Hitting the Mark: Improving Antibiotic Dosing in Patients with Altered Renal States

Monday, December 3, 2018
2:00 PM – 3:30 PM

Presenters:
Doug Fish, Pharm.D., BCCCP, BCPS-AQ ID
N. Jim Rhodes, Pharm.D., M.Sc., BCPS-AQ ID
Bruce A. Mueller, Pharm.D., FASN, FCCP, FNKF
Disclosures

All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.
Learning Objectives

• Identify critical factors that influence antibiotic exposure in patients with altered renal states.
• Evaluate alternative antibiotic dosing schemes to improve outcomes and facilitate care transitions.
• Select appropriate antibiotic regimens for patients with altered renal states.
Hitting the Mark: Improving Antibiotic Dosing in Patients with Altered Renal States

Douglas Fish, Pharm.D., BCCCP, BCPS-AQ ID
Professor, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Science, Aurora, CO
Clinical Specialist in Critical Care/Infectious Diseases
University of Colorado Hospital, Aurora, CO
Objective

• Identify critical factors that influence antibiotic exposure in patients with altered renal states
Patient Case #1: K.G.

- K.G. is a 76 y.o., 75 kg male who resides in a long-term care facility. He has a PMH significant for Type 2 DM, HTN, CAD, and stage 2 CKD. He has NKDA. He was hospitalized 2 weeks ago due to acutely altered mental status and chest pain.
- He now develops fever, increasing SOB, right-sided chest pain, and cough productive of purulent sputum. He is transported to the ED where the following are noted: BP 115/55 mm Hg, HR 121/min, RR 26/min, and Temp 38.9°C; the patient is alert and oriented x 1. His BUN/SCr are 53/1.5 with UO = 20 mL/hr; chest X-ray is consistent with RLL pneumonia.
- He is given 2 L NS and started on cefepime + vancomycin.
Based on K.G.’s history and clinical presentation, which of the following pharmacokinetic changes (compared to healthy individuals) would you expect to affect his antibiotics?

A. Decreased clearance
B. Increased volume of distribution
C. Decreased protein binding
D. All of the above
Renal Impairment in Hospitalized Patients

• Acute kidney injury (AKI) reported to occur in 4% - 23% of all hospitalized patients
  — Associated with infection in 10% - 30% of cases
• AKI occurs in up to 80% of patients with sepsis
  — Associated with increased mortality, hospital LOS, ICU LOS, cost
• One study found 31% of all infection-related hospitalizations occurred in patients with chronic kidney disease (CKD)
  — CKD also associated with increased hospital mortality, LOS, cost

Relationship Between Pharmacokinetics and Pharmacodynamics

- Concentration at Target Site
- Concentration In Plasma
- PK
- PD
- Drug Administration
- Host Factors
  - Pharmacological Effects
  - Clinical Efficacy and Toxicity
Alterations of Organ/Body Systems in Critically Ill Patients

Gastrointestinal dysfunction

Hepatic dysfunction

CNS dysfunction

Cardiovascular dysfunction

Neuromuscular dysfunction

Immunologic dysfunction

Respiratory dysfunction

Renal dysfunction

Endothelial dysfunction

Endocrine dysfunction

The Critically Ill Patient
## Potential PK Alterations Related to Physiochemical Properties of Antibiotics

<table>
<thead>
<tr>
<th></th>
<th>Hydrophilic Drugs</th>
<th>Lipophilic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume of Distribution (Vd)</strong></td>
<td>Small (0.1 – 0.8 L/kg)</td>
<td>Large (≥1 L/kg)</td>
</tr>
<tr>
<td><strong>Area of Distribution</strong></td>
<td>Primarily in extracellular fluids</td>
<td>Extensive intracellular penetration</td>
</tr>
<tr>
<td><strong>Elimination (CL)</strong></td>
<td>Predominantly renal</td>
<td>Predominant liver metabolism</td>
</tr>
<tr>
<td><strong>Volume of distribution (Vd)</strong></td>
<td>Vd ↑ or ↓ according to fluid shifts, fluctuations in body water</td>
<td>Not highly affected by fluid status</td>
</tr>
<tr>
<td><strong>Changes in drug CL in critically ill patients</strong></td>
<td>CL ↑ or ↓ according to changes in renal function</td>
<td>CL ↑ or ↓ according to changes in hepatic function</td>
</tr>
</tbody>
</table>

Physiochemical Classification of Antibiotics

- **Hydrophilic antibiotics**
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Aztreonam
  - Vancomycin
  - Linezolid
  - Polymyxins
  - Fluconazole
  - Aminoglycosides
  - Daptomycin
  - (Fluoroquinolones)
  - Acyclovir

- **Lipophilic antibiotics**
  - (Fluoroquinolones)
  - Macrolides
  - Tetracyclines
  - Rifampin
  - Clindamycin
  - Voriconazole
  - Posaconazole
PK/PD Alterations in Renal Impairment: More Than Just Decreased Renal Clearance

• Bioavailability
  – Alterations in absorption and/or time to Cmax for PO drugs

• Protein binding
  – Decreased due to albuminemia, ↓ binding affinity, competition for binding sites

• Volume of distribution
  – Often significantly increased due to fluid overload, ↓ protein or tissue binding

• Nonrenal clearance
  – Altered hepatic enzyme metabolism or transporter function
  – Nonrenal clearance may be ↑ in AKI and ↓ in chronic renal failure

• Pharmacodynamic alterations
  – Drug receptor site changes
PK Alterations: Volumes of Distribution (Vd)

• Attributed to numerous factors:
  – AKI and CKD
  – Aggressive volume resuscitation
  – Capillary leak syndromes
  – Hypoalbuminemia
  – Cachexia and muscle mass depletion
  – Ascites, peritoneal exudates, mediastinitis, large pleural effusions
  – Heart failure
  – Malnutrition
  – Acid-base disturbances
  – Burn injuries

• Alterations in Vd are not accurately predictable among individual patients
  – Individuals may also display significant changes in Vd over time

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Creatinine clearance (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1: &gt;100</td>
</tr>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>3.1 ± 2.6</td>
</tr>
<tr>
<td>CL (L/hr)</td>
<td>7.0 ± 4.3</td>
</tr>
<tr>
<td>$V_{ss}$ (L/kg)</td>
<td>0.28 ± 0.25</td>
</tr>
</tbody>
</table>

Factors Affecting Drug PK in ICU Patients and Clinical Recommendations

Protein Binding Considerations in ICU Patients

- Random sampling of 100 MICU patients at the University of Colorado Hospital found decreased albumin levels in 91%
  - Similar alterations found in SICU patients
- Total protein levels were also altered:
  - 47% of patients with decreased levels
  - Another 46% of patients had TP levels in lower half of normal range

<table>
<thead>
<tr>
<th>Albumin (gm/dL)</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.0</td>
<td>12%</td>
</tr>
<tr>
<td>2.1 - 3.3</td>
<td>79%</td>
</tr>
<tr>
<td>3.4 - 4.0</td>
<td>6%</td>
</tr>
<tr>
<td>4.0 - 5.0</td>
<td>3%</td>
</tr>
</tbody>
</table>

Normal range = 3.4 – 5.0 gm/dL

Fish DN, unpublished data.
Altered Protein Binding of Drugs in the ICU

- Protein binding of levofloxacin determined in 20 MICU & Burn ICU patients at several time points
  - Binding in ICU (mean ± SD): 17.2 ± 8.4%
  - Normal binding: 24 - 38%
- Similar alterations reported for linezolid
  - Binding in sepsis/septic shock: 6.9 – 22.4%
  - Normal binding: 31%
- Pharmacodynamic relevance of these changes not clear

Case #1 Revisited:

Based on K.G.’s history and clinical presentation, which of the following pharmacokinetic changes (compared to healthy individuals) would you expect to affect his antibiotics?

A. Decreased clearance
B. Increased volume of distribution
C. Decreased protein binding
D. All of the above
What are Appropriate Pharmacodynamic Targets?

- **Penicillins**
  - $fT > \text{MIC of } \geq 50\%$ of dosing interval
- **Cephalosporins**
  - $fT > \text{MIC of } \geq 60-70\%$ of dosing interval
- **Carbapenems**
  - $fT > \text{MIC of } \geq 40\%$ of dosing interval
- **Fluoroquinolones**
  - Gram-positive (*S. pneumoniae*): AUC/MIC $> 30$
  - Gram-negative: AUC/MIC $> 125-250$
- **Aminoglycosides**
  - Cmax/MIC $> 8-10$
- **Vancomycin**
  - AUC/MIC $> 350-400$

Cefepime Pharmacodynamics in Patients with Varying Renal Function

CrCL = 50-120 mL/min

- 2 gm q12h over 0.5h
- 2 gm q12h over 3h
- 1 gm q8h over 0.5h
- 1 gm q8h over 3h

CrCL = 30-49 mL/min

Augmented Renal Clearance

- Generally defined as creatinine clearance >130 mL/min/1.73m²
- Attributed to systemic inflammatory responses leading to ↑ cardiac output, ↑ renal perfusion
- Estimated to occur in 30%-65% of general ICU patients, up to 100% of patients with sepsis, trauma, CNS disorders such as TBI, SAH, infection
- Duration may be 1 week or more
- Difficult to accurately evaluate

Case #2
LF is to be treated with ertapenem for a severe intraabdominal infection. He is septic with AKI; his estimated creatinine clearance is 27 mL/min. The infection is known to be caused by a *Klebsiella*; susceptibilities are not yet known. Which of the following factors will likely have the most significant impact on achievement of desired antibiotic pharmacodynamic targets?

A. Alterations in Vd, CL
B. Pathogen MIC
C. Decreased protein binding
D. All of the above are equally important
Factors Affecting Drug Removal during Renal Replacement Therapy (RRT)

<table>
<thead>
<tr>
<th>Elimination pathway</th>
<th>Renally eliminated drugs more readily removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of distribution ($V_d$)</td>
<td>$&gt; 0.7$ L/kg: “large” $V_d$, not readily removed</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>$&lt; 500$ daltons: readily removed</td>
</tr>
<tr>
<td></td>
<td>$&lt; 1,500$ daltons: potentially removed</td>
</tr>
<tr>
<td>Plasma protein-binding</td>
<td>$&gt; 80$ to $90%$: highly protein-bound, not readily removed</td>
</tr>
<tr>
<td>Dialysis membrane</td>
<td>Membrane material</td>
</tr>
<tr>
<td></td>
<td>Membrane surface area</td>
</tr>
<tr>
<td></td>
<td>Membrane permeability / pore size</td>
</tr>
<tr>
<td>Dialyzer system</td>
<td>Type of dialysis</td>
</tr>
<tr>
<td></td>
<td>Flow rates of dialysate, blood, ultrafiltrate</td>
</tr>
<tr>
<td></td>
<td>Pre- vs. post-filter replacement fluids</td>
</tr>
<tr>
<td></td>
<td>Duration of dialysis</td>
</tr>
<tr>
<td></td>
<td>Filter age</td>
</tr>
</tbody>
</table>
Comparison of RRT Modalities

<table>
<thead>
<tr>
<th>Modality</th>
<th>Volume control</th>
<th>Solute removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent HD</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>SLED</td>
<td>++++/+++++</td>
<td>++++</td>
</tr>
<tr>
<td>CVVH</td>
<td>++++</td>
<td>++++/+++++</td>
</tr>
<tr>
<td>CVVHD</td>
<td>++++</td>
<td>++++/+++++</td>
</tr>
<tr>
<td>CVVHDF</td>
<td>++++</td>
<td>++++</td>
</tr>
</tbody>
</table>

- Drug clearance at any given dialysate/ultrafiltrate flow rates:
  - CVVHDF > CVVHD > CVVH > SLED ≥ IHD

HD = hemodialysis; CVVH = continuous veno-venous hemofiltration; CVVHD = continuous veno-venous hemofiltration; CVVHDF = continuous veno-venous hemofiltration; SLED = sustained low-efficiency dialysis.
General Principles of Drug Dosing during CRRT are Often Difficult to Apply

- CRRT is performed differently at almost every institution...
  - CVVH, CVVHD, CVVHDF, etc
  - IV replacement solutions given pre- or post-filter
  - Anticoagulation strategies
    - Citrate
    - Heparin
    - Nothing
  - Wide ranging effluent rates
Clinical Consequences of PK/PD Alterations on Drug Dosing

• Less predictable dose/response relationships
• Need for dosing changes, either higher or lower, to achieve desired responses
• Altered time to steady state & stable drug effects
• Potential for significant drug accumulation
• Increased potential for adverse effects/toxicities
Dosage Adjustment for Renal Impairment: Pharmacodynamic Considerations

• “Proper” adjustments may be clinically effective while reducing total drug exposure, drug cost & adverse effects

HOWEVER
• PK/PD of even high doses of many drugs already marginal
• Creatinine-based methods of assessing renal function notoriously inaccurate in many patients
• Trying to “fine tune” dose adjustments may place many patients at risk of treatment failure

THEREFORE
• Consider risks vs. benefits
• Don’t be too hasty in making dosing adjustments
KEY TAKEAWAYS

1) Significant PK alterations in patients with renal impairment may include changes in both CL and Vd
   – Protein binding alterations are common but of unclear clinical relevance

2) PK/PD alterations are difficult to accurately predict due to great variability in patient-specific parameters, RRT practices, etc.

3) Aggressive dosing of antimicrobials (at least during empiric therapy in high-risk patients) is often necessary optimize PK/PD performance
   – Renal impairment may require higher daily doses of some drugs, not lower
Session: Hitting the Mark: Improving Antibiotic Dosing in Patients with Altered Renal States

N. Jim Rhodes, Pharm.D., M.Sc., BCPS-AQ ID
Assistant Professor of Pharmacy Practice
Midwestern University, Downers Grove, IL
Infectious Diseases Pharmacist
Northwestern Medicine, Chicago, IL
Emphasis of discussion

• Evaluate alternative antibiotic dosing schemes as they relate to
  – Improving clinical outcomes
  – Facilitating transitions in care
Case #2

- AJ is a 51 year old male presenting with fever, tachycardia, and night sweats.
  - HPI: Reports 4 day history of increasingly fatigue and night sweats after a recent road trip. Recalls leg was struck by piece of luggage with increasing tenderness.
  - PMH: significant for DM type 2 and hypertension
  - Allergies/AE: sulfamethoxazole-trimethoprim (rash), cefpodoxime (rash)
  - ROS: tachycardic and diaphoretic.
    - Skin: 2 x 4 cm LLE purulent rash. A/O x 3.
  - PE: Unwell appearing 5’6” 150 kg male. Normal heart sounds no murmur noted.
    - Vitals: BP 100/75, RR 20, HR 118, Tmax 38.4°C, Sat. 95% on RA.
  - Initial lab results:
    - WBC: 13,000 cells/mm$^3$, PLT: 300,000 cells/mm$^3$, Tbili: 0.6 mg/dL, Scr: 0.5 mg/dL
  - ED course
    - Blood cultures are obtained
    - 2 L of normal saline and a one-time 2 gram dose of vancomycin

- AJ is admitted to the general medical service
  - Initial antibiotics: vancomycin 1.5 grams every 8 hr for sepsis d/t cellulitis
Case #2 Question 1

• Which of the following places AJ at a higher risk of augmented renal clearance?
  A. Receipt of a vancomycin loading dose
  B. Age ≥ 50 years
  C. Receipt of 2 L of intravenous fluids
  D. SOFA score ≤ 4
Altered renal states require altered dosing

- Proposed mechanisms of augmented clearance
  - Elevated cardiac index
  - Receipt of vasopressors

- Various risk factors
  - Trauma, sepsis
  - Previously healthy
  - Younger (<50 years)
  - Febrile neutropenia

Impact of Augmented Clearance on PK

PK/PD Measures

AUC = Area under the concentration–time curve
MIC = Minimum Inhibitory Concentration
$C_{\text{max}}$ = Maximum or peak plasma concentration
$C_{\text{min}}$ = Minimum or trough plasma concentration

Critically ill patients: short on time

Probability of target attainment for piperacillin/tazobactam with goal $T_{\text{MIC}}$ of 50%


Augmented clearance – decreased exposure

Case # 2 Continued

• Six hours into his hospital admission, AJ becomes hypotensive with a blood pressure of 84/50 mmHg. His blood pressure has not responded to fluid resuscitation and the rapid response team is called to transfer him to the MICU.
  – A code sepsis alert is triggered and the pharmacist on call is tasked with initiating broad spectrum antibiotics.
  – The following dosing parameters are available:
    • TBW: 150 kg
    • IBW: 63.8 kg
    • ABW: 98.3 kg
    • Scr: 1.0 mg/dL
Case # 2 Question 2

- Which of the following best describes AJ’s current renal function?
  A. 49 mL/min/1.73m² (Jelliffe & Jelliffe, TBW, BSA-Adjusted)
  B. 71 mL/min/1.73m² (Chiou & Hsu, TBW, BSA-adjusted)
  C. 85 mL/min/1.73m² (Cockcroft Gault, ABW, BSA-adjusted)
  D. 129 mL/min/1.73m² (Cockcroft Gault, TBW, BSA-adjusted)
  E. AJ’s renal function is unclear because urine creatinine is unavailable
Augmented renal clearance (ARC for short)

• Enhanced or supra-physiologic elimination of drug by kidneys
  – Quantifying renal clearance is difficult and time intensive
    • 8-hour urine collection
    • 24-hour urine collection
  – Defining “hyperfiltration” based on urinary creatinine
    • Glomerular hyperfiltration -> “Augmented Renal Clearance”
      – Consensus definition: > 130 mL/min/1.73m²
      – Higher and lower cut points have also been proposed
  – Incidence varies 16-100% depending on population and definition
    • Etiology remains unclear
      – Increased cardiac output
      – Increased intravascular volume
      – Administration of vasoactive agents

ARC you kidding me...

The relationship between CL and CRCL is complex...
For patients with high CRCL, linear adjustments to doses are unlikely to achieve PK/PD goals

Piperacillin PK in ICU (n=89) $R^2 = 0.1354$

Reasons for TDM:
- Increase efficacy
- Avoid toxicity
- Navigate PK complexities
- Monitor compliance

Augmented clearance and outcomes

- **BLING II ARC sub-study**
  - CI or II beta-lactam
    - ARC define with 8 hr urine
    - CRCL >130 mL/min
  - Total eligible n=254
    - ARC present in 17.7%
  - Majority
    - On piperacillin (67%)
    - Pulmonary source (51%)

- **Outcomes (ARC vs not)**
  - ICU free days at D90
    - 21 vs 21 days (P=0.89)
  - Clinical cure at D14
    - 55 vs 73% (P=0.024 unadjusted)
  - Mortality at D90
    - 13.3 vs 19.6% (P=0.33)

Continuous infusions (CI) to the rescue?

Roberts et al. [CI vs. IB]
- 30-day mortality
  - RR 0.73 (0.55-0.98)
- ICU mortality
  - RR 0.82 (0.58-1.16)
- Clinical cure
  - RR 1.32 (0.97-1.80)

Rhodes et al. [EI or CI vs. IB]
- All-cause mortality
  - OR 0.69 (0.56-0.84)
- Clinical cure
  - OR 1.77 (1.24-2.53)
- Microbiological cure
  - OR 1.22 (0.84-1.77)


Augmented clearance: identify and mitigate

• Clinical risk assessment
  – ARC risk-factor score
    • Age $\leq$ 50 years
      – aOR 28.6 (95% CI 4.4-187.2)
    • Trauma
      – aOR 16.1 (95% CI 3.0-87.7)
    • Modified SOFA $\leq$ 4
      – aOR 5.1 (95% CI 1.0-25.0)

• Exposure assessment
  – Population PK approach
    • Modeling concentrations
    • Predicting exposures
    • Simulating regimens
  – Adaptive PK approach
    • Bayesian forecasting
    • Individualized dosing
Predicting PK in critically ill patients

- Individualization
  - Population values
    - Easy fixed values
    - Lacks flexibility
  - Nomograms
    - Easy but static
    - Limited to original population of study


This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Learning from the past to predict the future

Adaptive feedback: Planning future regimen
Making and revising plans based on patient-specific PK

\[ AUC_{24} \text{ revised } \sim 250 \]

If MIC \leq 0.5, still meeting “goal” but perhaps safer

\[ AUC_{24} \text{ initial } \sim 550 \]

Lodise TP et al. Session 985. IDweek 2017. San Diego
Case #2 Continued

- AJ is treated with empiric vancomycin 1.5 g IV every 8 hours and piperacillin-tazobactam 3.375 g IV every 6 hours over 4 hr for sepsis and cellulitis.
  - Hospital day 1: blood culture Gram stain reveals Gram-positive Cocci.
  - Hospital day 2: Surgical drainage and debridement of pyomyositis performed
  - Hospital day 3: blood cultures speciate as *Staphylococcus aureus* (MSSA)
  - Hospital day 4: Surgical cultures speciate MSSA and *E. coli*.
    - Relevant susceptibilities and MICs for the *E. coli* are as follows:
      - R ≥32 mcg/mL Ampicillin
      - R ≥32 mcg/mL Ampicillin/Sulbactam
      - R ≥8 mcg/mL Cefazolin
      - S ≤1 mcg/mL Ceftriaxone
      - S 4 mcg/mL Cefepime
      - R >4 mcg/mL Ciprofloxacin
      - S ≤0.25 mcg/mL Meropenem
      - S 8 mcg/mL Piperacillin-tazobactam
      - R >4/76 mcg/mL Trimethoprim/sulfamethoxazole
Case #2 Question 3

- It is currently hospital day 5 and AJ is clinically improved and stabilized on the general medicine floor. Which of the following regimens would be the most appropriate for an outpatient transition for AJ?
  - A. Ertapenem 1 gram every 24 hr IVP
  - B. Cefepime 3 g / 24 hr via elastometric pump
  - C. Ceftriaxone 2 g every 24 hr IVP
  - D. Piperacillin-tazobactam 12 g / 24hr via elastometric pump
Making plans that work in-house and at home

- Elastomeric pumps
  - 10 mL/hr over 24hr
    - Piperacillin 12 g/day
    - Cefazolin 6 g/day
    - Cefepime 3 g/day
    - Flucloxacillin 8 g/day

- Stability at 0, 12, and 24 h
  - Mean change in concentration
    - -2%
    - +4%
    - -4%
    - -11%

Mean (SD) temperatures during pump use:
- Kept at waist at night: 30.9°C (0.9°C)
- Kept at head of bed: 26.2°C (1.0°C)
- Outdoor excursions: 26.2°C (3.3°C)

KEY TAKEAWAYS

1) KEY TAKEAWAY
Augmented renal clearance is of increasing interest and intense focus among critically ill population due to reduced PK/PD target attainment.

2) KEY TAKEAWAY
Pharmacists have at their disposal the means and expertise to identify and mitigate augmented clearance using individualized assessments.

3) KEY TAKEAWAY
Patients receiving extended or continuous infusions are at increased risk for medication errors during care transitions. Judicious use of outpatient infusions may be necessary to optimize PK/PD for serious infections.
Session: Hitting the Mark: Improving Antibiotic Dosing in Patients with Altered Renal States

Bruce A. Mueller, Pharm.D., FCCP, FASN, FNKF
Professor & Associate Dean of Academic Affairs
University of Michigan College of Pharmacy
Ann Arbor, Michigan
Objective

- Select appropriate antibiotic regimens for patients with altered renal states
Patient Case 1

49 KG male is admitted to the ICU with an AKI secondary to sepsis. Patient is oliguric with SCR 4.3mg/dL. Due to the AKI, the patient is started on CRRT at 2L/hr effluent rate.

If Cefepime started, how should it be dosed?

Pkg Insert – no CRRT recommendations, but 1g LD followed by 500 mg Q24 is HD recommendation.

Aronoff et al. Green Book - 1-2 g q12h

Trotman et al. CID 2005 - 2 g q12h
What cefepime dose do you choose?

A. 1gm LD followed by 500 Q 24
B. 1 Gm Q 12h
C. 2 Gm Q 12h
D. More?
Patient Case 2

129 KG male is admitted to the ICU with an AKI secondary to sepsis. Patient is oliguric with SCr 4.3mg/dL. Due to the AKI, the patient is started on CRRT at 2L/hr effluent rate.

If Cefepime started, how should it be dosed?

Pkg Insert – no CRRT recommendations, but 1g LD followed by 500 mg Q24 is HD recommendation.

Aronoff et al. Green Book - 1-2 g q12h

Trotman et al. CID 2005 - 2 g q12h
What cefepime dose do you choose?

A. 1gm LD followed by 500 Q 24
B. 1 Gm Q 12h
C. 2 Gm Q 12h
D. More?
Dosing in critically ill patients with AKI...

“There are known knowns. These are things we know that we know.

There are known unknowns. That is to say, there are things that we know we don't know.

But there are also unknown unknowns. There are things we don't know we don't know.”

Donald Rumsfeld
When dosing in RRT we have few metrics to base drug dosing on…

<table>
<thead>
<tr>
<th>Known Knowns</th>
<th>Known Unknowns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics (age, weight, sex, race)</td>
<td>Serum concentrations at site of action</td>
</tr>
<tr>
<td>RRT Operating Characteristics (rates, frequency, HD filters)</td>
<td>Volume of Distribution</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>Non-Renal Clearance</td>
</tr>
<tr>
<td>Urine Output</td>
<td>Actual GFR</td>
</tr>
</tbody>
</table>
Monte Carlo Simulations for Cases 1 & 2

• Build virtual patients with pharmacokinetic parameters gleaned from published studies in patient population
  – Critically ill patients receiving CRRT (4 cefepime trials)
  – Of size (84.1 ± 19.6 kg) seen in CRRT patients (ATN Trial)
  – Receiving contemporary CRRT rates (25 mL/kg/h) (ATN Trial)

• Choose pharmacodynamic targets associated with good outcomes (e.g. >60% time free drug concentration >MIC)

• Dose 5000 virtual patients with each dosing regimen and see how many meet pharmacodynamic targets. (>90% is goal)
  – U Michigan P4s, Kristina Kan & Andrew Dodson presenting their results at student posters at this ASHP meeting.
MCS of Cefepime & Patient Size:
PD Target = 4X MIC of either 4 or 8 mg/L for 60% of dosing interval

4X MIC of 8mg/L

4X MIC of 4mg/L

Weight Quintiles
- Smallest (40-67 kg)
- Middle 3 (68-100 kg)
- Largest (>100 kg)

Cefepime 2g q12h

N=5000
Data from Andrew Dodson 2018
ASHP Midyear Poster
Monte Carlo Sim Results: PTA for daptomycin 8mg/kg Q24h by body weight: 24-48h

<table>
<thead>
<tr>
<th></th>
<th>AUC/MIC≥ 666</th>
<th>AUC/MIC&lt;666</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallest 1000 pts</td>
<td>873</td>
<td>127</td>
<td>1000</td>
</tr>
<tr>
<td>body weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Largest 1000 pts</td>
<td>969</td>
<td>31</td>
<td>1000</td>
</tr>
<tr>
<td>body weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1842</td>
<td>158</td>
<td>2000</td>
</tr>
</tbody>
</table>

Chi Square  p< 0.0001

Data from Kristina Kan, UMich P4 Student
2018 ASHP Midyear Poster

Smallest 1000 body weight (kg): 60 ± 5.6 (46 - 68)
Largest 1000 body weight (kg): 114 ± 13 (101 - 177)
When dosing in RRT we have few metrics to base drug dosing on...

<table>
<thead>
<tr>
<th>Known Knowns</th>
<th>Known Unknowns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics (age, weight, sex, race)</td>
<td>Serum concentrations at site of action</td>
</tr>
<tr>
<td>RRT Operating Characteristics (rates, frequency, HD filters)</td>
<td>Volume of Distribution</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>Non-Renal Clearance</td>
</tr>
<tr>
<td>Urine Output</td>
<td>Actual GFR</td>
</tr>
</tbody>
</table>
Can I break the renal dosing rules?

• Patient size (Known Known) in our cases should be “permission” for you to break rules.
  — Therapeutic Index

• When else can/should I break the rules?
  — Adjusting doses for renal function at admission
  — Adjusting doses for renal function in ICU AKI
85 kg, 61 yo AA male is admitted to the hospital with apparent pneumonia. Patient’s admission SCr 2.0mg/dL. Broad spectrum antibiotics to be started as we wait for culture results.
Upon which of the following should renal dose adjustments should be made?

MDRD “e-GFR”: 39 mL/min
CKD-EPI: 40 mL/min
Cockcroft Gault: 47 mL/min
Modified CG for wt 41 mL/min
Pharmacists should ALWAYS adjust antibiotics for renal impairment, right?

- Patients admitted to Michigan Medicine with infectious diagnoses between January 2006 and April 2018 (n= 18,650)
  - Pneumonia
  - Complicated intra-abdominal infection
  - Complicated urinary tract infection
  - Acute bacterial skin/skin structure infection

- 3256 (17.5%) had AKI with an absolute increase in SCr of 0.3 mg/dL

- 57.2% of those diagnosed with AKI met no KDIGO criteria for AKI at 48 hours

RL Crass, KA Rodvold, BA Mueller, MP Pai; Renal Dosing of Antibiotics: Are We Jumping the Gun? Clinical Infectious Diseases 2018 (in press)
Serum Creatinine for First 48 hrs of Admission

A

Fractional Change in Scr

N = 18,650 (100%)

Baseline 0 24 48 72 96

Time (hours)

B

Fractional Change in Scr

N = 3,256 (17.5%)

Baseline 0 24 48 72 96

Time (hours)

All admissions

Patients with AKI at admission

Adapted from RL Crass, KA Rodvold, BA Mueller, MP Pai. Clin Infect Dis 2018
Serum Creatinine for First 48 hrs of Admission

Adapted from RL Crass, KA Rodvold, BA Mueller, MP Pai. Clin Infect Dis 2018
85 kg, 61 yo AA male is admitted to the hospital with apparent pneumonia. Patient’s admission SCr 2.0mg/dL. Broad spectrum antibiotics to be started as we wait for culture results.

Upon which of the following should renal dose adjustments should be made?

- **MDRD “e-GFR”**: 39 mL/min
- **CKD-EPI**: 40 mL/min
- **Cockcroft Gault**: 47 mL/min
- **Modified CG for wt**: 41 mL/min
The mortality rate of CRRT patients is 30-50%, and the #1 cause of death is infection...

Of last 10 CRRT patients at your institution...
How many experienced symptoms of **too high** antibiotic concentrations?

A. 0-1 patient
B. 2-3 patients
C. 3-4 patients
D. 4 or more patients
Difficult Balance in Antibiotic Dosing: Clinicians’ Dilemma

Higher Doses:
- Ensure Adequate Conc at Target Site
- Increased Abx Resistance
- Extracorporeal Drug clearance
- ↑ Volume of Distribution

Lower Doses:
- Reduce cost
- Decreased Renal Clearance
- Toxicity Concern

Adapted from Lewis SJ, Mueller BA. J Intensive Care Med. 2014
Do We Meet Pharmacodynamic Targets in CRRT?

- 53 CRRT patients receiving meropenem, pip-tazo, cefepime or ceftazidime had serum assayed.
- Serum concentrations remained >4X MIC of Pseudomonas spp. for the recommended time
  - 81% patients treated with Meropenem 1000mg Q 12h
  - 71% with Piperacillin/Tazobactam 4.0/0.5 g Q 6h
  - 53% with Ceftazidime 2000 mg Q 12h
  - 0% with Cefepime 2000 mg Q 12h

- Seyler L et al: Recommended b-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. Crit Care 2011;15:R137
<table>
<thead>
<tr>
<th>PK Change</th>
<th>Ability to Reach Pharmacodynamic Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid Overload</td>
<td>Reduced Ability</td>
</tr>
<tr>
<td>↓ Serum Albumin / ↓ Protein Binding</td>
<td>Mixed Effects</td>
</tr>
<tr>
<td>Retained Non-renal Clearance</td>
<td>Reduced Ability</td>
</tr>
<tr>
<td>Aggressive CRRT</td>
<td>Reduced Ability</td>
</tr>
<tr>
<td>Augmented Renal Clearance</td>
<td>Reduced Ability</td>
</tr>
</tbody>
</table>
How should a clinician decide on antibiotic dosing in ICU RRT patients??

• Therapeutic Index for most antibiotics is pretty wide (PCNs, Ceph, Carbapenems, etc)

• Will AKI at admission persist?
  – (Known Unknown)

• Should I give everyone a “normal renal” dose for their entire admission to be sure they are “therapeutic?”
What if I give “normal” antibiotic doses in CRRT patients?


• 50 consecutive CRRT patients got Full Dose Antibiotics
  – Ceftaz/Cefepime 2g Q8  
  – Pip-Tazo 4 g Q6  
  – Meropenem 1 g Q8

• 90% patients met or exceeded pharmacodynamic goals
• 53% had dangerously high antibiotic levels
Can we improve ICU survival in patients with AKI?

Antibiotic Levels
KEY TAKEAWAYS

1) PHARMACOKINETIC CHANGES IN AKI MIGHT BE A REASON TO BREAK RENAL DOSING RULES
   Example: Fluid overload might mean larger doses, esp loading doses.

2) CONSIDERING RRT IS IMPORTANT, CONSIDERING PATIENT IS MORE IMPORTANT
   Example: A large patient often needs larger doses, in spite of pkg insert. Consider whole patient, not just RRT

3) SOMETIMES BREAKING RENAL DOSING RULES IS OKAY
   1. AKI often transient. Dosing as normal renal function for first day or two unlikely to cause toxicity and ensures adequate concentrations
   2. Augmented Renal Clearance
Session: Hitting the Mark: Improving Antibiotic Dosing in Patients with Altered Renal States

Monday, December 3, 2018
2:00 PM – 3:30 PM

Presenters:
Doug Fish, Pharm.D., BCCCP, BCPS-AQ ID
N. Jim Rhodes, Pharm.D., M.Sc., BCPS-AQ ID
Bruce A. Mueller, Pharm.D., FASN, FCCP, FNKF