

Chapter 2

Renal Complications

Elizabeth J. Lechner and Michael G. Risbano

Abstract Acute kidney injury (AKI) is a common problem in critically ill patients and is associated with adverse clinical outcomes, including increased mortality. Elevation in serum creatinine is the primary diagnostic indicator of AKI. Critically ill patients pose a diagnostic and therapeutic challenge as their clinical circumstances are frequently changing, and alterations in serum creatinine and glomerular filtration rate often lag behind the onset of renal injury. Analysis of urine sediment, osmolality, electrolytes, and renal ultrasound can aid in the diagnosis of AKI and distinguish between prerenal, postrenal and intrinsic causes of renal failure. Some of the most common causes of AKI encountered by intensivists will be discussed here, including ischemic injury, medication-related nephrotoxicity, rhabdomyolysis, acute tubulointerstitial nephritis, and vascular processes. Treatment of AKI depends on the etiology and often includes removal of an injurious medication or exposure. In addition, fluid administration is a major component of therapy in most cases. Renal replacement therapy is available for more severe cases of AKI with critical electrolyte abnormalities, severe acidemia, or massive volume overload refractory to non-invasive medical treatment.

Keywords Acute kidney injury • Acute renal failure • Prerenal, postrenal and acute tubular necrosis • Renal replacement therapy • Acidosis • Fluid management

E.J. Lechner, M.D.

University of Pittsburgh Medical Center, Montefiore Hospital,
3459 Fifth Avenue, NW 628, Pittsburgh, PA 15213, USA
e-mail: lechnerlj@upmc.edu

M.G. Risbano, M.D., M.A., F.C.C.P. (✉)

Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh
Medical Center, Montefiore Hospital, 3459 Fifth Avenue, NW 628, Pittsburgh,
PA 15213, USA
e-mail: risbanomg@upmc.edu

Introduction

Contemporary preferred terminology for acute renal failure (ARF) is acute kidney injury (AKI) [1]. AKI is not a disease process in isolation, rather it is a clinical syndrome that occurs rapidly and impairs the kidney's ability to eliminate waste products. Critically ill patients often develop AKI, and AKI is associated with adverse clinical outcomes including increased hospital length of stay and mortality. Even modest increases in serum creatinine (0.3–0.4 mg/dL) advances mortality [2]. Recognizing and diagnosing AKI in critically ill patients is challenging due to dynamic and frequently changing clinical circumstances. In this chapter we review the broad categories of AKI encountered in critically ill patients and discuss how to address contemporary diagnostic strategies and treatment options.

Epidemiology

Due to the variety of definitions associated with AKI, the estimated prevalence of AKI in critically ill patients can greatly vary. AKI affects up to 25 % of intensive care unit (ICU) patients with a reported mortality ranging from 15 to 60 % [3]. AKI requiring renal replacement therapy (RRT) is an independent risk factor for in-hospital mortality, which can be as high as 70 %. AKI is associated with increased health care costs, length of stay, and risk of developing chronic kidney disease. Risk factors for the development of AKI are variable and include advanced age, sepsis, cardiac surgery, diabetes, rhabdomyolysis, pre-existing renal disease, hypovolemia and shock. While kidney injury occurring outside the hospital can usually be attributed to an isolated cause, AKI that evolves during hospitalization, particularly during critical illness, generally has a worse prognosis and may result from multiple renal insults including hypovolemia, surgery, decreased cardiac output, medication effects (anesthetics, diuretics, nephrotoxic drugs), or radiographic contrast agents.

Definition of Acute Kidney Injury

In a broad sense, ARF is defined as a rapid decrease in the glomerular filtration rate (GFR), occurring over a period of minutes to days. As the rate of production of metabolic waste exceeds the rate of renal excretion, serum urea and creatinine concentrations rise [2]. However, the lack of a precise and universally accepted definition for ARF has limited clinical and translational research. Consensus conferences and publications from the Acute Dialysis Quality Initiative (ADQI), American Society of Nephrology (ASN), ARF Advisory group, the International Society of Nephrology (ISN), National Kidney Foundations (NKF), and the Kidney Disease Improving Global Outcomes (KDIGO) groups have worked to identify and correct these knowledge gaps and to develop a universal definition.

Table 2.1 Comparison of RIFLE, AKIN and KDIGO criteria for acute kidney injury

		Serum creatinine criteria	Urine output criteria
RIFLE	Risk	1.5-fold increase in creatinine OR decrease in GFR by 25 %	<0.5 mL/kg/h for 6 h
	Injury	Two-fold increase in creatinine or decrease in GFR by 50 %	<0.5 mL/kg/h for 12 h
	Failure	Three-fold increase in creatinine or decrease in GFR by 75 %	<0.3 mL/kg/h for 24 h or anuria for 12 h
	Loss	Need for renal replacement therapy for more than 4 weeks	
	ESRD	Need for renal replacement therapy for more than 3 months	
AKIN	Stage 1	Increase to ≥ 0.3 mg/dL or ≥ 1.5 to <2.0 times baseline)	<0.5 mL/kg/h for 6 h
	Stage 2	Increase to ≥ 2.0 to <3.0 times baseline	<0.5 mL/kg/h for 12 h
	Stage 3	Increase to ≥ 3.0 times baseline	<0.3 mL/kg/h for 24 h or anuria for 12 h
KDIGO	Stage 1	Increase to 1.5–1.9 times baseline OR ≥ 0.3 mg/dL	<0.5 mL/kg/h for 6–12 h
	Stage 2	Increase to 2.0–2.9 times baseline	<0.5 mL/kg/h for ≥ 12 h
	Stage 3	Increase to 3.0 times baseline OR increase to ≥ 4.0 mg/dL	<0.3 mL/kg/h for ≥ 24 h OR anuria for ≥ 12 h OR initiation of renal replacement therapy

In 2007, a collaborative research focus group between the ASN, ISN, NKF and the European Society of Intensive Care Medicine recommended that the term *acute kidney injury* replace the term *acute renal failure*. This emphasizes that an acute decline in kidney function is often secondary to an injury causing functional or structural changes in the kidneys [4, 5]. The ADQI developed the Risk, Injury, Failure, Loss and End-stage kidney (RIFLE) criteria (Table 2.1) which defines AKI as an increase in serum creatinine by $\geq 1.5\times$ baseline within 7 (or fewer) days. This RIFLE criterion stratifies patients into three categories of severity: risk, injury, and failure, and defines two outcomes of AKI: need for RRT for >4 weeks (loss) and permanent kidney failure (end-stage renal disease or ESRD) based on serum creatinine, GFR, and urine output. The Acute Kidney Injury Network (AKIN) group subsequently modified the definition of AKI to be an abrupt (within 48 h) increase in serum creatinine concentration of ≥ 0.3 mg/dL from baseline, a percentage increase in serum creatinine concentration of ≥ 50 %, or oliguria. The AKIN criteria removed criteria for GFR used by the RIFLE definition and focused on changes in serum creatinine and urine output to define three stages of AKI. Additionally, patients were categorized as having *Failure* if they were initiated on RRT, regardless of serum creatinine or urine output at the time of initiating RRT (Table 2.1). Most recently, the KDIGO guidelines further modified both the RIFLE and AKIN criteria, utilizing changes only in serum creatinine and urine output, and not changes in GFR, for staging. KDIGO maintains the AKIN definition that the absolute increase in serum creatinine of 0.3 mg/dL must occur within 48 h, but the time frame for a 50 % increase in serum creatinine is 7 days, as defined by the RIFLE criteria. When using any of these criteria, patients are classified according to the parameter that classifies them in the most severe stage of injury.

Diagnosis and Assessment of Kidney Injury

History

Obtaining a patient's history is important in determining the etiology of AKI. Many critically ill patients have hypertension, diabetes, vascular disease, chronic glomerulonephritis, and other chronic underlying conditions that can cause chronic kidney disease. Knowledge of the patient's baseline creatinine (if available) is essential, as is knowledge of prior episodes of AKI or prior need for RRT. Confirming the patient's medications and any recent medication changes should be done, as NSAIDs, ACE inhibitors, diuretics and antibiotics may contribute to renal dysfunction. Additionally, recent episodes of hypotension or administration of intravenous contrast should be noted.

Signs and Symptoms

AKI can be asymptomatic in ICU patients, but some patients may complain of nausea, vomiting, anorexia, hiccups, lethargy or gastrointestinal bleeding. Uremic patients may experience asterixis, altered level of consciousness, and/or seizures. Uremic acidosis may cause Kussmaul breathing, and hyperkalemia may cause cardiac arrhythmias.

Assessment of Intravascular Volume

A focused physical exam, with an emphasis on assessing intravascular volume status, is important in evaluating patients with AKI. Decreased skin turgor and mucosal dehydration, tachycardia, orthostatic blood pressure, and/or decreased urine output all indicate an increased likelihood of whole body volume depletion. Reciprocally, lower extremity or sacral edema, elevated jugular venous distention, cardiac rubs/gallops, ascites, pleural effusions and/or pulmonary crackles may indicate volume overload.

Intravascular volume assessment of the ICU patient by the physical exam alone is often not sensitive or specific, and adjunctive studies are often needed to increase the accuracy of clinical volume assessment. Measuring central venous pressure (CVP) either noninvasively or with a central venous catheter has been traditionally utilized as an indicator of volume status and responsiveness to fluid challenge; however, the clinical utility of measuring CVP has recently been challenged [6]. Regardless, use of CVP as a target for intravascular volume assessment and volume responsiveness continues to be widely used in clinical practice.

Laboratory Data

Serum Creatinine

While diagnosing AKI in critically ill patients is complicated by patients' dynamic and frequently changing clinical conditions, serum creatinine remains the primary means of assessing renal function and dysfunction. Age, sex, race, muscle mass, catabolic state and medications, however, can adversely affect renal function and must be considered when interpreting creatinine levels. Formulae for estimating GFR from serum creatinine, such as the Modification of Diet in Renal Disease (MDRD) formula or the Cockcroft and Gault equation, estimate steady-state creatinine clearance. Creatinine is primarily produced by muscle tissue and released into the circulation at a rate of 15–25 mg/kg/day and 10–20 mg/kg/day for middle-aged males and females, respectively. Creatinine excretion primarily depends on glomerular filtration, with very little creatinine secreted into the tubules or reabsorbed into the systemic circulation. Therefore, for the serum creatinine concentration to increase >1 mg/dL, the GFR must decrease by half. As such, serum creatinine concentration is not a particularly reliable measure of renal function in critically ill patients, as patients' renal function may rapidly change with only an associated modest change in creatinine. As changes in serum creatinine often lag behind acute renal injury, creatinine initially underestimates the degree of injury. Thus, other indicators of kidney injury must be utilized in conjunction with creatinine to reliably and accurately detect early AKI. Specifically, urine output, urine sediment, osmolality, electrolytes, and renal ultrasound may increase the precision with which early AKI is detected, as well as assist in identifying possible etiologies (Fig. 2.1). Often, depending upon the clinical scenario, critically ill patients with AKI will have a variety of these diagnostic studies performed simultaneously.

Serum Urea

Urea is a nitrogen-containing breakdown product of protein catabolism primarily excreted by the kidneys. Under normal conditions urea is filtered and 35–50 % is reabsorbed by the renal tubules. At times of decreased renal perfusion, up to 90 % of urea may be reabsorbed. As creatinine is not reabsorbed, urea increases more rapidly with decreased renal blood flow, and particularly with prerenal failure. Prerenal failure is suspected when a blood urea nitrogen to creatinine ratio (BUN:Cr) is increased from the normal ratio of 10:1 to $\geq 20:1$. Of note, BUN levels can increase in the absence of renal failure, due to corticosteroid use, upper gastrointestinal (GI) bleeding with metabolism of blood and reabsorption of urea from the GI tract, and increased protein load from overfeeding or starvation (both of which result in increased protein metabolism and urea production).

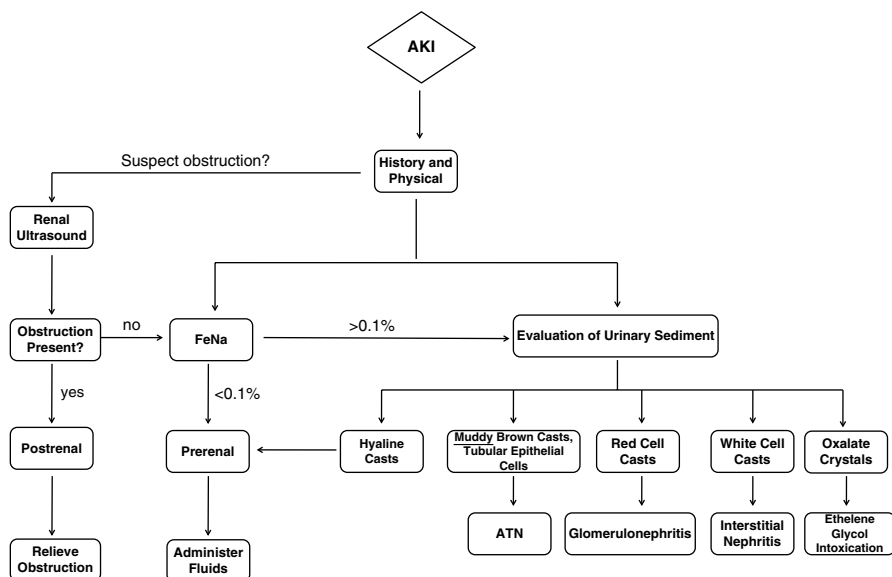


Fig. 2.1 Algorithm for diagnosis and treatment of acute kidney injury. Renal ultrasound may help diagnose obstructive uropathy by identifying hydronephrosis or bladder distension. Fractional excretion of sodium (FeNa) can distinguish between prerenal and intrinsic causes. The intrinsic cause can be identified through examination of the urinary sediment

Other Diagnostic Lab Tests

Other blood tests can be used in conjunction with serum creatinine and urea nitrogen to help determine the etiology of the AKI. Hypercalcemia and hyperuricemia may indicate an underlying malignancy. Elevated creatine kinase may signify rhabdomyolysis. Serum immunoelectrophoresis is abnormal in myeloma. Peripheral eosinophilia is suggestive of allergic interstitial nephritis. An osmolal gap (difference between measured and calculated osmolalities) suggests ethylene glycol or other non-ethanol alcohol toxicity [5].

Urine Output

Acute oliguria is defined as less than 400 mL of urine output per day, and may be the earliest sign of impaired renal function. Unfortunately, oliguria is an insensitive indicator of impending renal failure, as the absence of oliguria does not preclude nonoliguric renal failure.

Urine Sediment

Examination of the urinary sediment is helpful in distinguishing between the various causes of renal failure. In prerenal failure, hyaline and fine granular casts are usually present. In intrinsic renal failure due to acute tubular necrosis (ATN), muddy brown granular casts and tubular epithelial cells can predominate. White-cell casts and eosinophils may represent interstitial nephritis, and red-cell casts are typical in glomerulonephritis [5]. Heme-positive urine in the absence of erythrocytes suggests myoglobinuria or hemoglobinuria, and supports the diagnosis of rhabdomyolysis or transfusion reaction. The presence of oxalate crystals in the urine suggests ethylene glycol intoxication [5].

Urine Electrolytes and Osmolality

Urine osmolality, urine sodium concentration, fractional excretion of sodium (FE_{Na}), and the ratio of urine to plasma creatinine can differentiate between the causes of AKI. FE_{Na} distinguishes between prerenal azotemia and ATN:

$$FE_{Na} = \frac{\text{Urine Na (mEq / L)}}{\text{Urine Cr (mg / dL)}} \times \frac{\text{Serum Cr (mg / dL)}}{\text{Serum Na (mEq / L)}} \times 100$$

One of the earliest signs of tubular damage is decreased ability to concentrate the urine. ATN is characterized by a urine osmolality of less than 350 mOsm/kg, U_{Na} concentration greater than 40 mmol/L, and FE_{Na} greater than 1.0 % [6]. Prerenal azotemia is associated with a urine osmolality greater than 500 mOsm/kg, a U_{Na} concentration less than 20 mmol/L, and a FE_{Na} of less than 1.0 %. The accuracy of these indices is decreased with volume resuscitation, dopamine, mannitol, and diuretics. Therefore, urine specimens used to determine urine osmolality, U_{Na} (urinary concentration of sodium) and FE_{Na} should be collected before any such therapies are initiated. If a patient has recently received diuretics, the fractional excretion of urea (FE_{Ur}) can be used instead of the FE_{Na} .

$$FE_{Ur} = \frac{\text{Urine Ur (mg / dL)}}{\text{Urine Cr (mg / dL)}} \times \frac{\text{Serum Cr (mg / dL)}}{\text{Serum Ur (mg / dL)}} \times 100$$

Normal values of FE_{Ur} are 50–65 %, and a FE_{Ur} of <35 % indicates renal hypoperfusion. Note that the FE_{Ur} cannot distinguish between prerenal failure and ATN. Furthermore, the FE_{Ur} may be less accurate in patients experiencing osmotic diuresis.

Imaging Studies

Renal ultrasound (US) is often the first line imaging technique for critically ill patients with AKI. Renal US can accurately measure kidney size and detect hydronephrosis without the use of intravenous (IV) contrast. Small kidneys (evidence of chronic kidney disease) and horseshoe or unilateral kidney (evidence of congenital abnormalities) can assist in contextualizing a patient with AKI. Although evaluation of renal perfusion can be assessed by Doppler can determine renal viability by presence or absence of flow, the measurements are not quantitative. Obtaining accurate US images in ICU patients can be technically difficult and may require an experienced operator. In obstructive renal failure, computed tomography (CT) imaging can evaluate the level and site of obstruction. The decision to administer IV contrast for vascular assessment is often made on an individual patient basis.

Biomarkers

As serum creatinine is a slow and sometimes insensitive marker of kidney injury, several novel biomarkers for AKI are under investigation, though they are not yet available for routine use. Cystatin-C, a cysteine–proteinase inhibitor, is a small protein produced by nucleated cells that is freely filtered across the glomerulus, and therefore reflects GFR. Cystatin-C levels rise earlier than creatinine in critically ill patients with AKI. Cystatin-C levels are independent of muscle mass, allowing for more accurate estimation of GFR than serum creatinine [7]. Neutrophil gelatinase (NGAL), a 25-kDa protein, is up-regulated rapidly after AKI and can be measured in the urine or serum using enzyme-linked immunosorbent assay (ELISA) or fluorescence immunoassay. It has shown particular promise as a marker of AKI in patients with liver failure, with recent studies demonstrating that urinary NGAL can detect AKI in cirrhotic patients and can distinguish hepatorenal syndrome (HRS) from other causes of renal injury [7].

Causes of AKI

Some of the most common causes of AKI in critically ill patients are listed in Table 2.2. The causes are usually classified into one of three categories: prerenal, postrenal, or intrinsic.

Prerenal

Prerenal failure occurs due to decreased circulating blood volume, due to hypovolemia or a relative decrease in effective blood volume due to sepsis, hepatic failure, anaphylaxis, or vasodilatory drugs. Hemorrhage, gastrointestinal fluid loss

Table 2.2 Common causes of prerenal, intrinsic, and postrenal AKI in the ICU

Prerenal	Intrinsic	Postrenal
Sepsis	Acute tubular necrosis	Prostatic hypertrophy
Hypovolemia	Drugs	Prostate or cervical tumors
Hemorrhage	Toxins	Ureteral or urethral stones
GI fluid loss	Microcapillary occlusion	Neurogenic bladder
Surgery	Glomerular occlusion	Ureteral obstruction
Burns	Rhabdomyolysis	(i.e., from RP)
Anaphylaxis	Hemolysis (HUS/TTP)	lymphadenopathy)
Hepatic failure	Tumor lysis syndrome	Intra-abdominal hypertension
Vasodilatory drugs	Vascular	
Renal-artery or renal-vein occlusion	Glomerulonephritis	
	Acute interstitial nephritis	
	Intra-abdominal hypertension	

(diarrhea, vomiting, or nasogastric suction), renal losses (diuretics or glycosuria), trauma, surgery, and burns are other common etiologies of prerenal failure in critically ill patients. The renal structure and microstructure remain preserved early in prerenal failure. A reduction in the GFR coupled with an increased stimulus for salt and water reabsorption leads to high urine-to-plasma creatinine ratio. Urine sodium concentration is typically low. Elderly patients are particularly susceptible to prerenal azotemia due to a predisposition to hypovolemia and high prevalence of renal-artery atherosclerotic disease. Concomitant exposure to certain medications including angiotensin converting enzyme (ACE) inhibitors, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), tacrolimus, and cyclosporine can also precipitate prerenal azotemia. Prerenal AKI is usually fully reversible if the underlying cause is rapidly identified and treated [5].

Postrenal

Postrenal AKI, caused by obstruction of the urinary outflow tract, leads to hydronephrosis and enlargement of the renal pelvic cavity, with minimal distention of the renal papilla and few microscopic changes. It usually occurs due to ureteral or bladder-outlet obstruction from external compression with mass effect, tumor, or intrarenal obstruction due to crystals or renal calculi. Prostatic hypertrophy, prostate or cervical cancers, or retroperitoneal disorders are the most common causes. Neurogenic bladder can also result in functional obstruction. Renal ultrasound can be used to visualize obstructive uropathy and hydronephrosis and make the diagnosis. Like prerenal AKI, the potential for full recovery is good if the etiology of postrenal failure is determined and the obstruction is relieved quickly. The potential for recovery is inversely related to the duration of the obstruction.

Table 2.3 Nephrotoxic medications and mechanism of injury

Drugs that may cause acute renal failure in the ICU and possible mechanisms of injury
Radiocontrast agents (mechanism unknown)
Aminoglycosides (direct cellular toxicity from tubular cell accumulation)
Amphotericin (direct tubular cell toxicity)
Nonsteroidal anti-inflammatory drugs (prostaglandin blockade with afferent arteriolar vasoconstriction)
Angiotensin-converting enzyme inhibitors (efferent arteriolar vasodilatation)
Angiotensin receptor blockers (efferent arteriolar vasodilatation)
β -Lactam antibiotics (interstitial nephropathy)
Cisplatin (tubular cell toxicity)
Cyclosporin A (afferent arteriolar vasoconstriction and interstitial nephropathy)
FK-506 (tacrolimus) (afferent arteriolar vasoconstriction and interstitial nephropathy)

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Intrinsic

Intrinsic AKI is due to parenchymal injury of the blood vessels, glomeruli, tubules, or interstitium, and most commonly occurs after periods of prolonged or severe ischemia or exposure to nephrotoxins [2]. Damage to the tubular epithelium leads to sloughing of cellular debris and formation of casts which can occlude the tubular lumen. Prerenal AKI can lead to ATN if the renal perfusion is severe and the duration is long enough to cause tubular cell death. Congestive heart failure, cirrhosis and HRS, medications, sepsis, and renal vascular diseases such as renal artery thrombosis, renal artery stenosis, vasculitides, malignant hypertension, and hemolytic uremic syndrome are common causes [5].

Drugs and toxins can cause intrinsic renal failure by direct damage to the renal tubular cells, reduction in renal perfusion, rhabdomyolysis, drug precipitation causing intratubular obstruction, or allergic interstitial nephritis. Antimicrobials, radiocontrast agents, and chemotherapeutic agents are common causes of drug-induced AKI (Table 2.3).

Specific Etiologies of AKI

Ischemic Injury

When renal perfusion pressure drops, autoregulation maintains normal blood flow and GFR. Prostaglandins mediate a drop in afferent glomerular arteriolar resistance and sustain glomerular capillary pressure. An increase in efferent glomerular arteriolar resistance mediated by angiotensin II also supports glomerular capillary pressure. However, when renal perfusion pressure drops below the autoregulatory range,

endogenous vasoconstrictors increase afferent arteriolar resistance, which reduces glomerular capillary pressure and GFR, resulting in functional prerenal pathophysiology. Initially, the postglomerular capillary bed perfusing the renal tubules has diminished blood flow and pressures, but the tubules remain intact. Increasing severity and duration of ischemia, however, causes structural tubular damage and further renal dysfunction. Impaired sodium reabsorption by injured tubular epithelial cells increases sodium concentration in the tubular lumen and leads to polymerization of the Tamm–Horsfall protein, which contributes to cast formation [2].

Depletion of ATP leads to a number of critical alterations in metabolism. Cytoskeletal disruption leads to sloughing of cells from the brush-border membrane and obstruction of downstream tubules. Proteases and phospholipases are activated and cause oxidant injury to tubular cells and endothelial cells of the peritubular capillaries. Oxidant injury together with an increase in production of vasoconstrictors such as endothelin leads to vasoconstriction, congestion, hypoperfusion, and expression of adhesion molecules, which initiates leukocyte infiltration causing obstruction of the microcirculation and release of proinflammatory and chemotactic cytokines, reactive oxygen species, and proteolytic enzymes which damage tubular cells [2].

Elderly patients or those with atherosclerosis, hypertension, or pre-existing chronic renal failure are particularly susceptible to acute ischemic injury. While ischemic AKI classically occurs after an acute drop in systolic blood pressure below 90 mmHg during shock, normotensive ischemic ARF can also occur, involving milder degrees of low-perfusion states, in patients with increased susceptibility.

Contrast-Induced Nephropathy

Contrast-induced nephropathy (CIN) is acute deterioration of renal function after intravenous radiocontrast administration. Generally there is an increase in serum creatinine concentration more than 0.5 mg/dL or 25 % above baseline within 48 h of contrast administration [8]. The exact mechanism behind CIN is not clear. Though the incidence of CIN is low in the general population, critically ill patients are at increased risk due to multiple coexisting renal insults including hypotension, concomitant administration of nephrotoxic medications, sepsis, diabetes, cirrhosis, nephritic syndrome, and congestive heart failure.

There is no specific treatment for CIN once it develops, so prevention is a major focus. Ascorbic acid, fenoldopam, atrial natriuretic peptides, calcium channel blockers, prostaglandin E1, and endothelin receptor antagonist have been studied as preventative medications, but none have demonstrated an absolute benefit [9]. *N*-acetylcysteine (NAC) has also been proposed as a preventive therapy against CIN, but results across multiple studies remain inconsistent [10]. Contemporary management therefore centers upon intravenous fluid loading and using iso-osmolar contrast agents to minimize the risk of CIN [11]. Some studies have shown that sodium bicarbonate may confer more protection against CIN as compared to saline [12, 13]. The Renal Insufficiency Following Contrast Media Administration (REMEDIAL) study compared 326 at-risk patients with chronic kidney disease receiving

intravenous contrast, and demonstrated that sodium bicarbonate and NAC infusions prevented CIN compared to normal saline and NAC [12]. Additionally, the Reno-Protective Effect of Hydration with Sodium Bicarbonate Plus N-Acetylcysteine in Patients Undergoing Emergency Percutaneous Coronary Intervention (RENO) study evaluated 111 patients undergoing emergency percutaneous coronary intervention and demonstrated that rapid infusion of sodium bicarbonate plus NAC before contrast injection was both safe and effective in preventing CIN [13]. Follow-up studies, however, have reported conflicting results, [14, 15], and a meta-analysis concluded that patient heterogeneity may significantly influence the benefit of sodium bicarbonate [16]. In high-risk patients with chronic renal failure, hemofiltration has been reported to prevent CIN, though the clinical applicability of this is limited [17].

Nephrotoxic Drugs

Many drugs commonly administered in the ICU have nephrotoxic potential. Direct nephrotoxicity can lead to prerenal AKI, intrinsic AKI, or tubular obstruction. Renal syndromes such as renal tubular acidosis, Fanconi-like syndrome, and nephrogenic diabetes insipidus may also occur. Indirect nephrotoxicity occurs when agents damage non-renal tissues and produce breakdown products that cause renal failure (drug-induced hemolytic anemia or rhabdomyolysis), or when they interfere with the metabolism of other nephrotoxic medications. Though many medications may cause renal damage, anti-infective agents are some of the most commonly administered agents with nephrotoxic potential. Risk factors for development of AKI induced by antimicrobials include duration of therapy, excessive drug serum levels, pre-existing impaired kidney function, renal hypoperfusion, sepsis, and concurrent use of other nephrotoxic medications. The most successful strategy to prevent antimicrobial-induced kidney insufficiency is to decrease a patient's exposure to these agents, including limiting use based on pathogen susceptibility and limiting treatment duration to recommended treatment courses for the specific infection. For renally cleared agents, dosing should be adjusted according to creatinine clearance, acknowledging this may only be a rough estimate of GFR in critically ill patients. Monitoring medication serum concentrations may also help prevent dose-related renal toxicity. Of note, serum creatinine levels can increase with use of trimethoprim-sulfamethoxazole as this medication competes with creatinine for tubular secretion, not due to an actual decrease in GFR.

Vancomycin

Vancomycin is a key antibiotic for treating Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin is primarily eliminated by renal excretion through glomerular filtration as well as active tubular secretion. The exact mechanism of vancomycin-induced nephrotoxicity is not well

understood, but is thought to involve proximal renal tubular cell necrosis, oxidative stress, and mitochondrial damage [18].

Elevated vancomycin trough levels are a significant predictor of nephrotoxicity. A retrospective analysis of patients with MRSA pneumonia treated with vancomycin demonstrated that patients with higher vancomycin trough levels (levels ≥ 15 $\mu\text{g/mL}$) and prolonged treatment duration (courses ≥ 14 days) were more likely to develop renal toxicity, defined as a 0.5 mg/dL or greater than 50 % increase in baseline serum creatinine [19]. However, as the temporal relationship between elevated trough concentrations and development of nephrotoxicity was unclear, it is difficult to discern whether elevated trough levels represent a cause or effect of the accompanying renal failure. The concomitant use of vancomycin and aminoglycosides also significantly increases the risk of renal toxicity even more than when receiving any one therapy alone [18].

Patients typically recover from vancomycin-induced nephrotoxicity if the antibiotic is discontinued or dosage is appropriately adjusted [18].

Aminoglycosides

Aminoglycosides cover both Gram-negative bacilli and Gram-positive cocci, and despite years of use, bacterial resistance to aminoglycosides has not significantly increased. The most common complication of aminoglycoside administration is nephrotoxicity, estimated to occur in 10–20 % of patients receiving aminoglycosides [20]. Risk factors for development of aminoglycoside nephrotoxicity include increased age, diabetes, cirrhosis, chronic kidney disease, metabolic disturbances, concomitant use of other potentially nephrotoxic drugs (furosemide, ACE inhibitor, NSAIDs, vancomycin, colistin, cephalosporins, piperacillin, clindamycin, or iodinated contrast media), prolonged duration of therapy, or high concentrations of the drug.

Aminoglycosides are primarily cleared through the kidneys. They are filtered by the glomerulus, after which they reach the proximal tubule epithelial cells and bind to the brush-border membrane. Accumulation of aminoglycosides in endosomes and lysosomes results in cellular apoptosis and necrosis and decreased GFR [20].

Nephrotoxicity due to aminoglycosides generally occurs during treatment or a few days after discontinuation of treatment, with a mean delay of 9 days between first administration of the drug and resultant nephrotoxicity. However, increases in plasma creatinine associated with aminoglycoside toxicity have been reported to occur as late as 21 days after initiation of therapy. Recovery of renal function usually occurs after discontinuation of the drug without the need for RRT.

Standard (multiple-daily) and once-daily dosing regimens are equivalent with regard to bacteriologic cure, although once-daily dosing reduces mortality and incidence of nephrotoxicity [20]. The convenience of once-daily dosing and cost-reduction are additional benefits.

Nephrotoxic anti-infective agents should be used with caution, especially in patients with additional risk factors for kidney injury. However, in some cases prompt treatment of life-threatening infections must take precedence over the

potential for nephrotoxicity. Guidelines recommend monitoring of drug levels when possible to ensure appropriate dosing, and limiting the duration of treatment to the minimum time needed to treat the infection [21].

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs cause AKI by inhibiting prostaglandins. Prostaglandins are produced from cell membrane lipid precursors through enzymatic activity of cyclooxygenases. Prostaglandins are vasodilators, and are particularly important for maintaining renal perfusion in conditions of prolonged vasoconstriction such as chronic kidney disease, volume depletion, effective arterial volume depletion (heart failure, nephrotic syndrome, and cirrhosis), prolonged use of vasoactive medications such as norepinephrine or vasopressin, or severe hypercalcemia with renal arteriolar vasoconstriction. NSAIDs inhibit cyclooxygenase, leading to a reduction in prostaglandin synthesis, which can result in reversible renal ischemia, decreased glomerular filtration and AKI [22].

Increase in plasma creatinine concentration can occur at any time during NSAID use but usually occurs during the first 3–7 days of therapy. Urinalysis generally does not demonstrate hematuria or proteinuria. Hyaline casts or renal tubular epithelial cell casts may be seen.

NSAID-induced AKI can be minimized by limiting or avoiding NSAID use in high-risk patients. In addition, NSAIDs should be avoided in patients requiring iodinated contrast or other nephrotoxic medications. NSAID-induced AKI is treated by discontinuing the offending agent. Volume resuscitation may also benefit patients with coexisting volume depletion. Renal recovery may occur quickly; however, time to recovery is affected by the presence of underlying chronic kidney disease or concomitant renal insults. Further evaluation, including possible renal biopsy, should be considered if recovery does not occur within 3–7 days.

Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) is an allergic reaction caused by a variety of drugs, including penicillins, cephalosporins, ciprofloxacin, rifampin, sulfonamides, cimetidine, allopurinol, and NSAIDs. AIN can also be due to infectious (Legionnaire's disease, cytomegalovirus, and Hantavirus), autoimmune (lupus), alloimmune (renal transplant rejection), and infiltrative (sarcoidosis, leukemia, and lymphoma) processes. AIN is associated with a classic triad of fever, rash, and eosinophilia. Urinalysis may show leukocyturia with eosinophils, leukocyte casts, and low-grade proteinuria. Tubular dysfunction occurs in the majority of patients with AIN, with interstitial infiltrates composed of lymphocytes, macrophages, eosinophils, and plasma cells. The diagnosis is usually made based on clinical history and supported by laboratory findings, and can be confirmed by renal biopsy. AIN is usually

reversible after discontinuing the offending agent or treating the underlying disease. Corticosteroids administered early (within 7 days of diagnosis) can improve the recovery of renal function [23].

Glomerulonephritis/Vasculitis

Acute glomerulonephritis and vasculitis often results in transfer to the ICU for management of associated renal or respiratory failure. Renal failure due to glomerulonephritis and vasculitis includes: postinfectious glomerulonephritis, rickettsial infection, bacterial endocarditis, Goodpasture's syndrome, systemic lupus erythematosus, granulomatosis with polyangiitis, and Henoch–Schönlein purpura. Diagnosis is based on clinical presentation. Urinalysis typically shows nephritic sediment with red cells as well as white and red cell casts. Additional laboratory studies include antinuclear antibody, anti-GBM antibodies, serum complement levels (C3, C4), anti-neutrophil cytoplasmic antibodies, and antistreptolysin antibodies. Renal biopsy is typically recommended to obtain the correct diagnosis and guide management.

Rhabdomyolysis

AKI is a complication of rhabdomyolysis, and represents 7–10 % of all cases of AKI in the USA. The outcome of rhabdomyolysis is worse when complicated by AKI, with a reported mortality of 59 % among critically ill patients with the coexisting conditions [24]. The exact mechanism by which rhabdomyolysis impairs glomerular filtration is unclear, but intrarenal vasoconstriction, direct and ischemic tubule injury, and tubular obstruction all likely play a role [24]. Myoglobin is concentrated in the renal tubules and precipitates in the tubules with the Tamm–Horsfall protein. This process is enhanced by volume depletion, renal vasoconstriction, and acidosis. Though there is no defined threshold value of serum creatine kinase above which the risk of AKI is certain, AKI is unlikely when initial creatine kinase levels are less than 15,000–20,000 U/L.

Patients with AKI due to rhabdomyolysis usually experience volume depletion due to sequestration of water in injured muscles. The mainstay of treatment is early, aggressive volume repletion, with some patients requiring up to 10 L of fluid per day [24]. The type of fluid used for repletion remains controversial. The use of sodium bicarbonate to alkalize the urine has been considered to have potential benefit, but studies have not been definitive [24]. Large volumes of normal saline may be required to resuscitate a patient with rhabdomyolysis. This can result in the development of a hyperchloremic metabolic acidosis. Therefore changing IV fluids to either sodium bicarbonate or lactated ringers may be a reasonable option. As an osmotic agent, there is hypothetical benefit for mannitol in rhabdomyolysis as it increases urinary flow and mobilizes fluid from injured muscles; however, studies

have not shown benefit from its use [24]. Loop diuretics have also been studied but have also not shown any clear benefit.

Electrolyte abnormalities can occur as a result of the release of cellular components during rhabdomyolysis, particularly hyperkalemia, hyperphosphatemia, hyperuricemia, high anion-gap metabolic acidosis, and hypermagnesemia, and further complicate and exacerbate accompanying AKI. In cases of severe AKI with refractory hyperkalemia, acidosis, or volume overload, RRT may be necessary. Conventional hemodialysis does not remove myoglobin effectively due to its molecular size. Continuous venovenous hemofiltration or hemodiafiltration may have some efficacy in removing myoglobin, but larger studies are needed to assess the effect on outcomes.

Vascular Causes of ARF

Vascular diseases are an important yet often overlooked cause of AKI. Vascular processes can be divided into small-vessel and large-vessel diseases.

Small-Vessel Disease

Atherosclerosis with embolization of atherosclerotic plaques to the kidneys is an increasingly common cause of small vessel disease in the elderly population. Scleroderma can lead to fibrosis and narrowing of the small arteries in the kidneys. Although uncommon, scleroderma renal crisis is the sudden onset of oliguric renal failure, hypertension, and grade 3 or 4 hypertensive retinopathy in patients with scleroderma. Malignant hypertension can lead to acute renal vascular damage with fibrinoid necrosis and intimal thickening of the small arteries and arterioles. Clinical signs may include oliguria, proteinuria, hematuria, thrombocytopenia, and microangiopathic hemolytic anemia. The most common cause of malignant hypertension is underlying renal disease, though essential hypertension and medication noncompliance are also frequently responsible. Other less common causes of malignant hypertension that should be considered, particularly in difficult to treat cases, include renal artery stenosis, primary aldosteronism, and pheochromocytoma [25].

Other rare causes of small vessel renovascular disease include hemolytic-uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), and acute cortical necrosis.

Large-Vessel Disease

Renal artery stenosis (RAS) is usually caused by atherosclerosis of the main renal arteries; fibromuscular hyperplasia is a rare cause of RAS. RAS leads to decreased perfusion pressure and release of renin by the kidneys, which leads to hypertension. Over time, the kidneys decrease in size and become atrophic, glomerular filtration

decreases, and oliguria/anuria ensues. Serum renin levels, radionuclide scans after administration of captopril, Doppler studies, or renal arteriography may be useful for confirming a suspected diagnosis of RAS. Renal infarction, caused by acute embolism or thrombosis, most commonly occurs in older patients with coronary disease or atrial fibrillation [25].

Hepatorenal Syndrome

Hepatic and renal failure commonly coincide in critically ill patients, frequently due to drug intoxication and/or infections. Prerenal azotemia associated with advanced cirrhosis is common phenomena, and prerenal azotemia refractory to volume resuscitation is termed HRS. In HRS, splanchnic vasodilation leads to decreased effective arterial circulating volume and compensatory activation of the renin-angiotensin and sympathetic systems to maintain blood pressure. Catecholamine and angiotensin production increases, causing intrarenal vasoconstriction [7], resulting in a pre-renal state with low urine sodium (<10 mEq/L) and low FE_{Ur} (<20 %), and a bland urine sediment.

HRS is associated with a very high mortality. Etiologies of HRS include GI hemorrhage, spontaneous bacterial peritonitis and excessive diuretic use. When a cirrhotic patient demonstrates signs of prerenal failure, aggressive fluid resuscitation with crystalloid or albumin is indicated to attempt to reverse the process. Extravascular volume overload may limit resuscitation efforts; however, in hypoalbuminemic patients with prohibitive pleural effusions or ascites, thoracentesis or paracentesis with concomitant IV albumin replacement may be indicated.

Pharmacologic management of HRS includes α -agonists, norepinephrine, vasopressin analogs, and combination therapies, which may improve or reverse HRS in a minority of patients. Pentoxifylline may decrease the incidence of AKI in patients with acute alcoholic hepatitis. Intravenous albumin significantly reduces the incidence of AKI and mortality in cirrhotic patients with spontaneous bacterial peritonitis, and decreases the incidence of AKI after large-volume paracentesis. RRT can be a bridge to transplantation in patients with HRS and liver failure, but does not significantly change outcomes in the absence of liver transplantation [7].

Complications of Renal Failure

Bleeding

Increased risk of bleeding has long been recognized as a complication of renal injury; however, the pathophysiology remains poorly understood. Prolonged bleeding from puncture sites, subdural hematomas, and bleeding from mucous membranes including nasal, gastrointestinal, and genitourinary sites are the most common manifestations [26]. Although platelet counts and coagulation factors are

often normal in patients with AKI, platelet adhesiveness is reduced [27]. Prolonged bleeding time is a useful clinical laboratory test for assessment of bleeding risk [26]. Anticoagulation during hemodialysis can transiently worsen bleeding risk. However, RRT can improve the bleeding defect. Other medical therapies such as administration of cryoprecipitate, desmopressin, and estrogens can also improve bleeding due to AKI and uremia. Platelet transfusion is generally ineffective because transfused platelets will behave like the patient's own uremic platelets. Red blood cell transfusion in anemic patients can correct prolonged bleeding time. Erythropoietin can improve anemia associated with renal insufficiency and reduce the need for repeated transfusions, but it acts slowly and may not be useful in the acute setting [26].

Cardiovascular/Infectious/Neurologic Complications

Cardiovascular complications such as congestive heart failure, pulmonary edema, and hypertension may occur as a result of salt and water retention. Arrhythmias have been reported to occur in 10–30 % of patients. Infections are a leading cause of morbidity and mortality in patients with AKI, primarily respiratory or urinary tract infections. Neurologic problems may also be seen and include confusion, ataxia, somnolence, and seizures [5].

Nephrogenic Systemic Fibrosis

Administration of IV gadolinium in the setting of kidney injury is associated with increased risk of nephrogenic systemic fibrosis (NSF). NSF has been described in chronic renal failure with or without dependence on hemodialysis, in AKI, and in renal transplant patients. The precise extent of renal failure that is associated with NSF is not clear, though a GFR <30 mL/min/1.73 m² increases risk. High doses of IV gadolinium have been implicated as a cause, as gadolinium has been found within the tissue of patients with NSF. In patients with renal dysfunction, hemodialysis can remove approximately 93 % of infused gadolinium [28]. The American College of Radiology recommends that use of gadolinium contrast in patients with a GFR <30 mL/min/1.73 m² be reserved for absolutely essential cases and notes that no single gadolinium contrast in renal dysfunction can be safely administered [29]. If gadolinium must be given to a patient on hemodialysis, several sessions of hemodialysis performed after administration of gadolinium may decrease the risk of developing NSF [29].

Treatment

Treatment of AKI in the ICU is complicated as AKI is usually due to multifactorial etiologies, and is not necessarily due to a single process or insult.

Fluid Management in the Critically Ill

The mainstay of treatment for renal hypoperfusion due to hypovolemia from septic shock is goal-directed fluid resuscitation to rapidly and aggressively restore end-organ perfusion. Rivers' seminal paper on goal-directed fluid therapy targeted CVP (8–12 mmHg) or pulmonary capillary wedge pressure, mixed venous saturations (>70 %) and improved cardiac output as physiological endpoints [30]. This algorithm for volume resuscitation requires rapid administration of fluids or blood within a 6-h window. In a post-hoc analysis of the Vasopressin in Septic Shock Trial, patients in the highest quartile of CVP (>12 mmHg) had lowest survival at both 12 h and 4 days, and those with CVP <8 mmHg had better survival. Current sepsis guidelines recommend maintaining mean arterial pressure (MAP) greater than or equal to 65 mmHg with crystalloid, colloids or vasopressors [31]. It is unknown whether this is adequate to prevent renal failure. The Fluids and Catheters Treatment Trial (FACTT) suggested that in patients with acute lung injury, conservative fluid management may not be detrimental to kidney function. Specifically there was no significant difference in need for RRT between patients in the conservative versus liberal fluid strategy groups, although creatinine concentration was slightly higher in the conservative-strategy group [32]. Given these considerations, once appropriate resuscitation is achieved it is reasonable to transition to either maintaining euvolemia or even actively removing fluid [31].

Crystalloids Versus Colloids

Crystalloids and colloids are the two main types of fluids used for resuscitation, and there has been long-standing debate regarding the superiority and safety of one versus the other. Crystalloid solutions are inexpensive and readily available. Colloid solutions can be synthetic (hydroxyethyl starches) or natural (albumin). Due to their larger molecular weight, colloids remain in the bloodstream longer than crystalloids. However, colloids confer no survival advantage as compared to crystalloids [33, 34]. In addition, some hyperosmotic colloids have been associated with development of renal failure [35].

Hydroxyethyl starch is a synthetic colloid derived from partially hydrolyzed and variably hydroxyethylated plant starch. A systematic review of 38 randomized controlled trials comparing hydroxyethyl starch to crystalloids, albumin, or gelatin for acute fluid resuscitation in critically ill patients found that hydroxyethyl starch was associated with increased mortality, increased AKI, and increased need for RRT after exclusion of seven trials for scientific misconduct [36]. The Saline versus Albumin Fluid Evaluation (SAFE) Study randomized and evaluated 6,997 patients admitted to the ICU to receive either 4 % albumin or normal saline for fluid resuscitation. Although patients in the normal saline infusion arm initially received more IV fluids, blood products, had a positive fluid balance, and had higher CVPs, there was no difference in 28-day mortality or need for RRT between groups [37].

Despite the increased cost associated with use of albumin, the Surviving Sepsis Guidelines advocate using crystalloid or albumin for volume resuscitation in patients with sepsis with hypovolemic shock [31]. They recommend against the use of hydroxyethyl starch [31].

Vasopressors

In patients with persistent hypotension despite adequate fluid resuscitation, vasopressors should be used to increase MAP and/or cardiac output to optimize organ perfusion. The impact of vasopressors can be inferred from observed increases in urine output and creatinine clearance, and decreases in serum creatinine levels. However, there are no data to support the use of one vasopressor over another for improving renal function [21]. Though the Vasopressin and Septic Shock Trial (VASST) did suggest that vasopressin could reduce progression to severe AKI compared with norepinephrine in a small subgroup of patients with less severe septic shock, this study is not generalizable to a large population [37]. Dopamine stimulates renal dopamine receptor-1 and can increase renal blood flow and diuresis. Though initially thought to have a protective effect against kidney injury, this has not been proven in human studies and dopamine's use for this purpose is not recommended by consensus guidelines [21].

Nutrition

Adequate nutrition should be ensured, as malnutrition is associated with increased morbidity and mortality in patients with AKI. Critically ill patients have accelerated protein breakdown and increased caloric needs, and daily caloric intake of 25–30 kcal/kg of body weight may be required [2, 5]. Intake of potassium and phosphate is typically restricted for patients with renal dysfunction because of impaired renal excretion. Hypokalemia and hypophosphatemia due to cellular uptake or external losses can occur, and patients should be monitored for need of careful supplementation.

Renal Replacement Therapy

Acute dialysis-dependent renal failure portends a poor prognosis and is associated with in-hospital mortality of 60–70 %. Indications for RRT include electrolyte abnormalities (elevated potassium or phosphate), acidemia, or volume overload refractory to medical management. The need for RRT can occur with or without a significantly elevated serum creatinine concentration. Encephalopathy, pericarditis, and coagulopathy are late complications of AKI requiring RRT.

Optimal timing of initiation of RRT is controversial. Though it is reasonable to conclude that early initiation of RRT may be beneficial in order to avoid dangerous

metabolic, fluid, and electrolyte derangements of uremia, there are no outcomes data to support this sentiment [38]. In fact, some have argued to withhold RRT until definite indications are present to minimize risks of complications associated with catheter placement, hemodynamic instability and cardiac arrhythmias during dialysis, or delayed renal recovery [2].

Types of RRT

Types of renal replacement for AKI include peritoneal dialysis, intermittent hemodialysis, and continuous renal replacement therapy (CRRT). Acute peritoneal dialysis is infrequently used in developed countries and will not be discussed in this chapter.

Intermittent hemodialysis is performed using venovenous access for a few hours a day at variable intervals. Sustained, low efficiency dialysis (SLED) or extended daily dialysis are forms of intermittent hemodialysis in which the duration of dialysis is extended to 6–12 h to allow for more gradual removal of solutes and fluid. CRRT is performed continuously (24 h per day) through either arteriovenous or venovenous vascular access using much slower blood flow rates and achieving slower solute clearance per unit of time compared to intermittent hemodialysis. Continuous venovenous hemofiltration, continuous venovenous hemodialysis, and continuous venovenous hemodiafiltration are the most common sub-modalities of CRRT. CRRT requires continuous anticoagulation, thus increasing risk of bleeding. Additionally, continuous exposure to an extracorporeal circuit can result in nutritional depletion, subtherapeutic antibiotic levels, or infection.

A systematic review of randomized controlled trials and prospective cohort studies found intermittent hemodialysis and CRRT lead to similar clinical outcomes in patients with AKI [38]. A recent randomized trial of intermittent hemodialysis versus CRRT demonstrated that even sicker patients could be safely treated with intermittent hemodialysis. Thus, given the significantly higher cost of CRRT, intermittent hemodialysis may be preferable in patients with AKI requiring RRT. However, in patients with severe hemodynamic instability, CRRT is still preferred.

Anticoagulation with unfractionated heparin is recommended to maintain activated partial thromboplastin time between 1 and 1.4 times the upper limit of normal. In patients with high risk of bleeding, regional citrate anticoagulation can be administered.

Acid–Base Regulation by the Kidneys

The systemic acid–base balance is maintained when the renal net acid excretion equals the body's net endogenous acid production. Under normal conditions, the 80–85 % of filtered bicarbonate (HCO_3^-) is reabsorbed through the proximal convoluted tubules (PCT), where carbonic anhydrase II (CA II) splits cytosolic H_2CO_3 into H^+ and HCO_3^- . Bicarbonate then exits the cell through the basolateral

Table 2.4 Causes of metabolic acidosis

High anion gap metabolic acidosis	Normal (hyperchloremic) anion gap metabolic acidosis
Acute kidney injury	Administration of normal saline
Chronic kidney disease	Chronic kidney disease
Diabetic ketoacidosis ^a	Adrenal insufficiency
Alcoholic ketoacidosis	Hyporeninemic hypoaldosteronism
Lactic acidosis	Proximal renal tubular acidosis
Salicylate intoxication	Distal renal tubular acidosis
Toxic alcohol intoxication	Diarrhea
(methanol, ethylene glycol, diethylene glycol, propylene glycol)	Intestinal, pancreatic, or biliary fistulae
Pyroglutamic acidosis	Pseudoaldosteronism
Fasting ketoacidosis	Drugs (spironolactone, prostaglandin inhibitors, triamterene, amiloride, trimethoprim, pentamidine)
Toluene intoxication ^a	Ureterosigmoidostomy, ureteroileostomy
	Diabetic ketoacidosis ^a
	Toluene intoxication ^a

^aCan have a high or normal anion gap

$\text{Na}^+/\text{HCO}_3^-$ co-transporter. Carbonic anhydrase IV (CA IV), which is located in the lumen of the tubule, promotes dissociation of luminal H_2CO_3 into CO_2 and H_2O to prevent buildup of a proton gradient. The major determinants of HCO_3^- reabsorption include luminal HCO_3^- concentration, luminal pH, luminal flow rate, peritubular partial pressure of CO_2 ($p\text{CO}_2$), and luminal and peritubular concentrations of angiotensin II. HCO_3^- that is not reabsorbed in the PCT gets reabsorbed by the thick ascending limb of the loop of Henle via the NHE_3 Na^+/H^+ exchanger and an electrogenic H^+ -ATPase. Some HCO_3^- is also reabsorbed in the collecting duct via an H^+ -ATPase. With normal renal function, very little HCO_3^- is excreted in the urine and the urine pH is usually below 6.0 [39].

Metabolic Acidosis

Metabolic acidosis is common in critically ill patients, characterized by a primary reduction in the serum HCO_3^- concentration, resulting in a decrease in the arterial partial pressure of carbon dioxide ($P_a\text{CO}_2$) and a decrease in blood pH. Metabolic acidosis occurs when the body's normal mechanisms of acid–base homeostasis are overwhelmed by an increased acid production or bicarbonate loss (Table 2.4).

In response to acidosis, increase in H^+ and HCO_3^- transport along the nephron, increased ammoniagenesis, and increased availability of urinary buffers such as phosphate leads to reduction (or elimination) of HCO_3^- from the urine, and increased NH_4 excretion. Endothelin-1, produced by endothelial cells and proximal tubule cells in response to acidosis, stimulates renal H^+ and HCO_3^- transport. Cortisol is secreted by the adrenal cortex in response to acidosis and stimulates renal H^+ and HCO_3^- transport in the proximal tubule. Parathyroid hormone acts on the proximal tubule to inhibit phosphate reabsorption, which acts as a urinary buffer [39].

Metabolic acidosis triggers a secondary ventilatory response to decrease $P_a\text{CO}_2$. The expected $P_a\text{CO}_2$ for the serum HCO_3^- concentration can be calculated using Winter's formula ($P_a\text{CO}_2 = 1.5[\text{HCO}_3^-] + 8 \pm 2$). A measured $P_a\text{CO}_2$ different than the value calculated using Winter's formula indicates the presence of a coexisting primary respiratory alkalosis or acidosis [39].

The serum anion gap ($[\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$) may be useful in determining the etiology of a metabolic acidosis. Normal anion gap is 6–12 mmol/L. Low serum albumin reduces the calculated anion gap by ~2.3 mmol/L for every 1.0 g/dL decrease in serum albumin concentration. When the change in HCO_3^- concentration exceeds the change in anion gap, it can be inferred that a coexisting hyperchloremic acidosis is present. Conversely, if the change in HCO_3^- concentration is lower than the change in anion gap, a coexisting metabolic alkalosis is present [39].

Acute metabolic acidoses are treated by addressing the underlying disorder. Administration of sodium bicarbonate has not been shown to be clinically beneficial. However, sodium bicarbonate should be considered in patients with ketoacidosis and serum pH below 7.1 or hemodynamic instability. Bicarbonate may also be considered in severe lactic acidosis with significant acidemia and/or hemodynamic instability. Increasing minute ventilation in mechanically ventilated patients to reduce the $P_a\text{CO}_2$ or dialysis may also be appropriate in some cases [39].

Summary of Key Points

- Acute kidney injury (AKI) has largely replaced the term acute renal failure.
- Serum creatinine concentration remains the primary measurement for the diagnosis of AKI.
- The causes of AKI can be classified into prerenal, postrenal, and intrinsic. Urinary sediment and urine electrolytes can be used to differentiate between the various causes.
- The mainstay of therapy is fluid resuscitation with crystalloid solutions. There is no survival benefit of colloids over crystalloids.
- Intermittent hemodialysis and CRRT result in similar clinical outcomes; however, patients with severe hemodynamic instability may still require CRRT.
- The kidneys are important for maintaining normal acid–base balance.

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