Introduction to Antimicrobial Therapy

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Objectives

• Review the classification of antimicrobials
• Define pharmacokinetic and pharmacodynamic principles and their relationship to effective antimicrobial therapy
• Review relevant microbiologic information as it relates to choosing an antimicrobial
• Discuss patient and drug related factors that influence the selection of the appropriate antimicrobial agent
• Identify monitoring parameters to evaluate antimicrobial therapy

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
  – Macrolides
  – Clindamycin
  – Streptogramins (quinupristin/dalfopristin)
  – Oxazolidinones (linezolid)
  – Aminoglycosides
• Alter nucleic acid metabolism
  – Rifamycins
  – Quinolones
• Inhibit folate metabolism
  – Trimethoprim
  – Sulfamethoxazole
• Miscellaneous
  – Metronidazole
  – Daptomycin
• Inhibit folate metabolism

Case Presentation #1

• S.I. is a 72 y.o. male with history of SAH s/p aneurysm clipping about 2 months ago. His post-op course was complicated by ventilator-associated pneumonia, hydrocephalus requiring a VP shunt, and renal failure. Now admitted with acute mental status changes and fever.
• PMH: SAH, DM, HTN, hypercholesterolemia
• FH: non-contributory
• SH: +tobacco (4 cigarettes/day)
• Allergies: NKDA
• Occupation: attorney

• PE:
  – T 102.7°F,
  – Tachycardic

• Labs:
  – WBC 14.7, Hct 34.3, plts 295
  – Na 138, K 4.1, Cl 102, HCO3 25, BUN 26, SCr 1.4
  – LFTs well
  – Cultures pending
  – CSF: WBC 725 (96% neutrophils); protein 148; glucose 39

• Diagnosis: VP shunt infection

• Treatment: Antibiotics and shunt removal
  – Antibiotics?
  – Route?
  – Dose?
Case Presentation #2

- 43 y.o. male with congenital bladder extrophy (s/p multiple surgeries now with ureterocolostomy and colostomy), residual short bowel syndrome, multiple hospital admissions for UTIs, sepsis, recently admitted for 1 month with polymicrobial line sepsis, line removed, PICC placed. Returns 10 days later complaining of abdominal pain, N/V.
- PMH: HTN
- FH: non-contributory
- SH: no tobacco, occasional alcohol use
- Allergies: PCN

PE:
- T 99.7°F
- Lungs clear
- Abdomen soft, but indurated area below urostomy bag

Labs:
- WBC 12.4 (↑ from 7.1), Hct 34.8, Plts 290
- Na 139, K 3.7, Cl 105, HCO3 20, BUN 40, SCr 1.8
- LFTs wnl
- UA: 20 WBCs

CT scan:
- Abdominal cystic mass in pelvis with new hydronephrosis

4 days into hospital admission, the cystic collection spontaneously drains. Patient febrile to 101.7°F, tachycardic, increased WBC to 26.4. Cultures drawn. Started on broad spectrum antibiotics.

Selecting an Antimicrobial

- Confirm the presence of infection
  - History and physical
  - Signs and symptoms
  - Predisposing factors
- Identification of pathogen
  - Collection of infected material
  - Stains
  - Bacteriologies
  - Culture and sensitivity
- Selection of presumptive therapy
  - Drug factors
  - Host factors
- Monitor therapeutic response
  - Clinical assessment
  - Lab tests
  - Assessment of therapeutic failure

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

Is the Patient Infected???

- CAREFUL history and physical exam including relevant laboratory data and signs and symptoms
  - Temperature
  - White blood cell count (WBC)
    - WBC in normally sterile fluids (e.g. CSF)
  - Any swelling or erythema at a particular site
  - Purulent drainage from a visible site
  - Patient complaints
- Predisposing factors
  - Surgery, procedures, physical limitations, etc.
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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)

- Broth Dilution
Susceptibility Testing Methods

- E-test (epilometer test)

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Drug 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, 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

Pharmacodynamics

- Attempts to relate drug concentrations to their effect in the body
  - Desirable = bacterial killing
  - Undesirable = drug side effects
- Bacteriostatic
  - Inhibit growth or replication
- Bactericidal
  - Cause cell death
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

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

AUC/MIC and Survival Relationship for Quinolones

AUC/MIC and Outcomes Relationship for Ciprofloxacin

Pharmacodynamic Parameters and Colony Count after 24 hours for Cefotaxime in *K. pneumoniae*

Antimicrobial Pharmacodynamic Parameters

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>Pharmacodynamic Characteristics</th>
<th>Goal of Regimen</th>
<th>Parameter Correlating with In Vivo Efficacy</th>
</tr>
</thead>
</table>
| Aminoglycosides | Concentration-dependent killing | Maximization of Concentrations | Peak/MIC
| Quinolones    |                                  |                 | AUC/MIC, AUC/24h/MIC                     |
| Metronidazole |                                  |                 |                                          |
| Cephalosporins| Time-dependent Killing           |                 |                                          |
| Aztreonam     |                                 |                 |                                          |
| Penicillins   | Time-dependent Killing           |                 |                                          |
| Cephalosporins| NO Persistent Effects            |                 |                                          |
| Cefotaxime    |                                  |                 |                                          |
| Vancomycin    | Time-dependent Killing           |                 |                                          |
| Clindamycin   |                                 |                 |                                          |
| Macrolides    |                                 |                 |                                          |
| Daptomycin    |                                 |                 |                                          |
Post Antibiotic Effect (PAE)

- Delayed regrowth of bacteria following exposure to an antibiotic
  - Varies according to drug-bug combination
- Gram-positive organisms
  - Most antibiotics (beta-lactams) exhibit PAE ~1-2 hours
  - Aminoglycosides exhibit PAE < 1 hour
- Gram-negative organisms
  - Most beta-lactams (except imipenem) have a negligible PAE
  - Aminoglycosides and quinolones have PAE ≥ 2 hours
- Clinical significance unknown
  - Helps choose appropriate dosing interval

Aminoglycoside Concentrations

- 1.7 mg/kg q8h dosing
- 5 mg/kg q24h dosing

Aminoglycoside Concentrations

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

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 (1-5-10% cross reactivity)
- Age
  - May assist in predicting likely pathogens and guide empiric therapy
  - Renal and hepatic function vary with age
    - Neonates and elderly
- Pregnancy
  - Fetus at risk of drug teratogenicity
    - All 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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**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

**Site of Infection**

Will the antibiotic get there?

- Choice of agent, dose, and route important
  - Oral vs. IV administration
    - Bioavailability, severity of infection, site of infection, function of GI tract
  - Blood and tissue concentrations
    - Ampicillin/piperacillin $\rightarrow$ ↑ concentrations in bile
    - Fluoroquinolones $\rightarrow$ ↑ concentrations in bone
    - Cephalosporins, TMP/SMX, cephalaxin, amoxicillin $\rightarrow$ ↑ concentrations in prostate
  - Ability to cross blood-brain barrier
    - Dependent on inflammation, lipophilicity, low mw, low protein binding, low degree of ionization
    - 3rd or 4th generation cephalosporins, chloramphenicol, ampicillin, PCN, oxacillin
  - Local infection problems
    - Aminoglycosides inactivated by low pH and low oxygen tension
    - Beta-lactams $\rightarrow$ inoculum effect

**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
  - Pharmacokinetic interactions
    - Alter drug absorption, distribution, metabolism, or excretion
  - Pharmacodynamic interactions
    - Alter pharmacologic response of a drug
    - Selection of combination antimicrobial therapy ($\geq$ 2 agents) requires understanding of the interaction potential

**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
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Monitoring

- Efficacy and toxicity of antimicrobials
- Clinical assessment
  - Improvement in signs and symptoms
    - Fever curve, ↓ WBC
    - ↓ erythema, pain, cough, drainage, etc.
- Antimicrobial regimen
  - Serum levels
  - Renal and/or hepatic function
  - Other lab tests as needed
  - Consider IV to PO switch
- Microbiology reports
  - Modify antimicrobial regimen to susceptibility results if necessary
    - Resistance?
    - “Narrow” spectrum of antimicrobial if appropriate

Antimicrobial Factors in Drug Selection

- Factors to consider:
  - Site of infection (likely organisms gram positive and gram negative)
  - Recently hospitalized
  - Neurosurgery
  - Antibiotic penetration into CSF
  - Route of administration
  - Age
  - Renal function
- Patient empirically started on vancomycin 1 gram IV Q24h and cefepime 2 grams IV Q12h.

Case Presentation #1

- Factors to consider:
  - Most likely abdominal source (gram negative and anaerobic organisms)
  - PCN allergy
  - Renal/hepatic function
  - Multiple admissions and multiple infections
  - ?resistant organisms
  - IV vs. PO antibiotics
  - Short bowel syndrome
- Patient received empiric levofloxacin 500 mg IV Q24h, metronidazole 500 mg IV Q12h, and vancomycin 1g IV Q24h.

Cultures grew MSSA, patient’s therapy changed to oxacillin + rifampin.

Shunt removed. WBC ↓. Patient completed course of IV antibiotics.

Monitor for resolution of infection

Monitor hepatic profile
Cultures grew...

Levofloxacin and metronidazole continued to complete a course of therapy. Surgical intervention. Vancomycin discontinued.

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, 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
- Use antimicrobials only when needed for as short a time period as needed to treat the infection in order to limit the emergence of bacterial resistance

QUESTIONS?