Principles of Antimicrobial Therapy

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Disclosures

• None

Obtaining an Accurate Diagnosis

• Determine site of Infection
• Define the Host
  – Diabetic ?
  – Immunocompromised ?
  – Age ?
• Establishing a microbiologic diagnosis when possible
  – Can also exclude non infectious diagnosis

Obtaining an Accurate Diagnosis

• Obtain specimens PRIOR to initiating antimicrobials
  – endocarditis
  – osteomyelitis
• Obtain exposure/travel history
• Initiate empiric therapy based on most likely organisms i.e cellulitis, CAP

Location, Location, Location

• Antimicrobial concentrations at some sites( e.g. CSF, abscess cavity, prostate & bone) are much lower than serum levels
  – First and Second Generation Cephalosporins and macrolides do not cross BBB
  – Fluoroquinolones achieve high concentrations in the prostate
  – Daptomycin excellent against GP bacteria is deactivated by lung surfactant

Empiric Antimicrobial Therapy

• Most Likely Organisms (IDSA guidelines)
• Community Acquired versus Health Care Acquired
• Timing
  – Delay > 60 minutes ^ Morbidity and Mortality and ^ LOS
• Narrow spectrum when C&S available

**Interpretation of Susceptibility Testing**

- **Minimum Inhibitory Concentration**
  - Lowest concentration of an antibiotic that inhibits growth of a microorganism
  - Reported as “susceptible”, “intermediate” or “resistant”
  - Important for lab to know site of specimen

**Extended Spectrum Beta-Lactamases**

- Enzymes that mediate resistance to almost all B-lactams except carbapenems
- Clinically suspect ESBL if Rx failure with B-lactams

**KPC**

**Considerations for Empiric Therapy for Health Care Acquired Infections**

- Site of Infection
- Most Likely Organisms
- Knowledge of known colonizer (MRSA)
- Resistance Patterns/Antibiogram

**Bactericidal VS Bacteriostatic**

- **Bactericidal**
  - Cause death & disruption of the bacterial cell
- **Bacteriostatic**
  - Inhibit replication but do NOT kill the organism

**Use of Antimicrobial Combinations**

- Agents that are synergistic
  - B-Lactams and aminoglycoside for Rx of endocarditis caused by enterococcus
- Critically Ill/Empiric Therapy
  - “Double Cover” pseudomonas
- Extend Spectrum for Polymicrobial Infections
  - i.e. intra-abdominal infections
- Prevent Drug Resistance
  - i.e. TB and HIV
Host Factors

- Renal & Hepatic Function
- Age
- Genetic Variations
  - G6PD deficiency (African Americans)
  - Hemolysis if exposed to dapsone or nitrofurantoin
  - Antiretroviral abacavir asc. with a potentially fatal hypersensitivity Rxn shown to have a greater incidence in pts w HLA-B 5701


Host Factors

- Allergy/Intolerance
- Recent Antimicrobial Use
  - Exposure in past 3 months
- Pregnancy and Lactation
  - PCNs, cephalosporins and macrolides safest
  - Limited data

Oral Vs IV Therapy

- IV Therapy
  - Critically ill
  - ? GI function
  - More serious infections e.g. Infective endocarditis or meningitis
- Oral
  - NI GI function
  - If therapy for invasive organisms select agent w excellent bioavailability e.g. fluoroquinolones, linezolid and metronidazole

Pharmacodynamic Considerations

Time vs Concentration

- Time dependent (B lactams and Vancomycin)
  - Slow bactericidal activity
  - Important serum concentration exceeds the MIC for the duration of the dosing interval (continuous infusions or frequent dosing)
- Dose/Concentration dependent
  - (aminoglycosides, fluoroquinolones, metronidazole)
  - Enhanced activity as serum concentration is increased
  - "peak" concentration, not frequency of dosing interval is associated w efficacy

Outpatient Parenteral Antimicrobial Therapy (OPAT)

- Less Frequent Administration
  - Cont infusion pump
- Chemically Stable for 24 hrs
- Minimal toxicity and monitoring

70 yo female w Cr Cl 30 mL/min is being treated for pyelonephritis caused by E Coli w Ciprofloxacin. Dosing guidelines suggested either 250mg Q 12 or 500mg Q 24 hr for her reduced renal function. Which is more appropriate? Hint – Cipro is concentration dependent
Duration of Therapy

• Shorter Courses
• Follow IDSA guidelines
• Longer course for MDRO
• Longer course for invasive fungal, Osteo, endocarditis, intra abdominal abscesses

Assessing Response

• Clinical
  - Resolution of fever, tachycardia, confusion, BP stability
• Radiologic lag behind
• Microbiological
  - Negative Blood Cx

Adverse Effects

Direct
• Allergy
• Toxicity
• Drug-drug interaction
• Therapeutic failure

Indirect
• Effects on environmental flora
• Effects on commensal flora
  – C-Diff

Allergic Reactions

• Document allergy and response
• Antibiotics 1/5 ER visits for ADR
• Most common for children < 18
• Only 10-20% of PCN allergic were truly allergic when allergy tested
• Desensitization can occur with guidance from allergist

Non-allergic Drug Toxicity

• Associated w higher doses and/or prolonged use in renal or hepatic dysfunction
• Drug-drug interactions
• Cytochrome P450
  – rifampin is an inducer
  – macrolides and azoles are inhibitors
• Periodic clinical or drug monitoring
  – CPK w Dapto; CBC w diff w B Lactams, Bactrim and Linezolid, Cr w aminoglycosides

Judicious Use of Antimicrobials
Examples of Misuse

• Prescribing unnecessarily
• Delaying administration in critically ill pts
• Spectrum too broad or too narrow
• Wrong duration
• Failure to deescalate

Antimicrobial Stewardship

• Optimize antibiotic selection/dosing and duration while minimizing unintended consequences
• Cost Savings
• Improved Outcomes

Illnesses and Deaths Caused by Antibiotic Resistance

2,049,442 Illnesses
23,000 Deaths

Leadership and Culture
Primary Drivers
Secondary Drivers
Tightly and appropriately antibiotic utilization in the acute care setting
Optimize antibiotic selection/dosing and duration while minimizing unintended consequences
Tightly and appropriate initiation of antibiotics
Optimize antibiotic selection/dosing and duration while minimizing unintended consequences

Antibiotic stewardship
Cost Savings
Improved Outcomes

Resistances Doubles

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<tr>
<th>Year</th>
<th>Percentage</th>
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<td>2006</td>
<td>20%</td>
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<td>2008</td>
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CDC.gov 2013
50% of Antibiotic Use in Hospitals Unnecessary or Inappropriate

What Can NP’s Do?
- Do not treat viral infections
- Right drug/dose/duration
- Document indications and planned duration in clinical notes
- Re-evaluate need/Antibiotic time out
- Narrow spectrum when susceptibility data back

What Can NP’s Do?
- Send specimens to micro for Cx before initiating Rx
- Stop antibiotics if no sign of infection
- Consult ID experts for complex infections
- Educate Pts and families

Improving antibiotic use is a public health imperative
- Antibiotics are the only drug where use in one patient can impact the effectiveness in another.
- If everyone does not use antibiotics well, we will all suffer the consequences.