Introduction to Antimicrobial Therapy

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Case #1
- L.G. is a 78 yo woman admitted for cardiac cath. 3-vessel disease was identified and she was taken to the OR for CABG.
- Post-op in CTICU - patient did well. Extubated on POD #2.
- Transferred to the floor POD #4
- POD #6: spiked a temp to 101.7 with respiratory distress. Re-intubated and transferred back to the ICU. Blood, urine, sputum cultures were obtained.

Case #1 (cont.)
- The decision is made to start the patient on broad-spectrum antibiotics for presumed pneumonia
- The Surgery Resident, being his first week, is unsure which antibiotic to start, but remembers that piperacillin/tazobactam is "a broad-spectrum antibiotic"
- What questions should the resident ask himself in deciding which antibiotic to choose?

Case #2
- 68 y.o. female with HTN, anxiety with chest pain symptoms
- 7/27/05: Cath - 3 vessel CAD with normal LV function
- 9/12/05: admitted for CABG x 4 with LIMA without complications
- 9/13/05: extubated, diffuse ECG changes c/w pericarditis, a-fib, worsening hypotension, increased pressor requirements, re-explored in OR (RV failure)
- 9/14/05: hypotension with low filling pressures, severe cardiogenic shock with ARDS, VF arrest, emergent sternotomy, IABP placed
- 9/18/05: IABP d/c, d, duotube placed
- 9/19/05: extubated
- 9/21/05: re-intubated

Case #2 (cont.)
- 9/23/05: febrile, increase in pressor requirements, blood cultures drawn, started empiric antibiotics: vancomycin 1g IV q24h + piperacillin/tazobactam 4.5 g IV q8h
- Question: Are these empiric antibiotics appropriate?
  - Spectrum?
  - Consider existing culture and susceptibility results
  - Doses?
  - Consider existing or potential microbiology
  - Consider site of infection
  - Consider end-organ function
- 9/25/05: blood cultures + P. aeruginosa, tobramycin 160 mg IV q24h added, central lines changed (cordis, PA catheter)
- 9/27/05: cath tip + P. aeruginosa, C. albicans; additional blood cultures drawn
- Question: Is the addition of tobramycin appropriate?
  - Synergy?
  - Dose?

What You Need to Know to Treat with Antibiotics...
- Know the drugs
- Know the microbiology
- Know the patient
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What are Antimicrobials???
- Antimicrobials are drugs that destroy microbes, prevent their multiplication or growth, or prevent their pathogenic action
  - Differ in their physical, chemical, and pharmacological properties
  - Differ in antibacterial spectrum of activity
  - Differ in their mechanism of action

Classification of Antimicrobials
- Inhibit cell wall synthesis
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Monobactams (aztreonam)
  - Vancomycin
- Inhibit protein synthesis
  - Chloramphenicol
  - Tetracyclines
  - Glycylcycline (tigecycline)
  - Macrolides
  - Chloramphenicol
  - Streptogramins (quinupristin/dalfopristin)
  - Oxazolidinones (linezolid)
  - Aminoglycosides
- Alter nucleic acid metabolism
  - Rifamycins
  - Quinolones
- Inhibit folate metabolism
  - Trimethoprim
  - Sulfonamides
- Miscellaneous
  - Metronidazole
  - Daptomycin
  - Polymyxins

Beta-lactams

Vancomycin
**Protein Synthesis Inhibitors**

Mechanisms of Action – Protein Synthesis Inhibitors

- **Linezolid**
- **Tigecycline**
- **Streptogramins**

Rifamycins inhibit the β subunit of DNA-dependent RNA polymerase. Binding does not allow initiation of chain formation in RNA synthesis.

**Quinolones**

Inhibit the activity of topoisomerases, which are enzymes responsible for the supercoiling of the DNA (DNA gyrase) and relaxation of the supercoiled DNA (topoisomerase IV).

**Inhibitors of Folate Metabolism**

- **Daptomycin**
  - Calcium-dependent binding and insertion of the lipophilic tail into gram-positive cytoplasmic membrane
  - Oligomerization and channel formation occurs
  - Ion leakage and collapse of organisms leads to cell death

- **Metronidazole**
  - Metronidazole enters a bacterium where, via the electron transport protein fermentation, it is reduced. The drug then binds to DNA and DNA breakage occurs.

**Miscellaneous**

- **Daptomycin**
- **Metronidazole**
Antimicrobial therapy

- Empiric
  - Infecting organism(s) not yet identified
  - More "broad spectrum"

- Definitive
  - Organism(s) identified and specific therapy chosen
  - More "narrow" spectrum

- Prophylactic or preventative
  - Prevent an initial infection or its recurrence after infection

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Culture Results

- Minimum inhibitory concentration (MIC)
  - The lowest concentration of drug that prevents visible bacterial growth after 24 hours of incubation in a specified growth medium
  - Organism and antimicrobial specific
  - Interpretation:
    - Pharmacokinetics of the drug in humans
    - Drug's activity versus the organism
    - Site of infection
    - Drug resistance mechanisms

- Report organism(s) and susceptibilities to antimicrobials
  - Susceptible (S)
  - Intermediate (I)
  - Resistant (R)

Susceptibility Testing Methods

- Disk Diffusion (Kirby-Bauer disks)
**Susceptibility Testing Methods**
- Broth Dilution

**Pharmacokinetics, Pharmacodynamics, and the MIC**
- Concentration vs. time-dependent killing agents
  - Concentration-dependent agents: bacterial killing as the drug concentrations exceed the MIC
  - Peak/MIC (AUC/MIC) ratio important
  - Quinolones, aminoglycosides
    - Time-depending agents kill bacteria when the drug concentrations exceed the MIC
    - Time/MIC important
    - Penicillins, cephalosporins

- Post-antibiotic effect (PAE)
  - Delayed regrowth of bacteria following exposure to the antimicrobial
  - Varies according to drug-bug combination

**Concentration-dependent and Time-dependent agents vs. *Pseudomonas aeruginosa***

**Antimicrobial Pharmacodynamic Parameters**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Pattern of Activity</th>
<th>PK/PD parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta lactams</td>
<td>Time-dependent killing and minimal persistent effects</td>
<td>$T &gt; MIC$</td>
</tr>
<tr>
<td>PCNs, Carbapenems</td>
<td>Time-dependent killing and prolonged persistent effects</td>
<td>$T &gt; MIC$</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Time-dependent killing and prolonged persistent effects</td>
<td>Peak / MIC</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Concentration-dependent killing and prolonged persistent effects</td>
<td>$24\ h\ AUC / MIC$</td>
</tr>
<tr>
<td>Macrolides, Clindamycin, Tetracyclines, Ketolides, Linezolid</td>
<td>Time-dependent killing and prolonged persistent effects</td>
<td>$24\ h\ AUC / MIC$</td>
</tr>
</tbody>
</table>
Rationale for Extended-Interval Aminoglycoside Dosing
- Concentration-dependent killing
- Post-antibiotic effect
- Tissue penetration
- Negligible troughs potentially reduce toxicity
  - Renal accumulation is saturable

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Site of Infection
- Most important factor to consider in antimicrobial selection
- Defines the most likely organisms
  - Especially helpful in empiric antimicrobial selection
- Determines the dose and route of administration of antimicrobial
  - Efficacy determined by adequate concentrations of antimicrobial at site of infection
  - Serum concentrations vs. tissue concentrations and relationship to MIC

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Host Factors
- Allergy
  - Can be severe and life threatening
  - Previous allergic reaction most reliable factor for development of a subsequent allergic reaction
  - Obtain thorough allergy history
  - Penicillin allergy
    - Avoid penicillins, cephalosporins, and carbapenems in patients with true anaphylaxis, bronchospasm
    - Potential to use cephalosporins in patients with a history of rash (~5-10% cross-reactivity)
- Age
  - May assist in predicting likely pathogens and guide empiric therapy
  - Renal and hepatic function vary with age
    - Neonates and elderly
Host Factors

- Pregnancy
  - Fetus at risk of drug teratogenicity
- Renal and hepatic function
  - All antimicrobials become the plasma in varying degrees
- Genetic or metabolic abnormalities
  - Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Underlying disease states
  - Predispose to particular infectious diseases or alter most likely organisms

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Drug/PK/PD Factors

- Absorption
  - IM, SC, topical
  - GI via oral, tube, or rectal administration
  - Bioavailability = amount of drug that reaches the systemic circulation
- Distribution
  - Affected by the drug’s lipophilicity, partition coefficient, blood flow to tissues, pH, and protein binding
- Metabolism
  - Phase I
    - Generally inactivate the substrate into a more polar compound
    - Dealkylation, hydroxylation, oxidation, deamination
    - Cytochrome P-450 system (CYP3A4, CYP2D6, CYP2C9, CYP1A2, CYP2E1)
  - Phase II
    - Conjugation of the parent compound with larger molecules, increasing the polarity
    - Glucuronidation, sulfation, acetylation

Pharmacokinetics

- Elimination
  - Total body clearance
  - Renal + non-renal clearance
  - Affects half-life (t_{1/2})
  - Renal clearance
  - Glomerular filtration, tubular secretion, passive diffusion
  - Dialysis
  - Non-renal clearance
  - Sum of clearance pathways not involving the kidneys
  - Usually hepatic clearance, but also via bile tree, intestines, skin
  - Half-life
    - Steady state concentrations reached after 4-5 half lives
    - Varies from patient to patient
    - Affected by changes in end-organ function and protein binding
**Concomitant Drug Therapy**

- Influences the selection of appropriate drug therapy, the dosage, and necessary monitoring

**Drug Interactions**

- Risk of toxicity or potential for loss of efficacy of antimicrobial
- May affect the patient and/or the organisms
- Selection of combination antimicrobial therapy (≥ 2 agents)
- Requires understanding of the interaction potential
- Pharmacokinetic interactions
- Pharmacodynamic interactions

**Drug Interactions**

- Pharmacokinetic
  - An alteration in one or more of the object drug's basic parameters
- Pharmacodynamic
  - An alteration in the drug's desired effects
- Absorption
  - Bioavailability
- Distribution
  - Protein binding
- Metabolism
  - CYP450
- Elimination
  - Renal

**Synergistic/additive**

- May lead to desired or toxic effect

**Antagonistic**

- May lead to detrimental effects

**Indirect effects**

- Effect of one drug alters effect of another

**Combination Antimicrobial Therapy**

- Synergistic
- Antagonistic
- Indifferent

**Other Drug Factors**

- Adverse effect profile and potential toxicity

- Cost
  - Acquisition cost + storage + preparation + distribution + administration
  - Monitoring
  - Length of hospitalization + readmissions
  - Patient quality of life

- Resistance
  - Effects of the drug on the potential for the development of resistant bacteria in the patient, on the ward, and throughout the institution

**Antimicrobial Therapy**

- Site of infection / Microbiology
  - Where is it?
  - Which organisms need to be covered?
  - Gram-positive, gram-negative, anaerobes
  - What are the organisms in the unit?
- Antibiotic
  - Does the patient have any allergies?
  - Will the antibiotic reach sufficient concentrations at the site of infection?
  - Renal function
  - How is the antibiotic cleared?
  - What are the potential toxicities?
  - What is the impact on resistance?
  - Drug interactions?
- Patient
  - Comorbid illness
  - Any recent likely organisms and potential sites of infection
  - Tissue
  - End-organ function
  - Age/weight

**Summary**

- Antimicrobials are essential components to treating infections
- Appropriate selection of antimicrobials is more complicated than matching a drug to a bug
- While a number of antimicrobials potentially can be considered, spectrum, clinical efficacy, adverse effect profile, pharmacokinetic disposition, and cost ultimately guide therapy
- Once an agent has been chosen, the dosage must be based upon the size of the patient, site of infection, route of elimination, and other factors
- Optimize therapy for each patient and try to avoid patient harm
QUESTIONS?