertapenem has a role in abdominal or broad spectrum coverage. Cheaper than pip/tazo (Zosyn)
Monobactam

- Aztreonam (IV) [Azactam]
- Pharmacokinetics
  - similar to cephalosporins & penicillins
  - does not provide synergy with other beta-lactams
  - modest CSF penetration
- Spectrum
  - exclusively aerobic gram negative rods
  - includes some Pseudomonas activity
- Toxicity
  - no renal toxicity
  - similar to cephalosporins & penicillins
  - minimal (no?) cross reaction with penicillin allergy
- Cost: High
- Role
  - monotherapy for gram negative infections
  - when the renal toxicity of aminoglycosides must be avoided.
Vancomycin

Pharmacokinetics
- Renal elimination
- The MIC is gradually increasing
- Narrow therapeutic index
  - some (not all) advise following trough levels

Spectrum

- Almost all gram positive organisms
- No other coverage

Toxicity
- Red man syndrome
  - seen following rapid IV administration
  - Erythema ± hypotension
- Vestibular
- Renal is now very infrequent

Cost: high

Role
- Gram positive infections where the likelihood of resistance is high.
  Restricted because of the development of Vancomycin Resistance in Enterococci (VRE)
Aminoglycosides

Examples
- Gentamycin, Tobramycin, Amikacin

Pharmacokinetics
- renal elimination
- low therapeutic index, drug level monitoring important
- not active in an acid environment (limits activity in abscesses, pneumonia)
- do not penetrate the CNS

Spectrum: Gram negative rods.

Activity against GPC is usually not enough alone.

synergy noted with some organisms
Pseudomonas aeruginosa

Toxicity
- renal toxicity in 5-25 %
  - correlates with trough levels > 2
- auditory and vestibular toxicity
- rare neuromuscular junction blockade

Cost
- drug is very cheap
- monitoring adds to this cost

Role
- serious gram negative infections
- combination therapy against gram negatives or gram positives
Macrolides

Erythromycin & Analogues

- Examples
  - Erythromycin (IV, PO)
  - Azithromycin (PO) [Zithromax]
  - Clarithromycin (PO) [Biaxin]
- Pharmacokinetics
  - Excellent tissue penetration (but not CSF)
  - Concentrates within cells (Azithromycin > Clarithromycin >> erythromycin)
    May have higher concentrations at site of infection than in serum.
- Very long tissue half life for Azithromycin

- Spectrum

  **Gram Negative**
  - Streptococcus
  - Staphylococcus
  - Chlamydia
  - Legionella
  - Mycoplasma
  - Mycobacteria

  **Gram Positive**
  - Community acquired

  **Anaerobes**
  - Limited gram negative coverage
    azithromycin and clarithromycin have some activity against H. influenza

- Toxicity
  - GI toxicity
    greatest with erythromycin (10-20%)
    even when taken IV
  - Thrombophlebitis
  - Cost: low to high (0.60 to 6.00/day)
• Role
  • respiratory tract infections
  • treating streptococcal or staphylococcal infections in the presence of serious penicillin allergy

Clindamycin (IV, PO) [Cleocin]

• Pharmacokinetics
  • Well absorbed by mouth

• Spectrum
  • Gram negative
  • Gram positive
  • Anaerobes
  • Other
  • Chlamydia

• Toxicity
  • notorious correlation with *C. difficile* colitis
  • allergy

• Cost: Moderate

• Role
  • anaerobic infections
  • mixed infections (usually in combination)
  • deep seated gram positive infections
Folate Antagonists

Examples
• Sulfa drugs (many)
• Trimethoprim/sulfamethoxazole (IV, PO) [Bactrim, Septra]

Pharmacokinetics
• Excellent tissue penetration (including CNS)
• Bacteriostatic

Spectrum

Toxicity
• Allergy may be severe
• GI
• Hepatic
• Megaloblastic anemia

Cost: Low

Role
• Urinary tract infections
• Traveler’s diarrhea
Quinolones

Examples:
- Ciprofloxacin [Cipro]
- Norfloxacin [Noroxin]
- Ofloxacin [Floxin], Levofloxacin [Levaquin]
- Gemifloxacin [Factiv]
- Moxifloxacin [Avalelox]

Pharmacokinetics
- Well absorbed orally, reaching IV levels

Spectrum

Ciprofloxacin

- Gram negative
- Gram positive
- Anaerobes
- Other

Urine Only

Respiratory quinolones

- Gram negative
- Gram positive
- Mycobacterium
- Legionella
- Anaerobes
- Other

- Gram negative bacilli
- Gram positive cocci
  - enterococcus in urine only
  - resistance among streptococci and staphylococci is growing rapidly
- Good potential in atypical infections

Toxicity
- Must not be used in children <18 or in pregnancy
- Allergy
- CNS

Role
- Urinary tract infections & Traveler’s diarrhea
- 2\textsuperscript{nd} line for respiratory infections.
Others

Metronidazole

- **Mechanism**
  - Anaerobic cleavage of DNA
- **Pharmacokinetics**
  - Oral absorption is excellent
- **Spectrum**
- **Toxicity**
  - CNS (rare)
  - Disulfiram reaction with alcohol
  - Peripheral neuropathy
- **Use**
  - Treating mixed infections
  - C. difficile colitis

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Tetracycline

- **Examples**
  - Tetracycline (po)
  - Doxycycline (po) [Vibramycin]
  - Minocycline
  - Tigecycline [Tygacil]
- **Mechanism**
  - Interferes with protein synthesis at the 30S part of the ribosome
- **Pharmacokinetics**
  - Good tissue penetration
- **Spectrum**
- **Toxicity**
  - Do not use in children < 8 yo (teeth & bones)
Chloramphenicol

• Pharmacokinetics
  - Well absorbed.
  - Excellent CSF penetration
• Broad spectrum
  - Anaerobes
  - Atypical
    - Chlamydia
    - Rickettsia
    - Mycoplasma
    - spirochetes
• Gram negative
  - includes Salmonella
• Toxicity
  - Hematologic
    - dose related anemia (4g/day)
    - aplastic anemia 1:24,000-40,000
• Gray Baby Syndrome (Neonatal)
• Optic neuritis

Rifamycins

Example
  - Rifampin, rifabutin, rifaxamin
Mechanism
  - Interferes with synthesis of RNA polymerase, needed for protein synthesis.
Pharmacokinetics
  - Well absorbed
  - Widely distributed
Spectrum

Toxicity
  - Allergic
  - Body fluids tinged orange
  - Aggravates hepatic injury by other drugs.
Role
  - Treat TB, Leprosy
  - Synergy in treating prosthetic devices
Oxazolidinones

Example
Linezolid (Zyvox) IV, PO

Mechanism
Interferes with protein synthesis.

Pharmacokinetics
Well absorbed
Widely distributed

Spectrum
Gram positive
Gram negative
Anaerobes
Other

Toxicity
Thrombocytopenia, marrow suppression
Serotonin syndrome (MAOI)

Role
Resistant Gram positive Infections
Etiologies of common Infections

Urinary Tract Infections

Almost all *E. coli*, other GNR, and *Enterococcus*

Cellulitis

Almost all *Streptococcus pyogenes* (and other β-hemolytic Streptococci) with some *Staphylococcus aureus*. 
Wound Infections

*Staphylococcus aureus* is the leading etiology; Streptococci still play a significant role. A greater diversity of organisms than simple cellulitis. With antibiotic exposure and over time, it shifts toward GNR and resistant organisms. Anaerobes are seen most often when there is dead or ischemic tissue.

Community acquired pneumonia

*Streptococcus pneumoniae* plays a prominent role in almost every population.