Acute Kidney Injury and Continuous Renal Replacement Therapy

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LEARNING OBJECTIVES

1. Evaluate acute kidney injury (AKI) by etiology and severity of insult.
2. Assess general treatment strategies and the role of diuretics in AKI.
3. Apply the principles of drug dosing guided by the impact of pharmacokinetic and pharmacodynamic changes in AKI.
4. Distinguish the various types of renal replacement therapy and their unique drug and solute removal characteristics.
5. Design a medication regimen for patients receiving continuous renal replacement therapy.

ABBREVIATIONS IN THIS CHAPTER

AKI	Acute kidney injury
CRRT	Continuous renal replacement therapy
CVVH	Continuous venovenous hemofiltration
CVVHD	Continuous venovenous hemodialysis
CVVHDF	Continuous venovenous hemodiafiltration
IHD	Intermittent hemodialysis
KDIGO	Kidney Disease: Improving Global Outcomes
MAP	Mean arterial pressure
MRSA	Methicillin-resistant *Staphylococcus aureus*
PB	Protein binding
RRT	Renal replacement therapy
SA	Saturation coefficient
SC	Sieving coefficient
Vd	Volume of distribution

Table of other common abbreviations.

INTRODUCTION

Management of AKI remains a challenge for clinicians working in the acute care environment, with estimates of up to 20% of hospitalized patients experiencing AKI (Silver 2017). In the critically ill population, the proportion of patients with incident AKI increases to more than 50% (Ronco 2019; Silver 2017). Because the kidney is responsible for elimination of solutes, including toxins, drugs, and electrolytes, acute reductions in kidney function can lead to secondary complications such as electrolyte abnormalities and altered drug disposition. Furthermore, AKI alters the normal regulation of fluid status, blood pressure, and metabolism of certain substances by the kidney, which may require initiation of new drug therapy, alterations in drug dosing regimens, and nonpharmacologic interventions such as RRT.

Development of AKI in hospitalized patients leads to increased mortality, hospital costs, and length of stay. Estimates of AKI that requires RRT in the critically ill patient range from 3% to 13%. Of these patients, about 40% are predicted to require continued RRT beyond 90 days (Lee 2019). With annual fee-for-service expenditures estimated to be around $93,000 per-person-per-year for patients on hemodialysis, the economic impact of AKI that requires RRT is staggering (United States Renal Data System 2020). In addition, recent economic analyses have associated AKI with increased hospital costs starting at $5400 with costs for more severe AKI up to $34,000 (Silver 2017). Mortality rates for hospitalized patients have been reported to be as high as 25%, increasing to about 50% in critically ill patients who require RRT (Silver 2017; Gaudry 2016; Zarbock 2016). Length of stay estimates report increases of up to 8 days in those who develop severe AKI (Chertow 2005).

CLASSIFICATION OF AKI

Acute kidney injury is a broad term to describe an acute decline in kidney function, often identified based on acute elevations in serum creatinine and/or reduced urine output. Box 1 presents the definition of AKI by the Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for Acute Kidney Injury.

Etiologies

Acute kidney injury is categorized as *pre-renal*, *intrinsic*, or *post-renal/obstructive* (Makris 2016). Table 1 further describes the potential causes of AKI and definitions of these categories.

Both pre- and post-renal AKI are caused by factors outside of the kidney that alter renal hemodynamics or filtration capability, including dehydration or urinary outlet obstruction. For pre-renal AKI, a useful diagnostic tool is the fractional excretion of sodium. Because pre-renal AKI is associated with hypovolemic states, urinary excretion of sodium should be low; therefore, the fractional excretion of sodium should be less than 1% (Makris 2016).

In contrast to pre- and post-renal AKI, intrinsic AKI is secondary to direct damage to the renal tubules, vasculature, glomeruli, or interstitium (Makris 2016). The most common form of intrinsic AKI is acute tubular necrosis, which is characterized by direct damage to the renal tubules causing sloughing of luminal cells and the diagnostic criteria of "muddy brown casts" in the urine. Left untreated, pre-renal and post-renal AKI can result in renal ischemia that precipitates acute tubular necrosis and intrinsic kidney injury.

Box 1. KDIGO Acute Kidney Injury Definition

↑ SCr ≥0.3 mg/dL within 48 hr

—or—

↑ SCr ≥1.5 × baseline known or presumed to have occurred within the past 7 days

—or—

Urine output <0.5 mL/kg/hr × 6 hr

Information from: Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl 2012;2:1-138.

Grading Severity

The three grading systems developed to define and stage the severity of AKI are the Risk, Injury, Failure, Loss, and End-Stage Renal Failure (RIFLE), Acute Kidney Injury Network (AKIN), and KDIGO 2012 criteria (Khwaja 2012; Mehta 2007; Bellomo 2004). The KDIGO criteria incorporate aspects from both the AKIN and RIFLE criteria and have been more widely adopted to describe AKI. Table 2 details and compares the three sets of AKI criteria.

In addition to the development of AKI grading systems, some effort has focused on defining new terms to provide uniformity in describing kidney diseases. The term *acute kidney diseases and disorders* describes the phase of kidney injury after the initial insult but before qualifying as *chronic kidney disease*, which is defined by a duration of 3 months or more. In this context, use of the term *acute kidney diseases and disorders* replaces the terms *acute renal failure* or *acute renal insufficiency* (Levey 2020).

EARLY DETECTION OF AKI

Although creatinine has remained the standard biomarker used in definitions and classification of AKI, recent research has been focused on the identification and clinical use of alternative biomarkers to detect and prevent AKI. These biomarkers include neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, interleukin-18, liver-type fatty acid binding protein, insulin-like growth factor binding protein 7 (IGFBP-7), and tissue inhibitor of metalloproteinase-2 (TIMP-2). For many of these biomarkers, the understanding of the appropriate use in clinical practice still requires further research. However, the development of commercially available tests and clinical validation of biomarkers such as TIMP-2 and IGFBP-7 for the early detection of AKI have helped

BASELINE KNOWLEDGE STATEMENTS

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

- General understanding of renal anatomy and primary functions
- General knowledge of pharmacokinetic and pharmacodynamic concepts
- Estimation of a drug's volume of distribution
- Basic pharmacokinetic equations
- Knowledge of fluids and antimicrobials commonly used in the ICU setting

Table of common laboratory reference values.

ADDITIONAL READINGS

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

- Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1-138.
- Villa G, Neri M, Bellomo R, et al. Nomenclature for renal replacement therapy and blood purification techniques in critically ill patients: practical applications. Crit Care 2016;20:283.

Table 1. Etiologies of Acute Kidney Injury

Category	Etiology	Common pathologies
Pre-renal	Altered hemodynamics resulting in decreased renal blood flow and reduced GFR	Hypotension, shock, dehydration, cardiac failure, drug-induced reduction of glomerular pressure caused ACEis, ARBs, loop diuretics
Intrinsic	Cellular damage to renal anatomy	Nephrotoxin exposure, renal tubular ischemia, allergic interstitial nephritis
Post-renal (obstructive)	Obstruction in the urine collection system that impairs urine drainage, resulting in subsequent GFR decline	Stones, benign prostatic hypertrophy, urethral stricture

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; GFR = glomerular filtration rate.

Information from: Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. Clin Biochem Rev 2016;37:85-98.

further solidify the role of biomarkers in clinical practice. Validation studies for TIMP-2 and IGFBP-7 have been compared in the acute postsurgical populations, both for cardiac and major abdominal surgery. In these trials, bundled preventive AKI care such as fluid status optimization, nephrotoxin removal, and hemodynamic support were provided if urinary [TIMP-2] × [IGFBP-7] was 0.3 or more. Using this biomarker triggered approach and pre-emptive interventions, rates of AKI were reduced in the studied abdominal surgery and cardiac surgery populations by about 21% and 17%, respectively

Table 2. Acute Kidney Injury Staging Criteria

Staging System	Stage	SCr/GFR Criteria	Urine Output Criteria
RIFLE	Risk	↑ SCr ≥1.5 × baseline **or** ↓ in eGFR ≥25%	<0.5 mL/kg/hr for 6 hr
	Injury	↑ SCr ≥2 × baseline **or** ↓ in eGFR ≥50%	<0.5 mL/kg/hr for 12 hr
	Failure	↑ SCr ≥3 × baseline **or** SCr ≥4 mg/dL **or** ↓ in eGFR ≥75%	<0.3 mL/kg/hr for 24 hr or anuria for 12 hr
	Loss	Complete loss of kidney function for >4 wk	N/A
	ESKD	End stage kidney disease (>3 mo)	N/A
AKIN	1	↑ SCr ≥1.5 × baseline **or** ↓ in eGFR ≥25% **or** SCr ↑ ≥0.3 mg/dL	<0.5 mL/kg/hr for >6 hr
	2	↑ SCr ≥2 × baseline **or** ↓ in eGFR ≥50%	<0.5 mL/kg/hr for >12 hr
	3	↑ SCr ≥3 × baseline or SCr ≥4 mg/dL **or** ↓ in eGFR ≥75% **or** initiation of RRT	<0.3 mL/kg/hr for 24 hr or anuria for 12 hr
KDIGO	1	↑ SCr 1.5–1.9 × baseline **or** ↑ ≥0.3 mg/dL	<0.5 mL/kg/hr for 6–12 hr
	2	↑ SCr 2.0–2.9 × baseline	<0.5 mL/kg/hr for ≥12 hr
	3	↑ SCr 3.0 × baseline or SCr ≥4.0 mg/dL or initiation of RRT	<0.3 mL/kg/hr for ≥24 hr or anuria for ≥12 hr

AKIN = Acute Kidney Injury Network; eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease; KDIGO = Kidney Disease: Improving Global Outcomes; RIFLE = Risk, Injury, Failure, Loss, and End-Stage Renal Failure; RRT = renal replacement therapy.

Information from: Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-12; Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120:c179-84; Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.

(Gocze 2018; Meersch 2017). Although these trials are limited to a few hundred patients and are not large multi-center populations, these data may help drive further research in biomarker-guided therapy.

TREATMENT OF AKI

The treatment of AKI revolves around eliminating the insult, when possible; providing supportive care, in the form of volume resuscitation, hemodynamic support, medication optimization, and nutrition; and treating associated complications. The most recent consensus guidelines addressing the treatment of AKI were released in 2012 by KDIGO; the updated guidelines have yet to be published. No pharmacologic treatments exist for AKI, and management continues to rely on the principles just described.

Fluid Resuscitation

Volume depletion and shock are common insults that may cause AKI (Montomoli 2019). Resultant altered renal hemodynamics lead to renal hypoperfusion and can cause a pre-renal AKI that, if uncorrected, leads to renal ischemia and intrinsic AKI. Limited data exist to compare fluid resuscitation with placebo. However, the physiologic mechanisms by which fluid resuscitation may be beneficial in AKI have solidified the optimization of fluid status as a staple intervention for AKI. Crystalloid volume resuscitation has been recommended over colloidal resuscitation because of similar outcomes in the need for RRT and mortality, as well as reduced costs (Finfer 2004; Khwaja 2012). In addition, the use of starches has been associated with an increased risk for the development of AKI and recommendations against the use of starches and gelatins have been made (Khwaja 2012).

Controversy exists regarding the type and electrolyte content when choosing a crystalloid solution for volume resuscitation, mainly regarding 0.9% sodium chloride versus balanced crystalloid solutions. One hypothesis is that elevated serum chloride levels, and resultant hyperchloremic metabolic acidosis, imparted by 0.9% sodium chloride infusions increase renal vasoconstriction, which decreases renal cortical perfusion, causes interstitial edema, and contributes to AKI risk (Yessayan 2017). Balanced solutions that contain a significantly lower chloride load are associated with lower rates of hyperchloremia, mortality, AKI, and the need for CRRT (Semler 2018). However, these positive data are limited to single-center cluster-randomized studies. Larger multicenter trials to confirm these effects across a broader patient population are needed. Several retrospective cohort trials in ICUs, postoperative, and mixed medical–surgical populations have shown varying associations for hyperchloremia on the development of AKI (Lombardi 2020; Oh 2018; Sadan 2017).

Although volume resuscitation is an important component of AKI management, volume overload as a result of overaggressive resuscitation may worsen outcomes, including the risk of AKI and mortality (Moore 2018; Salahuddin 2017). A recent systematic review and meta-analysis found an associated increased risk of mortality in patients with AKI, sepsis, or respiratory failure who had fluid overload and positive fluid balance (Messmer 2020). Current recommendations suggest rigorous assessment for volume responsiveness and judicious use of fluid resuscitation (Moore 2018).

The association between fluid type and dose administered with patient outcomes highlights the need to recognize intravenous fluids as drugs. Although fluids are not typically managed by pharmacists, the opportunity exists for pharmacist stewardship with fluid administration to include concentrating fluids, modifying diluents used for drugs, and limiting fluid volumes administered.

Hemodynamic Support

Hypotension is a well-established risk factor for the development of AKI. Increases in the severity or duration of hypotension worsen the risk of AKI and the need for hemodynamic support (Lehman 2010). The current recommendations from the Surviving Sepsis Campaign Guidelines target a MAP of 65 mm Hg or more to increase tissue perfusion and decrease the risk of vasopressor-induced adverse events (Rhodes 2017). However, a specific MAP target has not been established for AKI risk mitigation. One proposal is that higher MAP targets (80–85 mm Hg) may reduce the risk of AKI and the need for RRT in patients with chronic hypertension (Beloncle 2016), but further clinical research is needed to support this target. Consequently, an individualized risk-benefit analysis of the adverse effects associated with increased use of vasopressors and the presence of baseline hypertension is warranted (Asfar 2014).

Avoidance of Nephrotoxins and Antimicrobial Optimization

Nephrotoxins are drugs or substances that cause direct impairment of kidney function. Although a staple intervention for any patient at risk of AKI, avoidance of nephrotoxins can often be complicated by comorbid conditions and acute illnesses that occur in the intensive care setting. It is important to note that although a drug may require dose adjustment in the setting of reduced kidney function to prevent renal accumulation, it may not be a nephrotoxin. Common nephrotoxins include antimicrobials, NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and iodinated contrast media. These drugs should be avoided when possible in patients with or at risk of AKI. As avoidance of nephrotoxins has been discussed in the acute kidney injury chapter of book 2 of the 2017 CCSAP, 2 the remainder of this section will focus on antimicrobials.

Septic patients often require initiation of empiric broad-spectrum antimicrobials, which can include nephrotoxins such as vancomycin, aminoglycosides, acyclovir, and amphotericin. Judicious use and concomitant monitoring of drug therapy is required to prevent AKI and allow for timely

mitigation when AKI occurs. Reports of development of AKI with the combination of vancomycin and piperacillin/tazobactam have heightened concerns with using these antibiotics. Rates of AKI associated with this combination range from 15%–35%, with a rate of about 33% in single-center retrospective cohort study (Karino 2016). The potential for AKI with the individual agents is known, but the mechanism for an increased risk with combination therapy is not yet understood. With increasing awareness of AKI risk, the combination of vancomycin and piperacillin/tazobactam should be avoided in high-risk patients when possible.

The combination of vancomycin and cefepime has been associated with about 50% of the risk of AKI compared with vancomycin and piperacillin/tazobactam in a retrospective cohort study, with only 12.5% AKI developing in the vancomycin and cefepime group versus 21.4% in the vancomycin and piperacillin/tazobactam group (Rutter 2017). Beyond the increased rates of AKI with combination therapy, higher doses of beta-lactam antibiotics are often required to reach the recommended AUC targets (i.e., 2 to 5 times the MIC of the organism) for critically ill patients (Abdul 2020). With the comorbid conditions in this population, in addition to pharmacokinetic changes and risk of infection with resistant pathogens, the AUC targets are often difficult to achieve.

One strategy to optimize therapeutic target attainment without drastically increasing drug doses is to use extended infusion times or continuous infusions. For β-lactam antibiotics, which display time-dependent microbial killing, this strategy has been validated for such drugs as piperacillin/tazobactam, meropenem, and cefepime (Chen 2019). In addition to validation in the general population, extended interval dosing strategies for piperacillin/tazobactam (infusion over 4 hours) and cefepime (infusion over 4 hours) have been demonstrated to achieve the therapeutic target of 2 to 5 times the MIC in patients undergoing CRRT (Philpott 2019; Shotwell 2016). Continuous infusion of antimicrobials such as piperacillin/achieves therapeutic targets and improves outcomes compared with standard infusions (Goncalves-Pereira 2012).

In addition to extended infusion β-lactam antibiotics, antimicrobial dosing optimization has broadened to include the recently published consensus guideline for vancomycin therapeutic monitoring, which proposes use of the AUC/MIC to reduce the risk of vancomycin-induced nephrotoxicity and to maximize clinical efficacy. After the publication of the previous vancomycin dosing guidelines, a meta-analysis by van Hal and colleagues that examined rates of AKI with trough goals of greater than 15 mcg/mL versus less than 15 mcg/mL found that the more intensive vancomycin trough goal increased the risk of AKI (OR, 2.67; 95% CI, 1.95–3.65) (van Hal 2013). These data and other studies have led to the recommendation for AUC-based monitoring to eliminate trough levels as surrogate markers for therapeutic target attainment.

The new recommendations promote an AUC/MIC target of 400–600 mg*h/L and that vancomycin AUC levels less than 400 mg*hour/L lead to vancomycin resistance. The prospective PROVIDE trial demonstrated similar rates of efficacy in AUC groups targeted above and below 650 mg*hour/L with higher rates of nephrotoxicity in the group with the higher AUC goal (Lodise 2020; Rybak 2020). For a therapeutic target in MRSA, AUC/MIC 400–600 mg*h/L is recommended over traditional trough goals of 15–20 mcg/mL to provide safe and effective vancomycin therapy (Rybak 2020). However, these therapeutic targets have not been validated in nonMRSA infections, and the results should be extrapolated cautiously. With the publication of the new guidelines, many institutions are transitioning to AUC/MIC-based dosing from trough-guided dosing to reduce vancomycin exposure and the incidence of vancomycin associated AKI (Rybak 2020). A single-center retrospective analysis characterizing the transition to this dosing strategy from trough-guided dosing reported an OR of 0.52 (95% CI, 0.34–0.80) for development of AKI using AUC/MIC-based dosing versus traditional trough-based dosing (Finch 2017). Although these data are promising, as with trough-guided dosing, AUC/MIC dosing is not ideal for patients with fluctuating kidney function or those requiring RRT. In these scenarios, weight-based dosing with serum concentration monitoring is recommended (Rybak 2020).

Nutrition

Protein-calorie malnutrition is a significant complication in hospitalized patients with AKI. Induced protein hypercatabolism places patients with AKI at high risk of malnutrition and collective recommendations for nutrition support have not radically changed in recent years. As put forth by the 2012 KDIGO guidelines, enteral nutrition is preferred when possible. Table 3 summarizes the recommended daily intake.

For the general critically ill population, the 2016 American Society for Parenteral and Enteral Nutrition/Society of Critical Care Medicine guidelines for nutrition support in

Table 3. 2012 KDIGO Nutrition Recommendations for Patients with AKI

Parameter	Recommendation
Total energy intake	20 –30 kcal/kg/day
Protein intake	
• Noncatabolic, not receiving RRT	• 0.8–1 g/kg/day
• Receiving RRT	• –1.5 g/kg/day
• Hypercatabolic, receiving CRRT	• Up to 1.7 g/kg/day

AKI = acute kidney injury; CRRT = continuous renal replacement therapy; KDIGO = Kidney Disease: Improving Global Outcomes; RRT = renal replacement therapy.

Information from: Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1-138.

the critically ill population recommend calculation of nutritional requirements using indirect calorimetry or, when unavailable, a weight-based calculation of 25–30 kcal/kg/day to estimate energy requirements (McClave 2016). Their recommendations for patients with AKI follow their standard for critically ill patients regarding energy requirements and protein intake (1.2–2 g/kg/day of actual body weight) with special consideration of the need for low phosphorus- and potassium-containing enteral formulas. For patients on hemodialysis or CRRT, the American Society for Parenteral and Enteral Nutrition guidelines recommend increased protein intake up to a maximum of 2.5 g/kg/day to account for loss of amino acids in the RRT effluent (McClave 2016).

Role of Diuretics

Loop diuretics have long been used in patients with AKI. However, data have not been established regarding their efficacy for kidney-related outcomes, including the need for RRT and time to renal recovery. In addition, clinical trials have failed to establish a benefit for the use of diuretics to prevent AKI (Patschan 2019). The 2012 KDIGO guidelines recommend against the use of diuretics to prevent and/or treat AKI, and no recent data have contradicted this recommendation (Khwaja 2012). Therefore, diuretic use in the setting of AKI is limited to management of volume overload. Research is ongoing to address diuretic challenges as a prognostic indicator of AKI. For example, evidence from a small single-center study supports a poor response to a furosemide stress test as a predictor of AKI progression (Rewa 2019). This study defined a poor response as less than 200 mL of urine flow in the 2 hours after administration of 1 mg/kg or 1.5 mg/kg furosemide equivalents for diuretic-naive patients and those with previous diuretic exposure, respectively (Rewa 2019). Further data and clinical validation of such a test is needed to provide recommendations for its use.

Overcoming diuretic resistance during AKI is beyond the scope of this chapter, but strategies to optimize loop diuretic therapy include increasing doses (up to the specific ceiling dose for the agent), modifying frequency based on drug half-life to avoid post-diuretic sodium retention, addition of thiazide-like diuretics, and/or use of continuous infusion loop diuretics.

PHARMACOKINETIC AND PHARMACODYNAMIC ALTERATIONS

Pharmacokinetic Alterations

Acute kidney injury affects pharmacokinetic variables far beyond the elimination of drugs and substances in the urine. Rapid shifts in kidney function and the associated complications can affect most, if not all, of the major pharmacokinetic variables. Table 4 outlines potential pharmacokinetic changes in absorption, distribution, metabolism, and excretion (ADME) that may occur in AKI. However, it should be noted that although these changes may significantly alter ADME, they are often difficult to quantify when applied to drug dosing. In addition, the rapidly changing clinical context of AKI requires constant modification of dosing regimens and leads to high variance in these values.

Table 4. Pharmacokinetic Alterations ADME in Acute Kidney Injury

Pharmacokinetic Process	Change in AKI
Absorption	No change or decreased
Distribution	No change or increased
Metabolism	No change or decreased
Excretion	Renal: decreased Nonrenal: no change or decreased

ADME = absorption, distribution, metabolism, and excretion.

Information from: Roberts DM, Sevastos J, Carland JE, et al. Clinical pharmacokinetics in kidney disease application to rational design of dosing regimens. Clin J Am Soc Nephrol 2018;13:1254-63.

Absorption

Acute kidney injury, especially in the critically ill, may lead to decreased drug absorption through several mechanisms. First, gut edema with fluid overload and impaired motility of the gastrointestinal tract may reduce the absorbed fraction of drug. In addition, the use of concomitant drugs such as gastric acid suppressants for stress ulcer prophylaxis and potassium-binding drugs (i.e., sodium zirconium cyclosilicate) may alter gastric pH and subsequently reduce bioavailability of drugs with pH-dependent absorption. The use of vasopressors for hemodynamic support may lead to intestinal vasoconstriction and decreased perfusion, resulting in decreased bioavailability (Ackland 2000).

Distribution

Critical illness and AKI may significantly modify the Vd, often resulting in an increased Vd. Rapid fluid shifts associated with aggressive fluid resuscitation, impaired elimination of free water, and sepsis-mediated capillary leak may result in an expanded Vd for hydrophilic compounds. For drugs that are highly protein bound, the catabolic and often malnourished state in acute illness and AKI may result in lower serum protein concentrations and therefore a higher fraction of unbound drug.

Metabolism

Impaired metabolism in AKI may result from direct reductions in the ability of the kidney to metabolize and eliminate drugs such as insulin, which undergoes filtration and proximal tubule

Patient Care Scenario

A 74-year-old man (height 72 inches, weight 110 kg [242.5 lb]) is transferred to the ICU from the ED for sepsis secondary to pneumonia. His medical history is significant for hypertension, diabetes mellitus type 2, hyperlipidemia, obesity, and recent treatment with 5 days of azithromycin for community-acquired pneumonia. His home drugs include amlodipine 10 mg, lisinopril 40 mg/day, hydrochlorothiazide 25 mg/day, metformin 1000 mg twice daily, atorvastatin 40 mg/day, and cholecalciferol 1000 units/day, none of which were restarted on admission. In the emergency department he was placed on noninvasive ventilation and started on norepinephrine at 2 mcg/minute with titration guidelines to maintain a MAP 65 mm Hg or more. In addition, treatment was initiated with vancomycin (goal AUC/MIC, 400–600) and piperacillin/tazobactam 3.375 g intravenously every 8 hours administered over 4 hours, and 2 L of normal saline was administered.

On hospital day 3, he is noted to have an increased serum creatinine and an acute decline in his urine output. Vital signs are temperature 98.6 °F (37.0°C), blood pressure 102/58 mm Hg, heart rate 85 beats/minute, and respiratory rate 20 breaths/minute. His pertinent laboratory values continue to worsen through hospital day 5 as follows:

Laboratory Parameter	Admission	Day 2	Day 3	Day 4	Day 5
WBC (× 10^3/mm^3)	24	22	18	15	10
Vancomycin AUC (calculated)	—	—	743	—	—
SCr (mg/dL)	0.84	0.95	1.75	2.54	3.02
Estimated glomerular filtration rate (mL/min/1.73 m^2)	>60	>60	38	25	20
Blood culture	No growth	No growth	No growth	No growth	No growth
MRSA nasal swab	—	—	Negative	—	—

What is the etiology of this patient's AKI? How should this patient's AKI be managed?

ANSWER

The etiology of this patient's AKI is likely multifactorial with prerenal and intrinsic causes. His initial presentation with hypotension and sepsis may have contributed to an initial decline in glomerular filtration rate because of renal hypoperfusion. In addition, as an outpatient he was taking an angiotensin-converting enzyme inhibitor, which was held on admission. This drug may contribute to decreased intraglomerular pressure in combination with systemic hypotension because it prevents angiotensin II-mediated compensatory vasoconstriction of the efferent arteriole. This decrease in compensatory vasoconstriction limits the ability to maintain adequate glomerular capillary pressure. Prompt and temporary discontinuation of lisinopril may have helped mitigate the initial renal insult. In addition, intrinsic nephrotoxicity may have occurred because a calculated AUCs greater than 650 have been associated with AKI. In addition to the elevated vancomycin level, the patient was also co-prescribed piperacillin/tazobactam, a combination associated with increased rates of AKI.

Management of his AKI requires prompt recognition and medical management. Discontinuing vancomycin is appropriate for several reasons, as follows: the potential to cause AKI; accumulation, which is indicated by the elevated AUC; and the negative MRSA nares screen. In addition, because vancomycin will likely still be present in significant serum concentrations with his impaired clearance, alternative empiric therapy for his pneumonia or de-escalation of therapy would be reasonable. Dose adjustments of the antimicrobial regimen should be done with caution because his kidney function is not yet stable and estimation using serum creatinine will not be accurate. Because there is no direct pharmacologic therapy for AKI, evaluation of fluid status and prompt resuscitation with normal saline should be completed. In addition, hemodynamic support should be continued as required to prevent conditions of decreased perfusion, and other potential nephrotoxins should be avoided.

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1-138.
2. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2020;77:835-64.
3. Lodise TP, Rosenkranz SL, Finnemeyer M, et al. The Emperor's New Clothes: prospective observational evaluation of the association between initial vancomycin exposure and failure rates among adult hospitalized patients with methicillin-resistant staphylococcus aureus bloodstream infections (PROVIDE). Clin Infect Dis 2020;70:1536-45.

uptake and degradation (Duckworth 1998). Alternatively, impaired CYP enzymatic degradation in the liver may occur in severe AKI through up-regulation of inflammatory cytokines that cause a decline in liver enzymatic function. Interleukin-6 has been implicated in the down-regulation of CYP isoform enzymatic activity, and its concentration increases sooner in the setting of AKI and sepsis (Dixon 2014). The clinical impact of this enzyme impairment is difficult to quantify but may significantly affect drug clearance.

Excretion

The impact of reduced renal clearance may be the most obvious of the pharmacokinetic changes as a result of AKI. Dosing regimens of drugs that undergo significant renal clearance must be evaluated and altered to avoid accumulation, especially considering the potential impact of reduced nonrenal clearance as previously discussed. Drugs that are primarily eliminated by the kidneys and display linear pharmacokinetics should have a decline in clearance proportional to the decline in kidney function; however, some drugs may undergo compensatory nonrenal clearance when kidney function declines. For example, ciprofloxacin undergoes increased biliary excretion in patients with reduced kidney function and may be difficult to dose based on assessment of kidney function alone (Jones 1997).

Pharmacodynamic Alterations

Pharmacodynamic changes in AKI are generally limited to reduced efficacy at the site of action or toxicity secondary to drug accumulation. Dosing strategies to overcome impaired drug delivery or efficacy at the site of action include increasing dosages and frequency of administration. Drugs that may accumulate and cause toxicity often require dose reduction and/or extension of the dosing interval.

PRINCIPLES OF DRUG DOSING

Estimation of Kidney Function

Estimating kidney function can be difficult in AKI. With common and often wide variations in kidney function, determining renal clearance of drugs or other substances can present a unique challenge. Current formulas used for the estimation of kidney function primarily rely on stable kidney function, and rapid changes in serum creatinine greatly limit their applicability and use. Equations such as Cockcroft-Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration are examples of such kidney function estimation equations that have been validated in patients with stable kidney function (Levey 1999; Levey 2009; Cockcroft 1976). Use of alternative biomarkers such as cystatin C has been proposed to improve the accuracy of characterization of the glomerular filtration rate versus using serum creatinine alone (Inker 2012). Cystatin C is an endogenously produced compound that improves the accuracy of estimated glomerular filtration rate prediction when used in combination with serum creatinine and applied to the chronic kidney disease–Epidemiology Collaboration creatinine-cystatin C equation (Inker 2012). The role of cystatin C in development of drug dosing regimens remains unclear, but cystatin C use led to greater attainment of the vancomycin therapeutic target in one cohort study (Frazee 2014).

Because of the lag time between serum creatinine accumulation and AKI, use of these equations may represent an overestimation of kidney function during an AKI episode or an underestimation of kidney function during the recovery period. For example, a rapid short-term (24-hour) increase in serum creatinine likely represents virtually no filtration during that period because creatinine accumulates as it is generated. In this fluctuant state, characterizing the trend of change in the serum creatinine may be more beneficial than using equations to estimate creatinine clearance.

In a 2018 retrospective analysis of AKI patients who were not receiving RRT but were receiving antimicrobials, adjustment of the antimicrobial dose based on kidney function was only appropriate 80% of cases based on creatinine clearance by the Cockcroft-Gault equation (Awdishu 2018). In addition, the same study found a discordance rate of up to 16% between antimicrobial dosing regimens using alternative kidney function estimation equations compared with Cockcroft-Gault as the standard (Awdishu 2018). Discordance between the estimated kidney function shown by steady state equations versus equations intended for use in patients with changing kidney function (Jelliffe equation) can lead to widely different drug dosing in the setting of acute illness (Jelliffe 2002). It has been suggested that such formulas such as the Jelliffe equation that use two creatinine values in a 24-hour period may provide a more accurate estimation of kidney function in AKI. However, this equation and other equations have not been widely used in clinical practice, and data from the Jelliffe study suggest that use of this equation can result in supratherapeutic drug dosing in a variety of patients (Awdishu 2018).

Alternatively, other methods, including the kinetic estimated glomerular filtration (KeGFR), have been developed to help characterize kidney function during periods of instability (Chen 2013). This equation is derived from several patient-specific variables, including changes in creatinine over time, the rate of creatinine production, and the steady-state creatinine. Although the KeGFR may be useful to provide a more accurate representation of unstable kidney function, its use has not become widespread and strategies for drug dosing using this equation are limited to small pilot studies (Bairy 2020).

Clinical Considerations for Dose Adjustments in Kidney Disease

Major indications for adjusting drugs for reduced kidney function are outlined in the following text; however, but it should be noted that most data surrounding adjustment for kidney function are based on trials of chronic kidney

disease patients. This basis may introduce some confounding because patients with chronic kidney disease can develop compensatory clearance of drugs and solutes through nonrenal mechanisms.

Preventing Toxicity

Prevention of toxicity is the primary concern during periods of AKI for most drugs that undergo significant elimination by the kidneys. This prevention is particularly important for drugs with a narrow therapeutic index, for which accumulation even to a relatively mild extent can result in toxicities. With the difficulty in estimating kidney function in nonsteady state conditions as with AKI, clinical decision-making relies on patient-specific and drug-specific guidelines as well as therapeutic drug monitoring when possible. The ideal characteristics of a drug for administration during AKI would be a wide therapeutic index, a high degree of nonrenal clearance, and a low cost. However, if therapeutic drug monitoring and established dose adjustments exist for reduced kidney function, drugs with a high degree of renal clearance can be used relatively safely.

Maintaining Efficacy

Although dose adjustments often focus on the prevention of toxicity, maintaining drug efficacy must be considered as well, especially in the critically ill population. Drug dose reduction may come at the expense of decreased therapeutic target attainment, and consideration of the patient's clinical status versus risk of drug accumulation is essential. In addition, because kidney function in the acute setting often fluctuates rapidly, increases in the dose or decreases in the dosing interval must be made when kidney function improves. For some drugs (i.e., loop diuretics), the pharmacodynamic effect relies on delivery of the drug to the lumen of the renal tubules by secretion. In these situations, the dose must be increased to maintain therapeutic efficacy in individuals with reduced kidney function.

Dose Modification vs. Interval Extension

Adjustments in drug regimens for reduced kidney function can be accomplished by two methods—dose reduction and/or interval extension. Considering the pharmacodynamics and pharmacokinetics of the drug in question is integral in determining which method to use. The primary consideration, in the case of antibiotics, is the mode of microbial killing. For concentration-dependent antibiotics such as aminoglycosides or fluoroquinolones, it is preferable to maintain peak concentrations, and thus would require similar dosages. To achieve adequate clearance and prevent drug accumulation in this situation, the dosing interval would need to be extended. Conversely, for antimicrobials relying on time above MIC to exert their antimicrobial effect (i.e., β-lactams), interval extension would lead to therapeutic concentrations falling below the required MIC for the organism. For these drugs, modifying the dose and maintaining the same dosing interval would prevent accumulation. However, patients for whom kidney function is extremely poor, both methods may be required to prevent accumulation and toxicity. These points illustrate the importance of clinical judgement that considers the clinical status of the patient in conjunction with drug characteristics and disposition.

INDICATIONS FOR RRT

The indications for RRT are often indicated by the mnemonic *AEIOU*, as follows: metabolic acidosis (pH less than 7.1), electrolyte imbalance (hyperkalemia), intoxication (for drugs with characteristics that make removal by RRT likely), volume overload, and uremia that are refractory to medical management. Initiating RRT early may allow better fluid and electrolyte management and uremic/toxin removal to prevent complications such as metabolic encephalopathy. However, delaying RRT initiation may allow time to recognize stabilization or recovery of kidney function before RRT is initiated. The KDIGO guideline suggests starting RRT for AKI classification stage 3 (see Table 2) (Khwaja 2012).

Timing of RRT Initiation

Some indirect evidence showed early RRT initiation had potential survival benefits (Vaara 2014; Bagshaw 2009; Gibney 2008). However, several multicenter, randomized, controlled trials found no significant difference in mortality between early and delayed initiation of RRT (STARRT-AKI Investigators 2020; Barbar 2018; Gaudry 2016). The AKIKI Study showed no significant difference in overall survival at day 60 between early and delayed initiation of RRT, with mortality rates of 48.5% and 49.7% (p=0.8), respectively (Gaudry 2016). They observed that 49% of the delayed RRT cohort did not receive any RRT. Catheter-related bloodstream infections were higher in the early RRT cohort (10%) than in the delayed RRT cohort (5%; p=0.03). In addition, the IDEAL-ICU Trial Investigators found no significant difference between an early RRT group (initiation within 12 hours after AKI) compared with a delayed RRT group (initiation after 48 hours of AKI) in overall mortality at 90 days (Barbar 2018). Lastly, STARRT-AKI Investigators have conducted a multinational, randomized, controlled trial (STARRT-AKI Investigators 2020). The early intervention group initiated RRT within 12 hours of AKI, whereas RRT was discouraged in the standard group unless conventional indications developed or AKI persisted for more than 72 hours. The mortality rate was 44% in both the early intervention and the standard groups at 90 days (RR, 1.00; 95% CI, 0.93 to 1.09; p=0.9). A higher rate of adverse events were reported in the early intervention group (23.0%) compared with the standard group (16.5%; p<0.001). The optimal timing of RRT initiation for AKI is still undefined and controversial in both the 2012 KDIGO AKI guidelines and recommendations from the 2020 KDIGO AKI Controversies Conference, with the latter supporting evaluation of the complication risks, potential for

recovery, fluid status, and global prognosis, as well as patient preferences when deciding to initiate RRT (Ostermann 2020; Khwaja 2012).

Modalities: IHD vs. CRRT vs. Hybrid RRT

Three RRT modalities are commonly used in critically ill patients with AKI: 1) IHD; 2) CRRT; and 3) hybrid RRT. *Intermittent hemodialysis* is a process of RRT in which blood and dialysate are perfused on opposite sides of a semipermeable membrane. Solutes are removed predominantly by diffusion from blood to dialysate and volume removal is controlled by the rate of ultrafiltration prescribed. This modality is commonly used as the chronic RRT modality for patients with end-stage kidney disease (ESKD) and typically performed three times weekly. For patients with AKI, IHD may be performed more often, even daily, based on indications for RRT to achieve better fluid and solute control. Drug dosing recommendations for IHD are predominantly derived based on drug disposition in patients with ESKD. This basis is important because critically ill patients with AKI and patients with ESKD have different pharmacokinetic values; critically ill patients may have a higher Vd, lower PB, and higher nonrenal clearance (Jang 2020). Because IHD is not an optimal RRT choice for hemodynamically unstable patients, other RRT modalities such as CRRT and hybrid RRT are preferred in the ICU.

Lower blood and dialysate (if used) flow rates are used with CRRT compared with IHD, and CRRT is intended to run 24 hours/day; however, CRRT interruptions often occur in critically ill patients (see the section on dose delivery and prescription of CRRT). Three different CRRT modalities are available: 1) *continuous venovenous hemofiltration* (*CVVH*); 2) *continuous venovenous hemodialysis* (*CVVHD*); and 3) *continuous venovenous hemodiafiltration* (*CVVHDF*). Solute removal by these modalities depends on convection with CVVH, hemodialysis (primarily diffusion) for CVVHD, and both convection and diffusion for CVVHDF. These CRRT modalities have the slowest effluent flow rates with the longest RRT duration compared with the other RRT modalities (IHD and hybrid RRT). The effluent flow rates include ultrafiltration flow rate for CVVH, dialysate flow rate for CVVHD, and combination of ultrafiltration and dialysate flow rates for CVVHDF. Figure 1, Figure 2, and Figure 3 illustrate the three different CRRT circuits: CVVH, CVVHD, and CVVHDF.

Hybrid RRT is often called *sustained low-efficiency dialysis or prolonged intermittent RRT*. Typically, the flow rates are higher than CRRT but slower than IHD. Duration of hybrid RRT must be considered because a longer treatment will yield a higher drug clearance when all other factors are consistently maintained. Inconsistency with hybrid regimens complicates drug dosing regardless of its advantage, such as planned downtime from RRT for procedures and physical therapy without limiting dialytic treatment. Table 5 summarizes the different characteristics of the available RRT modalities, including blood, dialysate and ultrafiltration flow rates, treatment duration, and frequency.

CONTINUOUS RENAL REPLACEMENT THERAPY

The current KDIGO clinical practice guideline recommends a CRRT dose of 20–25 mL/kg/hour (KDIGO Acute Kidney Injury Work Group 2012) based on two clinical trials that compared

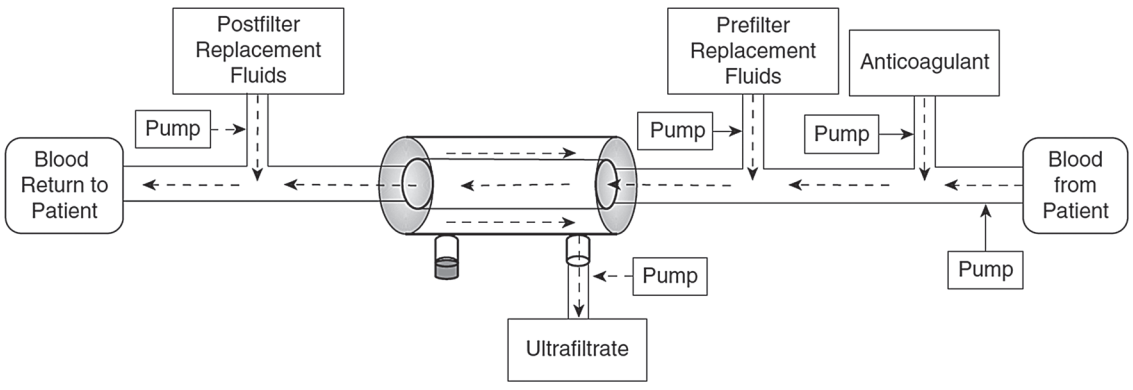

Figure 1. Continuous venovenous hemofiltration (CVVH) circuit incorporating pre- and post-filter replacement fluids. Because CVVH requires the production of a large amount of ultrafiltrate, replacement fluids are added to the circuit.

Reprinted from: Joy MS, Bentley ML, Gist KM. Drug dosing in acute kidney injury and extracorporeal therapies. In: Erstad BL, ed. American College of Clinical Pharmacy. Critical Care Pharmacotherapy. Lenexa, KS: American College of Clinical Pharmacy, 2016:538-69.

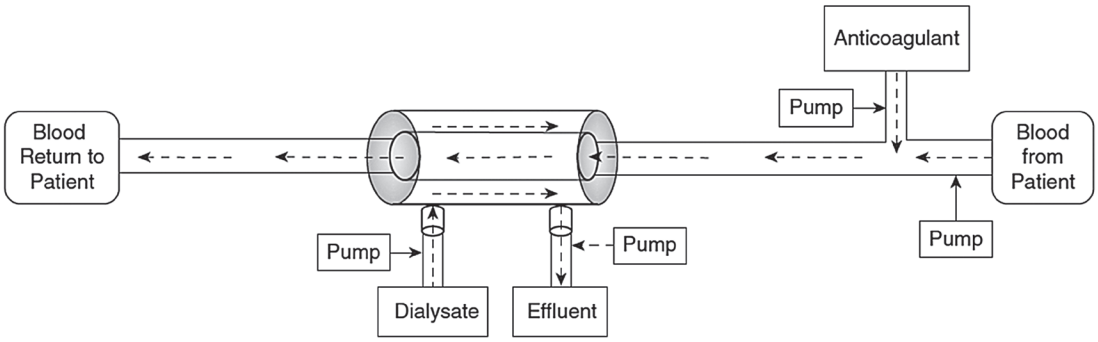

Figure 2. Continuous venovenous hemodialysis circuit, which uses a concentration gradient to remove solute. The resultant fluid is a combination of waste products and spent dialysate.

Reprinted from: Joy MS, Bentley ML, Gist KM. Drug dosing in acute kidney injury and extracorporeal therapies. In: Erstad BL, ed. American College of Clinical Pharmacy. Critical Care Pharmacotherapy. Lenexa, KS: American College of Clinical Pharmacy, 2016:538-69.

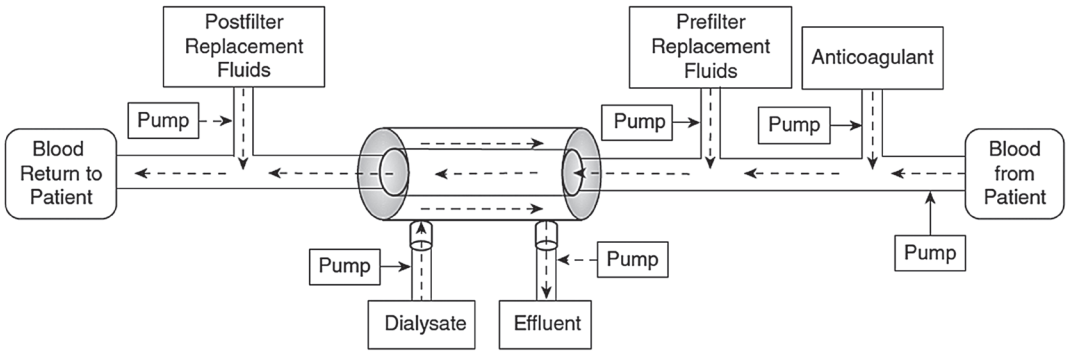

Figure 3. Continuous venovenous hemodiafiltration (CVVHDF). The process of CVVHDF is shown using pre- and post-filter replacement and a dialysate.

Reprinted from: Joy MS, Bentley ML, Gist KM. Drug dosing in acute kidney injury and extracorporeal therapies. In: Erstad BL, ed. American College of Clinical Pharmacy. Critical Care Pharmacotherapy. Lenexa, KS: American College of Clinical Pharmacy, 2016:538-69.

low-intensity CRRT (20–25 mL/kg/hour) with high-intensity CRRT (35 mL/kg/hour). These large multicenter clinical trials—the RENAL Replacement Therapy Study and the VA/NIH ATN Study—showed no mortality benefit between the cohorts (RENAL Replacement Therapy Study Investigators 2009; VA/NIH Acute Renal Failure Trial Network 2008).

Dose Delivered and Prescription of CRRT

The Acute Disease Quality Initiative Consensus Group recommends that clinicians routinely monitor and reassess CRRT dose delivery at least once every 24 hour and modify the dose accordingly (Bagshaw 2016). Clinicians may assess CRRT dose delivery by estimating intensity (mL/kg/hour × the number of treatment hours) or time-averaged delivery (average mL/kg/hour over 24 hour or other duration). This estimation is based on research data supporting that the CRRT prescribed dose often does not match the CRRT delivered dose based on the effluent flow rate (Lyndon 2012; Claure-Del Granado 2011; Macedo 2011). One study that compared the CRRT effluent rate prescribed, the total effluent volume (TEV), and the measured urea nitrogen and creatinine in the effluent found significant differences between the prescribed dose and measured TEV dose ($p<0.001$) (Lyndon 2012). In another study that also compared measured urea clearance to the prescribed CRRT dose based on an effluent rate, the prescribed CRRT dose was overestimated by 23.8%

Table 5. Modalities of RRT

Variable	IHD	Hybrid (PIRRT/SLED)	CRRT
Blood flow rate	250–450 mL/min	150–400 mL/min	150–250 mL/min
Dialysate flow rate	500–800 mL/min	100–300 mL/min	1–3 L/hr for CVVHD and CVVHDF
Ultrafiltrate rate	1–3 L per 3–5 hr	1–4 L per 6–12 hr	1–3 L/hr for CVVH and CVVHDF
Daily duration	3–5 hr	6–12 hr	24 hr
Frequency	3+ times/week[a]	3–7 times/wk	24 hr/day

[a]Typical frequency for end-stage kidney disease is 3 times per week but, more frequent IHD may be required in critically ill with AKI.

CVVH = continuous venovenous hemofiltration; CVVHD = continuous venovenous hemodialysis; CVVHDF = continuous venovenous hemodiafiltration; CRRT = continuous renal replacement therapy; IHD = intermittent hemodialysis; PIRRT = prolonged intermittent renal replacement therapy; RRT = renal replacement therapy; SLED = sustained low-efficiency dialysis.

Information from: Jang SM, Mueller BA. Dosing considerations in patients with AKI and CRRT. Boucher BA, Haas CE, ed. American College of Clinical Pharmacy. Critical Care Self-Assessment Program. Lenexa, KS: American College of Clinical Pharmacy, 2017.

compared with the actual delivered CRRT dose (Claure-Del Granado 2011). These authors recommended measurement of solute clearance to assess CRRT adequacy rather than effluent volume because the effluent volume significantly overestimates delivered CRRT dose.

The current clinical practice guidelines recommend a less-intensive CRRT dose (20–25 mL/kg/hour versus 35 mL/kg/hour) based on survival outcome data (RENAL Replacement Therapy Study Investigators 2009; VA/NIH Acute Renal Failure Trial Network 2008). Clinical outcome showed no difference between a less-intensive versus intensive CRRT dose. Some research findings suggest that the survival outcome is affected by antibiotic concentration because patients receiving high-intensity CRRT may have had lower antibiotic concentrations compared with patients receiving low-intensity CRRT. However, in a study that analyzed antibiotic samples from the RENAL Replacement Therapy Study to determine if CRRT intensity affected antibiotic concentrations, a higher CRRT dose generally did not result in a statistically significant change in antibiotic clearance for ciprofloxacin, meropenem, and piperacillin-tazobactam (RENAL Replacement Therapy Study Investigators 2009). Only vancomycin showed significantly increased CRRT clearance (28 vs. 22 mL/minute; p=0.0003) with higher intensity CRRT (Roberts 2015). This finding is consistent with a 2019 article (Jang 2019) that compared antibiotic exposure (cefepime, ceftazidime, piperacillin/tazobactam, imipenem and meropenem) between two CRRT intensity cohorts from the RENAL Replacement Therapy Study and VA/NIH ATN Study (RENAL Replacement Therapy Study Investigators 2009; VA/NIH Acute Renal Failure Trial Network 2008). Drug pharmacokinetics and demographic information from the RENAL and VA/NIH ATN studies were used to predict antibiotic exposure by a Monte Carlo simulation. Different β-lactam antibiotic regimens, PD targets (1 × MIC vs. 4 × MIC vs. 100% time above the MIC for the free antibiotic concentration), CRRT modalities, and percent of the dose delivered were applied within the model. Conclusions were that a higher CRRT dose did not substantially influence the probability of target attainments.

Anticoagulation in CRRT

The 2012 KDIGO clinical practice guideline for AKI recommends several anticoagulation options during CRRT, including no anticoagulation, regional citrate anticoagulation (RCA), and heparin. The guideline recommends avoiding anticoagulation if the patients cannot use RCA and are at increased bleeding risk. Regional citrate anticoagulation is recommended for patients who are without an increased bleeding risk or impaired anticoagulation and who are not receiving anticoagulation for another indication. However, calcium levels must be monitored and maintained to prevent excessive bleeding. Heparin can be used in patients if RCA is contraindicated and no additional bleeding risks are present such as impaired coagulation or receiving systemic anticoagulation. Typically systemic heparin is used when a patient has another indication for anticoagulation, such as deep vein thrombosis. Table 6 summarizes the KDIGO recommendations and considerations for anticoagulation during CRRT (Khwaja 2012).

DRUG DOSING IN CRRT

Drug dosing in critically ill patients receiving CRRT must account for advancements in CRRT technology. Tertiary drug references may still use pharmacokinetics data from older CRRT equipment and/or hemodiafilter membranes, which may not be applicable in current clinical practice. This lackof consistency may result in inappropriate drug dosing regimens and lead to inadequate drug concentration. Drug clearance during CRRT can be calculated based on the CRRT

Table 6. Anticoagulation in CRRT in the 2012 KDIGO Guideline

Anticoagulation Option	Clinical Considerations
No anticoagulation	• Avoid anticoagulation in patients with increased bleeding risk who cannot use RCA • Ensure patient has a good vascular access, a biocompatible CRRT hemodiafilter, and reduced resistance in the circuit • If patient is receiving CVVH, use pre-dilution replacement fluid to prevent clotting
Regional citrate anticoagulation	• RCA is recommended for: ◦ Patients without increased bleeding risk or impaired coagulation and not receiving effective systemic anticoagulation ◦ Patients with increased bleeding risk and not receiving anticoagulation • Post-filter ionized Ca^{2+} concentration is 0.25–0.5 mmol/L to maintain circuit patency and prevent excessive bleeding • Use systemic Ca^{2+} to maintain ionized Ca^{2+} level of 1–1.2 mmol/L to prevent bleeding • Monitor bicarbonate production, free Ca^{2+} and citrate toxicity • Caution with hepatic injury
Heparin	• Use UFH or LMWH if a patient has a contraindication for RCA and is without increased bleeding risk or impaired coagulation and not receiving effective systemic anticoagulation • Can be given regionally and systemically • Systemic UFH is used if a patient has another indication for anticoagulation, such as deep vein thrombosis • Monitor a prefilter aPTT (45–55 seconds or 1.5 × baseline) and HIT

aPTT= activated partial thromboplastin time; Ca^{2+}= calcium; CRRT = continuous renal replacement therapy; CVVH = continuous venovenous hemofiltration; DVT = HIT = heparin-induced thrombocytopenia; KDIGO = Kidney Disease: Improving Global Outcomes; LMWH = low molecular weight heparin; RCA = regional citrate anticoagulation; UFH = unfractionated heparin.

Information from: Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl 2012;2:1-138; Bentley ML. Continuous renal replacement therapies. In: Boucher BA, Haas CE, eds. American College of Clinical Pharmacy Critical Care Self-Assessment Program. Lenexa, KS: American College of Clinical Pharmacy, 2017.

effluent flow rates and SC/SA, defined as the ability of the drug to cross the membrane.

Principles of Drug Dosing in CRRT

When clinicians develop a dosing regimen in patients receiving CRRT, they must assess and interpret the pharmacokinetic values of the drug and the available literature on drug disposition during the procedure. This section will focus on antibiotic drug dosing because many other drugs used in this population can be titrated to effect, such as sedatives, vasopressors, and pain medications. Table 7 lists 18 elements that should be included in CRRT pharmacokinetic research articles to appropriately calculate a drug dosing regimen and the importance of these elements in developing a drug dosing regimen in CRRT.

Calculating Drug Clearance by CRRT Modality

In general, the slowest rate between blood or the effluent (dialysate plus ultrafiltration) rate is the one that ultimately determines a solute clearance. *Pre-dilution*, defined as when a replacement fluid is administered before the hemodiafilter, and *post-dilution*, defined as when a replacement fluid is administered after the hemodiafilter, CVVH require different equations to calculate drug clearance because pre-dilution CVVH results in decreased drug removal (because of dilution of blood). The ability of the drug to cross the hemodiafilter membrane is described as a *sieving coefficient* or *saturation coefficient*. The SC and SA can range from 0 (drug does not cross the membrane) to 1 (drug freely crosses the membrane), and these coefficients can be used interchangeably in general. When SC or SA information is unavailable for the calculation, it can be estimated as SC = 1 protein binding (PB) because the molecular weight of the drug and its PB influence SC/SA. It is important to note that critically ill patients often have decreased PB compared with healthy patients. Thus, using the PB data derived from critically ill patients to estimate SC/SA is vital. Table 8 shows the equations for a drug clearance among different CRRT modalities. To calculate CVVHDF solute clearance, ultrafiltration flow rate (Q_{uf}) from hemofiltration and dialysate flow rate (Q_d) from hemodialysis need to be combined. Then, these combined flow rates can be called an *effluent rate*, which will be multiplied by SA to determine the drug clearance. For example, in a patient receiving CVVHDF with blood flow rate (Q_b) of 150 mL/minute, Q_{uf} of 1 L/hour and Q_d of 1 L/hour, the Q_b (9 L/hour) is disregarded because the effluent rate (2 L/hour) is slower than Q_b.

Table 7. PK and Patient Data to Assess When Interpreting CRRT Antibiotic PK Literature

Type	Data Element	Importance in Developing a Dose in CRRT
Drug data	Antibiotic assayed	Is this antibiotic concentration- or time-dependent?
	Specified target concentration	Sensitivity patterns differ between organisms—did the serum concentration reported target match your situation?
	Dose recommendation	What PK/PD targets were used by authors to make their dose recommendation? Are these targets that same as your targets?
Patient demographics	Age	Do patients described in the report match your patients, such as pediatric patients vs. older adults?
	Weight	Is the drug dosed using mg/kg or "flat" dosing? Do patients described in the report match your patients?
	Severity of illness	Multiorgan failure will have different PK variables from isolated AKI
	Residual kidney function	Occasionally CRRT is used in nonoliguric fluid-overloaded patients, and CL_{renal} should be added to CL_{RRT}
	Hepatic function	Impaired liver function affects CL_{NR} and PB
Basic PK	Vd	Vd is used to calculate initial/loading dose (dose = target concentration × Vd), which provides an assessment of fluid overload
	CL_{tot}	Required to calculate dosing interval ($CL_{tot} = CL_{RRT} + CL_{non\text{-}RRT}$)
	PB(%)/serum albumin	Only unbound drug can cross the hemodiafilter membrane, and PB usually depends on the patient's serum albumin concentration
CRRT clearance	CL_{CRRT}	CL_{CRRT} should be compared with CL_{tot} to determine if CRRT meaningfully contributes to drug removal
	Mode of CRRT	Clearance of larger drugs is more efficient with convection than diffusion; for convective therapies, site of fluid replacement may affect CL_{CRRT}
	Filter membrane/ surface area	Permeability (approximate pore size) influences CRRT clearance of larger drugs
	SC/SA	Used as a measure of the drug's ability to cross membrane
	Q_b	The slowest flow rate between Q_b and Q_d/Q_{eff} will be a rate-limiting step of CL_{CRRT}; typically Q_d/Q_{eff} is slower than Q_b
	Q_d/Q_{eff}	
	Hct	Hct is used to calculate the plasma flow rate through hemodiafilter. $Q_b(1 - Hct) = Q_p$

AKI = acute kidney injury; CL_{CRRT} = continuous renal replacement therapy clearance; CL_{NR} = nonrenal clearance; CL_{renal} = renal clearance; CL_{tot} = total body clearance; CRRT = continuous renal replacement therapy; PB = protein binding; PD = pharmacodynamics; PK = pharmacokinetics; Q_b = blood flow rate; Q_{eff} = effluent flow rate; Q_p = plasma flow rate; SC = sieving coefficient; SA = saturation coefficient; Vd = volume of distribution.

Reprinted from: Jang SM, Mueller BA. Dosing considerations in patients with AKI and CRRT. Boucher BA, Haas CE, eds. American College of Clinical Pharmacy Critical Care Self-Assessment Program. Lenexa, KS: American College of Clinical Pharmacy, 2017.

If a solute has a PB of 0.4, then SC/SA can be estimated to be 0.6. Thus, the solute clearance will be 1.2 L/hour [(1 L/hour + 1 L/hour) × 0.6].

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) is common for aminoglycosides and vancomycin in the United States. In 2020, a position paper was published and endorsed by four organizations (including Infection Section of European Society of Intensive Care Medicine and Pharmacokinetic/Pharmacodynamic and Critically Ill Patient Study Groups of European Society of Clinical Microbiology and Infectious Diseases) suggesting TDM to assess antimicrobial concentrations in critically ill adult patients (Abdul-Aziz 2020). A wide inter-patient variability in critically ill patients receiving CRRT was observed with meropenem, piperacillin, tazobactam and ciprofloxacin in the RENAL study (Roberts 2012). The variability in trough concentrations were 6.7-fold for

Table 8. Equations for Calculating Drug Clearance by CRRT

Mode of CRRT	Calculation of CRRT Clearance	Predominant Solute Removal Process
CVVH pre-dilution	$CL_{CVVH(pre)} = Q_{eff} \times SC \times \left(\frac{Q_b}{Q_b + Q_{rep}}\right)$	Convection
CVVH post-dilution	$CL_{CVVH(post)} = Q_{eff} \times SC$	Convection
CVVHD	$CL_{CVVHD} = Q_d \times SA$	Diffusion
CVVHDF	$CL_{CVVHDF} = (Q_{uf} + Q_d) \times SA$	Convection + diffusion

CVVH (pre) = pre-dilution continuous venovenous hemofiltration; CVVH (post) = post-dilution continuous venovenous hemofiltration; CVVHD = continuous venovenous hemodialysis; CVVHDF = continuous venovenous hemodiafiltration; SA = saturation coefficient; SC = sieving coefficient; Q_b = blood flow rate; Q_d = dialysate flow rate; Q_{eff} = effluent flow rate; Q_{rep} = replacement fluid rate; Q_{uf} = ultrafiltration rate.

Adapted from: Jang SM, Mueller BA. Dosing considerations in patients with AKI and CRRT. Boucher BA, Haas CE, eds. American College of Clinical Pharmacy Critical Care Self-Assessment Program. Lenexa, KS: American College of Clinical Pharmacy, 2017.

meropenem, 3.8-fold for piperacillin, 10.5-fold for tazobactam, and 3.9-fold for ciprofloxacin. Overall, 15% of dosing intervals (n=40) did not achieve the antibiotic therapeutic targets. The data showed that 40% did not achieve the higher target concentrations whereas 10% exceeded the target concentrations in critically ill patients receiving CRRT. In addition, in a retrospective study that assessed the influence of β-lactam TDM in a tertiary ICU, TDM identified a necessary dose change in 35% of patients (Economou 2017). Most of these CRRT patients had excessive β-lactam concentrations. Thus, clinicians should be aware of a wide inter-patient variability with β-lactams. The experts strongly suggest the use of personalized dosing and TDM when using β-lactams in critically ill patients (Guilhaumou 2019). However, ability to do TDM for β-lactams is limited in most clinical practice areas in United States.

CONCLUSION

Acute kidney injury is a complex syndrome that affects many aspects of patient care and management of acute illness. It is associated with increased mortality, hospital length of stay, and health care costs. Defining and detecting AKI, determining the etiology, and providing supportive care are paramount in the treatment of this syndrome. Drug dosing for patients with AKI receiving CRRT are one of the most challenging endeavors for a critical care pharmacist. The pharmacokinetic and pharmacodynamic changes in this special population are highly specific and complex. The principles, drug dosing considerations, and calculations outlined in this chapter can be used to care for patients with AKI who are either receiving or not receiving CRRT and nonantibiotic drugs.

Practice Points

Acute kidney injury is a complex syndrome that can significantly impact patient outcomes. Prompt recognition and management is necessary to reduce negative outcomes and optimize medication therapy. This management is achieved through therapeutic interventions that include the following:

- **Determination of the severity and etiology of the AKI for swift therapeutic intervention to correct the underlying cause and promote renal recovery.**
- **Early detection and treatment of AKI using biomarker-guided care plans may be reasonable in patients with high risk of AKI, specifically the surgical population; however, more data are needed to validate the widespread use of this intervention.**
- **Although no direct pharmacologic interventions are available to treat AKI, supportive care, including fluid replacement and hemodynamic support, is paramount. Crystalloid fluid replacement with 0.9% sodium chloride is preferred over colloid fluid replacement. Maintenance of a MAP greater than 65 mm Hg using vasopressors selected based on the patient's clinical scenario is recommended.**
- **Diuretic use in AKI should be limited to management of volume overload because few data to support the use of diuretics to prevent or treat AKI.**
- **Avoidance of nephrotoxins and optimization of therapeutic regimens to attain therapeutic targets are key interventions that pharmacists can perform to improve outcomes in AKI.**
- **Although AKI impacts pharmacokinetic variables beyond the renal elimination of drugs, these changes are difficult to quantify. If possible, however, quantification may lead to significant changes in drug clearance.**
- **Estimation of creatinine clearance (a surrogate for glomerular filtration rate) in the setting of rapidly fluctuating kidney function can be difficult. Traditional methods rely on stable kidney function and should be avoided. Modified equations using several serum creatinine values or direct measurement of creatinine clearance may be considered but clinical judgement should be used when interpreting the results.**
- **Therapeutic index, risk of toxicity, and clinical situation should be considered to determine when, why, and how to perform renal dose adjustments. Interval extension and/or dose reduction of the drug should be considered based on the pharmacokinetics and pharmacodynamics.**

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Self-Assessment Questions

Questions 1 and 2 pertain to the following case.

K.D. is a 74-year-old man (height 70 inches, weight 85 kg [187.4 lb]) admitted with sepsis secondary to presumed bacteremia. Because he is hypotensive requiring pressors, K.D. is given 2 L of intravenous 0.9% sodium chloride; he also is promptly started on empiric antibiotics. K.D.'s baseline SCr from an outpatient visit 1 month ago is 0.94 mg/dL; today, his SCr is 3.26 mg/dL. K.D.'s urine output in the past 6 hours has been 200 mL.

1. According to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, which one of the following best classifies K.D.'s acute kidney injury (AKI)?

   A. Stage 1
   B. Stage 2
   C. Stage 3
   D. End-stage kidney disease

2. K.D. has a mean arterial pressure (MAP) of 60 mm Hg on norepinephrine running at 4 mcg/minute. He is started on empiric vancomycin (dosed by pharmacy) and piperacillin/tazobactam 3.375 g intravenously every 8 hours (administered over 4 hours). K.D.'s home drugs include metoprolol succinate 25 mg/day, lisinopril 40 mg/day, atorvastatin 40 mg/day, and cholecalciferol 2000 units/day. Currently, all his drugs are held. Which one of the following is the most likely cause of K.D.'s AKI?

   A. Obstructive nephropathy
   B. Acute interstitial nephritis
   C. Vancomycin induced nephrotoxicity
   D. Pre-renal AKI

3. A 54-year-old woman is admitted to the medical ICU for acute respiratory failure requiring intubation. On admission, vancomycin and piperacillin/tazobactam are initiated for empiric pneumonia treatment. On day 3 of admission, the patient's SCr begins to increase from a baseline of 0.7 mg/dL to 1.5 mg/dL. Urine output has declined to 400 mL in the past 24 hours but on examination she has 3+ pitting edema of both lower extremities. The patient's MAP remains more than 65 mm Hg without vasopressor support and her heart rate is 85 beats/minute. Blood and sputum cultures remain negative. Which one of the following is best to recommend for this patient?

   A. Discontinue vancomycin.
   B. Stop scheduled vancomycin and obtain a random vancomycin level before redosing.
   C. Discontinue vancomycin and transition to alternative MRSA coverage.
   D. Administer 25 g of intravenous albumin.

4. A critically ill 83-year-old woman is admitted to the ICU from the intermediate unit for respiratory failure secondary to hospital acquired pneumonia. On admission she has a positive MRSA screen, and the decision is made to place the patient on vancomycin and piperacillin/tazobactam. She was hypotensive but has improved after a 1000 mL bolus of 0.9% sodium chloride. Which one of the following is best to recommend to reduce this patient's risk of AKI?

   A. Transition to gentamicin and linezolid.
   B. Dose vancomycin using AUC-based monitoring with a goal AUC:MIC of 650.
   C. Change piperacillin/tazobactam to extended-infusion cefepime and metronidazole.
   D. Begin a continuous furosemide infusion and add metolazone 5 mg orally daily.

5. A 39-year-old man (height 65 inches, weight 120 kg [264.5 lb]) is admitted for bacteremia secondary to intravenous drug use and suspected endocarditis. He is initiated on vancomycin 2 g intravenously every 8 hours. The patient's SCr on admission was 0.7 mg/dL; today (36 hours later), his SCr has increased to 2.1 mg/dL. A random vancomycin level drawn 8 hours after his last dose was 42 mcg/mL. Which one of the following CrCl values best represents this patient's current kidney function?

   A. 41 mL/minute
   B. 120 mL/minute
   C. Less than 20 mL/minute
   D. 57 mL/minute

6. A critically ill 54-year-old man has a KDIGO stage 3 AKI and is becoming severely fluid overloaded. He has bilateral 3+ pitting edema of his extremities and a recent chest radiography exhibits mild pulmonary edema. Nephrology is consulted and wants to attempt diuresis before resorting to RRT. Which one of the following is best to recommend for this patient?

   A. Torsemide 20 mg intravenously once
   B. Furosemide 80 mg intravenously every 6 hours
   C. Bumetanide 1 mg/day orally
   D. Chlorothiazide 500 mg intravenously for 1 dose and furosemide 40 mg orally

7. Drug X was recently approved by the FDA under an emergency use authorization to treat coronavirus disease 2019 pneumonia. The mechanism of the drug relies on peak concentrations to exhibit its antiviral effects. There are few data regarding dose adjustments for reduced kidney function; however, pharmacokinetic data reveals that it is primarily excreted via the kidneys (about 80%)

and you would like to perform a pharmacokinetic study in patients with reduced kidney function (estimated glomerular filtration of 30–60 mL/minute/1.73 m^2). Which one of the following dose adjustment methods is best to use on the patients enrolled in your study?

A. Interval extension
B. Dose reduction
C. Interval reduction
D. Dose increase

8. You receive a vancomycin dosing consult for a patient admitted to your ICU. The patient is a 74-year-old man (height 68.5 inches, weight 80 kg [176.3 lb]) admitted with diabetic ketoacidosis and MRSA bacteremia from a central line that was inserted for outpatient treatment of osteomyelitis. On receiving the consult, the patient's SCr is 1.9 mg/dL. You do not have a baseline value and you are unable to determine if he has a medical history of chronic kidney disease. Which one of the following is the best initial vancomycin dosing strategy to recommend for this patient?

   A. Vancomycin 2 g intravenous load followed by 1250 mg every 36 hours for a predicted AUC of 517 mg*hour/L
   B. Vancomycin 2 g intravenous loading dose followed by a random level with morning labs
   C. Discontinuing vancomycin and initiating linezolid 600 mg intravenously every 12 hours
   D. Vancomycin 1 g intravenously every 36 hours for a predicted trough of 15.9 mcg/mL

9. A man with septic shock is admitted to the ICU. He has an elevated SCr (about 3 mg/dL) and his baseline kidney function is unknown. Considering a scenario in which all drugs have a relatively similar efficacy and available therapeutic drug laboratory monitoring strategies, which of the following characteristics would be best in this patient with unstable kidney function?

   A. Wide therapeutic index, high degree of renal clearance, low cost
   B. Narrow therapeutic index, high degree of nonrenal clearance, high cost
   C. Wide therapeutic index, high degree of nonrenal clearance, high cost
   D. Narrow therapeutic index, high degree of renal clearance, low cost

10. A critically ill 45-year-old woman (weight 75 kg [165.3 lb]) presents with non-*Enterobacteriaceae* nosocomial sepsis. She has a small amount of residual kidney function and needs renal replacement therapy and amikacin. The care team discusses how to maximize the amikacin pharmacodynamics by altering the drug administration technique. Which one of the following plans for administration of amikacin would be best to recommend to meet pharmacodynamic targets for this patient?

    A. Continuous infusion (24-hour infusion)
    B. Delayed infusion (12-hour infusion)
    C. Extended infusion (4-hour infusion)
    D. Intermittent infusion (30-minute infusion)

11. A man receives continuous venovenous hemodiafiltration (CVVHDF) with an ultrafiltration flow rate at 1 L/hour and a dialysate flow rate is running at 2 L/hour. The patient needs a drug (SC 0.9), and the average drug serum concentration is 3 mg/L. Which one of the following best describes how many milligrams of drug are removed in 5 hours in this patient?

    A. 3
    B. 8
    C. 25
    D. 41

12. A 55-year-old man is scheduled to start CVVHD this afternoon. The patient has no pertinent medical history. The medical team found no increased bleeding risk or impaired coagulation. The patient's hepatic function is within normal range. Which one of the following is best to recommend for this patient's anticoagulation?

    A. No anticoagulation is needed.
    B. Start regional citrate anticoagulation.
    C. Start regional anticoagulation using unfractionated heparin.
    D. Start systemic anticoagulation using unfractionated heparin.

13. A 60-year-old man (weight 66 kg [145.5 lb]) receives fluid resuscitation for septic shock. Six hours later, his weight is 76 kg [167.6 lb], and he is receiving high-dose norepinephrine, resulting in anuria. The patient is receiving CRRT, and the care team wants to start cefepime (time-dependent antibiotic) which has Vd of 0.5 L/kg, free fraction of 0.79, nonrenal clearance of 24 mL/minute, and sieving coefficient (SC) of 0.9 in critically ill patients. Which one of the following is the best cefepime dosing to recommend for this patient?

    A. 2 g loading dose, then 1 g every 12 hours
    B. 2 g as a continuous infusion
    C. 1 g every 24 hours
    D. 500 mg every 8 hours

14. A 55-year-old woman (weight 85 kg [187.3 lb]) who is granulocytopenic has AKI and needs CRRT. The care team wants to initiate meropenem (time-dependent drug) and wants the serum concentration to stay above the organism MIC of 2 mg/L for 24 hours/day while avoiding toxicity. To meet the pharmacodynamic targets, which one of the following is the best meropenem infusion and loading dose strategy to recommend for this patient?

    A. Continuous infusion with loading dose
    B. Continuous infusion without loading dose
    C. Intermittent infusion with loading dose
    D. Intermittent infusion without loading dose

15. A woman (weight 80 kg [176.3 lb]) is receiving CVVHD at a Q_{eff} of 40 mL/minute. The patient does not have native renal clearance. She also receives piperacillin/tazobactam 4.5 g every 8 hours (4:00 a.m., noon, 8:00 p.m.). The patient is scheduled to go to surgery tomorrow at 6:00 a.m. She is likely to be off CVVHD for at least 12 hours. It is the evening before the surgery. Which one of the following is best to recommend for this patient's CVVHD interruption?

    A. Discontinue piperacillin/tazobactam after the 8:00 p.m. dose before surgery and reinitiate when CVVHD is restarted.
    B. Discontinue piperacillin/tazobactam after 4:00 a.m. dose on the morning of surgery and reinitiate when CVVHD is restarted.
    C. After the 4:00 a.m. dose on the morning of surgery, give the next dose at 4:00 p.m.
    D. Make no changes; maintain piperacillin/tazobactam at 4.5 g every 8 hours.