Practical Antimicrobial Therapy

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Objectives

- Introduction to basic antimicrobial principles
- Pharmacokinetics
- Pharmacodynamics
- Provide an overview of some of the most common antimicrobial drug classes
  - β-lactam antibiotics
  - Aminoglycosides
  - Fluoroquinolones
  - A few others...

Background

- Basic mechanism of action:
  - Time-dependent killing
  - Concentration-dependent killing
- Pharmacokinetics (PK)
  - Peak & Trough serum concentrations
  - Half-life ($T_{1/2}$)
  - Source of metabolism
  - Source of excretion (kidney, GI, etc)
- Pharmacodynamics (PD) – relationship between PK & minimum inhibitory concentration (MIC)

PD Principals

- Area Under the Curve (AUC) : MIC ratio
  - $\geq 30-60:1$
  - $\geq 125:1$
- Time above MIC ratio
  - $\geq 50-60\%$ of the dosing interval
- Peak Concentration : MIC ratio
  - $\geq 10:1$
- Aminoglycosides vs. Gram(-) organisms
- Fluoroquinolones vs. Gram(-) organs

PD Goals

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<th>Parameter</th>
<th>Goal</th>
<th>Antimicrobial Drug Classes</th>
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<td>Time above MIC</td>
<td>$&gt;50-60%$ of the dosing interval</td>
<td>All β-lactams, Macrolides, Linezolid</td>
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<td>Peak Conc : MIC ratio</td>
<td>$\geq 10:1$</td>
<td>Aminoglycosides vs. Gram(-) organisms</td>
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<td>Area under the Curve (AUC) : MIC</td>
<td>$\geq 30-60:1$ $\geq 125:1$</td>
<td>Fluoroquinolones vs. Gram(-) vs. Gram(+) organs</td>
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Patient Case: JR

- 73yom s/p AAA repair & then L-carotid endarterectomy
- *Pseudomonas* pneumonia:
  - S: Zosyn (MIC=64), Tobramycin (MIC≤1)
  - L: Cefepime (MIC=16)
- Current Antibiotics:
  - Cefepime 1g IV q6h
  - Tobramycin 540mg IV q48 (7mg/kg)

Is this adequate therapy?
Antibiotic Therapy – Kara Birrer, PharmD

Mechanisms of Action

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<th>Antibacterial Family</th>
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<td>Inhibition of protein</td>
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<td>Inhibition of folic acid</td>
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<td>Disruption of cell</td>
<td>• Daptomycin</td>
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<td>membrane integrity</td>
<td>• Polymyxin B, E (Colistin)</td>
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<td>Other</td>
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<td>• Nitrofuransulfonamide</td>
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Penicillins

- Bactericidal cell-wall synthesis inhibitors
- Gram(+) activity maintained across spectrum
- Gram(-) activity dependent on ability to cross porin channels
- β-lactamase inhibitor combinations:
  - Methicillin-Resistant S. aureus (MRSA) coverage
  - Enhanced anaerobic activity

PCN Gram(-) Spectrum of Activity
**Penicillins**

- Major Adverse Events:
  - Anaphylaxis
  - Rash and/or hives
  - Seizures
- Anti-
  - Staphylococcus aureus Penicillins
  - Resistant to β-lactamase
  - NO Gram(-) activity
- ORMC Formulary: Nafcillin 2g IV q4 (no renal adjustment)

**Extended-Spectrum Penicillins**

- Piperacillin/Tazobactam (Zosyn®)
  - Sodium content 1.85 mEq per gram
  - Dosing:
    - Serious infection/Pneumonia: 4.5g IV q6
    - Other infections: 3.375g IV q6
- Ticarcillin/Clavulanic Acid (Timentin®)
  - Sodium content 5.2 mEq per gram
  - 2nd Line agent for Stenotrophomonas maltophilia

**Cephalosporins**

- Bactericidal cell-wall synthesis inhibitors
- DO NOT treat Enterococcus spp.
- Gram(+) activity generally decreases with each generation
- Gram(-) activity increases with generation
- Weak anaerobic activity with 2nd generation

**Cephalosporin Spectrum of Activity**

1. **1st Generation (EX: Cefazolin)**
   - Excellent MSSA activity
   - Some Gram(+) activity – E. coli, Klebsiella
   - Major role in surgical prophylaxis
2. **2nd Generation (EX: Cefotetan, Cefoxitin)**
   - Good Gram(-), moderate Gram(+) & anaerobic coverage
   - Primarily used for abdominal surgery prophylaxis
3. **3rd Generation (EX: Ceftriaxone, Ceftazidime)**
   - 1st β-lactams with Pseudomonas coverage (Ceftazidime)
   - Ceftazidime selects out multi-drug resistant organisms (MDR Gram(-), VRE, C. difficile, MRSA)
   - Ceftriaxone –
     - Excellent CSF penetration
     - Excellent Streptococcus pneumoniae drug
4. **4th Generation (EX: Ceftazime)**
   - Excellent MSSA and Pseudomonas spp coverage
**Cephalosporins**

- Major Adverse Events
  - Rash
  - Anaphylaxis
  - Seizures
- Cross-Sensitivity with Penicillins
  - 1-10%
  - Concern if patient has history of anaphylaxis

**Carbapenems**

- Bactericidal cell-wall synthesis inhibitors
- Broadest-spectrum antimicrobials available
- Stable against most β-lactamases
- Some intrinsic Resistance:
  - *Enterococcus faecium*
  - *MRSA*
  - *Stenotrophomonas maltophilia*
  - *Burkholderia spp.*
  - PCN-resistant *S. pneumoniae*

**Carbapenems**

- 4 Drugs:
  - Imipenem/Cilastatin (*Primaxin*®)
  - Meropenem (*Merrem*®)
  - Ertapenem (*Invanz*®)
  - Doripenem (*Doribax*®)
- Incomplete class cross-resistance
- Major Adverse Events:
  - Seizures (Imi >> Mero >> Dori)
  - Rash
  - Anaphylaxis
- Cross-Sensitivity with Penicillins < 1%

**Monobactam**

- Bactericidal cell wall synthesis inhibitor
- Pure Gram(-) coverage –
  - including *Pseudomonas*
- No cross-sensitivity with penicillins / cephalosporins
- Major Adverse Events:
  - Rash
  - GI upset
  - Injection-site thrombophlebitis

**Fluoroquinolones**

- DNA synthesis inhibitors:
  - DNA-gyrase inhibitor in Gram(-) bacteria
  - Topoisomerase IV inhibitor in Gram(+) bacteria
- Concentration dependant killers
  - Gram(-) AUC:MIC Goal ≥ 125:1
  - Gram(+) AUC:MIC Goal ≥ 10:1

**Fluoroquinolones**

- Anti-Pseudomonal Agents:
  - Ciprofloxacin
  - Levofloxacin (non-formulary)
**Fluoroquinolones**

- **Gram(+) Coverage:**
  - Class has POOR *Staphylococcus aureus* drugs
  - Select out MRSA
  - Newer agents excellent *Strep. pneumoniae* coverage
- **Major Adverse Events:**
  - QT Prolongation
    - Moxifloxacin >>> levofloxacin >>> ciprofloxacin
  - *C. difficile* colitis
- **Drug Interactions:** phenytoin, warfarin

**Aminoglycosides**

- **Inhibit bacterial protein synthesis at 30S & 50S ribosomal subunits**
- **Concentration-dependant killers**
  - Goal Peak : MIC = 10 : 1
  - Post-antibiotic effect

**Aminoglycosides**

- **Place in Therapy:**
  - Treatment of Gram(-) Infections
    - Gentamicin for Gram(+) synergy in combination with a β-lactam or vancomycin
- **Major Adverse Events:**
  - Nephrotoxicity (high trough)
  - Ototoxicity (prolonged duration of therapy)
- **Drug Interactions:**
  - Neuromuscular blockers

**Aminoglycosides**

- **Gentamicin/Tobramycin**
  - Gram(-) non-Burn: 7mg/kg IV q24
  - Gram(-) Burn: 2.5-3mg/kg IV q8-12h
  - Gentamicin Gram(+) Synergy: 1mg/kg IV q8
- **Amikacin**
  - Gram(-) non-Burn: 15-20mg IV Q24
  - Gram(-) Burn: 7.5 mg/kg IV Q8

Dose Calculator: [www.surgicalcriticalcare.net](http://www.surgicalcriticalcare.net)

**Aminoglycosides**

- **Colistin (Polymyxin E)**
  - Reserved for multi-drug resistant Gram(-) orgs
  - Nebulized: 150mg inhaled q12h
  - IV (VERY nephrotoxic): 2.5 mg/kg IV q8-12
- **Polymyxin B**
  - Also reserved for multi-drug resistant orgs
  - IV: 15,000-25,000 units/kg/day divided q12
- **No way to monitor levels for IV polymyxins**

**Aminoglycosides**

- **Polymyxin B & Colistin**
  - **Major Adverse Events:**
    - Nephrotoxicity
    - Neurotoxicity
  - **Drug Interactions:**
    - Neuromuscular blockers
**Vancomycin**
- Inhibits bacterial cell wall synthesis
- Time-dependant killer (time above MIC)
  - Some concentration-dependant characteristics
- Uses:
  - IV: treatment of Gram(+) infections
  - PO: treatment of *C. difficile* colitis

**Linezolid (Zyvox®)**
- Oxazolidindione – inhibits bacterial protein synthesis
  - Bacteriostatic: *Enterococcus*, *Staphylococcus*
  - Bacteriocal: *Streptococcus*
- DOC: VRE
- Large volume of distribution
- Dosing: 600mg IV/PO q12

**Synercid®**
- Quinupristin/Dalfopristin – inhibits bacterial protein synthesis
- Major organisms:
  - VRE
  - MSSA & MRSA
  - *Streptococcus pyogenes*
- Dose:
  - 7.5mg/kg IV q8-12 (no renal adjustment)

**Vancomycin**
- Dosing:
  - IV: 20mg/kg IV x1, then 15mg/kg IV q8-12h
  - PO: 125-250mg PO q6h
- Major Adverse Events:
  - Red Man Syndrome – slow down infusion
  - Not nephrotoxic – but accumulates

**Linezolid (Zyvox®)**
- Major Adverse Events
  - Thrombocytopenia/Pancytopenia
  - Blurred vision
  - Serotonin Syndrome
- Drug Interactions
  - Selective Serotonin Reuptake Inhibitors (SSRIs)

**Synercid®**
- Major Adverse Events
  - Hyperbilirubinemia
  - Infusion site reaction
  - Infusion-related arthralgias/myalgias
- Drug Interactions
  - No significant
**Daptomycin**
- Cell membrane disruption leading to inhibition of DNA/RNA/protein synthesis
- Bacteremia, Endocarditis, Skin/Soft Tissue infections
- Does NOT treat pneumonia!
- Spectrum of Activity:
  - MRSA
  - VRE

**Daptomycin**
- Dose:
  - 4-6mg/kg IV q24
  - Adjust for renal dysfunction
- Major Adverse Events:
  - Anemia
  - Constipation/NV
  - Injection-site reactions

**Bactrim®**
- Sulfamethoxazole/Trimethoprim
- Interferes with bacterial folic acid synthesis
- Drug of Choice:
  - Stenotrophomonas maltophilia
  - Pneumocystis carinii pneumonia (PCP)
  - Alternative for MRSA

**Bactrim®**
- Dosing:
  - Based on Trimethoprim (TMP) component
  - UTI: Bactrim® DS (800/160) 1 po bid
  - Severe Infections (MRSA/PCP/Stenotrophomonas):
    - 5 mg TMP/kg IV/PO/PT q6-8h
    - Adjust for renal dysfunction
- Major Adverse Events:
  - Stevens-Johnson Syndrome
  - Rash
  - Hyponatremia (IV)
  - Hyperkalemia
  - GI upset (large PO doses)

**Tetracyclines**
- Inhibit bacterial protein synthesis
- Bacteriostatic
- Spectrum of Activity
  - Gram (+) including MRSA
  - Gram (-)
  - Atypicals (Mycoplasma, Chlamydia, Rickettsia)
  - Alternative for H. pylori
**Tetracyclines**

- **3 Agents:**
  - Tetracycline 250-500mg po q6
  - Doxycycline 100mg po/IV q12
  - Minocycline

- **Major Adverse Events:**
  - Photosensitivity
  - Teeth/enamel discoloration in children
  - Hepatotoxicity

**Tigecycline**

- **A glycycline – protein synthesis inhibitor**
- **Spectrum of Activity:**
  - Gram (+) including MRSA and VRE
  - Gram (-) including E. coli & Klebsiella
  - Anaerobes
- **Does not cover:**
  - *Pseudomonas spp.*
  - *Proteus spp.*

**Macrolides**

- **Inhibit RNA-dependant protein synthesis**
- **Spectrum of Activity**
  - Gram (+) – including MSSA
  - Gram (-) (Haemophilus spp)
  - Atypical (Chlamydia spp, Mycoplasma, Legionella)
- **Several Agents:**
  - Erythromycin
  - Clarithromycin
  - Azithromycin

**Clindamycin**

- **Inhibits bacterial protein synthesis**
- **Spectrum of Activity**
  - Gram (+) – MSSA, Streptococcus, some MRSA
  - Anaerobes
- **Excellent alternative for Penicillin-allergic patients**
- **Major Adverse Events:**
  - Diarrhea
**Metronidazole**

- Interacts with DNA causing strand breakage and ultimately inhibits protein synthesis
- Spectrum of Activity: Anaerobes
  - *Clostridium difficile* diarrhea
- Major Adverse Events:
  - N/V
  - Diarrhea
- Dosing:
  - *C. difficile*: 500mg PO/PT q6

**Antimicrobial Resistance**

- Unsuppressed production of β-lactamase
  - AMPc
  - ESBL
- Alteration in bacterial cell membrane
  - Vancomycin-resistant *Enterococcus*
- *Pseudomonas spp.*
  - Aminoglycoside-altering enzymes
  - Efflux pump – pump out drug
  - Alter porin channel – drug can't get in

**Take Home Points**

- Penicillins – increase Gram(-) and maintain Gram(+)
- Addition of β-lactamase inhibitor = anaerobic coverage
- Cephalosporins – avoid 3rd generation
- Carbapenems – reserve for last resort
- Vancomycin – aim high trough
- Pharmacodynamic-based drug dosing