Optimizing Antimicrobials in the ICU using Pharmacodynamic and Pharmacokinetic Principles

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Objectives

1. Discuss the pathophysiologic changes in critically ill patients that affect PK/PD parameters in the context of antimicrobial therapy.

2. Identify ways to optimize antimicrobial therapy in critically ill patients in the context of altered PK/PD from critical illness.
Case: Patient XX

ID: 68 F admitted with S. pneuomo CAP and septic shock

PMH: DM2, HTN, CAD, Afib

Course in Hospital – MOF (CVS, RESP, RENAL, METAB)

Interventions – aggressive fluid resuscitation, mechanical ventilation, appropriate antibiotics, vasopressors, inotropes, enteral nutrition, stress steroids, glucose control, CRRT

Outcome: Death from MOF after 7 day ICU course
Why did Mrs. XX die?

“Well, Strep can be a very virulent organism!”

“Well, she presented late with established organ failure. With 4 failing organs she only had a 20% chance of survival anyways!”

“Well, she had no chance given her age and co-morbidities!”

“Well, with APC off the market, what do you expect?”

“Well, maybe we didn’t treat her like a critically ill patient…”
Maybe we chose the right antibiotic but we didn’t dose it appropriately

Where do you get your antimicrobial dosing information from?

Uptodate…Sandford Guide…Micromedex

Where do they get their dosing information from?

Product monographs…clinical trials

In what kind of patients are these doses established?

Healthy volunteers? Non-critically ill patients?

Can we extrapolate this data to critically ill patients?
<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Pharmacodynamics</th>
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<tbody>
<tr>
<td>Time course of drug absorption, distribution, metabolism, and excretion</td>
<td>Relationship between drug concentration and effect/toxicity</td>
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**Clinical Pharmacokinetics**

The application of PK principles to optimize drug therapy in an individual patient
Key Concepts

• Each antibiotic has its own pharmacokinetic profile

• Each class of antimicrobials has a different pharmacodynamic profile based on different kill/inhibitory characteristics on bacteria

• Individualized dosing regimens using known PK/PD characteristics are important to optimize patient outcomes and minimize antimicrobial resistance.

• PK profiles change over time in critically ill patients – warranting periodic reconsideration of dosing regimens
Figure 1. Pharmacokinetic and pharmacodynamic parameters of antibiotics on a concentration vs. time curve. Key: $T > MIC$—The time for which a drug’s plasma concentration remains above the minimum inhibitory concentration (MIC) for a dosing period; $C_{\text{max}}/\text{MIC}$, the ratio of the maximum plasma antibiotic concentration ($C_{\text{max}}$) to MIC; $AUC/\text{MIC}$, the ratio of the area under the concentration time curve during a 24-hour time period ($AUC_{0-24}$) to MIC.
PD Targets for Different Antibiotics

Time Dependent (T>MIC)
- Beta Lactams
- Carbapenems
- Linezolid
- Erythromycin
- Clarithromycin
- Clindamycin

Concentration Dependent (C\text{max}:MIC)
- Aminoglycosides
- Metronidazole
- Fluoroquinolones
- Daptomycin

Both (AUC:MIC)
- Fluoroquinolones
- Aminoglycosides
- Azithromycin
- Tetracyclines
- Vancomycin
- Tigecycline
- Linezolid

PMID: 19237886
Pharmacokinetic changes are highly variable in the ICU but may be more predictable if...

A. You know basic antibiotic characteristics
   - lipophilic or hydrophilic

B. You can trend the changes in patient characteristics
   - Volume status
   - End organ function/perfusion

C. You can trend pathophysiologic characteristics
   - Systemic inflammation
   - Hemodynamics
Hydrophilic or Lipophilic and Why do I Care?

<table>
<thead>
<tr>
<th>Hydrophilic Antibiotics:</th>
<th>Lipophilic Antibiotics:</th>
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<tbody>
<tr>
<td>• Beta Lactams</td>
<td>• Fluoroquinolones</td>
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<tr>
<td>• Aminoglycosides</td>
<td>• Macrolides</td>
</tr>
<tr>
<td>• Vancomycin</td>
<td>• Clindamycin</td>
</tr>
<tr>
<td>• Linezolid</td>
<td>• Tigecycline</td>
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<tr>
<td>• Colistin</td>
<td></td>
</tr>
<tr>
<td>Low Vd</td>
<td>High Vd</td>
</tr>
<tr>
<td>Predominantly renal clearance</td>
<td>Predominantly hepatic clearance</td>
</tr>
<tr>
<td>Low intracellular penetration</td>
<td>Good intracellular penetration</td>
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</tbody>
</table>
Critical illness (disease level and patient level) has the greatest influence on:

**Volume of Distribution** ($V_d$)

**Clearance** ($Cl$)

Increased Risk of Treatment Failure

Increased Risk of Antimicrobial Resistance
Characteristics of Sepsis and the Septic Patient affecting Vd

- Systemic inflammation/Capillary leak
- Serum Concentration (Hydrophilic drugs: aminoglycosides, beta-lactams, etc)

- Aggressive fluid resuscitation
- Third-spacing of albumin

- High output fistulas, post surgical drains
- Extracorporeal circuits (CRRT, plasma exchange, cardiopulmonary bypass)
Characteristics of Sepsis and the Septic Patient affecting Drug Clearance

- Hyperdynamic states (pharmacologically or pathophysiologically enhanced) can increase CrCl and hepatic perfusion
  - Increased clearance
- End-organ dysfunction can reduce metabolism and elimination of active drug
  - Reduced clearance
- Renal replacement therapies have variable effects on clearance depending on type and drug
  - Increased for some drugs like Pip/Tazo, Meropenem
- We have adaptive methods for increasing drug clearance during states of MOF
  - Gastrointestinal clearance of ciprofloxacin is increased in renal failure
  - Biliary clearance of piperacillin increases in renal failure
How does Vd and Cl affect Half Life ($T_{1/2}$)?

\[ T_{1/2} = \frac{0.693 \times V_d}{C_l} \]

The Obvious: decrease clearance $\rightarrow$ prolong Half Life

The Less Obvious: increase volume of distribution $\rightarrow$ prolong Half Life
What about protein binding?

- Significant changes in free fractions of drug are only relevant for highly protein bound drugs (>95%)
  - Small changes in protein binding result in huge relative changes in free (unbound) drug

- Changes in protein binding will affect both Cl and Vd

- Most antibiotics have low protein binding (<90%)
  - Exceptions: Ceftriaxone (95% bound to albumin), ertapenem, teicoplanin, aztreonam, daptomycin,

PMID: 21142293
Pharmacokinetics of Ceftriaxone in Critically Ill Adults

- 11 patients with sepsis
- Mean serum albumin 22 g/dL
- 2 patients with renal failure (no dialysis)
- Everyone receives Ceftriaxone 2g IV q24h

PMID: 11266414
Pharmacokinetics of Ceftriaxone in Critically Ill Adults

Figure 2. Scatter graph showing the relationship between blood concentration and percentage free fraction of ceftriaxone in patients with normal renal function (●) and patients with renal failure (○).
Pharmacokinetics of Ceftriaxone in Critically Ill Adults

Figure 1. Total plasma ceftriaxone concentrations of individual patients (logarithmic scale) over 24 h following iv administration. The curves drawn with a short-dashed (---) line represent the patients with renal failure. The long-dashed (———) line, representing the desired MIC, is at 8 mg/L.
Optimizing Antimicrobials in the ICU: Continuous/Prolonged Infusions of Beta Lactams

Cefotaxime vs Klebsiella in mouse lung model
Optimizing Antimicrobials in the ICU: Continuous/Prolonged Infusions of Beta Lactams

Retrospective studies and Quazi-experimental studies:
• Improved clinical cure rates
• Shorter ICU LOS
• Improved mortality

PMID: 17205441, 18313273, 21074370, 19150225

Reviews and Meta-analyses:
• Large volume of low level evidence suggest benefit
• Magnitude of benefit greatest in ICU populations

PMID: 21730935, 21914174, 20124468

One international multicenter RCT of 60 patients
• Improved clinical cure rates

PMID: 23074313
Optimizing Abx in the ICU: Extended Interval Aminoglycosides

• WHY?
  • Rapid bactericidal activity
  • Lowest rate of resistance

• Three PK/PD concepts we can take advantage of to maximize efficacy and minimize toxicity
  • Concentration dependent killing
  • Time dependent toxicity
  • Post-antibiotic effect
Aminoglycosides—Relationship Between $C_{\text{max}}:\text{MIC}$ Ratio and Clinical Response

Clinical response (%)

- 2: 55
- 4: 65
- 6: 70
- 8: 83
- 10: 89
- 12+: 92

Once-daily vs. Conventional Three-times Daily Aminoglycoside Regimens

Concentration (mg/L)

Time (hours)

Once-daily regimen
Conventional (three-times daily regimen)
Summary

The Problem:

- Inter and intra patient PK variability is huge
- We don’t know how reliable our dosing strategies are in the ICU to reach PD targets
- Therapeutic drug monitoring for only a few drugs
- Most micro labs do not report actual MICs

Solution?

- Therapeutic drug monitoring to identify patients in whom alternate dosing strategies are required?
- Periodic re-evaluation of antimicrobial dosing as Vd and Cl change over time?