Acute Kidney Injury

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LEARNING OBJECTIVES

1. Distinguish among the different types of acute kidney injury (AKI) and identify drug-induced causes.
2. Apply knowledge of organ cross-talk to predict changes in drug pharmacokinetics.
3. Demonstrate knowledge of protein, caloric, electrolyte, and trace element requirements in AKI with and without renal replacement therapy (RRT).
4. Compare and contrast the use of the various RRTs.
5. Estimate renal function, and formulate an appropriate drug-dose regimen for a patient with AKI not receiving RRT.

ABBREVIATIONS IN THIS CHAPTER

AIN	Acute interstitial nephritis
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ATN	Acute tubular necrosis
CKD	Chronic kidney disease
CRRT	Continuous renal replacement therapy
eGFR	Estimated glomerular filtration rate
IHD	Intermittent hemodialysis
KDIGO	Kidney Disease: Improving Global Outcomes
KIM-1	Kidney injury molecule-1
NGAL	Neutrophil gelatinase-associated lipocalin
RIFLE	Risk, injury, failure, loss, end-stage
RRT	Renal replacement therapy

Table of other common abbreviations.

INTRODUCTION

Acute kidney injury (AKI) results in the abrupt loss of kidney function, leading to the retention of waste products, electrolyte disturbances, and volume status changes. The term *AKI* has replaced *acute renal failure* because smaller changes in kidney function without overt failure can result in significant clinical consequences and increased morbidity and mortality.

Changes in kidney function are detected by a change in biomarkers, the most common biomarker being serum creatinine (SCr). Serum creatinine is an imperfect biomarker for recognizing AKI, given that an increase in SCr often lags (48–72 hours) behind the onset of injury. In addition, SCr is not in a steady-state condition in critically ill patients, leading to inaccurate estimates of glomerular filtration rates (eGFRs). Using an imperfect biomarker for AKI definition, recognition, and management may affect patient outcomes. Despite improvements in renal replacement therapy (RRT), AKI outcomes are not optimal (Mehta 2003). This chapter reviews the identification and management of AKI in critically ill patients.

DEFINING AKI

Prior studies of AKI used different quantitative definitions, leading to challenges for clinicians in interpreting and applying study findings. Some definitions used were complex and difficult to apply because the increase in SCr was different depending on the presence and severity of underlying chronic kidney disease (CKD). Several consensus definitions of AKI have been developed over time to improve the recognition and reporting of AKI.

RIFLE Classification

In 2004, the Acute Dialysis Quality Initiative published the risk, injury, failure, loss, end-stage (RIFLE) criteria. The RIFLE classification is

Table 1-1. Comparison of RIFLE and AKIN Criteria for AKI Definition

RIFLE		AKIN		RIFLE/AKIN
Category	**SCr or ↓ GFR**	**Stage**	**Increase in SCr**	**Urinary Output Change**
Risk	1.5-fold ↑ SCr **or** 25% ↓ GFR	1	1.5- to 1.9-fold ↑ SCr or ↑ SCr ≥ 0.3 mg/dL	< 0.5 mL/kg/hr for 6–12 hr
Injury	2-fold ↑ SCr **or** 50% ↓ GFR	2	2- to 2.9-fold ↑ SCr	< 0.5 mL/kg/hr for ≥ 12 hr
Failure	3-fold ↑ SCr **or** SCr > 4 mg/dL with acute risk > 0.5 mg/dL **or** 75% ↓ GFR	3	3-fold SCr **or** SCr > 4 mg/dL with acute risk > 0.5 mg/dL **or** RRT	< 0.3 mL/kg/hr for ≥ 24 hr or anuria for ≥ 12 hr

AKI = acute kidney injury; 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.

based on changes in two markers: SCr and urinary output. The classification includes three graded stages of AKI – risk, injury, and failure – with two outcomes: loss of kidney function greater than 4 weeks and end-stage renal disease greater than 3 months (Lopes 2013). The RIFLE-defined period for change in SCr or urinary output was 7 days.

After implementing the RIFLE classification, clinicians and investigators noted two problematic issues. First, AKI outcomes were worse in patients who developed AKI by SCr than by urinary output criteria. Second, the defined change in SCr value did not equate to the defined change in GFR (i.e., a 50% increase in SCr corresponds with a 33% decrease in GFR). Subsequently, GFR was not included in the Acute Kidney Injury Network (AKIN) or Kidney Disease: Improving Global Outcomes (KDIGO) definitions.

BASELINE KNOWLEDGE STATEMENTS

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

- General knowledge of the pathophysiology that leads to acute kidney injury
- Kidney Disease Outcome Quality Initiative criteria
- CKD stages
- Estimate and measure CrCl and GFR
- General knowledge of renal replacement therapy

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). Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl 2012;2:1-138.
- Medscape. Acute Kidney Injury. 2017 [homepage on the Internet]

AKIN Criteria

In 2007, AKIN updated and modified the RIFLE criteria to define AKI and the staging system. The definition of AKI is an abrupt increase in SCr of 0.3 mg/dL over baseline within 48 hours, a 50% or greater increase in SCr within 7 days, or urinary output of less than 0.5 mL/kg/hour for more than 6 hours. Studies had shown significantly increased mortality with small elevations in SCr (0.3–0.5 mg/dL) over a short period (24–48 hours). The AKIN staging system corresponds with the RIFLE categories. The loss and end-stage renal disease categories are removed from staging and considered outcomes (Table 1-1).

KDIGO Guidelines

In 2012, the KDIGO clinical practice guidelines defined AKI as an SCr increase of 0.3 mg/dL within 48 hours or a 50% increase in SCr within the previous 7 days (KDIGO 2012). The staging system was maintained the same as AKIN; however, a GFR of less than 35 mL/minute/1.73 m^2 was added for pediatric patients as a criterion for stage 3 AKI.

Biomarkers

Serum creatinine is a well-recognized marker of kidney function and not a sensitive kidney injury marker, given that it may lag 48–72 hours from the time of injury. Kidney injury biomarkers are needed to improve AKI detection and will likely replace SCr in the definition and staging of AKI. Kidney damage biomarkers, including kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), interleukin (IL)-18, liver-type fatty acid binding protein (L-FABP), insulin-like growth factor binding protein 7 (IGFBP-7), and tissue

inhibitor of metalloproteinase-2 (TIMP-2), may be elevated before an SCr increase, enhancing the detection of kidney damage without functional change (Murray 2014; Haase 2012). The combination of damage and functional biomarkers may enhance the detection, differential diagnosis, and subsequent management of AKI.

The biomarker, KIM-1, is a type 1 transmembrane protein with low expression in the normal kidney. It is up-regulated after ischemic injury and plays a role in the phagocytosis of apoptotic cells and debris. This has implications for remodeling and renal recovery. This biomarker was shown to be specific for acute tubular necrosis (ATN); a 1-unit increase in normalized KIM-1 was associated with an OR of 12.4 (95% CI, 1.2–119) for the presence of ATN after adjusting for other covariates (Han 2002). This biomarker plays a role as a diagnostic discriminator and may help further adjudicate drug-induced kidney disease.

Neutrophil gelatinase-associated lipocalin is a 25-kDa protein from the lipocalin family. It is up-regulated after ischemic or nephrotoxic AKI, is detected in the urine 3 hours post-injury, and peaks 6 hours post-injury. Injury to the kidney is mitigated by NGAL through the inhibition of apoptosis and increased proliferation of renal tubule cells. In the TRIBE-AKI study of 1219 adults undergoing cardiac surgery, urine and plasma NGAL concentrations peaked within 6 hours after surgery (Parikh 2011). Elevated postoperative concentrations (within 6 hours of arrival to the ICU) were associated with a higher risk of AKI, increased mortality, and increased hospital length of stay. Neutrophil gelatinase-associated lipocalin can identify patients who may be at higher risk of kidney injury. Future studies will need to determine how early detection may improve monitoring, aid in decision-making, and minimize exposure to additional nephrotoxins.

Interleukin-18 is a pro-inflammatory cytokine formed in the proximal tubule. Urine IL-18 concentrations are elevated within the first 6 hours post-AKI and peak 12–18 hours post-injury. Interleukin-18 plays a role in the inflammation that exacerbates tubular necrosis. Elevated urinary concentration of IL-18 post-cardiac surgery is an early marker of AKI and an independent predictor of dialysis or death in critically ill patients, with an OR of 6.8 (Parikh 2011).

Liver-type fatty acid binding protein is a 14-kDa protein localized in the proximal tubule and a marker of renal hypoxia. A meta-analysis has shown that L-FABP can detect AKI and predict the need for RRT and in-hospital mortality in patients at risk of AKI (Susantitaphong 2013). Liver-type fatty acid binding protein is approved in Japan as a tubular biomarker to aid in the early prediction of AKI before an increase in SCr in critically ill patients.

Insulin-like growth factor binding protein 7 and TIMP-2 are inducers of cell cycle arrest, which is an implicated mechanism in the pathophysiology of AKI. Together, these biomarkers had an AUC of 0.8 for predicting stage 2 or 3 AKI, which is improved over other biomarker prediction models. When added to clinical variables, the biomarkers improved the risk stratification of patients. Risk of death, dialysis, or persistent renal dysfunction at 30 days increased when the product of the biomarker concentrations (IGFBP-7 × TIMP-2) was above 0.3 and doubled when it was above 2 (Kashani 2013).

Future studies will delineate the most appropriate biomarker for risk assessment, differential diagnosis, and causality assessment and prognosis. The TRIBE-AKI consortium study data have provided preliminary data on the biomarker concentration ranges in various subpopulations and preliminary information on the ability to predict AKI (Parikh 2016; Murray 2014; McCullough 2013). However, the relationship between biomarker changes to mechanisms of injury over time requires delineation to best assess use.

EPIDEMIOLOGY

After standardizing the definition and grading of AKI, the epidemiology was first characterized using the RIFLE criteria in an international multicenter observational study of 29,269 critically ill patients. Around 5.7% of patients developed AKI, 10% of patients developed risk, 5% developed injury, and 3.5% developed failure, according to maximal AKI severity. The most common AKI etiology was septic shock at 47.5%. Overall hospital mortality was 60.3%, and mortality increased linearly with increasing AKI severity (Uchino 2005).

The Acute Kidney Injury-Epidemiologic Prospective Investigation was an international cross-sectional study of 1802 critically ill patients examining the incidence of AKI, by the KDIGO definition. This study showed that 57.3% of ICU patients developed AKI, with 18.4% developing stage 1, 8.9% stage 2, and 30% stage 3. Mortality increased with increasing AKI severity. In this study, a large proportion of patients, 47.7%, had residual injury at discharge, as measured by a GFR of less than 60 mL/minute/1.73 m^2 (Hoste 2015).

These studies show differing rates of AKI, depending on which criteria are used. In the 2005 study, a more severe definition of AKI was used for the overall incidence (Uchino 2005). Including the 0.3-mg/dL increase in SCr over 48 hours as a definition of AKI likely drives the change. Both studies show increased mortality with increased severity of AKI.

RISK FACTORS

Risk factors for AKI include age, comorbid diseases, proteinuria, nephrotoxic exposures, major surgery, sepsis, fluid resuscitation, and volume status. Older age increases the risk of AKI, but older patients are less likely to receive RRT (Hsu 2008).

Comorbid conditions including CKD, diabetes, hypertension, coronary artery disease, heart failure, liver disease, and chronic obstructive pulmonary disease are risk factors for AKI. Proteinuria with a GFR greater than 60 mL/minute/1.73 m^2 or an elevated urinary albumin/creatinine

ratio is associated with an increased risk of AKI, as shown in a post-cardiac surgery cohort.

Hospitalized patients, especially critically ill patients, are often exposed to several nephrotoxins and contrast exposure. Antimicrobials, NSAIDs, and proton pump inhibitors are common medications administered in this population. Acute kidney injury is common after cardiac surgery and is less common in the non-cardiac surgery population. Sepsis is a common predisposing factor to AKI, and the development of AKI further increases the risk of mortality.

Choice of fluid for resuscitation may be a risk factor for AKI because hydroxyethyl starch has been associated with increased risk of AKI compared with crystalloids (Mutter 2013). High-volume resuscitation with crystalloids has a higher risk of AKI than balanced salt solutions because of the deleterious effects of chloride loading. Fluid overload and therapies to treat volume overload increase the risk of AKI. Fluids are the mainstay for preventing and treating AKI. However, certain fluids have been associated with an increased risk of AKI (discussed later in the chapter).

CLASSIFICATION OF AKI

Causes of AKI can be classified into three broad groups: (1) pre-renal or hemodynamic (i.e., hypoperfusion to the kidney), (2) intrinsic (i.e., structural damage to the kidney), and (3) post-renal (i.e., obstruction of urinary outflow). It is important to determine the cause and assess for reversibility in order to identify appropriate strategies for minimizing the severity of injury.

Pre-renal Causes

Pre-renal AKI is the leading cause of kidney injury. Decreased renal perfusion of the kidney can cause AKI with or without systemic arterial hypotension. Inadequate fluid intake, excessive vomiting, diarrhea, and fever can lead to dehydration. Trauma resulting in massive hemorrhage decreases circulating volume, resulting in hypoperfusion to the kidney. Sepsis, heart failure, and cirrhosis are disease states in which there is reduced perfusion to the kidneys.

Sepsis and septic shock are the most common causes of AKI in the ICU. Although the mechanism that causes sepsis and septic shock is still unknown, it likely involves the inflammatory response to infection that leads to hypoperfusion and multi-organ failure. Cardiac surgery and heart failure are the second most common causes of AKI. Cardiopulmonary bypass pump can trigger exogenous and endogenous toxins, metabolic abnormalities, ischemia, reperfusion injury, inflammation, and oxidative stress. Several studies are investigating the use of biomarkers such as IL-18 and NGAL to predict AKI post-cardiac surgery. Hepatorenal syndrome, burns, and trauma can also cause hypoperfusion of the kidneys. The mechanisms are thought to be from shock, abdominal compartment syndrome, inflammatory mediators, and changes in tissue perfusion (Ibrahim 2013).

Box 1-1. Drugs Associated with AKI

Prerenal
- ACEIs/ARBs
- Calcineurin inhibitors
- COX-2 inhibitors
- Diuretics
- NSAIDs

Glomerular Injury
- Interferon
- Pamidronate

Acute Interstitial Nephritis
- Allopurinol
- Azathioprine
- Chinese herbs – *Stephania tetrandra*, *Magnolia officinalis*, *Aristolochia fangchi*
- Cimetidine
- Diuretics (thiazides, furosemide)
- NSAIDs
- Phenytoin
- Proton pump inhibitors
- Quinolones
- Rifampin
- Semisynthetic penicillins (ampicillin, nafcillin, oxacillin)
- Sulfonamides
- Vancomycin

Acute Tubular Necrosis
- Aminoglycosides
- Amphotericin B
- Carboplatin
- Cisplatin
- Cyclophosphamide
- Ifosfamide
- Pentamidine
- Radiocontrast media
- Vancomycin

Crystal Nephropathy
- Acyclovir
- Allopurinol
- Indinavir
- Methotrexate
- Nelfinavir
- Quinolones
- Sulfonamides
- Triamterene

ACEI = angiotensin converting enzyme inhibitors; AIN = acute interstitial nephritis; AKI = acute kidney injury; ARB = angiotensin II receptor blockers; ATN = acute tubular nephritis; COX II = cyclooxygenase 2.

Medications implicated in reducing blood flow to the kidneys are listed in Box 1-1. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) cause vasodilation of the efferent arteriole, reducing intraglomerular pressure and causing a decrease in GFR and increase in SCr. A transient increase in SCr is an expected outcome of the reduced GFR when initiating renin-angiotensin-aldosterone (RAAS) agents. However, certain

conditions may predispose the patient to develop AKI while taking a RAAS agent, specifically volume depletion, hypotension, or concurrent nephrotoxins. In these circumstances, RAAS agents should be held until these conditions have been addressed and may be considered for re-initiation once the AKI has resolved. Nonsteroidal anti-inflammatory drugs inhibit the synthesis of vasodilatory prostaglandins, resulting in vasoconstriction of the afferent arteriole. They also cause sodium and water retention and may increase blood pressure. Calcineurin inhibitors (e.g., cyclosporine and tacrolimus) can cause acute and chronic nephrotoxicity. Acute toxicity results from afferent arteriole vasoconstriction because of the upregulation of angiotensin II. Toxicity is usually associated with high trough concentrations. This is typically reversible by holding the dose and allowing concentrations to decline to the target range. Over-diuresis with loop diuretics may result in decreased circulating volume and decreased renal perfusion, especially in patients with conditions that increase their susceptibility to hemodynamic changes, such as cirrhosis and heart failure.

Intrinsic Causes

Intrinsic kidney injury includes damage to the glomerulus, tubules, interstitium, and vasculature. These conditions are quite different from a pathophysiologic standpoint and include a wide spectrum of etiologies, disease conditions, or offending drugs. The immune system plays a large role in glomerular disorders, interstitial injury, and vascular injury. Drugs causing intrinsic injury may be direct nephrotoxins, or they may stimulate an immune response. In some cases, drugs can cause injury through more than one mechanism (i.e., tubular injury and interstitial injury).

Glomerular

Autoimmune disorders play a large role in the etiology of glomerular injury. Glomerular injury may occur from immune-mediated diseases or conditions such as lupus nephritis, immunoglobulin A nephropathy, Wegner syndrome, polyarteritis nodosa, or post-streptococcal infection. Oncology drugs are the most commonly implicated agents in glomerular injury, with increasing recognition of kidney injury from new therapies targeting the immune system. The hallmark biomarker is the presence of proteinuria and increased SCr with a delayed onset of injury (i.e., weeks). Other evidence of glomerular injury includes hematuria and the presence of RBCs, WBCs, and casts on urinalysis. A kidney biopsy is often required to determine the etiology of the glomerular injury and guide management. Medications causing glomerular injury include interferon, pamidronate, gemcitabine, and vascular endothelial growth factor inhibitors. Interferon can affect podocytes, leading to minimal change disease or focal segmental glomerulosclerosis (FSGS). Pamidronate, a bisphosphonate used to treat hypercalcemia in oncology, has also been associated with FSGS. Gemcitabine has been associated with proteinuria and glomerular injury caused by thrombotic microangiopathy. Vascular endothelial growth factor inhibitors disrupt glomerular endothelial cells and slit diaphragms, leading to changes in glomerular permeability. Renal injury is accompanied by hypertension caused by decreased endothelial nitric oxide production.

Tubular

Tubular injury is commonly caused by antimicrobials and nephrotoxic drugs. Acute tubular necrosis is a common etiology of AKI in critically ill patients and is the most common type of AKI caused by ischemia or exposure to nephrotoxins. Ischemic ATN occurs when renal hypoperfusion overwhelms autoregulatory mechanisms, initiating cell injury and death. Causes of ischemic ATN include hypovolemic states (i.e., hemorrhage, GI, and insensible losses), low cardiac output in heart failure, and systemic vasodilation with sepsis. Nephrotoxic ATN may be caused by drugs, multiple myeloma, rhabdomyolysis, and contrast media.

The kidney is vulnerable to the untoward effects of medications. The kidney receives 25% of cardiac output, is rich in blood supply, and is an eliminating organ for medications. Aminoglycoside-associated ATN can occur in 11%–60% of adults and 12% of neonates. Injury includes ATN, distal tubule concentrating defects, and proximal tubular dysfunction with electrolyte abnormalities (e.g., hypomagnesemia, hypocalcemia, and hypokalemia). The injury is usually reversible if tubular regeneration processes are still intact. Risk factors for aminoglycoside toxicity include advanced age, volume depletion, sepsis, diabetes, liver disease, CKD, electrolyte disturbances, concomitant nephrotoxins (e.g., diuretics, NSAIDs, ACEIs/ARBs, and vancomycin), prolonged therapy duration (i.e., greater than 5 days), frequency of dosing (e.g., every 12 hours or every 8 hours), peak and trough concentrations greater than 10 and 2 mcg/mL, respectively (for gentamicin and tobramycin), an increase in trough concentration by 1 mcg/mL or more for amikacin, and specific agent used (i.e., gentamicin > tobramycin > amikacin). Aminoglycoside-associated nephrotoxicity is often multifactorial, making differentiation from other disease-related etiologies or concurrent nephrotoxins difficult.

Conventional amphotericin B can cause AKI in around 28% of cases. It causes vasoconstriction of afferent arterioles, reducing blood flow and oxygen delivery. It also binds to epithelial cell membranes, creating pores that disrupt permeability and lead to tubular injury. Amphotericin B may cause significant potassium and magnesium wasting as well as a distal renal tubular acidosis. Risk factors for amphotericin nephrotoxicity include concurrent nephrotoxins, conventional amphotericin B dose (i.e., greater than 0.5 mg/kg/day), and preexisting CKD. Lipid-based formulations such as liposomal amphotericin B are associated with less nephrotoxicity than conventional amphotericin B. Liposomal amphotericin B has the lowest rate of nephrotoxicity and has largely replaced use

of the conventional formulation. Nephrotoxicity from amphotericin B is usually reversible with therapy discontinuation.

Vancomycin nephrotoxicity is a topic of much debate. Controversy exists in determining a causal relationship. Many clinicians believe that vancomycin is not nephrotoxic and that high serum concentrations are a result of AKI but not the cause of AKI. Rates of AKI associated with vancomycin have increased, with new guidelines that advocate trough concentrations of 15–20 mg/L or higher in some cases for the treatment of complicated infections such as pneumonia (Rybak 2009). Retrospective studies have shown an association between high trough concentrations, total daily dose, concurrent administration of an aminoglycoside or piperacillin/tazobactam, and development of AKI (Burgess 2014; Gomes 2014; Meaney 2014; Lodise 2009; Lodise 2008). In a prospective study of vancomycin versus linezolid for nosocomial pneumonia, the rate of nephrotoxicity was higher with vancomycin than with linezolid (18.2% vs. 8.4%) (Wunderink 2012). The mechanism for nephrotoxicity had previously been attributed to the formulation because rates of nephrotoxicity decreased after reformulation and has recently increased with new target concentrations. Animal studies have shown that vancomycin induces oxidative stress, mitochondrial damage, and ischemic injury to the kidney. This widely used antibiotic requires careful monitoring of therapeutic drug concentrations and renal function and attention to dosing.

Contrast-induced nephrotoxicity occurs in 3%–30% of patients. Contrast agents cause ATN likely by renal vasoconstriction, increasing medullary hypoxia and direct cytotoxicity. In contrast to nephrotoxin-associated ATN, the fractional excretion of sodium (FENa) may be less than 1%, suggesting a prerenal contribution as well. The onset of injury is 48 hours with a return to baseline SCr in 3–7 days. Risk factors for contrast-induced nephrotoxicity include age, preexisting CKD, diabetes, heart failure, anemia, type of procedure, type of contrast agent, and volume of contrast. Risk-scoring tools have been published. Contrast agents are classified as high (iothalamate), low (iohexol), or iso-osmolar (iodixanol), depending on their osmolality in relation to blood. Iso-osmotic contrast media such as iodixanol (Visipaque) have a lower rate of nephrotoxicity than iohexol but no lower than other low-osmolar agents (Rudnick 2008; Solomon 2007; Aspelin 2003). In high-risk patients, iso-osmolar agents should be used, when possible, to reduce the risk of nephrotoxicity.

Interstitial

Interstitial damage is commonly a diagnosis of exclusion, given the lack of sensitive or specific biomarkers of interstitial injury. Acute interstitial nephritis (AIN) may be caused by infections, medications, or immune disorders. The most common infection includes pyelonephritis, but AIN can also be associated with renal tuberculosis and fungal nephritis. Medications most commonly implicated in AIN include antibiotics, NSAIDs, and diuretics (see Box 1-1). Additionally, some drugs may crystallize and deposit in the interstitium leading to an immune response. A detailed drug exposure history may help establish a temporal association. Immune-mediated disorders such as glomerulonephritis may cause AIN. Classic findings of fever, rash, and arthralgias as documented in methicillin-associated AIN may be absent in up to two-thirds of patients. Urinary eosinophils may be absent and are not a sensitive marker for AIN. Renal gallium scanning may provide some diagnostic evidence for AIN but cannot exclude the diagnosis. Renal biopsy remains the gold standard for diagnosis, but the risk-benefit of biopsy must be considered, especially in mild cases when drug discontinuation leads to clinical improvement.

Vascular/Thrombotic

Renal vascular disorders, which may cause AKI, include vasculitis, malignant hypertension, scleroderma, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome, thrombotic microangiopathies, disseminated intravascular coagulation, mechanical renal artery occlusion (surgery, emboli, thrombotic occlusion), and renal venous thrombosis. Thrombotic microangiopathy describes a disease of microvascular thrombosis, consumptive thrombocytopenia, and microangiopathic hemolytic anemia. Some chemotherapeutic agents have been associated with thrombotic microangiopathies, including gemcitabine, cisplatin, mitomycin C, and vascular endothelial growth factor inhibitors.

Post-renal Causes

Post-renal AKI is the result of kidney obstruction. The most common causes of post-renal AKI include nephrolithiasis, benign prostatic hypertrophy, and surgical causes. The four main chemical types of renal calculi are calcium, uric acid, struvite, and cysteine, with calcium stones being the most common type. Certain drugs have relatively low solubility in the urine and may crystallize, obstructing the collecting system (see Box 1-1).

CLINICAL WORKUP

Medical History and Physical Examination

Acute kidney injury is a syndrome that results from multiple insults. The etiology of AKI includes many different conditions, and often, the injury is worsened by the existence of risk factors. It may be difficult to distinguish the primary cause from contributing factors, and a thorough medical history and physical examination are essential to establish the strength of relationship and temporal association for causality. A complete medical history should include fluid losses; previous SCr and electrolytes; comorbid conditions such as diabetes, hypertension, cancer, transplantation, and heart and liver disease; history of pyelonephritis or UTI; recent surgery; radiographic procedures; and known infections (e.g., HIV, hepatitis) and exposures to possible infectious sources (e.g., sewage, waterways, rodents). A complete medication

Table 1-2. Summary of Urinary Indices for Differential Diagnosis

Urine Indices	Pre-renal/Hemodynamic	Acute Tubular Necrosis	Postrenal Obstruction
Urine sodium (mEq/L)	< 20	> 40	> 40
FENa (%)	< 1	> 2	> 1
Urine osmolality (mOsm/k)	Up to 1200	< 300	< 300
Urine creatinine/ plasma SCr ratio	> 40:1	< 20:1	< 20:1
Specific gravity	> 1.010	< 1.010	Variable

history should include OTC and prescription therapies as well as herbal medications and recreational drugs. Each drug should be assessed for its potential to cause drug-induced kidney disease (Awdishu 2016). The known onset of injury for the drug together with the laboratory findings can be used to establish causality. Physical examination should include assessment of volume status, signs and symptoms of acute and chronic heart failure, emboli, infection, and sepsis.

Laboratory Studies

Laboratory tests should include serum chemistry, CBC, urinalysis, urinary chemistry, and urine sediment. The urine sediment is often the window to etiology. Gross or microscopic hematuria suggests injury to the glomerulus, vasculature, or interstitium (e.g., stone, tumor, infection, or trauma). Red blood cell casts indicate a glomerular or vascular cause of AKI. Hyaline casts suggest hemodynamic injury. The presence of WBCs or WBC casts may indicate pyelonephritis or autoimmune causes. Crystals may point to drug-induced kidney disease from drugs such as sulfonamides, indinavir, triamterene, or acyclovir.

Urine chemistry, including urine sodium and calculation of the FENa, is useful to distinguish between a pre-renal AKI and other etiologies (Table 1-2). A FENa less than 1% indicates pre-renal AKI. When diuretics are administered, a low fractional excretion of urea (less than 35%) is a more sensitive marker for pre-renal AKI.

Radiographic Studies

Renal ultrasonography is necessary to look for reversible causes of AKI, such as obstruction from a kidney stone. Findings of decreased kidney size or echogenicity indicate CKD. Renal Doppler ultrasonography may help identify ischemic AKI and reduced renal blood flow. Typically, resistive indices are high (i.e., greater than 0.75) in this setting of reduced perfusion.

Renal Biopsy

Renal biopsy is helpful in patients whose ultrasound findings are normal and who have not recovered after 3–4 weeks when intrinsic kidney disease is suspected. Renal biopsy should be considered if information from the biopsy would change the patient's treatment. For example, consider a patient with epilepsy who is recently initiated on phenytoin with good response but who has an increase in SCr; the patient's etiology of kidney injury is unclear but thought to be phenytoin associated. The decision to change anticonvulsants carries a risk of breakthrough seizures. A biopsy confirming AIN would assist in clinical decision-making because this would warrant a change in the anticonvulsant regimen.

ORGAN CROSS-TALK

Organ cross-talk describes the effects of one malfunctioning organ on the function of another. Acute kidney injury has deleterious effects on lung, heart, brain, and liver function. The impact of AKI on other organs goes beyond the effects of uremia alone and is likely related to immune system up-regulation.

Lung dysfunction is an important systemic consequence of AKI, with mortality rates greater than 80% for combined AKI/lung injury in critically ill patients. Acute kidney injury can lead to lung injury and inflammation. Lung injury with its attendant hypoxemia, hypercapnia, and mechanical ventilation–associated high positive-end expiratory pressure can also worsen renal hemodynamics and function.

Acute kidney injury is associated with development of left ventricular dilatation and cardiorenal syndrome. In addition, ventricular fibrillation is more common in cardiac ischemia with AKI. Azotemia and water retention can result in cardiac failure after renal dysfunction.

Up-regulation of IL-1, tumor necrosis factor alpha, and intercellular adhesion molecule-1 messenger RNA expression has been suggested to occur in myocytes post-AKI. These changes result in cell death mediated by myocyte apoptosis and leukocyte infiltration.

Neurologic complications of AKI include decreased mental awareness, seizures, and encephalopathy. Animal models have shown that AKI leads to inflammation, microvascular permeability, and behavioral dysfunction. Fluid and electrolyte disturbances as well as drug toxicities are common in patients with kidney failure and can produce CNS depression with encephalopathy (Brouns 2004). Patients with AKI are

more susceptible to encephalopathy than are those with CKD because there is less time to adapt to uremia.

Acute kidney injury leads to increases in systemic pro-inflammatory cytokines, apoptosis, and cell damage in the liver. An increase in IL-6 activates Kupffer cells to produce further inflammatory cytokines, including IL-10. An increase in tumor necrosis factor alpha results in increased myeloperoxidase activity and oxidative stress in the liver. Liver damage in AKI complicates treatment because of the liver's critical role in metabolizing drugs and mediating remote organ injury.

PHARMACOLOGIC THERAPY FOR AKI

Therapy for AKI focuses on treating the underlying cause. The KDIGO international guidelines on AKI describe the general treatment strategies (Figure 1-1).

Fluid Replacement

Crystalloids and colloids are common solutions used for volume repletion in patients with pre-renal AKI. Crystalloid solutions are more commonly used than colloids for resuscitation, especially in the initial resuscitation phase in patients with AKI (Mutter 2013). Large-volume infusions of sodium chloride are now increasingly recognized as possibly having deleterious effects of hyperchloremic metabolic acidosis, leading to AKI and use of RRT (Yunos 2012). However, the SPLIT study found no significant difference in the incidence of AKI between sodium chloride 0.9% and plasmalyte (Young 2015). Yet the median volume of all solutions used in this study was low, 1–2 L, and the study did not address high-volume fluid use. Moreover, this study did not address whether hyperchloremic metabolic acidosis occurred because chloride concentrations were not reported. In addition, this study did not compare normal saline with Lactated Ringer solution, which is commonly used for fluid resuscitation. What this study does provide is evidence that 0.9% sodium chloride is not hazardous when the total doses of less than 2 liters is used in patients at low to moderate risk.

Colloid solutions include semisynthetic solutions like gelatins, dextrans, and starches and natural solutions such as albumin. Resuscitation with colloid solutions increases intravascular oncotic pressure and shifts fluid from the

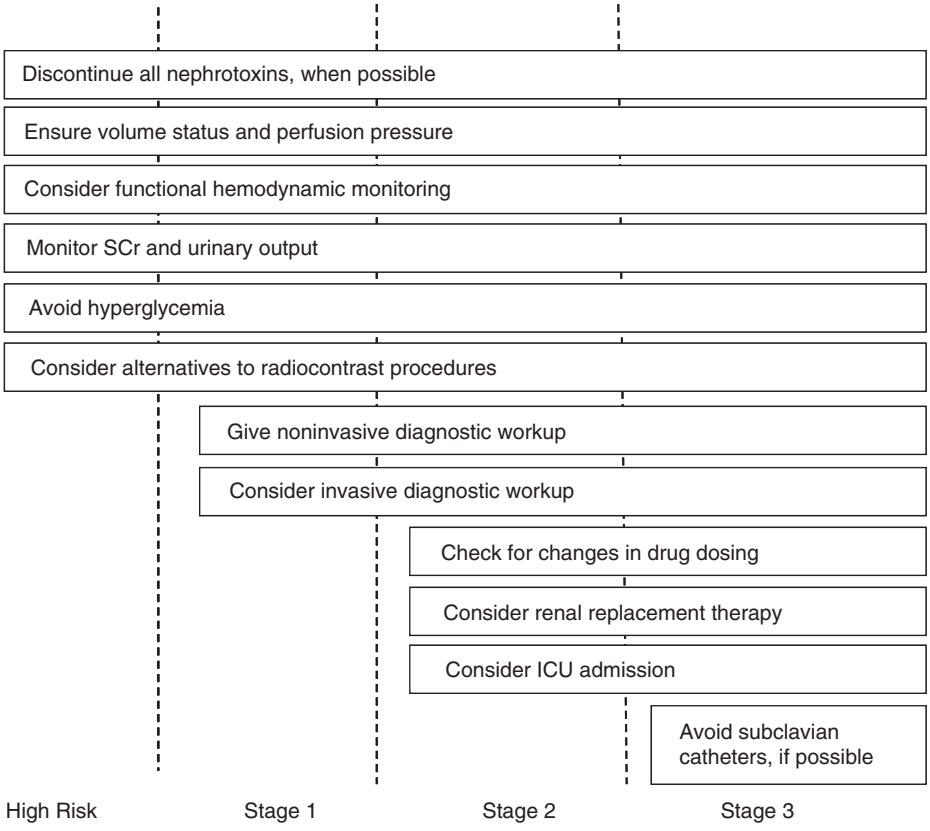

Figure 1-1. Stage-based management of AKI.

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cellular and extracellular space into the vasculature. Albumin, a purified blood product, is the most commonly used colloid. The SAFE trial examined the effects of fluid resuscitation on mortality using albumin 4% or 0.9% sodium chloride (Finfer 2004). There was no difference in death in the first 28 days in critically ill patients receiving colloids or crystalloids. However, patients in the albumin arm received 27% less fluid than patients in the saline arm, and most patients did not receive large volumes of fluid. The KDIGO guideline states that in the absence of hemorrhagic shock, isotonic crystalloids are the fluid of choice for intravascular volume expansion. Hydroxyethylstarch is relatively inexpensive compared with human albumin for correcting hypovolemia. Hydroxyethylstarch has been associated with adverse effects such as impaired coagulopathies and kidney dysfunction. They should be avoided until further studies can show their benefit or safety over crystalloids (Perel 2007). Colloids such as albumin may still play a role in patients requiring large volumes of fluid.

Diuretics

Diuretics have long been a mainstay in preventing and treating AKI. Volume overload is common, and diuretics facilitate fluid management. Studies have investigated the renoprotective effect of furosemide in reducing oxygen demand and improving clearance of necrotic debris (Ludens 1968). However, these preliminary data are outweighed by randomized controlled trials showing increased harm in patients receiving furosemide to prevent AKI after cardiac surgery or in those exposed to contrast (Ho 2006; Cantarovich 2004; Lombardi 2003; Lassnigg 2000; Solomon 1994).

Systematic reviews have shown that furosemide does not reduce the need for RRT or reduce mortality when used to treat AKI (Ho 2010). At this time, loop diuretics are recommended for treating volume overload and hyperkalemia as consequences of AKI, but they play no role in preventing or treating AKI (i.e., treatment of oliguria).

Vasopressors

Vasopressors are used to maintain an adequate mean arterial pressure (MAP) for organ and tissue perfusion. Often, fluid resuscitation alone is insufficient, and vasoactive agents must be considered. Persistent hypotension, even after fluid resuscitation, increases the risk of AKI. No one vasopressor is most effective in AKI; rather, choice of vasopressor depends on the cause of hypotension and hypoperfusion.

Of the vasopressors, dopamine was long considered preferred because low doses may improve renal blood flow. However, clinical trials have shown no improvement in the need for RRT or mortality, and dopamine plays no role in AKI (Kellum 2001). Use of dopamine has declined in favor of norepinephrine after studies showed that dopamine increases the risk of arrhythmia compared with norepinephrine and may negatively affect mortality (De Backer 2010). Fenoldopam, another dopamine agonist, is not recommended in treating or preventing AKI because of its lack of efficacy. Norepinephrine is the most commonly used vasopressor and is the current vasopressor of choice in sepsis. It has greater effects on α-receptors than on β-receptors. Adverse effects include ischemia from vasoconstriction and deleterious cardiac effects. Vasopressin is a non-adrenergic vasopressor. It is an endogenous hormone that increases vascular tone, improves blood pressure, and enhances diuresis. Vasopressin use has increased in the treatment of shock refractory to norepinephrine. The VASST trial showed no difference in mortality between vasopressin and norepinephrine, but subgroup analysis found that high doses administered with steroids reduced mortality and organ dysfunction (Russell 2008). The VANISH trial enrolled adult patients with septic shock requiring vasopressors despite fluid resuscitation within a maximum of 6 hours after the onset of shock (Gordon 2016). The trial used a 2 × 2 factorial design with treatment arms of (1) vasopressin and hydrocortisone, (2) vasopressin and placebo, (3) norepinephrine and hydrocortisone, and (4) norepinephrine and placebo to measure the effects of the different treatment arm on the primary outcome of kidney failure–free days within 28 days after randomization. The number of survivors who did not develop AKI did not differ between vasopressin and norepinephrine. However, fewer patients required RRT in the vasopressin arm. This trial shows that vasopressin cannot replace norepinephrine as the initial vasopressor for septic shock (Gordon 2016).

NUTRITION

Malnutrition, specifically protein energy wasting, is an important predictor of in-hospital mortality in patients with AKI independent of complications and comorbidities. Up to 42% of patients with AKI are malnourished on admission to the hospital (Fiaccadori 2008). Enteral nutrition is associated with improved ICU outcomes and is preferred to parenteral nutrition. There are no randomized clinical trials for nutrition in patients with AKI. All recommendations are based on expert consensus. The KDIGO guidelines recommend a total daily energy provision of 20–30 kcal/kg/day with 3–5 g/kg/day in carbohydrates and 0.8–1 g/kg/day in fat for all stages of AKI. The KDIGO guidelines on protein prescription suggest 0.8–1.0 g/kg/day in non-catabolic patients with AKI not receiving dialysis, 1.0–1.5 g/kg/day in patients with AKI receiving RRT, and up to 1.7 g/kg/day in patients receiving continuous renal replacement therapy (CRRT) and in hypercatabolic patients (KDIGO 2012). This year, the Society for Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition updated the guidelines on nutrition support in critically ill patients. They suggest using indirect calorimetry to determine caloric needs or a simple weight-based equation of 25–30 kcal/kg/day.

Expert consensus suggests that ICU patients with AKI be placed on a standard enteral formulation and that standard ICU recommendations for protein (1.2–2 g/kg of actual body weight per day) and energy (25–30 kcal/kg/day) provision be followed. Usual body weight should be used for patients at or near their ideal body weight, and ideal body weight should be used for critically ill patients and patients with obesity. Critically ill patients with AKI receiving hemodialysis or CRRT have increased nitrogen losses. Catabolic states such as sepsis and trauma can lead to multi-organ failure and an increase in protein turnover rate, which can lead to a negative nitrogen balance. Hemofiltration and hemodiafiltration can bind up to 10% of the infused amino acids. These patients have increased protein requirements, up to 2.5 g/kg/day. Energy requirements are 25–30 kcal/kg/day, indicating the need for higher protein feeds or protein-rich supplements to attain an increased nitrogen/calorie ratio. These two guidelines have differing recommendations on protein requirements. The recent American Society for Parenteral and Enteral Nutrition guidelines argue that higher protein prescriptions are needed to achieve a positive nitrogen balance.

RRT FOR AKI

Renal replacement therapy is required in 5%–6% of critically ill patients who develop AKI and is associated with increased mortality and health care costs. Despite advances in RRT, questions arise on how to optimize RRT for AKI to improve patient outcomes. Factors to consider in the prescription and delivery of RRT include timing of RRT, modality of RRT, treatment dose or intensity, and type of clearance provided by RRT (e.g., diffusion, convection). We will discuss the impact of these factors on patient outcomes and the implications for practicing pharmacists.

Timing

Until recently, a fundamental question on the optimal timing of dialysis for AKI was unaddressed in the literature. Debate centered on the risk-benefit ratio of early versus late initiation of dialysis. Clinically, most nephrologists initiate RRT in patients with AKI and volume overload or solute imbalances (i.e., acidosis or hyperkalemia). However, a recent randomized, single-center, clinical trial showed that early initiation (i.e., within 8 hours of developing stage 2 AKI) of continuous venovenous hemodiafiltration was associated with significantly reduced mortality at 90 days compared with delayed initiation (within 12 hours of stage 3 AKI) (Zarbock 2016). Additional benefits were shown for improved renal recovery and shorter time on RRT, duration of mechanical ventilation, and hospital length of stay. Additional studies are needed to confirm these results because early initiation was associated with a large reduction in mortality not previously shown. Earlier initiation of RRT will affect the assessment of renal function for drug dosing, given that patients with stage 2 AKI may have some residual renal function. Residual renal function should be considered in addition to the clearance provided by dialysis.

Modality

Supportive therapy for AKI includes intermittent or continuous RRT and hybrid therapies (Table 1-3). Intermittent hemodialysis (IHD) involves renal support for 3–6 hours per session three or four times weekly. Continuous therapies are

Table 1-3. RRT Modalities for AKI

Therapy	Advantage	Disadvantage
IHD	Short duration allows patient "off time" for procedures More rapid removal of small solutes (treatment of hyperkalemia) Less resource intensive[a]	Hypotension
CRRT	Hemodynamic stability Better control of volume and solute removal	Need for continuous anticoagulation and bleeding risks Downtime for procedures or tests may be reduced Resource intensive[a] Will not rapidly correct electrolyte disturbances Electrolyte wasting with continued therapy
SLED or EDD	Less resource intensive[a] Allows for "off time" for procedures Less anticoagulation than CRRT	Fewer studies on drug dosing Lower efficiency than CRRT Staff training/expertise

[a]Resources include nursing staff, nursing time, and equipment.

CRRT = continuous renal replacement therapy; EDD = extended daily dialysis; IHD = intermittent hemodialysis; SLED = sustained low-efficiency dialysis.

delivered theoretically 24 hours a day, 7 days a week. Hybrid therapies combine the advantages of both intermittent and continuous therapies, delivering a prolonged, gentler IHD treatment to improve patient tolerability and increase treatment efficiency compared with traditional IHD. Studies to date have not shown improved mortality between intermittent and continuous modalities (Liang 2016; Rabindranath 2007). The KDIGO guidelines suggest CRRT in patients with hemodynamic instability, excessive volume overload, or significant acid-base imbalances. Continuous renal replacement therapies are advantageous over intermittent RRT in achieving euvolemia, which is a critical factor in the ICU population.

Dose

The RRT dose is the prescribed clearance provided by the treatment and a measure of the quantity of blood purified from waste products and toxins. Clearance is defined as the volume of blood purified of urea per unit of time and is typically expressed in milliliters per minute. For IHD, the therapy is provided at least three times weekly with a goal of achieving a *Kt*/*V* (clearance of urea/unit time/volume of blood) of around 1.3. For CRRT, most centers use a dose of 25–35 mL/kg/hour. Historically, much attention was focused on whether higher clearance would remove inflammatory mediators in sepsis and improve patient outcomes. Several studies have investigated whether higher CRRT doses improve mortality or renal recovery. In a study of critically ill patients with AKI and non-renal organ failure or sepsis, increasing the intensity of IHD (six vs. three times weekly) or CRRT (35 vs. 20 mL/kg/hour) did not change mortality, renal recovery, or non-renal organ failure (VA/NIH Acute Renal Failure Trial Network 2008). Subsequently, additional trials of adult and pediatric patients from other countries similarly found no survival benefit with increasing the CRRT intensity to a dose of 35–40 mL/kg/hour.

An important consideration for pharmacists is that the prescribed clearance is not equivalent to the delivered clearance, given that the therapies may often be interrupted because of procedures, tests, or filter clotting. To determine the actual clearance provided by the treatment, the pharmacist should review the treatment flow sheet to calculate the net effluent delivered in the previous 24 hours and convert this value to milliliters per minute. For example, if a patient is initiated on continuous venovenous hemodiafiltration at a flow rate of 1 L/hour of dialysate and 1 L/hour of ultrafiltration, the prescribed clearance is 2 L/hour, or 33 mL/minute. However, if the patient is off treatment for a CT scan and is taken to the operating room for surgery, the prescribed clearance is not the same as the delivered clearance. After reviewing the treatment flow sheet, the effluent volume is determined to be 36 L. The delivered clearance is actually 25 mL/minute (i.e., 36 L/24 hours/60 minutes). This discrepancy in clearance often leads to unexpected drug concentrations during the therapeutic drug monitoring of antibiotics. Pharmacists are encouraged to be aware of this issue and to verify delivered clearances.

DRUG DOSING IN AKI

Pharmacokinetic Alterations

Acute kidney injury is associated not only with reduced renal clearance and renal metabolism of drugs but also with other impairments, such as changes in absorption, hepatic metabolism, plasma protein binding, and drug distribution. These changes may be particularly prominent in patients with severely impaired renal function and may occur even when the renal route is not the primary route of drug elimination. However, the FDA does not require pharmacokinetic studies of drugs in patients with AKI for drug applications/submissions. Information on pharmacokinetic alterations in AKI is largely extrapolated from studies of patients with CKD. However, such extrapolations may be inappropriate, given differences in the inflammatory milieu and organ cross-talk in AKI. Rapidly evolving changes in kidney function can lead to variable pharmacokinetic parameters during a patient's hospital stay.

In critically ill patients, drug absorption may be impaired because of decreased GI motility. Patients with sepsis may be receiving vasopressors, which may reduce gut perfusion, altering the bioavailability of orally administered drugs. Use of histamine receptor blockers and proton pump inhibitors to prevent stress ulcers increases gastric pH and may reduce the absorption of azole antifungals such as itraconazole or ketoconazole.

Acute kidney injury may significantly affect the volume of distribution (Vd) of drugs because of changes in total body water and distribution of body water. Sepsis causes endothelial damage and capillary leak, resulting in fluid shifts from the vasculature to the interstitium. Patients with sepsis may have effective volume depletion with increased total body stores of water. This may affect the Vd of hydrophilic drugs such as aminoglycosides, β-lactams, and glycopeptides. For example, the Vd of aminoglycosides was 0.35 L/kg in patients with AKI compared with 0.25 L/kg in patients with normal renal function. To determine changes in Vd, peak drug concentrations should be obtained for drugs with therapeutic drug monitoring. In CRRT, more rapid attainment of euvolemia and continuous re-equilibration between the different compartments minimize fluctuations in Vd.

Protein binding of drugs is altered in AKI for several reasons. Decreased synthesis of proteins, such as albumin in critical illness, can elevate the free fraction of drugs, leading to toxicity. In addition, albumin-binding capacity is decreased, likely because of the binding of endogenous inhibitors and pH changes. In CKD, uremia alters the conformational binding of substrates to albumin, leading to decreases in the protein binding of drugs such as phenytoin. Uremia likely has the

same effects in AKI, but the extent of protein binding changes is unknown, given the acuteness of the injury.

Acute kidney injury generally reduces total clearance for drugs with significant clearance by the kidneys (i.e., renal clearance less than 30% of total clearance). Reduced GFR and CrCl correspond well with reduced clearance of drugs such as antimicrobials. Sepsis may also alter renal tubular function, but this has not been fully elucidated. For example, renal elimination of fluconazole is primarily by filtration, but fluconazole also undergoes significant tubular reabsorption. In anuric patients, the drug is not filtered or reabsorbed and requires significant dose reduction. When CRRT is applied, fluconazole is filtered into the effluent; however, tubular reabsorption is not restored, resulting

Patient Care Scenario

A 53-year-old woman (weight 71 kg, height 62 in) is transferred from a community hospital to an academic medical center for sepsis secondary to a recurrent LLE cellulitis. Her medical history includes open-reduction, internal fixation of the left ankle; recurrent LLE cellulitis; HTN; and hypothyroidism. At the community hospital she was treated with intravenous clindamycin. She has worsening pain, erythema, swelling to LLE with new open wound to left lateral ankle. Her home drugs include carvedilol 12.5 mg orally twice daily, lisinopril 20 mg orally daily, clindamycin 300 mg orally three times daily, and levothyroxine 137 mcg orally daily. Her vital signs include BP 90/65 mm Hg, heart rate 98 beats/minute, respiratory rate 16 breaths/minute, O_2 saturation 98%, and pain score 8/10. She is started on intravenous fluids, vancomycin (goal trough 15-20 mg/L), and piperacillin/tazobactam. Her oral anti-hypertensives are discontinued. On day 2 of her admission she develops AKI, which continues to worsen over the next few days.

Laboratory parameters	Admission	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
SCR (mg/dL)	0.89	1.68	2.29	2.35	2.31	2.34	2.45
GFR (mL/min/1.73 m^2)	>60	32	22	22	22	22	21
Vancomycin concentration (mg/dL)		18.8		20.8			
WBC (x 10^3 cells/mm^3)	22.4	21.9	13.1	12.8	14.7	12.6	12.3

What is the etiology of her AKI and what is best to recommend for this patient?

ANSWER

The most likely etiology would be hemodynamic or pre-renal AKI secondary to sepsis. The patient presented with low blood pressure secondary to her infection as well as anti-hypertensive therapy. Lisinopril would be considered a risk factor for her development of AKI. Angiotensin converting enzyme inhibitors dilate the efferent arteriole and reduce intraglomerular pressure, which can be problematic in the setting of hypoperfusion and volume depletion. Vancomycin and piperacillin/tazobactam therapies have been associated with an increased risk of AKI in several retrospective studies. However, in this case, the rise in SCr by day 2 suggests that injury occurred prior to the administration of vancomycin and piperacillin/tazobactam. Vancomycin and piperacillin/tazobactam may have contributed to the severity of injury as the SCr continued to increase.

This case is difficult to manage because the patient requires adequate antibiotic therapy to treat sepsis but also mitigation of AKI risk factors to reduce severity of AKI, mortality and improve recovery of renal function. Fluids represent the initial therapy of choice for hemodynamic AKI to restore volume and improve perfusion. Normal saline remains the solution of choice for the treatment of AKI. If hemodynamics do not improve with fluid replacement, then vasopressors would be considered. By day 2 of the admission, the SCr is 1.68 mg/dL almost double her baseline. Estimates of kidney function include her GFR of 32, CLcr 31 by Cockcroft Gault equation, CLcr 25 mL/min by Jelliffe equation. The MDRD and Cockcroft Gault equations lead to overestimates of her kidney function since SCr is not in steady state. Re-evaluation of her antibiotic dosing is imperative with frequent therapeutic drug monitoring. Reassessment of the goal vancomycin trough is needed to minimize further injury since studies have demonstrated increased risks with troughs > 20 mg/L. In the case of cellulitis, a lower trough goal of 15 mg/L would provide adequate exposure while reducing her ongoing AKI risk. Exposures to other nephrotoxins should be minimized if possible (e.g., NSAIDs, contrast agents). Initiation of dialysis in this case would depend on additional factors including acid-base balance, volume status and electrolyte disturbances. Close monitoring of kidney function should be continued with follow-up at hospital discharge if the injury has not fully resolved.

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in drug clearance approximating normal clearance (Patel 2011). Knowledge of these pharmacokinetic changes when RRT is initiated in AKI is essential to recognize the need for dose adjustment.

Reductions in non-renal clearance (i.e., CYP metabolism) have been documented in AKI, as have changes in transporter function (e.g., P-glycoprotein); however, most data are from animal models or in vitro studies. Alterations in the non-renal clearance of vancomycin, imipenem, and meropenem have been documented and show that total clearance of these antibiotics is reduced in patients with AKI compared with healthy subjects but is higher than in patients with end-stage renal disease, indicating some preservation of hepatic function in AKI. The impact of AKI on transporter function and non-renal clearance requires further study.

Estimation of Renal Function

Most estimating equations used for drug dosing, such as Cockcroft-Gault (CG) or CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), are derived from conditions in which the SCr is at steady state in various populations, from healthy subjects to patients with CKD. Pharmacists often use the CG equation to estimate renal clearance and adjust medications because most of the approved dosing information from drug manufacturers was developed from pharmacokinetic studies using CG estimates of kidney function. However, CG and other steady-state equations will overestimate GFR in AKI because SCr is fluctuating.

In AKI, SCr changes lag behind the actual timing of the kidney insult, resulting in overestimation of renal clearance by steady-state equations. For example, consider a patient with a critical illness whose SCr changes from 1 mg/dL to 2 mg/dL overnight. This reflects significant injury to the kidney, given that the resultant GFR would have to be zero to have caused the doubling in SCr. Applying the linear relationship between SCr and GFR or using steady-state equations in this instance incorrectly estimates kidney function.

In addition, in studies of critically ill patients with a normal SCr, urinary excretion of creatinine was markedly reduced because of reduced muscle mass and creatinine generation. Using SCr to predict kidney function is insensitive in the critically ill population but is the most widely used biomarker of renal function. Measuring a 24-hour CrCl is feasible because ICU patients may have an indwelling catheter, and a nurse can complete the collection. However, several studies have shown that measured CrCl overestimates GFR in the critically ill population (Bragadottir 2013; Robert 1993). Measured GFR using iohexol or iothalamate is more accurate and is the gold standard for determining kidney function during AKI, but these tests are not widely available.

In these circumstances, equations for non–steady-state SCr should be used to estimate renal clearance. These include Jelliffe, Chiou, and Brater (Table 1-4). The difference between them is that the Jelliffe and Brater equations assume at least a 24-hour period between two SCr values, whereas the Chiou equation allows for determining clearance on an hourly basis. The Jelliffe equation has been evaluated in registries of patients with AKI, and newer versions have been developed that consider patient volume status. We recommend using the Jelliffe equation in AKI when urine collection is not feasible.

General Principles for Drug Dosing Alterations

The loading dose of a drug mainly depends on the Vd. In most instances, the loading dose does not require adjustment in AKI. Clinicians should critically appraise the patient's weight and volume status to determine whether a loading dose requires a titration of drugs that distribute in body water. In addition, some drugs have decreased tissue binding in renal failure, such as digoxin, and require a taper in loading dose. The maintenance dose depends on clearance and consequently requires dose adjustment. Dose adjustment can be made by reducing the dose, extending the interval, or using a combination of dose and interval modification.

Therapeutic Drug Monitoring

Therapeutic drug monitoring serves many purposes in AKI. Therapeutic drug monitoring fulfills the primary purpose of appropriately dosing drugs such as antimicrobials to ensure efficacy with minimal toxicity. If a patient with AKI is initiated on an antibiotic with serum concentration monitoring, population-based estimates of Vd may not be accurate, and obtaining a peak drug concentration will improve the determination of Vd. Therapeutic drug monitoring software will adjust Vd and clearance estimates to "fit" concentration data, and having an accurate estimate of Vd will minimize variability in the data. Recognizing that the patient with AKI is not at steady state and that the drug half-life will be changing, trough concentration monitoring should be used at intervals frequent enough to ensure efficacy and minimal toxicity, recognizing the limitation in concentration data. If a patient has been initiated on antibiotics and develops AKI, serum concentrations should be obtained as soon as AKI has been recognized to minimize the potential of accumulation and toxicity.

Therapeutic drug monitoring can assist in quantifying renal function. Clearances of antibiotics such as vancomycin or aminoglycosides correlate with CrCl. For example, vancomycin and gentamicin clearances are 20%–25% and 15%–20% lower than CrCl, respectively. Renal estimating equations have shown that gentamicin clearance performs as well as a 24-hour CrCl for estimating kidney function. Because serum concentration monitoring is usually used for aminoglycosides, using aminoglycoside clearance as a second measure of kidney function is a practical alternative to a measured clearance. These clearance estimates can aid in quantifying renal function, given the limitations in steady-state

Table 1-4. Estimating Equations for Fluctuating SCr

Author	Equation
Brater	CrCl (mL/min/1.73 m^2/70 kg) = [[293 − (2.03 × age)] × [1.035 − 0.01685 × (SCr1 + SCr2)]]/(SCr1 + SCr2) + [49 × (SCr1 − SCr2)]/(SCr1 + SCr2) × (time difference in days) SCr1 = first serum creatinine value. SCr2 = second serum creatinine value. Females: male value × 0.86.
Chiou	Male: CrCl (mL/min/1.73 m^2) = [2 × IBW × [28 − 0.2 (age)]/14.4 × (SCr1 + SCr2)] + [2 × [Vd(SCr1 − SCr2)]/[(SCr1 + SCr2) × (time difference (minutes))]] − [nonrenal CrCl × IBW] Female: CrCl (mL/min/1.73 m^2) = [2 × IBW × [22.4 − 0.16 (age)]/14.4 × (SCr1 + SCr2)] + [2 × [Vd(SCr1 − SCr2)]/[(SCr1 + SCr2) × (time difference (minutes))]] − [nonrenal CrCl × IBW] Vd (creat) = 0.6 L/kg. Nonrenal CrCl = 0.048 mL/min/kg IBW = ideal body weight. SCr1 = first serum creatinine value. SCr2 = second serum creatinine value.
Jelliffe	1. Estimate urinary creatinine excretion rate E1 males = Wt × (29.305 − [0.203 × (age)]) E1 females = Wt × (25.3 − [0.18 × (age)]) where: Wt = lean body weight[a] or adjusted body weight[b] if patient has obesity 2. Correct for rising SCr E2 = E1 − [4 × Wt × (SCr1 − SCr2)]/D where: Wt = lean body weight[a] or adjusted body weight[b] if patient has obesity. SCr1 = the latest serum creatinine. SCr2 = the earlier serum creatinine. D = the number of days between SCr values. 3. Calculate corrected creatinine clearance (CrCl) CrCl = (E2 × 0.12)/(SCr × BSA) where SCr = most recent serum creatinine.

[a]Lean body weight = male: (9270 × weight)/(6680 + 216 × BMI); female: (9270 × weight)/(8780 + 244 × BMI).

[b]Adjusted body weight = IBW + (actual body weight − IBW) × 0.4.

estimating equations. Furthermore, these estimates may be used to dose other drugs that do not have serum concentration monitoring, such as β-lactams.

RECOVERY OF KIDNEY FUNCTION

Quantifying Renal Recovery

Quantifying renal recovery is extremely challenging, and standardizing the definition is essential to the evaluation of management strategies for AKI. Renal recovery has been categorized into complete, partial, and non-recovery. Complete recovery is defined as a return to pre-AKI renal function, assessed as the eGFR ± 10% of baseline. Non-recovery is defined as a persistent requirement for RRT. Partial recovery is defined as a persistent impairment in GFR but no requirement for RRT.

Long-term Management and Follow-up

Patients who develop AKI during a hospitalization should be assessed for a nephrology follow-up post-discharge. Specialized ambulatory AKI clinics often focus on the first 90 days post-injury to assess the extent of recovery from the injury, quantify renal function, identify patient-specific risk factors, minimize further nephrotoxic exposures, and make referrals for CKD management if the patient does not recover. This focused evaluation and management is important because, depending on the degree of recovery,

the patient may have acute kidney disease, and exposure to nephrotoxins in this period may result in a secondary injury. Recurrent AKI episodes have been documented as a risk factor for CKD progression. In addition, patients require education on their AKI episode, avoidance of nephrotoxins, kidney function estimates, and modifiable risk factors to prevent progression to CKD.

CONCLUSION

Acute kidney injury can be caused by several conditions and should be considered a syndrome rather than an injury alone because of the many complications and effects on other organs. Pharmacists are uniquely positioned because of their knowledge base to improve AKI outcomes by identifying and avoiding nephrotoxins, optimizing medication therapy during an AKI episode, and accurately estimating kidney function in patients receiving or not receiving dialysis. Pharmacists can play a special role in educating patients on appropriate follow-up and avoiding nephrotoxins to minimize the risk of recurrent AKI and progression to CKD.

Practice Points

AKI is a syndrome caused by a spectrum of different etiologies and has many significant consequences on patient outcomes. Early recognition of AKI provides opportunity to improve patient outcomes through the following interventions:

- **Treatment of the underlying etiology of AKI. Determining the etiology is paramount to implementing therapy to reverse AKI.**
- **In pre-renal or hemodynamic AKI, fluid replacement and hemodynamic monitoring is key to reversing the injury. Normal saline is the preferred fluid for replacement since sodium chloride loading reduces tubuloglomerular feedback and pre-renal injury. There is no vasopressor of choice for pre-renal AKI. The selection of a vasopressor should be based on the etiology of AKI.**
- **Drugs are a common cause of intrinsic AKI, often necessitating the discontinuation of the offending drug. Novel chemotherapeutic agents are being recognized as an increasing cause of intrinsic AKI. Data regarding the benefit of steroids for acute interstitial nephritis is controversial and steroids are used more commonly in refractory cases that do not improve after drug discontinuation.**
- **During an AKI episode, clinicians should be cautious to avoid or minimize concurrent nephrotoxin exposures.**
- **Loop diuretics should be reserved for the management of volume overload or hyperkalemia.**
- **Assessment of renal function should be done using a measured creatinine clearance or the Jelliffe equation. Concurrent medications should be evaluated on a daily basis for dosage adjustment. Therapeutic drug monitoring should be employed when possible to guide drug dosing.**
- **Early initiation of dialysis (i.e., within 8 hours of Stage 2 AKI) may improve outcomes. There is no superior form of renal replacement therapy for AKI and increased dose of dialysis does not appear to confer a mortality benefit.**
- **Patients who experience an episode of AKI should be evaluated for resolution of injury with follow-up within the first 90 days to evaluate for the development of chronic kidney disease.**

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Self-Assessment Questions

Questions 1–10 pertain to the following case.

Z.M. is a 33-year-old woman (height 64 inches, weight 65 kg) with no known allergies; her medical history includes alcohol use disorder. Z.M. drinks 2 glasses of wine per day and 4 or 5 glasses per evening, socially. She had been feeling unwell with the flu, subjective fevers, nausea/vomiting, and abdominal pain, and she was taking acetaminophen at home for pain and fever. Upon admission to a community hospital, her vital signs were blood pressure 89/43 mm Hg, heart rate 89 beats/minute, temperature 98.4°F, and O_2 96% on room air. Her SCr was 0.78 mg/dL on admission, and over the next 24 hours, her urinary output was 875 mL. Blood cultures were positive for *Escherichia coli*. Z.M. was treated with levofloxacin for an upper respiratory infection. Five days later, she was transferred to the ICU for acute hepatic failure, upper respiratory illness, and witnessed seizure. On physical examination, Z.M. is alert and oriented, and she has ascites, jaundiced skin, and scleral icterus with 3 mm edema up to her shins. Blood pressure is 85/48 mm Hg. Repeat chemistry and CBC are significant for SCr 2.39 mg/dL, BUN 52 mg/dL, Na 131 mEq/L, K 3.3 mEq/L, WBC 27.1 × 10^3 cells/mm^3, and Hgb 8.4 g/dL. Her urinary output is now 10 mL/hour. Urinalysis shows specific gravity 1.03, 1+ protein, 5–10 RBCs, 2–5 WBCs, and few hyaline casts. Blood, urine, and respiratory cultures are pending. Z.M. is initiated on vancomycin and meropenem for presumed sepsis. A CT scan of her abdomen is ordered with contrast.

1. Which one of the following best categorizes Z.M.'s stage of AKI?

   A. 1
   B. 2
   C. 3
   D. 4

2. In addition to liver failure, which one of the following risk factors most likely contributed to Z.M.'s AKI?

   A. Contrast
   B. Acetaminophen
   C. Sepsis
   D. Levofloxacin

3. After the urine chemistry laboratory tests are completed, which one of the following tests would best assist in Z.M.'s diagnosis?

   A. Urine sediment
   B. Complement titers, antinuclear antibodies and antineutrophil cytoplasmic antibodies
   C. Renal ultrasonography
   D. Renal biopsy

4. Which one of the following is the most likely etiology of Z.M.'s AKI?

   A. Prerenal or hemodynamic AKI
   B. Acute tubular necrosis (ATN)
   C. Acute interstitial nephritis (AIN)
   D. Obstructive

5. Which one of the following treatment strategies is best to recommend first for Z.M.?

   A. Albumin 4% 250 mL
   B. Fluid resuscitation with 0.9% sodium chloride
   C. Furosemide 40 mg intravenous bolus dose
   D. Norepinephrine continuous infusion

6. Which one of the following estimates of Z.M.'s CrCl should be used for drug dosing?

   A. Less than 10 mL/minute/1.73 m^2
   B. 10–20 mL/minute/1.73 m^2
   C. 21–30 mL/minute/1.73 m^2
   D. 31–40 mL/minute/1.73 m^2

7. Which one of the following best describes when Z.M. should be initiated on renal replacement therapy (RRT)?

   A. Immediately
   B. When serum potassium is 6 mEq/L
   C. When blood gases show a pH less than 7.1
   D. When volume overload is unresponsive to diuretics

8. Which one of the following RRT modalities is best to initiate for Z.M.?

   A. Peritoneal dialysis using a cycler
   B. Intermittent hemodialysis (IHD) three times weekly
   C. Continuous venovenous hemofiltration
   D. Sustained low-efficiency dialysis

9. Which one of the following best represents the optimal dose of clearance by continuous renal replacement therapy (CRRT) for Z.M.?

   A. 650–1300 mL/hour
   B. 1300–1625 mL/hour
   C. 1625–2275 mL/hour
   D. 2275–2600 mL/hour

10. Z.M. is initiated on continuous venovenous hemodiafiltration (CVVHDF) at a rate of dialysate 1.5 L/hour and ultrafiltration 1 L/hour. She is taken to radiology for her CT scan. Her total effluent volume from the procedure over the past 24 hours is 43.2 L. Which one of the following best represents the ideal CrCl to use for dosing Z.M.'s meropenem?

    A. Less than 10 mL/minute/1.73 m^2
    B. 23 mL/minute/1.73 m^2
    C. 33 mL/minute/1.73 m^2
    D. 43 mL/minute/1.73 m^2

Questions 11–13 pertain to the following case.

M.S. is an 18-year-old previously healthy woman (height 66 inches, weight 65 kg) who is admitted to the hospital for a facial rash and pain that is of concern for herpes simplex virus (HSV) conjunctivitis. Laboratory findings on admission are significant for mild leukopenia, WBC 3.9 × 10^3 cells/mm^3, SCr within normal range of 0.75 mg/dL (eGFR 135 mL/minute/1.73 m^2), BUN 12 mg/dL, and urinary output 1550 mL/24 hours. M.S. is initiated on acyclovir 1250 mg intravenously every 8 hours for HSV conjunctivitis. On treatment day 4, her SCr is 1.8 mg/dL (eGFR 47 mL/minute/1.73 m^2). The therapy is changed, and she is administered 2 L of 0.9% sodium chloride. Her urinary output after fluids is 4250 mL/24 hours. Seven days later, on hospital discharge, M.S. has an SCr of 1.2 mg/dL (eGFR 76 mL/minute/1.73 m^2).

11. Which one of the following is the most likely etiology of M.S.'s AKI?

    A. Prerenal
    B. AIN
    C. ATN
    D. Postrenal

12. Which one of the following best characterizes M.S.'s prognosis?

    A. Complete recovery
    B. Partial recovery
    C. Delayed recovery
    D. Non-recovery

13. Which one of the following is best to recommend as a follow-up for M.S.?

    A. Referral to the AKI clinic in the first 90 days post-injury
    B. Referral to the CKD clinic
    C. Follow-up with primary care provider
    D. No follow-up required

14. A 56-year-old man is admitted to the hospital with a 3-week history of productive cough, upper lobe infiltrates on chest radiography, and fever. He has a history of hypertension and chronic obstructive pulmonary disease and takes inhalers as well as lisinopril 10 mg by mouth daily. The patient has been a smoker for 30 years. Electrolytes, CBC, and renal function are normal on admission. Sputum cultures grow *Mycobacterium tuberculosis*. The patient is treated with clarithromycin, rifampin, and ethambutol. Two weeks later, his fever recurs; 3 days later, his SCr increases from 1 mg/dL to 1.5 mg/dL. During the next 3 days, his SCr increases to 1.7 mg/dL, 1.9 mg/dL, and 2.1 mg/dL. No rash is noted. His urinalysis is positive for WBCs 5–8/high-power field (HPF) and RBCs 2–5/HPF. Eosinophils are detected in the urine, and FENa (fractional excretion of sodium) is greater than 1%. Renal ultrasonography is negative for hydronephrosis. Which one of the following is most likely etiology of this patient's AKI?

    A. Prerenal AKI from lisinopril
    B. AIN from rifampin
    C. ATN from ethambutol
    D. Postrenal obstruction from renal tuberculosis

15. A 60-year-old woman is scheduled for elective coronary artery bypass grafting of three vessels. She has a history of hypertension, hyperlipidemia, and hypothyroidism. Which one of the following biomarkers would best help predict AKI post-surgery for this patient?

    A. SCr
    B. TIMP-2
    C. Kidney injury molecule-1 (KIM-1)
    D. Neutrophil gelatinase-associated lipocalin (NGAL)

Questions 16–18 pertain to the following case.

M.T., a 72-year-old-man, is found down on his boat. He is admitted to the ICU for hypotension, septic shock, and second-degree sunburns. His vital signs are blood pressure 69/49 mm Hg and heart rate 95 beats/minute. Laboratory values are AST 31 IU/L, ALT 15 IU/L, total bilirubin 0.3 mg/dL, WBC 12 × 10^3 cells/mm^3, SCr 2.3 mg/dL, Na 145 mEq/L, Cl 106 mEq/L, K 4 mEq/L, HCO_3 20 mEq/L, and pre-albumin 17 mg/dL. M.T.'s medical history includes coronary artery disease, hypertension, and diabetes.

16. Which one of the following is best to recommend as the immediate course of action for M.T.?

    A. Albumin
    B. Sodium chloride
    C. Lactated Ringer
    D. Dextrose 5% in water

17. M.T. responds marginally to fluid resuscitation (blood pressure 80/55 mm Hg). Which one of the following vasopressors is best to recommend to improve M.T.'s hemodynamics and organ perfusion?

    A. Norepinephrine
    B. Vasopressin
    C. Dopamine
    D. Phenylephrine

18. M.T. is initiated on vancomycin and piperacillin/tazobactam empirically for septic shock after fluid resuscitation. Which one of the following is the best option for monitoring M.T.'s vancomycin concentrations?

    A. Check peak concentration on same day
    B. Check peak concentration after second dose, trough concentration in 2 days
    C. Check trough concentration in 2 days
    D. Check trough concentration in 4 days

Questions 19 and 20 pertain to the following case.

V.O. is a 57-year-old woman (height 64 inches, weight 90 kg) receiving chronic dialysis. She has been in the ICU for the past 3 days with methicillin-resistant *Staphylococcus aureus* bacteremia. She is hypotensive and febrile, progressing to sepsis. V.O. has been initiated on CVVHDF.

19. The ICU team would like to initiate nutrition for V.O. Which one of the following is best to recommend for V.O.?

    A. Give enteral nutrition.
    B. Give parenteral nutrition.
    C. Hold nutrition.
    D. Give only clear soup.

20. One week later, V.O. is initiated on parenteral nutrition. The nutritionist asks you to help estimate the patient's protein needs. In grams of protein per day, which one of the following is best to recommend for V.O. to receive?

    A. 66
    B. 138
    C. 173
    D. 225