Acute renal failure (ARF) has been defined as a syndrome in which an abrupt (hours to days) decrease in renal function produces retention of nitrogenous waste products. Translating this abstract description into a clinically useful, accurate, and widely accepted definition has been challenging, in large part because of the focus on serum creatinine concentration, which is easily obtained but has the inherent limitation of poor detection of rapid or subtle, but clinically important, changes in the glomerular filtration rate (GFR). Standard clinical criteria for ARF have been an increase in serum creatinine of 0.5 mg/dL when the baseline serum creatinine is normal or a 25% increase in serum creatinine when the serum creatinine at baseline is abnormal. However, it is now recognized that even a modest rise in serum creatinine of 0.3 mg/dL during hospitalization is associated with increased mortality and morbidity. In recent years, therefore, the term *acute kidney injury* (AKI) has replaced ARF because AKI denotes the entire clinical spectrum from mild increases in serum creatinine to overt renal failure. The field was also hampered by the lack of a standard definition of AKI, prompting an international conference that ultimately produced an acceptable staging system that is termed Risk-Injury-Failure-Loss-ESRD (RIFLE) criteria and is based on serum creatinine concentration and urine flow rate [see Table 1]. The Acute Kidney Injury Network (AKIN) subsequently modified the definition further and divided AKI into three stages. This definition also used serum creatinine concentration and urine flow rates, and AKIN stages are identical to the first three stages of RIFLE, except that the criteria for AKIN stage I included an absolute increase in serum creatinine by ≥0.3 mg/dL within 48 hours. In addition, patients receiving renal replacement therapy were considered to have met the criteria for stage III. The two staging criteria, RIFLE and AKIN, have been compared by examining outcomes in 120,123 critically ill patients, and only small differences between the two staging systems were noted in the numbers of patients classified as having AKI. Receiver operator characteristic (ROC) analysis for hospital mortality was 0.66 for RIFLE and 0.67 for AKIN. Thus, the two criteria were similar in predictive ability and classification of AKI in the intensive care unit (ICU).

Because of difficulties with the use of serum creatinine as a determinant of AKI, a variety of serum and urine biomarkers of AKI are currently undergoing intense investigation. These biomarkers, which include kidney injury molecule–1 (KIM-1), neutrophil gelatinase–associated lipoctin (NGAL), cystatin C, N-acetyl-[β-D-glucosaminidase (NAG), liver-type fatty acid–binding protein (L-FABP), and interleukin-18 (IL-18), potentially offer the opportunity to provide earlier detection of AKI and may provide additional assessment of outcome in AKI but presently are available for preclinical analyses only. Until a more sensitive determinant of GFR or novel biomarker becomes clinically available, serum creatinine concentration remains the mainstay feature in the diagnosis of AKI.

### Epidemiology

The incidence of AKI varies depending on the clinical setting and the definition that was used in the analysis. Hospital-acquired AKI appears to be increasing, from 49 admissions per 1,000 noted in 1983 to 71 admissions per 1,000 in 2002. These rates translate to approximately 35,000 patients in 1979 and 650,000 in 2002, producing an annual increase in the incidence rate of more than 13%. The increased incidence was also validated within a single

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**Table 1** Risk-Injury-Failure-Loss-ESRD (RIFLE) and Acute Kidney Injury Network (AKIN) Criteria in Acute Kidney Injury

<table>
<thead>
<tr>
<th>RIFLE</th>
<th>AKIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Increased creatinine × 1.5 or GFR decrease &gt; 25% (for AKIN, definition also met if creatinine increase is ≥0.3 mg/dL [26.2 µmol/L])</td>
</tr>
<tr>
<td>Injury</td>
<td>Increased creatinine × 2 or GFR decrease &gt; 50%</td>
</tr>
<tr>
<td>Failure</td>
<td>Increased creatinine × 3 or GFR decrease &gt; 75% or creatinine &gt; 4 mg/dL (for AKIN, definition also met if renal replacement therapy initiated)</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent AKI with complete loss of kidney function for &gt; 4 wk</td>
</tr>
<tr>
<td>ESRD</td>
<td>End-stage renal disease</td>
</tr>
</tbody>
</table>

AKI = acute kidney injury; GFR = glomerular filtration rate.

* The authors and editors gratefully acknowledge Mary Jo Shaver, MD, and Sudhir V. Shah, MD, for their contributions to the previous edition, from which this present version was updated.
patient population, where annual incidence rates of both dialysis-requiring and nondialysis-requiring AKI from 1996 through 2003 progressively increased. As the complexity of medical care increases, it is likely that the rate of nosocomial AKI will continue to increase.

The incidence of AKI has been cited as 1% on admission to the hospital, from 2% to 5% during hospitalization, in as many as 37% of patients treated in ICUs, and in 4 to 15% of patients after cardiovascular surgery. Overall, the incidence of AKI has been estimated to be 209 patients per million population per year, with 36% of patients with AKI requiring renal replacement therapy. In the 600,820 hospitalized member Kaiser Permanente Northern California database, 1,764 members (0.29%) developed dialysis-requiring nosocomial AKI in the period from 1996 to 2003. Although diabetes mellitus, hypertension, and proteinuria were independent risk factors, the propensity to develop severe AKI increased with each stage of underlying chronic kidney disease (CKD), as determined using preexisting serum creatinine concentrations. Seventy-four percent had an estimated GFR of less than 60 mL/min per 1.73 m².11 Although all hospitalized patients are at risk for developing AKI related either to their presenting illness or to an iatrogenic event, in preventive management, along with rapid correction of hypovolemia, patients with these risk factors, particularly CKD,11 should be considered at high risk for development of nosocomial AKI and managed and monitored carefully during their admission.

The short-term consequences of AKI are staggering. Despite major advances in dialysis and intensive care, the mortality rates for severe AKI in population-based studies remain elevated between 35 and 60%. In a large population of 19,982 hospitalized adults, AKI was associated not only with increased mortality but also lengthened hospital stay and higher overall costs. Outcome was directly related to the severity of the AKI, as characterized by a change in serum creatinine concentration, with increases as low as 0.3 mg/dL conferring increased short-term morbidity and mortality. The long-term consequences of AKI have also been examined. In the patient population enrolled in Kaiser Permanente of Northern California, patients who recovered from a bout of dialysis-requiring AKI subsequently had a 28-fold increase in the risk of developing CKD stages IV and V and more than a twofold increased risk of death following discharge from the hospital despite having an estimated GFR of greater than 45 mL/min per 1.73 m² prior to the event. Because even a minor decline in renal function is associated with poor patient outcome, prevention and early diagnosis of AKI are the cornerstones of management.

Pathophysiologic Classification of AKI

The syndrome of AKI may be defined pathophysiologically [see Figure 1], depending on whether it results from a decrease in renal blood flow (prerenal azotemia), intrinsic renal parenchymal diseases (renal azotemia), or obstruction of urine flow (postrenal azotemia).16

Prerenal azotemia is the single most common cause of AKI, accounting for 30 to 60% of all cases. Prerenal AKI occurs when glomerular perfusion falls as a result of either an absolute reduction in the volume of extracellular fluid or a reduction in circulating volume despite a normal total extracellular fluid volume, as may occur in conditions such as left ventricular failure, advanced cirrhosis, and sepsis. The kidney has the capacity to autoregulate GFR and blood flow simultaneously during renal hypoperfusion through the independent regulation of afferent and efferent arterial tone. Whereas the afferent arteriole dilates in response to renal hypoperfusion, the efferent arteriole constricts, maintaining glomerular intracapillary pressure, which is the driving force for glomerular filtration. Thus, during the early phase of mild to moderate prerenal conditions, renal blood flow and GFR are maintained within normal ranges, and blood urea nitrogen (BUN) and creatinine levels remain normal. When prerenal conditions become severe and renal adaptive mechanisms cannot compensate, GFR falls and the BUN and creatinine levels begin to increase. Impaired autoregulation of renal blood flow, which has been shown to occur in CKD in rodents, may be a mechanism of susceptibility to AKI. In addition, following a bout of AKI, renal autoregulation is impaired and potentially results in exacerbation of AKI following even mild decreases in systemic blood pressure.

Renal hypoperfusion, a high ratio (> 20) of BUN to serum creatinine, and a low urine volume characterize prerenal AKI. Levels of antidiuretic hormone are elevated, thus increasing the reabsorption of both water and urea. Prerenal failure is a response to severe volume depletion, heart failure, hepatorenal syndrome (HRS), or sepsis. In the proper setting, hemodynamically mediated prerenal failure may also occur with use of some pharmaceutical agents that include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and nonsteroidal antiinflammatory drugs (NSAIDs). Prerenal failure can also occur with the presentation of a large solute load to the kidney, along with stimulation of volume loss by an osmotic diuresis, as occurs in hyperglycemia.

Intrinsic renal diseases that cause AKI can involve the glomeruli, vasculature, or tubulointerstitium. The most
common intrinsic renal disease that leads to AKI is acute tubular necrosis (ATN). When prerenal and postrenal causes of AKI have been excluded, about 75% of hospitalized patients with AKI have ATN. Clinical recognition is based largely on exclusion of prerenal and postrenal causes of sudden azotemia, followed by exclusion of other causes of intrinsic AKI (e.g., postinfectious acute glomerulonephritis, atheroembolic renal disease, acute interstitial nephritis [AIN]).

Multiple insults are usually present, but prerenal azotemia is often a predisposing factor. Iatrogenic causes, including catheter-related sepsis and exposure to nephrotoxins (e.g., antibiotics, radiocontrast material), contribute to a significant portion of these cases. Approximately 40 to 60% of ATN cases occur in the postoperative or trauma setting.

 Depending on the clinical setting, other diagnoses to be considered are AIN (e.g., secondary to use of antibiotics), glomerulonephritis, atheromatous emboli (in association with previous aortic surgery, aortography, or anticoagulation), ureteral obstruction (in association with pelvic or abdominal pathology or secondary to complications of pelvic or abdominal surgery), or intrarenal obstruction (e.g., acute urate nephropathy or acute phosphate nephropathy).

In the hospital setting, postrenal azotemia accounts for about 10% of cases of AKI. AKI associated with postrenal azotemia should especially be a consideration in elderly men, particularly if they are receiving medications that could impair bladder function. Partial obstruction may present with AKI and associated polyuria because of the inhibitory effect of intrarenal pressures on renal concentrating ability. Besides abrupt anuria, urine flow rate is a poor indicator of postrenal AKI.

### Diagnostic Approach to AKI

To determine the cause of AKI, the physician must follow a systematic approach, which should start with excluding or correcting both prerenal and postrenal azotemia. Often the difficulty in arriving at a correct etiologic diagnosis of AKI in a hospitalized patient is not in identifying a possible cause but rather in selecting the actual cause from among several possible choices.
Correct diagnosis depends on basic knowledge of the natural history of AKI from different causes, review of the chronological sequence of events in the deterioration in the patient’s renal function, and analysis of the available patient data. Despite the exhaustive list of conditions that can cause acute azotemia in hospitalized patients, a careful history and physical examination and simple laboratory tests often suffice for diagnosis. Occasionally, it is difficult to determine if a patient presenting with renal failure has AKI or CKD, although there are clues that help differentiate the two syndromes [see Table 4].

In a hospital setting, AKI is most commonly recognized when patients exhibit oliguria, rising BUN and creatinine levels, or both oliguria and rising BUN and creatinine.

**CHART REVIEW, HISTORY, AND PHYSICAL EXAMINATION**

Evaluation of the patient with AKI should start with a complete medical history and a review of the hospital records. Some of the important data that should be sought from chart review are presented [see Table 5, Table 6, and Figure 2]. Particular attention should be paid to finding a recent serum creatinine concentration or other evidence of underlying kidney disease prior to admission, evidence of a

**Table 4** Features that Help Differentiate between Acute Kidney Injury and Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Feature</th>
<th>AKI</th>
<th>CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous laboratory assay</td>
<td>Normal creatinine just prior to event is single best evidence of AKI</td>
<td>Abnormal renal function is documented on old laboratory studies</td>
</tr>
<tr>
<td>Medical history</td>
<td>None</td>
<td>Long-standing and poorly controlled diabetes, hypertension, and severe vascular disease are risk factors</td>
</tr>
<tr>
<td>Renal ultrasonography</td>
<td>Normal</td>
<td>Small, echogenic kidneys support CKD, but patients with diabetes, HIV infection, multiple myeloma/amyloidosis, and polycystic kidney disease may have normal or enlarged kidneys</td>
</tr>
<tr>
<td>Bone films</td>
<td>Normal</td>
<td>Evidence of renal osteodystrophy with osteitis fibrosa, osteomalacia, mixed and dynamic bone lesions, and dialysis-related amyloidosis; subperiosteal erosions of the phalanges and tuft; bone cysts with amyloidosis all support CKD</td>
</tr>
<tr>
<td>Hemoglobin/hematocrit</td>
<td>Anemia is possible, but a normal hemoglobin level in a patient with advanced azotemia is presumptive evidence of AKI</td>
<td>Anemia is common in CKD</td>
</tr>
<tr>
<td>Urine sediment</td>
<td>Dirty-brown casts, tubular epithelial cells/casts suggestive of AKI</td>
<td>Broad, waxy casts</td>
</tr>
</tbody>
</table>

AKI = acute kidney injury; CKD = chronic kidney disease.
systemic disease process, and a detailed medication record. Even medical treatment previously thought to be innocuous should be considered. For example, acute phosphate nephropathy can develop after administration of an oral sodium phosphate bowel purgative in preparation for colonoscopy (see below). Another subtle historical finding is prior use of Chinese herbs, which might contain a nephrotoxin known as aristolochic acid (see description below).22

A patient presenting with AKI may have very nonspecific complaints, including fatigue, weakness, restlessness, loss of appetite, nausea, vomiting, decreased urine output, swelling, and hiccups. When levels of uremic toxins are markedly elevated, changes in mental status and seizures may occur. A history of nausea, vomiting, diarrhea, or other volume losses suggests AKI resulting from a prerenal condition. Recent trauma with muscle injury suggests rhabdomyolysis as the cause of AKI.

Extracellular fluid volume status is a critical part of the physical examination. Reduced body weight, marked orthostatic decrease in blood pressure, an increase in pulse, and a lack of jugular venous distention all suggest a
reduction in extracellular fluid volume. Patients with prerenal azotemia can appear to be experiencing volume overload in association with extracellular fluid expansion (e.g., cardiac failure, cirrhosis, nephrotic syndrome), but the effective blood volume is decreased and, thus, renal perfusion is impaired.

Careful abdominal examination may reveal a distended, tender bladder, indicating lower urinary tract obstruction.

Table 6  Daily Evaluation and Management of the Hospitalized Patient with Acute Kidney Injury

<table>
<thead>
<tr>
<th>Type of Evaluation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>Weight loss of 0.5 to 1 lb/day in a patient with ATN will help prevent volume overload</td>
</tr>
<tr>
<td>Jugular vein distention or crackles</td>
<td>Indicate volume overload with possible congestive heart failure; restrict volume, add diuretics, consider dialysis</td>
</tr>
<tr>
<td>CVP, PCWP</td>
<td>Assessment of these parameters may be indicated to differentiate volume overload from the presence of noncardiogenic pulmonary infiltrates; low PCWP suggests noncardiogenic pulmonary edema</td>
</tr>
<tr>
<td>Intake/output</td>
<td>In euvolemic patients, assess volume of previous day’s urine output (in stable patients, add 400 mL for insensible losses); insensible losses may be higher in catabolic, febrile, or agitated patients</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>Disproportionately high values suggest gastrointestinal bleeding, steroid use, hypercatabolic state, or prerenal AKI</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Disproportionately high values suggest muscle breakdown, as caused by rhabdomyolysis</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>[see Complications, in text]</td>
</tr>
</tbody>
</table>

AKI = acute kidney injury; ATN = acute tubular necrosis; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure.

Figure 2  This worksheet for the evaluation of acute kidney injury (AKI) in hospitalized patients may be used to chart a chronological outline of the events that may have contributed to the insult. In using such an approach, particular attention should be paid to the events that occurred a few days before the acute rise in the serum creatinine level. BUN = blood urea nitrogen; CO₂ = carbon dioxide; Hgb = hemoglobin; Hct = hematocrit; WBC = white blood cell count.
In men in whom lower tract obstruction is suspected as a cause of acute azotemia, examination of the prostate and a sterile postvoid bladder catheterization should be performed. Additional examination findings that may be helpful include fever, skin rash, and joint pains, which raise the possibility of a rheumatic disease, such as systemic lupus erythematosus, vasculitis, endocarditis, or drug allergy with AIN. A history of a recent aortic catheterization (e.g., cardiac catheterization) and the finding of livedo reticularis are diagnostic clues for cholesterol or atheromatous emboli. Abrupt anuria suggests acute obstruction, severe glomerulonephritis, or a sudden vascular event. Painless hematuria suggests acute glomerulonephritis, whereas painful hematuria is more consistent with obstruction.

Differentiating prerenal azotemia from ATN may be difficult, partly because of the difficulty in evaluating the volume status in a critically ill patient and also because prerenal azotemia from any cause, if severe enough, may lead to ATN. Evaluation of the urine volume and urine sediment and a number of urinary indices (useful only in patients with oliguria) are particularly helpful in making the correct diagnosis [see Table 7].

**Laboratory Tests**

**Ratio of BUN to Creatinine**

Initial laboratory tests include measurement of BUN and serum creatinine, sodium, chloride, potassium, and bicarbonate levels. These tests are important not only for the diagnosis but also for assessment of complications of AKI. In prerenal conditions resulting from enhanced salt and water avidity, there is a disproportionate increase in the ratio of BUN to creatinine (> 20:1). Other causes of BUN elevation include gastrointestinal (GI) bleeding, use of systemic steroids, catabolism caused by the underlying medical condition, or a high-protein diet. An elevation in the creatinine level that exceeds the elevation in BUN suggests rhabdomyolysis; such patients will also have an elevated creatine kinase (CK) or myoglobin level.

**Urine Flow Rate**

AKI is traditionally divided into anuric (urine output of < 100 mL/day), oliguric (urine output of 100 to 400 mL/day), and nonoliguric (urine output of > 400 mL/day). In a hospitalized patient, a normal urine output in the face of a rise in creatinine level more often signifies an intrinsic renal defect because prerenal azotemia should lead to oliguria. Wide variations in daily urinary output suggest obstruction.

Complete anuria (no urine output) suggests obstruction or an acute vascular catastrophe, such as renal vein or renal artery thrombosis or large emboli in the renal arteries, although it can be seen in ATN and AIN. To cause total anuria, a vascular event must affect both kidneys or a single functioning kidney.

**Urinalysis and Urine Sediment**

Microscopic examination of the urine has recently been validated as a useful approach to improve the differential diagnosis of AKI.2 The following is a list of findings on urinalysis, including urine sediment analysis, and their implications for AKI:

1. In prerenal failure, a moderate number of hyaline and finely granular casts may be seen, but coarsely granular and cellular casts are infrequent. Finely granular, broad and waxy casts can also be seen in the sediment of patients with CKD.
2. In ATN, a characteristic sediment is found in 70 to 80% of patients, particularly those with oliguric ATN; it consists of dirty-brown, coarse, granular casts; free renal tubular epithelial cells; and epithelial cell casts. With more severe renal injury, there may be a 24- to 48-hour delay before the appearance of dirty-brown casts.
3. A seemingly benign urine sediment containing few formed elements suggests possible obstruction.
4. Proliferative glomerulonephritis is characterized by urine containing 3+ to 4+ protein, 2+ to 3+ blood, and active sediment, defined as sediment containing red blood cells (RBCs) and RBC casts. An accurate history and careful physical examination (which may, for example, suggest systemic lupus erythematosus), determination of complement levels, antinuclear antibody testing, and kidney biopsy (if the kidney is of normal size) generally help clarify the diagnosis.
5. Findings of only a few RBCs in the urine sediment and strongly heme-positive urine or heme-positive urine supernatant (after removal of the RBCs by centrifugation) usually indicate myoglobinuria or hemoglobinuria. Patients with rhabdomyolysis have a marked increase in the level of muscle enzyme, such as CK. The urine sediment in patients with myoglobinuria may show RBCs, pigmented casts, granular casts, and numerous uric acid crystals.
6. The presence of white blood cells (WBCs) in clumps and casts, in the absence of evidence of bacteria, suggests AIN. This can be associated with microscopic hematuria and even RBC casts. Although the presence of eosinophils

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**Table 7** Serum and Urinary Diagnostic Indices

<table>
<thead>
<tr>
<th>Index</th>
<th>Prerenal Azotemia</th>
<th>Acute Tubular Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary sodium (U_\text{Na}) (mEq/L)</td>
<td>&lt; 20</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>Urine osmolality (U_{\text{osm}}) (mOsm/kg H_2O)</td>
<td>&gt; 500</td>
<td>&lt; 450</td>
</tr>
<tr>
<td>Fractional excretion of sodium (\text{UNa}\text{P}_{\text{Cr}}/\text{PNa}\text{UCr} (\times 100)</td>
<td>&lt; 1%</td>
<td>&gt; 1%</td>
</tr>
<tr>
<td>BUN-to-creatinine ratio</td>
<td>&gt; 20:1</td>
<td>—</td>
</tr>
<tr>
<td>Urine creatinine–plasma creatinine [U_{\text{Cr}} (mg/dL)/P_{\text{Cr}} (mg/dL)]</td>
<td>&gt; 40</td>
<td>&lt; 20</td>
</tr>
</tbody>
</table>

BUN = blood urea nitrogen; P_{\text{Cr}} = plasma creatinine; P_{\text{Na}} = plasma sodium; UNa = urine sodium; UCr = urine creatinine; UOsm = urine osmolality.
in the urine is not specific for AIN, this test should be performed when the diagnosis of the AKI is in question. 7. A urine sediment with abundant uric acid crystals or oxalate crystals suggests uric acid deposition (associated with hyperuricemia after chemotherapy) or intratubular oxalate (e.g., methoxyflurane anesthesia), respectively.

Urinary Indices

Urinary indices are practical determinants of tubular cell function and are often used to differentiate prerenal azotemia from ATN in oliguric conditions. However, interpretation of urinary indices in a patient with CKD is often difficult because of underlying sodium wasting in the baseline state that cannot be corrected rapidly with volume depletion. The rationale for the use of these indices is as follows: because creatinine concentrations increase along the nephron as fluid is removed by tubular processing of the glomerular ultrafiltrate, the ratio of urine to plasma creatinine (U/P Cr) provides an index of the fraction of filtered water excreted. If it is assumed that all of the creatinine filtered at the glomerulus is excreted into the urine and that relatively little is added by secretion, any incremental increase in the concentration of creatinine in urine over that in plasma must be the result of the removal of water. In prerenal azotemia, because of the reduction in the amount of glomerular filtrate entering each nephron and because of an increase in the retention of salt and water, U/P Cr typically is considerably greater than it is in ATN, and urinary sodium concentrations are characteristically lower [see Table 7]. In contrast, in ATN, the nephrons excrete a large fraction of their filtered sodium and water, resulting in lower U/P Cr and a higher fractional excretion of sodium (FE Na). Fractional excretion of urea (FE Urea) has also been reported to help differentiate prerenal azotemia from renal azotemia [see Table 7]. The use of FE Urea may have a particular diagnostic advantage over FE Na in patients who have been receiving diuretics; in one study, the FE Na was low in only 48% of diuretic-treated patients with prerenal azotemia.24 It must be kept in mind, however, that FE Urea values in CKD have not been standardized.

Interpretations of urinary indices must be made in conjunction with other assessments of the patient because there are clinically important exceptions to these generalizations. For example, patients with certain types of ATN, such as radiographic dye-induced renal injury or sepsis, may present with all the clinical characteristics of ATN but with FE Na rates of less than 1%.

Imaging Studies

If the diagnosis of prerenal azotemia or ATN is reasonably certain and the clinical situation does not require that other causes of acute azotemia be excluded, generally, no further diagnostic evaluation is necessary. Further diagnostic evaluation is indicated under the following circumstances: (1) the diagnosis is uncertain, especially if the clinical situation suggests other possibilities (e.g., obstruction or vascular accident); (2) clinical findings (e.g., total anuria) make the diagnosis of prerenal azotemia or ATN less likely; or (3) the oliguria persists longer than 4 weeks.

Renal ultrasonography is the initial diagnostic procedure of choice in renal failure because it is noninvasive and reliable. A finding of normal-sized kidneys in a patient with advanced azotemia generally suggests AKI rather than CKD; however, several important causes of CKD, including diabetes mellitus, HIV infection, multiple myeloma, polycystic kidney disease, and amyloidosis, may be associated with normal-sized or large kidneys. The renal ultrasound examination is helpful in confirming or excluding obstruction, identifying polycystic kidney disease, determining whether one or two kidneys are present, and localizing the kidney for renal biopsy. The concomitant use of Doppler flow analysis can also provide information regarding vascular patency.

A high-resolution noncontrast computed tomographic scan is considered the test of choice for suspected urinary tract calculi. Radionuclide methods are available for assessing renal blood flow and excretory (secretory) function. Blood flow studies can be used to easily determine whether the kidneys are perfused and, if so, whether blood flow to the two kidneys is symmetrical; such tests are less accurate in quantifying flow rates. Magnetic resonance imaging without contrast is now recommended to evaluate renal arterial or venous thrombosis. Radiouclide-tagged WBC scans have a limited role in diagnosing AIN.

Renal biopsy

Renal biopsy is rarely required for AKI that develops in the hospital setting. In contrast, renal biopsy is indicated somewhat more frequently for AKI that occurs outside the hospital.

Tubulointerstitial Lesions Associated with AKI

Tubulointerstitial renal damage that produces AKI can be generally divided into direct tubular epithelial cell injury (ATN), intratubular obstruction, and AIN.

Acute Tubular Necrosis

ATN is a clinical syndrome of abrupt and sustained decline in GFR that is triggered by an acute ischemic or nephrotoxic event and develops within minutes to days after the insult. Leakage of glomerular ultrafiltrate from the tubular lumen into the interstitial space across the damaged renal tubular cells, obstruction of flow within the tubule by debris or crystals in the lumen, and a decrease in the glomerular capillary ultrafiltration coefficient have all been proposed as playing pathophysiologic roles in ATN.

A variety of biochemical and cellular changes may be involved in cell injury in AKI. These include mitochondrial dysfunction, adenosine triphosphate (ATP) depletion, phospholipid degradation, elevation in cytosolic free calcium levels, a decrease in sodium pump (Na+,K+-ATPase) activity, alterations in substrate metabolism, lysosomal changes, and the production of oxygen free radicals. It is not clear yet which changes are causative and which are by-products of advanced cell injury.

Ischemia-induced ATN is a very complex physiologic process resulting from a mismatch between oxygen and nutrient delivery and energy demand of the nephrons. The most important pathophysiologic component of ischemic AKI may be a reduction in the local blood flow to the outer medulla.25 There appears to be an excess of constrictor hormones relative to hormones that dilate the afferent arterioles.
arteriole; subsequently, there is a drop in glomerular perfusion pressure and depression of the GFR. The brunt of the posts ischemic injury is in the proximal tubular cells, with loss of cell polarity and redistribution of Na+/K+-ATPase from its normal location on the basolateral plasma membrane. This leads to an increase in the delivery of sodium to the macula densa that stimulates afferent arteriolar vasoconstriction.26

Inflammatory cells are also involved in the pathogenesis of ATN.27 In addition, whereas previous studies focused on the renal tubular injury to epithelial cells, current research also emphasizes the importance of endothelial cells in ATN. As endothelial cells are injured, the cells swell, cell adhesion molecules are expressed, leukocytes are activated, and renal injury is potentiated. Vasoactive mediators promote vasoconstriction and further compromise in local blood flow and tubular cell metabolism.28

The role of the proximal tubule in reabsorbing solutes trapped in the ultrafiltrate produced by glomerular filtration, as well as absorption of solutes from the bloodstream and secretion into the tubular lumen, makes this cellular compartment particularly vulnerable to toxic injury. Exogenous cytotoxic agents, such as aminoglycosides or nucleoside reverse transcriptase inhibitors, and endogenous nephrotoxins, including immunoglobulin light chains and myoglobin, are concentrated in the proximal tubule and can produce AKI. Nucleoside reverse transcriptase inhibitors (e.g., adefovir and tenofovir) can produce a peculiar syndrome that consists of AKI, from proximal tubulopathy, and lactic acidosis, both of which appear to be related to drug-induced mitochondrial dysfunction.29

Cell death in either ischemic or nephrotoxic ATN may be of two kinds: apoptotic or necrotic. Advances in the understanding of cell death have led to the recognition that the pathways traditionally associated with apoptosis may be critical in determining the form of cell injury associated with necrosis. Apoptotic pathways, in which endonucleases play an important role, appear to be regulated by mediators such as oxidants, caspases, and ceramide. Which pathway the cell follows seems to depend on both the nature and the severity of the insult. It is likely that the pathway followed is to a large extent affected by the expression of the many genes involved in cell cycle regulation and by inflammatory and chemotactic genes. It is also likely that the cascades that lead to either apoptotic or necrotic cell death are activated almost simultaneously and may share some common pathways.

Persistent renal impairment from ATN may be oliguric or nonoliguric and typically lasts for 1 to 2 weeks, but it can persist for 4 to 6 weeks. This is often followed by a diuretic phase, which eventually leads to normalization of kidney function over a few days to a week. Most patients achieve recovery of renal function, except for a small, persistent decrease in GFR and some defect in the concentrating ability of the kidney. However, there is increased recognition that long-term consequences of a bout of AKI might include end-stage renal disease (ESRD) and progression of CKD [see Epidemiology, above].

AKI FROM INTRATUBULAR OBSTRUCTION

Several endogenous and exogenous molecules can precipitate in the tubular lumen to produce AKI. These include urate, calcium phosphate, immunoglobulin light chains, myoglobin, and medications. Some medications, including methotrexate, acyclovir, sulfadiazine, indinavir, sodium phosphate–containing cathartics, and triamterene, are concentrated in the tubular lumen and can form crystals that cause AKI from obstruction of urine flow. Medication-induced crystal nephropathy is typically observed in the setting of underlying CKD or volume depletion or following administration of high doses of these medications.

ACUTE INTERSTITIAL NEPHRITIS

AIN is often underdiagnosed as a cause of AKI. The diagnosis should not be overlooked, because this disorder requires specific intervention. Antibiotics are a major cause of AIN. This etiology is especially important to consider when a patient who is recovering from sepsis-induced AKI develops AKI while receiving antibiotics.

AIN is sometimes an immunologically induced hypersensitivity reaction to an antigen, usually a drug. AIN is detected in 2 to 3% of all renal biopsies but in up to 25% of renal biopsies that are performed specifically in the setting of drug-induced AKI. The drugs most commonly involved in the induction of AIN are NSAIDs and antibiotics [see Table 8].

AIN is suggested by laboratory findings that indicate an abrupt deterioration of renal function and by urinalysis and urine sediment findings of blood, protein, and WBCs in clumps and in casts in the absence of evidence of infection. Clinically, the only complaint may be flank pain, caused by distention of the renal capsule; there may also be systemic signs and symptoms of a hypersensitivity reaction, such as rash, joint pain, and fever. The complete blood count may reveal eosinophilia.

Definitive diagnosis is made by renal biopsy. Noninvasive techniques suggestive of AIN, which may include an increased urinary eosinophil count (using Hansel stain) and a positive gallium scan, are not specific. Treatment is aimed primarily at identifying and removing the offending agent. Prompt institution of corticosteroids appears to improve outcome in biopsy-proven drug-induced AIN, with serum

<table>
<thead>
<tr>
<th>Table 8 Drugs that Cause Acute Kidney Injury</th>
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<tbody>
<tr>
<td><strong>Cytotoxic</strong></td>
</tr>
<tr>
<td>Antibiotics (aminoglycosides, amphotericin B, nucleoside reverse transcriptase inhibitors [e.g., adefovir, tenofovir], cidofovir, others)</td>
</tr>
<tr>
<td>Cisplatin</td>
</tr>
<tr>
<td>Aristolochic acid (botanicals)</td>
</tr>
<tr>
<td>Ethylene glycol</td>
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<tr>
<td><strong>Crystallogenic</strong></td>
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<tr>
<td>Methotrexate</td>
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<tr>
<td>Antibiotics (acyclovir, sulfadiazine, indinavir, triamterene)</td>
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<tr>
<td>Sodium phosphate–containing cathartics</td>
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<tr>
<td>Associated with AIN</td>
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<tr>
<td>Antibiotics (β-lactams, sulfonamides, fluoroquinolones, others)</td>
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<tr>
<td>NSAIDs</td>
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<td>Proton pump inhibitors</td>
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<td>Diuretics</td>
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<tr>
<td>Allopurinol</td>
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<tr>
<td>Phenytoin</td>
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</table>

AIN = acute interstitial nephritis, NSAID = nonsteroidal antiinflammatory drug.
creatinine returning closer to baseline in treated, compared to untreated, patients.35

**SELECTED NEPHROTOXIC MEDICATIONS**

An impressive array of pharmaceuticals can produce AKI. Some medications are cytotoxic, whereas others produce so-called crystal nephropathies that occur when the medication crystallizes in the tubular lumen to produce AKI. Other medications produce allergic reactions in the form of AIN. A list of medications that produce AKI is provided in Table 8. A selected number of medications are discussed below.

**Aminoglycosides**

The most important manifestation of aminoglycoside nephrotoxicity is AKI secondary to ATN, which occurs in about 10 to 20% of patients receiving aminoglycosides (e.g., tobramycin, gentamicin, amikacin).31,32 Maintaining blood levels in the therapeutic range reduces but does not eliminate the risk of nephrotoxicity. Aminoglycoside-associated AKI is usually mild and nonoliguric; it is manifested by an increase in the serum creatinine level after about 1 week of aminoglycoside therapy. Patients with aminoglycoside nephrotoxicity may present with polyuria and hypomagnesemia; these conditions occur as a result of a decrease in the urinary concentrating ability and enhanced urinary loss, respectively.33 Several clinical factors or conditions can potentiate the effect of aminoglycosides on the kidney and can thus aggravate nephrotoxicity; these include renal ischemia induced by hypotension or volume depletion, the dosing schedule and the serum levels of aminoglycosides, sepsis, administration of other nephrotoxins, and liver disease. Once-daily dosing of aminoglycosides appears to be as effective in controlling infection as more frequent dosing, with a less nephrotoxic effect and without increased incidence of ototoxicity, compared to more frequent dosing.33 Individualized pharmacokinetic dosing of aminoglycosides has been shown to reduce the incidence of nephrotoxicity while allowing for higher doses of the drug to be administered.34

Presently, the only treatment for aminoglycoside nephrotoxicity is to discontinue the medication and to support the patient during the period of AKI. The prognosis for recovery of renal function after several days is excellent, although some patients may need dialysis before full recovery is achieved.

**Amphotericin B**

Amphotericin B is a relatively frequent cause of AKI. Hydration with normal saline before the infusion of amphotericin B decreases the incidence of AKI from this medication. Amphotericin B in lipid emulsion may be less nephrotoxic than nonlipid formulations and is recommended for patients at high risk for nephrotoxicity. Irreversible CKD and ESRD from amphotericin B nephrotoxicity are uncommon but do occur.

**Nonsteroidal Antiinflammatory Drugs**

NSAIDs are potent inhibitors of prostaglandin synthesis, a property that contributes to their nephrotoxic potential in certain high-risk patients who require prostaglandins for maintaining renal vasodilatation. The most frequent pattern of injury related to the use of NSAIDs is prerenal azotemia; this is particularly the case for patients with volume depletion or a reduced effective circulating volume. Susceptible patients include those with heart failure, cirrhosis, diabetes, CKD, nephrotic syndrome, and septic shock, as well as those of advanced age or who require use of a diuretic.35

A hyperchloremic metabolic acidosis, often associated with hyperkalemia, has also been recognized as an effect of NSAIDs, particularly in patients with preexisting chronic interstitial renal disease. In such persons, hyporeninemic hypoaldosteronism occurs during states of renal prostaglandin inhibition. NSAIDs have been associated with the development of AIN, which is often associated with renal insufficiency and marked proteinuria.36 This complication appears to be an idiosyncratic hypersensitivity drug reaction, which can develop days to months after starting the NSAID.37 In contrast to AIN associated with other drugs, AIN associated with NSAIDs is marked by a paucity of clinical manifestations of hypersensitivity, including eosinophilia and eosinophiluria. This disorder usually resolves with discontinuance of the offending agent.37 High-risk patients, such as the elderly and those with CKD, should be educated about the risk of using NSAIDs and should be advised to avoid these medications if possible. AKI caused by selective cyclooxygenase-2 inhibitors has been reported; thus, the same cautions apply to these agents as to nonspecific NSAIDs.

**Cisplatin**

Renal injury is a well-recognized complication of the use of cisplatin for the management of many solid-organ cancers. Cisplatin-associated nephrotoxicity affects a significant percentage of such patients; 25 to 35% develop a mild and reversible decrease in GFR after their first dose of cisplatin. With subsequent doses, the incidence and severity of renal failure increase, until irreversible renal injury occurs. Hypomagnesemia caused by renal losses of magnesium may be severe and can occur in as many as 50% of patients. Patients should be well hydrated with normal saline (200 to 250 mL/hr) before administration of cisplatin; other known nephrotoxins should be avoided whenever possible.38 The resultant ATN can be severe or irreversible, resulting in CKD or ESRD.

**ACE Inhibitors**

AKI that is associated with the use of ACE inhibitors is thought to be hemodynamic in origin; it is believed to occur as a result of the loss of autoregulation of renal blood flow and has typically been reported when ACE inhibitors are given to patients with bilateral renal artery stenosis. A 25 to 30% increase from baseline in serum creatinine levels when ACE inhibitors are initiated is considered acceptable by some investigators.39 If the serum creatinine level continues to rise, the ACE inhibitor should be discontinued, and an investigation for renal vascular disease should be considered. ACE inhibitors are not directly nephrotoxic; therefore, discontinuation of the medication should allow renal function to return to baseline if no other insults have occurred.
AKI in Special Situations

Rhabdomyolysis

Since the first description of the causative association between rhabdomyolysis and AKI in victims of crush injuries in World War II, the spectrum of recognized causes of rhabdomyolysis, myoglobinuria, and renal failure has markedly broadened. The most frequent causes are trauma or other injury that leads to muscle compression; ischemia; excess muscle activity, such as occurs during exercise or seizures; metabolic derangements; drugs; genetic defects; body temperature dysregulation; and infections. Some important metabolic derangements that can cause rhabdomyolysis include potassium and phosphate depletion; the risk of rhabdomyolysis associated with these electrolyte imbalances is increased in patients with chronic alcoholism. Cocaine use, neuroleptic malignant syndrome, and the use of statin drugs can also contribute to or cause rhabdomyolysis.

Muscle pain and dark-brown urine that is positive for blood on dipstick testing (orthotoluidine positive) but that does not contain RBCs are important diagnostic clues. However, the diagnosis must be confirmed by findings of elevated CK and myoglobin levels. About one third of patients with rhabdomyolysis develop AKI; the etiology appears to be related to renal vasoconstriction, proximal tubular cell injury from oxidant stress, and intranephronal of elevated CK and myoglobin levels. About one third of nephrotoxicity of myoglobin and urate.40 This therapy con-

tered in the field should receive immediate treatment with intravenous normal saline, 200 to 300 mL/hr. If urine output increases in 4 to 6 hours, the infusion should be continued (at a rate that matches the urine output) until the rhabdomyolysis resolves. However, if the patient continues to be oliguric (i.e., urine output is less than 400 mL/day), the infusion should be discontinued and the patient treated for AKI. Experience from recent disasters has shown that early aggressive hydration and alkalinization can prevent myoglobinuric AKI by protecting the kidney from the nephrotoxicity of myoglobin and urate.40 This therapy consists of isotonic sodium bicarbonate in 5% dextrose in water (D5W) or in sterile water, infused at a rate of 250 mL/hr. Urinary alkalinization is controversial; some investigators advocate urine alkalinization using isotonic bicarbonate solutions, whereas others consider it no better than saline diuresis.

A clinical presentation that is similar to that of rhabdo-

myolysis occurs after the release of heme pigments after intravascular hemolysis.

Aristolochic Acid Nephropathy (Formerly Chinese Herb Nephropathy)

Aristolochic acid, which has also been incriminated as the etiologic agent in Balkan nephropathy, is cytotoxic and produces proximal tubular epithelial cell death with subsequent tubular atrophy and interstitial fibrosis. Many botanicals may be contaminated with aristolochic acid and are listed in the review by Debelle and colleagues. Despite warnings, herbs containing aristolochic acid may be obtained through the Internet.

Acute Urate Nephropathy

AKI may occur in patients with malignancies that are associated with a high rate of tumor cell turnover (tumor lysis syndrome). Such turnover may occur either spontaneously or after chemotherapy; high cell turnover is particularly associated with poorly differentiated lymphomas and acute lymphoblastic leukemia. Uric acid production and hyperuricosuria may increase, resulting in intratubular crystallization of urate and development of acute urate nephropathy. In addition, during massive cell lysis, phosphate and potassium are released in large amounts and can produce hyperphosphatemia and hyperkalemia. In some patients, the precipitation of calcium and phosphate in the renal tubules can induce AKI independently of and in addition to uric acid deposition. The peak uric acid level often exceeds 20 mg/dL, and a ratio of urinary uric acid to creatinine concentrations greater than 1 to 1 suggests the diagnosis of acute urate nephropathy.

Conventional management includes aggressive intravenous hydration, diuretic therapy, urinary alkalinization, and inhibition of urate production by high-dose allopurinol. Prevention of AKI from tumor lysis syndrome involves establishing a urine output of greater than 3 to 5 L/24 hr and initiating treatment with allopurinol before institution of cytotoxic therapy. Establishing a high urinary output results in high intratubular pressure and thereby helps prevent intratubular obstruction. Allopurinol, which blocks the synthesis of uric acid by inhibiting xanthine oxidase, should be administered in dosages of 300 to 600 mg/day; therapy should begin 3 days before initiation of chemotherapy. In patients with underlying renal impairment, the allopurinol dose should be adjusted for renal function. In patients with initial hyperuricemia, allopurinol should be started and chemotherapy delayed until the serum uric acid concentration has become normal. Urinary alkalinization increases the solubility of xanthine and enhances its excretion. Urinary alkalinization can be achieved by the infusion of sodium bicarbonate in amounts sufficient to keep the urinary pH above 7 or by the administration of acetazolamide, which inhibits the reabsorption of sodium bicarbonate in the proximal tubule, thereby making the tubular fluid and the urine alkaline. Sodium bicarbonate and acetazolamide can be used in combination.

A recombinant form of urate oxidase, rasburicase, is a nonhuman proteolytic enzyme that oxidizes uric acid to allantoin. Rasburicase has been shown to reduce serum uric acid levels with associated diuresis more effectively and much faster than allopurinol and should be considered in the prevention of hyperuricemia and AKI.44

References

The development of oliguria with hyperuricemia may be an indication for dialysis. Early dialysis in these patients, started before severe renal impairment or uremia manifests, can help minimize further injury.

**ACUTE PHOSPHATE NEPHROPATHY**

The syndrome of acute phosphate nephropathy was characterized in greater detail. In this disease, AKI, with tubular cell injury and concomitant tubular and interstitial calcium phosphate deposits, occurs following the administration of an oral sodium phosphate bowel purgative, for example, in preparation for colonoscopy. Hypertensive elderly patients with CKD are particularly prone to develop this form of AKI following exposure to high doses of sodium phosphate. Treatment is best aimed at prevention; generous hydration should be pursued if susceptible patients must be exposed to high doses of sodium phosphate.

**AKI IN MULTIPLE MYELOMA**

Tubulointerstitial renal disease is commonly seen in multiple myeloma and is usually related to the overproduction of nephrotoxic monoclonal free light chains (FLCs), which is usually a component of immunoglobulin. AKI is a manifestation of FLC-associated AKI. A separate mechanism of FLCs is cytotoxic and promotes proximal tubular cell injury. Some monoclonal FLCs are cytotoxic and promote proximal tubular cell injury that can manifest as AKI. A study that should be considered. Renal biopsy to confirm that the etiology of the AKI was cast nephropathy was not performed; in perhaps one third of patients with myeloma and AKI, the etiology is not cast nephropathy but is related instead to extrarenal obstruction (nephrolithiasis, papillary necrosis, and amyloid deposition in the ureters), hypercalcemia, hyperviscosity syndrome, or other etiology, such as drug-related AIN or contrast-induced nephropathy (CIN). Also, serum FLCs were not determined either before or after the plasma exchange. Until additional data are provided, however, it is prudent not to recommend plasmapheresis for every patient with AKI, although a subset of patients may respond to plasma exchange. If plasma exchange is performed, demonstration of the efficacy of treatment by quantifying changes in serum FLC levels should be performed. Finally, hyperviscosity syndrome remains an indication for plasma exchange.

Hemodialysis using dialyzers that have very large effective pore size (about 50 kDa) effectively reduces serum FLC concentrations, providing the potential to accelerate recovery from AKI. In two small trials involving patients who had AKI from biopsy-proven cast nephropathy, this approach produced a promising renal response.

**ETHYLENE GLYCOL POISONING**

Ethylene glycol is a colorless, odorless, sweet-tasting liquid found in solvents and antifreeze. Ingestion of ethylene glycol, usually in the form of antifreeze, produces a syndrome of severe metabolic acidosis characterized by a high anion gap and a large osmolar gap. Anion gap and osmolar gap are defined as follows:

\[
\text{Anion gap} = [\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])
\]

\[
\text{Plasma osmolality (calculated)} = 2[\text{Na}^+] + (\text{BUN}/2.8) + ([\text{glucose}/18] + ([\text{ethanol}/4.7])
\]

\[
\text{Osmolar gap} = \text{measured osmolality} - \text{calculated osmolality}
\]

The normal value for the anion gap has been 12 ± 4 mEq/L. However, in a retrospective analysis of 222 patients with normal serum creatinine and albumin levels, the range for the anion gap was found to be much narrower, 6.6 ± 2 mEq/L, although the normal anion gap is typically standardized in each laboratory. This reduction in the anion gap is the result of implementation of automated laboratory analysis techniques that use ion-selective electrodes.

The osmolar gap is the difference between the measured and the calculated osmolality. The calculated osmolar gap is derived by use of the serum sodium, glucose, and urea levels. The addition of solutes to plasma can contribute to the osmolar gap; if such solutes are contributing to the osmolar gap, the measured osmolality will be found to be higher than the calculated osmolality. Alcohol intoxication is probably the most common cause of an osmolar gap.

Ethylene glycol is metabolized by alcohol dehydrogenase to glycolic acid, which is believed to be the major contributor to acidosis. The key clinical findings in patients who have ingested ethylene glycol are initial disorientation and agitation, with progression to central nervous system depression, AKI, metabolic acidosis, respiratory failure, and circulatory insufficiency. Hypocalcemia is a prominent feature that occurs as a result of the deposition of calcium oxalate in multiple tissues; it may be aggravated by a decrease in parathyroid hormone response. Calcium oxalate crystals are typically found in the urine sediment. Kidney
biopsy demonstrates deposition of calcium oxalate crystals in proximal tubular cells and is the presumed pathogenesis of AKI in this setting. AKI generally manifests after 48 to 72 hours. Aggressive intervention should be initiated at the time of diagnosis. Intervention should consist of intravenous infusion of sodium bicarbonate to enhance renal clearance of glycolate through ion trapping; intravenous infusions of ethanol or fomepizole to block the metabolism of ethylene glycol; and hemodialysis for the removal of ethylene glycol and glycolate. Regular monitoring of the osmolar gap (corrected for ethanol level if intravenous ethanol is administered during treatment) and the anion gap may help guide therapy during hemodialysis.

**CONTRAST-INDUCED NEPHROPATHY**

CIN is a common cause of AKI. In patients with normal renal function who have no other risk factors for AKI, the incidence of contrast-induced renal injury is low (<1%). The incidence of CIN is approximately 150,000 cases a year in the United States.57,58 CIN is defined as AKI occurring shortly after exposure to intravenous contrast—typically within 48 hours—in the absence of other causes of renal failure. The most important risk factor is preexisting renal insufficiency; other risk factors include diabetes mellitus, volume depletion, advanced age, heart failure, states of reduced renal perfusion, high total dose of contrast, preexistent use of NSAIDs, and concomitant exposure to other nephrotoxins.57,58 A meta-analysis of 31 randomized controlled trials, which included more than 5,000 patients, compared high-osmolar agents with low-osmolar agents; in all but nine studies, a favorable outcome was reported for patients receiving low-osmolar agents.40 The odds ratio for an increase in serum creatinine of greater than 0.5 mg/dL (44 µmol/L) with low-osmolar agents was 0.61 times that of the odds ratio associated with high-osmolar agents. Low-osmolar contrast media are the first choice for patients at risk for contrast media–induced AKI. Ioxilanol, a nonionic, iso-osmolar contrast medium, has been shown to be beneficial in preventing contrast nephropathy in high-risk patients.61 There appears to be no role for diuretics and mannitol in the prevention of CIN. For patients at high risk for contrast-induced AKI, consideration should be given to the volume of contrast used because there is an increased risk of renal injury with higher doses and with doses that are repeated within 48 hours. In high-risk patients, consideration should be given to the use of diagnostic procedures that do not require contrast.

Hydration with sodium bicarbonate before administration of contrast medium appears to be more effective than hydration with sodium chloride. In a randomized controlled trial in 199 patients whose serum creatinine level was at least 1.1 mg/dL (1.1 to 3.7 mg/dL), CIN occurred in eight patients (13.6%) who received sodium chloride by infusion but in only one patient (1.7%) who received sodium bicarbonate.62 Whereas this trial showed clear benefit of isotonic bicarbonate infusion in prevention of CIN, subsequent studies provided conflicting findings, suggesting the need for a large, multicenter trial.63 One interesting perspective is that the dose of bicarbonate that was used in these studies tended to vary. Negative effects were typically observed when the total administered dose of bicarbonate was 0.75–1.4 mEq/kg, whereas beneficial effects were observed when the dose was greater than 1.5 mEq/kg. In the typical hydration protocol, 150 mEq/L of sodium bicarbonate in D5W was infused at a rate of 3 mL/kg/hr for 1 hour immediately before contrast administration, followed by 1 mL/kg/hr during contrast administration and for 6 hours after the procedure. If the dose of bicarbonate becomes important, then delays in the initiation of therapy could produce negative results.

N-Acetylcysteine is commonly used to minimize toxicity of contrast in high-risk patients. Clinical studies of acetylcysteine for preventing contrast media–induced AKI have yielded conflicting results, however, and further studies are in order before this measure can be routinely recommended.64,65 The use of fenoldopam, a selective D1 dopamine receptor agonist that causes both systemic and renal arteriolar vasodilatation, has been advocated for helping to prevent CIN. In a randomized, controlled, multicenter study of patients with CKD, however, fenoldopam was ineffective in preventing further deterioration of renal function after administration of contrast dye.66

**AKI IN SEPSIS**

Sepsis is one of the major causes of death in the United States. The mortality rate of severe sepsis is quite high (=70%) and is a substantial health resource burden, with costs exceeding $10 billion per year in the United States.1,42 The incidence of sepsis has been increasing largely because of physicians taking care of an older population, underlying chronic illnesses, and complex hospital interventions.67–69 In a recent prospective observational study of 29,269 ICU patients, AKI was seen in approximately 6% of the patients, with the most common cause being septic shock (47.5%), and was associated with an overall mortality rate of 60%.70 The advent of newer antibiotics has greatly improved morbidity and mortality associated with sepsis; however, host inflammatory and hemodynamic responses invariably lead to multiple organ failure and adverse outcomes. AKI is particularly common in the setting of sepsis, and the presence of both sepsis and AKI portends an even higher mortality rate.71

The pathogenesis of sepsis-associated AKI is complex and multifactorial, involving systemic and intrarenal hemodynamic changes, immune and inflammatory responses mediated by a variety of cytokines, chemokines, endotoxin and reactive oxygen species, activation of the complement and coagulation cascades, and endothelial and tubular dysfunction.71 The use of changes in serum creatinine for diagnosis of sepsis-associated AKI is problematic because sepsis is associated with decreased production of creatinine, thereby limiting early detection of AKI.72 In addition, serum creatinine does not accurately reflect changes in GFR, particularly in ICU patients with volume overload. The utility of new biomarkers for early detection of sepsis-induced AKI (e.g., NGAL, KIM-1, L-FABP, IL-18) is very encouraging and would clearly obviate this problem. Many of these biomarkers are in various phases of development toward their routine and approved use in the clinical setting.73 These emerging biomarkers to recognize AKI before structural and functional injury become apparent will allow early
diagnosis and will facilitate institution of preventive and therapeutic strategies.

A major impediment to our understanding and application of potential therapies for sepsis-associated AKI has been the lack of animal models that closely mimic human sepsis syndromes. However, recent developments in this area have been highly encouraging and have led to several new clinically relevant animal models of sepsis. The goals for treatment of sepsis-associated AKI are largely directed at supportive interventions such as maintenance of hemodynamic status with fluids and vasopressors, control of the underlying cause of sepsis, antibiotics (appropriately dose modified for the degree of renal dysfunction), tight metabolic and glycemic control, and distant organ protection, particularly the lung, with low tidal volume ventilation. Agents such as activated protein C, caspase inhibitors, and corticosteroids remain controversial, but recent large clinical trials have reported negative results.

The indications for dialysis for patients with sepsis-associated AKI include volume overload, pulmonary edema, hyperkalemia, acidosis, and encephalopathy and are similar to those for patients with AKI not associated with sepsis [see Management of AKI, below].

**Hepatorenal Syndrome**

The HRS is defined as kidney failure in patients with severely compromised liver function in the absence of clinical, laboratory, or anatomic evidence of other known causes of renal failure. HRS closely resembles prerenal failure, except that it does not respond to conventional volume replacement. The etiology of HRS is thought to involve significant reductions in renal perfusion associated with splanchnic vasodilatation. In the United States and Europe, the great majority of HRS cases occur in patients with advanced alcoholic cirrhosis. In persons who have cirrhosis with ascites, the probability of developing HRS is 18% at 1 year and 39% at 5 years.

HRS may appear suddenly and cause severe azotemia within days (so-called type 1 HRS) or may begin insidiously over a period of weeks to months (type 2 HRS). Common precipitating causes are deterioration of liver function, sepsis, spontaneous bacterial peritonitis, the use of nephrotoxic antibiotics or NSAIDs, overzealous use of diuretics, diarrhea, or GI bleeding. Large-volume paracentesis has the potential to initiate and exacerbate hepatorenal dysfunction. Support with intravenous albumin infusion during large-volume paracentesis may prevent circulatory dysfunction and decreased renal perfusion. HRS can, however, occur without any apparent precipitating cause. The diagnosis is one of exclusion and should be suspected in any patient with advanced acute or chronic liver disease, portal hypertension, and progressive renal insufficiency associated with an increase in serum BUN and creatinine levels.

The initial step in management is to search diligently for and treat correctable causes of azotemia. All nephrotoxic agents should be discontinued. It is important to exclude reversible prerenal azotemia. Because HRS and prerenal azotemia produce similar urinary diagnostic indices, differentiating these two entities often requires a functional approach, such as volume expansion. Once a diagnosis of HRS is established, there is no specific treatment; management is conservative. If the patient is hypotensive, normalization of blood pressure may lead to improvement in renal perfusion and thus to stabilization of renal function. In patients with spontaneous bacterial peritonitis, intravenous albumin infusion (1.5 g/kg at the time of diagnosis followed by 1 g/kg on day 3) plus antibiotic treatment has proved more effective than antibiotic treatment alone in decreasing the incidence of renal impairment and death.

Several agents have been investigated for pharmacologic treatment of HRS; all are intended to increase renal blood flow. Octreotide is known to cause selective splanchnic vasoconstriction and may be beneficial for prolonged therapy and subcutaneous administration while patients await liver transplantation. Midodrine, octreotide, and albumin therapy followed by a transjugular portosystemic stent shunt has been shown to be beneficial in a few cases of type 1 HRS, which is characterized by rapid and progressive renal impairment (doubling of the serum creatinine level to more than 2.5 mg/dl in less than 2 weeks, commonly with associated oliguria or anuria) and typically is precipitated by spontaneous bacterial peritonitis. The combination of albumin infusion with the vasopressin analogue terlipressin has proved effective in reversing HRS in cirrhotic patients.

The prognosis for patients with HRS is poor unless their liver function can be improved. This typically requires liver transplantation.
has been associated with AKI in up to 7.7% of pregnant patients.

Postpartum AKI, also known as postpartum hemolytic-uremic syndrome (HUS), is characterized by hypertension and microangiopathic hemolytic anemia. It can occur from postpartum day 1 to several months after delivery, but peak onset is from postpartum week 2 to week 5. Glomerular lesions resemble those found in adult HUS and are characterized by fibrin deposition, thickened capillary walls, and subendothelial swelling associated with large granular subendothelial deposits. Genetic factors may be involved in the etiology of postpartum HUS, given that women who have experienced one episode are at increased risk for recurrence with subsequent pregnancies, and occurrence of the disease has been documented in sisters. Postpartum HUS is associated with elevations in the lactate dehydrogenase level; the HELLP syndrome, in contrast, is associated with elevations in transaminase levels. This difference is useful in distinguishing between these two syndromes. The mainstay of treatment for postpartum HUS is plasma exchange. Before the advent of plasma exchange therapy, mortality was 90%; current maternal survival rates are 70 to 80%.83

Other renal disorders may cause AKI during pregnancy. If active urine sediment occurs in a pregnant patient before the 20th week of gestation, acute glomerulonephritis should be considered. Lupus nephritis may develop during pregnancy in patients with a prior history of lupus nephritis or extrarenal lupus. Because complement levels are typically elevated during pregnancy, the finding of low complement levels in a pregnant woman (with additional supportive serology) is especially suggestive of lupus nephritis. Renal biopsy is not contraindicated during pregnancy. If a proliferative lesion is suspected, renal biopsy should be performed to facilitate early initiation of aggressive therapy. Any of the other prerenal and nephrotoxic causes of AKI can affect pregnant patients and should be considered. After the 20th week of gestation, AKI in a patient with hypertension is most likely the result of preeclampsia.

Management of AKI

Management of AKI entails close monitoring of the patient, supportive therapy, and targeted treatment of specific complications that may arise. The signs and symptoms of AKI reflect loss of the regulatory, excretory, and endocrine functions of the kidney. The loss of the excretory ability of the kidney is reflected in a rise in the plasma concentration of specific substances normally excreted by the kidney. The most widely monitored indices are the concentrations of BUN and creatinine in the serum. In patients without complications, BUN increases by 10 to 20 mg/dL/day, and bicarbonate decreases to a steady-state level of 16 to 18 mEq/L. The serum potassium concentration need not rise appreciably unless the patient experiences a hypercatabolic state, GI bleeding, or extensive tissue trauma.

PREVENTION

AKI places an overwhelming burden on the health care system. The estimated cost of dialysis and aggressive care of critically ill patients with AKI is over $10 billion per year in the United States.167 Thus, prevention is the cornerstone of patient care.

Approximately 25% of all hospital-acquired cases of AKI are related to the use of one or more nephrotoxic agents. Consequently, the best strategy for prevention of AKI is to avoid drug-related nephrotoxicity, especially in high-risk situations. Patients at risk are the elderly, those with preexisting renal disease, and those with volume depletion. The serum creatinine level is a poor marker of actual renal function, especially in elderly persons and in those with sepsis-associated AKI. An estimate of renal function is needed, especially in elderly patients, to permit proper management of the drug levels of all potential nephrotoxic agents and to enhance awareness of diminished renal function when the serum creatinine level falls within the normal range. The Modification of Diet in Renal Disease (MDRD) formula gives an acceptable estimate of GFR. Calculators for the MDRD GFR are available on the Internet (http://www.kidney.org/professionals/KDOQI/gfr_calculator.cfm or http://nkddep.nih.gov/professionals/gfr_calculators/index.htm).

Correcting fluid deficiencies before surgery and providing adequate hydration for patients who are particularly at risk before use of radiocontrast studies are useful measures. Hydration with sodium bicarbonate before contrast administration and N-acetylcysteine can be used to minimize contrast-induced nephrotoxicity [see Contrast-Induced Nephropathy, above]. A recent meta-analysis that evaluated the efficacy of preventive interventions in CIN found that the administration of N-acetylcysteine was renoprotective, particularly in high-risk patients, and given its low cost, availability, and few side effects, it should be used as a prophylactic agent.84 Nephrotoxic drugs should be used only when necessary; when such drugs are used, the patient should be monitored carefully. Pretreatment with allopurinol or rasburicase before chemotherapy of massive tumors diminishes uric acid excretion and thus lowers the potential for nephrotoxicity.

EMERGENT INTERVENTION

Hyperkalemia is a life-threatening complication of AKI that often necessitates urgent intervention [see Treatment of Complications, Hyperkalemia, below]. The electromechanical effects of hyperkalemia on the heart are potentiated by hypocalcemia, acidosis, and hyponatremia. Thus, the electrocardiogram (ECG), which measures the summation of these effects, is a better guide to therapy than a single determination of serum potassium. It must be emphasized that hyperkalemia is the biochemical abnormality that is most often responsible for death in patients with AKI. In contrast, moderate acidosis is generally well tolerated and usually does not require treatment; treatment may be necessary as adjunct therapy to control hyperkalemia or if the plasma bicarbonate level falls below 15 mEq/L.

SUPPORTIVE THERAPY

Patients with AKI in the ICU setting generally lose about 0.5 lb a day. Further weight loss may be minimized by providing adequate calories (1,800 to 2,500 kcal or 35 kcal/kg/day) and about 1.0 to 1.4 g protein/kg/day. The
use of hyperalimentation with 50% dextrose and essential amino acids has had little effect on reducing mortality and morbidity in patients with AKI, except in patients who also have significant burns.

DIALYSIS

Indications for initiating dialysis are as follows: (1) severe hyperkalemia, acidosis that is not easily controlled by medical treatment, or both; (2) fluid overload that is not responsive to fluid restriction, diuretics, or both; and (3) signs or symptoms of uremia (e.g., a pericardial friction rub, asterixis, mental status changes that are not accounted for by some other disorder, or seizures). In the absence of any of these indications, most nephrologists advocate dialysis when the BUN level reaches 80 to 100 mg/dL because the goal of modern therapy is to avoid the occurrence of uremic symptoms. Thus, the patient undergoes dialysis as frequently as necessary to keep the BUN level below 80 mg/dL. When this approach is used, most patients do not develop uremic symptoms, the diet and fluid intake can be liberalized, and the overall management of the patient is easier. It is critical to carefully review the indications for, and the doses of, all drugs administered to patients with AKI. Monitoring of blood concentrations of drugs is an important adjunct to effective treatment.

Both intermittent and continuous renal replacement therapy (CRRT) can be used, and the ultimate choice would depend on the hemodynamic status, experience of the center, and presence or absence of intracranial hypertension. In patients with hemodynamic compromise, intermittent dialysis is not feasible, and continuous venovenous hemodialysis or hemofiltration is the preferred modality. CRRT is also preferred in patients with raised intracranial tension or those at risk for cerebral edema. CRRT offers several advantages, including better hemodynamic stability, reduced incidence of cardiac arrhythmias, improved oxygenation, better nutritional support, and fluid and metabolic control. There is currently no consensus on the timing of intervention with dialysis, and early intervention should be based on the clinical criteria and volume status rather than just biochemical parameters. There is no role for prophylactic dialysis. Two recent studies have shown that the intensity of dialysis or dialysis dose per se does not affect overall survival and outcomes in AKI. Most continuous modalities use citrate-based regional anticoagulation protocols, and in patients with concomitant liver failure, citrate toxicity should be monitored. Continuous high-flux dialysis membranes have higher filtration rates, are more permissive to “middle molecules,” and have enhanced cytokine removal compared to low-flux dialyzers. However, whether removal of cytokines by CRRT is beneficial in improving survival in sepsis-associated AKI remains to be conclusively determined.

In a patient who receives appropriate therapy with early dialysis, many of the uremic manifestations associated with AKI either do not develop or are minimal. Infection remains the main cause of death despite vigorous dialysis. Thus, meticulous aseptic care of intravenous catheters and wounds and avoidance of the use of indwelling urinary catheters are important in the management of such patients.

DOPAMINE

In both animal and human studies, use of low-dose dopamine is associated with an increase in renal blood flow and natriuresis in the context of euvolemia and normal renal function. However, there are no clinical data to support the use of low-dose dopamine for the protection or improvement of renal function in patients with AKI. In several large studies comparing dopamine with placebo, dopamine was not found to improve survival or eliminate the need for dialysis. A recent meta-analysis concluded that low-dose dopamine resulted in transient increases in urine output but had no beneficial effects on preventing AKI or outcomes.

TREATMENT OF COMPLICATIONS

Volume Overload

Volume overload is one of the first manifestations of AKI caused by salt and water retention secondary to a decrease in GFR. In addition, volume overload may be exacerbated by intravenous fluids given in an aggressive resuscitation attempt or to treat oliguria. Volume overload can delay a diagnosis of AKI if changes in serum creatinine are used as the main “biomarker” of AKI. Untreated volume overload also adversely affects outcomes in AKI. Consequently, volume status needs to be evaluated daily in patients with AKI. This evaluation includes assessment of weight, central pressures if possible, blood pressure, and heart rate. Physical examination is also important and should be directed specifically toward the detection of skin turgor, peripheral edema, pulmonary edema, and a third heart sound.

Records of the patient’s daily fluid intake and output should be reviewed, but insensible fluid losses, as well as weight loss resulting from a high catabolic state, must be taken into consideration. A normal adult loses about 200 to 300 g of body weight a day as a result of catabolism, and the average 70 kg person has insensible losses of around 850 to 1,000 mL/day. With fever, the insensible water loss increases by about 13% for each degree Celsius rise above normal (7% for each degree Fahrenheit). Daily assessment and modification of fluid therapy are essential. Water is continuously generated from endogenous sources by the oxidation of protein (41 mL/100 g), fat (107 mL/100 g), and carbohydrates (55 mL/100 g). Adequate carbohydrates will help reduce protein metabolism, with a small decrease in water generation.

The most useful therapy for volume overload is a loop diuretic. Furosemide can be given intravenously in a bolus or by continuous infusion [see Table 9]. If started in the early stages of AKI, this intervention, along with fluid restriction, can be very beneficial in preventing or minimizing volume overload. Loop diuretics may be combined with thiazide diuretics (e.g., metolazone, chlorothiazide sodium) (which act on distal nephron segments) for an additive effect. In such cases, the thiazide diuretic should be administered 30 minutes prior to the loop diuretic. The main risk of using high doses of furosemide is deafness, which can be permanent. This risk is increased if the serum albumin level is low and if other ototoxic medications are being used simultaneously with furosemide. There is no good evidence that the use of diuretics alters the course of AKI; however, in patients with fluid overload, diuretics may be useful in
increasing urine output and preventing the need for dialysis. If the patient is unresponsive to diuretic treatment and remains oliguric, early intervention with dialysis should be considered.

Hyponatremia

Hyponatremia is a common problem in patients who have AKI that is related to a decrease in GFR and impaired tubular function. Usually, such hyponatremia is associated with hypervolemia. Sources of excess water intake include the administration of hypotonic solutions such as D5W or free-water intake through enteral or parenteral feeding.

The clinical manifestations of hyponatremia are primarily neurologic in nature. Symptoms are related to cell swelling and may include headache, behavioral disturbances, lethargy, ataxia, and seizures; symptoms can progress to coma, respiratory depression, and death.

Symptomatic hyponatremia should be treated aggressively but also with caution because overly aggressive correction of a low serum sodium level can lead to central pontine myelinolysis if the duration of electrolyte imbalance has been longer than 48 hours. The initial approach in a patient who has volume overload and hyponatremia is to restrict free water and administer loop diuretics. If symptoms of hyponatremia occur in a patient with AKI that is unresponsive to diuretics or saline replacement, the removal of free water may be warranted as the initial step in renal replacement therapy. Vasopressin receptor antagonists are a new class of agents that have shown benefit in treating hyponatremia in euvoletic and hypervolemic states.\(^2,23\) Tolvaptan is an orally administered selective vasopressin V2 receptor antagonist and approved for euvoletic and hypervolemic hyponatremia. Conivaptan is a nonpeptide dual arginine vasopressin V1A and V2 receptor antagonist administered intravenously for the management of euvoletic hyponatremia. Correction of hyponatremia should proceed gradually, with the rise in sodium level targeted at a rate of 1 to 2 mEq/L/hr until symptoms resolve or until the serum sodium level approaches 120 mEq/L. Therefore, continuous monitoring of the patient’s condition and measurement of serum electrolytes every 1 to 2 hours are warranted.

Hyperkalemia

Hyperkalemia is common in patients with AKI. Causal factors include a decrease in GFR, a low rate of urinary flow to the collecting duct, distal tubular damage, and comorbid conditions that contributed to or are associated with AKI, such as rhabdomyolysis, acidosis, and the hypercatabolic state. ACE inhibitors, potassium-sparing diuretics (e.g., spironolactone, triamterene), and NSAIDs may also play a role.

A small portion of the total-body potassium—1.5 to 2.5%, or around 60 mEq—is found in the extracellular compartment. The intracellular compartment has a potassium concentration about 38-fold higher than that of the extracellular compartment. Thus, any process that leads to cellular destruction can contribute to hyperkalemia, especially in patients with AKI.

The cardiac effects of hyperkalemia are primarily associated with the blunting of the magnitude of the action potential in response to a depolarizing stimulus. The sequential ECG changes observed in hyperkalemia are peaked T waves, prolongation of the PR interval, widening of the QRS complex, and a sine wave pattern [see Figure 3, left panel]; these findings call for emergent treatment. Early ECG changes with peaked T waves are usually first seen on the anterior chest leads (V2 to V5) [see Figure 3, right panel]. Other symptoms consistent with hyperkalemia include paresthesias, muscular weakness, and depressed deep tendon reflexes. These symptoms can progress to flaccid paralysis and ARF. Severe hyperkalemia is life-threatening and should be considered a medical emergency.

The treatment of hyperkalemia associated with ECG changes starts with the administration of calcium chloride or calcium gluconate, which immediately antagonizes the effect of potassium on cardiac conduction. Insulin and glucose, inhaled beta agonists, or intravenous sodium bicarbonate in patients known to have acidosis will help redistribute potassium to the intracellular space [see Table 10].\(^4\) These measures require 30 to 60 minutes to take effect and have a short duration of action. In patients with significant renal failure, the only certain way of lowering the potassium is to remove it from the body by using sodium polystyrene sulfonate (orally or as an enema), dialysis, or both. It is important to continue medical management of severe hyperkalemia with calcium, glucose, and insulin as well as sodium polystyrene sulfonate until dialysis can be initiated.

Dietary intake of potassium should be restricted to less than 50 mEq/day; intravenous or oral sources of potassium should be discontinued, and medications that inhibit potassium excretion (e.g., potassium-sparing diuretics, NSAIDs, ACE inhibitors, and ARBs) should be stopped.

Acidosis

The kidney plays a major role in acid-base balance through the excretion of nonvolatile acids and by the reabsorption
and regeneration of bicarbonate. A healthy adult produces 1 mEq/kg/day of hydrogen ions; this production is influenced to a large degree by dietary intake. In patients with AKI, the serum bicarbonate level decreases by 1 to 2 mEq/day and typically stabilizes around 16 to 18 mEq/L. A more severe drop may be precipitated by a hypercatabolic state, infection, inadequate nutrition, and other causes of metabolic acidosis. Patients with obstructive uropathy (postrenal causes) can manifest a type 4 renal tubular acidosis with marked acidosis and hyperkalemia.

Clinical manifestations of acidosis are partly related to the rapidity with which the acidosis develops. When metabolic acidosis develops rapidly, the body’s attempt to compensate by blowing off carbon dioxide may result in Kussmaul respiration, which is characterized by deep inspiration and a normal or reduced respiratory rate. Other clinical consequences include cardiac arrhythmias, depressed myocardial contractility, peripheral vasodilatation, abdominal pain, nausea and vomiting, headache and lethargy, and an increased catabolic rate.

Metabolic acidosis is defined as a low arterial pH in conjunction with a low serum bicarbonate level. Mild to moderate metabolic acidosis with a pH greater than 7.2 can be treated with oral sodium bicarbonate. Severe metabolic acidosis with a pH of 7.1 or less that is associated with AKI should be treated more aggressively, with intravenous sodium bicarbonate, renal replacement therapy, or both; CRRT is the preferred approach. Because intravenous sodium bicarbonate replacement poses many risks, critically ill patients who receive it require close monitoring. If needed, intravenous bicarbonate can be administered as an isotonic solution by adding 3 ampules of sodium bicarbonate (50 mEq/50 mL) to 1 L of D5W; the solution is infused at a variable but slow rate, depending on the patient’s condition and volume status. Particular attention should be given to cardiac, respiratory, and hemodynamic status. Serum electrolyte levels, including the serum calcium level, should be monitored and corrected as needed.

Early in the recovery phase of AKI, there may be modest reductions in GFR and in the ability to concentrate and acidify the urine. Thus, patients may continue to need support with intravenous fluids and oral or intravenous bicarbonate.

### Calcium and Phosphate Balance

It is important to note that changes in calcium and phosphate balance occur in AKI and do not necessarily indicate the presence of CKD. Hypocalcemia is a common finding in patients with AKI, but it rarely requires intervention. In patients with AKI, hypocalcemia can result from several mechanisms, the most common being hyperphosphatemia. Resistance to parathyroid hormone, altered vitamin D metabolism, and calcium sequestration in tissues all play a role. Transfusions of blood products that have been stored in citrate and infusions of sodium bicarbonate can contribute to a decrease in the serum calcium level. Calcium supplementation should be undertaken only if it is clinically indicated and should be carried out with caution.

<table>
<thead>
<tr>
<th>Table 10</th>
<th>Treatment Modalities for Hyperkalemia</th>
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<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td><strong>Onset</strong></td>
</tr>
<tr>
<td>Calcium gluconate 10% solution, 10 mL IV over 10–15 min</td>
<td>1–3 min</td>
</tr>
<tr>
<td>Regular insulin, 10 U IV with dextrose, 50% 50 mL if plasma glucose is &lt; 250 mg/dL</td>
<td>30 min</td>
</tr>
<tr>
<td>Beta2 agonist—nebulized albuterol, 10 mg</td>
<td>30 min</td>
</tr>
<tr>
<td>Sodium polystyrene sulfonate, 60 g p.o. in 20% sorbitol or 60 g per retention enema</td>
<td>1–2 hr</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Immediate</td>
</tr>
</tbody>
</table>

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**Figure 3** The progression of changes from peaked T waves, prolonged PR interval to a sine wave pattern is shown in the left panel. Early changes of peaked T waves are usually seen in the anterior chest leads (right panel).
Hypercalcemia is rare in patients with AKI and may be indicative of other underlying medical conditions. The most common underlying disorders are malignancies, particularly multiple myeloma. Hypercalcemia occurs in about 30% of patients during the recovery phase of AKI-associated rhabdomyolysis.

Hyperphosphatemia is common in patients with AKI. The elevation in the phosphate level results primarily from a decrease in renal excretion; tissue destruction and shifts from the intracellular to the extracellular space as a result of acidosis and catabolism can be contributing factors. In patients who can ingest food, hyperphosphatemia should be treated with phosphate binders; these agents prevent absorption of dietary phosphorus into the bloodstream. Phosphate binders include calcium salts (calcium carbonate or calcium acetate), aluminum hydroxide (should be avoided), sevelamer, which is a cationic polymer that binds phosphate through ion exchange, and lanthanum carbonate. If the calcium-times-phosphorus product is high (i.e., > 70), a non–calcium-based binder such as sevelamer should be administered to minimize metastatic calcification in soft tissues.

Anemia

A normochromic-normocytic anemia develops in 65 to 95% of patients with AKI. These patients have normal serum iron levels and normal or hypercellular bone marrow. An increase in the rate of destruction of RBCs as a result of increased erythrocyte fragility may play a role in the early decrease in the hemoglobin level in patients with AKI. The most important cause of AKI-associated anemia is inadequate production of erythropoietin, but in critically ill patients, a decrease in erythropoietin responsiveness also plays a role.

Blood loss may contribute to anemia in patients with AKI. These patients have an increased tendency to bleed because of platelet dysfunction secondary to azotemia. Conjugated estrogen and 1-desamino-8-arginine vasopressin (DDAVP or desmopressin) may help correct this bleeding tendency. DDAVP is given at a dosage of 0.3 mg/kg infused intravenously over 20 to 30 minutes.

Because anemia can produce significant complications in critically ill patients, hemoglobin levels should be maintained above 10 g/L. Erythropoietin is increasingly used in such patients to reverse anemia and to reduce the need for blood transfusions.

Prognosis of Patients with AKI

Mortality can be as high as 50 to 80% in patients who have AKI in association with sepsis, hypotension, and respiratory failure. The prognosis for hospitalized patients with AKI depends largely on the setting (i.e., hospital ward or ICU); the presence of comorbidities; the underlying cause of the renal failure; the severity of the renal failure; and how early in its course the condition is diagnosed and treatment is initiated. In a review of 22,589 patients who underwent cardiac surgery, mortality was 61.2% in those with AKI requiring dialysis, 14.1% in those with AKI not requiring dialysis, and only 0.68% in those who did not develop AKI. In a study of ICU patients with AKI, 64% required dialysis; in-hospital mortality was 37%, and 50% of patients died or failed to recover renal function.

In hospitalized patients with AKI caused by ATN, about one fourth to one third of deaths occur during the diuretic phase. This is not surprising, because with the availability of dialysis, the most important determinant of the outcome is not the uremia itself but, rather, the underlying disease causing AKI. Infection is a common cause of death in patients with AKI. In the majority of patients who survive the acute episode, renal function essentially returns to normal. However, recent data indicate that an increasing proportion of AKI survivors progress to CKD and ultimately to ESRD, particularly in the elderly population. It has also been suggested that repeated episodes of AKI may accelerate progression of kidney disease.

The authors have no commercial relationships with manufacturers of products or providers of services discussed in this chapter.

References


54. Hutchinson CA, Bradwell AR, Cook M, et al. Treatment of acute renal failure secondary to multiple myeloma with


