Does One Dose Fit All?
Antibiotic Dosing in Special Populations

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Objectives (Pharmacist Track)
• Describe how pharmacokinetics may be altered in certain patient populations
• Predict how pharmacokinetic alterations may affect antibiotic exposure, efficacy, and toxicity
• Review current strategies to dose antibiotics in special populations (e.g. obese, critically-ill)

Objectives (Pharmacy Technician Track)
• List the special patient populations where alternative antibiotic dosing may be required
• Describe how antibiotic exposure may be altered in special populations
• Review current strategies to dose antibiotics in special populations (e.g. obese, critically-ill)

Current Dosing Practices

One Standard Dose OR A little, A bit more, A lot…

Dosing Strategies
• Fixed Dosing
  • Majority of antiinfectives
    • Dosage adjustment for renal impairment often required
• Weight-Based Dosing
  • 21% (36/175) of weight-based drugs
    • Dosage adjustment for renal impairment in 83.3% (30/36)
• Body Surface Area-Based Dosing
  • 0% of antiinfectives (but 85% of antineoplastics)

Disclosure
I have a vested interest in or affiliation with the following companies or organizations
• Cempra Pharmaceuticals: Advisory Board Member

**Optimal Antibiotic Dosing**

- Based on specific pharmacokinetic-pharmacodynamic (PK-PD) target of bug-drug combination
  - $C_{\text{max}}/\text{MIC}$
  - AUC/MIC
  - $\%T>MIC$

**Target PK-PD Index for Antibiotic Activity by Drug Class**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>$C_{\text{max}}/\text{MIC}$</th>
<th>AUC/MIC</th>
<th>$%T&gt;MIC$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Aminoglycosides</td>
<td></td>
<td>Beta-lactams</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Fluoroquinolones</td>
<td></td>
<td>Penicillins</td>
</tr>
<tr>
<td>Cyclic lipopeptides</td>
<td>Glycopeptides</td>
<td></td>
<td>Cephalosporins</td>
</tr>
<tr>
<td>(daptomycin)</td>
<td>(vancomycin)</td>
<td></td>
<td>Carbapenems</td>
</tr>
<tr>
<td>Oxa/Alloquinolones</td>
<td>(linezolid)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td>Polymyxins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Penicillins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(linezolid)</td>
<td>Cephalosporins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mcrolides</td>
<td>Carbapenems</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Therapeutic Index**

Example: Time-dependent bacterial killing of cefepime

**Pharmacokinetic Alterations in Special Populations**

### Obesity

- Definition per the World Health Organization, WHO:
  
  Body Mass Index (BMI) = Weight in kg / (Height in m)$^2$

<table>
<thead>
<tr>
<th>BMI Classification</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 – 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 – 29.9</td>
</tr>
<tr>
<td>Obese</td>
<td>≥ 30.0</td>
</tr>
<tr>
<td>Obese Class I</td>
<td>30.0 – 34.9</td>
</tr>
<tr>
<td>Obese Class II</td>
<td>35.0 – 39.9</td>
</tr>
<tr>
<td>Obese Class III</td>
<td>≥ 40.0</td>
</tr>
</tbody>
</table>

**Prevalence of obesity (%)**

- World Health Organization, 2013
- Accessed February 13, 2014
- https://www.who.int/mediacentre/factsheets/fs311/en/


Prevalence* of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2011

*Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

Source: Behavioral Risk Factor Surveillance System, CDC.

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Obesity & Pharmacokinetics

Drug Distribution ($V_d$)
- Body composition
- Blood flow
- Drug lipophilicity
- Plasma protein binding

Drug Clearance ($CL$)
- Hepatic metabolism
  - Effects of obesity poorly characterized
- Renal clearance
  - GFR with obesity

Obesity & Drug Distribution

Hydrophilic Drug
$\leftrightarrow V_d$

Lipophilic Drug
$\uparrow V_d$

**Hydrophilicity/Lipophilicity of Antibiotics**

<table>
<thead>
<tr>
<th>Hydrophilic Antibiotics</th>
<th>Lipophilic Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Beta-lactams</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Lincosamides (clindamycin)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Macrolides</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Glycopeptides (vancomycin)</td>
<td>Sulfamethoxazole-Trimethoprim</td>
</tr>
<tr>
<td>Polymyxins</td>
<td>Tetracyclines</td>
</tr>
</tbody>
</table>

- Note: Water content in adipose tissue ~30% of other tissues

**PK Alterations Across Body Size Spectrum**

- Relationship between body size and physiology → Power Law
  \[ P = a \cdot W^b \]
- Change in PK parameter with every additional kg of TBW

**Pharmacokinetic Alterations in Special Populations**

### Critical Illness

- High antimicrobial utilization rates in this population
- Severe Sepsis
  - Incidence: 300 cases per 100,000 population
  - Intensive care unit (ICU) admission ~50%
  - Mortality: 25% (approaching 50% in septic shock)
  - Most common cause of death in non-coronary ICUs
- Dosing particularly challenging in these dynamic hosts
  - Rapid decline in organ function
  - Massive fluid shifts

**Obesity & Drug Clearance**

- Glomerular hyperdynamics (aka augmented renal clearance)
  - \( GFR \uparrow 51\% \) and renal plasma flow \( \uparrow 31\% \)
- Suggests renal vasodilatation of the afferent arteriole
  - \( \uparrow \) transcapillary hydraulic pressure difference
- Significantly affects clearance of multiple compounds
  - Albumin (fractional clearance \( \uparrow 70\% \))
  - Renally-cleared antibiotics

**Critical Illness & Pharmacokinetics**

### Drug Distribution \( \uparrow V_s \)

- Capillary leak syndrome
- Hypocalbuminemia
- Therapeutic Interventions
- Fluid replacement
- Mechanical ventilation
- Extracorporeal circuits
- Surgical drains
- Plasma protein binding

### Drug Clearance \( \uparrow \) or \( \downarrow CL \)

- \( \downarrow \) CL
  - Acute Kidney Injury
  - Hypoperfusion, vasopressors
  - Chronic Kidney Disease
  - Chronic Hepatic Disease
  - \( \downarrow \) CL
  - Augmented renal clearance
  - Hypocalbuminemia
Critical Illness & Drug Distribution

- Hydrophilic Drug
  - \( V_d \) increases
- Lipophilic Drug
  - \( V_d \) decreases

Critical Illness & Clearance

- Diminished Clearance (renal or hepatic)
  - May result in supratherapeutic antibiotic concentrations
  - Fairly good representation in modern PK studies
  - Dosage adjustment recommendations exist (renal>hepatic)
- Augmented Clearance (especially renal)
  - May result in subtherapeutic antibiotic concentrations
  - Often under recognized/represented in PK studies
  - Negligible dosing recommendations, yet emerging area of research

Lean Critically Ill
- Diminished Clearance
  - May result in supratherapeutic antibiotic concentrations
  - Fairly good representation in modern PK studies
  - Dosage adjustment recommendations exist (renal>hepatic)

Dosing Strategies

- Fixed Dosing
  - Ex: Ceftaroline 600mg IV Q12h

- Weight-Based Dosing
  - Ex: Daptomycin 6 mg/kg IV Q24h

Predicting Antibiotic Exposure Based on PK Alterations

- Case Study: Aminoglycosides (Weight-based Dosing)
  - \( V_d \) has to increase in proportion to body weight to ensure equivalent \( C_{max} \)

\[ C_{max} = \frac{Dose}{V_d} \]

- Scenario #1: Septic shock patient receiving massive fluid resuscitation

Scenario #2: Morbidly obese male with a complicated UTI

Which scenario affects \( V_d \) (and in turn \( C_{max} \))?
**C\text{max}\cdot\text{MIC}**

\[C_{\text{max}} = \frac{\text{Dose}}{V_d}\]

- Scenario #2: Morbidly obese male with a complicated UTI
  - Key Concept:
    - Aminoglycosides are hydrophilic so minimal anticipated effect of excess body weight on \(V_d\) (water content of adipose tissue ~30%)
  - Solution:
    - Utilize adjusted body weight (ABW) to calculate initial dose
      \[\text{ABW} = \text{IBW} + 0.4 (\text{TBW} - \text{IBW})\]
      \[\text{IBW} = \text{Ideal Body Weight}, \text{TBW} = \text{Total Body Weight}\]

**AUC:MIC**

\[\text{AUC} = \frac{\text{Dose}}{\text{CL}}\]

- Case Study: Vancomycin (Weight-based Dosing)
  - CL has to increase in proportion to body weight to ensure equivalent AUC across weight spectrum

- Scenario #1: Septic shock patient receiving massive fluid resuscitation
- Scenario #2: Morbidly obese male with a complicated cellulitis
  Which scenario affects CL (and in turn AUC)?

**%T>\text{MIC}**

\[t_{\frac{1}{2}} = \frac{V_d}{0.693/\text{CL}}\]

- Case Study: Beta-lactams
  - \(V_d\) and CL have to increase in proportion to body weight to ensure equivalent \(t_{\frac{1}{2}}\) across weight spectrum

- Scenario #1: Septic shock patient receiving massive fluid resuscitation
- Scenario #2: Morbidly obese male with a complicated UTI
  Which scenario affects \(V_d\) and CL (and in turn \(t_{\frac{1}{2}}\))?
**Importance of Renal Function**

- Main component of antibiotic clearance (CL)
- Changes in CL particularly drive AUC-MIC and %T>MIC (and Cmin)

**Augmented Renal Clearance (ARC)**

- Defined as creatinine clearance (CrCl) ≥ 130 mL/min
- Obese patients with minimal comorbid conditions
- Trauma patients, burn patients, other hyperdynamic kidney states
- ↓ Probability of achieving target AUC-MIC and %T>MIC
- Antibiotics affected: Vancomycin, Beta-lactams, etc.
- Difficult to detect at the bedside without measuring CrCl via timed urine collection
- Estimated CrCl equations often poorly correlate with ARC
  - Cockcroft-Gault
  - Modification of Diet in Renal Disease (MDRD)

**Augmented Renal Clearance (ARC)**

- N = 49 ICU patients in Malaysia
- Median age 34 years, 57% trauma admissions
- 39% with ARC (CrCl > 130 mL/min) based on measured CrCl
- In ARC group:
  - Emergent admissions significantly more common than elective ones
  - Measured CrCl not correlated to Cockcroft-Gault (G-G) CrCl

**Current Dosing Strategies in Special Populations**

**Fixed-Dosed Antibiotics in Obesity**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Standard Dosing</th>
<th>Modification in Obesity</th>
<th>Effect of Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenems</td>
<td>Varies: Management 5-6 g Q8h, 2-3 g Q6h for meningitis</td>
<td><strong>Consider meningal dosing in other invasive diseases</strong></td>
<td>Increased Vd and CL</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>2g IV Q8h</td>
<td>3g IV Q8h if ≥ 100 kg</td>
<td>Increased Vd and CL</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>2g IV Q6h</td>
<td>3g IV Q6h if ≥ 100 kg</td>
<td>Increased Vd and CL</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1800mg IV Q12h</td>
<td>1800-2000mg IV Q12h or 300mg PO Q12h</td>
<td>Increased CL, Decreased tissue penetration</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600mg IV/PO Q12h</td>
<td>600mg IV/PO Q12h or 900mg PO Q12h</td>
<td>Increased Vd and CL</td>
</tr>
</tbody>
</table>

**Weight-Based Antibiotics in Obesity**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Recommended Dosing Weight in Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Adjusted Body Weight (add 40% of TBW/IBW)</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>TBW (even in high-dose)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>TBW (consider max of 2500mg per infusion)</td>
</tr>
<tr>
<td>Sulfamethoxazole- trimethoprim</td>
<td>TBW</td>
</tr>
<tr>
<td>Isoniazid, Pyrazinamide, Ethambutol</td>
<td>IBW</td>
</tr>
</tbody>
</table>
**Beta-lactams**

- Extended/continuous infusions may improve clinical outcomes.
- Systematic review and meta-analysis: 13 RCTs and 13 cohort studies evaluated clinical outcomes with extended/continuous (E/C) vs. intermittent infusion (I)
  - Mainly beta-lactams (2 vancomycin)
  - RR 0.83 (95% CI 0.66, 1.00)

**Risk of Target Non-Attainment in Critical Illness**

- Subject PK data from DALI study: N=343 critically ill patients, 8 different beta-lactams
- Target non-attainment for beta-lactams:
  - Failed to achieve 50% ft>MIC: 12.8% (66/343) patients
  - Failed to achieve 100% ft>MIC: 31.4% (142/343) patients
- Risk factors for target non-attainment per multivariable logistic regression model:
  - Intermittent infusion (both targets)
  - Adjusted odds of non-attainment 41.4% lower with extended or continuous infusion (P=0.001 and P=0.027)
  - ^CICl (100% ft>MIC only)
  - aOR 1.012 per ml/min, P=0.001

**Therapeutic Drug Monitoring**

- Remains an important tool to tailor antibiotic regimens to these patients who do not match population PK
- When possible, recommend getting at least 2 concentrations (steady state preferred):
  1. Post-distributional peak or mid-dose concentration
  2. Trough concentration
- Ongoing research to implement TDM of additional antibiotics: Beta-lactams (penicillins, cephalosporins, and carbapenems)
- Polymyxins (colistin, polymyxin B)
- Clinical data associating PK-PD target attainment with clinical outcomes still lacking - requires TDM in real patients

**Key Points**

- Few generalizations exist to guide antibiotic dosing in obesity or critical illness
  - Case-by-case basis
  - Knowledge of underlying PK helpful in predicting altered exposure
- Weight-based dosing based on concept of CL and Vd increasing proportionally with body size
  - May not always be true at extremes of weight or in certain clinical scenarios
  - Alternative body size descriptors or dosing strategies may be needed
- Augmented renal clearance is under-recognized
  - May result in subtherapeutic antibiotic exposures in both obese and critically ill patients

**Bottom Line**

**One dose does NOT fit all**

Consider special populations in antibiotic dosing much like renal function and other comorbidities

**SCSHP 2015 Annual Meeting**

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