Pharmacokinetics/ Pharmacodynamics

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Learning Objectives

1. Describe the changes in critically ill patients that alter drug absorption.
2. Explain how critical illness affects the distribution of drugs.
3. Depict the effects of changing hepatic blood flow and protein binding on drug metabolism.
4. Differentiate between different critically ill patient populations and the expected pharmacokinetic (PK) changes.
5. Incorporate the PK changes in a critically ill patient into the design and evaluation of an appropriate drug regimen.
6. Identify the desired pharmacodynamic parameters associated with efficacy in select drugs.

Abbreviations in This Chapter

AAG	α_1-Acid glycoprotein
AKI	Acute kidney injury
aPTT	Activated partial thromboplastin time
ARC	Augmented renal clearance
AUC	Area under the curve
AUC/MIC	Ratio of area under the curve to the minimum inhibitory concentration for the bacterial pathogen
$AUC_{0\text{-}24}$/MIC	Ratio of area under the curve for 24 hours to the minimum inhibitory concentration for the bacterial pathogen
CKD	Chronic kidney disease
Cmax/MIC	Ratio between the maximum drug concentration and the minimum inhibitory concentration for the bacterial pathogen
*f*T>MIC	Free drug concentration time above the minimum inhibitory concentration for the bacterial pathogen
GFR	Glomerular filtration rate
ICU	Intensive care unit
KDIGO	Kidney Disease Improving Global Outcomes
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
SIRS	Systemic inflammatory response syndrome
TBI	Traumatic brain injury
Vd	Volume of distribution

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. J.H. is a 30-year-old man admitted to the intensive care unit (ICU) for septic shock. He initially received 30 mL/kg of normal saline for intravenous fluid resuscitation. He required further fluid administration to achieve a central venous pressure greater than 8 mm Hg. Despite prophylaxis with enoxaparin 30 mg subcutaneously every 12 hours, J.H. has a proximal deep venous thrombosis. Which is the most likely pharmacokinetic (PK) alteration contributing to this therapeutic failure?
   A. Decreased antifactor Xa (anti-Xa) activity secondary to decreased volume of distribution (Vd).
   B. Decreased anti-Xa activity secondary to decreased absorption.
   C. Increased anti-Xa activity secondary to decreased hepatic metabolism.
   D. Increased anti-Xa activity secondary to decreased renal elimination.

Questions 2–4 pertain to the following case.

E.W. is a 48-year-old man (height 70 inches, weight 85 kg) admitted to the trauma ICU after a motorcycle collision. E.W. presents with a traumatic brain injury (TBI; head computed tomography [CT] reveals a depressed skull fracture, frontal subarachnoid hemorrhage, and right intraparenchymal hemorrhage), right acetabulum fracture, bilateral rib fractures, and abdominal trauma. According to his abdominal CT, E.W. must go to the operating room for an exploratory laparotomy to undergo repair of several serosal tears. After surgery, E.W. requires significant resuscitation in his first 24 hours of admission (12 L of normal saline). He is made NPO (nothing by mouth) to allow bowel rest.

E.W.'s laboratory values are as follows: serum creatinine (SCr) 1.1 mg/dL, blood urea nitrogen (BUN) 17 mg/dL, and white blood cell count (WBC) 19×10^3 cells/mm^3. Pulmonary artery catheterization values are cardiac index 4.2 L/minute/m^2 (normal 2.8–3.6 L/minute/m^2) and central venous pressure 9 mm Hg. His medication therapy includes a fentanyl continuous infusion of 75 mcg/hour, a propofol continuous infusion of 15 mcg/

kg/minute, pantoprazole 40 mg intravenously every 24 hours, enoxaparin 30 mg subcutaneously every 12 hours, and phenytoin 150 mg intravenously every 8 hours.

2. Which is the most accurate assessment of risk factors for the decreased absorption of enterally administered drugs?
   A. Intestinal atrophy, pantoprazole therapy, abdominal surgery.
   B. TBI, fentanyl therapy, cardiac output.
   C. Abdominal surgery, pantoprazole therapy, TBI.
   D. Intestinal atrophy, cardiac output, fentanyl therapy.

3. Before E.W.'s admission to the ICU, his albumin concentration was 3.8 g/dL, but after surgery, it declines to 2.1 g/dL. Given this change in albumin, which change in total concentration and unbound concentration of propofol would be most likely?
   A. Increased total concentration, decreased unbound concentration.
   B. No change in total concentration, increased unbound concentration.
   C. Increased total concentration, no change in unbound concentration.
   D. Decreased total concentration, increased unbound concentration.

4. On postoperative day 3, E.W.'s serum creatinine (SCr) increases to 3 mg/dL. On postoperative day 4, his SCr is 3.2 mg/dL. Which variable for assessing kidney function would be most important for determining dosing adjustments in E.W.?
   A. BUN/SCr ratio.
   B. Total daily urine output.
   C. Estimation of glomerular filtration rate (GFR).
   D. History of chronic kidney disease (CKD).

Questions 5 and 6 pertain to the following case.
S.H. is a 35-year-old man (height 70 inches, weight 85 kg) admitted to the medical ICU because of sepsis caused by health care–associated pneumonia. He is empirically treated with vancomycin, piperacillin/tazobactam, and ciprofloxacin for health care–associated pneumonia. His laboratory values are as follows: SCr 1 mg/dL, BUN 12 mg/dL, and WBC 18×10^3 cells/mm^3.

5. According to the known PK changes in S.H., which would be the most appropriate intravenous loading dose of vancomycin?
   A. A. 1500 mg.
   B. B. 2000 mg.
   C. C. 2500 mg.
   D. D. 3000 mg.

6. S.H. is given a diagnosis of methicillin-resistant *Staphylococcus aureus* health care–associated pneumonia. On day 10 of vancomycin therapy, he has a vancomycin trough of 25 mcg/mL. On his current vancomycin dosing, he was previously therapeutic (trough of 19 mcg/mL). Which most likely explains what transpired?
   A. Augmented renal excretion returned to normal.
   B. Vd increased to larger than normal.
   C. Tissue penetration decreased to below normal.
   D. Liver blood flow returned to normal.

7. B.B. is 40-year-old woman with a surgical site infection caused by *Pseudomonas aeruginosa*. She is initiated on a piperacillin/tazobactam 3.375g intravenous infusion over 4 hours every 8 hours. Which is the most likely benefit of this approach with piperacillin/tazobactam?
   A. Decreased mortality supported by prospective controlled studies.
   B. Decreased neurotoxicity supported by prospective controlled studies.
   C. Decreased mortality supported by retrospective reviews.
   D. Decreased neurotoxicity supported by retrospective reviews.

8. C.W. is a 52-year-old man admitted to the ICU for acute respiratory failure. He is given scheduled morphine for pain control. Which PK parameter would most likely affect the hepatic metabolism of morphine?
   A. Increased α_1-acid glycoprotein (AAG).
   B. Decreased albumin.
   C. Increased hepatic blood flow.
   D. Increased intrinsic clearance.

I. INTRODUCTION

Pharmacokinetics (PK) refers to the movement of a drug through the body, particularly the absorption, distribution, metabolism, and excretion of a drug, whereas pharmacodynamics (PD) addresses the biochemical and physiologic effects of a drug on the body according to the concentration. Physiologic changes in critically good patients cause alterations that affect the PK and PD of drugs. Although few studies evaluate the effect of these changes, clinicians must consider the general principles when making decisions about drug dosing in the critically ill. The most important consideration in critically ill patients is that changes can occur rapidly. A patient may have an altered PK variable on one day, only to experience changes that alter that variable in a completely different way. The best example is of a critically ill patient with an increased renal elimination of a drug who experiences acute kidney injury (AKI) and ultimately has a decreased renal elimination of that same drug. Therefore, it is important for the critical care pharmacist to know how the principles can be altered and to continually anticipate changes during a patient's stay in the ICU.

II. ROUTES OF ADMINISTRATION

A. Intravenous
   1. The intravenous route is the most widely used method of drug administration in the critically ill population. The bioavailability of an intravenously administered drug is 100%, thus ensuring the entire dose reaches the systemic circulation.
   2. Although intravenous drug administration is the most popular method used in the ICU, it still poses several problems. The intravenous route does not guarantee penetration of the drug into sites outside the circulatory system. Examples of this include poor penetration of drugs into various tissues such as the meninges, pulmonary tissue, and bone. In conditions such as septic shock, drug penetration into muscle and subcutaneous tissue is lower than expected. Finally, reports of inadvertent extravascular administration of a drug contain documented severe adverse effects. Several reports of drug (cytotoxic and non-cytotoxic) extravasation highlight this potential complication of intravenous administration.

B. Enteral/Oral – Using the enteral or oral route of administration in critically ill patients results in variable drug bioavailability. The predominant concern for this route of administration in critically ill patients pertains to alterations in drug absorption. The issues pertaining to altered drug absorption are discussed in the next section. Of note, not all drugs show reduced absorption when administered enterally/orally to critically ill patients. One example comes from a study investigating the PK of atorvastatin. Compared with healthy volunteers, patients in the ICU had a significantly higher area under the curve (AUC) (110.5 ng/mL vs. 5.9 ng/mL, $p<0.01$) after a single dose of atorvastatin 20 mg. The increased AUC could only partly be explained by altered hepatic metabolism (Intensive Care Med 2009;35:717-21).

C. Subcutaneous/Intramuscular – Subcutaneous and intramuscular drug administration avoids first-pass metabolism by the liver and has the potential to increase the bioavailability of a drug. However, these routes still require the drug to be absorbed into the blood. Therefore, these routes are potentially affected by changes in absorption. Unlike the enteral or oral route, clinicians do not routinely abandon the use of subcutaneously or intramuscularly administered medications. Examples include the continued use of low-molecular-weight heparins and the antipsychotic haloperidol in patients for whom the absorption may be altered.

D. Inhalation – Administration of drugs directly into the lungs of critically ill patients is generally used for the local effect and not intended for systemic distribution. In fact, this route is often chosen to reduce systemic exposure of a drug. Ideally, an inhaled drug will achieve a high concentration in the pulmonary tissue, with little systemic exposure. The high local concentration is intended to maximize the therapeutic effect while reducing any adverse or unwanted affects. For example, the use of inhaled bronchodilators reduces unwanted systemic effects such as tachycardia. Antibiotics such as colistin and aminoglycosides are administered to improve the antibiotic concentrations in the lungs and reduce exposure to the kidneys. Drug particles between 1 and 5 micrometers have the best opportunity to be delivered to all areas of the lungs. Smaller particles will be exhaled without being deposited in the lower airways, whereas larger particles will be deposited in the large bronchi or the oropharynx. Several models of nebulizers are on the market that use different methods to achieve the desired particle sizes.

E. Intrathecal/Intraventricular – The intraventricular route is used with the same goal as the inhalation route. Increased local concentrations and reduced systemic concentrations are the desired effect. Data evaluating the efficacy of this route of administration are lacking in the general population and mostly limited to case series. Despite the lack of data, clinicians use this route when treating multidrug-resistant meningitis.

Patient Case

1. M.J. is a 70-year-old man admitted to the neurosurgical ICU for an aneurysmal subarachnoid hemorrhage. His initial management included placement of an external ventricular drain. Subsequently, he had a maximum temperature of 101.5°F, a WBC of 15×10^3 cells/mm^3, and a cerebral spinal fluid culture positive for methicillin-resistant *S. aureus*. Intraventricular vancomycin 20 mg is used for therapy. Which is the best rationale for this approach?
   A. Demonstrated superiority to intravenous antibiotics.
   B. Maximizing localized antibiotic concentrations.
   C. Reducing the nephrotoxicity of vancomycin.
   D. Reducing the ototoxicity of vancomycin.

III. ABSORPTION

A. Bioavailability refers to the percentage of an administered dose of drug that reaches the systemic circulation. Bioavailability from subcutaneous, intramuscular, or enteral administration is affected by absorption and first-pass metabolism (enterally administered drugs). Few studies directly assess the enteral absorption of drugs in critically ill patients, and the results vary. In addition, studies of enterally administered drugs do not differentiate whether plasma concentrations are altered because of changes in absorption or first-pass metabolism. Although data on absorption in critically ill patients are limited, clinicians must consider several factors if a route of administration other than intravenous is desired.

B. Gastrointestinal (GI) Perfusion – Hypotension and/or shock are known to cause the shunting of blood toward the vital organs (brain, heart, lungs) and away from the less vital organs (muscles, skin, splanchnic organs).
   1. GI absorption: No studies clearly show the effect of hypotension or shock on the oral or enteral absorption of drugs. Clinicians extrapolate changes in splanchnic blood flow to the likelihood that GI absorption is altered. Redistribution of blood away from the splanchnic circulation is thought to decrease drug absorption from the GI tract. The hyperdynamic phase of sepsis or septic shock can increase cardiac output, and studies have shown an increase in hepatosplanchnic (portal vein and hepatic artery) blood flow. In late-stage (decompensated) sepsis, it is thought that splanchnic blood

flow is decreased, but no studies have verified this. This uncertainty in splanchnic blood flow and GI absorption leads many clinicians to forgo the enteral route for drug administration.

2. Transdermal, subcutaneous, and intramuscular absorption: There are no studies evaluating the effect of hypotension or shock on transdermal, subcutaneous, or intramuscular absorption. Similar to splanchnic circulation, the shunting of blood to vital organs reduces blood flow to the skin and muscles, which is thought to reduce absorption from these sites. This assumption is supported by the observation that critically injured trauma patients with edema have significantly lower anti-Xa and antithrombin activity after treatment with subcutaneous enoxaparin (J Trauma 2005;59:1336-43). It is believed that altered absorption is a contributing factor to these results. However, this may not be generalized to all critically ill patients because anti-Xa activity was not significantly different in edematous compared with non-edematous medical-surgical ICU patients after dalteparin administration (Crit Care 2006;10:R93).
3. Vasopressor effect: Vasopressors may contribute to regional hypoperfusion, which could result in decreased absorption of drugs. Vasopressin reduces splanchnic blood flow in patients with distributive shock. In severe septic shock, use of epinephrine results in reduced splanchnic blood flow. Dopamine is not as effective as norepinephrine in maintaining splanchnic blood flow in patients with stable distributive shock. Conversely, when gut perfusion is compared between cardiac surgery patients with and without vasodilatory shock, norepinephrine use results in higher intestinal perfusion. However, this is countered by a worse splanchnic oxygen demand versus supply. The variable effect of vasopressors on splanchnic perfusion creates enough concern that most clinicians abandon the use of orally or enterally administered drugs when vasopressors are being used. One study investigated the anti-Xa activity of the low-molecular-weight heparin certoparin in critically ill patients. Less than 50% of patients receiving standard doses of certoparin had anti-Xa activity in the antithrombotic range (0.1–0.3 IU/mL) (Crit Care 2005;9:R541-8).

C. Intestinal Atrophy – After 3–5 days of fasting, gut mucosal crypt depth and villus height can be decreased. This correlates with an abnormal lactulose-mannitol test, indicating increased gut permeability. Splanchnic hypoperfusion can further worsen gut hypoxia, exacerbating gut permeability. However, the effect of intestinal atrophy on drug absorption has not been systematically evaluated. Atrophy and the corresponding loss of integrity of the tight junctions could lead to an increased absorption of drugs that are absorbed through passive diffusion. Conversely, cellular dysfunction caused by atrophy might decrease the absorption of drugs that require active transport for absorption. Currently, no studies can clarify this quandary.

D. GI Dysmotility – GI dysmotility has been clearly established in critically ill patients, with an incidence as high as 60%. Table 1 shows the conditions in critically ill patients that are associated with delayed gastric emptying caused by dysmotility. Acetaminophen kinetics show that GI dysmotility causes a delay in absorption and a reduced peak concentration in most studies. Concern regarding PK changes in the presence of delayed gastric emptying is a major factor contributing to the avoidance of orally or enterally administered drugs in critically ill patients. GI dysmotility is generally treated using prokinetic agents such as metoclopramide or erythromycin. There are no data regarding the effect of prokinetics on drug absorption in critically ill patients with dysmotility. Therefore, the effect of prokinetics on the PK of orally or enterally administered drugs in critically ill patients is unclear.

Table 1. Reasons for Delayed Gastric Emptying

Surgery	Postoperative Ileus	Trauma
Traumatic brain injury	Burns	Sepsis
Opioid analgesics	Mechanical ventilation	Electrolyte abnormalities
Hyperglycemia	Shock	Ileus

E. Intestinal Drug Transporters – Transmembrane proteins such as P-glycoprotein (PGP) and cytochrome P450 (CYP) enzymes play an integral role in the absorption of drugs. In general, these transporters serve to reduce the absorption of drug substrates. Therefore, decreased activity of these enzymes will theoretically increase the absorption of drugs that are substrates. Conversely, several intestinal transporters facilitate drug absorption and may thus decrease drug absorption. Unfortunately, there are no PK studies evaluating changes in drug absorption caused by changes in intestinal transporters that are specifically related to critical illness or conditions often present in these patients. As such, clinicians must understand the conditions that may affect transporter activity. Increased inflammatory cytokines in patients with systemic inflammatory response syndrome (SIRS) and sepsis affect PGP activity. Therefore, enteral drug absorption has the potential to be altered in these states. Unfortunately, no studies have directly investigated the effects of SIRS on drug absorption changes mediated by changes in PGP activity.

F. Physical Incompatibilities – Drugs administered through enteral feeding tubes come in contact with gastric secretions, intestinal secretions, and enteral nutrition formulas. All of these pose a problem for drug absorption.
   1. Drug enteral nutrition binding: Some drugs potentially interact with enteral nutrition. The degree of interaction and clinical significance varies.
      a. Ciprofloxacin bioavailability is reduced when it is administered with enteral nutrition, but most studies suggest that serum concentrations remain above the minimum inhibitory concentration (MIC) for most bacterial pathogens.
      b. Enteral nutrition has been reported to significantly reduce the absorption of levothyroxine, phenytoin, and warfarin. One case report showed a reduction in voriconazole serum concentrations when enteral nutrition was initiated (J Oncol Pharm Pract 2012;18:128-31).
      c. A suggested solution to this interaction is to hold the enteral nutrition 1–2 hours before and after drug administration. However, this poses two problems. First, interruption of enteral nutrition may contribute to inadequate nutrition support. Second, if enteral nutrition is not withheld, there is the potential for suboptimal effects of the interacting drug.
   2. pH changes: The state of ionization of a drug generally affects the lipophilicity and potentially the absorption. Examples from non-critically ill patients include increased gastric pH caused by histamine-2 receptor antagonists or proton pump inhibitors, resulting in decreased absorption of ketoconazole, itraconazole, atazanavir, cefpodoxime, and dipyridamole. Acid-suppressive drugs increased nifedipine and digoxin absorption, and alendronate had a 2-fold increase in bioavailability in the presence of these agents (Aliment Pharmacol Ther 2009;29:1219-29).

G. Important Considerations for Absorption
   1. The overall uncertainty of a patient's ability to absorb drugs from the GI tract often results in the clinician's avoidance of enterally administered drugs. The decision to use the GI route of administration is arbitrary. Many clinicians will anecdotally use tolerance of enteral feedings as a surrogate marker for normal drug absorption. If certain drugs are administered enterally, withholding the nutrition to avoid physical incompatibilities is warranted.
   2. Subcutaneous and intramuscular routes of administration present similar problems with absorption, but clinical practice has not abandoned these routes of administration. Some clinicians advocate for using larger doses of drugs being administered subcutaneously, but no studies have verified the safety or efficacy of this practice.

Patient Case

2. I.L. is a 32-year-old man receiving stress ulcer prophylaxis with esomeprazole 40 mg intravenously every day. Which drug will most likely have an increased absorption secondary to the increased gastric pH?
   A. Carvedilol.
   B. Ciprofloxacin.
   C. Diazepam.
   D. Digoxin.

IV. DISTRIBUTION

A. The Vd of a drug is a PK variable that relates the dose with the resultant serum concentration of said drug. A simple mathematical representation of this relationship is the following equation:

$$C = \frac{\text{dose}}{\text{Vd}}$$

where *C* is the initial serum concentration of an intravenously administered drug and Vd is the volume of distribution. However, the distribution of most drugs is more complex and is affected by several factors such as perfusion, degree of protein binding, tissue permeability, drug lipid solubility, drug pK_a, and pH of the environment. Critically ill patients may be subjected to changes in the above factors that could result in an altered Vd for some drugs.

B. Tissue Perfusion – As noted in the previous section, shock states cause the redistribution of blood flow. This results in decreased perfusion of the muscle, skin, and splanchnic organs. Hydrophilic drugs with a smaller Vd (ones that remain in the plasma water volume) may have decreased distribution to parts of the body with decreased blood flow. This is highlighted by animal studies of septic shock showing lower gentamicin concentrations in the microcirculation compared with the central vessels.

C. Fluid Shifts and Tissue Membrane Permeability – Critically ill patients can receive significant volumes of intravenous fluid for resuscitation purposes. This often results in increased volumes of total body water and interstitial fluid. In addition to fluid administration, disease states such as sepsis, thermal injury, acute respiratory distress syndrome, AKI, heart failure, and cirrhosis can cause increases in interstitial fluid volumes. In addition, surgery increases extracellular volume postoperatively. In this setting, the Vd for hydrophilic drugs is increased, whereas the Vd for lipophilic drugs is often unchanged. The increased interstitial water provides a larger compartment for hydrophilic drugs to distribute, thus decreasing the serum concentrations. In addition, because distribution is into a larger interstitial space, the drug concentration can be decreased in this space. This has been shown in microdialysis studies evaluating subcutaneous tissue concentrations for piperacillin. Compared with healthy volunteers, patients with septic shock had reduced piperacillin tissue concentrations. Unfortunately, increased Vd of drugs is not universally noted. Although one study found increases in aminoglycoside Vd, another study was unable to correlate fluid shifts with changes in the aminoglycoside Vd (Crit Care Med 1988;16:327-30).

D. Protein Binding – Drugs can bind to plasma proteins such as albumin, AAG, lipoproteins, and cortisol-binding protein. Albumin and AAG are important in critically ill patients. Albumin generally binds to acidic drugs (e.g., diazepam, phenytoin), whereas AAG binds to basic drugs (e.g., lidocaine, diltiazem). Of importance, their concentrations change during various states of critical illness. Albumin concentrations generally decrease under stress, whereas AAG concentrations increase. The following equation represents the calculation of Vd:

$$Vd = \left(\frac{f_u}{f_{uT}} \right) Vt + Vp$$

where f_u is the fraction unbound in the plasma, f_{ut} is the fraction unbound in the tissues, Vt is the volume of tissue, and Vp is the volume of plasma. When the plasma concentration of albumin decreases, the f_u of a drug increases. This increase results in an increased Vd. The converse is true for drugs bound to AAG.

1. The clinical relevance of this was noted when a decrease in the Vd of lidocaine correlated with an increase in AAG in post-cardiac surgery patients. It was suspected that arrhythmias were caused by these PK changes (Clin Pharmacol Ther 1984;35:617-26).
2. Table 2 provides examples of drugs used in critically ill patients that bind to albumin and AAG.

Table 2. Extraction Ratio and Protein Binding of Select Drugs Used in Critically Ill Patients

Protein Binding	High ER Drugs	Intermediate ER Drugs	Low ER Drugs
Albumin	Propofol Morphine Propranolol Verapamil	Aspirin Carvedilol Omeprazole Midazolam	Carbamazepine Ceftriaxone Dexamethasone Diazepam Itraconazole Phenytoin Valproic Acid Warfarin Diltiazem
AAG	Lidocaine Fentanyl Propranolol Verapamil	Midazolam	Carbamazepine Diltiazem

ER = extraction ratio.

E. pH – Acid-base disorders are common among the critically ill. Although these disorders are treatable, they create plasma pH changes that could affect drug distribution. Most drugs are either weak acids or bases and exist in either the ionized or the non-ionized state, depending on the surrounding environment. Non-ionized drugs penetrate cell membranes more easily than do ionized drugs. Therefore, it would be expected that a drug in the ionized state would have a smaller Vd than when in the non-ionized state. Theoretically, a drug that is a weak acid in a patient experiencing acidemia would be expected to have a larger Vd, and the converse would be true for a basic drug. Although the potential exists to correlate plasma pH changes with changes in drug Vd, evidence in humans is lacking.

Patient Cases

3. R.H. is 20-year-old man who presents to the emergency department with nausea and vomiting. His vital signs are significant for a heart rate of 130 beats/minute, blood pressure of 98/62 mm Hg, and respiratory rate of 28 breaths/minute. Laboratory tests reveal an arterial blood gas significant for a pH of 7.11, P_{CO_2} of 18 mm Hg, and sodium bicarbonate of 5.2 mEq/L. His basic metabolic panel is significant for a potassium level of 5 mEq/L, BUN of 22 mg/dL, SCr of 1.4 mg/dL, and blood glucose of 400 mg/dL. Which describes what would most likely happen to the Vd of a weak acid like ciprofloxacin in this patient?
   A. Increased because of decreased ionization.
   B. Decreased because of increased ionization.
   C. No change because of no change in ionization.
   D. Decreased because of decreased ionization.

4. B.B. is a 62-year-old woman admitted to the ICU for septic shock. She required 25 L of crystalloids during her resuscitation. Which antibiotic would be most likely to have a Vd similar to that in normal individuals?
   A. Tobramycin.
   B. Linezolid.
   C. Levofloxacin.
   D. Cefepime.

V. METABOLISM

A. Introduction – The predominant location for drug metabolism is the liver, but it can include tissues such as the GI tract, kidneys, lung, and brain. The greatest extent of knowledge regarding drug metabolism, and more importantly changes in critically ill patients, relates to hepatic metabolism. Therefore, this section will focus largely on changes in the hepatic metabolism of drugs.

B. Renal Metabolism – There is evidence that the kidneys express the CYP isoenzymes 2B6 and 3A5. Data suggest that CYP 2C8, 2C9, and 3A4 are also expressed in the kidneys. In addition, UGT (UDP-glucuronosyltransferase) enzymes 1A9 and 2B7 are abundantly expressed in the kidneys, and they play a role in the glucuronidation of drugs. Unfortunately, there are no data describing how changes in critically ill patients affect drug metabolism in the kidneys by these enzymes. Critically ill patients with AKI have clinically relevant changes in insulin metabolism, as evidenced by increased hypoglycemic events and lower insulin requirements upon developing AKI (Nutrition 2011;27:766-72).

C. Hepatic Metabolism – Hepatic clearance refers to the volume of blood that is completely cleared of drug by the liver per unit of time. The ability of the liver to metabolize drugs depends on three physiologic parameters: hepatic blood flow, drug protein binding, and the intrinsic activity of hepatic enzymes. When evaluating an intravenously administered drug (bioavailability of 1), clearance by the liver can be simply represented by the following equation:

$$CL_H = Q \times E$$

where CL_H is the hepatic clearance, Q is the hepatic blood flow, and E is the hepatic extraction ratio. The extraction ratio can be further described by the following equation:

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

where f_u is the fraction unbound in the plasma, CL_{int} is the intrinsic hepatic clearance, and Q is hepatic blood flow. The HER is classified by the fraction of drug removed during one pass through the liver and can range from 0 to 1. It can be separated into high (greater than 0.7), intermediate (0.3–0.7), and low (less than 0.3) categories. The extraction ratio would be zero when the liver does not metabolize a drug and 1 when CL_H is entirely dependent on hepatic blood flow. The effect of changes in critical illness depends on the extraction ratio of the drug. Table 2 provides a list of select high extraction ratio and low extraction ratio drugs.

D. High Extraction Ratio Drugs

1. Drugs with a high hepatic extraction ratio are highly metabolized by hepatic enzymes and are thus extensively cleared by the liver. In drugs with high extraction ratios, clearance dose not vary with changes in hepatic enzymatic activity and is primarily dependent on hepatic blood flow. Mathematically, this can be represented by:

$$f_u \times CL_{int} >>> Q$$

Given the above relationship, CL_H can be simplified to:

$$CL_H = Q$$

As previously stated, clearance of a drug pertains to removal of the drug from the blood. Therefore, the effect on plasma drug concentration will affect the efficacy of the drug. Because only the free drug is available to produce a clinical effect, the unbound steady-state concentration (Cssu) is extremely important. The steady-state concentration (Css) of hepatically metabolized drugs can be represented by the following equation:

$$C_{ss} = \frac{dose}{CL_H}$$

where Css is the steady-state concentration and dose is the rate of drug input. Because $CL_H = Q$ for high extraction ratio drugs, the equation can be modified to:

$$C_{ss} = \frac{dose}{Q}$$

The unbound steady-state concentration for a high extraction ratio is represented by the following equation:

$$C_{ssu} = \frac{f_u \times dose}{Q}$$

Figure 1 shows how a change in each variable of CL_H affects the Css and Cssu. For high extraction ratio drugs, altered hepatic blood flow affects both the Css and the Cssu, whereas changes in f_u affect only the Cssu.

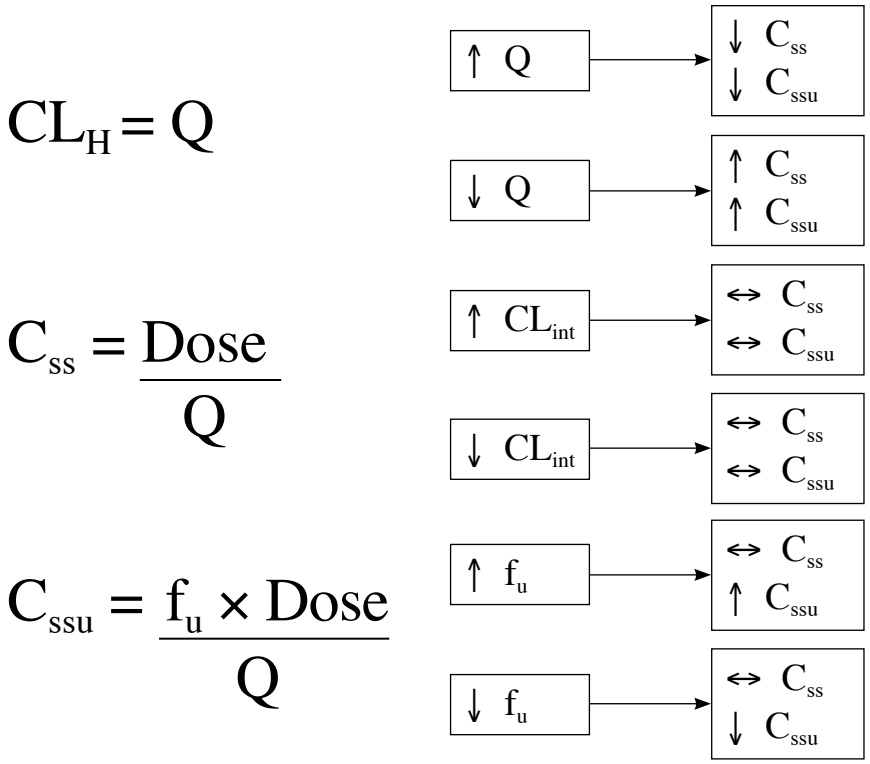

Figure 1. Effect of variable changes on steady-state and unbound steady-state concentrations of a high extraction ratio drug.

2. Effect of increased hepatic blood flow: Animal models have shown a clear increase in splanchnic perfusion during the hyperdynamic phase of sepsis. Critically ill patients in the hyperdynamic phase of sepsis or septic shock have an increased cardiac output and increased hepatosplanchnic blood flow. Unfortunately, a correlation directly relating cardiac output (or an increase in cardiac output) to an increase in splanchnic blood flow could not be established in some studies. Therefore, quantification of the increase in blood flow and the resultant increase in hepatic metabolism cannot be established. The clinician is left to assume the potential for increased metabolism of high extraction ratio drugs and the expected decrease in unbound steady-state concentration and possibly a reduced clinical efficacy.
3. Effect of decreased hepatic blood flow
    a. Conditions with a low cardiac output such as hypovolemic or hemorrhagic shock, late (hypodynamic) sepsis, myocardial infarction with or without cardiogenic shock, and acute heart failure exacerbation would be expected to cause a decrease in hepatic blood flow. Human studies to verify this assertion are lacking. Animal models of hypodynamic sepsis and cardiogenic shock show a reduction in hepatic blood flow.
    b. Mechanical ventilation produces an increased intrathoracic pressure. This pressure causes a decrease in venous return to the heart, compresses the ventricles, and reduces ventricular filling. The result is a decrease in cardiac output (N Engl J Med 1981;304:387-92) and hepatic blood flow (Crit Care Med 1982;10:703-5).
    c. Adding an inotrope would likely improve hepatic blood flow. Although data in humans are lacking, an animal model of endotoxemia found improvement in hepatic blood flow after the administration of dobutamine.

E. Low Extraction Ratio Drugs – Drugs with a low hepatic extraction ratio undergo a lower degree of hepatic enzyme metabolism; thus, they are not extracted from hepatic blood flow as high extraction ratio drugs. In drugs with low extraction ratios, clearance varies with changes in hepatic enzymatic activity, and clearance is independent of hepatic blood flow. Mathematically, this can be represented by:

$$f_u \times CL_{int} <<< Q$$

According to this relationship, CL_H can be simplified to:

$$CL_H = f_u \times CL_{int}$$

Again, the Css for hepatically metabolized drugs can be represented by the following equation:

$$C_{ss} = \frac{dose}{CL_H}$$

where Css is the steady-state concentration and dose is the rate of drug input. Because $CL_H = f_u \times CL_{int}$ for low extraction ratio drugs, the equation can be modified to:

$$C_{ss} = \frac{dose}{f_u \times CL_{int}}$$

The unbound steady-state concentration for a low extraction ratio drug is represented by the following equation:

$$C_{ssu} = \frac{dose}{CL_{int}}$$

Figure 2 on page 2-398 shows how a change in each variable of CL_H affects the Css and the Cssu. For low extraction ratio drugs, altered CL_{int} affects both the Css and the Cssu, whereas changes in the f_u affect only the Css.

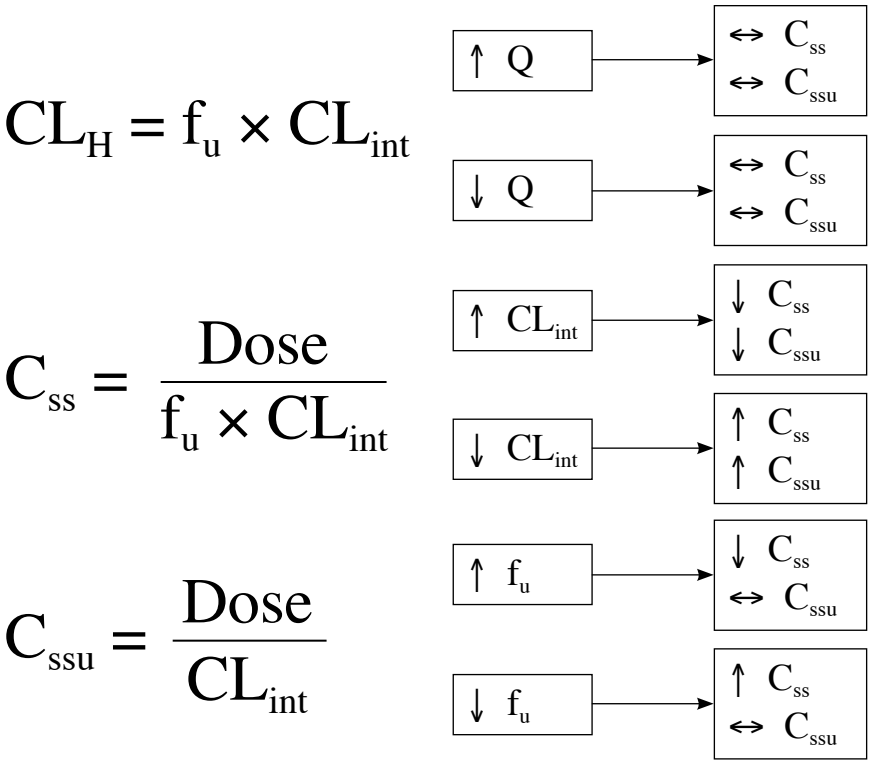

Figure 2. Effect of variable changes on steady-state and unbound steady-state concentrations of a low extraction ratio drug.

F. Effect of Changes in Intrinsic Clearance

1. Drug interactions – A major mechanism for altered intrinsic clearance is not caused by changes in critically ill patients, but it still poses a significant threat to altered metabolism of drugs. The CYP enzymes play an important role in phase I metabolism. Many drugs used in critically ill patients are substrates, inducers, inhibitors, or combinations of these. Critically ill patients often have complex pharmacotherapeutic regimens that create the potential for drug interactions through the CYP system. As in other patient populations, drug concentrations are increased when substrates are coadministered with inhibitors of the same CYP and decreased when substrates are coadministered with inducers.
2. Inflammation – SIRS plays an important role in altering CYP activity. The inflammatory cytokines interleukin (IL)-1α, IL-6, and TNFα (tumor necrosis factor alpha) decrease the expression and activity of CYP enzymes. Similarly, patients in early sepsis would have increased inflammatory cytokines with the resultant depressed CYP activity. This is supported by studies showing that endotoxin administration results in decreased CYP-mediated drug metabolism in healthy volunteers. Unfortunately, studies have not characterized a time course for the cytokine-mediated changes. Clinicians are left to use patient response and monitoring for toxicity to determine whether drug metabolism is altered or has returned to normal.

3. Hypothermia – Animal models have shown that hypothermia affects drugs metabolized through the CYP system. Drugs studied in animal models include fentanyl, pentobarbital, propranolol, and morphine. Human studies have investigated the effect of hypothermia on low extraction ratio drug kinetics. One example showed changes in phenytoin PK during mild hypothermia. Specifically, increased concentrations and reduced metabolism, but no changes in protein binding, were noted during hypothermia (Ther Drug Monit 2001;23:192-7). Other drugs noted to have decreased hepatic clearance during hypothermia are midazolam, fentanyl, remifentanil, phenobarbital, and vecuronium.
4. AKI – One study investigated the effects of AKI on the hepatic metabolism of midazolam. Patients with worsening AKI, as determined using the RIFLE (risk, injury, failure, loss) criteria, had increasing midazolam concentrations. The authors hypothesized that the increased concentrations were caused by impaired CYP3A activity (Intensive Care Med 2012;38:76-84).

G. Intermediate Extraction Ratio Drugs – Metabolism of an intermediate extraction ratio drug is dependent on hepatic blood flow, intrinsic clearance, and fraction of unbound drug. Essentially, intermediate extraction ratio drugs are dependent on the same variables as both the low extraction ratio and high extraction ratio drugs. As such, they are the most complex drugs for determining how hepatic clearance will be affected in critically ill patients. This is important because critically ill patients generally have more than one change occurring at the same time. For example, patients with septic shock may have increased hepatic blood flow secondary to increased cardiac output while having a decreased intrinsic clearance secondary to increased circulating inflammatory cytokines. Quantifying the overall effect is difficult in the ever-changing critically ill patient. The clinician is often left to monitor for the expected therapeutic outcome while being aware of the potential toxicities.

H. Other Factors
   1. TBI increases the hepatic clearance of some drugs.
      a. One study found that patients with TBI had increased hepatic clearance of phenytoin during the first 7–14 days. The authors alluded to the possibility that the increased clearance was associated with changes in protein binding, induction of metabolism, or stress on hepatic metabolic capacity (Clin Pharmacol Ther 1988;44:675-83).
      b. Another study noted a correlation between nutritional protein intake and increased phenytoin metabolism in patients with TBI.
      c. Phase II enzymatic activity may also be enhanced in patients with TBI, as evidenced by increased lorazepam clearance. Similar data for lorazepam were noted in thermally injured patients. These data suggest that phase II metabolism can be affected by critical illness.
   2. Hepatic failure – Hepatic failure will significantly affect drug dosing in the critically ill patient. See the Hepatic Failure/GI/Endocrine Emergencies chapter for more information regarding drug dosing in hepatic failure.

Patient Cases

5. A.P. is a 35-year-old woman admitted to the ICU for an acute asthma exacerbation. She was intubated and required mechanical ventilation. She is prescribed morphine for pain control. Which statement best describes the effect of mechanical ventilation on morphine unbound concentrations?

   A. Increases oxygenation delivery to the liver and increases the unbound concentration.
   B. Decreases hepatic blood flow and increases the unbound concentration.
   C. Increases cytokine production and decreases the unbound concentration.
   D. Cannot affect the unbound concentration.

6. J.M. is a 65-year-old woman in the ICU who develops atrial fibrillation. Her rate is controlled using a diltiazem infusion of 10 mg/hour. J.M. develops a fever and leukocytosis. She is empirically initiated on vancomycin 1 g intravenously every 12 hours, piperacillin/tazobactam 2.25 g intravenously every 6 hours, and fluconazole 400 mg intravenously every 24 hours. Which PD response would you most expect to see in J.M.?

   A. Increased heart rate caused by an increased intrinsic clearance of diltiazem.
   B. Decreased heart rate caused by a decreased intrinsic clearance of diltiazem.
   C. Increased heart rate caused by a decreased unbound fraction of diltiazem.
   D. Decreased heart rate caused by an increased unbound fraction of diltiazem.

7. P.M. is receiving phenytoin for the treatment of posttraumatic seizures. You measure a total phenytoin concentration, which is 8 mcg/mL. You calculate the adjusted concentration according to P.M.'s hypoalbuminemia (albumin of 2.5 g/dL) and determine the concentration to be around 13 mcg/mL. Which best depicts why this adjustment was needed?

   A. The unbound phenytoin concentration increased because of an increased unbound fraction of phenytoin.
   B. The total phenytoin concentration increased because of an increased unbound fraction of phenytoin.
   C. The unbound phenytoin concentration decreased because of an increased unbound fraction of phenytoin.
   D. The total phenytoin concentration decreased because of an increased unbound fraction of phenytoin.

8. C.P. is a 50-year-old man admitted to the medical ICU for diabetic ketoacidosis. His medical history is significant for hypertension, type 1 diabetes mellitus, and a myocardial infarction 2 years ago. He quit smoking last year and only drinks alcohol occasionally. His vital signs are significant for a heart rate of 125 beats/minute, blood pressure of 95/65 mm Hg, and respiratory rate of 22 breaths/minute. His significant dehydration contributed to the development of AKI. His current SCr is 2.8 mg/dL. His blood glucose is significantly elevated at 350 mg/dL. He will be initiated on a continuous intravenous infusion of insulin to correct his blood glucose. Which factor is most important to consider when dosing insulin in C.P.?

   A. Decreased renal metabolism of insulin.
   B. Increased Vd of insulin.
   C. Increased hepatic metabolism of insulin.
   D. Decreased receptor binding of insulin.

VI. EXCRETION

A. Renal Excretion

1. For most drugs, the kidneys are the primary site for excretion of the parent drug, metabolites, or both. Urinary excretion of a drug is dependent on filtration, secretion, and reabsorption. Patients in the ICU may experience increased, decreased, or normal renal excretion of drugs. The state of renal excretion depends on many variables and can change rapidly. This is especially true in ICU patients, where a clinical condition can contribute to both increased and decreased excretion, depending on how that condition progresses.
2. Filtration
    a. GFR is the variable most widely used to describe kidney function. The National Kidney Foundation defines normal kidney function as 140 ± 30 mL/minute/1.73m^2 for young healthy men and 126 ± 22 mL/minute/1.73m^2 for young healthy women. Although there is no standard definition for increased GFR (augmented renal clearance [ARC]), an increase of 10% above the upper end of normal (greater than 160 mL/minute/1.73m^2 in men and greater than 150 mL/minute/1.73m^2 in women) has been proposed (Crit Care 2013;17:R35).
    b. ARC – Conditions such as surgery, trauma, burns, and sepsis have been associated with increased renal blood flow. This is generally believed to be caused by an increased cardiac output coupled with vasodilation. The resulting ARC is believed to be a response to SIRS.
        i. One study found glomerular hyperfiltration present in 17.9% of patients admitted to the ICU. Most of these patients were younger and admitted for multi-trauma or surgery (Anaesth Intensive Care 2008;36:674-80). These data are supported by a study showing young postoperative trauma patients with peak creatinine clearance (CrCl) values as high as 190 mL/minute/1.73m^2. A more recent study found insignificant risk factors for the ARC to be age 50 years or younger, trauma, and a modified sequential organ failure score of 4 or less.
        ii. A study of burn patients found an increase in iohexol clearance with a median value of 155 mL/minute/1.73m^2 on day 1 of admission. In this small study, clearance had returned to the expected baseline of 122 mL/minute/1.73m^2 by day 7 (Burns 2010;36:1271-6). In addition, several studies have shown increased excretion of renally eliminated drugs in burn patients. Examples include vancomycin, ciprofloxacin, imipenem, fluconazole, and aminoglycosides.
        iii. Fluid administration would be expected to improve cardiac output and thus renal blood flow. Animal studies have confirmed that the administration of crystalloids can increase CrCl. Sheep administered normal saline and 3% hypertonic saline have a significantly higher calculated CrCl compared with controls. However, no human studies have verified ARC in critically ill patients after fluid administration.
        iv. Vasoactive drugs would be expected to improve cardiac output and thus renal blood flow. Unfortunately, human studies were only able to establish an improvement in CrCl in patients with impaired CrCl before norepinephrine administration. Although studies were unable to show ARC, patients receiving vasopressors for shock states might be expected to have normal renal blood flow and CrCl, assuming they are not experiencing AKI.
        v. The duration of ARC is not well established, but the peak CrCl appears to occur at about days 4–5 in most studies, with CrCl returning to normal by day 7 in one study.
    c. Impaired renal clearance
        i. Decreased renal excretion of drugs during AKI is the most widely applicable change occurring in critically ill patients. Depending on the patient population and definition used, the incidence of AKI in ICU patients can be as high as 78%. AKI significantly affects the excretion of renally eliminated drugs, and dosing modifications must be made in these situations.

ii. The guidelines recommend that staging of AKI be done using the Kidney Disease Improving Global Outcomes (KDIGO) AKI criteria. However, these guidelines do not make specific recommendations regarding drug dosing.
iii. A clinical update to the 2010 guidelines does provide recommendations on how to approach drug dosing in critically ill patients with AKI. Because of the complicated picture of AKI in critically ill patients, however, the recommendations are not as precise as recommendations for drug dosing in CKD. In fact, the authors note that most renal dose adjustment recommendations in the literature and from the FDA (U.S. Food and Drug Administration) are based on data from patients with CKD (Kidney Int 2011;80:1122-37).
iv. The update recommends a stepwise approach to adjusting drug-dosing regimens in patients with AKI (Box 1).

Box 1. Recommended Steps for Assessing and Adjusting Drug Regimens in Patients with AKI

Step 1 – Assess the following • Demographic information • Past medical history (including history of renal disease) • Current clinical information • Current laboratory information • DNA polymorphisms
Step 2 – Estimate eGFR or CL_{cr} using: • Age • Body size • Ethnicity • Concomitant diseases
Step 3 – Review current medications • Identify drugs needing individualized dosing
Step 4 – Calculate individualized treatment regimen • Determine treatment goals (PK or PD values) • Calculate dosage regimen (based on drug PK and changes noted in the patient)
Step 5 – Monitor regimen • Drug response • Signs or symptoms of toxicity • Drug levels (if available)
Step 6 – Revise regimen • Adjust regimen according to patient response • Adjust regimen according to changes in patient status

v. The recommendations include using the estimated GFR (eGFR) or CrCl to assess renal function for drug dosing. The estimated GFR equation is described as follows:

$$GFR = 175.6 \times SCr^{-1.154} \times age^{-0.212} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}$$

where GFR is in milliliters per minute/1.73m^2, SCr is measured in the laboratory using isotope dilution mass spectroscopy (IDMS), and age is in years. If the laboratory measuring the SCr does not use IDMS, the following equation should be used:

$$GFR = 186.3 \times SCr^{-1.154} \times age^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}$$

vi. The Cockcroft-Gault equation is used to estimate the CrCl as follows:

$$\text{CrCl} = \frac{(140 - \text{age})\,\text{weight}}{\text{SCr} \times 72} \times 0.85 \text{ (if female)}$$

where CrCl is in milliliters per minute, weight is in kilograms, and SCr is in milligrams per deciliter.

vii. The update also notes that the most important factor when determining kidney function is having at least one GFR estimate for all patients.

viii. A more detailed discussion of assessment of AKI can be found in the Renal Disorders chapter.

3. Secretion and reabsorption: Unfortunately, it is difficult to study changes in drug secretion and reabsorption in patients. Therefore, data are not available to describe the clinically important changes in these two variables in critically ill patients.
4. Renal replacement therapies:
   a. Patients having a diagnosis of AKI may require hemodialysis. The choice of dialytic technique depends on the institution, expertise of the clinician, patient hemodynamic stability, and access to various types of dialysis machines. Drug removal by dialysis depends on the method of dialysis used.
   b. Acute intermittent hemodialysis
      i. Intermittent hemodialysis can significantly contribute to the excretion of drugs, whereas other drugs are not appreciably removed by hemodialysis. Removal of drugs during hemodialysis depends on the size of the molecule, Vd, protein binding, and type of dialysis filter (specifically the membrane size).
      ii. See the Renal Disorders chapter for more specific recommendations on drug dosing when a critically ill patient is undergoing intermittent hemodialysis.
   c. Continuous renal replacement therapies (CRRTs)
      i. CRRT refers to several methods of renal replacement. Many studies have investigated the effect of CRRT on drug removal. Considerable variability exists in the type of CRRT used. The 2010 clinical update to the KDIGO guidelines suggests the following equation as one option to determine the appropriate dose of a drug in CRRT:

$$\text{dose} = \text{dose}_n \left(\frac{\text{CL}_{\text{nonrenal}} + (\text{Q}_{\text{eff}} \times \text{SC})}{\text{CL}_{\text{norm}}} \right)$$

where dose is the desired dose for CRRT, dose_n is the normal dose of a drug, $\text{CL}_{\text{nonrenal}}$ is the nonrenal clearance of a drug, Q_{eff} is the effluent rate, SC is the sieving coefficient, and CL_{norm} is the normal clearance of the drug.

      ii. See the Renal Disorders chapter for more specific recommendations of drug dosing during CRRT.

B. Hepatic Excretion – Hepatic excretion of drugs is less important for most drugs than renal excretion. However, excretion of drug in the bile can potentially be affected by critical illness. This is evidenced by changes in the clearance of some neuromuscular blocking agents.
   1. A study of nine patients undergoing surgery for total biliary obstruction showed a significant increase in pancuronium half-life compared with normal patients (270 minutes vs. 132 minutes, $p<0.001$). The urinary excretion of pancuronium and its metabolites did not change. This suggests that the increased half-life was caused by the decreased hepatic excretion of pancuronium (Br J Anaesth 1977;49:1103-8).

2. Similar results were found for vecuronium in patients with cholestasis, where the mean half-life was 98 minutes in patients with cholestasis and 58 minutes in normal patients (Br J Anaesth 1986;58:983-7).

C. Pulmonary Excretion – Pulmonary excretion is important for volatile gases such as anesthetics. It can be hypothesized that impaired gas exchange (e.g., acute respiratory distress syndrome) has an effect on the body's ability to remove volatile gases. However, data are lacking regarding changes in critically ill patients that affect their ability to excrete anesthetics.

VII. PHARMACODYNAMICS

A. *Pharmacodynamics* refers to the biochemical and physiologic effects of a drug, specifically those related to the mechanism of action. This term also pertains to drug/receptor binding and clinical effect. Most clinicians use the term to refer to the physically identifiable effect of a drug in a patient. For example, the PD effect of an opioid is the relief of pain reported by the patient. However, the PD effect of some drugs is not readily observable. For example, the PD effect of proton pump inhibitors is an increase in gastric pH. Few PD studies of critically ill patients are reported in the medical literature, and most pertain to antibiotic therapy.
   1. Antibiotics general information: PD studies of antibiotics use models to estimate the combined effects of the patient population PK of specific antibiotics and the MIC for select bacteria. These techniques generally allow a calculation of the desired PD outcome. Antibiotics generally fall into three PD categories, which correlate with efficacy: (1) time-dependent killing (T>MIC), (2) concentration-dependent killing (Cmax/MIC), and (3) a combination of time- and concentration-dependent killing (AUC/MIC).
   2. β-Lactam antibiotics: For β-lactam antibiotics, the PD parameter of the free drug concentration time above the MIC (*f*T>MIC) is used to predict treatment success. This is reported as a percentage of time the free drug concentration remains above the MIC. The ideal *f*T>MIC is 100%. However, PD studies of β-lactam antibiotic use in critically ill patients have found that a very low percentage of patients will achieve the desired PD targets (Crit Care 2011;15:R206). These failures are often attributed to clinically important changes that can occur rapidly in critically ill patients (e.g., ARC). As such, epidemiologic studies have tried to determine a breakpoint at which clinical success is achieved. Studies vary, and the suggested breakpoint ranges from 50% to 100% (*f*T>MIC) (Br J Clin Pharmacol 2012;73:27-36). Modeling generally suggests improved PD of β-lactams when using prolonged or continuous infusions. Many institutions have adopted the practice of prolonged infusions. This is supported by quasi-experimental and retrospective studies showing improved outcomes such as improved clinical cure, improved microbiological cure, and reduced morbidity and mortality. Unfortunately, prospective controlled clinical trials have not found such dramatic differences (J Crit Care 2014;29:1089-95). There are many reasons why there appears to be a discrepancy between PD modeling studies and controlled clinical trials, but patient variability, dosing variability, and disease severity seem to be important factors (Ann Intensive Care 2012;2:37).
   3. Aminoglycosides: Aminoglycoside bacterial killing is based on the ratio between the maximum drug concentration and the MIC for the bacterial pathogen (Cmax/MIC), or concentration-dependent killing. Efficacy was noted when patients were pooled from four controlled clinical trials and peak concentrations, MIC values, and clinical response were evaluated. Peak-to-MIC ratios of 8–10 resulted in around 90% clinical response (J Infect Dis 1987;155:93-9). In patients with gram-negative bacteremia, early therapeutic peak concentrations were a significant discriminating factor for morality. According to these and other data, once-daily aminoglycoside dosing has been used. Taking advantage of high peak concentrations maximizes the PD of aminoglycosides. Variability in the Vd of aminoglycosides in critically ill patients, together with concern for ARC in this population, raises

issues about appropriately dosing these agents, especially in critically injured trauma patients, whose drug levels can be undetectable for more than 12 hours (J Trauma 2000;49:869-87).

4. Vancomycin: The PD parameter that best describes vancomycin efficacy is the AUC/MIC. Several studies have evaluated the free 24-hour AUC/MIC ($fAUC_{0-24}$/MIC), or the AUC × 50% protein binding/MIC. Current guidelines use the available literature to recommend an AUC/MIC of 400 or greater (Am J Health Syst Pharm 2009;66:82-98). The guidelines suggest that continuous-infusion regimens are unlikely to improve patient outcomes and that standard intermittent infusions should be sufficient to achieve the desired PD end points. Of interest is a retrospective study of vancomycin-associated nephrotoxicity in critically ill patients. In this study, intermittent dosing was associated with a significantly higher risk of nephrotoxicity compared with continuous infusion (odds ratio 8.2; $p \leq 0.001$) (Crit Care Med 2014;42:2527-36). Of note, more aggressive dosing may be required in critically ill patients. Doses as high as 20 mg/kg administered as often as every 6 hours were needed to optimize PK parameters in critically injured trauma patients being treated for ventilator-associated pneumonia (J Trauma Acute Care Surg 2012;72:1478-83).
5. Fluoroquinolones: Similar to the efficacy of aminoglycosides, efficacy of the fluoroquinolones is based on a Cmax/MIC (10 or greater), and the fluoroquinolones have a post-antibiotic effect against gram-negative and gram-positive bacteria. PD studies have shown that the $fAUC_{0-24}$/MIC is associated with bacterial eradication. In one study of lower respiratory tract infections treated with ciprofloxacin, an AUC_{0-24}/MIC of 125 was associated with the percent probability of 80% for clinical cure (Antimicrob Agents Chemother 1993;37:1073-81). Unfortunately, it is difficult to incorporate these PD parameters into fluoroquinolone dosing in individual critically ill patients.
6. Non-antibiotic drugs: PD studies of other drugs in critically ill patients are sparse.
    a. The PD parameter for continuous infusions of many anticoagulants is change in the activated partial thromboplastin time (aPTT). Unfractionated heparin infusions are generally predictable in most patient populations. However, in critically ill patients, just under one-half (44%) did not reach a therapeutic aPTT within 24 hours of starting a heparin continuous infusion (Neth J Med 2013;71:466-71). Concern for a variable response in critically ill patients has led to the development of dosing nomograms/protocols. Researchers have found a shortened time to therapeutic aPTTs in critically ill patients receiving unfractionated heparin and direct thrombin inhibitors (argatroban and bivalirudin).
    b. As with antibiotic PD studies, most PD studies of other drugs have shown a decreased response in critically ill patients. For example, critically ill patients in septic shock had a reduced response to dobutamine compared with critically ill patients without septic shock and with normal volunteers (Crit Care Med 1993;21:31-9). Trauma patients with edema have lower AUCs for anti-Xa activity compared with non-edematous patients (J Trauma 2005;59:1336-43). Mechanically ventilated patients with chronic obstructive pulmonary disease were studied for covariates affecting acetazolamide therapy. Mixed-effects modeling found the Simplified Acute Physiology Score II, serum chloride, and concomitant corticosteroids to be the main covariates interacting with acetazolamide PD.

VIII. THERAPEUTIC DRUG MONITORING

A. Therapeutic drug monitoring (TDM) refers to the measurement of medication concentrations in the blood. The focus of TDM is on drugs with a narrow therapeutic index and aims to achieve two things: (1) maximize efficacy and (2) reduce toxicity. Use of TDM in critically ill patients is extremely important because changes in the PK variables previously described can result in less-than-desirable drug concentrations. Table 3 highlights some commonly used medications in the ICU and their therapeutic

ranges. One of the main limitations of TDM is the lack of clinically available assays. In addition, assays for some drugs may not be cost-effective to routinely conduct in certain institutions. These issues generally result in TDM for a very limited spectrum of drugs.

1. Monitoring of blood concentrations is dependent on the intended use and interpretation of those concentrations. Most TDM occurs as a method to confirm a therapeutic concentration in a patient with signs and/or symptoms of toxicity or decreased efficacy. In this case, a concentration is measured during the appropriate timeframe (Table 3), and a clinician interprets the concentration. If needed, the clinician modifies the drug dosing according to clinical experience. This method may produce variable results. The critically ill patient requires important considerations. For example, if extended-interval dosing is being used, the likelihood of an increased Vd must be considered. Patients with ARC have the potential to have a prolonged drug-free period. Finally, the status of a critically ill patient can change rapidly. Monitoring for decreased kidney function is essential to avoid accumulation.

Table 3. Therapeutic Drug Monitoring Ranges for Select Drugs Used in Critically Ill Patients

Drug	Timing of Blood Sample	Therapeutic Range
Amikacin	Trough Peak (traditional)	< 8 mg/L 20–30 mg/L
Phenobarbital	Trough	10–40 mg/L
Carbamazepine	Trough	4–12 mg/L
Cyclosporin	Trough	50–500 mcg/L
Digoxin	Trough (8–24 hours postdose)	0.6–2 mcg/L
Gentamicin	Trough (traditional) Trough (extended interval) Peak	< 2 mg/L Undetectable 5–10 mg/L
Lidocaine	Peak	1.5–5 mg/L
Phenytoin	Trough	10–20 mg/L
Tobramycin	Trough (traditional) Trough (extended interval) Peak	< 2 mg/L Undetectable 5–10 mg/L
Vancomycin	Trough (complicated infections) Trough (uncomplicated infections)	15–20 mg/L 10–15 mg/L

2. For certain intravenously administered drugs (e.g., aminoglycosides, vancomycin), several concentrations can be measured when the drug is at steady state. The patient's specific PK can be determined and used to tailor the drug-dosing regimen. The following PK equations can be used to calculate the various kinetic parameters.

Determination of the elimination rate constant:

$$k_e = \frac{\ln \frac{C_1}{C_2}}{\Delta \text{ in time}}$$

where k_e is the elimination rate constant, C_1 is the measured peak concentration, C_2 is the measured trough concentration, and Δ in time is the elapsed time from C_1 to C_2.

Determination of the drug half-life:

$$t_{1/2} = \frac{0.693}{k_e}$$

where $t_{1/2}$ is the calculated half-life.

Determination of the calculated peak concentration:

$$Cmax = C_1 (e^{ke(t')})$$

where Cmax is the calculated peak concentration and t´ is the time between the C_1 and the end of the intravenous infusion.

Determination of the calculated trough concentration:

$$Cmin = C_2 (e^{-ke(t')})$$

where Cmin is the calculated trough concentration and t´ is the time between C_2 and the beginning of the next dose.

Determination of the drug Vd:

$$Vd = \frac{dose}{t_{inf} \times k_e} \times \frac{(1 - e^{-ke(tinf)})}{Cmax - Cmin \times e^{-ke(tinf)}}$$

where t_{inf} is the duration of the drug infusion.

Determination of the new dosing interval:

$$\tau = \frac{\ln\left(\frac{C_{max,desired}}{C_{min,desired}}\right)}{k_e} + t_{inf}$$

where τ (tau) is the new dosing interval, $C_{max,desired}$ is the desired peak concentration for the new dosing regimen, and $C_{min,desired}$ is the desired trough concentration for the new dosing regimen.

Determination of the new dose:

$$dose = C_{max,desired} \times k_e \times Vd \times t_{inf} \times \frac{(1 - e^{-ke(\tau)})}{(1 - e^{-ke(tinf)})}$$

3. One drawback of this method is that it assumes the PK variables obtained (e.g., vancomycin trough) correlate with PD parameters (AUC/MIC). Although this may be true in many cases, some advocate for the incorporation of PD into individualized drug dosing. Alternative methods use PK parameters from previous patients (population PK) to estimate the PK in an individual patient. These methods generally require complicated mathematical calculations, many of which are not practical for use clinically. However, with the development of PK software, clinicians can carry out complex calculations. Many software programs are available for clinician use in patient care. More advanced modeling using the Bayesian method has also been proposed to address the issues posed by using population PK in patient groups that may not be well represented in the population. Using software with population PK parameters from non-critically ill patients in the interpretation of PK in critically ill patients could result in errors in designing the appropriate drug-dosing regimen.

B. Drug Nomograms/Protocols – A nomogram is a diagram representing the relationship between three or more variables using scales arranged in a manner such that one variable can be determined if the other variables are known. A classic drug-dosing example is the once-daily aminoglycoside nomogram (Antimicrob Agents Chemother 1995;39:650-5). The nomogram itself allows the user to determine only one variable (generally the dosing interval) using other variables (time from infusion to drug concentration and the measured drug concentration). Many institutions incorporate nomograms into drug-dosing protocols or pathways but still call them drug-dosing nomograms. One of the most commonly used drug-dosing nomograms was developed for continuous infusions of unfractionated heparin. As previously noted, a heparin nomogram can improve time to therapeutic aPTT when developed specifically for critically ill patients. It is important to consider the patient population used to develop a nomogram because the variables may not apply to all patient populations. An example of this occurs with protocols for insulin infusions in critically ill patients. As previously noted, patients with AKI are at a greater risk of hypoglycemia if treated with an insulin infusion protocol developed in critically ill patients without kidney impairment.

IX. CONCLUSION

There are marked differences in the ways in which critically ill patients handle drugs. Research in this area has noted significant changes in the PK and PD of certain medications in select critically ill populations. Although these studies have highlighted important issues, considerable work is still needed to better define these changes in different critically ill populations. As research continues to advance, together with our knowledge of how patients handle drugs differently, critical care clinicians must stay abreast of new information and the ways in which it will affect the care of their patients.

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MARKETING AND EXPLANATIONS TO PATIENT CASES

1. Answer: B.
Increasing the concentration of an antibiotic at the site of an infection is most important (Answer B is correct). Although there are case reports describing the use of intraventricular antibiotics in the treatment of meningitis, they have not shown superiority (Answer A is incorrect). Although there is the potential to reduce vancomycin-induced nephrotoxicity, no studies have compared the nephrotoxicity of intraventricular antibiotics with that of intravenous antibiotics, likely because this is not the rationale for their use (Answer C is incorrect). Ototoxicity could also be reduced, but this was not the intent of the locally instilled antibiotics (Answer D is incorrect).

2. Answer: D.
Three studies have documented an increase in digoxin absorption when the gastric pH is increased, with two studies noting the cause of increased gastric pH from a proton pump inhibitor (Answer D is correct). However, no studies have shown a decreased absorption of carvedilol (Answer A is incorrect), ciprofloxacin (Answer B is incorrect), or diazepam (Answer C is incorrect).

3. Answer: A.
A decrease in the ionization of a drug allows the drug to more easily pass through membranes. Increasing the ionization would decrease the Vd by decreasing its ability to pass through membranes. A weak acid would be less ionized in a more acidic environment. The patient is likely in diabetic ketoacidosis with a definite acidosis. Aspirin (a weak acid) is less likely to be ionized and would have an increased Vd (Answer A is correct; Answers B–D are incorrect).

4. Answer: C.
Levofloxacin has a large Vd. The increase in interstitial fluid volume caused by 25 L of crystalloids would increase the Vd of hydrophilic drugs but would have no appreciable effect on the Vd of a drug like levofloxacin, which already has a large Vd (Answer C is correct). Tobramycin, linezolid, and cefepime have relatively small volumes of distribution and are increased in patients with increased interstitial volumes (Answers A, B, and D are incorrect).

5. Answer: B.
Morphine is a high extraction ratio drug. Mechanical ventilation can decrease cardiac output and thus decrease liver blood flow. The decrease in liver blood flow is inversely proportional to the unbound steady-state concentration. Therefore, it both decreases the hepatic blood flow and increases the unbound concentration (Answer B is correct). The effects of mechanical ventilation on cardiac output would likely decrease oxygen delivery (Answer A is incorrect). Cytokines affect intrinsic clearance but would not affect the concentration of a high extraction ratio drug (Answer C is incorrect). Mechanical ventilation can indirectly affect the unbound concentration (Answer D is incorrect).

6. Answer: B.
This patient has sepsis, which is associated with an increased production of inflammatory cytokines. These cytokines can decrease the activity of the CYP enzymes and decrease intrinsic clearance. Also, fluconazole inhibits the activity of CYP 3A4. Diltiazem is a low extraction ratio drug. The hepatic clearance of diltiazem is affected by changes in intrinsic clearance (inlcuding CYP 3A4 activity). The unbound steady-state concentration would be increased, with a decrease in intrinsic clearance caused by the inflammatory cytokines. The increased unbound steady-state concentrations would cause a decrease in the heart rate (Answer B is correct). There is no cause for an increase in intrinsic clearance and a corresponding increase in heart rate (Answer A is incorrect). There is no reason for this patient to have a decrease in the unbound fraction of diltiazem (Answer C is incorrect). A decrease in albumin could occur with sepsis and would result in an increase in the unbound fraction of diltiazem. The increase in unbound fraction would not affect the unbound steady-state concentration, nor would it affect the heart rate (Answer D is incorrect).

7. Answer: D.
Using the equations for low extraction drugs like phenytoin, it is clear that unbound fraction is inversely proportional to the steady-state concentration and has no effect on the unbound steady-state concentration (Answer D is correct; Answers A and C are incorrect). An increase in the unbound fraction of phenytoin would not result in an increase in the total concentration (Answer B is incorrect).

8. Answer: A.

The kidney plays a role in the excretion and metabolism of insulin. Acute kidney injury will decrease the ability of the kidney to metabolize insulin. This will increase circulating insulin and contribute to hypoglycemia (Answer A is correct). The Vd of insulin in AKI is not well studied and has not been tied to episodes of hypoglycemia (Answer B is incorrect). Hepatic impairment may increase the risk of hypoglycemia with insulin, but an increase in hepatic metabolism is unlikely to affect the risk of hypoglycemia in AKI (Answer C is incorrect). There have been reports of insulin resistance in patients with AKI, but this would not contribute to hypoglycemia (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B.
Decreased anti-Xa activity occurs in critically ill patients receiving several different low-molecular-weight heparins. This patient received the standard fluid bolus and then required more fluid to raise his central venous pressure. This suggests that the patient has redistributed the fluids to the extravascular space. The data showing that edematous patients have lower anti-Xa activity compared with non-edematous patients supports the connection between anti-Xa activity and absorption (Answer B is correct). Given the patient's fluid distribution, the Vd of enoxaparin would likely be increased, not decreased (Answer A is incorrect). Enoxaparin is not hepatically metabolized (Answer C is incorrect). Although a patient could have an increased anti-Xa activity secondary to decreased renal elimination, this would require a CrCl of less than 30 mL/minute. That the patient experienced a deep venous thrombosis does not correlate with increased activity (Answer D is incorrect).

2. Answer: C.
Abdominal surgery has been identified as a risk factor for ileus. Antisecretory agents such as pantoprazole alter the absorption of drugs. Traumatic brain injury is significantly associated with intolerance of enteral nutrition, as indicated by increased gastric residuals. This indicates delayed gastric emptying and the risk of altered absorption. Therefore, the combination of abdominal surgery, pantoprazole therapy, and TBI contains the three variables identified in the literature to alter absorption. Theoretically, intestinal atrophy could cause changes in absorption, but no data are available to confirm this theory (Answers A and D are incorrect). Changes in cardiac output have been correlated with changes in hepatosplanchnic blood flow. These changes in blood flow are thought to affect absorption, but again, no data have correlated increased cardiac output with increased absorption of drugs (Answer B is incorrect).

3. Answer: B.
Propofol is a high extraction ratio drug that is bound to albumin. When the albumin concentration decreases, there is an expected increase in the free fraction of propofol. Using the equations describing the total and unbound concentrations of a high extraction ratio drug, the total concentration is not affected by changes in the free fraction, but unbound concentrations are increased when the free fraction increases (Answer B is correct; Answers A, C, and D are incorrect).

4. Answer: C.
The update to the KDIGO guidelines notes that the most important factor in determining kidney function is having at least one estimate of GFR. The update recommends that the GFR or the CrCl be estimated to make this determination (Answer C is correct). The BUN value can be used to help identify the BUN/SCr ratio indicating intravascular volume contraction, and potentially a prerenal cause to the patient's AKI, but it is not helpful in drug dosing (Answer A is incorrect). Total daily urine output is helpful in the diagnosis of AKI (oliguric vs. non-oliguric AKI) and in the staging of AKI (using a urine output of less than 0.5 mL/kg/hour) but not in the dosing of drugs (Answer B is incorrect). A history of CKD is helpful in determining a baseline kidney function, but the GFR is still needed for changes in drug dosing (Answer D is incorrect).

5. Answer: C.
The ASHP (American Society of Health-System Pharmacists) vancomycin dosing guidelines recommend a 25- to 30-mg/kg loading dose of vancomycin for serious infections. Given the patient's sepsis, he is likely to have more interstitial fluid. This fluid will increase the Vd of hydrophilic drugs like vancomycin. The 2500-mg dose is near the top end of the recommended 25- to 30-mg/kg loading dose (Answer C is correct). The other doses are outside the recommended 25- to 30-mg/kg loading dose range (Answers A, B, and D are incorrect).

6. Answer: A.
Critically ill patients younger than 50 years are more likely to have augmented renal excretion. Vancomycin is excreted unchanged in the urine. The initial dosing would result in a therapeutic trough concentration, given the increased (augmented) renal excretion of vancomycin. Augmented renal excretion usually returns to normal around day 7. An increased vancomycin trough after a previously therapeutic trough is most likely associated with a decline in renal excretion at day 10 of therapy (Answer A is correct). There is no

indication that the Vd has changed, which would likely result in lower or unchanged concentrations (Answer B is incorrect). Vancomycin tissue penetration may be better if inflammation is present, but there are no documented studies correlating decreased inflammation with increased serum concentrations (Answer C is incorrect). The liver does not appreciably metabolize vancomycin, and liver blood flow would not be a factor in the vancomycin concentration (Answer D is incorrect).

7. Answer: C.

Prospective controlled studies of prolonged infusions of piperacillin/tazobactam have not shown an improvement in mortality (Answer A is incorrect). No studies have reported neurotoxicity as an outcome (Answers B and D are incorrect). Only retrospective studies have shown improvements in mortality with the use of prolonged or continuous infusions of piperacillin/tazobactam (Answer C is correct).

8. Answer: C.

Morphine is a high extraction ratio drug. As such, its hepatic metabolism or hepatic clearance depends only on hepatic blood flow. Hepatic clearance equals hepatic blood flow (Answer C is correct). Morphine does not bind to AAG (Answer A is incorrect). Because hepatic blood flow is the major determinant of hepatic metabolism of morphine, changes in protein binding do not affect metabolism (Answer B is incorrect). Changes in intrinsic clearance do not affect the metabolism of morphine as significantly as does hepatic blood flow (Answer D is incorrect).