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 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
What You Need to Know to Treat with Antibiotics…

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Classification of Antimicrobials

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
  - Clindamycin
  - Streptogramins (quinupristin/dalfopristin)
  - Oxazolidinones (linezolid)
  - Aminoglycosides
- Alter nucleic acid metabolism
  - Rifamycins
  - Quinolones
- Inhibit folate metabolism
  - Trimethoprim
  - Sulfonamides
- Miscellaneous
  - Metronidazole
  - Daptomycin

Beta-lactams

Vancomycin
Protein Synthesis Inhibitors

Inhibitors of Folate Metabolism

Rifamycins

Quinolones

Miscellaneous

Antimicrobial therapy

**Protein Synthesis Inhibitors**
- Aminoglycosides
- Micafungin
- Trityls
- Chloramphenicol
- Penicillins
- Tetraacyclines
- Erythromycin

**Inhibitors of Folate Metabolism**
- Dihydropteroate synthase
- 5-MTHF reductase
- Tetrahydrofolic acid

**Rifamycins**
- Rifampin

**Quinolones**
- Ciprofloxacin

**Miscellaneous**
- Daptomycin
- Metronidazole

**Antimicrobial therapy**
- **Empiric**
  - Infection(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
What You Need to Know to Treat with Antibiotics…

■ Know the drugs
■ Know the microbiology
■ Know the patient

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
Susceptibility Testing Methods
- E-test (epsilometer test)

What You Need to Know to Treat with Antibiotics...
- Know the drugs
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- Know the patient

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
  - Time-dependent agents: kill bacteria when the drug concentrations exceed the MIC
    - Time>MIC important
    - Pencillins, 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>
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<tr>
<td>Beta lactams</td>
<td>Time-dependent killing and prolonged persistent effects</td>
<td>T &gt; MIC</td>
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Rationale for Extended-Interval Aminoglycoside Dosing
- Concentration-dependent killing
- Post-antibiotic effect
- Tissue penetration
- Negligible troughs potentially reduce toxicity
  - Renal accumulation is saturable
What You Need to Know to Treat with Antibiotics…

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- Know the patient

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

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
- **Pregnancy**
  - Fetus at risk of drug teratogenicity
  - Most antimicrobials cross the placenta in varying degrees
  - Penicillins, cephalosporins, and erythromycin appear safe
  - Altered drug disposition
  - Penicillins, cephalosporins, and aminoglycosides are cleared more rapidly during pregnancy
  - ↑ intravascular volume, ↑ glomerular filtration rate, ↑ hepatic and metabolic activities
- **Genetic or metabolic abnormalities**
  - Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- **Renal and hepatic function**
  - Accumulation of drug metabolized and/or excreted by these routes with impaired function
  - ↑ risk of drug toxicity unless doses adjusted accordingly
  - Renal excretion is the most important route of elimination for the majority of antimicrobials
- **Underlying disease states**
  - Predispose to particular infectious diseases or alter most likely organisms
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Pharmacokinetics

- 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
    - General 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
    - Generally inactivate the parent compound
    - Glucuronidation, sulfation, acetylation

Pharmacokinetics

- Elimination
  - Total body clearance
    - Renal + non-renal clearance
  - 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 biliary 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

Drug/PK/PD Factors

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

- Drug interactions
  - ↑ risk of toxicity or potential for ↓ 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

Concomitant Drug Therapy
Drug Interactions

- Pharmacokinetic
  - An alteration in one or more of the object drug’s basic parameters
- Absorption
  - Bioavailability
- Distribution
  - Protein binding
- Metabolism
  - CYP450
- Elimination
  - renal

Pharmacodynamic
- An alteration in the drug’s desired effects
- 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

Antimicrobial Therapy

- Site of infection / Microbiology
  - Where is it?
  - What organisms need to be covered?
  - Gram positives, gram-negatives, anaerobes
  - If anaerobic, MRSA
  - 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?
  - Penetration
    - Blood-brain barrier
  - How is the antibiotic cleared?
  - What are the potential toxicities?
  - What is the impact on resistance?
  - Drug interactions?
    - Good vs. bad
- Patient
  - Comorbidity
  - Ate risk likely organisms and potential sites of infection
  - Toxicities
  - End-organ function
  - Age/weight

Combination Antimicrobial Therapy

- Synergistic
- Antagonistic
- Indifferent

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  - Ate risk likely organisms and potential sites of infection
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  - 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

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

QUESTIONS?