Fundamental Antimicrobial Concepts

**Objectives**

1. Describe the different pharmacokinetic characteristics of antibiotics
2. Interpret important data from an antibiogram
3. Understand antibiotic selection and therapy by becoming familiar with major classes and spectrum of activity
4. Analyze newer antibiotic agents and their role in the treating infections

* **Minimum Inhibitory Concentration (MIC)**
  1. The lowest concentration of an antimicrobial that will inhibit the growth of the bacteria
* **Minimum Bactericidal Concentration (MBC)**
  1. The lowest concentration of an antimicrobial that will kill a bacteria
* **Area Under the Time Concentration Curve (AUC)**
  1. Pharmacodynamic parameter that represents the total drug exposure or concentration over time. It is dependent on the rate of elimination of a drug from the body.
* **Concentration-Dependent Killing**
  1. Bacteria are killed by achieving high concentrations. The rate and extent of bacterial killing are directly related to the concentration of the antibiotic at the binding site.
  2. The most important pharmacodynamic parameter for these types of antibiotics is peak/MIC
  3. The target is a concentration that is ≥10 above the MIC
* **Time-Dependent Killing**
  1. The rate of bacterial killing remains unchanged regardless of concentration as long as the antibiotic remains above the MIC ≥ 50% of the time
  2. The most important pharmacodynamic parameter for these types of antibiotics is time > MIC
* **Post Antibiotic Effect (PAE)**
  1. The continued suppression of bacterial growth after the antibiotic has finished being administered and its concentration is below the MIC
* **Bacteriostatic vs Bactericidal**
  1. Bactericidal antibiotics kill bacteria directly and bactericidal antibiotics keep the bacteria from growing



|  |  |  |
| --- | --- | --- |
| **Time-Dependent**  **(with minimal or no PAE)** | **Time-Dependent**  **(concentration enhanced with PAE)** | **Concentration-Dependent**  **(with PAE)** |
| * Beta-lactams * Vancomycin | * Macrolides (clarithromycin and erythromycin * Lincosamides * Oxazolidinones * Tetracyclines * Glycylcyclines * Carbapenems * Vancomycin | * Aminoglycosides * Macrolide (azithromycin) * Fluoroquinolones * Metronidazole * Ketolides * Daptomycin |

|  |  |
| --- | --- |
| **Bacteriostatic** | **Bactericidal** |
| * Tetracycline * Macrolides * Lincosamides * Oxazolidinones | * Penicillins * Cephalosporins * Monobactams * Carbapenems * Vancomycin * Aminoglycosides * Fluoroquinolones * Metronidazole * Sulfonamides * Daptomycin * Nitrofurantoin |

* **Common Mechanisms of Resistance**
  1. Decreased permeability – fewer porins or active efflux proteins that keep drugs out
  2. Metabolic proteins – proteins that degrade the drug, i.e. beta-lactamases
  3. Alteration of substrate – affinity for the drug is reduced because the target has been changed – if the drug can’t bind then it can’t have an effect.
  + **Penicillin and cephalosporin:** beta-lactamases; change in PBPs; change in porins
  + **Aminoglycosides:** formation of enzymes that inactivate drugs by conjugation reactions
  + **Macrolides:** altered drug binding sites; active transport out of cells
  + **Tetracyclines:** efflux pumps
  + **Sulfonamides:** alteration of substrate
  + **Fluoroquinolones:** alteration of substrate; efflux pumps
* **Antibiotic Review**

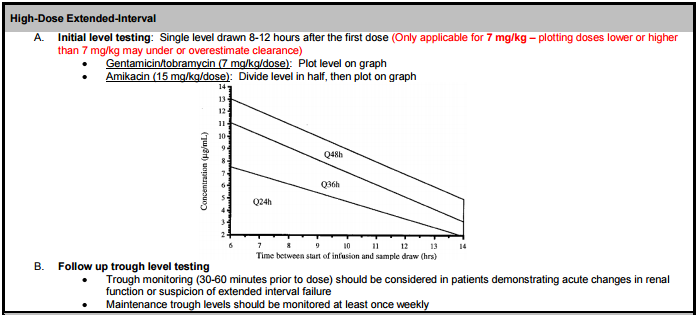
1. **Penicillin**

* **Natural penicillin** – Penicillin V (oral) and Penicillin G (IV)
  + **Mechanism of Action (MOA)**: Inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs)
  + **Antimicrobial spectrum:** *Streptococcus* species and oral cavity anaerobes
  + Take without food
* **Penicillinase-resistant penicillin**: Methicillin, nafcillin, oxacillin, dicloxacillin
  + **MOA:** Inhibits bacterial cell wall synthesis by binding to PBPs
  + **Antimicrobial spectrum:** *Staphylococcus (not MRSA) and streptococcus* species
* **Aminopenicillin** – Ampicillin and Amoxicillin
  + **MOA**:Inhibits bacterial cell wall synthesis by binding to PBPs
  + **Antimicrobial spectrum:** same as Pen VK plus *listeria monocytogenes, Enterococcus, Proteus mirabilis,*  and some strains of *E coli*
  + Amoxicillin has the same chemical structure as ampicillin but with an added hydroxyl group for increased oral absorption and decreased dose interval
* **Beta-lactam/beta-lactamase inhibitor:** Amoxicillin-clavulanate
  + **MOA:** Inhibits bacterial cell wall synthesis by binding to PBPs
  + **Antimicrobial spectrum:** same as Aminopenicillin but added beta-lactamase producing strains of MSSA, *Haemophilus influenza*  and *Moraxella catarrhalis*
  + Know which pediatric dosage forms to use in pediatric infections and why
* **Expanded spectrum anti-pseudomonal penicillin**: Piperacillin-tazobactam
  + **MOA:** Inhibits bacterial cell wall synthesis by binding to PBPs
  + **Antimicrobial spectrum:** all of the above plus *Pseudomonas*  and anaerobic bacteria
  + Avoid use in suspected or proven ESBL gram negative bacilli infections
  + Continuous and extended infusions – 4.5gm over 30minutes then 3.375mg q8h infused over 4 hours

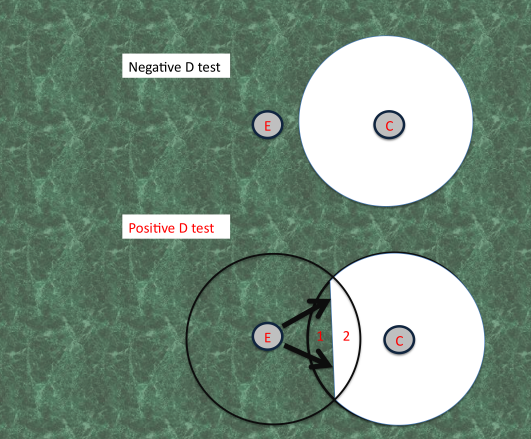
1. **Cephalosporin**

* **Beta-lactam allergy cross-reactivity**
  + Once believed that rate was 15-20% but in reality the true rate of reaction is < 2%
  + Rates of cross-reactivity increase with beta-lactams that share common side chains
    - Amoxicillin – Ampicillin – Cefadroxil – Cephalexin – Cefprozil
    - Ceftazidime – Aztreonam
    - Penicillin G – Cefoxitin
* **1st Generation** – Cephalexin (PO), cafadroxil (PO), cefazolin (IV)
  + **MOA:** Inhibits bacterial cell wall synthesis by binding to PBPs
  + **Antimicrobial spectrum**:
    - Gram +: MSSA, *Strep* Group A,B,C,F,G; Poor *Strep pnuemo* coverage
    - Gram - : *Proteus, E. Coli, Klebsiella* - **PEcK**
* **2nd Generation** – Cefprozil (PO), cefuroxime axetil (PO), cefuroxime (IV), cefoxitin (IV), cefotetan (IV)
  + **MOA:** Inhibits bacterial cell wall synthesis by binding to PBPs
  + **Antimicrobial spectrum**:
    - Gram +: MSSA, *Strep* Group A,B,C,F,G; Poor *Strep pnuemo* coverage
      * Action against Gram + cocci is generally not as strong as 1st generation
    - Gram - : *Haemophilus inf, Enterobacter, Neisseria, Proteus, E. Coli, Klebsiella, Serratia m* - **HEN** **PEcKs**
    - The cephamycins have added coverage against anaerobes
      * Cefoxitin and cefotetan
      * Active *in vitro* against ESBL bacteria but no clinical evidence to support
* **3rd Generation** – Cefdinir (PO), cefixime (PO), ceftriaxone (IV), cefotaxime (IV), ceftazidime (IV)
  + **MOA:** Inhibits bacterial cell wall synthesis by binding to PBPs
  + **Antimicrobial spectrum**: same as above generations but with better Gram + coverage and can now be used for *Strep pnuemo*
    - Added Gram – coverage to *Pseudomonas* for ceftazidime only
  + Ceftriaxone and and cefotaxime have good CNS penetration
  + Ceftriaxone and cefazolin (1st gen) have highest levels in the bile
* **4th Generation** – Cefepime (IV)
  + **MOA:** Inhibits bacterial cell wall synthesis by binding to PBPs
  + **Antimicrobial spectrum:**  added coverage for *Pseudomonas* and better coverage of MSSA than 3rd generation
  + Chemical structure allows for better penetration into gram negative bacilli
  + Can be used against most beta-lactamase producing bacteria
  + Can be used against ESBL producing gram negative bacilli if given at highest doses
    - Carbapenems still recommended for ESBL bacteria
* **5th Generation** – Ceftaroline (IV)
  + **MOA:** Inhibits bacterial cell wall synthesis by binding to PBPs
  + **Antimicrobial spectrum:** 
    - Binds to PBP 2a - active against MRSA and MRSE
    - Not active against *Psedomonas*
    - Similar gram negative coverage to ceftriaxone
    - Not recommended for *Enterococci* or anaerobic infections

1. **Carbapenems** – Ertapenem, meropenem, doripenem, imipenem-cilistatin (all IV)
   * **MOA:** Inhibits bacterial cell wall synthesis by binding to PBPs
   * **Antimicrobial spectrum:** Covers gram positive, gram negative and anaerobes with the exception of MRSA. All carbapenems cover *Pseudomonas*  except ertapenem
     + Broadest spectrum of any beta-lactam
   * Drug of choice for ESBL producing gram negative bacilli
     + If resistant to ESBL producing bacteria then ertapenem has the highest rates
   * Allergy cross-reactivity
   * Seizures
     + Most recent meta-analysis show that carbapenems have highest rate of seizures compares to other beta-lactams
     + Likely due to the drug binding to GABA receptors
2. **Aminoglycosides** – Gentamicin, tobramycin, amikacin
   * **MOA:** Interferes with bacterial protein synthesis by binding to 30S and 50S ribosomal subunits resulting in a defective bacterial cell membrane
   * **Antimicrobial spectrum:**
     + Aerobic gram-negative bacilli (including *Pseudomonas*)
     + No activity against anaerobic organisms
     + *Staphylococcus aureus* may be susceptible *in vitro* but is resistant when used as single therapy - often used in combination with other antibiotics for synergy
   * Hartford Nomogram



1. **Glycolipopeptides** – Vancomycin
   * **MOA:** Inhibits bacterial cell wall synthesis by blocking glycopeptide polymerization through binding tightly to the D-ala-D-ala portion of a cell wall precursor
   * **Antimicrobial spectrum:** 
     + Most common empiric antibiotic selection for MRSA or MRSE; no gram negative coverage
   * Initial doses are based on actual body weight (including the obese) and subsequent doses based on trough values
     + 25-30 mg/kg loading dose in severely ill followed by 15-20mg/kg/dose q8-12h
     + Draw trough prior to 4th dose
     + Target troughs of 15-20 mcg/ml
     + Peaks are not necessary
     + MIC > 4 then VISA
     + MIC > 8 then VRSA
   * Obesity (BMI > 40) and CrCl >50
     + 30mg/kg/day q8h
     + CrCl for morbidly obese – Salazar-Corcoran
2. **Fluoroquinolones** – Levofloxacin (IV, PO), ciprofloxacin (IV, PO), moxifloxacin (IV, PO)
   * **MOA:**  inhibits DNA-gyrase in susceptible organisms
   * **Antimicrobial spectrum:** 
     + Best activity is against gram negative bacilli - *Enterobacter, Pseudomonas* and *Haemopholis*
     + Also have activity against common respiratory pathogens – *Strep pneumo, Haemopholis, Moraxella, Legionella, Chlamydia and Mycoplasma*
   * Moxifloxacin has better anaerobic and *Staph* coverage
     + Does not need to be used in combination with metronidazole for the treatment of intra-abdominal infections whereas ciprofloxacin and levofloxacin do
   * Ciprofloxacin has the most potency against aerobic gram negative bacilli
   * Levofloxacin and moxifloxacin are more active against respiratory bacteria than ciprofloxacin
   * Ciprofloxacin has better *Pseudomonas* coverage and Levofloxacin and Moxifloxacin have better *Strep pneumo* coverage
3. **Macrolides** – Azithromycin (IV, PO), erythromycin (IV, PO), clarithromycin (PO)
   * **MOA:** Inhibits RNA-dependent protein synthesis at the chain elongation step and binds to the 50S ribosomal subunit
   * **Antimicrobial spectrum:** Aerobic and anaerobic gram-positive cocci (except for most *Enterococci* and many *Staphylococcus* strains); *Strep pneumo* and *Strep pyogenes* strains; also cover atypicals
   * Common is GI upset (20-25%) Erythromycin > Azithromycin and Clarithromycin
     + Activate motilin
   * Avoid use in QTc prolongation
4. **Lincosamide** – Clindamycin (IV, PO)
   * **MOA:** Reversibly binds to 50S ribosomal subunits preventing peptide bond formation, thus inhibiting bacterial protein synthesis
   * **Antimicrobial spectrum:**
     + *Strep* and *Staph*, *M. catarrhalis*
     + Good anaerobic coverage – *Bacteroides* and most *Clostridium*
     + Not active against *Enterococci, H influenza, or N meningitidis*
   * Often use in combination with other antibiotics to inhibit toxic shock and toxin production
   * D-test
     + A positive D-test indicates the presence of macrolide-inducible resistance to clindamycin



1. **Oxazolidinones** – Linezolid (IV, PO), tedizolid (IV, PO)
   * **MOA:** Inhibits bacterial protein synthesis by binding to bacterial 23S ribosomal RNA of the 50S subunit. This prevents the formation of a functional 70S initiation complex that is essential for the bacterial translation process
   * **Antimicrobial spectrum:** Gram positive cocci – MRSA, MSSA, VREF, *Enterococci* and *Strep* *pneumo*
   * Both with great oral bioavailability
   * MAOI…?
2. **Tetracyclines** – Doxycycline (IV, PO), minocycline (PO), tetracycline (PO)
   * **MOA:** Inhibits bacterial protein synthesis by binding with the 30S and possibly the 50S ribosomal subunits
   * **Antimicrobial spectrum:** 
     + Tetracyclines are considered broad-spectrum antibiotics that treat many aerobic gram-positive and gram-negative bacteria. They also have activity against many atypical pathogens.
   * Hyclate vs. monohydrate
     + Monohydrate may have reduced GI side effects due to slower dissolution but may also be less bioavailable at a higher pH