Introduction to Antimicrobials

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What are antimicrobials?

- Drugs that destroy microbes, prevent their multiplication or growth, or prevent their pathogenic action
- Differ in physical, chemical, pharmacological properties
- Differ in antibacterial spectrum of activity
- Differ in their mechanism of action

Antibiotic Classes (by mechanism of action)

- Inhibit cell wall synthesis
  - Penicillins
  - Cephalosporins
  - Monobactams (aztreonam)
  - Carbapenams
  - Glycopeptides (vancomycin)
- Inhibit protein synthesis
  - Aminoglycosides
  - Tetracyclines
  - Glycylcycline (tigecycline)
  - Macrolides (azithromycin, clarithromycin)
  - Lincosamides (clindamycin)
- Alter nucleic acid metabolism
  - Rifamycins
  - Quinolones
- Inhibit folate metabolism
  - Trimethoprim
  - Sulfonamides
- Inhibit protein synthesis
- Alter nucleic acid metabolism
- Inhibit folate metabolism
- Other mechanisms

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  - Sulfonamides
- Miscellaneous
  - Metronidazole
  - Lipopeptides (Daptomycin)
  - Polymyxins

Antibiotic Targets
**Beta-lactams**
- All contain the beta-lactam ring with 3 carbon atoms and one nitrogen atom
- Inhibit synthesis of the peptidoglycan layer of the cell wall by blocking the action of transpeptidases (penicillin binding proteins)
- Includes: penicillins, cephalosporins, monobactams, and carbapenams

**Vancomycin (Glycopeptide)**
- Inhibits cell wall synthesis by interfering with peptidoglycan synthesis.
- It does this by binding to the D-Ala-D-Ala terminals of N-acetylmuramic acid (NAM) and N-acetylglucosamine (NAG) peptide subunits localized at the outer surface of the cell membrane.
- As a result, these subunits cannot incorporate into the peptidoglycan matrix.
- With a rare exception, only active against gram positive bacteria

**Protein Synthesis Inhibitors**
(inhibit translation of bacterial proteins in various ways)
- **Rifamycins (rifampin)**
  - Mechanism of action:
    - Blocks mRNA synthesis (prevents transcription of bacterial DNA)
    - Does this by binding to the bacterial DNA-dependent RNA polymerase
  - Used in combination with other antimicrobials (only used alone as prophylaxis for *N. meningitidis*)
Quinolones

- Inhibit DNA synthesis
- Inhibit the topoisomerases responsible for supercoiling DNA (DNA gyrase) and relaxing the supercoiled DNA (topoisomerase IV)
- Examples: ciprofloxacin, levofloxacin, moxifloxacin

Inhibitors of Folate Metabolism

- Examples: trimethoprim, sulfonamides
- Often given in combination (example: trimethoprim-sulfamethoxazole)

Metronidazole

- Diffuses into the cell and is reduced
- Metronidazole free radicals interfere with organism DNA causing breakage, destabilization and cell death
- Active in anaerobes and select parasites such as Entamoeba and Giardia

Metronidazole: mechanism of action in anaerobes

Daptomycin (Lipopeptide)

- Binds to the cell membrane of gram-positive organisms in a calcium-dependent process and disrupts the bacterial cell membrane potential causing ion leakage and cell death.

Polymyxins

- Polymyxins destroy bacterial membranes with a surface detergent–like mechanism by interacting with membrane phospholipids and increasing cellular permeability.
- Only active against Gram negative bacteria (do not have access to the bacterial cell membrane in Gram positives and resistant Gram negatives)
How are antibiotics used?

- **Empiric therapy**
  - Often ‘broad spectrum’
- **Definitive therapy**
  - If possible, initial empiric therapy should be changed to an antibiotic with a narrower spectrum of activity
- **Prophylactic or preventative therapy**

Culture and Sensitivities

- Identify the pathogen
- Determine the sensitivity of the organism to various antibiotics
  - is it ‘sensitive’, ‘intermediate’, or ‘resistant’?
- Sensitivity is determined by the interpretation of the **minimum inhibitory concentration (MIC)** which is the lowest concentration of antibiotic that prevents visible bacterial growth after 24 hours of incubation in the appropriate culture media

Antibiotic Spectrum

- **Broad Spectrum**
  - Covers many potential pathogens (example: a carbapenam which has Gram positive, Gram negative, and anaerobic coverage)
- An antibiotic with a **narrower spectrum** has a more targeted spectrum of activity
  - Example: clindamycin which only has Gram positive and anaerobic coverage—no Gram negative coverage)

The MIC

- The MIC is organism and drug specific
- ‘Susceptible’ implies that the concentration of antibiotic that can be achieved at the site of infection is >MIC
- Numerous ways to determine the MIC
  - Kirby–Bauer disk diffusion
  - Broth dilution
  - E-test
When choosing and dosing an antibiotic, consider:

- **Pharmacodynamics** (what the drug does to the body/bacteria)
  - Desirable effects
    - Cidal vs static
    - Concentration vs time-dependent killing
    - Post antibiotic effect
  - Undesirable effects
    - Toxicity (e.g., nephrotoxic, hepatotoxic, ototoxic, etc)
    - Allergy
    - Antibiotic-associated diarrhea or *C. difficile* colitis

When choosing and dosing an antibiotic, also consider:

- **Pharmacokinetics** (what the body does to the drug):
  - Absorption (consider food/drug interactions)
  - Distribution (does it get where it needs to go in the right concentration?)
  - Metabolism (will it be metabolized properly, are there drug-drug interactions?)
  - Excretion
    - Renal vs nonrenal
    - Half life (time for the blood concentration to decrease by half)
Using antibiotics in combination

- Synergism
- Antagonism
- Indifference

Case

- A 19 YO college student complains to her friends that she has a headache and neck stiffness.
- The next morning her roommate is unable to wake her and EMS is called
- Exam: temp 102, RR 24, BP 90/45, P 120, patient is lethargic with nuchal rigidity, photophobia, and a petechial rash

Case Continued

- Bacterial meningitis is suspected in the ER.
- Before a lumbar puncture is performed, she is given broad spectrum coverage with vancomycin (glycopeptide) and ceftriaxone (3rd generation cephalosporin)
- Lumbar puncture draws cloudy fluid.
- CSF analysis reveals leukocytosis w/90% PMNs, low glucose and high protein, consistent with bacterial meningitis.

Case Continued

- Gram stain of the CSF reveals Gram negative diplococci
- Culture grows *Neisseria meningitidis* type B (not covered by vaccine)

Case Continued

- The diagnosis of meningococcal meningitis is made and vancomycin is discontinued (ceftriaxone is continued as definitive treatment).
- The health department is contacted and the patient’s close contacts, including her roommate and boyfriend, are given rifampin for prophylaxis.

Case Continued

- The patient requires treatment in the ICU, but recovers.
- Her boyfriend is shocked to discover that his pee turned orange after taking the rifampin (this is from rifampin, but no one warned him)!
**Case Continued**

- A health care worker who had almost no contact with the patient is paranoid that he will get infected and takes ciprofloxacin as prophylaxis, despite health department recommendations.
- This worker develops *C. difficile* colitis requiring treatment with metronidazole.
- No one tells him not to drink alcohol on the metronidazole. When he does he has a disulfiram–reaction (flushing, throbbing, headache, copious vomiting, etc!)

**Heed this Warning**

- Use discretion when prescribing antibiotics. Indiscriminate use promotes antibiotic resistance and unnecessarily puts patients at risk for adverse reactions.
- One of Lowy’s Laws: It is always the patient who didn’t need the antibiotic to begin with who has the worst reaction.

The End!

Good luck with your antibiotic choices!