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
What You Need to Know to Treat with Antibiotics…

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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
  - Clindamycin
  - Streptogramins (quinupristin/dalfopristin)
  - Oxazolidinones (linezolid)
  - Aminoglycosides

- **Alter nucleic acid metabolism**
  - Rifamycins
  - Quinolones

- **Inhibit folate metabolism**
  - Trimethoprim
  - Sulfonamides

- **Miscellaneous**
  - Metronidazole
  - Daptomycin
Beta-lactams

Vancomycin

Vancomycin-susceptible staphylococci

Inhibition of cell-wall synthesis

Tripeptide containing intermediates in cell-wall synthesis
Protein Synthesis Inhibitors

Aminoglycosides
Blocks the initiation of translation and causes the misreading of mRNA

Macrolides
Prevents the continuation of protein synthesis

Chloramphenicol
Prevents peptide bonds from being formed

Tetracyclines
Blocks the attachment of tRNA to the ribosome

Lincosamides
Prevents the continuation of protein synthesis

Streptogramins
Each interferes with a distinct step of protein synthesis

Oxazolidinones
Thought to interfere with the initiation of protein synthesis

Rifamycins

MODE OF ACTION OF RIFAMYCINS

DNA template
Recognition of the promoter

Binding of the first NDP
Formation of the phosphodiester bound and translocation of the growing chain

mRNA
Quinolones

Inhibitors of Folate Metabolism

- Dihydropteroate diphosphate + p-aminobenzoic acid (PABA)
- Dihydropteroate synthetase
- Dihydropteroic acid
- Dihydrofolate reductase
- Tetrahydrofolate acid

Sulfonamides

Trimethoprim
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
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)
## Culture Results

### Example

#### BLOOD CULTURE 2004-07-30 10:56

**SPECIMEN DESCRIPTION:** BLOOD

**CULTURE:** POSITIVE FOR ESCHERICHIA COLI (gram)

**CULTURE:** GRAM STAIN OF POSITIVE BOTTLE: GRAM NEGATIVE RODS

**REPORTED TO DR. **** AT 1119 ON 07/31/04**

**Collection time:** 2004-07-30 10:56  **Received time:** 2004-07-30 10:56

**Status:** Final, Access: F50319RCRBL00D47U

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#### BLOOD CULTURE 2004-06-02 10:42

**SPECIMEN DESCRIPTION:** BLOOD

**CULTURE:** POSITIVE FOR ESCHERICHIA COLI (gram)

**CULTURE:** GRAM STAIN OF POSITIVE BOTTLE: GRAM NEGATIVE RODS

**Collection time:** 2004-06-02 10:42  **Received time:** 2004-06-02 10:42

**Status:** Final, Access: W3019HCRBL00D462

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Susceptibility Testing Methods

- Disk Diffusion (Kirby-Bauer disks)

- Broth Dilution
Susceptibility Testing Methods

- E-test (epsilometer test)

What You Need to Know to Treat with Antibiotics...

- Know the drugs
- Know the microbiology
- 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
    - Quinolones, aminoglycosides
  - Time-dependent 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

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Concentration-dependent and Time-dependent agents vs. *Pseudomonas aeruginosa*
### Antimicrobial Pharmacodynamic Parameters

<table>
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<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 minimal persistent effects</td>
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<td>Aminoglycosides</td>
<td>Concentration-dependent killing and prolonged persistent effects</td>
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<td>24 h AUC / MIC</td>
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<td>Linezolid</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...

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

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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
    - All antimicrobials cross the placenta in varying degrees
    - Penicillins, cephalosporins, 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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Drug/PK/PD Factors

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
  - Generally inactivate the substrate into a more polar compound
  - Dealkylation, hydroxylation, oxidation, deamination
  - Cytochrome P-450 system (CYP3A4, CYP2B6, 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
    - 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 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

Concomitant Drug Therapy

- 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 ($\geq$ 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
  - 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

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 positives, gram-negatives, anaerobes
    - P. aeruginosa, 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
  - Comorbid illness
    - Alters most likely organisms and potential sites of infection
    - Toxicities
  - 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?