Chapter 31

Acute and Chronic Renal Failure and Management

Michael L. Bentley, PharmD, FCCM, and Ashita J. Tolwani, MD, MSc

Key words: acute kidney injury, acute renal failure, intrinsic acute kidney injury, prerenal acute kidney injury, continuous venovenous hemofiltration, continuous venovenous hemodialysis, continuous venovenous hemodiafiltration, sustained low-efficiency dialysis and extended daily dialysis

Disclosures: The authors have not disclosed any potential conflicts of interest.

Acute renal failure (ARF) is defined as a decrease in kidney function, occurring over a period of hours to days, resulting in the accumulation of creatinine, urea, and other metabolic waste products (azotemia). It can occur in patients with previously normal renal function or in patients with preexisting renal disease (acute-on-chronic renal failure). Acute renal failure is often accompanied by reductions in urine volume with associated salt and water retention and metabolic disturbances, such as metabolic acidosis and hyperkalemia. Anuria is defined as urine output less than 50 mL/d, and oliguria is urine output less than 400 mL/d. Oliguria is also defined as a urine output that is less than 1 mL/kg/h in infants or less than 0.5 mL/kg/h for 6 consecutive hours in children and adults.

Characterizing the epidemiology of ARF has been problematic given variations in the definition of ARF, differences in the causes and settings of ARF, and dissimilarities among patients developing ARF. Over recent years, there has been increasing recognition that relatively small increases in serum creatinine (SCr) are associated with morbidity and mortality. For this reason, the term acute kidney injury (AKI) has been used to recognize the importance of the disease as a spectrum of injury extending from less severe forms to more advanced injury, such as that requiring renal replacement therapy (RRT).
EPIDEMIOLOGICAL PATTERNS

The incidence of AKI varies widely and is dependent on the population studied and definition used. It accounts for 1% of hospital admissions in the United States.\(^3\)

The incidence of hospital-acquired AKI is 5% to 7%, exceeding that of community-acquired AKI by 5- to 10-fold, and has nearly doubled over the last 2 decades.\(^4\)

Acute tubular necrosis (ATN) remains the most common cause of hospital-acquired AKI and is often multifactorial (e.g., sepsis, postsurgical, contrast agents, medications).\(^5\) In the ICU, 5% to 20% of patients develop AKI, of whom approximately 6% require some form of RRT during their ICU stay. The incidence of ICU-related AKI has also increased over the last few decades. This is probably related to the increasing incidence of sepsis-related hospital admissions; increased prevalence of risk factors for AKI, including older age, chronic kidney disease (CKD), diabetes mellitus, and congestive heart failure; and expanded use of IV radiocontrast agents.

DEFINITION AND STAGING

The major obstacle to research in ARF has been the lack of a uniform definition, which has led to conflicting reports in the literature. Because of this lack of standardization, in 2002 the Acute Dialysis Quality Initiative workgroup devised the RIFLE definition and staging system for ARF, which categorizes ARF into 3 grades of increasing severity by incorporating levels of oliguria in addition to incremental Scr elevations: Risk (defined as oliguria \(>6\) hours or a Scr increase of at least \(1.5\)-fold), Injury, and Failure (both defined by a greater increase in Scr, or duration and severity of oliguria, compared with the Risk group) (Table 1 on page 595).

These categories—R, I, and F—were associated with 2 clinical outcomes: renal loss and end-stage renal disease (ESRD).\(^6\) Loss and ESRD were defined by the need for RRT for greater than 4 weeks and greater than 3 months, respectively. After emerging data demonstrated that even small alterations in renal function lead to adverse outcomes, the Acute Kidney Injury Network (AKIN) modified the RIFLE staging system and used the term AKI instead of ARF to encompass the entire spectrum of acute kidney dysfunction (Table 1 on page 595).\(^7\) The AKIN workgroup defined AKI as a reduction in kidney function occurring over no more than 48 hours manifest by an absolute increase in Scr level 0.3 mg/dL or more or a relative increase in Scr to \(1.5\)- to 2-fold, or documented oliguria less than 0.5 mL/kg/h for more than 6 hours despite adequate fluid resuscitation.\(^8\) Compared with the RIFLE classification, the AKIN definition includes lesser degrees of Scr elevation to diagnose AKI, identical grades of oliguria, and a similar severity staging system. In addition, the AKIN definition categorizes all patients requiring RRT for AKI in stage 3. For all practical purposes, RIFLE and AKIN criteria are the same. Multiple studies have validated the utility of these criteria to various populations, showing a correlation between more severe RIFLE stages and worse clinical outcomes.\(^9,10\)

DIFFERENTIAL DIAGNOSIS

Although specific tests do not exist for the diagnosis of AKI, a thorough history and complete physical examination should be undertaken to include rate of loss (acute versus a prolonged decline), symptoms if present, concurrent diseases, and review of both current and recent medications. Table 2 on page 596 lists several drugs known to cause or contribute to AKI. In addition, a review of blood chemistries (blood urea nitrogen, creatinine, serum electrolytes, albumin, and a complete blood count) and a complete evaluation of the urine (microscopy, sodium, creatinine, and osmolality) are essential. An often overlooked reason for acute oliguria is abdominal compartment syndrome. Abdominal compartment syndrome causes oliguria and AKI mainly by directly increasing renal outflow pressure and reducing renal perfusion. Therefore, measuring bladder pressure is essential in patients suspected of having abdominal compartment syndrome.

Ultrasoundography has limited utility for the majority of ICU patients given that prerenal azotemia and ATN represent the majority of cases. A reasonable initial approach may
## Table 1.

**RIFLE and AKIN Criteria for AKI**

<table>
<thead>
<tr>
<th>RIFLE Class</th>
<th>SCr Criteria/GFR</th>
<th>UOP Criteria (for both RIFLE and AKIN)</th>
<th>AKIN Stage</th>
<th>SCr Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Increase to 1.5-fold or GFR decrease &gt;25% from baseline</td>
<td>&lt;0.5 mL/kg/h for 6 h</td>
<td>1</td>
<td>Increase to 1.5- to 2-fold above baseline or by 0.3 mg/dL</td>
</tr>
<tr>
<td>I</td>
<td>Increase to 2-fold or GFR decrease &gt;50% from baseline</td>
<td>&lt;0.5 mL/kg/h for 12 h</td>
<td>2</td>
<td>Increase to 2- to 3-fold above baseline</td>
</tr>
<tr>
<td>F</td>
<td>Increase to 3-fold, GFR decrease &gt;75% from baseline, or SCr &gt;4 mg/dL (acute increase of at least 0.5 mg/dL)</td>
<td>&lt;0.3 mg/kg/h for 24 h or anuria for 12 h</td>
<td>3*</td>
<td>Increase &gt;3-fold above baseline or ≥4 mg/dL with an acute increase of ≥0.5 mg/dL</td>
</tr>
<tr>
<td>L</td>
<td>Complete loss of function for &gt;4 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Complete loss of function for &gt;3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; GFR, glomerular filtration rate; RIFLE, risk (R), injury (I), failure (F), loss (L), end-stage kidney disease (E); SCr, serum creatinine; UOP, urine output.

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

Include volume expansion and placement of a bladder catheter if absent, or if a bladder catheter is present, evaluation for obstruction. However, ultrasonography is warranted in high-risk patients, those presenting from the community (because obstruction is more common in community-acquired AKI), and after the initial evaluation has failed to reveal the potential cause of AKI. Although universal indications for renal biopsies are lacking, a biopsy may be necessary to assist in the diagnosis, determine the prognosis, and/or guide therapy. Renal biopsy is most useful in intrinsic renal failure not associated with ATN.

### CAUSES

Acute kidney injury generally is divided into 3 categories: prerenal, intrinsic, and postrenal. Several renal indices can help differentiate between prerenal AKI (also called prerenal azotemia) and ATN, as well as other causes of AKI (Table 3 on page 597). Although useful, these variables can be influenced by several nonrenal factors. For example, SCr, used to determine the ratio of blood urea nitrogen to SCr and to estimate glomerular filtration rate (GFR), can be influenced by both renal and nonrenal factors (Table 4 on page 597). In addition, reaching SCr steady state is often difficult given the variable rate of creatinine production, volume of distribution, and rate of elimination seen in the critically ill.\(^{1,3,16,18}\) The fractional excretion of sodium (FENa) is often used, and a FENa less than 1% suggests a prerenal cause. Fractional excretion of sodium measures the ratio of sodium excreted (urine sodium × volume) to sodium filtered (serum sodium × GFR):

\[
\text{FENa} = \frac{[\text{U}_\text{Na} \cdot S_\text{Na}]}{[S_\text{Na} \cdot U_\text{Na}]} \cdot 100
\]

where U = urine, Na = sodium, S = serum, and Cr = creatinine. Although FENa is very useful when evaluating AKI, sodium excretion can be influenced by common ICU medications, most notably loop diuretics.
### Table 2.

**Potential Causes of Drug-Induced Acute Kidney Injury**

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal</td>
<td></td>
</tr>
<tr>
<td>ECF volume depletion</td>
<td>Diuretics (excessive diuresis)</td>
</tr>
<tr>
<td>Decreased CO</td>
<td>Negative inotropic drugs (especially in severe or decompensated HF)</td>
</tr>
<tr>
<td>Decreased SVR</td>
<td>Vasodilator antihypertensive medications</td>
</tr>
<tr>
<td>Increased RVR</td>
<td>NSAIDs, cyclooxygenase inhibitors-2, cyclosporine, tacrolimus, anesthetics</td>
</tr>
<tr>
<td>Decreased TCP</td>
<td>ACEI, ARB</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>ATN</td>
<td>AG, amphotericin B, radiocontrast agents, cisplatin, zoledronate, cocaine, antiretrovirals (adefovir, cidofovir, tenofovir, and foscarinet)</td>
</tr>
<tr>
<td>AIN</td>
<td>Antimicrobials (penicillins, cephalosporins, sulfonamides, ciprofloxacin, vancomycin, macrolides, tetracyclines, and rifampin), NSAIDs, cyclooxygenase-2 inhibitors, omeprazole, lansoprazole, phenytoin, valproic acid, cimetidine, ranitidine, diuretics, cocaine</td>
</tr>
<tr>
<td>Acute GN</td>
<td>NSAIDs, ampicillin, rifampin, lithium, penicillamine, hydralazine, gold, mercury, heroin</td>
</tr>
<tr>
<td>Postrenal</td>
<td></td>
</tr>
<tr>
<td>Tubular precipitation</td>
<td>Acyclovir, methotrexate, sulfadiazine, foscarinet, indinavir, tenofovir, sulfonamides, triamterene, large-dose vitamin C (due to oxalate crystals), guaifenesin and ephedrine (nephrolithiasis)</td>
</tr>
<tr>
<td>Obstruction</td>
<td>Anticholinergic medications</td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ACEI, angiotensin-converting enzyme inhibitors; AG, aminoglycosides; acute GN, acute glomerulonephritis; AIN, acute interstitial nephritis; ATN, acute tubular necrosis; ARB, angiotensin receptor-blockers; CO, cardiac output; ECF, extracellular fluid; HF, heart failure; NSAIDs, nonsteroidal antiinflammatory drugs; RVR, renal vascular resistance; SVR, systemic vascular resistance; TCP, transcapillary pressure.

In this case, diuretics increase sodium excretion, making FENa less useful. In addition to FENa, a ratio of blood urea nitrogen to SCr greater than 20:1 and a urine osmolality greater than 800 mOsm/kg are suggestive of prerenal injury.

**Prerenal Acute Kidney Injury**

Prerenal acute kidney injury results from impaired renal blood flow and can be caused by several mechanisms.

Decreased perfusion may occur from intravascular volume depletion, decreased effective circulation, or medications.

Since the parenchyma is undamaged, the kidney responds by reabsorbing sodium in order to reabsorb water. This occurs when decreased perfusion is associated with intravascular volume depletion or when the effective circulating volume is decreased as suggested by a FENa.
Table 3.
Common Renal Indices Found in Acute Kidney Injury

<table>
<thead>
<tr>
<th>Type of Failure</th>
<th>BUN:SCr Ratio</th>
<th>UNa, mEq/L</th>
<th>FENa (FEUrea)</th>
<th>Urine Osmolality, mOsm/kg H₂O</th>
<th>Urinalysis/Sediment (typical findings²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal</td>
<td>&gt;20:1</td>
<td>&lt;20</td>
<td>&lt;1% (&lt;35%)</td>
<td>&gt;500</td>
<td>Specific gravity &gt;1.020; normal, hyaline cast</td>
</tr>
<tr>
<td>Intrinsic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| ATN            | <20:1         | >20  
(usually >40) | >1%b (<35%)  | <300                        | Specific gravity ~1.010; muddy-brown cast; epithelial cells, granular cast, WBCs, mild proteinuria |
| AIN            | <20:1         | Variable  
(usually >20) | <1% or >1%  
(>35%)   | Variable (usually <300) | Hematuria, WBCs and possible cast, RBCs, epithelial cells, ± eosinophils, low to moderate proteinuria |
| Acute GN       | >20:1         | <20        | <1% (<35%)    | Variable (usually >500)    | Dysmorphic RBCs and RBC cast, ± eosinophils, moderate to severe proteinuria |
| Acute vascular syndrome | — | >20        | Variable       | Variable                     | Hematuria |
| Postrenal      | >20:1         | >20        | Variable       | <400 but variable           | Variable (normal, hyaline cast, possible RBCs and/or WBCs, Bence-Jones proteinuria, crystals³) |

Abbreviations: acute GN, acute glomerulonephritis; AIN, acute interstitial nephritis; ATN, acute tubular necrosis; BUN, blood urea nitrogen; SCr, serum creatinine; FENa, fractional excretion of sodium; FEUrea, fractional excretion of urea; RBCs, red blood cells, WBCs, white blood cells.

*Not seen in all cases.

bFENa can be low in radiocontrast nephropathy and pigment nephropathy; FENa typically >3%.

³Calcium oxalate crystals with ethylene glycol ingestion; uric acid crystals in tumor lysis syndrome.

Table 4.
Factors Influencing Measured Serum Creatinine and Urea

<table>
<thead>
<tr>
<th>Serum creatinine</th>
<th>Urea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor (nonmedication)</td>
<td>Factor (medication)</td>
</tr>
<tr>
<td>Muscle mass, age, race, sex, diet, neuromuscular disease</td>
<td>Trimethoprim, cimetidine</td>
</tr>
<tr>
<td>Liver impairment, diet, trauma/burns, blood loss, internal</td>
<td>Corticosteroids, tetracycline</td>
</tr>
</tbody>
</table>
less than 1%. If not corrected in a timely fashion, the lack of perfusion will result in ATN.

Drug-induced prerenal AKI typically results either from decreased blood flow to the kidney or from intraglomerular hemodynamic alterations. Extracellular volume depletion can be seen with excess diuretic use or when diuretics are used in patients with decreased effective circulation. Drugs that are associated with prolonged hypotension can also lead to a further decrease in blood flow to the kidney. Drugs affecting the natural vasodilatation of the afferent arterioles or vasoconstriction of the efferent arterioles can result in prerenal AKI. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors decrease prostaglandins, which are partially responsible for vasodilating the afferent arteriole. Angiotensin-converting enzyme inhibitors and angiotensin receptor-blocking agents prevent efferent vasoconstriction by inhibiting the vasoconstrictor angiotensin II, therefore decreasing transcapillary pressure and the kidneys' ability to maintain an adequate perfusion pressure. Calcineurin inhibitors (eg, cyclosporine and tacrolimus) can also cause prerenal AKI. The mechanism is not well understood but is believed to result from afferent vasoconstriction, although efferent vasoconstriction probably also occurs. In addition, acute interstitial nephritis has been associated with these agents.11,20

Intrinsic Acute Kidney Injury

Intrinsic AKI occurs from injury to the renal tubules, glomerulus, vascular structures, or interstitium or obstruction of the renal tubules. The FENa may be greater than 1%, less than 1%, or variable depending on the mechanism of the insult. For example, in ATN, the renal tubule is damaged and unable to reabsorb sodium, resulting in a FENa greater than 1%. In the case of glomerulonephritis, the renal tubules are intact, allowing sodium to be reabsorbed; as a result, the FENa is less than 1%. 

Tubular Injury

Acute tubular necrosis is common in critical illness and often results from ischemia associated with a prolonged prerenal insult or a direct nephrotoxin. Renal injury is usually reversible but may take days to weeks and require short-term RRT. Irreversible damage is possible if ischemia is severe enough to cause cortical necrosis. Nephrotoxins most commonly associated with ATN include contrast agents, aminoglycosides, and amphotericin B, as well as several antiretrovirals.21-23

The urine sediment in ATN commonly demonstrates many tubular epithelial cells and coarse granular casts, often described as "muddy brown" casts. Acute tubular necrosis is characterized by failure to maximally dilute or concentrate urine (isosthenuria). In prerenal azotemia, urine osmolality is usually greater than 500 mOsm/kg, whereas in intrinsic renal disease, urine osmolality is less than 300 mOsm/kg. However, exceptions exist.

Interstitial Injury

Acute interstitial nephritis (AIN) is characterized by inflammatory infiltrates and edema within the interstitium. The clinical presentation may include fever and rash with laboratory evidence of eosinophilia. However, this classic triad is seen in only 10% to 30% of patients with AIN.24 It is relatively uncommon, identified in 1% to 3% of all renal biopsies,25 unless associated with AKI. In this group, biopsy-proven AIN accounts for 15% to 27% of cases.26

Although the cause of AIN varies, drug-associated AIN is most common, representing more than 75% of cases. Other causes include infections (5%-10%), idiopathic causes (5%-10%), and AIN associated with systemic diseases (10%-15%).27 Recovery is usually complete but may take weeks to several months. Early steroid administration has been suggested to limit damage associated with drug-induced disease.28 Acute interstitial nephritis associated with the chronic use of calcineurin inhibitors is often irreversible.

Glomerular Injury

Acute glomerulonephritis refers to a specific set of renal diseases in which an immunological mechanism triggers inflammation and proliferation of glomerular tissue that can result in damage to the basement membrane.
mesangium, or capillary endothelium. Urinary findings range from moderate to severe proteinuria (nephrotic category), dysmorphic erythrocytes, and erythrocyte casts (nephritic category). Rapidly progressive glomerulonephritis is frequently associated with systemic disorders such as lupus, hepatitis, vasculitis, and pulmonary renal syndromes. Typical complaints include fever, malaise, and arthralgia. Serological assays and kidney biopsy will identify most causes. Early recognition of this syndrome is extremely important because it can result in irreversible kidney damage, and in death, without prompt and aggressive treatment. Treatment with corticosteroids and cyclophosphamide has been shown to limit the disease.

**Vascular Injury**

Microvascular or macrovascular disease (major renal artery occlusion or severe abdominal aortic disease) can cause AKI. The classic microvascular diseases often present with microangiopathic hemolytic anemia and AKI occurring from glomerular capillary thrombosis, often with accompanying thrombocytopenia. Typical examples of these diseases are thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). Atheroembolic disease is another important cause of irreversible AKI. Patients with atherosclerotic disease who undergo an invasive vascular procedure are at increased risk for AKI induced by atheroemboli.

**Intratubular Obstruction**

Intratubular obstruction from precipitation of either protein or crystals within the tubular lumen can cause AKI. Examples include tubular obstruction from precipitated monoclonal light chains in multiple myeloma, uric acid from tumor lysis syndrome, calcium oxalate deposition from ethylene glycol, and drugs.

**Postrenal Acute Kidney Injury**

Postrenal AKI is uncommon in the critically ill. If it occurs, the obstruction may be seen anywhere between the renal pelvis and the external urethral meatus. Obstruction may be intraluminal, located in the wall, or extrinsic to the urinary tract. It may occur at the level of the bladder or urethra (lower tract obstruction) or at the level of the ureters or renal pelvis (upper tract obstruction). To cause AKI, upper tract obstruction must be bilateral or affect a solitary functioning kidney. The obstruction blocks the flow of urine, leading to hydrenephrosis with resultant damage to the renal parenchyma. If postrenal AKI is not treated promptly, the elevated tubular pressure can cause CKD.

If a urinary tract obstruction is expected, it can be ruled out with the placement of a bladder catheter. If a catheter is in place it should be evaluated for obstruction and, if obstruction is present, cleared or replaced. Ultrasound is the gold standard test for diagnosis of upper tract obstruction. However, upper urinary tract obstruction may not be initially detected by ultrasound in a patient who is volume depleted. It is therefore recommended to repeat the ultrasound if upper urinary tract obstruction is suspected once the patient is adequately fluid resuscitated.

**BIOMARKERS FOR ACUTE KIDNEY INJURY**

Serum creatinine is widely used in the diagnosis of AKI and is considered to be a specific but generally insensitive biomarker of renal dysfunction since several factors influence its production. Serum creatinine can change rapidly, resulting in non-steady-state levels that are misleading when used to estimate clearance. In addition, an increase in SCr is generally seen several days after injury has occurred. For these reasons, SCr is generally considered a poor marker of early AKI.

Identifying markers at the molecular–cellular level may allow for early intervention. They need to detect injury early, provide for a differential diagnosis, and predict prognosis. Several biomarkers are at differing stages of development and are being investigated in both adults and children with samples obtained from blood plasma, urine, or both. Those showing promise include neutrophil gelatinase–associated lipocalin (NGAL), cystatin C, interleukin-18, and kidney injury molecule-1 (KIM-1).
One of the most studied biomarkers in AKI is NGAL, a protein that is expressed in several tissues, including kidney, salivary gland, lung, trachea, stomach, colon, uterus, and prostate. Ischemic injury to the kidney upregulates this protein in the proximal tubule of the kidney, resulting in increased urine and plasma NGAL levels. This biomarker has shown promise in the following patient populations and conditions: pediatric and adult cardiac surgery, contrast induced-nephropathy, septic shock, trauma, and insulin following coronary angiography.

Cystatin C is synthesized by all nucleated cells. It is freely filtered by the glomerulus, reabsorbed by the proximal collecting tubule, and not secreted. In a small study (n = 85), cystatin C was found to identify AKI 1 to 2 days earlier than the RIFLE criteria. Interleukin-18 and KIM-1 have shown promise as well. Interleukin-18 is a proinflammatory cytokine that is induced in the proximal tubule following an insult to the kidney and detected in the urine. The transmembrane protein KIM-1 is overexpressed in the proximal tubule following ischemia and is detectable in urine.

Although most studies have investigated one biomarker, it is unlikely that a single biomarker will be able to identify AKI or predict outcome. It is more likely that a panel consisting of several biomarkers will be needed.

**COMMON CAUSES OF ACUTE KIDNEY INJURY IN CRITICAL ILLNESS**

**Hepatorenal Syndrome**

Hepatorenal syndrome (HRS) is a reversible, functional renal impairment that occurs in patients with advanced liver cirrhosis or those with fulminant hepatic failure. It is characterized by a marked reduction in GFR and renal plasma flow in the absence of other cause of renal failure. The hallmark of HRS is intense renal vasoconstriction with predominant peripheral arterial vasoconstriction. Notably, tubular function is preserved with the absence of proteinuria and lack of tubular histological changes.

**Definition and Incidence**

Two subtypes of HRS have been identified. Type 1 HRS is a rapidly progressive renal failure that is defined by doubling of initial SCR to a level more than 2.5 mg/dL or by 50% reduction in creatinine clearance to a level less than 20 mL/min in less than 2 weeks. Type 2 HRS is a moderate, steady renal failure with a SCR of more than 1.5 mg/dL. In type 1 HRS, a precipitating factor frequently is identified, whereas type 2 HRS arises spontaneously and is the main underlying mechanism of refractory ascites.

A multicenter, retrospective study of 423 patients with cirrhosis and AKI demonstrated that HRS (either type 1 or 2) caused AKI in 20 cases (6.6%), with the majority of AKI as either ATN (35%) or prerenal failure (32%).

**Pathophysiological Characteristics**

Splanchnic and systemic vasoconstriction together with intense renal vasoconstriction is the pathophysiological hallmark of HRS. Four interrelated pathways have been implicated in the pathophysiological process of HRS: (1) peripheral arterial vasoconstriction with hyperdynamic circulation and subsequent renal vasoconstriction, (2) stimulation of the renal sympathetic nervous system, (3) cardiac dysfunction contributing to the circulatory derangements and renal hypoperfusion, and (4) action of different cytokines and vasoactive mediators on the renal circulation and other vascular beds.

**Precipitating Factors**

A precipitating factor that worsens renal vasoconstriction can be identified in more than 70% to 100% of patients with type 1 HRS. It has been proposed that subclinical bacterial infections, which are potentially treatable or preventable, can act as precipitating factors. Twenty to thirty percent of patients with spontaneous bacterial peritonitis develop HRS despite appropriate treatment and resolution of infection. The extent to which intraabdominal hypertension or abdominal compartment syndrome contribute to HRS as precipitating factors is not known, yet it is speculated to be underrecognized in the critical care setting.
Diagnosis

Other causes of AKI must be excluded to make the diagnosis of HRS. Diuretic withdrawal and volume expansion are used to exclude a prerenal cause. Absence of shock and nephrotoxic drugs lessens the likelihood of ATN or AIN. The absence of significant proteinuria or hematuria excludes acute glomerular diseases sometimes seen in cirrhotic patients (cryoglobulinemia, membranoproliferative glomerulonephritis, and hepatitis C–related membranous nephropathy).

Both types of HRS require an increase in SCr above 1.5 mg/dL. The original diagnostic criteria contained minor criteria that are not needed to make the diagnosis of HRS but may be helpful in supporting the diagnosis. These minor criteria are serum sodium less than 130 mmol/L, urine osmolality more than serum osmolality, urine sodium less than 10 mmol/L, and urine output less than 500 mL/d. Low urine sodium and relatively high urine osmolality are seen in renal hypoperfusion states with functioning tubules. These markers were originally used to distinguish between ATN and HRS, yet low sensitivity and specificity limit their diagnostic accuracy.

Management

Management for HRS differs between type 1 and type 2, and given the dismal prognosis of patients with type 1 HRS, aggressive therapy usually is indicated only for patients who are waiting for a liver transplant or undergoing evaluation to determine candidacy for transplantation.64

General management includes withholding diuretics, continuing a low-sodium diet, restricting free water to less than 1 L/d for hyponatremic patients, excluding other causes for AKI, and looking for precipitating factors (especially spontaneous bacterial peritonitis). A therapeutic paracentesis is performed for patients with tense ascites in order to reduce abdominal pressures. Albumin is infused if more than 5 L of peritoneal fluid is removed to avoid precipitating volume contraction. Patients with type 2 HRS are typically less sick and can be managed as outpatients. Patients with type 1 HRS, however, require inpatient care with frequent monitoring of fluid intake, chemistries, and urine output. Beyond general management there are 4 major therapeutic interventions: pharmacological treatment with vasoconstrictors, transjugular intrahepatic portosystemic shunt, RRT, and liver transplantation. Of these, liver transplantation is the only one that affects long-term mortality.

Vasoconstrictor Therapy

Studies using vasoconstrictors designed to interrupt the splanchnic vasodilation have shown benefit and are now the most promising pharmacological agents for managing HRS. Vasoconstrictors studied include vasopressin analogs (omitressin and terlipressin), somatostatin analogues (octreotide), and the α-adrenergic agonists (midodrine and norepinephrine). Terlipressin is the most studied vasoconstrictor, and multiple small randomized trials62 as well as a metaanalysis63 showed improved renal function with reversal of HRS type 1 (SCr <1.5 mg/dL for up to 15 days), although 3-month survival was unchanged.64 Given these findings, terlipressin with albumin infusion is considered first-line therapy for HRS. Terlipressin, however, is not available in all countries, including the United States. Alternatives to terlipressin include vasopressin, midodrine, and octreotide.

Transjugular Intrahepatic Portosystemic Shunt

Transjugular intrahepatic portosystemic shunt is a nonsurgical method of portal decompression previously used as an alternative therapy for cirrhotic patients bleeding from esophageal or gastric varices who do not respond to endoscopic and medical treatment. A side-to-side portacaval shunt connects the portal and hepatic veins within the hepatic parenchyma. Transjugular intrahepatic portosystemic shunt reduces portal pressure and returns some of the volume of blood pooled in the splanchnic circulation to the systemic circulation.55 Transjugular intrahepatic portosystemic shunt is contraindicated in advanced cirrhosis since it can worsen liver failure and hepatic encephalopathy. It may benefit a select group of
patients by prolonging survival long enough for them to receive a liver transplant or avoid dialysis.

Renal Replacement Therapy
Initiation of dialysis is controversial in untreated patients who have HRS type 1 and are not candidates for liver transplantation because of the dismal chance of survival and the high morbidity and mortality rates associated with dialysis. The decision to initiate dialysis in these patients should be individualized.41 In patients awaiting a liver transplant who have failed pharmacological therapy or transjugular intrahepatic portosystemic shunt and have an indication for dialysis (intractable metabolic acidosis, volume overload, hyperkalemia), RRT may be a reasonable option as a bridge to liver transplantation.

Liver Transplantation
Liver transplantation remains the best treatment for suitable candidates with HRS because it offers a cure to both the diseased liver and the renal dysfunction.42 Following liver transplantation, evidence of resolving HRS is present in the first month with return of renal sodium excretion and normalization of hemodynamic abnormalities.56,57 Long-term renal function, however, remains affected.

Prognosis
The prognosis for patients with cirrhosis and renal failure is poor.61-67 The overall survival rate is approximately 50% at 1 month and 20% at 6 months, and HRS is associated with the worst prognosis.68 Untreated type 1 HRS carries a grim prognosis. Mortality is as high as 80% in 2 weeks, and only 10% of patients survive 3 months.58,59 Patients with type 2 HRS have a much better median survival, approximately 6 months.60

Cardiorenal Syndrome
The heart and kidney have a unique relationship. Diseases and processes that affect one organ will often affect the other. As an example, worsening heart failure leads to reduced renal perfusion and, if severe enough, results in prerenal AKI. However, patients with CKD have an increased risk of cardiovascular diseases.62,63 The situation in which acute or chronic dysfunction in one organ leads to acute or chronic dysfunction in the other has been referred to as the cardiorenal syndrome (CRS).

Definition and Incidence
Recently a new classification of the CRS was proposed,64 leading to a consensus conference under the auspices of the Acute Dialysis Quality Initiative.65 The syndrome has been divided into 5 subtypes whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other (Table 5 on page 603). Subtypes 1 and 3 account for acute changes in either the heart (type 1), leading to AKI, or the kidney (type 3), leading to cardiac dysfunction. Subtypes 2 and 4 account for chronic changes. In type 2, chronic heart disease leads to CKD, and type 4 CKD leads to chronic heart disease (left ventricular remodeling and dysfunction, acute heart failure [AHF], acute coronary syndrome). Secondary CRS (type 5) is preceded by a systemic event (e.g., sepsis) that leads to simultaneous injury and/or dysfunction of both the heart (AHF, acute coronary syndrome) and kidney (AKI, CKD).

The incidence of CRS depends on the definition used and whether the primary event was acute or chronic in nature and is typically derived indirectly. For example, AKI has been reported to occur in approximately 30% of patients hospitalized for AHF65,66 an estimate of type 1 CRS. The incidence of chronic CRS (types 2 and 4) may be as high as 60%, as reported from 2 studies identified in the chronic heart failure population.67,68 The true incidence of CRS may not be known, and studies are needed to better define this syndrome.

The pathophysiological progress, precipitating factors, management, and prognosis are related to the specific organs and their interdependency. Several recent reviews have been published.69,70

Tumor Lysis Syndrome
Tumor lysis syndrome (TLS) is characterized by a constellation of metabolic derangements caused by massive and abrupt release of intracellular components
Table 5.
Classification of Cardiorenal Syndrome

<table>
<thead>
<tr>
<th>CRS</th>
<th>Primary Event</th>
<th>Definition/Secondary Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>AHF or ACS or cardiogenic shock</td>
<td>Acute worsening of cardiac function leading to AKI</td>
</tr>
<tr>
<td>Type 2</td>
<td>Chronic heart disease</td>
<td>Chronic abnormalities in cardiac function leading to CKD</td>
</tr>
<tr>
<td>Type 3</td>
<td>AKI</td>
<td>Acute worsening of renal function leading to AHF, ACS, arrhythmias, shock</td>
</tr>
<tr>
<td>Type 4</td>
<td>CKD</td>
<td>CKD leading to cardiac injury (LV remodeling and dysfunction, diastolic dysfunction, AHF, ACS)</td>
</tr>
<tr>
<td>Type 5</td>
<td>Systemic disease (e.g., sepsis)</td>
<td>Simultaneous injury and/or dysfunction of heart and kidney due to acute or chronic disorders leading to AHF, ACS, AKI, CHD, CKD</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndrome; AHF, acute heart failure; AKI, acute kidney injury; CHD, congenital heart disease; CKD, chronic kidney disease; CRS, cardiorenal syndrome; LV, left ventricular.

into the blood following rapid lysis of malignant cells, leading to hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and uremia.\textsuperscript{71} It is typically seen after initiating cytotoxic therapy for hematological malignancies with large tumor burden or cell counts as in acute lymphoblastic leukemia, Burkitt lymphoma, or acute myeloid leukemia. These metabolic derangements place patients at risk for AKI, cardiac arrhythmias, seizures, and even death. Data suggest that AKI is a common complication of TLS, with incidences ranging from 7% to 45% in the adult population.\textsuperscript{72} Both hyperuricemia and hyperphosphatemia have been implicated in causing AKI.

**Pathophysiological Processes**

**Hyperuricemia**

Purines are catabolized to hypoxanthine and then to uric acid by xanthine oxidase. Uric acid is poorly soluble in water and solubility decreases with acidity; at a pH of 5 (the typical pH of urine), the solubility is 15 mg/dL.\textsuperscript{73} Rapid tumor lysis and the resulting purine catabolism exceed the renal clearance capacity of uric acid, which is normally 500 mg/d.\textsuperscript{74} The precipitation of uric acid in renal tubules can lead to tubular obstruction and AKI. Crystal-independent causes of AKI from uric acid, even with mild increases (5.7 ± 2 mg/dL), have been proposed and include renal vasoconstriction, alterations in renal autoregulation through inhibition of nitric oxide synthase 1, decreases in endothelial cell nitric oxide, and stimulation of the renin-angiotensin system.\textsuperscript{75}

**Hyperphosphatemia**

The level of phosphorus in malignant cells can be up to 4 times the level found in normal cells, and rapid release of these stores leads to hyperphosphatemia.\textsuperscript{71} Renal injury from hyperphosphatemia is thought to be related to crystals from calcium-phosphate precipitation in renal tubules. Risk of calcium-phosphate precipitation increases when the calcium phosphorus product exceeds 70.\textsuperscript{76} Hyperphosphatemia has also been implicated as the cause of AKI in acute phosphate nephropathy seen in patients receiving oral sodium phosphorus solution as a bowel preparation for colonoscopy.\textsuperscript{77}

**Diagnosis**

Diagnostic criteria for TLS were last modified by Cairo and Bishop in 2004\textsuperscript{74} and can be made based on laboratory findings or clinical condition (Table 6 on page 604).

**Management and Preventive Measures**

General principles for the management of patients at risk for or presenting with TLS are aggressive volume
Table 6.
Cairo-Bishop Definition of Laboratory and Clinical Tumor Lysis Syndrome

<table>
<thead>
<tr>
<th>Serum values in laboratory tumor lysis syndrome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid ≥8 mg/dL or 25% increase from baseline</td>
</tr>
<tr>
<td>Potassium ≥6 mEq/L or 25% increase from baseline</td>
</tr>
<tr>
<td>Phosphorus ≥6.5 mg/dL (children) or ≥4.5 mg/dL (adults) or 25% increase from baseline</td>
</tr>
<tr>
<td>Calcium ≤7 mg/dL or 25% decrease from baseline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical tumor lysis syndrome†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine ≥1.5 times the upper limit of normal for the age-adjusted normal range</td>
</tr>
<tr>
<td>Cardiac arrhythmia or sudden death</td>
</tr>
<tr>
<td>Seizure</td>
</tr>
</tbody>
</table>

*Laboratory tumor lysis syndrome is defined as having 2 or more of the serum values listed within a time period extending from 3 days before to 7 days after the initiation of chemotherapy.
†Clinical tumor lysis syndrome includes the presence of 1 or more of the listed clinical states.

expansion, treatment of hyperkalemia and secondary hypocalcemia, and preventive therapy for hyperuricemia.

**Volume Expansion**

Volume depletion can further increase uric acid or calcium-phosphate crystal precipitation in renal tubules. In patients at risk of or with TLS, volume expansion is one of the most important interventions because it maintains renal blood flow and urine flow, promoting urinary excretion of potassium, uric acid, and phosphate.78

**Hypouricemic Agents**

Hyperuricemia may be the main contributor to AKI in TLS. In a study conducted in 100 adults with aggressive non-Hodgkin lymphoma, AKI was avoided by preventing hyperuricemia.79 Urinary alkalization had been recommended in the past to reduce precipitation of uric acid crystals in the renal tubules; however, the higher urine pH causes an increase in calcium-phosphate crystal deposition. Therefore, urine alkalization has been removed as a recommendation for treatment.

Allopurinol in its active form, oxypurinol, acts as a competitive inhibitor of xanthine oxidase and decreases uric acid production. However, it cannot actively reduce preexisting high levels of serum uric acid, limiting its use to prevention. Also, the inhibition of xanthine oxidase blocks the catabolism of xanthine and hypoxanthine, increasing their levels. High xanthine levels could lead to xanthine crystal precipitation in renal tubules, also contributing to acute obstructive uropathy. Last, allopurinol reduces the clearance of 6-mercaptopurine and azathioprine, which are frequently used in leukemia treatment.

Rasburicase is effective in reducing high uric acid levels by directly catabolizing uric acid into allantoin. The urine solubility of allantoin is 5 to 10 times higher than uric acid, and allantoin crystal precipitation is largely nonexistent. The efficacy of rasburicase was compared with allopurinol in a study with 275 adults with hematological malignancies at risk of TLS in which patients were randomly assigned to 1 of 3 arms (rasburicase, allopurinol, or rasburicase plus allopurinol).80 Normalization of plasma uric acid levels was superior (87% versus 66%) and time to control of uric acid levels was shorter (4 hours versus 27 hours) in the rasburicase arm compared with the allopurinol arm. Results were similar in the rasburicase arm and rasburicase-plus-allopurinol arm.80 The rasburicase dose that is currently approved by the US Food and Drug Administration is 0.20 mg/kg/d for up to 5 days, yet several studies suggest that a shorter schedule may be sufficient to treat most patients.

The safety profile for rasburicase is good, although cases of hypersensitivity and methemoglobinemia have been reported.31,32 Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase or catalase deficiencies.31

**Electrolyte Management**

Electrolyte derangements seen in TLS include hyperkalemia, hyperphosphatemia, and hypocalcemia. In addition to using established measures to treat
these disturbances, it is useful to restrict potassium and phosphorus intake and avoid medications that antagonize the renin–angiotensin–aldosterone system. Administration of IV calcium should be restricted to symptomatic patients due to the risk of worsening calcium–phosphate precipitation and AKI.

**Prognosis**

Tumor lysis syndrome carries a poor overall prognosis. In the multicenter retrospective study by Annemans et al., 15% of patients with TLS died as a result of TLS complications.

No data exist for the long-term consequences of AKI in patients with TLS. It is known, however, that even mild AKI is associated with worsened outcomes. A review showed that hospitalized patients with 10% to 24% increases in SCR had a relative risk of death of 1.8 compared with controls. No studies to date have evaluated the renal recovery from urate nephropathy. In a study of patients with acute phosphate nephropathy from oral sodium phosphate solution, 19% developed end-stage renal disease and the remainder developed moderate CKD.

**Contrast-Induced Nephropathy**

Contrast-induced nephropathy (CIN) is the third most common cause of AKI in the hospital. Although CIN is reversible in most cases, it is associated with increased morbidity and mortality.

**Definition**

Contrast-induced nephropathy is defined as an increase in SCR within the first 24 hours after contrast exposure (peaking up to 5 days afterward) with an absolute increase in SCR of 0.5 to 1.0 mg/dL or as a proportional increase of 25% to 50% from baseline. Some investigators have used an increase in serum cystatin C by 15% to 25% as a marker of AKI after contrast exposure. Differing definitions have led to wide variations in the reported incidence and implications of CIN.

**Incidence of CIN**

The incidence of CIN varies from 0% to more than 50% depending on the definition used, predisposing risk factors, radiocontrast agent, type of radiographic procedure, differences in clinical settings, prophylaxis protocols, and study design. In patients with a GFR greater than 45 mL/min/1.73 m² body surface area, the incidence has been reported to be less than 1%, in patients with CKD and diabetes 4% to 38%, and in azotemic diabetic patients undergoing coronary angiography as high as 50%.

**Risk Factors for Contrast-Induced Nephropathy**

The most important and well-established risk factor for contrast-induced AKI is CKD, particularly in combination with diabetes and advanced age. Several additional risk factors have been identified, including advanced heart failure, decreased renal perfusion from hypovolemia, elevated fasting glucose independent of preexisting diabetes, anemia, nephrotoxic drugs, and multiple myeloma. Certain periprocedural risk factors and procedures are associated with a higher risk of CIN. Patients undergoing percutaneous coronary intervention (PCI) are at higher risk compared with those undergoing nonemergent contrast-enhanced procedures. The European Society of Urogenital Radiology recommends measuring serum creatinine level within 7 days prior to administration of contrast media in high-risk patients (patient with estimated GFR of less than 60 mL/min per 1.73 m² BSA or elevated serum creatinine), diabetic patients, patients receiving intra-arterial contrast media and those with a history suggesting possibility of reduced GFR). In patients undergoing emergent procedures serum creatinine should always be measured if the delay in the examination does not harm the patient, or these patients should be assumed to be high risk and treated appropriately.

Some studies have shown an increased risk of CIN with increasing volume of contrast administered. Newer (iso-osmolar nonionic) contrast agents have a lower risk of CIN compared with first-generation contrast agents.
(hyperosmolar ionic agents), but the benefit is not present when compared with second-generation low-osmolality agents.\textsuperscript{14,18} Table 7 on page 606 summarizes the types and properties of commonly used contrast agents. Table 8 on page 607 lists several risk factors for the development of CIN, and Table 9 on page 608 outlines a simple risk scoring system for predicting CIN in patients undergoing PCI.\textsuperscript{99}

**Pathophysiologica Process**

The pathogenesis of CIN is a complex interplay of various mechanisms that are not completely understood. Mechanisms include vasoconstriction and a decrease in renal blood flow, medullary hypoxia, oxidative stress, and direct tubular cytotoxicity. Patients exposed to first-generation contrast agents with high osmolality can develop direct tubular injury from osmotic nephrosis.\textsuperscript{100}

**Clinical Features**

An increase in SCr is noted within 24 to 48 hours following exposure. Renal failure is nonoliguric in the vast majority of patients. Kidney damage may be limited to a transient increase in SCr returning to baseline in 3 to 5 days, or it can present as persistent renal failure, especially in patients with preexisting renal disease combined with diabetes.\textsuperscript{12,24} In most cases, patients have a benign urinalysis with a FENa less than 1%.\textsuperscript{101} The diagnosis of CIN is based on the timeline and clinical course of the disease.

**Prevention**

Multiple strategies have been tried to prevent CIN, especially since it is associated with a huge clinical and economic burden. High-risk patients should be proactively identified and alternative methods of imaging considered. All nephrotoxic agents must be discontinued 24 hours before administration of contrast media. Despite numerous trials, little evidence is available on the use of pharmacotherapeutic agents to prevent CIN.

**Contrast Agent and Volume**

Studies have shown that the volume of contrast agent used is an independent risk factor for CIN; hence, the lowest possible volume of contrast agent should be used.\textsuperscript{92,94,102,103} Repetitive studies requiring contrast should be spaced several days apart.\textsuperscript{97} All generations of contrast agents seem to carry a similar risk of CIN in low-risk patients, but in high-risk patients, nonionic, lower osmolality agents (second-generation agents) have been associated with a lower incidence of CIN when compared with ionic, high-osmolality agents (first-generation agents).\textsuperscript{94,98,104} Iodixanol (290 mOsm/kg), the only nonionic iso-osmolar agent, has been associated with a lower incidence of CIN compared with iohexol (844 mOsm/kg) in high-risk patients\textsuperscript{105} but no advantage has been noted when compared with other nonionic low osmolar agents such as iopamidol (795 mOsm/kg).\textsuperscript{106-108}

**Hydration**

Multiple studies have shown that IV hydration is beneficial and reduces the incidence of CIN in high-risk patients. There is conflicting evidence as to whether IV bicarbonate-based solutions are advantageous over isotonic saline.\textsuperscript{109-113} It is currently recommended that either IV 0.9% sodium chloride or isotonic sodium bicarbonate be used for volume expansion in patients at risk of CIN.

### Table 7.

Types and Properties of Radiocontrast Agents

<table>
<thead>
<tr>
<th>Generation</th>
<th>Agents</th>
<th>Osmolality, mOsm/kg</th>
<th>Polarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Monomers: diatrizoate</td>
<td>1,400-1,800</td>
<td>Ionic</td>
</tr>
<tr>
<td>Second</td>
<td>Monomer: iohexol, ioversol</td>
<td>500-800</td>
<td>Nonionic</td>
</tr>
<tr>
<td></td>
<td>Monomer: ioxaglate</td>
<td></td>
<td>Ionic</td>
</tr>
<tr>
<td>Third</td>
<td>Dimer: iodixanol</td>
<td>~290</td>
<td>Nonionic</td>
</tr>
</tbody>
</table>
Acetylcysteine

Acetylcysteine (NAC) is a thiol-based antioxidant that scavenges oxygen free radicals and behaves as a vasodilator by increasing the biological effects of nitric oxide. The first beneficial effects of NAC were reported by Tepel et al., and since then other trials have been published about its benefit and role in preventing CIN. Conversely, several additional trials have not found a significant benefit of NAC in reducing the incidence of CIN. In a large metaanalysis, NAC reduced the risk of CIN by 38% compared with saline alone. Given the low risk of orally administered NAC, it is used at many institutions to prevent CIN. The use of IV NAC is controversial and is not generally recommended because of its potential side effects.

Hemofiltration, Hemodialysis, and Other Agents

Hemodialysis has been shown to remove contrast effectively from blood circulation in small studies but it does not prevent adverse effects such as vasoconstriction and AKI.

Several agents with vasodilator properties have been reported to reduce CIN; however, these results need to be validated in larger trials before incorporation in practice. Examples include theophylline, fenoldopam, and iloprost. Others have shown no benefit and may be detrimental.

Prognosis

Contrast-induced nephropathy has been associated with increased in-hospital morbidity and mortality in both retrospective and observational studies. In 1,826 patients undergoing PCI, the reported in-hospital mortality rate was 1.1% for patients without CIN compared with 7% for patients with CIN and 35.7% for patients with CIN requiring dialysis. Contrast-induced nephropathy also has major economic implications, with average in-hospital cost reported to be approximately US$10,000.

Table 8.

<table>
<thead>
<tr>
<th>Risk Factors for Contrast-Induced Nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
</tr>
<tr>
<td>Chronic kidney disease (GFR &lt;60 mL/min/1.73 m²</td>
</tr>
<tr>
<td>BSA)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Volume depletion</td>
</tr>
<tr>
<td>Nephrotoxic drug use (cyclosporine, NSAIDs, AG)</td>
</tr>
<tr>
<td>Other comorbidities: anemia, hypoalbuminemia,</td>
</tr>
<tr>
<td>paraproteinemia</td>
</tr>
<tr>
<td><strong>Procedural</strong></td>
</tr>
<tr>
<td>Higher volume of contrast</td>
</tr>
<tr>
<td>First-generation contrast agents</td>
</tr>
<tr>
<td>Emergent procedure</td>
</tr>
<tr>
<td>Length of procedure</td>
</tr>
<tr>
<td>Intra-arterial administration of contrast agent</td>
</tr>
<tr>
<td>Periprocedural hemodynamic instability</td>
</tr>
</tbody>
</table>

Abbreviations: AG, aminoglycosides; BSA, body surface area; GFR, glomerular filtration rate; NSAIDs, nonsteroidal antiinflammatory drugs.

Treatment

After establishing the correct diagnosis of CIN, treatment is primarily supportive.

GENERAL MANAGEMENT OF ACUTE KIDNEY INJURY

In the majority of cases AKI can be effectively treated by adequate volume replacement, treatment of the underlying medical condition, and avoidance of nephrotoxic medications. Up to 30% of AKI cases may be preventable, with a further significant percentage potentially reversible through simple interventions such as urgent relief of urinary tract obstruction, adequate fluid resuscitation to restore an effective circulating blood volume, prompt restoration of effective blood pressure, avoidance of fluid overload, and discontinuation of potentially nephrotoxic drugs. No specific pharmacological therapy is effective.
Table 9.
Contrast-Induced Nephropathy Risk Score

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Assigned Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension with systolic blood pressure &lt;80 mm Hg for at least 1 h with inotropic support</td>
<td>5</td>
</tr>
<tr>
<td>Intraaortic balloon pump</td>
<td>5</td>
</tr>
<tr>
<td>Congestive heart failure class III/IV and/or history of pulmonary edema</td>
<td>5</td>
</tr>
<tr>
<td>Age &gt;75 y</td>
<td>4</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
</tr>
<tr>
<td>Baseline hematocrit &lt;39% for men</td>
<td></td>
</tr>
<tr>
<td>Baseline hematocrit &lt;36% for women</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
</tr>
<tr>
<td>Contrast media volume</td>
<td>1 for each 100 mL of contrast</td>
</tr>
<tr>
<td>Serum creatinine &gt;1.5 mg/dL</td>
<td>4 for serum creatinine criteria</td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m²</td>
<td>2 for eGFR 40-60</td>
</tr>
<tr>
<td></td>
<td>4 for eGFR 20-40</td>
</tr>
<tr>
<td></td>
<td>6 for eGFR &lt;20</td>
</tr>
<tr>
<td>Total Calculated Score</td>
<td>% Risk of CIN</td>
</tr>
<tr>
<td>≤5</td>
<td>7.5</td>
</tr>
<tr>
<td>6-10</td>
<td>14.0</td>
</tr>
<tr>
<td>11-16</td>
<td>26.1</td>
</tr>
<tr>
<td>≥16</td>
<td>57.3</td>
</tr>
</tbody>
</table>

Abbreviations: CIN, contrast-induced nephropathy; eGFR, estimated glomerular filtration rate.

in established ATN. Although multiple agents including diuretics, renal vasodilators, and growth factors have shown promise in animal models, none have demonstrated efficacy in clinical trials. Potassium, magnesium, and phosphate should be restricted. Phosphate binders may be required to prevent severe hyperphosphatemia. Supplemental bicarbonate can be used to correct metabolic acidosis. Nutrition should be managed carefully to ensure adequate caloric and protein intake. In patients with severe AKI, there may be no other option than to initiate RRT.

**RENALE REPLACEMENT THERAPY FOR ACUTE KIDNEY INJURY**

Once a patient has developed AKI, the therapeutic options are limited, with the mainstay of treatment being RRT. There is a paucity of evidence to guide the optimal time to initiate RRT. In most instances, clinicians base RRT initiation on standard life-threatening indications, including drug intoxications, symptomatic uremia, volume overload, acidosis, and hyperkalemia, that prove refractory to medical management. Unfortunately, beyond this indication-based approach, there is limited evidence to
guide clinicians on when to initiate RRT for AKI. To date, there is no generally accepted azotemia threshold for RRT initiation. Given the well-known risks of the procedure, including complications of vascular access placement, infection, hypotension, and arrhythmias, the decision to initiate RRT is based most often on a wait-and-watch attitude. Thus, RRT is usually not started until the patient has clinical features of volume overload and biochemical features of solute and or electrolyte imbalance. Recent evidence suggests that early initiation of RRT may be associated with decreased mortality, but these data need to be confirmed by prospective randomized, controlled trials in order to enable clear recommendations. In the absence of well-designed randomized clinical trials, recommendations on the optimal timing for RRT initiation remain uncertain and the decision remains the choice of the individual physician.

Once a decision to initiate RRT is made, the key technical components of the prescription include the modality, anticoagulation, and the intensity of the treatment. Anticoagulation and intensity of treatment are beyond the scope of this chapter.

Modality

Renal replacement therapies are classified by the predominant transport process used to remove solutes and toxins. All forms of RRT rely on the principle of allowing water and solute transport through a semipermeable membrane and then discarding the waste products. Ultrafiltration is the process by which water is transported by a transmembrane pressure gradient across a semipermeable membrane. Diffusion and convection are the 2 processes by which solutes are transported across the membrane. Diffusion occurs by movement of solutes from an area of higher solute concentration to an area of lower concentration across a semipermeable membrane. The concentration gradient is maximized and maintained throughout the length of the membrane by running the dialysate (an electrolyte solution usually containing sodium, bicarbonate, chloride, magnesium, and calcium) countercurrent to the blood flow. Small-molecular-weight solutes, such as urea, are cleared efficiently by diffusion, but larger molecular-weight solutes are not. Convection occurs when the transmembrane pressure gradient drives water across a semipermeable membrane as in ultrafiltration but then "drags" with the water both small-molecular-weight (blood urea nitrogen, creatinine, potassium) and larger-molecular-weight (insulin, β₂-microglobulin, tumor necrosis factor, vitamin B₁₂) solutes. Membrane pore diameter limits the size of the large solutes that can pass.

The available RRT modalities use ultrafiltration for fluid removal and either diffusion, convection, or a combination of the latter 2 to achieve solute clearance. Options for RRT therapy for AKI include intermittent hemodialysis (IHD), peritoneal dialysis (PD), various forms of continuous renal replacement therapy (CRRT), and newer "hybrid" therapies such as extended duration dialysis (EDD) or a sustained low-efficiency dialysis (SLED).

Intermittent Hemodialysis

Traditionally, nephrologists have managed AKI with IHD, empirically delivered 3 to 6 times a week, 3 to 4 hours per session, with a blood flow rate of 200 to 300 mL/min and a dialysate flow rate of 500 to 800 mL/min. In IHD, solute clearance occurs mainly by diffusion, whereas volume is removed by ultrafiltration. Decisions regarding dialysis duration and frequency are based on patient metabolic control, volume status, and presence of any hemodynamic instability. Advantages of IHD include rapid solute and volume removal. This results in rapid correction of electrolyte disturbances, such as hyperkalemia, and rapid removal of drugs or other substances in fatal intoxications in a matter of hours. Intermittent hemodialysis also has a decreased requirement for anticoagulation compared with other types of RRT because of the faster blood flow rate and shorter duration of therapy. The main disadvantage of IHD is the risk of systemic hypotension caused by rapid electrolyte and fluid removal. Hypotension occurs in approximately 20% to 30% of hemodialysis treatments. Sodium modeling, cooling the dialysate, increasing the dialysate calcium concentration, and conducting intermittent ultrafiltration may improve hemodynamic stability during IHD. Despite this, approximately 10% of ARF patients cannot be treated with IHD because of
hemodynamic instability. Furthermore, rapid solute removal from the intravascular space can cause cerebral edema and increased intracranial pressure, limiting this therapy in patients with head trauma or hepatic encephalopathy.

**Peritoneal Dialysis**

In PD, the peritoneum is used as a semipermeable membrane for diffusive removal of solutes. A dialysate solution is administered into the peritoneal cavity through a catheter where it stays for a prescribed period of time and then is drained. The use of PD is limited by practical considerations. Acute PD requires the surgical insertion of a peritoneal dialysis catheter and often is complicated by catheter leakage and malfunction. The use of PD is limited by low solute clearance in hypercatabolic patients and potential pulmonary restriction due to the expansion of the peritoneal cavity. It is contraindicated in postoperative patients who need abdominal surgery or surgical drains. In addition, because PD is less predictive in fluid and solute removal in the ICU, it is used less widely than other therapies.

**Continuous Renal Replacement Therapy**

Continuous renal replacement therapy has emerged over the past decade as a viable modality for management of hemodynamically unstable patients with AKI. The different CRRT modalities can use diffusion, convection, or a combination of both for solute clearance. Unlike IHD, CRRT is performed continuously (24 h/d) with a typical blood flow of 100 to 250 mL/min and a dialysate flow of 17 to 40 mL/min if a diffusive CRRT modality is used. It is performed most commonly through a venous vascular access. The most commonly applied modalities of CRRT are continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). In CVVH, solute clearance occurs by convection. No dialysate is used. The rate at which ultrafiltration occurs is the major determinant of convective clearance. Intravenous “replacement fluid” is provided to replace the excess volume that is being removed and to replenish desired solutes. In CVVHD, solute removal occurs by diffusion. Unlike IHD, the dialysate flow rate is slower than the blood flow rate, allowing small solutes to equilibrate completely between the blood and dialysate. As a result, the dialysate flow rate approximates urea and creatinine clearance. Ultrafiltration is used for volume control. CVVHDF combines the convective solute removal of CVVH and the diffusive solute removal of CVVHD. As in CVVH, the high ultrafiltration rates used to provide convective clearance require the administration of IV replacement fluids.

The advantages of CRRT include hemodynamic tolerance caused by slower ultrafiltration. The gradual continuous volume removal makes control of volume status easier and allows administration of medications and nutrition with less concern for volume overload. Because it is a continuous modality, there is less fluctuation of solute concentrations over time and better control of azotemia, electrolytes, and acid-base status. It does not raise intracranial pressure like IHD. The main disadvantages of CRRT include access and filter clotting, the consequent need for anticoagulation, increased costs, and demands on ICU nurse time compared with IHD.

**Sustained Low-Efficiency Dialysis and Extended Daily Dialysis**

Sustained low-efficiency dialysis and EDD are slower dialytic modalities run for prolonged periods using conventional hemodialysis machines with modification of blood and dialysate flows. Typically, they use low blood-pump speeds of 200 mL/min and low dialysate flow rates of 300 mL/min for 6 to 12 hours daily. Sustained low-efficiency dialysis and EDD combine the advantages of CRRT and IHD. They allow for improved hemodynamic stability through gradual solute and volume removal as in CRRT. At the same time, they are able to provide high solute clearances as in IHD and remove the need for expensive CRRT machines, costly customized solutions, and trained staff. Because these treatments can be performed intermittently based on the needs of the patient, they also avoid the interruption of therapy for various diagnostic and therapeutic procedures that may be required in such patients.
Table 10 on page 611 summarizes several types of RRTs and their mechanism of solute removal.

Selecting RRT

Modality selection is hampered by lack of evidence for improved outcomes with specific modalities. Modality comparisons have failed to demonstrate any survival advantage for continuous versus intermittent therapy.\(^{155-164}\)
Three recent metaanalyses have reached similar conclusions—that the type of RRT does not have a major impact on survival or renal recovery.\(^ {160-164}\) However, the validity of the data from the studies is uncertain on account of issues related to study design, such as exclusion of patients with hemodynamic instability, improper randomization, differences in baseline characteristics between arms, and high crossover rates between modalities. Notably, even though the meta-analysis by Bagshaw et al.\(^ {162}\) found no statistical difference in survival between the 2 modalities, there was a higher occurrence of hemodynamic instability and greater cumulative fluid balance in the IHD groups.

Analysis of the currently published studies does not allow evidence-based guidelines for the selection of RRT modality for the treatment of AKI. The modality chosen should therefore be guided by the individual patient’s clinical status, local medical and nursing expertise, and the availability of RRT modality. It is now recognized that more than one therapy can be used to manage patients with AKI. Transitions in therapy are common and reflect the changing needs of patients during their hospital course. For instance, patients in the ICU may initially start on CRRT when they are hemodynamically unstable, transition to SLED/EDD when they improve, and leave the ICU receiving IHD.

Prognosis and Recovery

Acute kidney injury has a poor prognosis, with the mortality ranging from 10% to 80% depending on the patient population studied. Patients who present with uncomplicated AKI have a mortality rate of up to 10%.\(^ {5,165}\)
In contrast, patients presenting with AKI and multiorgan failure have been reported to have mortality rates greater than 50%. If RRT is required, the mortality rate can

Table 10.

Duration of Treatment and Characteristics of Solute Removal With Differing Modalities for Renal Replacement Therapy

<table>
<thead>
<tr>
<th>Technique</th>
<th>Duration, h(^a)</th>
<th>Process of Solute Removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard IHD</td>
<td>3-4</td>
<td>Diffusion</td>
</tr>
<tr>
<td>EDD/SLED</td>
<td>6-12</td>
<td>Diffusion</td>
</tr>
<tr>
<td>Continuous therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>Variable</td>
<td>Diffusion</td>
</tr>
<tr>
<td>CVWH</td>
<td>24</td>
<td>Convection</td>
</tr>
<tr>
<td>CVHHD</td>
<td>24</td>
<td>Diffusion</td>
</tr>
<tr>
<td>CVHDF</td>
<td>24</td>
<td>Diffusion and convection</td>
</tr>
</tbody>
</table>

Abbreviations: CVWH, continuous venovenous hemofiltration; CVHHD, continuous venovenous hemodialysis; CVHDF, continuous venovenous hemodiafiltration; EDD, extended daily dialysis; IHD, intermittent hemodialysis; PD, peritoneal dialysis; SLED, sustained low-efficiency dialysis.

\(^{a}\) Duration may vary depending on patient needs and circuit performance.
be as high as 80%. In a multinational, prospective, observational study of 29,269 critically ill patients with AKI in 54 hospitals in 23 countries, ICU mortality was 52%, with an additional 8% mortality in the hospital after ICU discharge for an overall hospital mortality of 60.3%. Among surviving patients, 13.8% continued to require RRT at the time of hospital discharge.

**SUMMARY**

- Acute kidney injury: A reduction in kidney function occurring over no more than 48 hours manifested by an absolute increase in serum creatinine of 0.3 mg/dL or more or a relative increase by 50% or more or documented oliguria less than 0.5 mL/kg/h for more than 6 hours despite adequate fluid resuscitation.

- Acute renal failure: A decrease in kidney function occurring over a period of hours to days, resulting in the accumulation of creatinine, urea, and other metabolic waste products.

- Intrinsic acute kidney injury: Injury to the renal tubules, glomerulus, vascular structures, and interstitium or obstruction of the renal tubules.

- Prerenal acute kidney injury: Injury resulting from impaired blood flow to the kidney that can be caused by several mechanisms.

- Continuous venovenous hemofiltration: Extracorporeal removal of solute by the process of convection.

- Continuous venovenous hemodialysis: Extracorporeal removal of solute by the process of diffusion.

- Continuous venovenous hemodiafiltration: Extracorporeal removal of solute by the process of diffusion and convection.

- Sustained low-efficiency dialysis and extended daily dialysis: Extracorporeal removal of solute via slower dialytic modalities using conventional hemodialysis machines with modification of blood and dialysate flows.

**REFERENCES**


