Antibiotic Dose Optimization in Critically Ill Patients: Providing Individualized Care

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CONFLICTS OF INTEREST

- None to report
LEARNING OBJECTIVES

- To describe the PKPD characteristics of antibiotics that support individualized dosing

- To explain the pathophysiological factors in the critically ill population that contribute to pharmacokinetic changes

- To justify individualized antibiotic dose optimization practices within institutions

- To formulate individualized dosing regimens for selected antimicrobials in critically ill patients
ANTIBIOTIC ICU TREATMENT GOALS

- Prompt initiation
  - Kumar et al.
    - 7.6% mean decrease in survival for each hour delay in appropriate antibiotics
- Correct selection
  - Gaieski et al.
    - 13.7% decrease in mortality when appropriate antimicrobial administered within 1-hour of triage
- Optimize drug properties
- De-escalation
- Discontinuation
PK/PD AND THE MIC

- Pharmacokinetics (PK)
  - Change in concentration over time
- Pharmacodynamics (PD)
  - Concentration required for optimal effect
  - Minimum inhibitory concentration (MIC)
    - Lowest concentration inhibiting growth of organism

**PK/PD Relationship**
<table>
<thead>
<tr>
<th>PK/PD Index</th>
<th>Time-dependent</th>
<th>Concentration-dependent</th>
<th>Time and Concentration-dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>$fT&gt;MIC$</td>
<td>$fC_{max}/MIC$</td>
<td>$fAUC_{0-24}/MIC$</td>
<td></td>
</tr>
<tr>
<td>Example</td>
<td>$\beta$-lactams</td>
<td>Aminoglycosides</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluoroquinolones</td>
<td>Lincosamides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lipopeptides</td>
<td>Macrolides</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oxazolidinones</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Goal</td>
<td>Maximize duration of exposure</td>
<td>Maximize concentration</td>
<td>Maximize exposure</td>
</tr>
</tbody>
</table>
$fT_{\text{MIC}}$

- Time in the dosing interval when the free concentration of antibiotic exceeds the MIC of the bacteria
  - **Penicillins**
    - 50% $fT_{\text{MIC}}$
  - **Cephalosporins**
    - 60-70% $fT_{\text{MIC}}$
  - **Carbapenems**
    - 40% $fT_{\text{MIC}}$

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</tbody>
</table>

**Time-dependent**

**\( fC_{\text{max}}/\text{MIC} \)**

- Ratio between the peak concentration and the MIC of the bacteria
- Aminoglycosides
  - 8-10:1 \( C_{\text{max}}/\text{MIC} \)

<table>
<thead>
<tr>
<th>Concentration-dependent</th>
<th>( fC_{\text{max}}/\text{MIC} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK/PD Index</td>
<td></td>
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<td></td>
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\( fAUC_{0-24}/MIC \)

- Ratio between the area under the concentration-time curve during a 24-hour period and the MIC of the bacteria
- Vancomycin
  - >400 AUC/MIC ratio

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<tbody>
<tr>
<td>Time and Concentration-dependent</td>
<td>Fluoroquinolones, Lincosamides, Macrolides, Oxazolidiones, Tetracyclines</td>
<td>Maximize exposure</td>
</tr>
</tbody>
</table>

THE MIC…

- Ciprofloxacin
  - PK/PD index = $fAUC_{0-24}/MIC$
  - Target $fAUC_{0-24}/MIC \geq 125$
  - Bacteria-1
    - MIC = 1 mcg/mL
    - Require $AUC_{0-24} 125 \rightarrow 125/1 \rightarrow 125$
  - Bacteria-2
    - MIC = 2 mcg/mL
    - Require $AUC_{0-24} 250 \rightarrow 250/2 \rightarrow 125$
  - Bacteria-3
    - MIC = 4 mcg/mL
    - Require $AUC_{0-24} 500 \rightarrow 500/4 \rightarrow 125$
What is the PK/PD index that describes the optimal killing of bacteria by β-lactam antibiotics?

A. $fT >_{\text{MIC}}$

B. $fC_{\text{max}}/\text{MIC}$

C. $fAUC_{0-24}/\text{MIC}$
What is the PK/PD index that describes the optimal killing of bacteria by β-lactam antibiotics?

A. $fT > \text{MIC}$

B. $fC_{\text{max}} / \text{MIC}$

C. $fAUC_{0-24} / \text{MIC}$
PK IN THE CRITICALLY ILL PATIENT

PK/PD Relationship

Patient specific factors

Patient outcomes

Dose → PK → Concentration → MIC → PD → Effect
PK IN THE CRITICALLY ILL PATIENT

❤️ CARDIOVASCULAR

🔍 Output → Drug clearance
🔍 Microvascular failure
🔍 Tissue perfusion
🔍 Distribution of antibiotics

RESPIRATORY

Chronic respiratory disease versus Acute lung injury

PK IN THE CRITICALLY ILL PATIENT

RENAL

Impairment $\rightarrow$ reduced clearance

Augmented renal clearance (ARC)

Enhanced renal elimination $\rightarrow$ sub-therapeutic levels

*Pharmacotherapy.* 2015;35:1063-75.
PK IN THE CRITICALLY ILL PATIENT

Volume of distribution (Vd)

Hydrophilic agents
- Aminoglycosides
- β-lactams
- Vancomycin
- Linezolid

Small ~0.2-0.3 L/kg
Increased Vd with fluid shifts

Hydrophobic agents
- Fluoroquinolones
- Tigecycline
- Clindamycin

Large Vd >1 L/kg
MONTE CARLO SIMULATION

- Computer-based simulation
- Integrates variables:
  - PK/PD
  - Antimicrobial concentrations
  - MIC of specific organisms
- Determines probability of successful regimen

PTA

- Probability of Target Attainment (PTA)
  - Probability that at least a specific value of a PK/PD Index is achieved at a given MIC
PTA - CEFEPIME

▲ 2g IV q8 hours
Δ 1g IV q4 hours
● 1g IV q6 hours
○ 2g IV q12 hours
■ 1g IV q12 hours

BAYESIAN ANALYSIS

- Computer-based simulation integrating:
  - Population model
  - Patient serum levels
HOW TO APPROACH TREATMENT PATIENT CASES
JS is a 92yoF with a PMH of COPD who was sent to the ED from the NH with worsening SOB, fever, and an oxygen saturation of 86% on room air. She had a low-grade fever 4 days ago and was started on Ceftriaxone IM by the NH physician. Despite this, she continued to worsen. Upon arrival and exam, she was started on Zosyn 4.5g IV q6h infused over 30 minutes and Levaquin 500mg IV daily.
BASELINE CHARACTERISTICS

Ht: 160cm  Wt: 45kg  SCr: 1.36
Tmin: 101.7  Tmax: 102.9  Flu swab: NEG
HR: 99  RR: 27  BP: 166/68
BUN: 19  WBC: 8.2

Estimated CrCl (Cockgroft-Gault): 18.7 mL/min

Is her current Zosyn regimen appropriate based on her characteristics?
TRENDING THREATS IN HOSPITALS TODAY

1) Alarming rise in antibiotic resistance
   - One of the greatest threats to human health worldwide
   - Extreme costs to U.S. healthcare: $21 to $34 billion per year
   - Result in > 8 million additional hospital days

2) Diminishing antibiotic pipeline as major drug companies withdraw from antibiotic market

HEALTHCARE-ASSOCIATED INFECTIONS

- Occur in ~2 million Americans per year
- Result in 99,000 deaths per year, mostly due to antibiotic-resistant pathogens (e.g. *Pseudomonas aeruginosa*)
- Pneumonia one of the most common healthcare-associated infection in America

DOSE OPTIMIZATION: REITERATION

- Maximize antibiotic efficacy by maximizing bacterial kill
- Prevent/reduce emergence of resistance
- Preserve antibiotic effectiveness
- Alternative dosing strategy: extended infusions of Beta-lactam antibiotics
- Evidence suggests extended infusion piperacillin-tazobactam (PIP-TAZ) is at least equivalent—and potentially superior—to standard dosing

WHAT IS EXTENDED-INFUSION PIP-TAZ?

- Infusion over a prolonged period of time (e.g. over 4 hours) instead of the shorter standard infusion time of 30 minutes
- Developed from PK/PD profiles of Beta-lactam antibiotics to maximize time-dependent bactericidal activity and improve PTA
- Especially beneficial in critically ill patients with infections that are severe or difficult to treat

IV ADMINISTRATION DEFINITIONS

- Intermittent IV administration: infusion lasting 30 to 60 minutes
- Extended IV administration: infusion lasting 3 to 4 hours
- Continuous IV administration: continuous infusion over a 24-hour period at a fixed rate
A NEW WAY TO OPTIMIZE DOSING

- fT>MIC is the biggest factor in predicting degree of bactericidal activity for Beta-lactams such as PIP-TAZ, as they exhibit time-dependent PD
- Traditional dosing of PIP-TAZ does not provide adequate fT>MIC for organisms with an MIC > 8 mg/L
- Thus, finding alternative dosing regimens that maximize fT>MIC is key
- This is where extended infusion practice comes in

Pharmacotherapy 2006;26(9):1320-1332
Clin Infect Dis 2007; 44:624
A NEW WAY TO OPTIMIZE DOSING

- The PK/PD index that maintains the bactericidal activity is when the free time remains above the MIC.
- The best strategy to optimize these properties in PIP-TAZ is to infuse 3.375g over 4 hours.
- A cohort study of patients treated with PIP-TAZ for Pseudomonas aeruginosa infections compared those receiving standard (n=92) vs. extended-infusion dosing (n=102).
  - In patients at greatest risk for mortality (APACHE II score ≥17) extended infusion significantly lowered 14-day mortality rates (12.2% vs. 32.6%, \( P = 0.04 \)) and median hospital length of stay (21 days vs. 38 days, \( P = 0.02 \)) compared with standard dosing.

*Pharmacotherapy* 2006; 26: 1320-1332.
*Clin Infect Dis.* 2007; 44:357-363
## DOSING REGIMEN BASED ON RENAL FUNCTION

<table>
<thead>
<tr>
<th>CrCl</th>
<th>&gt; 20 ml/min</th>
<th>CRRT</th>
<th>CrCl &lt;20 ml/min</th>
<th>Intermittent or Peritoneal Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>3.375g q8h over 4 hours</td>
<td>2.25g q8h over 4 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Pharmacotherapy* 2006; 26: 1320-1332.
*Clin Infect Dis.* 2007; 44:357-363
Current PIP-TAZ regimen ordered by physician: 4.5g IV q6h over 30 minutes
CrCl: 18.7 mL/min

What is the most appropriate regimen JS should be on?
A) PIP-TAZ 3.375g IV q8h over 4 hours
B) PIP-TAZ 2.25g IV q8h over 4 hours
JF is a 44yoF with a hx of insulin-dependent DM, diabetic neuropathy, osteomyelitis, and recurrent foot ulcers who was admitted with a CC of worsening bilateral foot ulcers. She has been getting consistent outpatient wound care and has been on Augmentin 500 mg PO BID at home for approximately 1 week prior to this admission. She reported that over the last month, the wounds on both of her feet were progressively getting worse with increasing drainage, pain, inflammation, and odor.

Baseline Characteristics:

- Height: 165 cm
- Weight: 81 kg
- SCr: 0.99
- BUN: 19
- WBC: 7.8
- Tmax: 98.5
- BP: 155/75
- Allergies: erythromycin base
A previous right-foot wound culture from 2 months prior grew Proteus species, Klebsiella oxytoca, and Staphylococcus aureus.

<table>
<thead>
<tr>
<th>Proteus species</th>
<th>MIC Dilution</th>
<th>MIC Interp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/Clavulanate</td>
<td>8</td>
<td>S</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>≥32</td>
<td>R</td>
</tr>
<tr>
<td>Ampicillin/Sulbactam</td>
<td>16</td>
<td>I</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>≥64</td>
<td>R</td>
</tr>
<tr>
<td>Cefepime</td>
<td>≤1</td>
<td>S</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>≤1</td>
<td>S</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>≤1</td>
<td>S</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤0.25</td>
<td>S</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>≤0.5</td>
<td>S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>≤1</td>
<td>S</td>
</tr>
<tr>
<td>Imipenem</td>
<td>4</td>
<td>S</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>≤0.12</td>
<td>S</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>≤4</td>
<td>S</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≤1</td>
<td>S</td>
</tr>
<tr>
<td>Trimethoprim/Sulfa</td>
<td>≤20</td>
<td>S</td>
</tr>
</tbody>
</table>
### Staphylococcus aureus

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC Dilution</th>
<th>MIC Interp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefoxitin</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td></td>
<td>R</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>0.25</td>
<td>S</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>≥8</td>
<td>R</td>
</tr>
<tr>
<td>Linezolid</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td><strong>Oxacillin</strong></td>
<td>≤0.25</td>
<td>S</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>≤0.5</td>
<td>S</td>
</tr>
<tr>
<td>Trimethoprim/Sulfa</td>
<td>≤10</td>
<td>S</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≥16</td>
<td>R</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>≤0.12</td>
<td>S</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>≤0.5</td>
<td>S</td>
</tr>
<tr>
<td><strong>Klebsiella oxytoca</strong></td>
<td>MIC Dilution</td>
<td>MIC Interp</td>
</tr>
<tr>
<td>------------------------</td>
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<td>S</td>
</tr>
<tr>
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<td>2</td>
<td>S</td>
</tr>
<tr>
<td><strong>ESBL confirmation test</strong></td>
<td>POSITIVE</td>
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</tr>
<tr>
<td>Gentamicin</td>
<td>4</td>
<td>S</td>
</tr>
<tr>
<td>Imipenem</td>
<td>8</td>
<td>I</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>≤0.12</td>
<td>S</td>
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<tr>
<td>Piperacillin/Tazobactam</td>
<td>≥128</td>
<td>R</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≥16</td>
<td>R</td>
</tr>
<tr>
<td>Trimethoprim/Sulfa</td>
<td>≥320</td>
<td>R</td>
</tr>
</tbody>
</table>
What would be the right empiric therapy selection in this patient until new cultures and testing can be done?
GRAM-NEGATIVE INFECTIONS: PROLONGED INFUSION OF B-LACTAMS

- fT>MIC required for maximal effect varies between different B-lactams
- Carbapenems fT>MIC: ~40%
  - Meropenem: extended infusion over 3 hours
Let’s go back to JF...
Based on the patient presentation, history, and previous cultures, which of the following antibiotic regimens is the most appropriate for empiric coverage?

- A) Piperacillin/Tazobactam 3.375g IV q8h infused over 4 hours
- B) Vancomycin 1000mg IV q12h + Piperacillin/Tazobactam 3.375g IV q8h infused over 4 hours
- C) Meropenem 2g IV q8h infused over 3 hours
MZ is a 67yoF with myelodysplastic syndrome who comes in with acute onset of 1-2 days of left knee pain, swelling, and fever of 101.7. The left knee is a site of TKR done 2 years ago.

Baseline characteristics:

Ht: 173 cm   Wt: 95kg   WBC: 1.2   RBC: 2.41
Plt: 58     ANC: 0.4 x 10^3/mcL   Segs: 36
Bands: 0    Tmax: 101.7     SCr: 1.31
BUN: 19     BP: 91/35      Alb: 1.3

Allergies: amoxicillin, levaquin, contrast dye
The attending physician was looking to empirically start vancomycin in this patient.
VANCOMYCIN PK/PD REVIEW

- Hydrophilic drug
- Clearance: based on estimated CrCl using Cockcroft-Gault equation utilizing TBW
- Most estimations of clearance are based on population PK parameters and values
- ~55% protein-bound in plasma
  - Low albumin (e.g. < 3) may result in elevated free serum vancomycin concentrations
- Bactericidal effect is present when concentration is 4 x MIC
- MRSA is susceptible to vancomycin if MIC ≤ 2
- AUC to MIC ratio is the recommended method of determining vancomycin efficacy
  - AUC:MIC > 400 ensures efficacy
VANCOMYCIN TROUGH TARGETS

- Trough should *always* be > 10 mg/L to prevent development of resistance
- Target 15 to 20 mg/L: bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia proven to be caused by *Staphylococcus aureus*
- Target 10 to 15 mg/L: most other indications (e.g. cellulitis, community-acquired pneumonia)
WHEN TO DRAW A VANCOMYCIN LEVEL

- A level should be checked:
  - Prior to the 4th dose
    - 85-90% steady-state if no loading dose utilized
    - ~100% steady-state if loading dose utilized
  - If renal function is unstable
  - If dosage adjustment is made, trough can be checked after 3 doses
  - If nephrotoxicity or ototoxicity is suspected
  - Changes in albumin level (if albumin < 3) while patient is on therapy
ESTIMATING VANCYMYCIN CLEARANCE

- Simple method: Clearance = CrCl x A
- A = 0.7 to 0.8 in non-obese individuals
- A = 0.9 to 1.1 in obese individuals
- This is to account for the protein-binding
Let’s go back to MZ…
The attending physician was looking to empirically start vancomycin, with a target trough level between 10 and 15 mcg/mL.

Use Bayesian pharmacokinetics to estimate the initial empiric regimen using the following formulas:

1. **Estimate CrCl:**
   - Cockgroft-Gault equation: 41.9 mL/min
   - Multiply CrCl for albumin by 0.8 = 33.5 mL/min

2. **Estimate population kinetics-based normalized Vd:**
   
   \[ Vd (L) = \frac{((0.17 \times \text{Age (years)}) + (0.22 \times \text{TBW (kg)}) + 15)}{42.5} \]

3. **Estimate 24-hour dose requirement for an AUC > 400 based on indication:**

   \[ \text{Dose in 24h (mg)} = \text{AUC} \times (((0.689 \times \text{Crcl} + 3.66 \text{ if age >60, CrCl if age < 61}) - (\text{Age (years)} \times 0.012 \text{ ml/min/kg when Age > 95 years })) \times 0.06) \times \text{Vd} \]

4. Determine dose and Interval based on dose needed in 24 hours.
Based on the empiric calculations, MZ’s regimen was estimated to be **1000mg IV q24h**. She received 3 doses over 3 days:

**Day 1:** 1000mg given at 7:12 AM  
SCr: 1.31

**Day 2:** 1000mg given at 6:49 AM  
SCr: 1.34

**Day 3:** 1000mg given at 6:20 AM  
SCr: 1.26

The first trough level was drawn prior to the 4th dose to check the patient’s steady-state concentration:

**Day 4:** Level drawn at 5:00 AM = **11.5**  
SCr: 1.20
<table>
<thead>
<tr>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
<th>Sex</th>
</tr>
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<tbody>
<tr>
<td>67 years</td>
<td>173 cm</td>
<td>95 kg</td>
<td>Female</td>
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</table>

**Vancomycin 1000 mg IV every 24 hours**

- **Current Regimen**
- **1000 mg q 24 h**
- **Observed Level**

- **Peak:** 23.6 mg/L
- **Trough:** 12.8 mg/L

- **ID:** 1
- **Kel:** 0.027 1/h
- **Vd:** 89 L
- **AUC:** 422.3 (mg/h L)
SAME PATIENT, NEW SCENARIO…

A blood sample was collected from MZ’s knee site on the day of admission and cultured, which resulted in GPC in clusters from both bottles.

What target range should the vancomycin trough be within?

A) 10 to 15 mg/L

B) 15 to 20 mg/L
<table>
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</tr>
</thead>
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**Vancomycin 1250 mg IV every 24 hours**

- Current Regimen
- 1250 mg q 24 h
- Observed Level

- Peak: 30.3 mg/L
- Trough: 15.3 mg/L

**Parameters**
- ID: 1
- Kel: 0.031 1/h
- Vd: 76.1 L
- AUC: 528.1 (mg/h L)
Therapeutic drug monitoring (TDM)
- High-performance liquid chromatography (HPLC) assays
- Roberts et al.
  - β-lactam TDM in 236 ICU-patients (53.5±18.3 years)
  - 175 (74.2%) patients required dose adjustments
  - 119 (50.4%) required dose increases
  - 206 (87.3%) positive treatment outcomes
- Further randomized trials needed
SUMMARY

- Baseline knowledge of PK/PD indices
- Changes in pathophysiology in critically ill patients impact antibiotic concentrations
- Use pharmacokinetic modeling to bring dose optimization to the bedside
- TDM for more agents in the future
Antibiotic Dose Optimization in Critically Ill Patients: Providing Individualized Care

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