Your Smartphone Doesn’t Always Have The Answers:
Evaluating Pharmacokinetic and Pharmacodynamic Changes in the Acutely Ill

Jason Haney, PharmD, BCPS, BCCCP
Assistant Professor, Clinical Pharmacy & Outcomes Sciences
Medical University of South Carolina - College of Pharmacy
Objectives

By the end of this session, the audience should be able to:

• explain how critical illness alters drug absorption and distribution;

• describe the effects of changing hepatic blood flow and protein binding on drug metabolism;

• differentiate methods of approximating renal clearance; and

• identify methods to optimize the pharmacodynamic activity of antibiotics in critically ill patients.
Disclosures

• I have no real or apparent conflicts of interest.
Critical illness

Anticipate and monitor changes

Dose adjustment and therapeutic drug monitoring

- Absorption
- Distribution
- Metabolism
- Excretion
- Pharmacodynamics
Absorption

• Bioavailability (F)
  – % of administered dose that reaches the systemic circulation

- Affected by absorption
- Affected by first-pass metabolism

SQ
Affected by absorption

PO/PT
Affected by first-pass metabolism

IM
Intravenous Delivery

• Most widely used
• Bioavailability 100%
• Concerns
  • Tissue penetration
  • IV compatibility
  • Extravasation

Enteral/Oral Absorption

• Bioavailability variable
• Concerns
  – Reduced absorption
  – Adequate mentation
  – Swallowing ability or access

GI perfusion

- Theoretical changes in absorption with changes in CO or regional hypoperfusion
- No data

Image: https://en.wikipedia.org/wiki/Circulatory_system
Intestinal atrophy

- Decreased crypt depth and villous height
- Increased gut permeability
- Possible increased absorption by passive diffusion
- Probable decreased absorption of drugs by active transport
- No data

https://commons.wikimedia.org/wiki/File:Villi_%26_microvilli_of_small_intestine.svg
GI dysmotility

• Delayed gastric emptying causes delayed absorption
• Reduced peak drug concentrations
• Very common and numerous causes
  – DM, surgery, TBI, Parkinsonism, many medications
• Anecdotal correlation between enteral feeding tolerance and enteral drug absorption
• Prokinetic agents have unknown effects on absorption
Intestinal drug transporters

• Decreased transporter and enzyme activity
  – Increased absorption of P-gp and CYP substrates
  – Decreased absorption of OATP and UGT substrates

• No PK studies in critically ill

![Intestinal lumen with drug transporters](https://commons.wikimedia.org/wiki/File:Villi_%26_microvilli_of_small_intestine.svg)

- BCRP
- MRP2
- P-gp
- OATP
- PEPT1
- ASBT
- MCT1

CYP3A, CYP2D6, CYP2J2, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT2B4, UGT2B7
Physical incompatibilities

- **Enteral nutrition**
  - Significance varies
  - Hold nutrition 1-2 hrs before and after drug administration
  - Ensure meeting nutritional needs

- **pH changes**
  - Affect ionization, lipophilicity, and potentially absorption
  - Commonly affected by acid-suppressive therapy
Subcutaneous, Intramuscular, and Transdermal Absorption

- Clinically not abandoned as quickly as enteral/oral
- Avoid first-pass metabolism
- Concerns
  - Changes in absorption
  - Not studied

Image - https://commons.wikimedia.org/wiki/File:Needle-insertion-angles-1.png
Inhaled Absorption

- Increases local concentrations
- Reduces systemic exposure
- 1-5 µm particle size is ideal
- Concerns
  - Drug-specific equipment
  - Bronchospasm
  - Altered lung architecture
  - V/Q mismatch


Patient Case - KH

• KH is a 36-year-old man who is admitted to a trauma ICU after a vehicular accident. He is diagnosed with a depressed skull fracture, multiple rib and upper extremity fractures, and abdominal trauma.

• The patient is taken to surgery for repair of multiple intestinal tears. After surgery, he requires significant volume resuscitation and is made NPO to allow bowel rest.

• It is now post-operative day #1. KH is treated with fentanyl IV 75 mcg/hr, propofol IV 15 mcg/kg/min, pantoprazole 40 mg IV daily, enoxaparin 30 mg SQ Q12H, and phenytoin 150 mg IV Q8H.
Patient Case - KH

All of the following are significant risk factors for decreased absorption of enteral medications in KH except:

a. Abdominal surgery
b. Traumatic brain injury
c. Propofol
d. Pantoprazole
e. Fentanyl
Critical illness

Anticipate and monitor changes

- Absorption
- Distribution
- Metabolism
- Excretion
- Pharmacodynamics

Dose adjustment and therapeutic drug monitoring
Distribution

- Dose = 10 mg
- C = 10 mg/L
- Vd = dose/C = 1L

Vd = dose/C = 1L

Tissue perfusion

Shock

Redistribution of blood flow

Decreased perfusion of muscle, skin, and splanchnic organs

Less distribution of hydrophilic drugs to these areas

Fluid shifts and membrane permeability

- Fluid Resuscitation
- Acute Conditions

TBW
Interstitial fluid
Hydrophilic drug
Vd

Hydrophilic drug concentrations

Image - https://hermentorcenter.com/2013/05/14/
Vancomycin PD

- AUC/MIC best describes its efficacy
- Recommend AUC/MIC ≥ 400
- Continuous infusion regimens are unlikely to improve outcomes
- Aggressive dosing may be required in critically ill patients
Protein binding

Image - https://superawesomveectors.deviantart.com/art/Pills-Vector-Illustration-643402348

Free drug
Plasma conc
Time
Bound drug
Free drug
Time
Plasma conc

Effect

Image - https://superawesomvectors.deviantart.com/art/Pills-Vector-Illustration-643402348

Bound drug
Free drug
Time
Protein Binding

• Albumin
  – Binds acidic drugs
  – Concentrations fluctuate
  – Lower levels under stress
    • $f_u$ increases
  – Drugs affected – Lots!
    • Morphine
    • Propofol
    • Aspirin
    • Midazolam, diazepam
    • Diltiazem, verapamil, carvedilol
    • Phenytoin, valproic acid

• $\alpha_1$-Acid glycoprotein
  – Binds basic drugs
  – Concentrations fluctuate
  – Higher levels under stress
    • $f_u$ decreases
  – Drugs affected
    • Fentanyl
    • Lidocaine
    • Midazolam
    • Diltiazem, verapamil
% unionized

Diazepam
Phenytoin

Lidocaine
Diltiazem

50%

pH = pKa

Weak acid

Weak base

6.8  pH  7.8

Diazepam
Phenytoin

Lidocaine
Diltiazem
• On postoperative day #2, KH is empirically treated with vancomycin, meropenem, and caspofungin for suspected sepsis.
• Labs: SCr 1.1 mg/dL, BUN 15 mg/dL, WBC 20.2 x 10³ cells/mm³
• Height: 72 in, weight 90 kg (baseline 82 kg)
• Which of the following would be the most appropriate IV loading dose of vancomycin?
  a. 1500 mg
  b. 2000 mg
  c. 2500 mg
  d. 3000 mg
Critical illness

Anticipate and monitor changes

Dose adjustment and therapeutic drug monitoring

• Absorption
• Distribution
• Metabolism
• Excretion
• Pharmacodynamics
Metabolism
Renal metabolism

- Significant metabolic capacity
- CYP 2B6, 2C8, 2C9, 3A4, and 3A5
- UGT 1A5, 1A6, 1A7, 1A9, 2B4, 2B7 and 2B17
- Unknown effect of critical illness on these enzymes
- Clinically significant changes in insulin metabolism with acute kidney injury
Hepatic clearance (CLₜₜ)

- Volume of blood that the liver clears of drug per unit of time
- For IV drugs (F = 1), $CL_H = Q \times E$
  - $Q$: hepatic blood flow
  - $E$: hepatic extraction ratio

Intrinsic hepatic enzyme activity
Drug protein binding
Hepatic blood flow
Hepatic extraction ratio

\[ E = \frac{f_u \times CL_{int}}{Q + f_u \times CL_{int}} \]

\( f_u \): fraction unbound in the plasma
\( CL_{int} \): intrinsic hepatic clearance
\( Q \): hepatic blood flow

No hepatic metabolism

<table>
<thead>
<tr>
<th>No hepatic metabolism</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0.3</td>
<td>0.7</td>
</tr>
</tbody>
</table>

\( CL_H \) entirely dependent on hepatic blood flow
High HER drugs (> 0.7)

- Highly metabolized by hepatic enzymes
- Unbound steady-state concentration (Css_u) is extremely important
- Clearance does not vary with changes in hepatic enzymatic activity

- Examples
  - Fentanyl
  - Lidocaine
  - Morphine
  - Propofol
  - Propranolol
  - Verapamil
High HER drugs (> 0.7)

- Clearance depends on hepatic blood flow \( (\text{CL}_H \approx Q) \)
  
- Increased CO (e.g., early sepsis)
  - Assume potential for increased metabolism
  - Expect decreased \( \text{C}_{su} \)
  - Possibly reduced efficacy

- Decreased CO (e.g., cardiogenic shock, mechanical ventilation)
  - Reduced hepatic blood flow is expected
  - Expect increased \( \text{C}_{su} \)
Low HER drugs (< 0.3)

- Lower degree of hepatic enzyme metabolism
- Clearance varies with changes in hepatic enzyme activity
- $\text{CL}_H = f_u \times \text{Cl}_{\text{int}}$
- Clearance does not vary with changes in hepatic blood flow

Examples
- Carbamazepine
- Ceftriaxone
- Dexamethasone
- Diazepam
- Diltiazem
- Lorazepam
- Phenytoin
- Valproic acid
- Warfarin
Low HER drugs and altered intrinsic clearance

• Complex drug interactions
  – CYP inhibitors, inducers, substrates

• Inflammation
  – Inflammatory cytokines decrease expression and activity of CYP enzymes

• Hypothermia
  – Decreased drug metabolism through the CYP system

• Acute kidney injury
  – May affect CYP and UGT metabolism by the kidneys
  – These changes may cause increased substrate concentrations
Intermediate HER drugs (0.3 – 0.7)

- Most complex drugs to determine effects of changes
  - Tenuous critically ill patients
  - Multiple simultaneous changes
- Monitor for expected therapeutic outcomes and possible toxicities
- Examples: aspirin, carvedilol, midazolam, omeprazole

\[ \text{Q} \]
\[ f_u \]
\[ \text{CL}_{\text{int}} \]
• Post-operatively, KH’s albumin concentration declined to 2.1 g/dL from 3.8 g/dL on admission. There are no estimated significant differences in cardiac output since admission.

• Which of the following changes in propofol concentrations would be most likely?
  a. Increased total, decreased unbound
  b. Unchanged total, increased unbound
  c. Increased total, unchanged unbound
  d. Decreased total, increased unbound

• Hint: propofol is a high HER drug that is bound to albumin.
Critical illness

Anticipate and monitor changes

Dose adjustment and therapeutic drug monitoring

• Absorption
• Distribution
• Metabolism
• Excretion
• Pharmacodynamics
Hepatic excretion

Renal excretion of BAs

Enterohepatic circulation of BAs

Fecal BA loss
Renal excretion

- Filtration
- Reabsorption
- Secretion

Urinary excretion
Glomerular filtration

• GFR is the most widely used variable to describe kidney function
• National Kidney Foundation defines normal kidney function as a GFR of:
  – $140 \pm 30 \text{ mL/min/1.73m}^2$ for young healthy men
  – $126 \pm 22 \text{ mL/min/1.73m}^2$ for young healthy women
Renal elimination

Excretion = Filtration – Reabsorption + Secretion
Cockcroft-Gault equation

\[
CrCl (mL/min) = \frac{(140 - age) \times weight}{SCr \times 72} \times 0.85 \text{ (if female)}
\]

- Historically used to estimate CrCl
- FDA standard for clinical trials and package inserts
- Validated only in the setting of stable renal function
- Low sensitivity in patients with reduced protein stores or malnourishment
- Adjust weight for overweight patients to avoid overestimation
- Poor correlation with measured CrCl (24-hr urine) in critically ill

Nephron 1976;16:31–41
Modification of Diet in Renal Disease (MDRD) study

• Applicable for CKD patients with GFR <60 mL/min/1.73m²
• Validated only with stable renal function
• Better estimate of renal function than C-G because it directly estimates GFR instead of CrCl
• Applicable to a wide population
  – Primarily Caucasians and African Americans
  – 18-70 years old
• Underestimates if GFR >60 mL/min/1.73m²
CKD-Epidemiology Collaboration (CKD-EPI) equation

• Applicable for CKD patients
• Validated only with stable renal function
• Better estimate of renal function than C-G because it directly estimates GFR instead of CrCl
• More accurate than MDRD for adults when GFR >60 mL/min/1.73m²
• Not adequately validated in African Americans with higher GFRs or in the elderly
Augmented renal clearance

• Occurs in 30-65% of ICU patients despite a normal SCr
• An increase of 10% above the upper end of normal GFR
  – > 160 mL/min/1.73m² in men
  – > 150 mL/min/1.73m² in women
• Associated with an increased CO and, thus, renal blood flow
• Significant risk factors: age ≤ 50 years, trauma, sepsis, burns, major surgery, TBI, SAH, pancreatitis, pregnancy
• Peak CrCl appears to occur around days 4-5 and may return to normal by day 7
Identifying augmented renal clearance

• Exclude patients with SCr ≥ 1.3 mg/dL
• Calculate ARC Score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Number of Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 50 yrs</td>
<td>6</td>
</tr>
<tr>
<td>Trauma admission</td>
<td>3</td>
</tr>
<tr>
<td>Modified Sequential Organ Failure Assessment (SOFA) score ≤ 4</td>
<td>1</td>
</tr>
</tbody>
</table>

• If ARC Score 7 – 10 or the patient has a TBI or SAH, obtain an 8-hr urine collection and calculate the CrCl

\[
\text{Measured CrCl} = \frac{UCr \times Uvol}{SCr \times Tmin}
\]

• If CrCl > 130 mL/min, higher doses are needed for similar drug exposure
Aminoglycoside PD

- Concentration-dependent killing
- Ideal peak: MIC = 8-10
- Post-antibiotic effect
- Once-daily dosing optimizes PD
- Vd variability and ARC cause concern for appropriate once-daily dosing
Impaired renal clearance

• Most common acute change in critically ill patients
• Most renal dose adjustment recommendations are based on data from patients with CKD
• Drug dosing recommendations are not as precise in AKI as with CKD
• Estimate GFR at least once for all patients when determining kidney function

Kidney Int 2011;80:1122-37
Identifying AKI

- Risk, Injury, Failure, Loss of kidney function, and End stage renal disease (RIFLE)
  - Abrupt (1 – 7 days) but sustained (> 24 hours) decrease in renal function

<table>
<thead>
<tr>
<th>Grade</th>
<th>SCr and GFR Criteria</th>
<th>Urine Output Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>SCr increase to 1.5-fold or GFR decrease &gt; 25% from baseline</td>
<td>&lt; 0.5 mL/kg/h for ≥ 6 hours</td>
</tr>
<tr>
<td>Injury</td>
<td>SCr increase to 2-fold or GFR decrease &gt; 50% from baseline</td>
<td>&lt; 0.5 mL/kg/h for ≥ 12 hours</td>
</tr>
<tr>
<td>Failure</td>
<td>SCr increase to 3-fold or GFR decrease &gt; 75% from baseline, or SCr ≥ 4 mg/dL with an acute increase of at least 0.5 mg/dL</td>
<td>&lt; 0.3 mL/kg/h for ≥24 hours or anuria for ≥ 12 hours</td>
</tr>
<tr>
<td>Loss</td>
<td>Complete loss of function (need for RRT) for &gt; 4 weeks</td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>Complete loss of function (need for RRT) for &gt; 3 months</td>
<td></td>
</tr>
</tbody>
</table>

Color key: Grades of severity | Outcomes

KDIGO Clinical Practice Guideline for Acute Kidney Injury 2012; http://www.kidney-international.org
Drug dosing in acute kidney injury

• Increase in SCr and decrease in estimated CrCl lags behind true change in renal function
• Drugs with primary renal elimination can accumulate in AKI
  – Degree depends on amount of renal elimination and type of elimination (e.g., filtration or secretion)
• In most cases, loading doses are not adjusted
  – Increase loading dose of hydrophilic drugs with hypervolemia
  – Decrease loading dose of drugs with decreased tissue binding

Drug dosing in acute kidney injury

- Dose adjustments based on conservative estimates of renal function
  - Weigh risk vs benefit
  - Reduce dose, extend interval, or both
  - Therapeutic drug monitoring for drugs with narrow therapeutic index
- Daily assessment of medication regimens (e.g., reassessment of kidney function, efficacy and adverse effects of therapy)
- Additional dosage adjustments needed if dialysis is initiated
**β-lactam antibiotic PD**

- Time-dependent killing
- $fT > MIC$ predicts treatment success
- Prolonged infusions improve PD

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Bacteriostasis</th>
<th>Bactericidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>35-40%</td>
<td>60-70%</td>
</tr>
<tr>
<td>Penicillins</td>
<td>30%</td>
<td>50%</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>20%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Patient Case - KH

• On day 9 of vancomycin therapy, KH has a vancomycin trough of 25 mcg/mL. On his current vancomycin dosing, he was previously therapeutic (trough of 18 mcg/mL, estimated AUC/MIC >400).

• Which most likely explains the change?
  a. Renal tubular secretion decreased to below normal
  b. Vd increased to larger than normal
  c. Tissue penetration decreased to below normal
  d. Augmented renal excretion returned to normal
Patient Case - KH

- KH’s current meropenem regimen is 1 g IV Q8h
- Which of the following would be the most appropriate dosing for meropenem to optimize the pharmacodynamics if KH experienced a non-oliguric acute kidney injury during the acute treatment of sepsis of unknown origin?
  a. 500 mg IV Q8h
  b. 1 g IV Q24h
  c. 500 mg IV Q24h
  d. 1 g IV Q8h
Renal replacement therapies

<table>
<thead>
<tr>
<th>RRT modality</th>
<th>Transport principle</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRRT</td>
<td>All intermittent therapies</td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>Diffusion</td>
<td>“Classic” hemodialysis</td>
</tr>
<tr>
<td>EDD</td>
<td>Diffusion</td>
<td>Longer dialysis times, slower blood/dialysate flows</td>
</tr>
<tr>
<td>SLEDD</td>
<td>Diffusion</td>
<td>Longer dialysis times, slower blood/dialysate flows</td>
</tr>
<tr>
<td>SCUF</td>
<td>Convection</td>
<td>Only ultrafiltration</td>
</tr>
<tr>
<td>CVVHDF</td>
<td>Convection &amp; diffusion</td>
<td>Hemofiltration combined with dialysis</td>
</tr>
<tr>
<td>CAVH</td>
<td>Convection</td>
<td>Without pumps, allows UF rates of only 10-15 L/d</td>
</tr>
<tr>
<td>CVVH</td>
<td>Convection</td>
<td>“Classic” hemofiltration</td>
</tr>
<tr>
<td>CRRT</td>
<td>Convection</td>
<td>All continuous therapies</td>
</tr>
</tbody>
</table>

CAVH = continuous arteriovenous hemofiltration; CRRT = continuous renal replacement therapy; CVVH = continuous venovenous hemofiltration; CVVHDF = continuous venovenous hemodiafiltration; EDD = extended daily dialysis; IHD = intermittent hemodialysis; IRRT = intermittent renal replacement therapy; SCUF = slow continuous ultrafiltration; SLEDD = slow low efficient daily dialysis.
Continuous renal replacement therapies

- Less severe fluid shifts leading to more hemodynamic stability
- Considerable variability exists in the type of CRRT used
- An equation to determine appropriate dosing in CRRT:

\[
Dose = dose_n \left( \frac{CL_{\text{nonrenal}} + (Q_{\text{eff}} \times SC)}{CL_{\text{norm}}} \right)
\]

- \(CL_{\text{nonrenal}}\) = nonrenal clearance of a drug
- \(CL_{\text{norm}}\) = normal clearance of the drug
- Dose = desired dose for CRRT
- \(dose_n\) = normal dose
- \(Q_{\text{eff}}\) = effluent rate
- \(SC\) = sieving coefficient
Drug dosing in CRRT

• Protein binding and molecular weight most influence drug removal
  – Drug removal is inversely proportional to % protein binding
  – Protein binding affects convection and diffusion
  – Drug clearance decreases as molecular weight increases
  – Most drugs are small enough to be cleared

• Volume of distribution and drug charge are less important
  – Slower rates allow equilibration between compartments
  – Hydrophilic drugs (Vd < 0.6 L/kg) are more likely to be removed
Drug dosing concepts in CRRT

- PK studies for CRRT are not FDA-required
- Residual renal function should be considered
- Most loading doses should not be adjusted
- Renally-cleared medications will be significantly impacted
- Drug-specific dosing literature should be used, if available
- Dose adjustment may be required if CRRT is interrupted
Steps for assessing and adjusting drug regimens in acutely ill patients:

1. Assess clinical information
2. Estimate ADME alterations
3. Review current medication
4. Calculate individualized dosing regimens
5. Monitor efficacy and toxicity
6. Adjust regimen as needed
Your Smartphone Doesn’t Always Have The Answers:
Evaluating Pharmacokinetic and Pharmacodynamic Changes in the Acutely Ill

Jason Haney, PharmD, BCPS, BCCCP
Assistant Professor, Clinical Pharmacy & Outcomes Sciences
Medical University of South Carolina - College of Pharmacy