Chapter 61: Acute Kidney Injury

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 75, Acute Kidney Injury.

KEY CONCEPTS

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1. Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines provide a classification system for diagnosing and staging acute kidney injury (AKI). This classification system is based on separate criteria for serum creatinine (S_{cr}) and urine output.

2. AKI is a common complication in critically ill patients that is different than chronic kidney disease and is associated with high morbidity and mortality.

3. AKI is typically categorized based on three types of injury: (a) prerenal—decreased renal blood flow, (b) intrinsic—structural damage within the kidney, and (c) postrenal—an obstruction within the urine collection system.

4. Serum creatinine, urea, and urine output are commonly used markers of kidney function in clinical practice. However, advances in AKI research have led to the development of multiple novel biomarkers that can be used for risk assessment, early detection, classification, and prognosis in AKI.

5. Conventional formulas used to estimate glomerular filtration rate (eGFR) are not recommended in AKI patients. In addition, medication dose adjustment recommendations are typically based on limited pharmacokinetic studies conducted in chronic kidney disease (CKD) patients and may not be reflective of pharmacokinetic changes and dosing requirements in AKI patients.

6. The most effective prevention strategies for AKI include limiting exposure to nephrotoxic medications and optimizing the patient's hemodynamic and fluid status. Incorporation of electronic health alerts may increase early detection and decrease risk of AKI progression.

7. Supportive management remains the primary approach to prevent or reduce complications associated with AKI or comorbid conditions. Supportive therapies include renal replacement therapy (RRT), nutritional support, identifying potential causes and avoidance of nephrotoxins, blood pressure management, and fluid management.

8. For patients with prolonged or severe AKI, RRT is the cornerstone of support along with aggressive fluid and electrolyte management.

9. Medication dosing for AKI patients receiving continuous renal replacement therapy (CRRT) or prolonged RRT is poorly characterized. Dosing requirements of agents primarily eliminated by the kidney may require individualization and may be higher than observed in CKD. Dosing requirements may need to be adjustment downward as kidney function declines, and then subsequently increase as AKI resolves. Therapeutic drug monitoring should be utilized whenever possible for any agent with a narrow therapeutic index.

PATIENT CARE PROCESS

Patient Care Process for Acute Kidney Injury

Collect

- Patient characteristics (eg, age, sex)
- Chief complaint/reason for admission
- Patient medical history including other relate comorbid conditions (eg, CKD, diabetes, HTN, cirrhosis)
- Current medication list
- Baseline serum creatinine (if available)
- Volume status (low fluid volume eg, dehydration), urine output
- Hemodynamic (eg, blood pressure, mean arterial pressure)
- Urinalysis results (eg, WBCs, RBCs, protein, granular casts, FE_{Na}) (see Table 61-2)
- Kidney imaging results (eg, obstruction, hydronephrosis)

Assess

- Stage and severity of AKI using KDIGO criteria (Table 61-1)
- Most likely type of AKI (Fig. 61-2)
- Presence of baseline CKD
- Presence of sepsis, severe sepsis, or septic shock
- Presence of electrolyte disturbances
- RRT modality and parameters if applicable (Fig. 61-3)

Plan*

- Assess direction and degree of changing kidney function
- Review all medications for appropriateness and ensure doses and frequencies are adjusted for patient's current kidney function and RRT
- Evaluate presence and eliminate any potential nephrotoxins
- Need for electrolyte corrections
- Identify any renally eliminated medications with narrow therapeutic indexes. Recommend therapeutic drug monitoring when necessary

Implement*

- Formulate a management plan for any necessary medication additions, deletions or dose alterations
- Communicate treatment plant to the patient's primary team and nephrology team (if consulted)
- Document therapy recommendations including dose adjustments and follow-up assessment plans in the patient's electronic health record or

chart

- Provide patient education regarding all elements of treatment plan (when possible)

Follow-up: Monitor and Evaluate (Table 61-7)

- Changes in kidney function (eg, changes in S_{cr}, urine output, continued need for RRT or changes in the RRT approach)
- Hemodynamic and volume status
- Electrolytes, acid-base status
- Response to the medication regimen including any potential adverse events
- Patient adherence to treatment plan using multiple sources of information
- Overall clinical status and management progression

**Collaborate with patient, caregivers, and other healthcare professionals.*

BEYOND THE BOOK

BEYOND THE BOOK

Watch the video entitled "Changing Glomerular Filtration Rate" in Khan Academy (https://youtu.be/x0pFo1RxTzM). This 4 min video provides a brief overview of how changes in afferent and efferent arteriolar tone control the glomerular filtration rate. This video is useful to enhance student understanding of the pathophysiology and medication-induced causes of AKI, as well as the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

Acute kidney injury (AKI) is a clinical syndrome generally defined by an abrupt reduction in kidney function as evidenced by changes in serum creatinine (S_{cr}), blood urea nitrogen (BUN), and urine output. The consequences of AKI can be serious, especially in hospitalized patients. Early recognition along with supportive therapy is the focus of management for those with established AKI, as there is no pharmacologic therapy that directly reverses the injury. Individuals at risk, such as those with history of chronic kidney disease (CKD), need to have their hemodynamic status carefully monitored and their exposure to nephrotoxins minimized. A thorough patient assessment including medical and surgical history, medication use, physical examination, and multiple laboratory tests is essential. Management goals include maintenance of blood pressure, fluid and electrolyte homeostasis, all of which may be dramatically altered in the presence of AKI, as well as the use of diuretics and renal support therapies. Additional therapies designed to eliminate or minimize the insult that precipitated AKI include discontinuation of any offending agents (ie, nephrotoxins), hydration, maintenance of renal perfusion, and renal replacement therapy (RRT).

In this chapter, the definition, classification, epidemiology, and common etiologies of AKI are presented. Methods to recognize and assess the extent of kidney function loss are also discussed. Unique considerations for medication dosing adjustments and finally, preventive strategies for patients at risk and management approaches for those with established AKI are reviewed.

DEFINITION AND CLASSIFICATION OF ACUTE KIDNEY INJURY

1 Several different definitions and classifications of AKI have been published, including the *R*isk, *I*njury, *F*ailure, *L*oss of Kidney Function, and *E*nd-Stage Kidney Disease (RIFLE), *A*cute *K*idney *I*njury *N*etwork (AKIN), and Kidney Disease: Improving Global Outcomes (KDIGO) classifications. Among these, the KDIGO criteria are the most commonly used for diagnosing and staging AKI (Table 61-1).[1-3] The KDIGO criteria have been validated across

different patient populations and their staging correlates closely with hospital mortality, cost, and length of stay.[4-6]

TABLE 61-1

RIFLE, AKIN, and KDIGO Classification Schemes for AKI[a]

RIFLE Category	S_{cr} and GFR[b] Criteria	Urine Output Criteria
Risk	S_{cr} increase to 1.5-fold or GFR decrease >25% from baseline	<0.5 mL/kg/hr for ≥6 hours
Injury	S_{cr} increase to twofold or GFR decrease >50% from baseline	<0.5 mL/kg/hr for ≥12 hours
Failure	S_{cr} increase to threefold or GFR decrease >75% from baseline, or S_{cr} ≥4 mg/dL (354 µmol/L) with an acute increase of at least 0.5 mg/dL (44 µmol/L)	Anuria for ≥12 hours
Loss	Complete loss of function (RRT) for >4 weeks	
ESKD	RRT >3 months	
AKIN Criteria	**S_{cr} Criteria**	**Urine Output Criteria**
Stage 1	S_{cr} increase ≥0.3 mg/dL (27 µmol/L) or 1.5- to 2-fold from baseline	<0.5 mL/kg/hr for ≥6 hours
Stage 2	S_{cr} increase >2- to 3-fold from baseline	<0.5 mL/kg/hr for ≥12 hours
Stage 3	S_{cr} increase >3-fold from baseline, or S_{cr} ≥4 mg/dL (354 µmol/L) with an acute increase of at least 0.5 mg/dL (44 µmol/L), or need for RRT	<0.3 mL/kg/hr for ≥24 hours or anuria for ≥12 hours
KDIGO Criteria	**S_{cr} Criteria**	**Urine Output Criteria**
Stage 1	S_{cr} increase ≥0.3 mg/dL (27 µmol/L) or 1.5-1.9 times from baseline	<0.5 mL/kg/hr for 6-12 hours
Stage 2	S_{cr} increase 2-2.9 times from baseline	<0.5 mL/kg/hr for ≥12 hours
Stage 3	S_{cr} increase three times from baseline, or S_{cr} ≥4 mg/dL (354 µmol/L), or need for RRT, or eGFR[c] <35 mL/min/1.73 m^2 in patients <18 years	Anuria for ≥12 hours

[a]For all staging systems, the criterion that leads to worst possible diagnosis should be used.

[b]GFR calculated using the Modification of Diet in Renal Disease (MDRD) equation.

[c]GFR calculated using the Schwartz formula.

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; hr, hours; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease; RRT, renal replacement therapy; S_{cr}, serum creatinine.

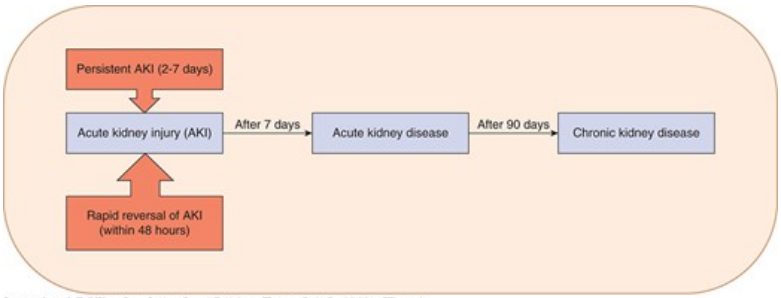
Since the KDIGO staging system depends on S_{cr} and urine output as the main diagnostic criteria, it is associated with some inherent weaknesses. An

increase in S_{cr} is usually evident roughly 1 or 2 days after development of AKI. This lag time in S_{cr} rise may delay diagnosis of AKI and adversely affect patient outcomes. Urine output decreases earlier and often is the first indicator of AKI but it is a fairly nonspecific marker. Documentation can be challenging, especially with patients able to independently void without ability to document urine output. In fact, patients with AKI can be nonoliguric (urine output greater than 500 mL/day), oliguric (urine output less than 500 mL/day), or anuric (urine output less than 50 mL/day). Urine output will also vary with volume status, diuretic administration or omission, and the presence of an obstruction.[7]

AKI becomes acute kidney disease (AKD) if kidney function is impaired beyond 7 days, and can ultimately transition into CKD if the duration exceeds 90 days (Fig. 61-1).[8] As such, there has been a growing recognition of the need to standardize AKI recovery. The Acute Disease Quality Initiative (ADQI) proposed to further subclassify AKI into those who recover within 48 hours of injury (rapid reversal of AKI) and those whose injury persists beyond 48 hours (persistent AKI).[8]

FIGURE 61-1

Continuum of impaired kidney function. Acute kidney injury is an abrupt decrease in kidney function that can either rapidly reverse within the first 48 hours or persist over a period of up to 7 days. Kidney impairment that persists beyond 7 days is termed acute kidney disease and can lead to chronic kidney disease if its duration exceeds 90 days.



EPIDEMIOLOGY

The epidemiology of AKI varies widely depending on the patient population studied and the criteria used to evaluate the patient. A recent CDC analysis from the National Inpatient Sample and the National Health Interview Surveys noted that the total number of AKI-related hospitalizations increased fourfold over the last two decades (from 953,926 in 2000 to 3,959,560 in 2014). Age-standardized rates of AKI hospitalizations increased 139% (23-55 per 1,000 persons) among diabetic adults and rose by 230% (3.5-11.7 per 1,000 persons) among non-diabetic adults.[9]

AKI occurs in 3.0% to 18.3% of hospitalized non-critically ill patients and 30% to 60% of critically ill adults.[10] Risk factors associated with AKI include the presence of CKD, diabetes, heart or liver disease, albuminuria, major surgery (especially cardiac surgery), acute decompensated heart failure, sepsis, hypotension, volume depletion (diarrhea, vomiting, or dehydration), medications (exposure to angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], aminoglycosides, etc.), advanced age, male gender, and African American race.[3,10-12]

2 Severity, duration, and frequency of AKI are important predictors of poor patient outcomes. Any degree of AKI is associated with an increased risk of death, and the odds increase with the severity of the insult.[10,12] For survivors of AKI, the development of some degree of CKD and need for RRT are other important considerations. In addition, AKI is associated with increased length of hospital stay, mortality, cost, readmission, ventilator days, and need for post-hospitalization care.[10,12,13]

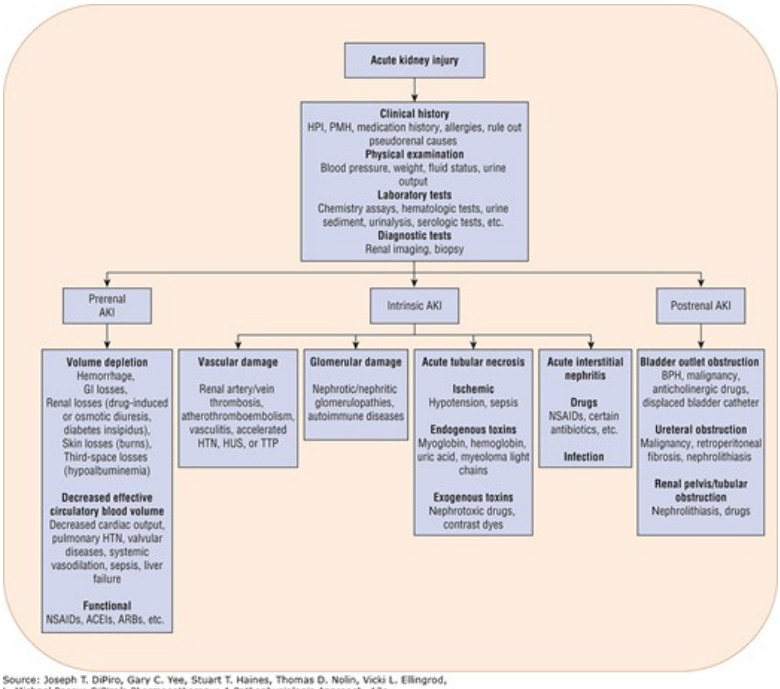
ETIOLOGY

3 The etiology of AKI can be divided into three broad categories based on the anatomic location of the injury associated with the precipitating factor(s). The management of patients presenting with this disorder is largely predicated on identification of the specific etiology responsible for the patient's AKI (Fig. 61-2). Traditionally, the causes of AKI have been categorized as (a) prerenal, which results from decreased renal perfusion in the

setting of undamaged parenchymal tissue, (b) intrinsic, the result of structural damage to the kidney, most commonly the tubule from an ischemic or toxic insult, and (c) postrenal, caused by obstruction of urine flow downstream from the kidney.

FIGURE 61-2

Classification of acute kidney injury (AKI) based on etiology. (ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BPH, benign prostatic hyperplasia; HPI, history of present illness; HTN, hypertension; HUS, hemolytic uremic syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs; PMH, past medical history; TTP, thrombotic thrombocytopenic purpura.)



The risk of AKI increases substantially with decreasing glomerular filtration rate (GFR) and presence of albuminuria and underlying CKD. A history of AKI has also been associated with high risk for developing additional episodes of AKI and subsequent complications such as CKD.[10,14]

PATHOPHYSIOLOGY

The pathophysiologic processes involved in the development of the three traditional categories of AKI: prerenal AKI, intrinsic AKI, and postrenal AKI are described below.

Prerenal Acute Kidney Injury

Prerenal AKI or prerenal azotemia results from hypoperfusion of the renal parenchyma, with or without systemic arterial hypotension. Renal hypoperfusion associated with systemic arterial hypotension may be caused by a decline in either the intravascular volume or the effective circulating blood volume. Intravascular volume depletion may result from several conditions, including hemorrhage, excessive gastrointestinal (GI) losses (severe vomiting or diarrhea), dehydration, extensive burns, and diuretic therapy. Effective circulating blood volume may be reduced in conditions associated with a decreased cardiac output or blood flow to the kidney and systemic vasodilation. Renal hypoperfusion without systemic hypotension is most commonly associated with bilateral renal artery occlusion or unilateral occlusion in a patient with a single functioning kidney.

Patients with a mild reduction in effective circulating blood volume or volume depletion are generally able to maintain a normal GFR by activating several compensatory mechanisms. Those initial physiologic responses by the body stimulate the sympathetic nervous and the renin–angiotensin–aldosterone system and release antidiuretic hormone if hypotension is present. These responses work together to directly maintain blood pressure via vasoconstriction and stimulation of thirst, which in conscious patients results in increased fluid intake, as well as sodium and water retention. Additionally, GFR may be maintained by afferent arteriole dilation (mediated by intrarenal production of vasodilatory prostaglandins, kallikrein, kinins,

and nitric oxide) and efferent arteriole constriction (mainly mediated by angiotensin II). In concert, these homeostatic mechanisms are often able to maintain arterial pressure and renal perfusion, potentially averting the progression to AKI.[15] If, however, the decreased renal perfusion is severe or prolonged, these compensatory mechanisms may be overwhelmed, and prerenal AKI will be clinically evident.

Patients at risk for prerenal AKI are particularly susceptible to changes in the afferent and efferent arteriolar tone, as they may not be able to compensate as readily. Some medications interfere with these renal adaptive responses, and the resulting reduction in the glomerular hydrostatic pressure precipitates an abrupt decline in GFR and is sometimes referred to as *functional AKI*. A common cause of this syndrome is a decrease in efferent arteriolar resistance as the result of initiation of an ACE inhibitor or ARB (see Chapter 65). For example, individuals with heart failure are often given an ACE inhibitor or ARB to help improve left ventricular function, but if the dose is titrated too rapidly, they may experience a decline in GFR. If the increase in the S_{cr} is less than 30% from baseline and potassium serum levels are within normal range, the medication can generally be continued.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may also precipitate AKI in susceptible individuals due to their impact on renal prostaglandin production and afferent arteriolar vasodilation, which some patients rely on to maintain GFR.[16]

Sepsis is one of the leading clinical conditions associated with AKI. The exact mechanism by which sepsis causes AKI is poorly understood. A complex interplay of different mechanisms may be involved in its pathogenesis, including disturbances in renal microcirculation, inflammation, and metabolic reprogramming.[17,18]

Intrinsic Acute Kidney Injury

Intrinsic AKI results from direct damage to the kidney and is categorized on the basis of the injured structures within the kidney: vasculature, glomeruli, tubules, and interstitium.

Renal Vasculature Damage

Occlusion of the larger renal vessels resulting in AKI is not common but can occur if large atheroemboli or thromboemboli occlude the bilateral renal arteries or one vessel of the patient with a single kidney. Atheroemboli most commonly develop during vascular procedures that cause atheroma dislodgement, such as angioplasty and aortic manipulations. Thromboemboli may arise from dislodgement of a mural thrombus in the left ventricle of a patient with severe heart failure or from the atria of a patient with atrial fibrillation. Renal artery thrombosis may occur in a similar fashion to coronary thrombosis, in which a thrombus forms in conjunction with an atherosclerotic plaque.

Although smaller vessels can also be obstructed by atheroemboli or thromboemboli, the damage is limited and the development of clinically significant AKI is unlikely. However, these small vessels are susceptible to inflammatory processes that lead to microvascular damage and vessel dysfunction when the renal capillaries are affected. Neutrophils invade the vessel wall, causing damage that can include thrombus formation, tissue infarction, and collagen deposition within the vessel structure. Diffuse renal vasculitis can be severe and promote concomitant ischemic acute tubular necrosis (ATN). Untreated hypertension may also compromise renal microvascular blood flow, causing diffuse renal capillary damage.

Glomerular Damage

Glomerular damage is an uncommon cause of AKI. The glomerulus serves to filter fluid and solute into the tubules while retaining proteins and other large blood components in the intravascular space. Kidney injury may develop when circulating immune complexes deposit in the glomeruli and cause an inflammatory reaction (eg, lupus nephritis, IgA nephropathy).[19] Details on the pathophysiology and specific therapeutic approaches to glomerulonephritis are described in Chapter e66.

Tubular Damage

Most intrinsic AKI cases are due to ATN, which can either result from renal ischemia or nephrotoxin exposure (eg, aminoglycosides, contrast dyes). The tubules located within the medulla of the kidney are particularly at risk for ischemic injury, as this portion of the kidney is metabolically active and thus has high oxygen requirements, yet, as compared with the cortex, receives relatively low oxygen delivery. Thus, ischemic conditions caused by severe hypotension or exposure to vasoconstrictive medications preferentially affect the tubules more than any other portion of the kidney.

The clinical evolution of ATN is characterized by four distinct phases: initiation, extension, maintenance, and recovery. Renal tubular epithelial cell

injury is the hallmark of the initiation phase that results from vasoconstriction and ischemia, and leads to GFR reduction. Contrary to its name, ATN is not only characterized by necrosis and cell death but by a large spectrum of cellular injury that usually involves sublethal damage to the cells. The extent of injury depends not only on the severity and duration of ischemia but also on the sensitivity of renal cells to the insult which may vary based on the cells' metabolic demands, physical location within the kidney, degree of regional blood perfusion, oxygenation status, and membrane permeability. Further, alterations in cytoskeletal structure lead to a loss of epithelial polarity and barrier function. As a result, the glomerular filtrate starts leaking back into the interstitium and is reabsorbed into the systemic circulation. Additionally, urine flow is obstructed by accumulation of sloughed epithelial cells, cellular debris, and formation of casts.[19,20]

The extension phase is characterized by continued hypoxia following the initial ischemic event and an inflammatory response. Both events are more pronounced in the outer medullary region and the GFR continues to decrease. During the maintenance phase, GFR reaches a nadir during which cellular repair processes are initiated in an attempt to reestablish and maintain cellular and tubular integrity. The surviving cells undergo repair, migration, dedifferentiation, and proliferation. The maintenance phase is eventually followed by a recovery phase, during which new tubule cells are regenerated through redifferentiation and epithelial polarity is reestablished.[19,20]

Interstitial Damage

Acute interstitial nephritis (AIN) is an idiosyncratic delayed hypersensitivity immune reaction that is most commonly caused by medications (see Chapter 65) and less commonly by infections, autoimmune diseases, or idiopathic causes. AIN is characterized by tubular and interstitial inflammation, and edema with lesions composed of mononuclear cells, with a predominance of lymphocytes (primarily CD4+ T lymphocytes) and monocytes or macrophages. The specific pathogenic process depends on the cause of AIN. Medication-induced disease is characterized by renal interstitial dendritic and renal tubular epithelial cells recognition of the offending agent as immunogenic and their activation of T lymphocytes which induce proinflammatory molecules. Once acute interstitial inflammation sets in, it can progress rapidly to a more destructive fibrogenic process marked by increased interstitial matrix, ischemia, tubular atrophy, and interstitial fibrosis.[21,22] The prognosis of AIN varies depending on the specific cause, baseline kidney function, and timely detection of the offending agent; however, it is estimated that almost a quarter of patients may not recover their baseline kidney function.[22]

Postrenal Acute Kidney Injury

Postrenal AKI accounts for less than 5% of all cases of AKI and may develop as the result of obstruction at any level within the urinary collection system (see Fig. 61-2). However, if the obstructing process is above the bladder, it must involve both kidneys (one kidney in a patient with a single functioning kidney) to cause clinically significant AKI, as one functioning kidney can generally maintain a near-normal GFR. Bladder outlet obstruction, the most common cause of obstructive nephropathy, is often the result of a prostatic process in males (hypertrophy, cancer, or infection), producing a physical impingement on the urethra and thereby preventing the passage of urine. It may also be the result of an improperly placed urinary catheter. Blockage may also occur at the ureter level secondary to nephrolithiasis, blood clots, sloughed renal papillae, or physical compression by an abdominal process. Crystal deposition within the tubules from oxalate and some medications severe enough to cause AKI is uncommon, but it is possible in patients with severe volume contraction and in those receiving large doses of a medication with relatively low urine solubility (see Chapter 65).[19] Typically, these patients have insufficient urine volume to prevent crystal precipitation in the urine. Extremely elevated uric acid concentrations from chemotherapy-induced tumor lysis syndrome can cause obstruction and direct tubular injury as well.[23] Wherever the location of the obstruction, urine will accumulate in the renal structures above the obstruction and cause increased pressure upstream. The ureters, renal pelvis, and calyces all expand, and the net result is a decline in GFR. If renal vasoconstriction ensues, a further decrement in GFR will be observed.

CLINICAL PRESENTATION

The initiating signs or symptoms of AKI are highly variable and largely dependent on the underlying etiology. It may be a change in urinary character (eg, decreased urine output or urine discoloration), edema, electrolyte disturbances, sudden weight gain, or severe abdominal or flank pain. Early recognition and cause identification are critical, as they directly affect the outcome of AKI. One of the first steps in the diagnostic process is to determine if the change in kidney function is acute, chronic, or the result of an acute change in a patient with known CKD (also called acute-on-chronic kidney failure). Patients should also be promptly evaluated for any changes in their fluid and electrolyte status. Patients presenting with AKI in the outpatient environment may have nonspecific or seemingly unrelated symptoms so that the time of onset of the injury can be difficult to determine. On

the other hand, AKI in hospitalized patients is often detected much earlier in its course due to frequent laboratory studies and daily (or hourly) patient assessments.

Patient Assessment

The assessment of a patient with AKI starts with a thorough review of his or her medical records, with a particular focus on chronic conditions, laboratory studies, procedures, and surgeries. An exhaustive review of prescription and nonprescription medicines, herbal products, and drugs of abuse may help determine if AKI was potentially precipitated by drug ingestion.

During the initial patient evaluation, presumptive signs and symptoms of AKI need to be differentiated from a potential new diagnosis of CKD. A medical history for kidney disease–related chronic conditions (eg, poorly controlled hypertension or diabetes mellitus), previous laboratory data documenting the presence of proteinuria or an elevated S_{cr}, and the finding of bilateral small kidneys on renal ultrasonography suggest the presence of new onset CKD rather than AKI. However, it is important to note that patients with CKD may develop episodes of AKI as well. In these patients, an abrupt rise in the baseline S_{cr} is one of the most useful indicators of the presence of an acute insult to the kidneys. The staging of AKI should also be assessed including the initial insult and decline in kidney function, stabilization of the decline in function, and recovery period.

An acute change in urinary habitus is another common and noticeable symptom associated with AKI. The presence of cola-colored urine is indicative of blood in the urine, a finding commonly associated with acute glomerulonephritis. In hospitalized patients, changes in urine output may be helpful in characterizing the cause of the patient's AKI. Acute anuria is typically caused by either complete urinary obstruction or a catastrophic event (eg, shock or acute cortical necrosis). Oliguria, which often develops over several days, suggests prerenal azotemia, whereas nonoliguric kidney failure usually results from acute intrinsic kidney failure or incomplete urinary obstruction.

Depending on the underlying cause of AKI, patients may present with a variety of symptoms affecting virtually any organ system of the body. Constitutional symptoms such as nausea, vomiting, fatigue, malaise, and weight gain are common but nonspecific. The onset of flank pain is suggestive of a urinary stone; however, if bilateral, it may suggest swelling of the kidneys secondary to acute glomerulonephritis or AIN. Complaints of severe headaches may suggest the presence of severe hypertension and vascular damage. The presence of fever, rash, and arthralgia may be indicative of medication-induced AIN or lupus nephritis.

A thorough physical examination is an important step in evaluating individuals with AKI, as clues regarding the etiology can be evident from the patient's head (eye examination) to toe (evidence of dependent edema) assessment. Evaluation of the patient's volume and hemodynamic status is critical as well, as it will guide management. For example, patients with prerenal AKI can present with either volume depletion or fluid overload. Volume depletion may be evidenced by the presence of postural hypotension, decreased jugular venous pressure (JVP), and dry mucous membranes. Fluid overload, on the other hand, is often reflected by elevated JVP, pitting edema, ascites, and pulmonary crackles.

Conventional Markers of Kidney Function

4 Common laboratory tests used to evaluate the patient with impaired kidney function are described in Chapter e60. Over the past four decades, S_{cr} has been the most widely used laboratory test for estimating creatinine clearance (CL_{cr}) and eGFR. However, there are several limitations associated with its use since it is affected by age, gender, muscle mass or evidence of acute breakdown, diet, hydration status, and stability of the values (eg, S_{cr}) utilized. For example, patients with reduced creatinine production, such as those with low muscle mass, may have low values (less than 0.6 mg/dL [53 µmol/L]); thus, the presence of a gradual rise to normal values (0.8-1.2 mg/dL [71-106 µmol/L]) may actually suggest the presence of AKI. However, in the presence of improved nutrition and a large muscle mass, a S_{cr} of 1.2 mg/dL (106 µmol/L) may be a true representation of a person's current renal status. Instead of using only the most current value to determine kidney function, changes in the value from a patient's baseline over the past few days need to be considered. S_{cr} is normally inversely proportional to GFR. However, rapid changes in GFR disrupt this equilibrium and make S_{cr} an insensitive marker. In fact, changes in S_{cr} will lag behind the GFR's decline by 1 to 2 days due to slow accumulation, increased tubular secretion, and increased extrarenal clearance.[24,25] This can lead to an overestimation of the patient's GFR in the early stages of AKI and consequently a potential delay in the diagnosis of the syndrome.

5 Because S_{cr} steady-state values are assumed when one uses several GFR calculation methods, such as the Cockcroft-Gault and Chronic Kidney

Disease Epidemiology Collaboration (CKD-EPI) equations, they should not be used to estimate GFR in AKI patients with unstable kidney function. These equations will typically overestimate GFR when the AKI is worsening and underestimate it when the AKI is resolving. Instead, it may be useful to evaluate changes in S_{cr} values from the patient's baseline and also consider the S_{cr} sequence values to determine if kidney function is potentially improving or worsening. The most recent S_{cr} reflects the time-averaged kidney function over the preceding time period. Several mathematical approaches to estimate GFR in patients with unstable S_{cr} that incorporate the principles of creatinine accumulation and elimination have been proposed and are discussed in detail in Chapter e60. However, these methods have not been extensively validated in the setting of AKI, and their value for adjusting medication dosing is questionable. Additionally, these equations are complex and are not commonly used in the clinical setting.

Two other widely available markers of kidney function are BUN and urine output. The value of the BUN in AKI is limited because urea production and renal clearance are heavily influenced by extrarenal factors such as critical illness, volume status, protein intake, and medications. Urine output measured over a specified period of time (eg, 4-24 hours) allows for short-term assessment of kidney function, but its utility is limited to cases in which it is significantly decreased. The presence of anuria suggests complete kidney failure, whereas oliguria indicates some degree of kidney damage. Urine output needs to be interpreted with caution, as it is dependent on several factors, such as hydration status and medications. As mentioned earlier in the chapter, a patient may have AKI and still maintain a normal urine output; this condition is referred to as *nonoliguric AKI*. Another approach to estimating kidney function is to directly measure CL_{cr} over a short period of time, for example, 4 to 12 hours.[26] Although, potentially precise and simple to do, its accuracy is questionable if the urine output is low or the urine collection is incomplete.

In addition to BUN and S_{cr}, selected blood and urine tests, and urinary sediment are routinely evaluated to differentiate the cause of AKI and guide patient management. For example, a complete blood cell count with differential can help rule out infectious causes of AKI. Serum electrolyte values may be abnormal because of the acute decline of the kidney's ability to regulate electrolyte excretion. Particular attention should be paid to serum potassium, calcium, magnesium, and phosphorus values, which can be markedly elevated and cause life-threatening complications.

Given the limited usefulness of solely using S_{cr} or BUN concentrations to differentiate the etiology of AKI, urinary electrolytes and osmolality should be determined, and both a microscopic and chemical analysis of the urine should be performed (Table 61-2). The finding of a high urinary specific gravity, in the absence of glucosuria or mannitol administration, suggests an intact urinary concentrating mechanism and that the cause of the patient's AKI is likely prerenal azotemia. The presence of urinary protein is often difficult to interpret, especially in the setting of acute or chronic kidney failure. A patient with CKD may have a baseline proteinuria, thus clouding the clinical presentation, unless this is known at the time of AKI assessment. Classically, proteinuria is a hallmark of glomerular damage. However, tubular damage can also result in proteinuria, as the tubules are responsible for reabsorbing small proteins that are normally filtered by all glomeruli. The presence of blood also results in a positive urine protein test, so this confounder must always be assessed when a positive urine protein is obtained. Hematuria suggests acute intrinsic AKI secondary to glomerular injury, catheter related trauma, infection, or a kidney stone. On microscopic examination, the key findings are cells, casts, and crystals, and the presence of one or more of these may suggest specific etiologies of the AKI (Table 61-3). The finding of urinary crystals may indicate nephrolithiasis and a postrenal obstruction. If red blood cells or red blood cell casts are present, one should consider the presence of a physical injury to the glomerulus, renal parenchyma, or vascular beds. The finding of white blood cells or white blood cell casts suggests interstitial inflammation (ie, interstitial nephritis), which can be secondary to an allergic, granulomatous, or infectious process.

TABLE 61-2

Diagnostic Parameters for Differentiating Causes of AKI[a]

Laboratory Test	Prerenal AKI	Intrinsic AKI	Postrenal AKI
Urine sediment	Hyaline casts, may be normal	Granular casts, cellular debris	Cellular debris
Urinary RBC	None	2-4+	Variable
Urinary WBC	None	2-4+	1+
Urine Na (mEq/L or mmol/L)	<20	>40	>40
FE_{Na} (%)	<1	>2	Variable
Urine specific gravity	>1.018	<1.012	Variable

[a]Common laboratory tests are used to classify the cause of AKI. Functional AKI, which is not included in this table, would have laboratory values similar to those seen in prerenal AKI. The laboratory results listed under intrinsic AKI are those seen in acute tubular necrosis, the most common cause of intrinsic AKI.

AKI, acute kidney injury; FE_{Na}, fractional excretion of sodium; S_{cr}, serum creatinine; RBC, red blood cell; WBC, white blood cell.

TABLE 61-3

Urinary Findings as a Guide to the Etiology of AKI

Type of Urinary Evaluation	Presence of	Suggestive of
Urinalysis	Leukocyte esterases	Pyelonephritis
	Nitrites	Pyelonephritis
	Protein	
	Mild (<0.5 g/day)	Tubular damage
	Moderate (0.5-3 g/day)	Glomerulonephritis, pyelonephritis, tubular damage
	Large (>3 g/day)	Glomerulonephritis, nephrotic syndrome
	Hemoglobin	Glomerulonephritis, pyelonephritis, renal infarction, renal tumors, kidney stones
	Myoglobin	Rhabdomyolysis-associated tubular necrosis
	Urobilinogen	Hemolysis-associated tubular necrosis
Urine sediment	Microorganisms	Pyelonephritis
Cells	Red blood cells	Glomerulonephritis, pyelonephritis, renal infarction, papillary necrosis, renal tumors, kidney stones
	White blood cells	Pyelonephritis, interstitial nephritis
	Eosinophils	Drug-induced interstitial nephritis, renal transplant rejection
	Epithelial cells	Tubular necrosis
Casts	Granular casts	Tubular necrosis
	Hyaline casts	Prerenal azotemia
	White blood cell casts	Pyelonephritis, interstitial nephritis
	Red blood cell casts	Glomerulonephritis, renal infarct, lupus nephritis, vasculitis
Crystals	Urate	Postrenal obstruction
	Calcium phosphate	Postrenal obstruction

AKI, acute kidney injury.

Simultaneous measurement of urine and serum electrolytes is also helpful in the setting of AKI (see Table 61-3). From these values, a fractional

excretion of sodium (FE_{Na}) can be calculated. The equation for the calculation of the FE_{Na} is as follows:

$$FE_{Na} = \frac{\text{Excreted Na}}{\text{Filtered Na}} \times 100 = \frac{U_{vol} \times U_{Na}}{GFR \times S_{Na}} \times 100$$ FENa=ExcretedNaFilteredNa×100=Uvol×UNaGFR×SNa×100

where

$$GFR = \frac{U_{vol} \times U_{cr}}{S_{cr} \times t}$$ GFR=Uvol×UcrScr×t

Thus:

$$FE_{Na} = \frac{U_{Na} \times S_{cr} \times 100}{U_{cr} \times S_N}$$ FENa=UNa×Scr×100Ucr×SN

where U_{vol} is the urine volume, U_{cr} is the urine creatinine concentration, U_{Na} is the urine sodium concentration, S_{cr} is the serum creatinine concentration, S_{Na} is the serum sodium concentration, which usually does not vary much, GFR is the glomerular filtration rate, and *t* is the time period over which the urine is collected.

The FE_{Na} is one of the better diagnostic parameters to differentiate the cause of AKI. A low urinary sodium concentration (less than 20 mEq/L [mmol/L]) and low FE_{Na} (less than 1%) in a patient with oliguria suggest that there is stimulation of the sodium-retentive mechanisms in the kidney and that tubular function is intact. These findings are most characteristic of prerenal azotemia. Unfortunately, diuretic use in the preceding days limits the usefulness of the FE_{Na} calculation by increasing natriuresis, even in hypovolemic patients. The fractional excretion of urea (FE_{Urea}), which can be calculated like FE_{Na}, is sometimes used as an alternative means to assess tubular function in patients receiving diuretics. The inability to concentrate urine results in a high FE_{Na} (greater than 2%), suggesting tubular damage as the primary cause of the intrinsic AKI. However, this is also not an absolute finding, as there are some intrinsic causes that can be associated with a low FE_{Na} (eg, contrast nephropathy, myoglobinuria, and interstitial nephritis). Highly concentrated urine (greater than 500 mOsm/kg [mmol/kg]) suggests stimulation of antidiuretic hormone and intact tubular function. These findings are consistent with prerenal azotemia.

Novel Biomarkers of Kidney Damage

A variety of biomarkers have been investigated to detect and predict the clinical outcomes of AKI. While they vary in their origin, function, distribution, and time of release following kidney injury, the large majority are molecules that are released as a result of direct kidney cell damage. The performance of most biomarkers is variable and depends on the patient population, cause of AKI, presence of comorbidities, and timing of biomarker measurements. In general, their ability to detect AKI is better within homogenous patient populations where the time of AKI is known than in heterogeneous populations with multiple comorbidities and unknown AKI time or cause such as critically ill patients. Even though some biomarker tests are now commercially available, these tests are not routinely available at most clinical practice sites.[27,28]

Two of the most promising biomarkers for use in AKI are tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7). Both molecules inhibit specific proteins that result in G1 cell cycle arrest noted to occur during the early phases of cellular stress or injury.[29] The combination of TIMP-2 and IGFBP7 was approved by the Food and Drug Administration (FDA) as the first point-of-care device (Nephrocheck®) to detect early AKI. The Nephrocheck® test uses a fluorescent immunoassay and reveals test results expressed as an AKI risk score within 20 minutes. A score over 0.3 $(ng/mL)^2/1{,}000$ indicates high risk for developing moderate to severe AKI within 12 hours of testing. The cutoff value of 0.3 has a sensitivity of 95% and a specificity of only 46%. TIMP-2 and IGFBP7 have greatest predictability in patients at high risk for AKI, particularly patients who are critically ill, septic, or undergoing major surgery.[30] Nephrocheck® is not to be used as a standalone test for the diagnosis of AKI and should be used in conjunction with other diagnostic and clinical findings. Further, Nephrocheck® should be avoided in patients experiencing severe albuminuria and hyperbilirubinuria, as they interfere with the test results.[31]

Other biomarkers of kidney damage include neutrophil gelatinase–associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), interleukin 18 (IL-18), liver-type fatty acid binding protein (L-FABP), and N-acetyl-beta-D-glucosaminidase (NAG). They have been used for risk assessment, early detection, classification, and prognosis of AKI.[28,32] Since novel AKI biomarkers are still not widely utilized in clinical practice, the ADQI published a consensus statement on how AKI biomarkers can be integrated into a patient-centered approach to improve AKI care.[33] The panel recommends using AKI biomarkers to identify patients at risk who would benefit from preventative treatment. Further, they suggest using biomarkers to guide AKI management and predict AKI recovery and duration. It is important to note that these biomarkers would be used in addition to and not as a

replacement for clinical assessment and standardized tests for kidney function such as S_{cr} and urine output.[32,33]

The advances in our knowledge of AKI pathophysiology as well as the advent of biomarkers has prompted ADQI to propose the use of two new terms "functional change" and "kidney damage." Functional change refers to changes in glomerular and tubular function and includes markers such as S_{cr}, eGFR, and cystatin C. Kidney damage describes the presence of tubular and/or glomerular injury and includes markers such as TIMP-2 and IGFBP7. The rationale behind the proposed changes in terminology stems from the recognition of subclinical kidney injury. According to this, kidney injury may be detected by changes in the plasma or urinary levels of specific biomarkers before overt changes in kidney function (decreased eGFR or increased S_{cr}) have occurred. As a result, a patient may have kidney damage without a change in kidney function. Since this patient group is at a greater risk of complications, a longer stay in intensive care unit, and has a higher risk of dying when compared with the group without kidney damage, they may benefit from preventative interventions geared toward minimizing progression and toxicity (ie, avoidance or cessation of nephrotoxic drugs). The ADQI group has proposed the use of functional and damage markers, along with clinical information, to improve diagnostic accuracy, etiology, and staging of AKI.[33] Table 61-4 summarizes the relationship between functional change and kidney damage.[34,35]

TABLE 61-4

Classification of AKI Based on Functional and Kidney Damage Biomarkers

Loss of function	Kidney Damage	
	No	Yes
No	No loss of function or damage Biomarker negative KDIGO negative	Kidney damage without loss of function Biomarker positive KDIGO negative
Yes	Loss of function but no kidney damage KDIGO positive Biomarker negative	Loss of function and presence of kidney damage KDIGO positive Biomarker positive

AKI, acute kidney injury; KDIGO, Kidney Disease Improving Renal Outcomes.

Diagnostic Considerations

When the source of kidney injury is unclear after reviewing the patient's history, physical examination, and assessment of laboratory values, imaging techniques such as abdominal radiography, including the kidneys, ureters, and bladder (KUB), computed tomography (CT), and ultrasonography may be helpful. These may reveal small, shrunken kidneys indicative of CKD. Postrenal obstruction can often be identified with a renal ultrasonography and/or CT scan. Renal ultrasonography is also useful in detecting obstruction or hydronephrosis. Nephrolithiasis as small as 5 nm or a narrowing of the ureteral tract can be detected by ultrasonography or more sensitive tests, such as KUB and CT. When the cause of AKI is not evident, renal biopsies are useful in determining the cause in most patients. Because of the associated risk of bleeding, a renal biopsy is rarely undertaken and should only be performed in those circumstances when a definitive diagnosis is needed to guide therapy, such as the precise etiology of glomerulonephritis (see Chapter e66).

PREVENTION OF ACUTE KIDNEY INJURY

Prevention of AKI is critical since there is no treatment to reverse the insult once it has developed. Several nonpharmacologic and pharmacologic options to reduce the risk of AKI are described below.

Desired Outcomes

The goals of AKI prevention are to (a) screen and identify patients at risk, (b) monitor high-risk patients until the risk has subsided, and (c) implement prevention strategies when appropriate.

General Approach to Prevention

6 The choice of preventive strategy depends on the patient's risk factors for AKI such as comorbidities, planned procedures, and medications, to name a few.

Sometimes, the risk of kidney injury is predictable, such as in the setting of decreased perfusion secondary to compromised cardiac function (eg, post coronary bypass surgery) or secondary to the administration of a nephrotoxic agent like radiocontrast dye. In these situations, the potential insult to the kidneys cannot be avoided but may be preventable or minimized with intravenous fluids and/or avoidance or removal of any additional insults. In the inpatient setting, volume status optimization, hemodynamic support, and careful assessment of the risk versus benefit of potentially nephrotoxic medications are commonly recommended strategies for the prevention of AKI.

Nonpharmacologic and Pharmacologic Strategies for Prevention of AKI

Electronic Alert Systems

Advances in electronic health record (EHR) systems have led to the development of clinical decision support systems and electronic alerts designed to improve and standardize care in certain high-risk patient populations. Electronic alerts have been used for early detection of AKI and increased surveillance of patients on nephrotoxic medications. In general, alerts lead to greater implementation of the intervention, lower loss of kidney function, and decreased exposure to nephrotoxins.[36-38] For example, use of an EHR generated screening tool to identify pediatric patients receiving nephrotoxic medications and to recommend daily S_{cr} monitoring, switching a nephrotoxic drug to a non-nephrotoxic alternative or therapeutic drug monitoring, as appropriate has resulted in a 23% decrease in AKI rates and 42% decrease in AKI intensity.[39] Electronic alerts have the potential to reduce AKI by focusing on more appropriate medication prescribing and monitoring.

In addition to EHR systems, advances in machine learning technology have led to development of AKI risk prediction models. So far, there is an increasing amount of evidence that these machine learning models are effective in predicting AKI, typically within the following 24 to 72 hours.[40-42] While the application of machine learning in nephrology is still relatively new and not widely available in clinical practice, it has potential to improve patient outcomes in the future.

Intravenous Fluids

Intravenous fluids are one of the primary interventions that have consistently shown benefit and are routinely used in the prevention of AKI, particularly in patients with hemodynamic instability secondary to intravascular volume depletion as well as in patients receiving radiocontrast agents before a radiologic procedure.

Hemodynamic instability and systemic hypotension increase the risk of AKI as they can lead to decreased renal perfusion and subsequent kidney injury. Both isotonic crystalloids and colloid-containing solutions have been used for intravascular volume replacement. Among colloids, synthetic products such as hyperoncotic hydroxyethyl starch (HES) have been associated with impaired kidney function and should generally be avoided.[43] Albumin does not increase the risk of AKI and specific patient populations such as those with cirrhosis and spontaneous bacterial peritonitis may benefit from its therapy.[44] It has been hypothesized that albumin may offer additional advantages to septic patients as it is the main protein responsible for maintaining plasma colloid osmotic pressure, it has antioxidant and anti-inflammatory properties, and acts as a scavenger for reactive oxygen and nitrogen species. However, major patient outcomes such as risk of AKI, need for RRT, and mortality are comparable between albumin replacement therapy and isotonic saline.[45] Now, the 2012 KDIGO guidelines recommend isotonic crystalloids over colloids for intravascular volume expansion in patients at risk for AKI.[3]

When using crystalloid solutions, options include either balanced solutions or isotonic saline. Use of balanced fluids over normal saline in acutely ill individuals likely decreases risk of AKI, need for RRT, and death.[46–48] The main concerns associated with the use of large amounts of saline are hyperchloremic acidosis since the chloride content in isotonic saline is 1.5 times that of plasma (154 mEq/L [mmol/L]). Hyperchloremia in turn can

decrease renal artery blood flow and renal tissue perfusion. Further, saline infusions cause a greater increase in interstitial fluid volume than balanced solutions, which may result in increased renal volume and intracapsular pressure, decreased microvascular blood flow, and impaired kidney function.[49] On the other hand, balanced solutions such as Ringer's lactate, Hartmann's solution, and PlasmaLyte have an electrolyte composition similar to human plasma, and do not increase risk of hyperchloremic acidosis.

In addition to correcting hemodynamic instability and hypovolemia, fluids are the mainstay of therapy for the prevention of contrast-induced acute kidney injury (CI-AKI). CI-AKI is a common cause of ATN in the inpatient setting (see Chapter 65 for a detailed discussion of CI-AKI).[50]

While administration of intravenous fluids clearly has a critical role in AKI prevention, fluids need to be used judiciously as volume overload can have deleterious effects on the kidneys. The majority of crystalloid solutions redistribute into the interstitial space and can lead to interstitial edema, increased intraabdominal pressure, decreased renal oxygen delivery, and decreased GFR. In fact, poorer outcomes may be observed in patients with fluid overload including increased risk of AKI and decreased recovery of kidney function.[51] Hence, fluid administration beyond reestablishing euvolemia is generally not recommended.

Glycemic Control

In critical illness, both hyper- and hypoglycemia are associated with adverse patient outcomes.[52] Hyperglycemia can occur secondary to stress, inflammation, or medications (eg, steroids) while hypoglycemia can develop secondary to decreased clearance of insulin, interruptions in nutrition support prior to procedures, or tight insulin protocols. Tight glycemic control with target glucose levels of 80 to 110 mg/dL (4.4-6.1 mmol/L) may significantly decrease the risk of AKI and this has been adopted in the ICU setting.[53,54] However, tight glycemic control protocols may also increase risk of hypoglycemia and mortality.[52,55,56] As a result, a more moderate approach to glycemic control is favored in the critically ill. Guidelines from the American Diabetes Association and Surviving Sepsis Campaign recommend a glycemic target range of 140 to 180 mg/dL (7.8-10 mmol/L) and less than 180 mg/dL (10 mmol/L), respectively, in critically ill patients.[57,58]

TREATMENT OF ACUTE KIDNEY INJURY

7 Since there is no specific treatment that can reverse AKI or hasten its recovery, supportive measures that focus on hemodynamics, fluid balance, acid-base balance, and electrolyte homeostasis are the mainstays of therapy.

Desired Outcomes

Short-term goals of AKI management include minimizing the degree of insult to the kidney, reducing extrarenal complications, and expediting the patient's recovery of kidney function. Therapy should focus on maintaining organ functions while sustaining mean arterial pressure goals. The ultimate goal is to have the patient's kidney function restored to pre-AKI baseline.

General Approach to Treatment

Identification and management of AKI should be prompt. At times, the most effective method for managing AKI may be treatment of the precipitating event. A review of a patient's medications should be conducted to determine if a nephrotoxic agent could be the potential cause of AKI. Additionally, if possible, exposure to nephrotoxic agents should be limited either by discontinuation or switching to a less nephrotoxic option. Prerenal AKI should be managed with hemodynamic support and volume replacement, intrinsic AKI management relies on managing the cause and providing supportive care, and postrenal AKI therapy should focus on removing the cause of the obstruction. At the same time, patient's comorbidities need to be reviewed, as disease states such as cardiac and liver failure may require introduce additional management challenges.

Pharmacologic and Nonpharmacologic Strategies for Treatment of AKI

There is no cure for AKI. Thus, management of AKI focuses on supportive care and managing resultant complications, which includes hemodynamic instability, fluid overload, electrolyte imbalances, and acid-base abnormalities. In initial stages of AKI or mild disease, pharmacologic therapy may be sufficient, but patients with more severe AKI, RRT may be necessary to maintain fluid, electrolyte, and acid-base balance while removing accumulating waste products or toxins.

Fluid Management

Maintaining an adequate fluid status is imperative but also challenging, working to balance the need for volume resuscitation and fluid overload. First-line therapies for volume resuscitation consist of intravenous fluids, while fluid overload may need to be treated with loop diuretics or RRT.[3] Additionally, administration of all intravenous fluids should also be evaluated to determine if any notable reduction in daily intake can be achieved. This can be accomplished by concentrating intravenous medications to deliver less fluid overall or switching intravenous medication to the enteral route.

Intravenous Fluids

The principle of fluid therapy is to maintain or restore effective intravascular volume to assure adequate renal perfusion. In selected settings such as sepsis, low oncotic pressures and leaky vasculature can pose a challenge by leading to excessive extracellular fluid and anasarca with intravenous fluid administration. Similar to preventative hydration strategies, intravenous fluids need to be used judiciously as both volume depletion and fluid overload can adversely affect kidney function and increase morbidity and mortality.

Intravenous fluids should be administered to patients who have a prerenal AKI caused by hypovolemia or patients experiencing hemodynamic instability resulting from hypovolemia. The goal of fluid administration should be to restore and maintain euvolemia. In order to reduce the risk for fluid overload, slower correction strategies with either small intravenous boluses or short-term infusions of crystalloid fluids should be administered. Frequent reassessment of volume and hemodynamic status should be completed to determine further need for or changes to fluid therapy. As previously noted, balanced crystalloid solutions may be preferred for patients requiring IV fluids (eg, resuscitation) since isotonic saline has been associated with hyperchloremic metabolic acidosis and death in critically ill adults.[47,59,60] The patient should be monitored for fluid intake (both enteral and intravenous), urine output, insensible losses (ie, vomiting, diarrhea, excessive perspiration) which may not be captured in overall documented daily totals of fluid loss, pulmonary and peripheral edema, blood pressure (target mean arterial pressure ≥65 mm Hg), and serum electrolytes. Urine output ≥0.5 mL/kg/hr is generally targeted during the initial fluid resuscitation phase.[57] Assessing documentation of fluid balance in the EHR should consider that a patient's independent drinking or urinary voiding or excessive perspiration may not be captured. When this occurs, changes in a patient's weight can assist in validating fluid status.

If AKI is a result of blood loss or is complicated by symptomatic anemia, red blood cell transfusion to a hemoglobin >7 g/dL (70 g/L; 4.34 mmol/L) is the treatment of choice.[57] Once a hemoglobin of >7 g/dL (70 g/L; 4.34 mmol/L) is reached, balanced solutions or normal saline can be used to restore intravascular volume. In patients with cardiac failure, fluids should only be administered if intravascular volume is depleted. Albumin is typically preferred in individuals with severe hypoalbuminemia secondary to cirrhosis or nephrotic syndrome.[44] In critically ill patients with vasodilatory shock, vasopressors such as norepinephrine and vasopressin may be used in conjunction with fluids in order to maintain adequate hemodynamics and renal perfusion.[3]

Diuretics

Loop diuretics are frequently prescribed for the management of fluid overload in patients with established kidney injury and often as a precursor to RRT. Loop diuretics have several theoretical advantages: increased urine output, decreased risk of ischemic injury by inhibiting the Na-K-Cl cotransporter and thus decreasing oxygen demand, and enhanced renal blood flow due to increased availability of renal prostaglandins. Enhancing urine output from oliguric to nonoliguric may be beneficial in itself, as nonoliguric AKI is associated with better outcomes than oliguric AKI.[61] However, even though loop diuretics increase urine output, they may not improve patient outcomes (ie, mortality, need for RRT) for patients with established AKI.[61,62] Therefore, the KDIGO guidelines recommend limiting the use of loop diuretics to the management of fluid overload and avoiding their use for the purpose of treatment of AKI.[3]

Diuretic resistance is a relatively common problem in patients with AKI for several reasons. Excessive sodium administration (eg, normal saline) may override the ability of the diuretics to eliminate sodium. Also, patients with ATN have a reduced number of functioning nephrons on which the diuretic may exert its action upon. In other clinical states such as glomerulonephritis, heavy proteinuria can occur. In these patients, intraluminal loop diuretics cannot exert their effect in the loop of Henle if they are extensively bound to proteins present in the urine. Still other patients may have greatly reduced bioavailability of oral furosemide because of intestinal edema, often associated with high preload states, which further reduces oral furosemide

absorption. Lastly, the braking phenomenon, which is a progressively decreasing response to natriuresis associated with repeated administration of a loop diuretic, may also lead to diuretic resistance.[61,63] Table 61-5 includes possible therapeutic options to counteract each form of diuretic resistance.

TABLE 61-5

Common Causes of Diuretic Resistance in Patients with AKI

Causes of Diuretic Resistance	Potential Therapeutic Solutions
Excessive sodium intake (sources may be dietary, IV fluids, and drugs)	Remove sodium from nutritional sources and medications
Inadequate diuretic dose or inappropriate regimen	Increase dose, increase frequency, use continuous infusion or add thiazide
Reduced oral bioavailability (usually furosemide)	Use parenteral therapy, switch to oral torsemide or bumetanide
Nephrotic syndrome (loop diuretic protein binding in tubule lumen)	Increase dose, add thiazide
Reduced renal blood flow	
Drugs (NSAIDs, ACEIs, vasodilators)	Discontinue these drugs if possible
Intravascular depletion	Intravascular volume expansion
Increased sodium resorption	
Distal nephron hyperthrophy	Add thiazide, sodium restriction
Postdiuretic sodium retention	Dietary sodium restriction, use continuous infusion
Heart failure	Assess effective circulatory volume, increase dose, increase frequency, use continuous infusion
Cirrhosis	Assess effective circulatory volume, consider paracentesis
Acute tubular necrosis	Increase diuretic dose, diuretic combination therapy

ACEIs, angiotensin-converting enzyme inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs.

The most common therapeutic option to overcome diuretic resistance is to use higher doses of intravenous loop diuretics. Often, patients with impaired kidney function have lower rates of diuretic secretion into the tubular fluid; consequently, higher doses of loop diuretics are prescribed. Caution must be taken when increasing intermittent bolus doses as the risk of adverse reactions such as ototoxicity also increases due to higher corresponding peak concentrations achieved too quickly. To avoid rapid high peak concentrations when using furosemide, doses of less than 160 mg can be administered undiluted no faster than a rate of 20 to 40 mg/minute, whereas doses exceeding 160 mg can be diluted and administered via a short infusion at a rate no faster than 4 mg/min. Another option to avoid high peak concentrations and post-diuretic sodium retention is to administer loop diuretics as a continuous infusion. Administration via a continuous infusion can achieve the same degree of diuresis with lower doses and results in no difference in mortality or hospital length of stay. An initial loading dose is recommended prior to the initiation of a continuous infusion of furosemide or its equivalent to decrease the time to the medication's onset of action.[63] One disadvantage of using a continuous infusion is it requires

more extensive and frequent monitoring, as infusion rates are usually based on an hourly urine output goal. Typically, increasing intermittent bolus doses or increasing dosing frequency are trialed before implementing the more labor-intensive continuous infusion strategy.

Another approach to overcome diuretic resistance in AKI is to use a loop diuretic in combination with a diuretic from a different pharmacologic class. Diuretics that work at the distal convoluted tubule (chlorothiazide and metolazone) or the collecting duct (amiloride, triamterene, and spironolactone) may have a synergistic effect when administered with loop diuretics by blocking the compensatory increase in sodium and chloride reabsorption (see Chapter 68, Disorders of Sodium and Water Homeostasis). Thiazide diuretics are most commonly used in combination with loop diuretics. Oral metolazone is used most often because, unlike other thiazides, it produces effective diuresis at a CL_{cr} less than 20 mL/min (0.33 mL/s). Oral metolazone is frequently given 30 minutes prior to intravenous loop diuretics to achieve peak effects at the same time to potentially enhance diuresis. The combination of thiazide and thiazide-type diuretics and a loop diuretic has been used successfully in the management of fluid overload. When such combinations are used, the regimen should be assessed for any improved or enhanced diuresis and determine if the regimen should be continued.[63]

While diuretic strategies are being used, symptoms of ototoxicity, fluid status, and serum creatinine and electrolytes (ie, potassium, sodium, magnesium, calcium, BUN) should be closely monitored, especially with aggressive strategies such as larger doses of diuretics and continuous infusions. The goal of diuretic therapy in the setting of fluid overload is to achieve adequate urine output to accomplish a net negative diuresis. Net negative diuresis, or achieving a fluid output that is higher than fluid intake, is desired. Strict intake and output measures are best accomplished when a patient has a urinary catheter to monitor urine volume or is located in the intensive care unit where any changes are frequently assessed and documented. In patients who do not have a urinary catheter, accurate assessment of urine output can be challenging and a patient's weight should be closely followed. Daily goals for diuretic therapy should be a net negative diuresis of 500 to 1,000 mL of urine per day or a weight loss of 0.5 to 1 kg per day as tolerated. Once a patient has reached euvolemic status, diuretics should either be discontinued or dose adjusted to maintain the patient's fluid balance.

Electrolyte and Acid-Base Management

The most common electrolyte disorder encountered in AKI patients is hyperkalemia, as >90% of potassium is renally eliminated. Life-threatening cardiac arrhythmias may occur with serum potassium concentrations greater than 6 mEq/L (mmol/L), so frequent monitoring of potassium is essential. Medications and foods with high amounts of potassium (antibiotics, oral phosphorous replacement powders, alkalinizers, potassium salt substitutes) should be avoided (see Chapter 70, Disorders of Potassium and Magnesium Homeostasis). Some medications may promote potassium retention by the kidneys (spironolactone, eplerenone, finerenone) and should also be avoided or closely monitored if used (see Chapter 70). In general, exogenous potassium supplementation should be avoided in patients with AKI unless warranted by the presence of hypokalemia. Medications that can cause an increase of potassium such as ACE inhibitors, ARBs, and sulfamethoxazole-trimethoprim should be avoided.

Other electrolytes abnormalities include hyperphosphatemia and hypocalcemia. These electrolytes are eliminated by the kidneys and, unlike potassium, are not efficiently removed by dialysis. Hyperphosphatemia can be particularly high in patients with tissue destruction (eg, trauma, rhabdomyolysis, and tumor lysis syndrome) due to substantial amounts of phosphorus released from the destroyed tissue. Typically, the dietary intake of phosphorus needs to be restricted in advanced stages of AKI. When phosphorus is particularly high, phosphate binding agents (eg, calcium acetate, sevelamer hydrochloride) may be considered. Caution should be taken when using calcium-containing phosphate binding agents or calcium-containing antacids in situations where hypercalcemia is present to prevent precipitation of calcium phosphate which can lead to soft tissue calcification. In contrast to the patient with CKD, AKI patients do not usually develop calcium imbalance secondary to the limited duration of the illness. Hypocalcemia can develop as a result of hyperphosphatemia; thus, the treatment of hyperphosphatemia should correct the imbalance. Additionally, hypocalcemia can be seen in patients who are receiving continuous renal replacement therapy (CRRT) along with a concomitant infusion of regional citrate being used for anticoagulation. Typically, citrate is infused before the renal replacement machine's dialyzer/hemofilter to bind serum calcium in order to prevent the extracorporeal circuit from clotting which leaves less calcium to return to circulation. Since severe hypocalcemia can result in arrhythmias or even death, frequent monitoring of unbound serum calcium concentrations and supplementation with parenteral calcium is necessary to maintain normocalcemia.

Metabolic acidosis can also occur in patients with severe AKI due to the kidney's inability to adequately excrete acid. This can be a result of AKI itself or from other conditions that are common in critically ill patients, such as shock due to severe hypoperfusion. Determining and correcting the underlying cause of the acid-base imbalance is imperative. Supplementation with bicarbonate therapy can be utilized in patients with mild acidosis to temporarily

correct the derangement. RRT may need to be initiated if the underlying cause cannot be reversed promptly or in patients with severe life-threatening acidosis.

Nutritional Considerations in AKI

Nutritional management of critically ill patients with AKI can be extremely complex, as it needs to account for metabolic derangements resulting from both impaired kidney function and underlying disease processes, as well as the effects of RRT on nutrient balance. Loss of the normal physiologic and metabolic functions of the kidney and the hypercatabolic response to stress and injury will have an impact on the metabolism of nutrients. Derangements in glucose, lipid, and protein metabolism result in hyperglycemia and insulin resistance, hypertriglyceridemia, protein catabolism, and negative nitrogen balance. The latter, in particular, is problematic to manage, as increased amino acid turnover and skeletal muscle breakdown lead to muscle wasting and malnutrition that does not respond well to increasing exogenous protein supplementation. The KDIGO guidelines recommend a caloric intake goal of 20 to 30 kcal/kg/day (84-126 kJ/kg/day) irrespective of the stage of kidney impairment and preferentially through the enteral route. In the setting of noncatabolic AKI without need for dialysis, 0.8 to 1 g/kg/day of protein is suggested and 1 to 1.5 g/kg/day if patient is receiving RRT.[3] CRRT is associated with an increased removal of small water-soluble molecules such as amino acids and certain nutrients. As a result, hypercatabolic patients receiving CRRT will typically have higher protein requirements up to a maximum of 1.7 g/kg/day.[3] The Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines for nutrition in patients with AKI recommend a caloric intake goal of 25 to 30 kcal/kg/day (105-126 kJ/kg/day). In the ICU setting, up to 2.5 g/kg/day of protein is suggested if patient is receiving RRT.[64]

Renal Replacement Therapy

Renal replacement therapy is often utilized to treat life threatening indications resulting from severe AKI. These indications include fluid overload, electrolyte disturbances (eg, hyperkalemia), acid-base imbalances, uremic complications, oliguria or anuria, and pulmonary edema from fluid overload. Multiple factors influence decisions to initiate dialysis including specific timing and type of modality.[3,65-69] The most common indications for initiation of RRT are summarized in Table 61-6. In the setting of AKI, the mode of delivery of RRT can be either intermittent hemodialysis or continuous RRT and the chosen modality usually depends on physician preference and the resources (ie, healthcare professionals, machines) available. No difference in mortality or dialysis dependence has been shown between patients who received continuous or intermittent forms of RRT; however, continuous RRT is generally preferred in hemodynamically unstable patients.[3,67,70]

TABLE 61-6

Common Indications for RRT

Indication for RRT	Clinical Setting
A: *a*cid-base abnormalities	Metabolic acidosis (especially if pH <7.2)
E: *e*lectrolyte imbalance	Severe hyperkalemia and/or hypermagnesemia
I: *i*ntoxications	Salicylates, lithium, methanol, ethylene glycol, theophylline, phenobarbital
O: fluid *o*verload	Fluid overload (especially pulmonary edema unresponsive to diuretics)
U: uremia	Uremia or associated complications (neuropathy, encephalopathy, pericarditis)

RRT, renal replacement therapy.

Intermittent Hemodialysis

Intermittent hemodialysis (IHD) is the most frequently used RRT (see Chapter 64). Hemodialysis treatments usually last 3 to 4 hours and thus can

achieve the rapid removal of volume and solutes and thereby contribute to correction of most of the electrolyte abnormalities associated with AKI. The primary challenge with this modality is hypotension, which is typically caused by the rapid removal of intravascular volume over a short period of time. Achieving prompt venous access for dialysis can be difficult in hypotensive patients and can limit the effectiveness of IHD. This can result in a lack of solute clearance, an inability to correct metabolic derangements, continued volume overload, and can lead to delayed recovery because of further ischemic insults to the kidneys. Patients with dialysis-dependent CKD generally achieve adequate solute and volume control with three times weekly dialysis, but hypercatabolic, fluid-overloaded patients with AKI may require more frequent hemodialysis treatments. Chapter 64 provides a detailed explanation of the principles and processes of IHD.

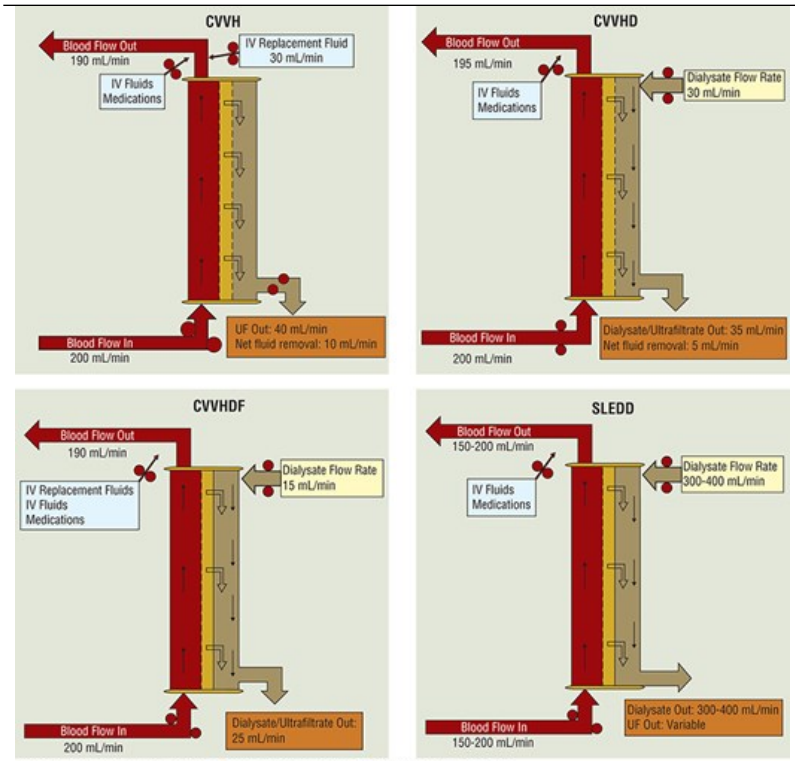
Continuous Renal Replacement Therapy

CRRT is a viable option to manage hemodynamically unstable patients with AKI, especially those who cannot tolerate rapid volume removal. Unlike IHD treatments that last a few hours, CRRT runs continuously 24 hours a day, providing a slower and more consistent removal of solutes and fluid over time. In general, CRRT can achieve a greater amount of solute removal with higher mean arterial pressures compared with IHD in critically ill patients with AKI.[70] CRRT use is most commonly considered for those patients with higher acuity because of their intolerance of IHD-associated hypotension. The KDIGO guidelines suggest using CRRT over IHD in hemodynamically unstable patients.[3]

Several CRRT variants have been developed, including continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). These modalities differ in the degree of both their solute removal as well as fluid clearance and the modality chosen is based on an individual patient's needs. The removal of solutes and fluid can be achieved via three different mechanisms: diffusion, convection, and membrane adsorption. In CVVH, solute and fluid clearance is primarily a result of convection, the active transport of drug molecules at the concentration at which they exist in plasma water into the ultrafiltrate using a pump-driven pressure gradient, known as "solvent drag," then fluid absent of solutes is replaced (Fig. 61-3). CVVHD provides a more extensive solute removal that works primarily by diffusion, where solute molecules passively move down a concentration gradient from an area of higher concentration (plasma) pass through the dialysis membrane to an area of lower concentration (dialysate). CVVHDF combines both convection and hemodialysis, achieving even higher solute and fluid removal rates (Fig. 61-3).

FIGURE 61-3

Several renal replacement therapies are commonly used in patients with acute kidney injury (AKI), including one of the three primary continuous renal replacement therapy (CRRT) variants: (a) continuous venovenous hemofiltration (CVVH), (b) continuous venovenous hemodialysis (CVVHD), (c) continuous venovenous hemodiafiltration (CVVHDF), and the hybrid intermittent hemodialysis therapy, and (d) sustained low-efficiency daily dialysis (SLEDD). The blood circuit in each diagram is represented in red, the hemofilter/dialyzer membrane is yellow, and the ultrafiltration/dialysate compartment is brown. Excess body water and accumulated endogenous waste products are removed solely by convection when CVVH is employed. With CVVHD, waste products are predominantly removed as the result of passive diffusion from the blood, where they are in high concentration to the dialysate. The degree of fluid removal that is accomplished by convection is usually minimal. CVVHDF uses convection to a degree similar to that employed during CVVH as well as diffusion, and thus is often associated with the highest clearance of medications and waste products. Finally, SLEDD employs lower blood and dialysate flow rates than intermittent hemodialysis (IHD), but because of its extended duration, it is a gentler means of achieving adequate waste product and fluid removal.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Optimal timing of CRRT initiation has not been clearly established. Whether early initiation of RRT has improved morbidity and mortality benefit versus delaying RRT to allow for the possibility for a patient to recover function without needing RRT has been the subject of considerable debate. In situations when severe or life-threatening complications of AKI are present such as oliguria, pulmonary edema, or metabolic disorders (eg, acidosis, hyperkalemia, uremia), the indication for CRRT is clear. However, in the absence of such complications, the exact timing of CRRT initiation is uncertain. In fact, early initiation of CRRT at the onset of AKI may not demonstrate a mortality benefit or improve patient outcomes.[66,71,72] Clinicians are advised to carefully consider the patient's overall clinical status, severity of kidney impairment and related complications, and trends in the patient's physiologic and laboratory values before deciding whether and when to initiate CRRT.[68]

Anticoagulation is a major consideration for patients receiving CRRT as circuit clotting and filter patency can limit CRRT performance. It is important to note that the drivers for thrombosis and bleeding in severe kidney impairment are unique to this population, creating some limitations in applying approaches utilized in patients with more intact function. Typical anticoagulation is achieved by the administration of parenteral agents such as unfractionated heparin or regional citrate. Unfractionated heparin is widely available and easy to monitor but it also systemically anticoagulates the patient leading to an increased risk of bleeding. Regional citrate chelates ionized calcium in the extracorporeal circuit and impairs progression of the coagulation cascade. In order to maintain physiologic levels of calcium in the patient's systemic circulation when using regional citrate, most protocols require infusion of parenteral calcium (ie, calcium chloride or calcium gluconate) prior to returning the blood to the patient as well as frequent monitoring of ionized calcium levels. When compared to unfractionated heparin, regional citrate is associated with less circuit clotting and longer filter lifetimes. Also, the risk of bleeding is lower as anticoagulation is limited to the extracorporeal circuit and does not extend to the patient. However, regional citrate increases the production of bicarbonate secondary to dissociation of the calcium-citrate complexes in the liver, which can increase the risk of metabolic alkalosis.[73] The goals of citrate anticoagulation are to maintain the circuit ionized calcium between 0.8 and 1.6 mg/dL (0.2-0.4 mmol/L), and the patient's systemic ionized calcium between 4.4 and 5.2 mg/dL (1.1-1.3 mmol/L).[3] Now, the KDIGO Work Group recommends regional citrate as the preferred anticoagulant of choice for patients receiving CRRT.[3]

Other anticoagulants may be used in patients receiving CRRT but their use is less common or only recommended in select circumstances. Low-molecular weight heparins are generally not recommended due to increased cost, poor removal by CRRT, and limited supporting data. Argatroban or bivalirudin, which are direct thrombin inhibitors, is typically reserved for patients with contraindications to heparin such as antithrombin deficiency or heparin-induced thrombocytopenia.[3,73] Overall, the specific approach to anticoagulation depends on whether there is a need to limit anticoagulation

to the circuit alone or extend it to systemically anticoagulate the patient. Many patients on CRRT require systemic anticoagulation for an underlying comorbidity (eg, atrial fibrillation and artificial heart valve) and will not need additional anticoagulation for RRT. As a result, the need for anticoagulation and the specific anticoagulant of choice should be tailored to individual patient requirements and corresponding indications.

Challenges with CRRT may include limited availability of the specialized equipment and other resources necessary to provide the treatments and to individualize the IV replacement, dialysate fluids, and medication therapy adjustments. Also, medication dosing requirements for patients who are receiving CRRT are complex and not clearly defined.[74] CRRT use is most commonly considered for those patients with higher acuity because of their intolerance of IHD-associated hypotension. The KDIGO guidelines suggest using CRRT over IHD in hemodynamically unstable patients.[3]

Prolonged Intermittent Renal Replacement Therapies

An alternative to CRRT is prolonged intermittent RRT (PIRRT), which has had a variety of names including extended-duration IHD, hybrid IHD, sustained low-efficiency dialysis (SLED), or sustained low efficiency daily dialysis (SLEDD) (see Fig. 61-3). These therapies use conventional dialysis machines but lower blood (150-200 mL/min) and dialysate (300-400 mL/min) flow rates with extended treatment periods of 6 to 12 hours. For critically ill patients with AKI, they are comparable to CRRT for hemodynamic control.[69] Although the use of PIRRT is increasing, our knowledge of its impact on medication removal is limited.[75] Differences in the prescribed parameters used in PIRRT, including frequency, duration, and dialysate flow rates, along with limited data on medication dosing in PIRRT present challenges to healthcare providers responsible for appropriate medication selection and dosing.[76-78]

Medication Dosing Considerations in AKI

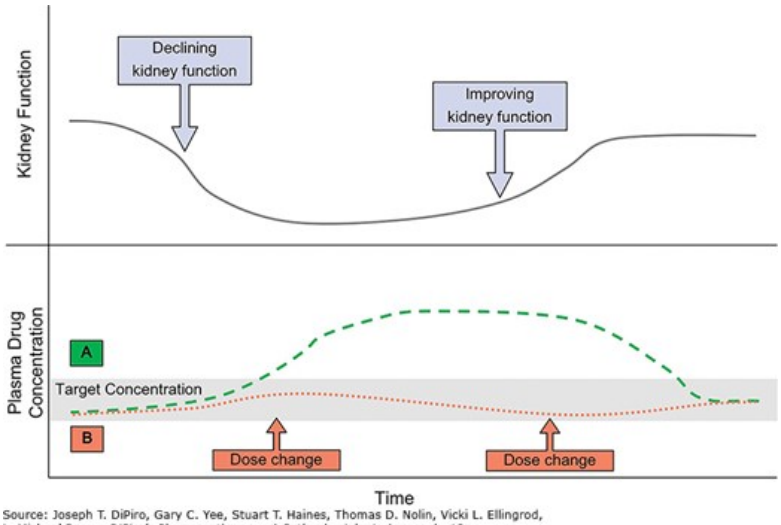
9 Optimization of medication therapy for patients experiencing AKI is often challenging. The multiple variables influencing responses to the medication regimen include the patient's residual drug clearance, fluid accumulation, comorbidities, and whether they need renal support with RRT. In addition, the patient's current kidney function state and corresponding drug elimination influenced by the decline, stabilization or recovery of AKI should be considered. For renally eliminated medications, particularly for agents with a narrow therapeutic range, serum drug concentration measurements and assessment of pharmacodynamic responses are likely to be necessary. If hepatic function is normal, choosing an agent eliminated primarily by the liver may be preferred. However, renally eliminated active metabolites may accumulate to a point where they may elicit an undesired pharmacologic effect. Kidney failure can also independently impair nonrenal drug elimination including metabolism through "organ crosstalk," where the dysfunction of one organ affects another.[79] Unfortunately, pharmacokinetic studies in patients with established AKI are limited.

The use of dosing guidelines based on data derived from patients with stable CKD may not reflect the clearance and volume of distribution in critically ill AKI patients. CKD dosing recommendations generally assume a stable rate of decline and do not take into account the dynamic changes seen in AKI (see Chapter 67).[74] In general, medication elimination may be more robust in AKI compared to CKD, suggesting some caution with utilizing CKD data for dosing decisions.[80] In some situations with sepsis and presence of AKI, immediate reductions in dosing for selected agents such as antibiotics should be cautioned as it may lead to under treatment. With the exception of vancomycin or aminoglycosides, full doses or extended infusions of antibiotics should be considered for the first 24 hours and reevaluated.[81]

Pharmacotherapy regimen decisions should take into consideration the four distinct phases of AKI described earlier, specifically initiation, extension, maintenance, and recovery phase. The initiation and extension phases occur right after the kidney insult. First, a clinical determination should be made about the severity of AKI and degree of residual renal clearance. Then, in order to determine if medication therapy modifications are needed, the clinician should consider the goals of therapy, the specific pharmacokinetics of the medication, the potential for increased risk for an adverse drug event, and therapeutic drug monitoring (if available) (see Fig. 61-4). In AKI, the severity and timing of the decline in kidney function is relatively unpredictable, so frequent monitoring and reevaluation of medication dosing is necessary. Urine output is a good surrogate marker to monitor kidney function and prospectively assess where kidney function is trending. S_{cr} measurements lag behind kidney function; that is, today's S_{cr} measurements typically reflect yesterday's kidney function, and thus, S_{cr} is not a good marker for monitoring kidney function. In the next phase, maintenance, kidney function stabilizes and medication therapy regimens may require fewer alterations. The fourth and final phase is recovery, where AKI begins to resolve and there may be a need to increase the medication dose due to enhanced renal clearance. It is critically important to follow the patient closely and recognize trends for decreasing or improving kidney function in an effort to achieve and maintain medication therapy management goals.

FIGURE 61-4

Relationship between kidney function changes in AKI and dosing of renally eliminated drugs. As kidney function fluctuates in AKI, plasma drug concentrations will be affected. (A) If no dosing adjustments are made, then this will lead to supratherapeutic concentrations [depicted by green line] which can lead to adverse effects. In order to maintain target drug concentrations, dosing adjustments should be made as fluctuations occur. (B) When kidney function declines, a dosing regimen should be adjusted by decreasing the dose or frequency to maintain plasma drug concentrations in the therapeutic range [depicted by red line]. When kidney function improves, the dosing regimen should be changed by increasing the dose or frequency.



Edema, which is common in AKI, can increase the volume of distribution of many medications, particularly water-soluble compounds with relatively small volumes of distribution. Increased fluid distribution into the tissues (ie, sepsis and anasarca in heart failure) can also contribute to a larger volume of distribution for many medications and thereby reduce the proportion of medication in the plasma that is available to be removed by the kidneys. Because AKI frequently occurs in critically ill patients, multisystem organ failure is often an accompanying problem. In addition to volume overload, reductions in cardiac output or liver function can alter the pharmacokinetic profile of most medications. For selected renally eliminated medications or related metabolites with narrow therapeutic windows, close follow-up and dosing adjustments may be necessary.[74,75]

If rapid onset of activity is desired, a loading dose may be necessary to promptly achieve desired serum concentrations because the expanded volume of distribution and the prolonged elimination half-life extend the time (3.5 times the half-life) needed to reach steady-state concentrations. Maintenance dosing regimens should be reviewed frequently and be based on the assessment of the patient's most current kidney function. A dose that provides the desired serum concentration on 1 day may be inappropriate a few days later if there is a change in the patient's fluid status or kidney function has dramatically changed, or if RRT is initiated, changed, or discontinued (see Fig. 61-4).[74]

Medication therapy individualization in patients with AKI is complicated by the fact that patients with AKI may have a higher residual nonrenal clearance than patients with CKD who have a similar CL_{cr}.[74] Alterations in the activity of some, but not all, cytochrome P450 enzymes have been demonstrated in patients with CKD.[79,80] This may be the result of less accumulation of uremic waste products that may alter hepatic function. If a patient with AKI has higher than anticipated nonrenal clearance, this would result in more robust elimination leading to lower than expected, possibly subtherapeutic, serum concentrations. For example, to maintain comparable serum concentrations, the imipenem dose requirement in patients with AKI would be 2,000 mg divided daily as compared with the recommended dosage for patients with ESRD of 1,000 mg daily. As AKI persists, the nonrenal clearance values approach those observed in patients with CKD.[82] Another challenge associated with medication dosing in patients with AKI is that much of the dosing-related data were acquired in patients with CKD, with initial pharmacokinetic assessments done after single-dose administration. The determination of pharmacokinetic parameters using a single-dose model may result in overestimated initial medication removal secondary to simultaneous distribution from the plasma to the tissue.[83] In conclusion, the application of dosing regimens derived from patients with CKD and ESRD in addition to the use of more aggressive RRT approaches may result in underdosing of certain medications and thereby contribute to less than optimal clinical outcomes.

Medication Dosing Considerations in RRT

There are several physicochemical and pharmacokinetic characteristics that can alter medication clearance during RRT, including molecular weight, protein binding, volume of distribution, and degree of renal clearance or fraction eliminated by the kidneys.[83,84] Medication dosage regimen design considerations specific to patients receiving peritoneal dialysis and IHD are presented in Chapter 67. However, medication-dosing requirements for patients with AKI or CKD who are receiving CRRT are complex and not as clearly defined as in IHD.[74,81] Inadequately dosed medications in critically ill patients with AKI requiring RRT may be one factor contributing to the lack of improving outcomes with newer RRT approaches.

In general, RRT-mediated medication clearance is inversely related to molecular weight, such that RRT medication clearance decreases as the weight of a medication increases. IHD efficiently clears medications with a small molecular weight (ie, <500 Da), whereas CRRTs can efficiently clear much larger solutes (ie, <15,000 Da). High protein binding (>80%) can also affect clearance in both IHD and CRRT as the drug-protein complexes increase molecular weight significantly (eg, >50,000 Da), thus making it difficult for the complexes to pass through the pores in the hemofilter.[83,84] Conversely, patients who are experiencing hypoalbuminemia will have a higher fraction of unbound drug, thus a larger amount of the agent may be removed during RRT depending on the weight of the drug and its primary mode of elimination (eg, liver, kidney). Compounds with a large volume of distribution (V_D) of >1 L/kg are extensively distributed to extravascular tissues, leaving only a small fraction of the drug in the vascular compartment and thereby limiting drug removal.[74,81,83] Renal clearance of a drug also plays a role in determining RRT removal. In general, medications that are predominantly cleared by the kidney are more likely to be cleared via CRRT than medications that are eliminated primarily by nonrenal mechanisms.

There are marked differences in medication removal between the different CRRT modalities. Since CVVH relies on convection, medication removal is independent of molecular size of the medication or presence of a concentration gradient. Thus, it is the most efficient means of removing larger molecules (<15,000 Da) and those that are primarily not protein bound in the plasma. Another parameter that can assist in determining the likelihood of medication removal during use of convective RRT modalities is the sieving coefficient (SC), which is the ratio of a solute or medication in the ultrafiltrate to that in plasma. An SC of 1 indicates free transport across the membrane where an SC of 0 indicates no transport across the membrane. The SC is often approximated by the fraction unbound (f_u), or the fraction of drug unbound to protein in the plasma, because the ratios are often similar, and this information may be more readily available than SC. In CVVHD, medication removal relies on diffusion, which is an efficient means of removal of smaller molecules (<500 Da). Since CVVHDF is a combination of both convection and diffusion, medication removal is enhanced.

Limitations of using IHD-based dosing recommendations in patients receiving RRT for AKI include variability in the patient's individual pharmacokinetic parameters, differences in the dialysis prescription, such as dialyzer blood flow or duration, unpredictability of dialysis timing based on availability, use of new hemodialyzers, and advances in the technology without knowing how medications are impacted. Pharmacokinetic and medication dosing assessments in patients with impaired kidney function often are performed after single dose administration to stable CKD subjects. Distribution and clearance estimates in this setting may not reflect those observed at steady and may be over-estimated.[84,85] The RRT approach used may also change on an hourly or daily basis, especially in hemodynamically unstable individuals. The approach can also be affected by a failure of the circuit, the need for a procedure, or the availability of a machine. Individualization of a dosing regimen may require daily assessment of the clinical status of the patient and any planned or administered hemodialysis. Renally eliminated drugs with narrow therapeutic ranges may benefit from additional orders to contact the patient's healthcare providers if dialysis is stopped.[86]

Overall, there are numerous potential pharmacokinetic and pharmacodynamic alterations to be aware of in the patient with AKI. Individualization of pharmacotherapy for a patient receiving RRT is dependent on the patient's residual kidney function, the clearance of the medication by CRRT, as well as the properties of the medication (ie, molecular weight, V_D, protein binding, and SC). In CRRT, the frequency of therapy interruptions will also impact medication removal and corresponding dosing requirements. Unfortunately, there is still a scarcity of data to quantify these changes, and even less evidence demonstrating that if one incorporates these considerations into patient care, the associated outcomes will be improved.

EVALUATION OF THERAPEUTIC OUTCOMES

Vigilant monitoring of patients with AKI is essential, particularly in those who are critically ill. Table 61-7 summarizes the main monitoring parameters for patients with established AKI.

TABLE 61-7

Key Monitoring Parameters for Patients with Established AKI[a]

Parameter	Frequency
Fluid ins & outs	Hourly/Every shift
Patient weight	Daily
Hemodynamics (blood pressure, heart rate, mean arterial pressure, etc.)	Hourly/Every shift
Blood chemistries	
Sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium	Daily
Blood urea nitrogen/serum creatinine	Daily
Drugs and their dosing regimens	Daily
Nutritional regimen	Daily
Blood glucose	Daily (minimum)
Therapeutic drug monitoring of renally cleared drugs (eg, vancomycin aminoglycosides)	Highly variable, about three times weekly
Times of administered doses	Daily
Doses relative to administration of renal replacement therapy	Daily (unless unanticipated changes occur)
Urinalysis	
Calculate measured creatinine clearance	Every time measured urine collection performed
Calculate fractional excretion of sodium	Every time measured urine collection performed
Plans for renal replacement therapy	Daily

[a]Phlebotomy should be coordinated to minimize excessive blood draws.

Once the laboratory-based tests (eg, urinalysis and FE_{Na} calculations) have been conducted to diagnose the cause of AKI, they usually do not have to be repeated. In established AKI, daily measurements of fluid intake and output are usually adequate. Urine output should be measured more frequently in critically ill, hemodynamic instability, or more severe AKI. Monitoring diuretic response is also important. Vital signs should be monitored at least daily, and more often if the acuity of illness warrants. Electrolytes, BUN, and S_{cr} should be considered routine and measured at least daily for hospitalized patients. Electrolytes may need to be monitored more frequently in patients who are receiving enhanced diuretic strategies or on RRT. For medications influenced by RRT, the need for dose adjustments should be assessed daily or anytime RRT is interrupted, discontinued, or a change in modality or rate has been made.

The presence of renally eliminated medications should be assessed frequently. Therapeutic drug monitoring should be performed for medications that have a narrow therapeutic index if results can be obtained in a timely fashion. For patients receiving IHD, measuring a pre-dialysis serum drug concentration has the advantage of allowing time for the result to be reported and the next dose calculated so that it can be administered soon after dialysis. This is especially important if the desired pharmacologic effects are lost during or after hemodialysis because the serum concentration has become subtherapeutic. Serum concentrations drawn right after hemodialysis may reflect plasma concentrations that are transiently depressed until the medication can reequilibrate from the tissues (ie, a redistribution or rebound effect). The advantage of collecting a post-dialysis sample is the greater accuracy in determining how much medication was removed during hemodialysis. The down side of this strategy is that it delays dosing calculations and the administration of the next dose and ultimately delays the reestablishment of the target concentrations.

CONCLUSION

The unique characteristics of AKI can lead to notable differences in how kidney function is measured and how treatment regimens are developed. Most management approaches involve both prevention and supportive strategies, so as to minimize the potential for additional harm to the kidney. Understanding the constantly changing status inherent to AKI and how to adjust medication regimens is a key component to optimizing therapy.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ADQI	acute dialysis quality initiative
AIN	acute interstitial nephritis
AKD	acute kidney disease
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
ARB	angiotensin receptor blocker
ATN	acute tubular necrosis
BUN	blood urea nitrogen
CI-AKI	contrast-induced acute kidney injury
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL_{cr}	creatinine clearance
CRRT	continuous renal replacement therapy
CT	computed tomography
CVVH	continuous venovenous hemofiltration
CVVHD	continuous venovenous hemodialysis

CVVHDF	continuous venovenous hemodiafiltration
eGFR	estimated glomerular filtration rate
EHR	electronic health record
ESKD	end-stage kidney disease
FDA	Food and Drug Administration
FE_{Na}	fractional excretion of sodium
FE_{Urea}	fractional excretion of urea
GI	gastrointestinal
GFR	glomerular filtration rate
IGFBP7	insulin growth-like factor binding protein 7
IHD	intermittent hemodialysis
JVP	jugular venous pressure
KDIGO	Kidney Disease: Improving Global Outcomes
KUB	kidneys, ureters, and bladder
NAC	*N*-acetylcysteine
NGAL	neutrophil gelatinase-associated lipocalin
NSAID	nonsteroidal anti-inflammatory drug
PIRRT	prolonged intermittent renal replacement therapy
RIFLE	Risk, Injury, Failure, Loss of kidney Function, and End-stage kidney disease
RRT	renal replacement therapy
SC	sieving coefficient
S_{cr}	serum creatinine
SLED	sustained low-efficiency dialysis
TIMP-2	tissue inhibitor of metalloproteinases 2
UFR	ultrafiltration rate

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SELF-ASSESSMENT QUESTIONS

1. A 71-year-old male, long-term care resident is admitted to the hospital with altered mental status. His admission laboratory values show a blood urea nitrogen (BUN) of 43 mg/dL (15.4 mmol/L), serum creatinine (Scr) of 2.8 mg/dL (248 µmol/L). Urinalysis reveals presence of white blood cells, red blood cells, and granular casts. His calculated fractional excretion of sodium (FeNa) is 2.2%. Whch of the following is the most likely etiology of his acute kidney injury?

   A. Intrinsic acute kidney injury

B. Bladder obstruction

C. Postrenal acute kidney injury

D. Functional acute kidney injury

2. A 56-year-old male presents to the hospital with acute kidney injury. Based on the Kidney Disease Improving Renal Outcomes (KDIGO) classification system, which of the following parameters should be used to determine the stage of his kidney injury?

A. Serum creatinine

B. Estimated glomerular filtration rate

C. Serum creatinine or blood urea nitrogen

D. Serum creatinine or urine output

3. A 52-year-old (80 kg) man is in the intensive care unit with sepsis and acute kidney injury. Over the last 24 hours, his serum creatinine increased from a baseline of 0.9 mg/dL to 1.9 mg/dL (80-168 µmol/L) and he has had 100 mL/hr of urine output for the last 6 hours. His urinalysis is positive for the presence of epithelial cells, granular casts, and WBCs. According to the Kidney Disease Improving Global Outcomes (KDIGO) AKI classification, which stage of acute kidney injury does this patient have?

A. Stage I

B. Stage II

C. Stage III

D. Stage IV

4. A 53-year-old male is receiving furosemide IV for the treatment of fluid overload. If his response to furosemide decreases, all of the following strategies can be utilized to overcome diuretic resistance EXCEPT ___

A. Increase dose of furosemide

B. Change furosemide to a continuous infusion

C. Change furosemide from intravenous to oral route

D. Add oral metolazone

5. A 36-year-old male is diagnosed with intrinsic acute kidney injury secondary to a prolonged exposure to intravenous tobramycin. Which of the following pathophysiologic processes has most likely occurred in this case?

A. Glomerular damage secondary to severe inflammation

B. Drug hypersensitivity reaction leading to interstitial inflammation

C. Bladder outlet obstruction

D. Tubular epithelial cell damage

6. A 82-year-old female is admitted to the medical intensive care unit with acute kidney injury (AKI). Her labs indicate the following: Na 133 mEq/L (mmol/L), K 4.8 mEq/L (mmol/L), Cl 95 mEq/L (mmol/L), CO_2 22 mEq/L (mmol/L), PO_4 6.6 mg/dL (2.13 mmol/L), Ca 8.1 mg/dL (2.03 mmol/L), BUN 33 mg/dL (11.8 mmol/L), and S_{cr} 2.8 mg/dL (248 µmol/L). Which of the following electrolyte abnormalities does she have that are commonly found in patients with AKI?

A. Hyperphosphatemia

B. Hyperkalemia

C. Hyponatremia

D. Hypercalcemia

7. Which of the following medications is most likely to cause of prerenal acute kidney injury in a 75-year-old hospitalized patient?

A. Tobramycin

B. Acyclovir

C. Contrast dyes

D. Lisinopril

8. Per 2012 KDIGO AKI guidelines, which of the following intravenous fluids is recommended as first-line therapy for the prevention of acute kidney injury?

A. 0.45% Saline

B. PlasmaLyte

C. 20% Albumin

D. 0.25% Saline

9. Which of the following dialysis modalities is/are most likely to cause hypotension?

A. Intermittent hemodialysis

B. CVVH

C. CVVHD

D. Sustained low-efficiency dialysis (SLED)

10. A 72-year-old critically ill male with acute kidney injury requires vancomycin, a renally cleared antibiotic, for the treatment of ventilator-associated pneumonia. When determining how to individualize vancomycin dosing for this patient, all of the following parameters need to be taken into account EXCEPT:

A. Serum phosphorus levels

B. Serum creatinine

C. Urine output

D. Utilization of renal replacement therapy

11. Which of the following statements about drug dosing considerations in renal replacement therapy is CORRECT?

A. Drug clearances attained by intermittent hemodialysis, continuous renal replacement therapy (CRRT), and hybrid renal replacement therapy are generally similar.

B. Drug clearance is dependent on a drug's physiochemical properties.

C. Drug clearance is similar across all CRRT modalities.

D. Principles of drug clearance are more clearly defined for CRRT than IHD.

12. Electronic health record alerts may prevent acute kidney injury by helping healthcare providers ___

A. Distinguish between patients with acute kidney injury and those with chronic kidney disease

B. Identify patients at risk for acute kidney injury

C. Renally dose medications

D. Identify patients requiring renal replacement therapy

13. One major advantage of novel biomarkers such as tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) is that they can _____

A. Detect early acute kidney injury (AKI)

B. Detect which patients will develop chronic kidney disease

C. Stage patient's severity of AKI

D. Predict recovery from chronic kidney disease

14. Which of the following is considered an indication for RRT?

A. Metabolic acidosis

B. Hypernatremia

C. Pneumonia

D. Cardiac failure

15. Which of the following anticoagulants used in CRRT is associated with hypocalcemia?

A. Unfractionated heparin

B. Fondaparinux

C. Bivalrudin

D. Regional citrate

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** Patient urinalysis and laboratory findings (particularly presence of granular casts and a FeNa >2%) indicate the presence of intrinsic acute kidney injury. Patients with prerenal functional AKI will typically have a FeNa <1% and no cells in their urinalysis. Patients with obstruction or postrenal AKI will need further diagnostic testing such as imaging to confirm presence of an obstruction. See the "Clinical Presentation" section and Table 61-3 for further details.

2. **D.** KDIGO Classification utilizes changes in serum creatinine and/or urine output to stage patients with acute kidney injury. For all staging systems, the criterion (eg, Scr, UOP, GFR) that leads to worst possible diagnosis should be used. See the "Definition and Classification" section for more information.

3. **B.** Patient's UOP is 1.25 mL/kg/hr for the last 6 hours, which doesn't fit any Stage Classification. However, his baseline serum creatinine increased 2

to 2.9 fold, which places him into Stage II. The criterion (eg, Scr, UOP, GFR) that leads to worst possible diagnosis should be used. See Table 61-1 for more information related to classification of patients with acute kidney injury.

4. **C.** All the listed interventions would be appropriate to overcome diuretic resistance except changing furosemide to oral route. Fluid overloaded patients may have intestinal edema which can reduce oral bioavailability of furosemide. As a result, intravenous route is preferred in most hospitalized patients. See the "Treatment" section and Table 61-7 for more information.

5. **D.** Intrinsic kidney injury is typically associated with tubular epithelial damage and is commonly observed with the administration of aminoglycosides such as tobramycin. See the "Pathophysiology" section for more information.

6. **A.** Patients with AKI will typically present with hyperphosphatemia and hyperkalemia as both phosphorus and potassium are mainly excreted by the kidneys. They can also develop hypocalcemia as a result of hyperphosphatemia or due to the use of regional citrate anticoagulation. Since the patient's serum potassium levels are within normal range, hyperphosphatemia is the most likely electrolyte abnormality associated with her AKI diagnosis. See the "Clinical Presentation" section for more information

7. **D.** ACE-inhibitors such as lisinopril are typically associated with prerenal acute kidney injury while other listed medications are not. See the "Pathophysiology" section for more information.

8. **B.** Isotonic fluids such as 0.9% saline or balanced solutions (ie, Plasmalyte) are preferred fluids for the prevention of acute kidney injury. Hypotonic fluids largely distribute intracellularly. Lastly, 20% albumin is typically reserved for hypoalbuminemic patients with cirrhosis or nephrotic syndrome. See the "Prevention" section for further information.

9. **A.** Intermittent hemodialysis is most likely to cause hypotension due to shorter duration and higher blood flow rates. See the "Renal Replacement Therapy" section for more information.

10. **A.** All of the listed parameters affect vancomycin clearance and need to be taken into account with the exception of serum phosphorus levels. Even though hyperphosphatemia is common in patients with AKI, it does not seem to interfere with vancomycin dosing recommendations. See the "Renal Replacement Therapy" section for more information.

11. **B.** Drug clearance is dependent on physiochemical properties such as protein binding and molecular weight. However, IHD and CRRT are all renal replacement modalities that vary in terms of efficiency of solute and water removal. Additionally, efficiency varies within each CRRT modality. See the "Drug Dosing Considerations in Renal Replacement Therapy" section for more information.

12. **B.** Electronic health record alerts may be useful in identifying patients at risk for acute kidney injury, for example, patients receiving multiple nephrotoxic medications. See the "Prevention" section for more information.

13. **A.** Novel biomarkers can detect early AKI. A score over 0.3 $(ng/mL)^2/1{,}000$ indicates high risk for developing moderate-to-severe AKI within 12 hours of testing. See the "Clinical Presentation" section for more information.

14. **A.** Life threatening complications of AKI are indications for RRT which includes fluid overload, electrolyte disturbances (eg, hyperkalemia), acid-base imbalances, uremic complications, oliguria or anuria, and pulmonary edema from fluid overload Metabolic acidosis. See the "Renal Replacement" section for more information.

15. **D.** Regional citrate is a preferred method of circuit anticoagulation in CRRT as it does not systemically anticoagulate the patient and it is associated with less circuit clotting. However, it works by chelating ionized calcium in the extracorporeal circuit, leading to less calcium that is returned to circulation. See the "Continuous Renal Replacement Therapy" section for more information.