Appropriate Antibiotic Selection

Elizabeth A. VandeWaa, Ph.D.
Professor, University of South Alabama
College of Nursing
Lecturer, Barkley and Associates

Misuses of Antibiotics
- For treatment of viral infections
- For treatment of FUO
  - except in the immunocompromised host
- In the absence of bacteriologic information
- In inappropriate dosage, patient
- In the absence of other interventions such as drainage, removal of foreign bodies, etc.

Host Factors Affecting Antibiotic Use
- Allergy
- Immune status
  - bactericidal drugs in the immunocompromised host
- Infection site complications
  - BBB, foreign bodies, perfusion
- Age
- Pregnancy and lactation
- Genetics

Selective Toxicity and Mechanism of Antibiotic Action
- Antibiotics have unique mechanisms of action that make them selectively toxic to bacteria
  - Disruption of bacterial cell walls or inhibition of cell wall synthesis
  - Lethal or nonlethal inhibition of bacterial protein synthesis
  - Inhibition of bacterial nucleic acid synthesis
  - Antimetabolites

Antibiotics and their MOA

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Who Should Receive Antibiotic Prophylaxis?

- Certain surgical patients
  - cardiac, peripheral vascular, orthopedic, GI, hysterectomy
- The severely neutropenic patient
- The patient at risk for bacterial endocarditis
- The patient with recurrent UTIs, severe rheumatic endocarditis

Indications for Antibiotic Combinations

- Initial therapy of severe infection
  - until invading organism(s) is identified
- In mixed infections
  - common in GI, pelvic, brain abscesses
- To prevent emergence of resistance
  - TB, HIV, certain parasites
- To decrease toxicity
- To promote a synergistic effect
  - Ampicillin + Gentamicin; Sulfasoxazole + Trimethoprim

Disadvantages of Antibiotic Combinations

- Increased risk of adverse effect such as allergy or toxicity
- Increased risk of suprainfection
- Increased chance for emergence of drug resistance
- Increased cost

Cell Wall Synthesis Inhibitors

- Penicillins
- Cephalosporins
- Carbapenems
- Aztreonam
- Vancomycin
- Teicoplanin
- Fosfomycin

Penicillins

- Inhibit transpeptidase necessary for cell wall synthesis and activate autolysis which cleave bonds in the cell wall. These targets are called PBPs: PBP1 and PBP3 are the most crucial targets.
- Resistance is due to inability of drug to reach the PBPs or enzymatic inactivation of the drug.

Effect Of Beta-lactamase On Penicillins

- The enzyme cleaves open the drug molecule

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**Penicillins: Antibacterial Spectrum**

- **Narrow-spectrum penicillinase sensitive**
  - Pen G, Pen V
  - Useful for Strep spp., Neisseria spp., many anaerobes, spirochetes
- **Narrow-spectrum penicillinase resistant**
  - Nafcillin, oxacillin, cloxacillin, dicloxacillin
  - Useful for Staph aureus

- **Broad-spectrum penicillins**
  - Ampicillin, amoxicillin, ticampicillin
  - Useful for H. influenzae, E. coli, P. mirabilis, N. gonorrhoeae, enterococci
- **Extended-spectrum penicillins**
  - Carbenicillin indanyl, ticarcillin, mezlocillin, piperacillin
  - Useful for same as above plus Pseudomonas, Enterobacter spp., Proteus, Bacterioides fragilis, many Klebsiella spp.

In the Patient with a PCN Allergy…

- Avoid PCNs entirely
- In cases of a mild allergy, a cephalosporin could be used; if anaphylaxis or severe allergy, avoid a ceph (5-10% cross-sensitivity)
- Vancomycin and Erythromycin may be alternatives
- In life-threatening infections when no alternative will do, give PCN according to a desensitization schedule

**Penicillins Combined with a Beta-Lactamase Inhibitor**

- These are extended spectrum agents with limited toxicity; useful against Pseudomonas
- Ampicillin + sulbactam (Unasyn)
- Amoxicillin + clavulanic acid (Augmentin)
- Ticarcillin + clavulanic acid (Timentin)
- Piperacillin + tazobactam (Zosyn)

**Penicillins: Antibacterial Spectrum**

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**Penicillins: Side Effects and Toxicities**

- Pain at IM injection site
- Rare neurotoxicity
- Reactions to procaine and potassium
- Allergy: immediate (2-30 min); accelerated (1-72 h); late (days to weeks)
- Anaphylactic reactions occur with PCNs more than with any other drugs. Incidence is about 0.02%, but mortality is 10%

Cephalosporins

- Most widely used antibacterials
- Are beta-lactam antibiotics that bind to PBPs
- Resistance to cephalosporins occurs due to beta-lactamases which cleave open the drugs
- These drugs are grouped into generations, which take into account spectrum of activity, susceptibility to beta-lactamases, and increasing ability to penetrate the CSF
Cephalosporins

- **First Generation**
  - Cefadroxil, Cefazolin, Cephalexin, Cephapirin, Cefradine
  - Good gram positive coverage

- **Second Generation**
  - Cefaclor, Cefmetazole, Cefonicid, Cefotetan, Cefoxitin, Cefprozil, Cefuroxime, Loracarbef
  - Some gram negative coverage

- **Third Generation**
  - Cefdinir, Cefditoren, Cefixime, Cefoperazone, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftibuten, Ceftizoxime, Ceftriaxone, Ceftriaxonil, Ceftaroline
  - Gram negative aerobes; ceftazidime is effective against *Pseudomonas*, ceftaroline is effective against MRSA

- **Fourth Generation**
  - Cefipime
  - Broadest spectrum

Cephalosporins: Side Effects and Toxicities

- Allergy
  - Maculopapular rash after several days is the most common manifestation
- Increased bleeding tendencies
  - Cefmetazole, cefoperazone, cefotetan
- Thrombophlebitis with IV infusion
- Alcohol intolerance
  - Cefmetazole, cefoperazone, cefotetan

Carbapenems

- Broad spectrum beta-lactam antibiotics
- Imipenem, Meropenem, Ertapenem (Invanz), Doripenem (Doribax)
- Imipenem (Primaxin) is the broadest spectrum of any antibacterial; good for mixed infections, often used with cilastatin
- Meropenem (Merrem IV) may be used for bacterial meningitis
- Ertapenem is indicated for acute pelvic infections, CAP, complicated GI, GU, skin soft tissue infections
- Doripenem is used for complicated intra-abdominal infections or complicated UTIs

Aztreonam

- *(Azactam)*: Beta-lactam called a monobactam
- Narrow spectrum, effective only against gram negatives.
- Safe for patients with other beta-lactam allergies
- Must be given parenterally

Vancomycin

- Reserved for serious infections
  - AAPMC (second choice to metronidazole), MRSA, serious infections in the PCN-allergic patient
- Binds to precursors for cell wall synthesis, but is not a beta-lactam
  - Adverse effects include ototoxicity at plasma levels > 30ug/mL, rashes, thrombophlebitis; no cross-reactivity in the PCN-allergic patient