Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics

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LEARNING OBJECTIVES

1. Evaluate the physiologic changes that affect drug absorption and distribution in critically ill patients.
2. Distinguish the effects of changing hemodynamics on drug metabolism and elimination and predict potential pharmacokinetic changes in critically ill patients.
3. Apply knowledge of how different drug properties affect the influence of physiologic changes on pharmacokinetics in critically ill patients.
4. Justify pharmacotherapy on the basis of pharmacodynamic parameters that correspond with the maximal efficacy of commonly used antimicrobials.
5. Demonstrate the value of pharmacogenomic applications with commonly used drugs in critically ill patients.

ABBREVIATIONS IN THIS CHAPTER

AKI	Acute kidney injury
Cl_h	Hepatic clearance
Cl_{int}	Intrinsic clearance
C_{max}	Maximum concentration
CYP450	Cytochrome P450
E_h	Hepatic extraction efficiency or ratio
F_u	Fraction unbound
GFR	Glomerular filtration rate
KDIGO	Kidney Disease: Improving Global Outcomes
LNPEP	Leucyl/cystinyl aminopeptidase
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PGx	Pharmacogenomics
PK	Pharmacokinetics
Q	Hepatic blood flow
TDM	Therapeutic drug monitoring
V_d	Volume of distribution

Table of other common abbreviations.

INTRODUCTION

Pharmacotherapy of critically ill patients is challenging. Given the relative dearth of data available specifically for patients in ICUs, critical care pharmacists must use a combination of data extrapolation and clinical intuition to design optimal therapeutic dosing plans. Furthermore, each critically ill patient is distinct, with a differing pathogenesis and a rapidly changing physiology, which may further complicate treatment choices. The development of an individualized therapeutic plan requires the selection of a dosing and monitoring regimen that balances available information with the highest likelihood of positive outcome and minimal adverse effects. To successfully develop individualized dosing regimens and administer them to critically ill patients, an understanding of pharmacokinetics (PK), pharmacodynamics (PD), and pharmacogenomics (PGx) is paramount.

Every drug entering the body follows an identical process of absorption, distribution, metabolism, and elimination—but one that is unique to that specific medication. That process ultimately determines how much drug is available at the targeted site of action. *Pharmacokinetics* refers to the sum of the processes the body is conducting on the drug. In contrast, *pharmacodynamics* refers to the physiologic and biochemical effects of the drug on the body. The intended effects of the drug, at a concentration that minimizes potential adverse effects, are determined by the intricate balance between PK and PD. *Pharmacogenomics* refers to a patient's possible shift in the balance of PK and PD through innate genetic polymorphisms, which can alter the way the body and the drug (or its metabolites)

interact with each other. The relationship between PK, PD, and PGx is further complicated by the rapid physiologic changes seen in critically ill patients. An understanding of the general principles of PK, PD, and PGx can assist clinicians in making the best choices when designing a drug regimen for critically ill patients. This chapter describes the general concepts behind PK, PD, and PGx and their use as principles in clinical examples seen in the critical care setting.

PK CONCEPTS AND DERANGEMENTS IN CRITICALLY ILL PATIENTS

Absorption

Absorption refers to the ability of a drug to migrate from the site of administration into the bloodstream. The extent of absorption is typically measured in terms of bioavailability, defined as the fraction of an administered dose that reaches the systemic circulation. All drugs administered outside the intravenous route are affected by absorption. However, few studies have directly evaluated the effects of critical illness on absorption.

A number of factors may affect enteral absorption in critically ill patients (e.g., gastric pH, GI motility, bowel wall edema, splanchnic perfusion, first-pass metabolism, feeding tube or enteral feed interactions). Furthermore, the physiologic and therapeutic changes that occur during critical illness are unpredictable, and summation of the results may lead to an increased, decreased, or net unchanged enteral absorption. Theoretically, in states of decreased perfusion, the body's natural physiologic response is to shunt blood toward vital organs and away from the GI tract, which may decrease the enteral absorption of drugs (Beale 2004). In patients requiring vasopressors for hemodynamic support, many studies have documented differing degrees of alterations in splanchnic perfusion (Hollenberg 2004).

Among the many reasons for decreased gastric motility in critically ill patients are abdominal surgery, opioid use, electrolyte abnormalities, ileus, immobility, and traumatic brain injury (Nguyen 2007). The delay in gastric emptying may alter absorption based on the drug's characteristics. Absorption from the stomach is usually slow and favors acidic drugs, whereas absorption from the small intestines is usually fast and favors basic drugs. Delayed gastric emptying may decrease the absorption of drugs normally absorbed in the small intestines, because increased transit time from the stomach can lead to degradation. On the other hand, for drugs absorbed in the stomach, delayed emptying may increase absorption because of more time spent at the site of absorption (Prescott 1974).

Another common factor that may affect drug absorption is the use of enteral feeding tubes and formulas. Drugs administered through enteral feeding tubes may adhere to the lumen of the tube or have physical incompatibilities that limit bioavailability. In critically ill patients, decreased absorption from feeding tube drug administration has occurred with amiodarone, carbamazepine, ciprofloxacin, phenytoin, theophylline, digoxin, and warfarin (Lourenco 2001, Zhu 2013). In general, many drug-nutrient interactions can be circumvented by withholding enteral nutrition for 1 to 2 hours both before and after drug administration, although using that practice for drugs frequently administered may lead to suboptimal nutritional support.

The conclusion that critical illness has unpredictable effects on enteral absorption is further corroborated by discrepant clinical PK evaluations of drugs administered enterally in critically ill patients. In an open-label, single-dose study of healthy volunteers, hospitalized general ward patients, and critically ill patients, atorvastatin maximal concentration (C_{max}) and AUC 0 to 24 hours after administration were about 18- and 15-fold higher, respectively, in critically ill patients with sepsis ($p<0.01$ for both C_{max} and AUC) compared with healthy volunteers. Notably, all doses were administered orally or, for those who could not swallow (23 of 25 critically ill patients), by way of a nasogastric tube. Although the results may have been influenced by the use of CYP inhibitors in some critically ill patients, similar results were observed in selected patients not receiving CYP inhibitors, wherein the mean AUC and C_{max} were about 10-fold higher. Notably, despite the 10-fold-higher C_{max} and AUC, those differences did

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Acute physiologic changes that occur during critical illness
- Basic pharmacokinetics and pharmacodynamics principles
- Pharmacology, pharmacokinetics, and spectrum of activity of antimicrobial agents
- Basic drug properties of commonly used drugs in critically ill patients
- Pharmacogenetic testing and results interpretation

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Roberts JA, Abdul-Aziz MH, Lipman J, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 2014;14:498-509.
- PharmGKB. Clinical Pharmacogenetics Implementation Consortium. Dosing Guidelines [home page on the Internet].

not reach statistical significance, most likely as a result of lack of study power (Kruger 2009).

The higher observed C_{max} and AUC in that study are in contrast with an evaluation ofthe effects of various clinical characteristics likely to affect paracetamol (acetaminophen) absorption. That study enrolled 27 ICU patients with normal hepatic and renal functions and no contraindications to nasogastric feeding. Of this group, 9 patients required the use of dopamine; those patients had significant decreases in paracetamol $AUC_{0-60min}$ compared with those who were hemodynamically stable (mean 337.4 vs. 728.2 $mg \cdot L^{-1} \cdot minute$, p=0.005) . Notably, the usual $AUC_{0-60min}$ in healthy volunteers is about 600 $mg \cdot L^{-1} \cdot minute$. This study also observed a considerable range in $AUC_{0-60min}$ among all of the ICU patients (61.2 to 1400.3 $mg \cdot L^{-1} \cdot minute$) (Tarling 1997).

Last, in a study of the enteric absorption and PK of oseltamivir in 41 critically ill patients with suspected H1N1 influenza, the median and trough plasma concentrations of oseltamivir and its metabolite were similar to those observed in other clinical trials involving ambulatory patients (Ariano 2010). The aforementioned data are representative of the degree of variability in enteric absorption that could be expected on the parts of critically patients. Taken together, the data further confirm that enteral absorption of drugs in critically ill patients is highly erratic. If possible, enteral routes of administration should be avoided in acutely ill patients until the clinical status has been stabilized. Using alternative routes of administration may be especially important with drugs that have narrow therapeutic indexes. Regarding drugs without parenteral alternatives, clinicians should be aware of unpredictable absorption and extra vigilant in monitoring efficacy and safety.

Critical illness can also affect absorption in the subcutaneous route. Given the physiologic shunting of blood to vital organs during shock, perfusion to subcutaneous tissue may be affected. In a study evaluating the antifactor Xa activity of a subcutaneously administered low-molecular-weight heparin for deep-vein thromboembolic prophylaxis, the use of a vasopressor was an independent predictor of having an undetectable peak anti-factor Xa level (Jochberger 2005). In a separate study, the antifactor Xa activities in patients on prophylactic doses of subcutaneously administered low-molecular-weight heparin while on vasopressors were compared with antifactor Xa activities in hemodynamically stable, critically ill patients and hospitalized non-ICU patients. When compared with the two other groups, patients who received vasopressors had significantly lower concentrations of antifactor Xa activity that was not within the recommended therapeutic range (Dorffler-Melly 2002). In addition to physiologic shunting of peripheral blood volume to vital organs, aggressive fluid resuscitation, vasodilatory states, and third-space shifts of intravascular volume may cause significant peripheral edema, further decreasing subcutaneous absorption.

The effects of edema in critically ill patients have been evaluated in several studies. In a study of 20 multiple-trauma patients, a PK evaluation on subcutaneously administered enoxaparin was performed on patients classified as nonedematous or edematous (presence of edema and increase in admitting body weight of 10 kg or more). That investigation demonstrated highly variable AUCs in the entire cohort. In addition, a significant decrease in antifactor Xa activity was seen in edematous patients compared with nonedematous patients. In fact, in 7 of the 10 edematous patients, the majority of the sampled antifactor Xa assays were below the lower limit of detection (Haas 2005).

That finding was similar to finding in other investigations, which corroborated the relatively low plasma antifactor Xa activity in critically ill patients receiving standard doses of subcutaneous enoxaparin for deep-vein thrombosis prophylaxis (Dorffler-Melly 2002, Mayr 2002, Priglinger 2003). However, a study of 14 patients in a mixed medical-surgical ICU revealed that the presence of edema did not affect the C_{max} or AUC of dalteparin (Rommers 2006). Notably, the definition of peripheral edema as used in this study was slightly more conservative than the one used in the study mentioned earlier; hence the lack of difference in dalteparin concentrations may reflect the relatively lower magnitude of edema and/or the small sample size.

In summary, the subcutaneous absorption in critically ill patients—especially those on vasopressors or with more than 10 kg of fluid weight gains during their ICU admissions—is highly variable and most likely suboptimal.

Distribution and Protein Binding

The distribution of a drug depends largely on the drug's hydrophilicity and its acid dissociation constant, which affects its binding to proteins and other macromolecules. Only a free drug, unbound by protein, can diffuse across tissue and have physiologic effect. Many acidic drugs are bound to albumin and many basic drugs are bound to α_1-acid glycoprotein. During states of critical illness, albumin concentration decreases as a result of increased vascular permeability, decreased production, and catabolism (Fleck 1985). In contrast, α_1-acid glycoprotein is an acute-phase reactant and tends to increase during states of stress (Edwards 1982). The changes in protein concentrations could affect both the amount of free drug available and the overall volume of distribution (V_d).

Decreased protein binding leads to an increased free fraction and overall V_d, whereas increased protein binding has the opposite effect. Although decreased binding would lower the total serum concentration, increased free fraction may lead to better therapeutic effects than normally observed. In one study of the effect of albumin concentration on total and free phenytoin concentrations, free fraction of phenytoin was inversely related to plasma albumin concentration in 10 critically ill trauma patients (Boucher 1988). Hence,

measurements of total drug concentration may inappropriately underestimate the true effects of phenytoin.

Aside from drug charge, protein binding, and the effects of critical illness on intrinsic protein concentrations, distribution could also be affected by the drug's hydrophilicity. Usually, hydrophilic drugs (high water solubility) have lower V_d than lipophilic drugs (high lipid solubility). Hydrophilic drugs (e.g., β-lactams, aminoglycosides, vancomycin, linezolid, colistin, morphine, hydromorphone) tend to distribute within the plasma volume, and distribution into tissue requires adequate perfusion of the tissue from blood volume. In contrast, lipophilic drugs (e.g., azithromycin, fluoroquinolones, tetracyclines, clindamycin, fentanyl, midazolam, propofol) have sufficient V_d to penetrate tissue independent of perfusion. Serum concentrations of lipophilic drugs are only minimally affected by fluid shifts and large-volume fluid resuscitation. Critically ill patients may have derangements in both plasma volume and tissue perfusion, which may affect the distribution of a drug to its intended site of action.

Hydrophilic drugs require tissue perfusion to bring concentrations from systemic circulation to a site of action. As previously mentioned, hemodynamic instability leads to redistribution of blood flow and decreased perfusion to peripheral areas. As a result, the delivery of hydrophilic drugs may become impaired. This was demonstrated in a study comparing the subcutaneous and skeletal muscle concentrations of piperacillin to plasma concentrations in six pairs of age- and sex-matched patients with septic shock and healthy patients. Using microdialysis methods, the investigators determined that in patients with septic shock, the piperacillin concentrations were 5- to 10-fold lower in the subcutaneous and skeletal muscle tissues compared with plasma concentrations. In the healthy volunteers, the free piperacillin concentrations in peripheral tissues were about 95% of those seen in plasma concentrations. Furthermore, the plasma concentrations were also significantly higher in healthy volunteers, which may reflect the increased V_d seen in critically ill patients (Joukhadar 2001). For hydrophilic drugs, aggressive fluid resuscitation may lead to increases in total body water, which results in a larger V_d and lower serum concentrations. That effect of aggressive fluid management has also been demonstrated among aminoglycosides and other β-lactam antibiotics (Dasta 1988,Triginer 1990).

In summary, critical illness may lead to changes in endogenous protein concentrations, tissue perfusion, and total plasma volume. The extent of those changes on each drug depends ultimately on the drug's properties. Table 1-1 describes drugs commonly used in critical care, their characteristics that may affect volume of distribution, and the potential effects caused by critical illness.

Table 1-1. Characteristics of Drugs Commonly Used in Critical Care

Drug Characteristic	Pharmacokinetic Characteristics	Examples	Critical-Illness Changes	Effect on V_d
Basic charge	Bound to α_1-acid glycoprotein	Azithromycin, carvedilol, fentanyl, lidocaine, meperidine, milrinone, nicardipine, olanzapine, phenobarbital, verapamil	α_1-acid glycoprotein is an acute phase reactant, which would increase in states of stress	Decreased volume of distribution Decreased free fraction
Acidic or neutral charge	Bound to albumin	Amiodarone, ceftriaxone, diazepam, midazolam, morphine, phenytoin, prednisolone, propofol, valproic acid, warfarin	Decreased production and increased vascular permeability and catabolism lead to hypoalbuminemic states	Increased volume of distribution Increased free fraction
Lipophilic	Distributes widely in tissue Large volume of distribution	Diazepam, fentanyl, fluoroquinolones, lorazepam, macrolides, midazolam, propofol, rifampin, tetracycline	Minimal changes	Minimal changes
Hydrophilic	Distribution primarily into serum Small volume of distribution	Aminoglycosides, β-lactams, daptomycin, hydromorphone, morphine, vancomycin	Fluid resuscitation Third spacing Reduced tissue perfusion	Increased volume of distribution Decreased serum concentration

Information from: Boucher BA, Wood GC, Swanson JM. Pharmacokinetic changes in critical illness. Crit Care Clin 2006;22:255-71; and Israili ZH, Dayton PG. Human alpha-1-glycoprotein and its interactions with drugs. Drug Metab Rev 2001;33:161-235.

Metabolism

The liver plays a major role in the metabolism of many drugs, and critical illness and drug properties can affect hepatic clearance. Intrinsic patient factors include volume status, perfusion, gut motility, and liver function. The major drug properties that affect the quantity of elimination by the liver include extraction ratio and protein binding (Rodighiero 1999). To fully understand the impact of critical illness on a medication's hepatic metabolism, an appreciation of the underlying determinants of hepatic clearance is necessary. Hepatic clearance (Cl_h) of a medication is a function of hepatic blood flow (Q) and the liver's extraction efficiency (ratio) for the particular drug (E_h) (Verbeeck 2008); this can be represented by the formula:

$$Cl_h = Q \times E_h$$

A particular drug's extraction efficiency depends on liver blood flow, intrinsic clearance of unbound drug (Cl_{int}), and the fraction of unbound (f_u) drug in the blood (Verbeeck 2008); it can be represented by the formula:

$$E_h = (f_u \times Cl_{int}) / (Q + (f_u \times Cl_{int}))$$

Together the equation for hepatic clearance is:

$$Cl_h = (Q \times f_u \times Cl_{int}) / (Q + (f_u \times Cl_{int}))$$

The equation contains the three primary components of hepatic drug elimination: blood flow, drug protein binding, and intrinsic clearance. Intrinsic clearance is based on the sum of all of the hepatic enzyme and transport activity involved in the removal of drug from the blood.

During acute illness, many pathophysiologic changes may affect drug metabolism and reduce Cl_{int}. During states of vasodilatory shock, cardiac output may be either normal, increased, or decreased depending on the progression of shock and the adequacy of fluid resuscitation. However, hepatic flow is likely to be impaired in states of low cardiac output—such as hypovolemia—or a state of cardiogenic or hemorrhagic shock. Furthermore, mechanical ventilation has decreased venous return, leading to decreased cardiac output and hepatic blood flow (Bonnet 1982). A reduction in liver perfusion may lead to a decrease in enzymatic activity. However, an increase in cardiac output may further increase the hepatic extraction of medications.

Two different types of reactions are primarily responsible for the liver's metabolizing capabilities: phase I oxidative metabolism and phase II glycosylation and glucuronidation. Phase I reactions, which are usually mediated by the CYP isoenzymes, require the presence of oxygen molecules and are therefore more susceptible to functional deficiencies caused by lack of oxygenation from decreased hepatic perfusion. Being less reliant on the presence of oxygen, conjugation phase II reactions such as glucuronidation are less susceptible to the effects of liver cirrhosis and hypoxia (Westphal 1997).

Each drug's extraction efficiency determines the extent to which its hepatic metabolism is affected by critical illness. Medications can be categorized according to the E_h: high (E_h >0.6), low (E_h <0.3), or intermediate (0.3 < E_h <0.6). Drugs with high extraction ratios depend on blood flow and are usually relatively insensitive to changes in protein binding or enzyme activity ($Cl_h \approx Q$). Drugs in this category are most influenced by cardiac output and hepatic blood flow. In fact, studies that evaluated drugs with intermediate to high extraction ratios have found increases in serum concentrations ranging from 2- to 12-fold from decreases in hepatic blood flow (Rodighiero 1999). On the other hand, drugs with low extraction efficiency are affected by changes in protein binding and intrinsic hepatic clearance ($Cl_h \approx f_u \times Cl_{int}$) (Verbeeck 2008). The hepatic elimination of those drugs depends more on hepatic enzymatic reactions and is more sensitive to decreases in metabolism from states of cirrhosis or acute liver dysfunction. Table 1-2 illustrates drugs commonly used in critical care and their respective extraction ratios.

Table 1-2. Hepatic Extraction of Drugs Commonly Used in Critical Care

Extraction Characteristic	Hepatic Extraction	Examples
Low extraction	<0.3	Amoxicillin, ceftriaxone, chlordiazepoxide, clarithromycin, clindamycin, diazepam, doxycycline, fluconazole, lansoprazole, lorazepam, methadone, methylprednisolone, metronidazole, mycophenolate, oxazepam, phenobarbital, phenytoin, prednisolone, prednisone, primidone, rifampin, theophylline, valproic acid
Intermediate extraction	0.3–0.6	Alfentanil, amiodarone, atorvastatin, azathioprine, carvedilol, codeine, diltiazem, erythromycin, itraconazole, lidocaine, meperidine, nifedipine, omeprazole, ranitidine
High extraction	>0.6	Fentanyl, isosorbide dinitrate, morphine, nitroglycerin, propofol, sufentanil

Information from: Delco F, Tchambaz L, Schlienger R, et al. Dose adjustment in patients with liver disease. Drug Saf 2005;28:529-45.

Elimination

Although drugs can be excreted through the biliary tract, feces, and respiration, the kidneys eliminate most drugs and metabolites in the critical care setting, and they are the ones most likely to be affected by physiologic changes during acute illness. Drugs are eliminated by the kidney through glomerular filtration and tubular secretion. Although tubular secretion function is not directly measureable, glomerular filtration rate (GFR) is a good marker of overall renal drug clearance.

Although much focus is on acute kidney injury (AKI) and reduction of renal function, critical illness could also lead to augmented renal clearance. There is no universally accepted definition of augmented renal clearance, although a value of 10% above the upper limit of normal (GFR >160 mL/minute/1.73m^2 in men and >150 mL/minute/1.73m^2 in women) has been proposed (Udy 2010). Critical care conditions that are likely to lead to augmented renal clearance include those that induce low systemic vascular resistance and high cardiac output. Although there are no robust epidemiologic study data on the incidence of augmented renal clearance, it has been reported as high as 85% of all patients at some point during their ICU stay (Udy 2010). Augmented renal clearances have generally been observed in patients who are younger (<55 years), are post-trauma (particularly head trauma), are postsurgery, have sepsis, are diagnosed with hematologic malignancies, or have significant burn injuries (Albanese 2004, Benmalek 1999, Brater 1986, Brown 1980, Conil 2007, Fuster-Lluch 2008, Lamoth 2009). Clinicians caring for patients with adequate urine output, no laboratory indications of AKI, and conditions in which renal blood flow may be increased should be aware of the possibility of augmented renal clearances and decreased serum concentrations of renally eliminated drugs. Of interest, direct correlations between augmented renal clearance and lower serum drug levels have been observed for many antimicrobial agents including β-lactams, aminoglycosides, and glycopeptides (Udy 2010).

Little is known about optimal adjustments to drug dosing in patients with AKI. The Kidney Disease: Improving Global Outcomes (KDIGO) society provides guidelines on drug-dosing considerations, but few details are offered for the management of patients with AKI (Matzke 2011). Box 1-1 lists recommended steps for assessing and adjusting drug regimens in patients with AKI or chronic kidney disease. Specifically for patients with chronic kidney disease, the KDIGO guidelines recommend that drug dosages be adjusted according to FDA-approved labeling. For patients with AKI, the guidelines acknowledge that there are few or no specific data. However, because of PK changes seen in AKI patients—including the potential for increases in V_d—and because of the inability to accurately estimate renal function, the guidelines recommend a liberal dosing approach. That approach entails, for hydrophilic drugs, administering an aggressive 25%–50% greater than normal loading dose, followed by a normal or near normal maintenance dosage (Matzke 2011). The rationale for such an aggressive approach is the importance of administering an adequate dose to quickly optimize pharmacologic activity, particularly for antimicrobials. In addition, in the setting of AKI, increased nonrenal clearances of some agents have been observed. The clinical applicability of that recommendation would clearly depend on the patient's clinical status and the assessment of the drug's therapeutic index with the potential for adverse reactions.

Critically ill patients with renal failure may require renal replacement therapy, which provides an extracorporeal mechanism for drug removal. The choice of dialytic technique depends on institutional practice and the patient's hemodynamic status. There are considerable institutional differences in the use of continuous renal replacement therapy and of extended daily dialysis as regards dialysis machines, flow rates, filter sizes, and indications. As such, the medical literature provides little guidance about selecting the most appropriate dosing regimens for each specific dialytic mechanism. To select a dosing regimen, the KDIGO guidelines recommend a strategy that accounts for extracorporeal clearance of the drug. One such method is to use the formula:

$$\text{Dose} = \text{Dose}_n \times [\text{Cl}_{\text{nonrenal}} + (Q_{\text{eff}} \times \text{SC})] / \text{Cl}_{\text{norm,}}$$

Box 1-1. Assessing and Adjusting Drug Regimens in Patients with Acute Kidney Injury or Chronic Kidney Disease

Step 1 – Assess the following
- Demographic information
- Medical history
- Current clinical information
- Current laboratory information
- DNA polymorphisms

Step 2 – Estimate eGFR or creatinine clearance by 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
- Therapeutic drug monitoring if applicable

Step 6 – Revise regimen
- Adjust regimen according to patient response

eGFR = estimated glomerular filtration rate; PD = pharmacodynamics; PK = pharmacokinetics.

Adapted with permission from Swanson LM. Pharmacokinetics /Pharmacodynamics. ACCP Updates in Therapeutics 2015: Critical Care Pharmacy Preparatory Review Course; 2:335-66.

Where $dose_n$ = normal dose; $Cl_{nonrenal}$ = nonrenal clearance; Q_{eff} = effluent rate; SC = saturation coefficient (or sieving coefficient if using hemofiltration modes of dialysis); and Cl_{norm} = normal clearance (Matzke 2011). Normal clearance in this case can also be interpreted as the total body clearance seen in usual population without organ dysfunction.

In the foregoing equation, the saturation coefficient (or sieving coefficient) is, in general, similar among different continuous renal replacement therapy machines and membranes. In situations when the saturation coefficient is not available, the fraction unbound provides a reasonable estimate. A nephrology team usually chooses an effluent rate based on a patient's weight and needs for solute removal. The extent of nonrenal clearance varies with the medication. In some instances, patients may also have residual renal function, which should be accounted for.

Given the complexity of the calculations, institutions should attempt to quantify their most common methods and practices associated with continuous dialytic methods and derive appropriate dosing guidelines for commonly administered drugs. The literature contains several continuous renal replacement therapy dosing reviews (Churchwell 2009, Heintz 2009, Kuang 2007, Trotman 2005), but most of these studies used older dialysis machines or filters in an era when dialysis and replacement fluid flow rates were relatively low. In other words, the doses described in clinical reviews may not be adequate for current dialytic modes and practices.

PK Summary

The effects of critical illness on PK are vast and unpredictable. Ultimately, serum concentrations of medications administered to critically ill patients depend on the interaction between physiologic derangements and drug properties. Figure 1-1 summarizes the physiologic effects of critical illness and the corresponding effects on drug concentrations. If medications are to exert their intended effects, the establishment of adequate serum concentrations in critically ill patients is important—especially when, for certain agents, the drug's PD rely on achieving a particular concentration target.

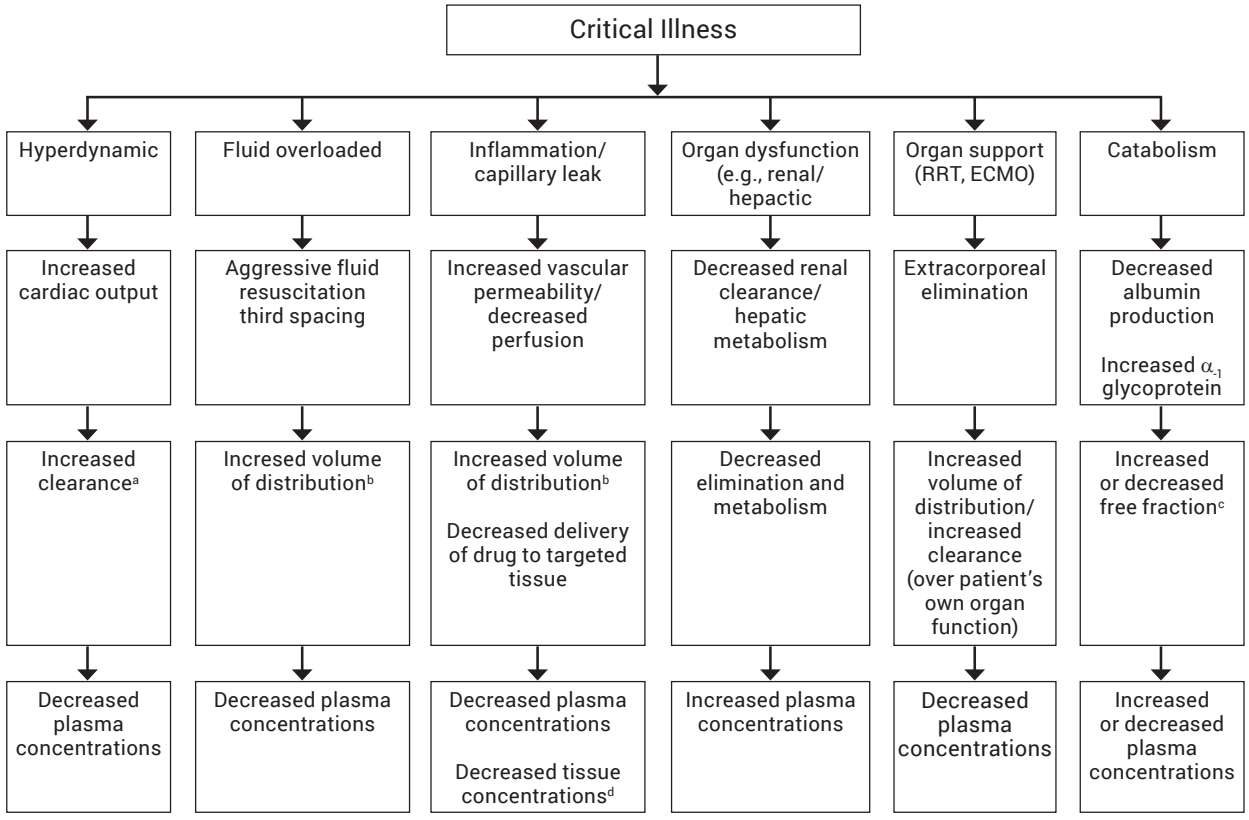

Figure 1-1. Effect of critical illness on pharmacokinetics of medications.

[a]Drugs excreted by kidneys are susceptible to augmented renal clearance.

[b]Applicable for hydrophilic medications.

[c]Acidic or neutral drugs usually bound to albumin increase their free fractions; basic drugs decrease their free fractions.

[d]Likely to affect hydrophilic drugs with a relatively small volume of distribution (less than plasma blood volume).

ECMO = extracorporeal membrane oxygenation; RRT = renal replacement therapy.

PHARMACODYNAMICS

Clinical Pharmacodynamic Applications in Antimicrobials

The majority of PD evaluations and applications for critically ill patients involve the management of antimicrobials, which is the focus of this section. Antimicrobials function through the inhibition of vital processes seen in microbiologic pathogens. For antimicrobials, the best PD responses, defined as improvements in microorganism clearance or in clinical outcomes, are more likely when certain targets are achieved. Table 1-3 summarizes known PD targets for some of the most commonly used antimicrobials in the ICU. The desired antimicrobial PD targets correspond to reaching a time, concentration, or AUC ratio above the organism's MIC. As such, the probability of antimicrobial PD target attainment and desired antimicrobial effect depends on the interplay between pathogen resistance and each patient's PK parameters.

Antibiotics such as aminoglycosides induce bacterial killing through concentration-dependent PD, wherein the rate and extent of the kill increases as the ratio between the maximum concentration and MIC increases. In an analysis of 236 patients treated with aminoglycosides for gram-negative

Table 1-3. Pharmacodynamic Targets of Antimicrobials

Antimicrobial PD Category and Corresponding Antibiotics	PD Targets
Concentration Dependent	
Aminoglycosides	C_{max}/MIC 8–10 (Drusano 2007); AUC/MIC >70 (Highet 1999)
Metronidazole	N/A
Time Dependent	
Penicillins	40–50% T > MIC (Craig 1996)
Cephalosporins	60–100% T > MIC (Crandon 2010; McKinnon 2008)
Carbapenems	50–75% T > MIC (Ariano 2005; Li 2007)
Concentration Dependent and Time Dependent	
Fluoroquinolones	AUC/MIC >125 (Ariano 2005; Li 2007)
Vancomycin	AUC/MIC >400 (Moise-Broder 2004)
Linezolid	AUC/MIC >80–120 (Rayner 2003)
Tigecycline	AUC/MIC 13–18 (Bhavnani 2012; Rubino 2012)
Daptomycin	AUC/MIC 38–171 (Dandekar 2003)
Colistin	AUC / MIC 7-23 (Dudhani 2010)
Fluconazole	AUC / MIC >12 (Baddley 2008)

C_{max} = maximal concentration; PD = pharmacodynamics; T > MIC = time above MIC during dosing interval.

Information from: Ariano RE, Nyhlen A, Donnelly JP, et al. Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. Ann Pharmacother 2005;39:32-8; Baddley JW, Patel M, Bhavnani SM, et al. Association of fluconazole pharmacodynamics with mortality in patients with candidemia. Antimicrob Agents Chemother 2008;52:3022-8; Bhavnani SM, Rubino CM, Hammel JP, et al. Pharmacological and patient-specific response determinants in patients with hospital-acquired pneumonia treated with tigecycline. Antimicrob Agents Chemother 2012;56:1065-72; Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. Pediatr Infect Dis J 1996;15:255-9; Crandon JL, Bulik CC, Kuti JL, et al. Clinical pharmacodynamics of cefepime in patients infected with *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2010;54:1111-6; Dandekar PK, Tessier PR, Williams P, et al. Pharmacodynamic profile of daptomycin against *Enterococcus* species and methicillin-resistant *Staphylococcus aureus* in a murine thigh infection model. J Antimicrob Chemother 2003;52:405-11; Drusano GL, Ambrose PG, Bhavnani SM, et al. Back to the future: using aminoglycosides again and how to dose them optimally. Clin Infect Dis 2007;45:753-60; Dudhani RV, Turnidge JD, Nation RL, et al. fAUC/MIC is the most predictive pharmacokinetic/pharmacodynamic index of colistin against *Acinetobacter baumannii* in murine thigh and lung infection models. J Antimicrob Chemother 2010;65:1984-90; Forrest A, Nix DE, Ballow CH, et al. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 1993;37:1073-81; Highet VS, Forrest A, Ballow CH, et al. Antibiotic dosing issues in lower respiratory tract infection: population-derived area under inhibitory curve is predictive of efficacy. J Antimicrob Chemother 1999;43 Suppl A:55-63; Li C, Du X, Kuti JL, et al. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother 2007;51:1725-30; McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 2008;31:345-51; Rayner CR, Forrest A, Meagher AK, et al. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use program. Clin Pharmacokinet 2003;42:1411-23; and Rubino CM, Bhavnani SM, Forrest A, et al. Pharmacokinetics-pharmacodynamics of tigecycline in patients with community-acquired pneumonia. Antimicrob Agents Chemother 2012;56:130-6.

infections, improvements in clinical response were seen in more than 90% of patients with peak:MIC ratios of 10 or more (Moore 1987). Similar findings were observed in patients with gram-negative nosocomial pneumonia (Kashuba 1999). Given the availability of aminoglycoside serum concentration monitoring and the variability in V_d observed in critically ill patients, clinicians should perform first-dose pharmacokinetic evaluations with a view to aggressive dosing of these antibiotics so as to target known PD parameters.

For antibiotics such as fluoroquinolones, when serum concentration monitoring is not readily available, clinicians should still be familiar with the targeted PD parameters and understand the importance of hitting those targets. Using modeling data, clinicians should be able to assess clinical scenarios in which the probability of PD goal target attainment is lower than ideal. For example, with fluoroquinolones, as the MIC approaches 1 mcg/mL (even with aggressive dosing regimens), the probability of PD target attainment drops off considerably (Drusano 2004b).

As demonstrated in the previous section, critically ill patients have a number of physiologic changes that may alter the PK of antimicrobials. The changed PK has the propensity to decrease the probability of antimicrobial PD target attainment. Indeed, using microbiologic data generated from 14 ICUs and Monte Carlo simulation of PK parameters garnered from published reports of infected patients, one team demonstrated that routine β-lactam dosing had a probability of target attainment as low as 45% (DeRyke 2007). Notably, simulations of high-dose ceftazidime and cefepime (2 g every 8 hours) against *Pseudomonas aeruginosa* exceeded the PD target more than 90% of the time. An open-label multicenter study evaluated the PK profiles of 80 critically ill patients treated with aggressively dosed β-lactam (e.g., piperacillin 4 g every 6 hours, cefepime 2 g every 8 hours, ceftazidime 2 g every 8 hours, meropenem 1 g every 8 hours); the proportion of patients who met prespecified PD targets for meropenem, ceftazidime, cefepime, and piperacillin-tazobactam were 75%, 28%, 16%, and 44%, respectively (Taccone 2010). Notably, that study's PD target was time greater than four times the MIC, which is considerably more aggressive than the target used in the DeRyke study.

In a recent prospective, multinational, PK point-prevalence study of 248 ICU patients treated with β-lactams, 16% of patients did not achieve the PD target of 50% of free drug concentration T > MIC. Patients who did not achieve the PD target had a 32% lower chance of achieving a positive clinical outcome (Roberts 2014c). In that point-prevalent study, the antibiotic dosing and administration methods were dictated by the treating physician and varied among the different sites.

Aside from the decreased propensity for critically ill patients to reach PD targets because of PK changes, evidence suggests that PD targets in critical care should be different and higher than those seen in non–critically ill patients. Indeed, few of the targets proposed in Table 1-3 have been validated in critically ill patients. In fact, many of the targets were derived from animal models, in vitro kill studies, or non–critically ill patients.

Although most clinicians assume that the PD targets should be the same in critically ill patients, the data to support that hypothesis is sparse; some studies suggest that higher PD targets are necessary. In a study of 76 patients with serious infections treated with either cefepime or ceftazidime, both clinical cure and bacteriologic cure were significantly higher if drug concentrations were above the MIC throughout the entire dosing interval (100% T > MIC) (McKinnon 2008). This begs the question of whether, for severe infections, a higher proportion of time spent above the MIC for β-lactams is warranted.

Traditional in vitro studies also suggest that, for β-lactams, further increases in concentration above the MIC do not produce additional bacteriologic killing (Drusano 2004a). However, in a PK study of 101 patients with lower respiratory tract infections being treated with meropenem, the only PD target significantly correlated with clinical success was 100% time spent above five times the MIC (Li 2007). Taken together, it appears that the optimal PD parameter for patients with severe infections might not be fully elucidated. In a recent survey of nine ICUs in which therapeutic drug monitoring (TDM) of β-lactams is routine, the PD targets ranged from 100% T > MIC to 100% T > 4xMIC (Wong 2014), which is considerably higher than traditionally recommended.

The potential need for higher PD targets poses additional challenges for critically ill patients. Aside from the high interpatient variability because of unpredictable PK, critically ill patients also have a higher risk of acquiring resistant organisms with higher MICs. In an epidemiologic study of resistance among gram-negative bacilli in ICU patients over a decade, consistent increases in resistance rates were observed (Lockhart 2007). The constellation of higher baseline MICs, the potential need for higher PD targets, PK changes that may lower serum concentrations, and dosing recommendations that are largely one size fits all based on healthy volunteers makes selection of an adequate antimicrobial dosing regimen for critical care patients a considerable challenge.

Two strategies have emerged as potential options for the application of antimicrobial PD principles in critically ill patients: TDM of antimicrobials (including ones not traditionally considered for TDM) and the use of alternative-dosing-administration techniques (e.g., continuous or extended infusions for β-lactams and once-daily dosing for aminoglycosides).

Evidence from pharmacokinetic modeling and Monte Carlo simulation suggests that the probability of PD target attainment for β-lactams is enhanced through continuous or extended infusion methods (Lodise 2006). However, whether the use of continuous- or extended-infusion β-lactams improves clinical outcomes remains a controversial topic, with meta-analyses demonstrating conflicting results (Falagas 2013, Roberts 2009). To address this controversy, a prospective, randomized, controlled, double-dummy trial compared β-lactams

(piperacillin-tazobactam, ticarcillin-clavulanate, or meropenem) with continuously administered and intermittent 30-minute β-lactam infusions in 432 patients with severe sepsis in 25 ICUs. The study attempted to address many of the study design issues that had precluded clinical interpretation from previous studies. The issues included administration of a loading dose, double-blind design, selection of severely ill patients, administration of the same total daily dose in each arm, and aggressive dosing regimens. The study did not perform pharmacokinetic evaluations to determine whether continuous infusions of β-lactams were in fact associated with improvements in target attainment. The study found no significant differences in any primary or secondary outcomes, which included ICU-free days, 90-day mortality, 14-day clinical cure, duration of bacteremia, and organ-failure-free days. In addition, no differences in adverse effects were observed (Dulhunty 2015).

Although this study found a lack of clinical outcome benefits with continuous infusions of β-lactams, several considerations remain. Of the 432 patients, only 83 actually had a pathogen isolated from blood. Furthermore, MIC information and differences in proportion of patients with PD target attainment were not evaluated. The median duration of study drug treatment was only 3.2 days in the study arm and 3.7 days in the intermittent arm. Furthermore, because the study did not evaluate serum concentrations, it is difficult to ascertain whether the lack of benefit was caused by the inability of continuous infusion to improve further on PD target attainment over aggressively dosed bolus administration of β-lactams. Although this study found evidence that continuous infusions of β-lactams may not be helpful for all patients with severe sepsis, it does not negate that such an administration technique has PK/PD benefits and may be of benefit in a more selective subpopulation.

Traditionally, TDM has been reserved for medications with narrow therapeutic indexes. Recently, TDM use has been suggested to ensure the optimization of the dosing of β-lactams in critically ill patients (Roberts 2014a). Several reports recently illustrated the feasibility of routine TDM use for dose optimization of β-lactams (Hites 2013, Patel 2012, Roberts 2014b). However, to date, no prospective studies have evaluated the clinical benefit associated with that practice. Furthermore, wide adoption of routine antimicrobial TDM is unlikely to occur until a quick turnaround and a reliable method for obtaining antimicrobial concentrations are available. Last, although dosing nomograms are available for certain antimicrobials (e.g., aminoglycosides, vancomycin), there are currently no standards for interpretation and dosing adjustments of other antimicrobials based on serum concentration. Until some of those barriers to TDM topple, it is unlikely that antimicrobial TDM will become routine at most institutions.

Patient Care Scenario

A 72-year-old man is admitted to a medical ICU with pneumonia and septic shock. Upon admission, he received 8 L of lactated Ringers and 1 L of 5% albumin. He has acute kidney injury requiring continuous renal replacement therapy and is currently receiving norepinephrine 45 mcg/minute, vasopressin 0.03 units/minute, cefepime, and levofloxacin. What physiologic changes are observed in this patient that could affect the pharmacokinetics and pharmacodynamics of the antimicrobials he is receiving?

ANSWER

This is a complicated patient with many physiologic changes that may affect antimicrobial PK and PD. Full ascertainment of the effects of the physiologic changes requires an assessment of the patient and the antimicrobial properties. Presumed changes, based on patient presentation, are larger intravascular volume from fluid resuscitation; decreased serum albumin concentration and increased α-acid glycoprotein, affecting protein binding; hemodynamic instability, decreasing perfusion and distribution of hydrophilic antimicrobials to intended site of action; and extracorporeal removal of drugs by way of continuous renal replacement therapy. The extent to which those physiologic changes would affect the PK and PD depends on the drugs' properties: Cefepime is a time-dependent antimicrobial with a small volume of distribution and low protein binding and is eliminated through the kidneys. For cefepime, the patient's physiologic changes are likely to lower serum concentration (increased volume of distribution), decrease distribution to active site of infection (hemodynamic instability), and decrease clearance (acute kidney injury). Regarding levofloxacin, this drug has a large volume of distribution, has low protein binding, and is also eliminated by the kidneys. Clearance is affected by acute kidney injury; however, serum concentration and delivery to site of infection should not be affected by the increase in intravascular volume. To effectively design a therapeutic regimen for this patient, a clinician must first weigh the potential effects of deranged PK and PD and then balance the safety and efficacy of potentially underdosing or overdosing the patient on any particular medication. An understanding of the antimicrobials' PD targets and local MIC patterns would also assist in designing a regimen.

1. Roberts JA, Abdul-Aziz MH, Lipman J, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 2014;14:498-509.
2. Smith BS, Yogaratnam D, Levasseur-Franklin KE, et al. Introduction to drug pharmacokinetics in the critically ill patient. Chest 2012;141:1327-36.

PHARMACOGENOMICS

Pharmacogenomics is the study of how genes affect a person's response to drugs. The application of PGx information is an opportunity to further provide personalized medicine for critically ill patients. Currently, a large number of drugs have known pharmacogenomic variations in PK or PD. However, given the current structure of evidence-based medicine and FDA drug development regulations, the majority of drug dosing and monitoring remains a one-size-fits-all paradigm. Furthermore, the application of PGx to critically ill patients will necessitate the availability of a rapid genetic test panel that targets known genes that may affect critical care pharmacotherapy. Unfortunately, no such commercially available genetic test panel currently exists, and most PGx tests (unless available through in-house assays) have turnaround times of 5–7 days, thus precluding rapid bedside decisions. As such, application of the PGx tests and clinical scenarios discussed in the following rely on information from rapid genetic testing or incidental findings from previously administered PGx test panels. The discussion also pinpoints specific areas where further PGx testing development could enhance clinical application.

Genetic Variations in CYP Metabolism

The CYP enzymes are responsible for the hepatic metabolism of about 75% of all drugs (Guengerich 2008). Almost all CYP isoenzymes have genetic variations reported; however, a few enzymes have particular clinical applicability in critically ill patients. These include CYP2D6, CYP2C9, and CYP2C19, which are responsible for hepatic metabolism of 25%, 15%, and 10% of all drugs, respectively (Zhou 2009). Although involved in the hepatic metabolism of 50% of drugs, the CYP3A4 polymorphisms are less as common, have minimal clinical impact, and are not discussed here.

Phenotypic variations of CYP enzymes can be categorized into four categories: poor metabolizers, intermediate metabolizers, extensive metabolizers, and ultrarapid metabolizers (Samer 2013). Extensive metabolizers are generally considered wild-type representatives (typically most common) and have the usual amount of enzyme activity. Poor metabolizers result from either the presence of two nonfunctional (null) alleles or the deletion of the entire gene. Intermediate metabolizers are usually found in individuals carrying one null allele or one with reduced function. Ultrarapid metabolizers often carry one or more duplicate functional genes. Furthermore, the distribution of common variant alleles of CYP genes varies among different ethnic populations. Common phenotypes of the three most-studied isoenzyme genetic polymorphisms—with their corresponding frequencies in ethnic groups—and potentially affected drugs as seen in critically ill patients are listed in Table 1-4.

Table 1-4. CYP Isoenzymes Commonly Seen in Critically Ill Patients

CYP Isoenzyme	Common Metabolizer Types	Whites (%)	Africans (%)	Asians (%)	Affected Drugs
CYP2D6	Poor	5–10	1–2	1–2	Antipsychotics, carvedilol, codeine, diltiazem, ethanol, hydrocortisone, metoprolol, oxycodone, propafenone, tramadol
	Intermediate	10–15	50	30	
	Ultrarapid	1–5[a]	0–2[b]	2[c]	
CYP2C19	Poor	3–16	7–15	14–46	Clopidogrel, diazepam, phenobarbital, phenytoin, prasugrel, propranolol, proton pump inhibitors, valproic acid, voriconazole, warfarin
	Ultrarapid	16–31	16–33	Rare	
CYP2C9	Poor	35%	Rare	0–2	Amiodarone, clopidogrel, metronidazole, pantoprazole, sulfamethoxazole, valproic acid, voriconazole

[a]Higher prevalence seen in southern European countries.

[b]As high as 30% of Ethiopians.

[c]As high as 30% of Saudi Arabians.

Information from: Bradford LD. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics 2002;3:229-43; Gaedigk A, Bradford LD, Marcucci KA, et al. Unique CYP2D6 activity distribution and genotype-phenotype discordance in black Americans. Clin Pharmacol Ther 2002;72:76-89; Guengerich FP. Cytochrome p450 and chemical toxicology. Chem Res Toxicol 2008;21:70-83; Owusu Obeng A, Egelund EF, Alsultan A, et al. CYP2C19 polymorphisms and therapeutic drug monitoring of voriconazole: are we ready for clinical implementation of pharmacogenomics? Pharmacotherapy 2014;34:703-18; Samer CF, Lorenzini KI, Rollason V, et al. Applications of CYP450 testing in the clinical setting. Mol Diagn Ther 2013;17:165-84; and Zhou SF, Liu JP, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. Drug Metab Rev 2009;41:89-295.

Clinical Application of CYP Polymorphisms

Clopidogrel

Clopidogrel is a thienopyridine prodrug that requires hepatic transformation to an active metabolite, which irreversibly inhibits the $P2Y_{12}$ receptor on the surface of blood platelets, causing decreased aggregation activity. Conversion of clopidogrel to its active metabolite requires two sequential oxidative steps involving several CYP enzymes (i.e., CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4). Patients with reduced CYP enzyme function may have decreased biotransformation of clopidogrel to its active metabolite.

Clopidogrel is often prescribed after percutaneous coronary intervention (PCI); however, patient response rates vary greatly, with up to 20% of patients being nonresponders or poor responders (Campo 2010). Several studies have linked CYP2C19 genetic polymorphisms with varying rates of clinical outcomes among post-PCI patients treated with clopidogrel (Collet 2009, Frere 2009, Giusti 2007, Mega 2009, Shuldiner 2009). Furthermore, meta-analysis has shown that patients treated with clopidogrel who are undergoing PCI and who are either homozygous (poor metabolizers) or heterozygous (intermediate metabolizers) with the CYP2C19 loss of functional allele(s) have an increased risk of major adverse cardiovascular events (Mega 2011). Furthermore, the relationship exhibits a stepwise increase in poor outcomes from intermediate metabolizers to poor metabolizers, which may further denote a physiologic or pharmacologic connection (HR for adverse cardiovascular event = 1.55; 95% CI, 1.11–2.17 for intermediate metabolizer; HR 1.76, 95% CI 1.24–2.50 for poor metabolizer).

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines provide specific guidance in the use of clopidogrel in patients who are post-PCI and are intermediate or poor metabolizers of CYP2C19; for these patients, an alternative antiplatelet agent such as prasugrel or ticagrelor should be considered. Those recommendations may assist clinicians prior to the decision to initiate clopidogrel, but they may be of limited applicability for patients with confirmation of adequate antiplatelet activity, such as those with evidence of inhibition on platelet aggregation tests. Notably, the benefit of prasugrel and ticagrelor over clopidogrel in patients with post–acute coronary syndrome—with the majority undergoing PCI for the prevention of cardiovascular death, myocardial infarction, or stroke—was most pronounced in those with loss of functional CYP2C19 alleles (Mega 2009,Wallentin 2010). The American College of Cardiology guidelines on the management of ST-elevation myocardial infarction say genetic testing of clopidogrel metabolism may be considered on an individual patient basis (O'Gara 2014).

Voriconazole

The CYP2C19 polymorphisms may also have implications in the use of voriconazole for treatment of invasive fungal infections. Voriconazole is a triazole antifungal agent that is recommended as a first-line therapy for the treatment of acute invasive aspergillosis. It is metabolized primarily by hepatic enzyme CYP2C19, with some additional metabolism by CYP2C9 and CYP3A4. Voriconazole has a narrow therapeutic index and nonlinear pharmacokinetics, and it exhibits large, interpatient pharmacokinetic variability with a more than 100-fold difference in plasma concentrations observed with usual dosing (Meletiadis 2006). Those properties make it an ideal agent for the combination of pharmacogenetic evaluation and TDM.

Numerous studies have consistently found a relationship between voriconazole serum concentrations and CYP2C19 polymorphisms (Hassan 2011, Scholz 2009). In addition, the use of TDM to maintain voriconazole levels within therapeutic ranges has correlated with improvements in efficacy and adverse effects (Park 2012). However, to date, no studies have definitively proved that CYP2C19 polymorphisms are linked directly to differences in patient outcomes. That lack of proof may be due to increased use of TDM and dose adjustments, as well as the influence of other patient baseline characteristics on outcomes associated with invasive fungal infections. However, despite the lack of clinical evidence, the use of pharmacogenetic information to guide initial dosing of voriconazole seems prudent, particularly if the information is already available and would not delay therapy. That initial-dose guidance may be especially important for patients known to be ultrarapid metabolizers and to have active fungal infections. Subsequent dosing of voriconazole could be directed through TDM.

Opioid Analgesics

A number of opioid analgesics (e.g., codeine, hydrocodone, oxycodone, tramadol) rely on in vivo conversion to more active opioids for their analgesic properties. Codeine metabolism entails conversion to norcodeine by CYP3A4, glucuronidation conversion to codeine-6-glucuronide, and CYP2D6 conversion to morphine. Although the CYP2D6 pathway is responsible for only 5%–10% of codeine metabolism, CYP2D6 is responsible for the majority of analgesic effect because the parent drug has a 200-fold weaker affinity for the μ-opioid receptor compared with morphine.

The association between genetic polymorphisms of CYP2D6 leading to phenotypic differences in metabolizing activity and PK and PD differences with codeine and morphine is well documented. In CYP2D6 ultrarapid metabolizers, PK studies have documented increased conversion of codeine to morphine (Kirchheiner 2007); in some cases, this has resulted in toxic systemic concentrations of morphine

and life-threatening adverse effects after normal doses of codeine (Gasche 2004). In contrast, poor metabolizers of CYP2D6 have been associated with decreased formation of morphine and lack of efficacy. CYP2D6 is also responsible for the biotransformation of tramadol, hydrocodone, and oxycodone to more-potent opioids. Although the clinical evidence surrounding PK changes associated with various CYP2D6 polymorphisms is not as robust as that for codeine, the CPIC guidelines provide similar therapeutic recommendations for all of these agents (Crews 2014). The guidelines recommend that alternative opioids that don't rely on CYP2D6 conversion (e.g., morphine, hydromorphone) should be considered for patients who are either ultrarapid metabolizers or poor metabolizers of CYP2D6 (Crews 2014).

Other Polymorphisms Relevant to Critical Care

Human Leukocyte Antigen

Human leukocyte antigen B (HLA-B) is a gene that is used for encoding a cell surface protein for antigen presentation to the immune system. It is responsible for the presentation of a variety of peptides for immune recognition. To date, there are more than 2000 identified HLA-B alleles. Of particular interest to critical care practitioners, HLA-B*15:02 is related to the development of severe cutaneous adverse drug reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) as caused by any of several antiepileptics, including carbamazepine, phenytoin, and oxcarbamazepine.

Unlike polymorphisms of CYP metabolizing enzymes, whose varying degrees of metabolizing activity depend on the presence or absence of one or both alleles, HLA-B*15:02 genotyping is considered positive if one or two copies of the allele are present; it is considered negative only when no copies are present. HLA-B*15:02 appears to have a distinctive ethnic and regional distribution, with the highest rates among East Asians and South or Central Asians. Rates of HLA-B*15:02 positivity have been as high as 36% in some areas of China. In general, areas of Hong Kong, Singapore, Thailand, and Malaysia have rates of 6%–12%. Among other Asians, Koreans and Japanese have relatively low rates of HLA-B*15:02 positivity, at 0.5% and 1%, respectively. Among patients with known ancestry associated with high probability of having an HLA-B*15:02 allele, the negative predictive value for severe cutaneous reactions in those treated with carbamazepine is 100% (Hung 2006). However, the positive predictive value is only 7.7%, suggesting that not all patients who possess the allele will develop severe reactions.

Currently, the FDA recommends that patients with ancestries in at-risk populations (East Asians and South or Central Asians) be screened for the presence of the HLA-B*15:02 allele before initiation of carbamazepine and phenytoin. Patients positive for HLA-B*15:02 should avoid initiation of relevant antiepileptics.

Leucyl/cystinyl Aminopeptidase (LNPEP) Variants

Currently, the surviving sepsis campaign has an ungraded recommendation suggesting that low-dose vasopressin may be added to norepinephrine for the hemodynamic support of patients in septic shock (Dellinger 2013). Vasopressin is currently administered as a fixed-dose infusion; therefore, it is understandable that patient variations may lead to differing serum concentrations.

One particular genetic variation associated with vasopressin therapy has significant correlations with outcomes among patients with septic shock. The clearance of vasopressin depends primarily on actions by the LNPEP enzyme. A single nucleotide polymorphism on the section of gene that encodes LNPEP generates genotypic differences and phenotypic variations in enzymatic activity. Using data from the Vasopressin and Septic Shock Trial and a validation cohort, Nakada and colleagues were able to determine that the TT genotype of a specific single nucleotide within the LNPEP gene was associated with increased enzymatic activity, leading to decreased vasopressin concentrations (Nakada 2011). The TT genotype, when compared with normal genotype (AA or AT), was also associated with increased 28-day mortality (51% vs. 34%, p=<0.001). Although the screening of this particular single-nucleotide polymorphism is not currently commercially available for clinical care and no studies support that a clinical decision based on this genetic variant would yield outcomes benefit, the trial by Nakada and colleagues demonstrates the potential vastness of the applicability of PGx.

CONCLUSION

The application of PK/PD/PGx principles is at a crossroad, and it is unlikely that a large-scale study would clearly demonstrate clinical outcome benefits associated with the application of those principles—as became evident by a study comparing continuous infusion β-lactams with intermittent infusions. This is most likely because the stringent procedure called for by a randomized controlled trial is contradictory to the patient-specific approach endorsed by the application of PK, PD, and PGx principles. As critical care pharmacists, we must decide whether each patient should receive personalized dosing and monitoring schemes based on a balance between the importance of the efficacy of a drug and the potential for adverse reactions associated with under- or overdosing of the medication. Application of the individualized PK, PD, and PGx principles may constitute deviation from a traditional, evidence-based therapeutic approach. However, as clinicians, we should not—based only on lack of evidence—negate the known physiologic and pathophysiologic changes seen in critically ill patients and the potential for dosing optimization.

Practice Points

In applying pharmacokinetic, pharmacodynamic, and pharmacogenomic principles to critically ill patients, clinicians should consider following these steps.

- **Quantify the patient's current clinical physiologic changes and note how each change could alter the pharmacokinetics of medications.**
- **For medications with narrow therapeutic indexes or ones for which meeting pharmacodynamic targets is crucial, specifically evaluate the potential effects of the patient's physiologic change on serum and tissue concentrations.**
- **Derive a pharmaceutical plan that applies a dosing strategy that optimizes the probability of pharmacodynamic target attainment without substantial increase in the risk of adverse effects.**
- **If using a dosing scheme that differs from the package insert's recommended doses, ensure proper documentation of the scheme's rationale and vigilantly monitor for both therapeutic and adverse effects.**
- **Adjust dosing and monitoring schemes accordingly based on observed effects and changes in the patient's physiology.**
- **The clinician should also realize that until the advent of real-time genetic testing, pharmacogenomics applications are currently restricted to incidental findings from previously evaluated patients,**

REFERENCES

Albanese J, Leone M, Garnier F, et al. Renal effects of norepinephrine in septic and nonseptic patients. Chest 2004;126:534-9.

Ariano RE, Sitar DS, Zelenitsky SA, et al. Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. CMAJ 2010;182:357-63.

Beale RJ, Hollenberg SM, Vincent JL, et al. Vasopressor and inotropic support in septic shock: an evidence-based review. Crit Care Med 2004;32:S455-65.

Benmalek F, Behforouz N, Benoist JF, et al. Renal effects of low-dose dopamine during vasopressor therapy for posttraumatic intracranial hypertension. Intensive Care Med 1999;25:399-405.

Bonnet F, Richard C, Glaser P, et al. Changes in hepatic flow induced by continuous positive pressure ventilation in critically ill patients. Crit Care Med 1982;10:703-5.

Boucher BA, Rodman JH, Jaresko GS, et al. Phenytoin pharmacokinetics in critically ill trauma patients. Clin Pharmacol Ther 1988;44:675-83.

Brater DC, Bawdon RE, Anderson SA, et al. Vancomycin elimination in patients with burn injury. Clin Pharmacol Ther 1986;39:631-4.

Brown R, Babcock R, Talbert J, et al. Renal function in critically ill postoperative patients: sequential assessment of creatinine osmolar and free water clearance. Crit Care Med 1980;8:68-72.

Campo G, Fileti L, Valgimigli M, et al. Poor response to clopidogrel: current and future options for its management. J Thromb Thrombolysis 2010;30:319-31.

Churchwell MD, Mueller BA. Drug dosing during continuous renal replacement therapy. Semin Dial 2009;22:185-8.

Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet 2009;373:309-17.

Conil JM, Georges B, Fourcade O, et al. Intermittent administration of ceftazidime to burns patients: influence of glomerular filtration. Int J Clin Pharmacol Ther 2007;45:133-42.

Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther 2014;95:376-82.

Dasta JF, Armstrong DK. Variability in aminoglycoside pharmacokinetics in critically ill surgical patients. Crit Care Med 1988;16:327-30.

Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.

DeRyke CA, Kuti JL, Nicolau DP. Pharmacodynamic target attainment of six beta-lactams and two fluoroquinolones against *Pseudomonas aeruginosa, Acinetobacter baumannii, Escherichia coli,* and *Klebsiella* species collected from United States intensive care units in 2004. Pharmacotherapy 2007;27:333-42.

Dorffler-Melly J, de Jonge E, Pont AC, et al. Bioavailability of subcutaneous low-molecular-weight heparin to patients on vasopressors. Lancet 2002;359:849-50.

Drusano GL. Antimicrobial pharmacodynamics: critical interactions of "bug and drug." Nat Rev Microbiol 2004a;2:289-300.

Drusano GL, Preston SL, Fowler C, et al. Relationship between fluoroquinolone area under the curve: minimum inhibitory concentration ratio and the probability of eradication of the infecting pathogen, in patients with nosocomial pneumonia. J Infect Dis 2004b;189:1590-7.

Dulhunty JM, Roberts JA, Davis JS, et al. A Multicenter Randomized Trial of Continuous versus Intermittent beta-Lactam Infusion in Severe Sepsis. Am J Respir Crit Care Med 2015;192:1298-305.

Edwards DJ, Lalka D, Cerra F, et al. Alpha1-acid glycoprotein concentration and protein binding in trauma. Clin Pharmacol Ther 1982;31:62-7.

Falagas ME, Tansarli GS, Ikawa K, et al. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. Clin Infect Dis 2013;56:272-82.

Fleck A, Raines G, Hawker F, et al. Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. Lancet 1985;1:781-4.

Frere C, Cuisset T, Gaborit B, et al. The CYP2C19*17 allele is associated with better platelet response to clopidogrel in patients admitted for non-ST acute coronary syndrome. J Thromb Haemost 2009;7:1409-11.

Fuster-Lluch O, Geronimo-Pardo M, Peyro-Garcia R, et al. Glomerular hyperfiltration and albuminuria in critically ill patients. Anaesth Intensive Care 2008;36:674-80.

Gasche Y, Daali Y, Fathi M, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med 2004;351:2827-31.

Giusti B, Gori AM, Marcucci R, et al. Cytochrome P450 2C19 loss-of-function polymorphism, but not CYP3A4 IVS10 + 12G/A and P2Y12 T744C polymorphisms, is associated with response variability to dual antiplatelet treatment in high-risk vascular patients. Pharmacogenet Genomics 2007;17:1057-64.

Guengerich FP. Cytochrome p450 and chemical toxicology. Chem Res Toxicol 2008;21:70-83.

Haas CE, Nelsen JL, Raghavendran K, et al. Pharmacokinetics and pharmacodynamics of enoxaparin in multiple trauma patients. J Trauma 2005;59:1336-43;discussion 43-4.

Hassan A, Burhenne J, Riedel KD, et al. Modulators of very low voriconazole concentrations in routine therapeutic drug monitoring. Ther Drug Monit 2011;33:86-93.

Heintz BH, Matzke GR, Dager WE. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. Pharmacotherapy 2009;29:562-77.

Hites M, Taccone FS, Wolff F, et al. Case-control study of drug monitoring of beta-lactams in obese critically ill patients. Antimicrob Agents Chemother 2013;57:708-15.

Hollenberg SM, Ahrens TS, Annane D, et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit Care Med 2004;32:1928-48.

Hung SI, Chung WH, Jee SH, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenet Genomics 2006;16:297-306.

Jochberger S, Mayr V, Luckner G, et al. Antifactor Xa activity in critically ill patients receiving antithrombotic prophylaxis with standard dosages of certoparin: a prospective, clinical study. Crit Care 2005;9:R541-8.

Joukhadar C, Frossard M, Mayer BX, et al. Impaired target site penetration of beta-lactams may account for therapeutic failure in patients with septic shock. Crit Care Med 2001;29:385-91.

Kashuba AD, Nafziger AN, Drusano GL, et al. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob Agents Chemother 1999;43:623-9.

Kirchheiner J, Schmidt H, Tzvetkov M, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. Pharmacogenomics J 2007;7:257-65.

Kruger PS, Freir NM, Venkatesh B, et al. A preliminary study of atorvastatin plasma concentrations in critically ill patients with sepsis. Intensive Care Med 2009;35:717-21.

Kuang D, Verbine A, Ronco C. Pharmacokinetics and antimicrobial dosing adjustment in critically ill patients during continuous renal replacement therapy. Clin Nephrol 2007;67:267-84.

Lamoth F, Buclin T, Csajka C, et al. Reassessment of recommended imipenem doses in febrile neutropenic patients with hematological malignancies. Antimicrob Agents Chemother 2009;53:785-7.

Li C, Du X, Kuti JL, et al. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother 2007;51:1725-30.

Lockhart SR, Abramson MA, Beekmann SE, et al. Antimicrobial resistance among Gram-negative bacilli causing infections in intensive care unit patients in the United States between 1993 and 2004. J Clin Microbiol 2007;45:3352-9.

Lodise TP, Lomaestro BM, and Drusano GL, et al. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on beta-lactam antibiotics: insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy 2006;26:1320-32.

Lourenco R. Enteral feeding: drug/nutrient interaction. Clin Nutr 2001;20:187-93.

Matzke GR, Aronoff GR, Atkinson AJ Jr., et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2011;80:1122-37.

Mayr AJ, Dunser M, Jochberger S, et al. Antifactor Xa activity in intensive care patients receiving thromboembolic prophylaxis with standard doses of enoxaparin. Thromb Res 2002;105:201-4.

McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 2008;31:345-51.

Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354-62.

Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA 2011;304:1821-30.

Meletiadis J, Chanock S, Walsh TJ. Human pharmacogenomic variations and their implications for antifungal efficacy. Clin Microbiol Rev 2006;19:763-87.

Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis 1987;155:93-9.

Nakada TA, Russell JA, Wellman H, et al. Leucyl/cystinyl aminopeptidase gene variants in septic shock. Chest 2011;139:1042-9.

Nguyen NQ, Ng MP, Chapman M, et al. The impact of admission diagnosis on gastric emptying in critically ill patients. Crit Care 2007;11:R16.

O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;61:e78-140.

Park WB, Kim NH, Kim KH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. Clin Infect Dis 2012;55:1080-7.

Patel BM, Paratz J, See NC, et al. Therapeutic drug monitoring of beta-lactam antibiotics in burns patients—a one-year prospective study. Ther Drug Monit 2012;34:160-4.

Prescott LF. Gastric emptying and drug absorption. Br J Clin Pharmacol 1974;1:189-90.

Priglinger U, Delle Karth G, Geppert A, et al. Prophylactic anticoagulation with enoxaparin: Is the subcutaneous route appropriate in the critically ill? Crit Care Med 2003;31:1405-9.

Roberts JA, Abdul-Aziz MH, Lipman J, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 2014a;14:498-509.

Roberts JA, Paul SK, Akova M, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014b;58:1072-83.

Roberts JA, Webb S, Paterson D, et al. A systematic review on clinical benefits of continuous administration of beta-lactam antibiotics. Crit Care Med 2009;37:2071-8.

Rodighiero V. Effects of liver disease on pharmacokinetics. An update. Clin Pharmacokinet 1999;37:399-431.

Rommers MK, Van der Lely N, Egberts TC, et al. Anti-Xa activity after subcutaneous administration of dalteparin in ICU patients with and without subcutaneous oedema: a pilot study. Crit Care 2006;10:R93.

Samer CF, Lorenzini KI, Rollason V, et al. Applications of CYP450 testing in the clinical setting. Mol Diagn Ther 2013;17:165-84.

Scholz I, Oberwittler H, Riedel KD, et al. Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to CYP2C19 genotype. Br J Clin Pharmacol 2009;68:906-15.

Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA 2009;302:849-57.

Taccone FS, Laterre PF, Dugernier T, et al. Insufficient beta-lactam concentrations in the early phase of severe sepsis and septic shock. Crit Care 2010;14:R126.

Tarling MM, Toner CC, Withington PS, et al. A model of gastric emptying using paracetamol absorption in intensive care patients. Intensive Care Med 1997;23:256-60.

Triginer C, Izquierdo I, Fernandez R, et al. Gentamicin volume of distribution in critically ill septic patients. Intensive Care Med 1990;16:303-6.

Trotman RL, Williamson JC, Shoemaker DM, et al. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. Clin Infect Dis 2005;41:1159-66.

Udy AA, Roberts JA, Boots RJ, et al. Augmented renal clearance: implications for antibacterial dosing in the critically ill. Clin Pharmacokinet 2010;49:1-16.

Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 2008;64:1147-61.

Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet 2010;376:1320-8.

Westphal JF, Brogard JM. Drug administration in chronic liver disease. Drug Saf 1997;17:47-73.

Wong G, Brinkman A, Benefield RJ, et al. An international, multicentre survey of beta-lactam antibiotic therapeutic drug monitoring practice in intensive care units. J Antimicrob Chemother 2014;69:1416-23.

Zhou SF, Liu JP, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. Drug Metab Rev 2009;41:89-295.

Zhu LL, Zhou Q. Therapeutic concerns when oral medications are administered nasogastrically. J Clin Pharm Ther 2013;38:272-6.

Self-Assessment Questions

Questions 1–6 pertain to the following case.

S.W. is a 54-year-old woman (weight 45 kg) admitted to the ICU with signs and symptoms of pneumonia and septic shock requiring intubation, aggressive fluid resuscitation, broad-spectrum antimicrobials, and hemodynamic support with norepinephrine. Her medical history is significant for seizures, for which she is taking phenytoin 100 mg orally three times daily. S.W. received a total of 7 L of crystalloid fluids in the first 24 hours after ICU admission. She is currently sedated with midazolam and fentanyl, and an orogastric tube was placed to initiate tube feeds. Her laboratory test results include WBC count 18.2 x 10^3 cells/mm, hemoglobin 8.0 g/dL, albumin 2.0 g/dL, lactate 2.2 mmol/L, SCr 0.8 mg/dL, and total phenytoin concentration 6.0 mcg/mL. Her physical examination reveals anasarca, and chest radiography demonstrates the presence of pulmonary edema. S.W.'s other current drugs, aside from norepinephrine, include pantoprazole 40 mg by mouth once daily, enoxaparin 30 mg subcutaneously every 12 hours, ceftriaxone 1 g intravenously every 24 hours, and azithromycin 500 mg intravenously every 24 hours.

1. Which one of the following physiologic changes is most likely to decrease S.W.'s absorption of oral pantoprazole?

   A. Increased α-1 glycoprotein concentrations
   B. Decreased albumin concentrations
   C. Decreased gastric emptying
   D. Increased splanchnic perfusion

2. Based on her clinical status and pharmacokinetic changes, which of the following recommendations is the most appropriate regarding S.W.'s current enoxaparin regimen?

   A. Decrease enoxaparin to 40 mg once daily.
   B. Continue current enoxaparin regimen.
   C. Check 4-hour peak anti-factor Xa level.
   D. Change to subcutaneous unfractionated heparin.

3. Which of the following best describes ceftriaxone's volume of distribution in S.W.?

   A. Decreased because of aggressive volume resuscitation
   B. Increased because of mechanical ventilation
   C. Decreased because of hypoalbuminemia
   D. Increased because of hypoalbuminemia

4. Which of the following statements best describes the total serum concentration of azithromycin in S.W.?

   A. Unaffected from aggressive fluid resuscitation
   B. Decreased because of aggressive fluid resuscitation
   C. Increased because of decreased protein binding
   D. Decreased because of increased protein binding

5. During daily patient rounds, you calculate S.W.'s adjusted phenytoin concentration, based on the current albumin concentration, to be about 12 mcg/mL. Which one of the following properties of phenytoin would best explain why an adjustment is necessary for S.W.?

   A. High protein binding, weakly acidic
   B. Moderate protein binding, weakly basic
   C. High protein binding, weakly basic
   D. Moderate protein binding, weakly acidic

6. Upon verifying the corrected phenytoin concentration, the team orders a home dose of oral phenytoin 100 mg three times daily for S.W. You recommended changing the drug to IV fosphenytoin. Which one of the following reasons best justifies this change to S.W.'s regimen?

   A. Concerns with diminished absorption because of orogastric tube interactions
   B. Vasodilatory shock leading to increased hepatic blood flow and first-pass metabolism
   C. Hypoalbuminemia leading to increased volume of distribution
   D. Mechanical ventilation leading to decreased hepatic blood flow and first-pass metabolism

7. Your coronary care ICU is gathering information in preparation for the possible development of routine pharmacogenomics evaluations. The ICU director wants your input on deciding which pharmacogenomics tests should be employed for post-percutaneous coronary intervention patients. Which of the following tests is most likely to have clinical applicability in your particular unit?

   A. CYP3A4 polymorphism
   B. LNPEP gene variants
   C. CYP2D6 polymorphisms
   D. HLA-B screening

8. A Chinese patient with a prolonged history of epilepsy is admitted to your neuro ICU with active seizures. The patient was chronically managed on carbamazepine and phenytoin as an outpatient, with stable doses for the past 2 years. On admission, the patient had a total phenytoin level of 6.2 mcg/mL. The patient received intravenous lorazepam, and the seizures have currently subsided. One of the neurology fellows recently read an article regarding the increased propensity for severe cutaneous reactions among certain individuals receiving carbamazepine and phenytoin and raises this concern during rounds while discussing whether this patient's home anti-epileptics should be continued. Which one of the following recommendations is best regarding this patient's home anti-epileptics?

A. Continue both carbamazepine and phenytoin and adjust dose as necessary.
B. Continue carbamazepine and hold phenytoin while screening for HLA-B*15:02.
C. Continue phenytoin and hold carbamazepine while screening for HLA-B*15:02.
D. Hold all anti-epileptic therapy until HLA-B*15:02 screening is pending.

9. Scheduled oxycodone/acetaminophen is included as part of a surgical pain management protocol in your mixed surgical ICU. During your daily evaluation of the patients in the unit, you notice that one patient has previously been tested for CYP2D6 polymorphisms and is an ultra-rapid metabolizer. Which one of the following recommendations is best regarding oxycodone/acetaminophen use in this patient?

   A. Therapy should continue as normal because CYP2D6 phenotypes do not affect oxycodone/acetaminophen.
   B. Oxycodone/acetaminophen should be initiated at a higher than usual dose because the patient is an ultra-rapid metabolizer.
   C. An alternative drug should be recommended because the patient has a CYP2D6 phenotype associated with poor analgesic response.
   D. An alternative drug should be recommended because the patient has a CYP2D6 phenotype associated with increased adverse effects.

10. Clopidogrel is routinely used in your coronary care ICU in patients who undergo cardiac catheterization and stent placement. Recently, CYP2C19 genetic polymorphisms and platelet aggregation tests (light transmission aggregometry) have been employed as part of routine patient care for the purpose of ensuring adequate clopidogrel dosing. The platelet aggregation test reports platelet activity as P2Y12 reaction units (PRU), with normal aggregation being in the range of 194–418. A patient who received a drug eluting stent 6 weeks ago and currently receiving clopidogrel 75 mg once daily has the following laboratory results: CYP2C19 phenotype: poor metabolizer, PRU: 112 suggesting inhibited platelet aggregation. Which one of the following recommendations is best regarding clopidogrel use in this patient?

   A. Increase dose
   B. Continue current dose
   C. Decrease dose
   D. Change to aspirin alone

Questions 11–15 pertain to the following case.

L.H. is a 25 year-old woman (weight 65 kg) admitted to the surgical-trauma ICU after a motor vehicle crash. She suffered blood loss, open bone fractures, and traumatic brain injury. L.H. is currently intubated and hypotensive requiring norepinephrine 15 mcg/min despite receiving large amounts of crystalloid, colloids, and blood products. She has no significant medical history. Upon admission, L.H. was started on piperacillin/tazobactam 3.375 g intravenously every 6 hours administered as 30-minute bolus infusions. Her current urine output is 150 mL/hour. Her relevant laboratory results are WBC count 16.7 x 10^3 cells/mm, hemoglobin 9.0 g/dL, albumin 2.4 g/dL, lactate 1.2 mmol/L, and SCr 0.3 mg/dL.

11. Which of the following is most likely to cause a lower than usual piperacillin/tazobactam serum concentration in L.H.?

   A. Hemodynamic instability
   B. Augmented renal clearance
   C. Hypoalbuminemia
   D. Decreased volume of distribution

12. Which one of the following interventions would best assist piperacillin/tazobactam pharmacodynamics target attainment in L.H.?

   A. Decrease infusion time from 30 min per dose to 10 min per dose.
   B. Administer total daily dose as one large bolus infusion.
   C. Change dosing regimen to 2.25 g intravenously every 4 hours.
   D. Change dosing regimen to 4.5 g intravenously every 8 hours.

13. Which one of the following statements best describes L.H.'s piperacillin/tazobactam pharmacodynamic target?

   A. Peak concentration should be at least 10 times higher than the pathogen's MIC.
   B. Minimum pharmacodynamic target is serum concentration being above the MIC for 50% of each dosing interval.
   C. Prolonged time of serum concentration above MIC beyond 50% is unnecessary.
   D. A higher AUC to MIC ratio than what is traditionally recommended is likely to improve bacterial killing.

14. You recommend administering piperacillin/tazobactam to L.H. in a fashion that maximizes the probability of pharmacodynamics target attainment. Which one of the following reasons best justifies this recommendation for L.H.?

   A. Proven mortality benefit
   B. Decreased ventilator days
   C. Decreased adverse effects
   D. Improved in vitro killing

15. In discussing L.H. with your PGY-2 critical care resident, you expressed concern regarding the increased volume of distribution with piperacillin/tazobactam and the corresponding decreased serum and tissue concentrations.

Which one of the following alternative regimens will be least likely to be affected by the pharmacokinetic changes seen in L.H.?

A. Cefepime
B. Levofloxacin
C. Gentamicin plus vancomycin
D. Aztreonam plus clindamycin

16. For the same dose, which of the following factors is the most important contributor to the probability of attaining pharmacodynamic (peak/MIC > 8) targets for aminoglycosides?

A. Serum protein concentrations
B. Volume of distribution
C. Pathogen resistance
D. Renal clearance

Question 17 and 18 pertain to the following case.

M.M. is a 40-year-old man admitted to your medical ICU. He is currently hemodynamically stable, mechanically ventilated, and anuric. Respiratory viral panel and bronchoalveolar lavage from admission demonstrate proven influenza infection. M.M. is worsening while on standard therapy, and your team would like to pursue a new oral antiviral agent that is available through a compassionate use program for patients with severe influenza unresponsive to standard therapy. M.M. is currently receiving continuous veno-venous hemodialysis (dialysate flow rate, 2 L/hour) and there are no dosing recommendations provided by the manufacturer for patients receiving continuous renal replacement therapy. The team approaches you for a dosing recommendation for this new compound. From the investigator brochure, you gather the following information: usual dose 100 mg once daily; adjust dose for CrCl < 30 mL/min to 50 mg once daily; total body clearance 1.2 L/hr; metabolized by the liver to inactive metabolites; low hepatic extraction efficiency; 60% of total clearance via kidneys as unchanged drug; protein binding 20%.

17. Which one of the following dosing regimens is best to recommend for M.M?

A. 50 mg once daily
B. 100 mg once daily
C. 130 mg once daily
D. 175 mg once daily

18. M.M. has been receiving the new oral antiviral agent through a naso-gastric feeding tube. On day 3 of therapy, M.M. develops hemodynamic instability. An ECG demonstrates new left-ventricle wall motion abnormality and a decreased ejection fraction from baseline. New laboratory results demonstrate an INR of 2.0 and total bilirubin of 4.5 mg/dL. Based on its pharmacokinetic profile, which one of the following changes in serum concentrations of the antiviral agent is most likely to happen as a result of M.M.'s hemodynamic instability and altered hepatic metabolism?

A. Decreased because of decreased hepatic blood flow
B. Increased because of decreased hepatic blood flow
C. Decreased because of decreased intrinsic hepatic clearance
D. Increased because of decreased intrinsic hepatic clearance

19. A 54-year-old Asian man (weight 70 kg) with acute myeloid leukemia is admitted to your medical ICU with neutropenic fever and respiratory failure requiring mechanical ventilation. The patient's chest CT scan demonstrates cavitary lesions suggestive of invasive fungal infection, and serum galactomannan assay is positive. The medical team decides to treat the patient's presumed invasive fungal infection with voriconazole. Your institution has a mechanism to obtain both CYP2C19 polymorphism and voriconazole serum concentration results by a send-out test. Which of the following recommendations is best for this patient?

A. Test for CYP2C19 polymorphisms to determine initial dose; adjust dose base on therapeutic drug monitoring.
B. Administer standard intravenous doses, adjust dose base on therapeutic drug monitoring.
C. Administer standard intravenous doses, and monitor for radiologic signs of efficacy.
D. Administer standard intravenous dose, adjust dose based on CYP2C19 polymorphism.

20. A 40-year-old woman (height 66 in, weight 56 kg) is admitted to your medical ICU with signs and symptoms of pyelonephritis and septic shock. The patient has a history of chronic UTIs and kidney stones requiring the placement of ureteral stents. The patient was profoundly dehydrated upon admission and required 8 L of crystalloid fluid in the first 24 hours to maintain her blood pressure. The patient was anuric upon admission, but upon fluid resuscitation and removal of ureteral stents her urine output is now 150 mL/hr. She was initially started on ciprofloxacin for her infection, but urine cultures now demonstrate the presence of an extended β-lactamase producing *K. pneumoniae*, which is sensitive to meropenem. Relevant laboratory results are WBC count 26.7 x 10^3 cells/mm, lactate 4.2 mmol/L, and SCr 2.3 mg/dL (baseline 0.5 mg/dL). Which one of the following meropenem regimens would be best to recommend for this patient?

A. 500 mg once daily
B. 500 mg every 12 hours
C. 500 mg every 8 hours
D. 1000 mg every 8 hours