

Principles of Estimating Renal Clearance, Acute Kidney Injury, and Renal Replacement in the Critically Ill Patient

Michael L. Bentley, Pharm.D., FCCP, FCCM, FNAP

Carilion Clinic
Roanoke, Virginia

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Learning Objectives

1. Discuss the limitations of using measured creatinine to estimate creatinine clearance (CrCl).
2. Understand how CrCl and glomerular filtration rate differ.
3. List common equations used to estimate CrCl.
4. Define acute kidney injury (AKI).
5. List common categories and give examples of drug-induced AKI.
6. With respect to renal replacement therapy, define diffusion and convection and describe their role in blood purification.
7. Discuss the role of dialysate and replacement fluids in continuous renal replacement therapy (CRRT).
8. Describe drug-dosing concepts in CRRT and sustained low-efficiency dialysis/extended daily dialysis.

Abbreviations in This Chapter

ACEI	Angiotensin-converting enzyme inhibitor
ADQI	Acute Dialysis Quality Initiative
AIN	Acute interstitial nephritis
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ARB	Angiotensin receptor blocker
ARF	Acute renal failure
ATN	Acute tubular necrosis
CG	Cockcroft-Gault (equation)
COX-2	Cyclooxygenase-2
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cr	Creatinine
CRRT	Continuous renal replacement therapy
CVVH	Continuous venovenous hemofiltration
CVVHD	Continuous venovenous hemodialysis
CVVHDF	Continuous venovenous hemodiafiltration
EDD	Extended daily dialysis
GFR	Glomerular filtration rate
ICU	Intensive care unit
IHD	Intermittent hemodialysis
MDRD	Modification of Diet in Renal Disease (study)
MW	Molecular weight
NSAID	Nonsteroidal anti-inflammatory disease

RRT	Renal replacement therapy
RIFLE	Risk, injury, failure, loss, end-stage renal disease
SLED	Sustained low-efficiency dialysis
Vd	Volume of distribution

Self-Assessment Questions

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

Questions 1–3 pertain to the following case.

G.W. is a 42-year-old obese man (height 64 inches, weight 112 kg) with stable chronic kidney disease (CKD). His creatinine clearance (CrCl) is estimated using the Cockcroft-Gault (CG) equation.

1. Which is one of the most important considerations when using this equation?
 - A. CG does not account for the sex of a patient.
 - B. Strongly consider using adjusted body weight in the calculation because this patient is obese.
 - C. CG can be used only if IDMS (isotope dilution mass spectroscopy)-standardized creatinine (Cr) is used.
 - D. CG is only validated to estimate CrCl in patients with acute kidney injury (AKI).
2. G.W.'s CrCl is estimated using the Modification of Diet in Renal Disease (MDRD) study equation. Which is one of the most important considerations when using this equation?
 - A. It has been studied and validated in patients with stable CKD.
 - B. It has been studied and validated in elderly patients (those older than 70 years).
 - C. In patients with glomerular filtration rates (GFRs) greater than 60 mL/minute per 1.73m², it overestimates clearance.
 - D. Compared with CG and measured CrCl, the MDRD study equation overestimates clearance.
3. G.W.'s CrCl is estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Which depicts one of the most important considerations when using this equation?

- A. It has been studied and validated in patients with AKI.
 - B. It has been studied and validated in patients who are 12 years or older but younger than 70 years.
 - C. It uses serum creatinine (SCr), age, and race, but not sex, in its calculation.
 - D. Compared with MDRD, it is more accurate when the GFR is greater than 60 mL/minute per 1.73m².
- 7. E.R. continues to worsen. He is now febrile with an increasing white blood cell count (WBC). You are asked to dose cefepime while he is receiving CVVH. Which would be the best place to begin looking for dosing recommendations?
 - A. Intermittent hemodialysis (IHD) guidelines.
 - B. Package insert.
 - C. Primary literature/dosing summaries.
 - D. Estimates using an estimated sieving coefficient.

Questions 4–7 pertain to the following case.

E.R. is a 67-year-old man admitted to your intensive care unit (ICU) several days ago with acute respiratory failure. He required mechanical ventilation and was placed on empiric antibiotics to cover likely community-acquired pneumonia. During the past 5 days, his renal function has worsened (SCr on admission 0.6 mg/dL; today, 2.4 mg/dL). He now requires renal replacement with continuous venovenous hemofiltration (CVVH). Current medications include ceftriaxone, azithromycin x 2 doses only, enoxaparin, and ranitidine. As a pharmacist, you are asked to evaluate E.R. for a possible cause of drug-induced AKI. You determine that the most likely drug is ceftriaxone.

- 4. Through which mechanism is ceftriaxone most likely to cause AKI?
 - A. Acute tubular necrosis (ATN).
 - B. Acute interstitial nephritis (AIN).
 - C. Glomerulonephritis.
 - D. Tubular precipitation.
- 5. Using the AKIN staging, which best describes the stage of AKI that E.R. is in?
 - A. Stage 1.
 - B. Stage 2.
 - C. Stage 3.
 - D. Unable to determine because urine output is not provided.
- 6. Which best describes the principle for clearance used for solute removal during CVVH?
 - A. Convection.
 - B. Diffusion.
 - C. Both convection and diffusion.
 - D. Membrane binding.
- 8. Which drug property is most important to consider when estimating whether a drug will be removed by continuous renal replacement therapy (CRRT)?
 - A. Protein binding.
 - B. Molecular weight (MW).
 - C. Volume of distribution (Vd).
 - D. Drug charge.

I. MEASUREMENT OF KIDNEY FUNCTION

A. Measuring GFR

1. Several exogenous compounds can be used to measure GFR, but they have limited clinical application, given their technically difficult administration technique, limited availability, and cost.
2. Although they are a less accurate measure of GFR, endogenous substances (i.e., Cr) are used clinically.
3. Estimated GFR urinary clearance of Cr can be determined by collecting urine over a 24-hour or shorter period. However, this, too, has limited utility, given the frequent collection errors and delay in results.

B. Limitations to Using SCr for Estimating GFR

1. Measured SCr is the product of what is produced and what is excreted. Cr is a byproduct of muscle metabolism and is influenced by muscle mass and diet, which may vary between individuals and affect estimated clearance.
2. Reaching a steady-state SCr concentration is often unpredictable in critically ill patients because the Cr production rate, its Vd, and the elimination rate may vary, further complicating drug-dosing estimates when SCr is used to estimate clearance.

C. Estimating CrCl (Table 1)

1. CG equation
 - a. Although several equations for estimating CrCl have been proposed, CG has historically been used.
 - b. Using body weight would seem logical, given the relationship between muscle metabolism and Cr production. However, for patients who are overweight, obese, or morbidly obese, using total body weight will likely overestimate CrCl. Although a consensus has not been reached, using an adjusted weight (with a factor of 0.4) provides a more accurate measurement, compared with Cr collected over 24 hours, than actual or ideal body weight in this patient group.
2. The MDRD study equation (estimated glomerular filtration rate [eGFR])
 - a. This equation was developed from a sample of patients with CKD using the urinary clearance of ^{125}I iothalamate.
 - b. It has been validated in a wide population, including whites and African Americans, between 18 and 70 years of age with reduced renal function (less than 60 mL/minute per 1.73m^2). However, these results should be interpreted with caution because most studies do not compare actual clearance.
 - c. In individuals with GFRs greater than 60 mL/minute per 1.73m^2 , the MDRD equation underestimates measured GFR.
 - d. MDRD should not be used when SCr is unstable (i.e., in hospitalized patients with rapidly changing renal function or in those with AKI).
3. CKD-Epidemiology Collaboration (CKD-EPI) Equation
 - a. CKD-EPI uses the same four variables (SCr, age, sex, and race) as the MDRD Study equation for predicting GFR in adults ≥ 18 years of age and has been shown to be more accurate when GFR is > 60 ml/min per 1.73 m^2 than MDRD.
 - b. Similar to the MDRD Study equation, and other equations used to estimate GFR from SCr, CKD-EPI should be used with caution in patients with non-steady-state creatinine production and elimination and in those with altered production of creatinine (ex., altered diets or muscle mass).
 - c. It has not been adequately validated in the elderly or in African Americans with higher GFR's.

Table 1. Common Equations for Estimating GFR

<p>CockcroftGault $\text{CrCl (mL/min)} = (140 - \text{age (years)} \times \text{weight (kg)} \times 0.85 [\text{female}]) / (\text{SCr (mg/dL)} \times 72)$</p> <p>MDRD (four-variable) study equation $\text{GFR (mL/min per } 1.73\text{m}^2) = 186.3 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 [\text{African American}] \times 0.742 [\text{female}]$</p> <p>MDRD (four-variable) study equation using IDMS SCr $\text{GFR (mL/min per } 1.73\text{m}^2) = 175.6 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 [\text{African American}] \times 0.742 [\text{female}]$</p> <p>CKD-EPI^a $\text{GFR}\alpha \text{ (mL/min per } 1.73\text{m}^2) = 141 \times \min(\text{SCr}/k, 1)^\alpha \times \max(\text{SCr}/k, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.159 [\text{black}] \times 1.018 [\text{female}]$</p>

Abbreviations: CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; CrCl, creatinine clearance; GFR, glomerular filtration rate; IDMS, isotope dilution mass spectroscopy; MDRD, Modification of Diet in Renal Disease

^aFor CKD-EPI, k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min is the minimum of SCr/k or 1, and max is the maximum of SCr/k or 1 and age is years.

D. Considerations for Drug Dosing

1. CKD: In patients with reduced kidney function, a dose adjustment in renally eliminated medications may be necessary. Information is often conflicting between what is recommended by the manufacturer and what is found in the postmarketing studies.
 - a. Drug-dosing recommendations: In 2010, the National Kidney Disease Education Program recommended that for adults, drug dosing be based on either the MDRD study equation (eGFR) or CrCl using the CG equation.
 - b. For very large or small patients, the eGFR should be multiplied by the estimated body surface area to give the eGFR in milliliters per minute.
2. AKI
 - a. Drug dosing in critically ill patients with AKI has been problematic. Several issues are unique to this population, including (1) rapid changes in SCr and the time needed to reach a new steady-state concentration; (2) influence of aggressive volume resuscitation – increased Vd; (3) increase in Cr secretion in early AKI; (4) increased non-renal clearance; (4) lack of evidence-based dosing; and (5) influence of renal replacement therapies (RRTs).
 - b. There is growing evidence that AKI alters the non-renal clearance of several medications. It is likely that the cytochrome P450 (CYP) enzymatic pathways of several organs are involved, as are uptake and efflux transporters. The impact of altered pathways on drug dosing is in its early stages of development. Currently, there are no global adjustment recommendations; however, the pharmacist should be aware that drug-specific data might be limited.

Patient Cases

1. R.J. is a 42-year-old man admitted to your ICU with septic shock. Before this admission, he had been healthy, taking no chronic medications. An initial basic metabolic panel showed an SCr of 2.2 mg/dL and a blood urea nitrogen (BUN) of 20 mg/dL. You wish to estimate his CrCl. Which best describes some of the limitations to using R.J.'s current SCr?
 - A. There are no limitations.
 - B. Drug-dosing recommendations consider acute changes in renal function.
 - C. R.J.'s SCr is likely not at steady state.
 - D. The laboratory will likely be unable to report a value, given R.J.'s acute change.

2. S.B. is a 69-year-old African American woman with a history of diabetes, hypertension, and stable CKD. You wish to estimate her CrCl for drug dosing. Which equation is most appropriate?
 - A. CG.
 - B. MDRD.
 - C. Either CG or MDRD.
 - D. CKD-EPI.

II. ACUTE KIDNEY INJURY**A. Epidemiology**

1. Defining the incidence of AKI has been a limiting factor in moving patient care and research forward. Reasons why this has been problematic include varying causes of and dissimilarities among those developing acute renal failure (ARF) and timing of onset.
2. Patients presenting with ARF at the time of hospital admission is uncommon, accounting for about 1% of hospital admissions; however, community-acquired ARF has been poorly studied.
3. Hospital-acquired AKI, although more common than community-acquired AKI, occurs infrequently (i.e., in 1.9%–7% of patients admitted to a medical center, except in elderly patients, for whom AKI has been reported to be as high as 60%).
4. Critically ill patients are at greatest risk of AKI.
 - a. ARF has been estimated to occur in 20%–30% of all patients admitted to an ICU.
 - b. Severe sepsis and septic shock are common causes of ATN, which is a leading cause of AKI in critical illness.
 - c. Other common risk factors include use of intravenous radiocontrast agents, major surgery (especially cardiothoracic), nephrotoxic medications, and chronic medical conditions (e.g., history of CKD, congestive heart failure, and diabetes mellitus). Most patients have more than one risk factor.

B. Definitions (Table 2a and 2b)

1. During the past several decades, many definitions have been used to define ARF, making it difficult to compare patient populations across studies. In 2002, the Acute Dialysis Quality Initiative (ADQI) workgroup developed the RIFLE (risk, injury, failure, loss, end-stage renal disease) definition and staging system.
 - a. RIFLE categorizes ARF into three grades of increasing severity and two clinical outcomes.

- b. For the acronym RIFLE, “risk” is defined as oliguria for more than 6 hours or an increase in SCr to 1.5 times baseline or greater. As renal function continues to worsen, the criteria for “injury” and “failure” are met. Clinical outcomes (“loss” and “end-stage renal disease”) are defined by the need for RRT for more than 4 weeks and more than 3 months.
2. According to emerging data suggesting that small changes in renal function (SCr of 0.3 mg/dL or greater) lead to worse outcomes, the ADQI workgroup formed the Acute Kidney Injury Network (AKIN).
 - a. This group defined AKI, using a staging system of 1–3, as a reduction in kidney function that occurs over no more than 48 hours using measures of SCr and urine output.
 - b. Stage 1 is an absolute increase in the SCr level of 0.3 mg/dL or greater or a relative increase to 1.5- to 2-fold above baseline or documented oliguria less than 0.5 mL/kg/hour for more than 6 hours, despite adequate fluid resuscitation.
 - c. Similar to RIFLE, stages 2 and 3 are met with worsening SCr and urine output.
 - d. The main difference between the two staging systems is that the AKIN definition initially includes a lesser degree of SCr elevation to diagnose AKI.
 - e. In patients requiring RRT, AKIN stage 3 is met regardless of the stage they are in at the time of RRT initiation.
 - f. Several studies have validated these criteria and show that the more severe the RIFLE class or AKIN stage, the worse the clinical outcome.

Table 2a. Criteria for AKI

RIFLE Class	SCr Criteria/GFR	UOP Criteria
R	Increase to 1.5-fold or GFR decrease > 25% from baseline	< 0.5 mL/kg/hour for 6 hours
I	Increase to 2-fold or GFR decrease > 50% from baseline	< 0.5 mL/kg/hour for 12 hours
F	Increase to 3-fold, GFR decrease > 75% from baseline or SCr ≥ 4 mg/dL (acute increase of at least 0.5 mg/dL)	< 0.3 mL/kg/hour for 24 hours or anuria for 12 hours
L	Complete loss of function for > 4 weeks	
E	Complete loss of function for > 3 months	

Table 2b. Criteria for AKI

AKIN Stage	SCr Criteria	UOP Criteria
1	Increase to 1.5- to 2-fold above baseline or by 0.3 mg/dL	< 0.5 mL/kg/hour for 6 hours
2	Increase to 2- to 3-fold above baseline	< 0.5 mL/kg/hour for 12 hours
3 ^a	Increase > 3-fold above baseline or ≥ 4 mg/dL with an acute rise of ≥ 0.5 mg/dL	< 0.3 mL/kg/hour for 24 hours or anuria for 12 hours

^aIndividuals who receive renal replacement therapy (RRT) are considered to have met the criteria for stage 3, irrespective of the stage they are in at the time of RRT.

AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; RIFLE = risk (R), injury (I), failure (F); loss (L); end-stage kidney disease (E); UOP = urine output.

3. In AKI and CKD, there are many reasons that changes may occur in the function and structure of the kidney. Moreover, even though changes may occur, it is possible that neither the AKI definition nor the CKD definition is met.
 - a. In its 2012 clinical practice guideline, KDIGO (Kidney Disease: Improving Global Outcomes) proposed an operational definition for acute kidney disease (AKD). The purpose was to identify patients with AKD in an attempt to offer therapies to restore kidney function and reverse kidney damage.
 - b. An operational definition of “no known kidney disease” (NKD) was also included for those not meeting other criteria.
 - c. Table 3 provides definitions of AKI, CKD, AKD, and NKD.

Table 3. Definition of AKI, CKD, AKD, and NKD According to Function and Structure

	Functional Criteria (change in SCr, GFR,^a or UOP)	Structural Criteria (damage^b or no damage and duration)
AKI	↑ in SCr by 50% within 7 days Or ↑ in SCr by 0.3 mg/dL within 2 days Or Oliguria	No criteria
CKD	GFR < 60 mL/min per 1.73m ² for > 3 months	Kidney damage for > 3 months
AKD	AKI Or GFR < 60 mL/min per 1.73m ² for < 3 months Or ↓ in GFR by ≥ 35% or ↑ in SCr by > 50% for < 3 months	Kidney damage for < 3 months
NKD	GFR ≥ 60 mL/min per 1.73m ² , stable SCr	No damage

^aAssessed from measured or estimated GFR.

^bKidney damage is assessed by pathology, biomarkers (urine or blood), imaging, and kidney transplantation (for CKD).

AKD = acute kidney disease and disorders; AKI = acute kidney injury; CKD = chronic kidney disease; NKD = no known kidney disease.

C. Differential Diagnosis

1. AKI cannot be diagnosed with a single specific test.
2. A thorough history and complete examination should be complete, including:
 - a. Rate of loss, symptoms, and coexisting diseases
 - b. A comprehensive review of current and recent medications should be completed. Drug-related injury is a leading cause of AKI.
3. Chemistries (BUN, Cr, serum electrolytes, albumin, and a complete blood cell count) and a urinalysis (microscopy, sodium, Cr, and osmolality) may assist in determining the type of failure (e.g., prerenal, intrinsic, postrenal).
4. If not present, a bladder catheter should be inserted. If present, it should be evaluated for obstruction.
5. Abdominal compartment syndrome should be ruled out if clinically suspected. Acute oliguria and AKI are the result of increasing renal outflow pressure and reduced renal perfusion.
6. Routine use of renal ultrasonography is limited because most ICU-related AKI is associated with prerenal azotemia and ATN. However, it may be useful in high-risk patients, those from the community, or after an initial evaluation fails to reveal the cause of AKI.

7. Renal biopsies have limited usefulness but may be necessary. They are most useful in intrinsic renal failure not associated with ATN.
- D. Causes of Drug-Induced AKI (Table 4) – Drug-induced AKI can result when medications are given to an otherwise normal, healthy patient, but injury is more common in the setting of several insults (i.e., disease plus drug) to the kidney.
1. Prerenal
 - a. Decreased blood flow to the kidney, which can result in injury, may be caused by several mechanisms. A reduction in intravascular volume from shock, resulting in decreased perfusion pressure, is most common.
 - b. Drugs typically cause prerenal AKI by one of two mechanisms: they either decrease blood flow to the kidney or influence intraglomerular hemodynamics. Included among drugs affecting blood flow is the excessive use of loop diuretics and several cardiovascular medications.
 - i. Loop diuretics can alter extracellular volume by causing excess volume depletion or reduced effective circulation.
 - ii. Cardiac medications can decrease cardiac output (e.g., those having a negative inotropic effect, especially in the setting of severe or decompensated heart failure) or alter systemic vascular resistance (e.g., antihypertensive medications that reduce systemic vascular resistance by causing vasodilatation).
 - iii. Normal hemodynamics of the kidney is maintained, in part, by vasodilatation of the afferent or vasoconstriction of the efferent arterioles. Increased renal vascular resistance or decreased transcapillary pressure can occur after medications that affect these vessels are administered.
 - iv. Vasodilatation of the afferent arteriole is partly caused by the effects of prostaglandins. Medications that decrease prostaglandin synthesis decrease the ability of the afferent arterioles to vasodilate. Common medications known to inhibit this synthesis are the nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors.
 - v. Vasoconstriction of the efferent arteriole is mediated through angiotensin II. Drugs that block angiotensin II (e.g., angiotensin-converting enzyme inhibitors [ACEIs] and angiotensin receptor blockers [ARBs]) prevent effective efferent vasoconstriction, leading to decreased transcapillary pressure. As a result, the kidney loses its ability to maintain adequate perfusion pressure.
 - vi. Calcineurin inhibitors (e.g., cyclosporine and tacrolimus) have been associated with prerenal AKI, although the exact mechanism has not been well established. Both afferent and efferent vasoconstriction may be involved. These drugs have also been associated with AIN.
 2. Renal (Intrinsic) – Drug-induced intrinsic AKI can be caused by several mechanisms and is the result of injury to the renal tubules, glomerulus, vascular structures, interstitium, or obstruction of the renal tubules.
 - a. Tubular injury
 - i. ATN is common in critical illness.
 - ii. Tubular injury results most often from prerenal insults (e.g., prolonged hypotension) or from nephrotoxic agents.
 - iii. Intravenous contrast agents, aminoglycosides, amphotericin B, and the antiretroviral agents are most commonly associated with ATN.
 - b. Interstitial injury
 - i. In the absence of AKI, AIN is uncommon. It occurs in only 1%–3% of all renal biopsy-proven cases. In the presence of AKI, the incidence is higher and accounts for 15%–27% of cases.

- ii. Interstitial injury is characterized by inflammatory infiltrates and edema within the interstitium. The clinical presentation is nonspecific and may include fever and rash with laboratory evidence of eosinophilia; however, this “classic triad” occurs in only 10%–30% of patients.
 - iii. Drug-induced AIN represents more than 75% of cases. Other causes include infections (5%–10%), idiopathic (5%–10%) or associated with systemic diseases (10%–15%).
 - iv. Several medications have been associated with AIN, including antimicrobials (e.g., penicillins, cephalosporins, sulfonamides, ciprofloxacin, vancomycin), NSAIDs and COX-2 inhibitors, omeprazole, lansoprazole, phenytoin, valproic acid, cimetidine, ranitidine, diuretics, and cocaine.
 - v. Renal recovery is usually complete once the offending agent has been removed; however, it may take weeks to several months. AIN associated with the chronic use of calcineurin inhibitors is often irreversible. In addition to removing the offending agent, steroids may be useful in limiting damage. However, steroid use remains controversial.
 - c. Glomerular injury
 - i. Acute glomerulonephritis (GN) is associated with inflammation and proliferation of glomerular tissue that results in damage to the basement membrane, mesangium, or capillary endothelium.
 - ii. Non-drug causes of GN include systemic disorders such as lupus, hepatitis, and vasculitis
 - iii. Drug-associated GN may include NSAIDs, ampicillin, rifampin, lithium, penicillamine, hydralazine, gold, mercury, and heroin.
 - iv. Fever, malaise, and/or arthralgia may occur.
 - v. Renal indices are non-specific and may mirror prerenal disease.
 - vi. It can be fatal and result in irreversible kidney damage.
 - vii. Treatment includes removal of the likely agent and may include the use of immunosuppressant’s, which may limit disease.
 - d. Vascular injury
 - i. Injury to the renal vascular system is more likely to be caused by either microvascular or macrovascular disease than induced by drugs.
 - (a) AKI associated with microvascular disease is usually associated with thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). It is often the result of glomerular capillary thrombosis.
 - (b) AKI associated with macrovascular disease is usually associated with renal artery occlusion or major abdominal aortic disease.
 - ii. Injury is often irreversible; it should be considered in patients with recent vascular procedures.
 - e. Intratubular obstruction
 - i. Intratubular obstruction is uncommon and can be associated with non-drug or drug causes.
 - ii. Non-drug causes include multiple myeloma and tumor lysis syndrome. Injury results from monoclonal light chains and uric acid that obstructs the tubule.
 - iii. Drug-associated intratubular obstruction can result from the calcium oxalate crystals associated with ethylene glycol ingestion.
3. Postrenal
- a. AKI associated with postrenal causes is uncommon in critically ill patients because a bladder catheter is usually in place. If an obstruction is suspected, it should be ruled out by evaluating the catheter, or by placing one if absent.
 - b. The obstruction may be in the luminal wall or extrinsic to the urinary tract. To cause AKI from upper tract obstruction, the blockage must be bilateral or affect a single functioning kidney.

- c. Medications known to cause tubular obstruction include acyclovir, methotrexate, sulfadiazine, foscarnet, indinavir, tenofovir, and triamterene.
- d. Risk factors include preexisting renal dysfunction and poor hydration.
- e. Ultrasonography is the gold standard test for diagnosis.

Table 4. Location, Mechanism of Injury, and Potential Causes of Drug-Induced Acute Kidney Injury

<p>Prerenal</p> <p>Hemodynamic alterations</p> <ul style="list-style-type: none"> • ↓ Cardiac output (e.g., negative inotropic drugs) • ↓ Systemic vascular resistance (e.g., vasodilators) • ↑ Renal vascular resistance – ex. NSAIDs, COX-2 inhibitors, cyclosporine, tacrolimus) • ↓ Transcapillary pressure – ex. ACEIs; ARBs <p>Extracellular volume depletion – ex. excessive diuretic use</p>
<p>Renal (Intrinsic)</p> <ul style="list-style-type: none"> • Acute tubular necrosis – ex. AG, amphotericin B, contrast agents, cocaine, antiretrovirals (adefovir, cidofovir, foscarnet, and tenofovir) • Acute interstitial nephritis – ex. antimicrobials (penicillins, cephalosporins, sulfonamides, ciprofloxacin, vancomycin, macrolides, tetracyclines, and rifampin), COX-2 inhibitors, NSAIDs, PPIs (omeprazole, lansoprazole, phenytoin, valproic acid, diuretics, cocaine, H₂RA (cimetidine, ranitidine) • Glomerulonephritis – ex. NSAIDs, antimicrobials (ampicillin, penicillamine, rifampin), lithium, hydralazine, gold, mercury, heroin
<p>Postrenal</p> <p>Precipitation of drug in renal tubules – ex. sulfonamides, antiretrovirals (acyclovir, foscarnet, indinavir, tenofovir), methotrexate, sulfadiazine, triamterene, vitamin C at large doses</p>
<p>Bladder Obstruction</p> <p>Ex. anticholinergics</p>

ACEI = angiotensin-converting enzyme inhibitor; AG = aminoglycoside; ARB = angiotensin receptor blocker; COX-2 = cyclooxygenase-2; GN = glomerulonephritis; H₂RA = histamine-2 receptor antagonist; NSAIDs = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.

Patient Case

Questions 3–5 pertain to the following case.

F.B. is a 68-year-old, 70 kg, man admitted to your ICU with fever, elevated WBC, respiratory failure requiring mechanical ventilation, and norepinephrine to support his blood pressure. His medical history is significant for chronic back pain, for which he takes acetaminophen as needed; diabetes, for which he takes glipizide; and enalapril for hypertension. Before this admission, he had been otherwise healthy, seeing his primary care provider about 1 week ago. At that time, his blood pressure was 140/80 mm Hg, and his A1C was 5.2. This laboratory workup was also unremarkable: WBC 5.0×10^3 cells/mm³, BUN 7 mg/dL, and SCr 0.9 mg/dL. Today, his WBC is 24×10^3 cells/mm³, BUN 38 mg/dL, and SCr 3.2 mg/dL, with about 325 mL of urine output since his admission 24 hours ago.

3. Which best describes F.B.'s AKI?
 - A. RIFLE class R.
 - B. AKIN stage 1.
 - C. RIFLE class F or AKIN stage 3.
 - D. RIFLE class E or AKIN stage 3.
4. Which medication is most likely contributing to his AKI?
 - A. Enalapril.
 - B. Glipizide.
 - C. Acetaminophen.
 - D. Enalapril and glipizide equally.
5. When evaluating F.B.'s potential causes of AKI, which additional information or test would be most important to consider or obtain?
 - A. Rate of loss, symptoms, and coexisting diseases and medications.
 - B. Renal evaluation using ultrasonography because this can determine the cause of AKI in most patients.
 - C. Review of blood chemistries because this will likely determine the cause of injury.
 - D. Renal evaluation using biopsy.

III. RENAL REPLACEMENT THERAPIES

- A. General Approaches to Managing AKI
 1. Once injury has occurred, therapy consists of supportive care and limiting additional insults, including nephrotoxins.
 2. In patients with shock, adequate fluid resuscitation should be initiated to restore effective circulation without producing volume overload.
 3. No specific pharmacologic therapy is effective in treating or reversing AKI.
 4. Metabolic control and patient volume should be followed closely, and RRT is initiated when other approaches have failed.
 5. Few data exist to suggest the timing or modality of therapy. Historically, RRT has been offered when severe acidosis (A) or electrolyte abnormalities – hyperkalemia (E) are present, in the setting of certain intoxicates (I), refractory volume overload (O), or symptomatic uremia (U). The AEIOUs of initiating RRT. Whether RRT is initiated largely depends on the treating physician, but recent evidence suggests that early initiation is associated with decreased mortality.

B. Mode of Renal Replacement for AKI

1. Differing modes of RRT include IHD, peritoneal dialysis (PD), CRRTs, and extended daily dialysis (EDD) or sustained low-efficiency dialysis (SLED).
2. Solute and water transport through a semipermeable membrane assists in defining the mode of RRT.
3. Solute removal requires diffusion, convection, or its combination.

C. Intermittent Hemodialysis

1. IHD has historically been used to manage critically ill patients with AKI.
2. However, hypotension can occur in about 20%–30% of patients treated with IHD.
3. IHD may also be problematic in patients with head trauma or hepatic encephalopathy because of rapid solute removal from the intravascular space, causing cerebral edema and increased intracranial pressure.

D. Continuous Renal Replacement Therapies

1. CRRT is the most commonly used modality of RRT in hemodynamically unstable ICU patients.
2. CRRT modalities include CVVH, continuous venovenous hemodialysis (CVVHD), or continuous venovenous hemodiafiltration (CVVHDF).
3. SCUF, or slow continuous ultrafiltration, is another type of CRRT that removes fluid without the need for replacement solutions. It has no impact on the removal of waste products (e.g., BUN) or electrolytes and cannot correct acid-base abnormalities.
4. Solute clearance during CVVHD occurs by diffusion. Diffusion is the movement of solutes from an area of higher solute concentration to an area of lower concentration. A concentration gradient is produced by running an electrolyte solution (i.e., dialysis fluid with a flow rate of 17–40 mL/minute) countercurrent to the flow of blood. Small-molecular-weight solutes are cleared efficiently.
5. Solute clearance during CVVH occurs by convection, and the ultrafiltration rate determines the clearance rate for most solutes. Convection uses the concept of “solute drag” and is capable of removing both small- and large-molecular-weight solutes. Solute removal occurs when the transmembrane pressure drives water and solute across a semipermeable membrane. This process involves the addition of replacement fluid to replace the excess volume that is being removed and replenish the desired electrolytes.
6. For CVVHDF, solute removal is by convection (i.e., CVVH) and diffusion (i.e., CVVHD).

E. SLED or EDD

1. These therapies are provided using conventional hemodialysis machines with low blood-pump speeds (around 200 mL/minute) and low dialysate flow rates (around 300 mL/minute) for extended periods: 6–12 hours a day versus 3–4 hours for IHD or 24 hours for CRRT.
2. Similar to CRRT, they allow for improved hemodynamic stability by producing gradual solute and volume removal compared with IHD.
3. These therapies have certain advantages over CRRT. They produce high solute clearances using existing IHD machines eliminating the need for external solutions and allow “time away” when various diagnostic and therapeutic procedures are needed. Disadvantages include limited data on drug clearance.

F. Choosing a Mode

1. Data are conflicting regarding the renal replacement mode of choice for critically ill patients.
2. Outcomes such as mortality and renal recovery appear to be no different between IHD and CRRT; however, most studies are limited by design, patient characteristics, and crossover between different modalities.

G. CRRT and Drug-Dosing Concepts

1. Drug properties that influence removal during CRRT include protein binding, MW, and Vd. Drug charge is less important.
 - a. The ability of a drug to bind to plasma protein (i.e., albumin) greatly influences how it is removed by CRRT. Removal is inversely proportional to the percent bound (i.e., the higher the percent bound, the less removed). Protein binding affects removal for both convection and diffusion.
 - b. In the absence of significant protein binding, the MW of most drugs has little impact on its overall clearance. Removal can be significant during CVVH because this therapy effectively removes drugs with an MW less than 15,000 kDa, and the pore sizes of most membranes are between 20,000 and 30,000 kDa, allowing drugs to pass freely. During CVVHD, the greatest impact on drug clearance occurs with drugs having an MW less than 500 kDa. As MW increases, clearance is reduced. Given that most drugs have an MW of less than 500 kDa, CVVH, CVVHD, and CVVHDF result in significant drug removal if protein binding is low.
 - c. Vd is less of an issue with CRRT compared with other RRTs. Because CRRT uses slower flow rates, time is allowed for drugs to equilibrate between body compartments. Drugs with a Vd less than 0.6 L/kg have a greater potential for removal.
2. CRRT modalities and their influence during therapy
 - a. CVVH
 - i. Solute removal during CVVH is by convection. Convection is influenced by the membrane pore size; the free fraction of drug, as discussed earlier; and the ultrafiltration rate.
 - ii. The ability of a substance to pass through a membrane by convection is termed *sieving coefficient* (SC). The SC ranges from 0 to 1. An SC of 1 represents free movement, whereas an SC of 0 represents no movement across a filter.
 - iii. SC can be calculated using a ratio of measured drug or other solute in the ultrafiltrate to its concentration in the plasma, $SC = C_{UF}/C_p$, where C_{UF} is concentration in the ultrafiltrate and C_p is concentration in the plasma.
 - iv. If a measured SC is not available, it can be estimated using the percent unbound to albumin, $SC = 1 - fb$, where fb is fraction bound.
 - (a) If replacement fluids are administered postfilter, the clearance rate can be estimated using the following equation:

$$CVVH_{\text{post-dilution}} = UF \times SC \text{ (mL/min)}$$

- (b) If pre-dilution (i.e., before the filter) fluids are used, clearance across the membrane is reduced. Clearance can be estimated using the following equation:

$$CVVH_{\text{pre-dilution}} = UF \times SC \times Qb / (Qb + Qrf)$$

where Qb is blood flow rate and Qrf is pre-dilution replacement fluid flow rate. For pre-dilution fluid replacement to affect overall clearance, the rate must be high. Increased clearance can also occur if both pre- and post-dilution fluids are used.

- b. CVVHD
 - i. Solute removal during CVVHD occurs by passive diffusion. The flow of dialysate is countercurrent to that of the blood. Movement of solute across the semipermeable membrane occurs because of a concentration gradient, with movement from an area of higher (blood) to an area of lower concentration (dialysate). This process occurs until equilibrium is established.
 - ii. Small substances (e.g., urea with an MW of 60 kDa) are cleared more rapidly than large substances (e.g., drugs with an MW approaching 500 kDa).

- iii. The ability of a drug to cross the dialysis filter during CVVHD is called the saturation coefficient (SA). Equations exist for estimating the SA when published data are unavailable. It can be calculated as $SA = C_E/C_p$, where C_E is the concentration in the effluent (spent dialysate) fluid and C_p is the concentration in plasma. C_p can be calculated as $C_p = (CA + CV)/2$, where CA is the concentration drawn from the prefilter port and CV is the concentration drawn from the postfilter port. This equation can be simplified to $SA \sim C_E/C_p$, but this is slightly less accurate. $CVVHD \sim Q_d \times SA$, where Q_d is the dialysate flow rate.
 - c. Continuous venovenous hemodiafiltration
 - i. Solute removal during CVVHDF is by diffusion and convection (i.e., both dialysate and replacement fluids are used).
 - ii. Clearances of small substances are about equal to the sum of the clearance from CVVH and CVVHD separately. However, as MW increases, this correlation no longer holds true.
 - iii. Clearance is estimated as $CVVHDF = (UF + Q_d) \times SA$.
 - d. SLED and EDD
 - i. As with IHD and CRRT, the most important factor influencing drug removal during SLED/EDD is protein binding.
 - ii. Other factors include blood and dialysis flow rates and membrane surface area and flux.
 - iii. Solute removal during SLED/EDD is greater than that during CVVHD when estimated over the same time interval because higher dialysis flow rates are used during SLED/EDD treatments.
 - e. Drug-Dosing Concepts
 - i. Drug dosing during CRRT and SLED is often unclear because this information is not included in product labeling. Manufacturers are not required to study how these therapies alter clearance.
 - ii. General dosing considerations for CRRT
 - (a) For most medications, loading doses require no adjustment.
 - (b) If a drug is normally cleared by the kidneys or is removed by other RRT modalities, CRRT will likely have a significant impact on its removal.
 - (c) When available, drug-specific literature should be used in determining dose and frequency to minimize the likelihood of dosing errors. Although CRRT is meant to be a continuous therapy, it is often interrupted. If therapy is held for an extended period, dose adjustment may be required.
 - iii. General dosing considerations for SLED
 - (a) The duration of SLED and its flow rates (dialysate, blood) vary between studies and institutions, making a general approach to dosing problematic.
 - (b) In addition, little information is available to guide drug dosing.
 - (c) Like IHD and CRRT, the most important factors determining drug removal are protein binding, water solubility, MW (less than 500 kDa), and V_d (less than 0.8 to 1 L/kg).

Patient Case

Questions 6–8 pertain to the previous case.

F.B. is a 68-year-old, 70 kg, man admitted to your ICU with fever, elevated WBC, respiratory failure requiring mechanical ventilation, and norepinephrine to support his blood pressure. His medical history is significant for chronic back pain, for which he takes acetaminophen as needed; diabetes, for which he takes glipizide; and enalapril for hypertension. Before this admission, he had been otherwise healthy, seeing his primary care provider about 1 week ago. At that time, his blood pressure was 140/80 mm Hg, and his A1C was 5.2. This laboratory workup was also unremarkable: WBC 5.0×10^3 cells/mm³, BUN 7 mg/dL, and SCr 0.9 mg/dL. Today, his WBC is 24×10^3 cells/mm³, BUN 38 mg/dL, and SCr 3.2 mg/dL, with about 325 mL of urine output since his admission 24-hours ago.

It is determined that F.B. needs RRT to manage his volume and control his metabolic derangements. He is currently on norepinephrine with a mean arterial pressure of 65 mmHg.

6. Which renal replacement mode will most likely be chosen?
 - A. IHD.
 - B. Slow-low extended daily dialysis.
 - C. CRRT.
 - D. PD.

7. You are asked to dose F.B.'s medications while he is on CRRT. Which propriety has the greatest influence on drug removal?
 - A. Protein binding.
 - B. MW.
 - C. Vd.
 - D. Drug charge.

8. F.B. is to start antimicrobial therapy, and you are asked to dose his medications. Which is the most reasonable approach to determining the appropriate dose and frequency?
 - A. Look up recommendations for IHD therapy because they are the same as for CRRT.
 - B. Perform a drug-specific literature search to determine the most appropriate IHD dose, and then use it to recommend dosing during CRRT.
 - C. Use only CRRT-based recommendations because drug removal is different between IHD and CRRT.
 - D. Once a dose and frequency are determined, they can be continued until the patient recovers his renal function.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C

Reaching a new SCr steady-state concentration requires several days and is often unpredictable. This is common in critically ill patients because the production rate, Vd, and elimination rate may depend on several factors. Drug-dosing recommendations do not account for rapid changes in renal function, and SCr does not accurately estimate CrCl. Although in 2005 the National Institute of Standards and Technology released materials traceable to a reference for Cr, this reference does not account for acute changes but only tries to standardize the measurement.

2. Answer: C

In 2010, the National Kidney Disease Education Program recommended that an adult's drug dosing be based on either the MDRD study equation or CrCl using the CG equation. Although the CKD-EPI equation is gaining acceptance it has not been adequately validated in the elderly or in African Americans with higher GFR's.

3. Answer: C

Both RIFLE class "F" and AKIN stage 3 are met using similar SCr and urine output criteria. For this case, the SCr increased by at least 3-fold above baseline, and the patient's urine output was less than 0.3 mL/kg/hour for 24 hours.

4. Answer: A

F.B. has at least severe sepsis that lead to decreased renal perfusion causing AKI. Enalapril likely contributed to the injury by altering renal hemodynamics. Both glipizide and acetaminophen are unlikely to cause AKI.

5. Answer: A

Acute kidney injury cannot be diagnosed with a specific test or study. The patient's rate of kidney loss, symptoms, and coexisting diseases are very important because these may lead to the cause of injury. Drug-induced AKI is most common in the setting of additional insults and may occur even after the drug is discontinued.

6. Answer: C

Intermittent hemodialysis (IHD) is often used in critically ill patients because many physicians are familiar with this therapy; however, about 20%–30% of patients on

IHD become hypotensive and require discontinuation or a switch to an alternative therapy. Although slow-low extended daily dialysis is an option, some form of continuous renal replacement therapy (CRRT) would likely be chosen because of this patient's unfavorable hemodynamics. Continuous renal replacement therapies such as CVVH, CVVHD, and CVVHDF are often used because they allow for slower flow rates and improved hemodynamics. However, there is no clear benefit with one therapy over another.

7. Answer: A

The greatest influence of drug removal during CRRT is binding to albumin (i.e., the higher the percent bound, the less drug removed). The MW of most drugs has little impact on the drug's overall clearance because most drugs are less than 500 kDa. Continuous venovenous hemofiltration can effectively remove drugs with an MW less than 15,000 kDa, whereas the greatest impact of removal during CVVHD occurs with drugs having an MW less than 500 kDa. Because CRRT is performed using slower flow rates, time is allowed for the drugs to equilibrate between body compartments, making Vd less of an issue. Although not well studied, binding to the filter is not important for most drugs.

8. Answer: C

Continuous renal replacement therapy presents unique challenges, and dosing considerations are not interchangeable between intermittent and continuous therapies. In general, if a drug is normally cleared by the kidneys or is removed by other RRT modalities, CRRT will likely have a significant impact on its clearance. In the absence of significant protein binding, removal can be expected. Drug-specific guidance can be obtained from the primary literature or from summary charts, but it should be reviewed with caution because flow rates during CRRT may vary. Although CRRT is meant to be a continuous therapy, it is often interrupted, and drug dose and frequency may need adjustment.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B

The CG equation has historically been used to estimate CrCl. Several patient factors may influence results (i.e., measured SCr, age, weight, and sex). For patients who are obese, using total body weight will likely overestimate CrCl. Although not universally accepted, using an adjusted weight (with a factor of 0.4) is more accurate, compared with a measured 24-hour CrCl, than actual or ideal body weight in this patient group. Only since 2005 has the National Institute of Standards and Technology released materials traceable to a reference for Cr, using isotope dilution mass spectroscopy, in an attempt to standardize measured SCr.

2. Answer: A

The MDRD study equation was developed from a sample of patients with CKD using a urinary clearance of ^{125}I iothalamate. It has been validated in white and African American patients between 18 and 70 years of age with reduced renal function. Compared with CG and measured CrCl from a 24-hour urine collection, MDRD has been shown to provide a better estimate of clearance, but additional studies are needed. The MDRD study equation underestimates the measured GFR when greater than 60 mL/minute per 1.73m^2 , and it should be used only when the SCr level is stable.

3. Answer: D

The CKD-EPI equation uses the same four variables (SCr, age, sex, and race) as the MDRD study equation for predicting the GFR in adults 18 years or older. The CKD-EPI equation has been shown to be more accurate than the MDRD equation when the GFR is greater than 60 mL/minute per 1.73m^2 . However, CKD-EPI should be used with caution in patients with non-steady-state Cr production and elimination.

4. Answer: B

Although AIN is an uncommon occurrence, drugs are associated with more than 75% of cases if it occurs. Several medications have been associated with AIN, including antimicrobials (e.g., penicillins, cephalosporins, sulfonamides, ciprofloxacin, vancomycin, macrolides) and histamine-2 receptor antagonists.

5. Answer: C

AKIN stage 3 is met, regardless of the patient's change in SCr or urine output, because he is receiving RRT.

6. Answer: A

Solute removal during CVVH is by convection, which is primarily influenced by membrane pore size, free fraction of drug, and ultrafiltration rate. Clearance is increased as fluid moves across the filter, "pulling" solute with it.

7. Answer: C

Drug-dosing recommendations for IHD can be found in many resources. However, dosing during CRRT and SLED is less clear. Primary literature and/or summary tables for CRRT and SLED should be referenced because these recommendations are not usually found in other sources. Use caution to ensure that identical modes of CRRT are referenced with similar flow rates.

8. Answer: A

Although protein binding, MW, Vd, and drug charge may influence removal, binding to plasma protein has the greatest impact because only unbound drugs can be cleared through the filter.

