

VI ACUTE RENAL FAILURE

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Definitions

Acute renal failure (ARF) can be broadly defined as an abrupt decrease in renal function sufficient to result in retention of nitrogenous waste (e.g., blood urea nitrogen [BUN] and creatinine). ARF can result from a decrease in renal blood flow (prerenal azotemia), intrinsic renal parenchymal diseases (renal azotemia), or obstruction of urine flow (postrenal azotemia) [see Table 1]. The most common intrinsic renal disease that leads to ARF is acute tubular necrosis (ATN). ATN is characterized by an abrupt and sustained decline in glomerular filtration rate (GFR) that occurs within minutes to days in response to an acute ischemic or nephrotoxic insult. Its clinical recognition is based largely on exclusion of prerenal and postrenal causes of sudden azotemia, followed by exclusion of other causes of intrinsic ARF (e.g., glomerulonephritis, acute interstitial nephritis, and vasculitis). Although the term acute tubular necrosis is not an entirely valid histologic description of this syndrome, the term is ingrained in clinical medicine and is therefore used in this subsection.

Epidemiology

The frequency of ARF varies greatly, depending on the clinical setting. The incidence of ARF has been cited as 1% on admission to the hospital and from 2% to 5% during hospitalization.^{1,3} In a study of 2,216 medical and surgical patients, 5% of patients developed ARF; of those cases, 55% were associated with iatrogenic factors—mostly adverse drug effects—and sepsis.¹

The incidence of severe ARF in adults in Western countries is approximately 140 per million population per year; 50 to 70 per million population per year require dialysis.⁴

Acute Renal Failure in the Hospitalized Patient

ETIOLOGY

In hospitalized adults, prerenal azotemia is the single most common cause of acute renal failure, accounting for 30% to 60% of all cases.⁵ In the hospital setting, 1% to 10% of cases of ARF are associated with postrenal azotemia; such cases are easily treated.⁵ ARF associated with postrenal azotemia is more of a consideration in the elderly male patient, especially if the patient is receiving medications that could impair bladder function. ATN is the most common intrinsic renal disease leading to ARF. Multiple insults are usually present, but often the predisposing factor is prerenal azotemia. Iatrogenic causes, including sepsis and nephrotoxins, cause a large portion of ARF cases. Approximately 40% to 60% of cases of ATN occur in the postoperative or trauma setting. When prerenal and postrenal causes of ARF have been excluded, about 75% of hospitalized patients with ARF will have ATN.⁵ Depending on the clinical setting, other diagnoses to be considered are acute interstitial nephritis (e.g., secondary to use of methicillin), glomerulonephritis, atheromatous emboli (in association with previous aortic surgery, aortography, or both), ureteral obstruction (in association with pelvic or abdominal pathology or secondary to complications of pelvic or abdominal surgery), or intrarenal obstruction (e.g., acute uric acid nephropathy).

PATHOPHYSIOLOGY

Prerenal Azotemia

Prerenal ARF occurs when there is a reduction in glomerular perfusion, either from an absolute reduction in the volume of extracellular fluid (e.g., hypovolemia) or in conditions in which the effective circulating volume is reduced despite a normal total extracellular fluid volume (e.g., congestive heart failure, advanced cirrhosis, and septic states). The kidney has the capacity to autoregulate GFR and blood flow simultaneously during renal hypoperfusion through the independent regulation of afferent and efferent arteriolar tone. While the afferent arteriole dilates in response to renal hypoperfusion, the efferent arteriole constricts, maintaining glomerular intracapillary pressure, 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 BUN and creatinine levels remain normal during this phase. Only when prerenal conditions become severe and renal adaptive mechanisms cannot compensate does GFR fall and do the BUN and creatinine levels begin to increase.

Table 1 Causes of Acute Renal Failure

- I. Prerenal azotemia
 - A. Absolute decrease in effective blood volume
Hemorrhage, skin losses (burns, sweating), gastrointestinal losses (diarrhea, vomiting), renal losses (diuretics, glycosuria), fluid pooling (peritonitis, burns)
 - B. Relative decrease in blood volume (ineffective arterial volume)
Congestive heart failure, sepsis, anaphylaxis, liver failure
 - C. Arterial occlusion
Bilateral thromboembolism, thromboembolism of solitary kidney
- II. Renal azotemia
 - A. Vascular causes
Vasculitis, malignant hypertension, microscopic polyarteritis
 - B. Acute glomerulonephritis
Postinfectious glomerulonephritis, anti-basement membrane-antibody disease
 - C. Acute interstitial nephritis
Drug-associated acute interstitial nephritis (methicillin nephrotoxicity)
 - D. Acute tubular necrosis
 1. Ischemia
Prerenal azotemia (if severe enough), postsurgical complication
 2. Sepsis syndrome
 3. Nephrotoxicity
 - a. Exogenous nephrotoxins
Antibiotics (aminoglycosides, cephalosporin, amphotericin B); iodinated contrast agents; chemotherapeutic agents (cisplatin); solvents (carbon tetrachloride, ethylene glycol)
 - b. Endogenous nephrotoxins
Intratubular pigments (hemoglobinuria, myoglobinuria), intratubular proteins (myeloma), intratubular crystals (uric acid, oxalate), tumor lysis syndrome
- III. Postrenal azotemia (obstruction of collecting system)
Bladder outlet obstruction, bilateral ureteral obstruction (unusual), ureteral obstruction in a solitary kidney

Table 2 Diagnostic Evaluation of a Patient with Acute Renal Failure

Types of Evaluation	Comments
<i>Chart Review</i>	
Previous renal function	Patients with previous renal insufficiency are more susceptible to ARF
Medications	Aminoglycosides are important causes of ATN in hospitalized patients (nonoliguric and in the first 2 wk of therapy); certain antibiotics, NSAIDs, and a host of medications can cause AIN; contrast agents are an important cause of ARF
Start date	
Drug levels	
Nephrotoxins?	
NSAIDs?	
Aminoglycosides?	
Amphotericin B?	
Contrast agent used?	
Surgery	Cardiac and vascular surgery patients are particularly susceptible to ATN
Type and duration	
Hemodynamics	
Blood loss	
Anesthetic used	Methoxyflurane and enflurane (which is related to methoxyflurane but is less toxic) can cause nonoliguric ATN
Infection	Infection or sepsis can cause ARF even in the absence of hypertension
Fever?	
Positive blood cultures?	
Hemodynamics	Hypotension can cause prerenal azotemia and ischemic ATN
Blood pressure	
Heart rate	
Weight (in and out)	
<i>Physical Examination</i>	
Volume status	
Edema?	Pretibial in the ambulatory patient, sacral in the bedridden patient
Jugular vein distention?	
Crackles?	
S ₃ gallop?	
Skin	
Diffuse rash?	
Livedo reticularis?	
Atheroemboli?	
Bladder	Distended bladder
Suprapubic fullness	To assess postvoid residual urinary volume and to relieve bladder obstruction
Bladder catheterization	
<i>Urinalysis and Sediment Analysis</i>	
Elements	
Protein and blood	
Cellular	
Cast	
<i>Urine Indices</i>	
See Table 4	
<i>Additional Tests</i>	
Renal ultrasonography	A finding of kidneys of different size suggests vascular disease in the smaller kidney
Size and symmetry	
Corticomedullary differentiation	
Obstruction	
Indication for renal biopsy	

AIN—acute interstitial necrosis ARF—acute renal failure ATN—acute tubular necrosis NSAIDs—nonsteroidal anti-inflammatory drugs

Acute Tubular Necrosis

Although an initial decrease in renal blood flow appears to be a requisite for the development of ischemic ATN, blood flow returns nearly to normal within 24 to 48 hours after the initial insult. Despite adequate renal blood flow, tubular dysfunction persists, and the GFR remains depressed. Leakage of glomerular ultrafiltrate from the tubular lumen into the renal interstitium across the damaged renal tubular cells, obstruction of flow by debris or crystals in the lumen of the tubules, and a decrease in the glomerular capillary ultrafiltration coefficient have all been proposed as playing a pathophysiologic role in ATN.

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

Despite the common use of the term acute tubular necrosis, necrosis of the tubules is seen infrequently in either ischemic or nephrotoxic ARF. Cell death may be of two kinds: apoptotic or necrotic. Recent advances in the understanding of cell death has led to the recognition that the pathways traditionally associated with apoptosis may be very critical in determining the form of cell injury associated with necrosis. Recent evidence indicates that apoptotic pathways, in which endonucleases play an important role, are regulated by mediators such as oxidants, caspases, and ceramide. The pathway that is followed by the cell is dependent on both the nature and the severity of insults. 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 proinflammatory and chemotactic genes. It is also likely that the cascades that lead to either the apoptotic or the necrotic mode of cell death are activated almost simultaneously and may share some common pathways.

Table 3 Daily Evaluation and Management of the Hospitalized Patient with Acute Renal Failure

Weight	Weight loss of 0.5 to 1 lb/day in a patient with ATN will help prevent volume overload
Jugular vein distention or crackles	Indicate volume overload with possible congestive heart failure; restrict volume, add diuretics, consider dialysis
CVP, PCWP	Assessment of these parameters may be indicated to differentiate volume overload from the presence of noncardiogenic pulmonary infiltrates; low PCWP suggests noncardiogenic pulmonary edema
Intake/output	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
Blood urea nitrogen	Disproportionately high values suggest gastrointestinal bleeding, steroid use, hypercatabolic state, or prerenal ARF
Creatinine	Disproportionately high values suggest muscle breakdown, as caused by rhabdomyolysis
Electrolytes	[see Complications, in text]

ARF—acute renal failure ATN—acute tubular necrosis CVP—central venous pressure PCWP—pulmonary capillary wedge pressure

					First Day for Elevated Creatinine		
Date							
Weight							
Input							
Output							
Blood Pressure							
Pulse							
Temperature							
BUN							
Creatinine							
Sodium							
Potassium							
Chloride							
CO ₂							
WBC							
Hgb							
Hct							
Platelet							
Surgery							
Contrast							
Medications							

Figure 1 This figure shows the timeline for the treatment of acute renal failure. The chart may be used to outline 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)

DIAGNOSIS

Clinical Presentation

Presenting symptoms suggestive of ARF include a decrease in urine output, dark urine, cola-colored urine, and symptoms suggestive of uremia, such as fatigue, weakness, nausea, vomiting, loss of appetite, metallic taste in the mouth, itching, confusion, fluid retention, and hypertension.

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.

Chart Review, History, and Physical Examination

Determination of the cause of ARF depends on a systematic approach, which should start by excluding and correcting both prerenal and postrenal azotemia. The difficulty in arriving at a correct diagnosis in a hospitalized patient is not in failing to identify a possible etiology for the ARF but often just the opposite—that is, the difficulty lies in determining the actual cause among several possible causes of ARF. Correct diagnosis depends on careful analysis of available data, on the clinical course of the individual patient with ARF, and on examining the chronologic sequence of events in the deterioration in renal function. The correct diagnosis also requires knowledge of the natural history of the different causes of ARF.

The evaluation of the patient with ARF 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 Tables 2 and 3 and Figure 1]. Reduced body weight, postural changes in blood pressure and pulse, and decreased jugular venous pulse 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 uncover a distended, tender bladder, indicating lower urinary tract obstruction. In any patient in whom lower tract obstruction is suspected as a cause of acute azotemia, examination of the prostate and a sterile diagnostic postvoid bladder catheterization should be performed as a part of the physical examination.

Additional findings that may be helpful are fever and rash, which occur in some patients with acute interstitial nephritis (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.

Differentiating prerenal azotemia from ATN may be difficult, partly because of the difficulty in evaluating the volume status in a critically ill patient and because any cause of prerenal azotemia, if severe enough, may lead to ATN. Evaluation of the

urine volume and urine sediment and a number of urinary indices (most useful in patients with oliguria) are particularly helpful in making the correct diagnosis.

LABORATORY TESTS

Ratio of Blood Urea Nitrogen to Creatinine

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 an elevation in BUN include gastrointestinal 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.

Urinary Volume

Urinary volume is often less than 400 ml/day in patients with oliguric ATN. Nonoliguric ATN is common and has various causes, including nephrotoxic antibiotic-induced ARF. On the other hand, anuria (i.e., urinary output of less than 100 ml/day) should suggest a diagnosis other than ATN, the most easily correctable being obstruction. Widely varying daily urinary output also suggests obstruction. Vascular events should be a consideration in a patient with abrupt anuria; such events include renal vein or renal artery thrombosis or large emboli in the renal arteries. To cause total anuria in a patient with two functioning kidneys, such a vascular event would have to affect both kidneys; naturally, if the patient had a single functioning kidney, the vascular event would only have to affect the functioning kidney.

Urinalysis and Urine Sediment

In prerenal failure, a moderate number of hyaline and finely granular casts may be seen on urinalysis; coarsely granular and cellular casts are seen infrequently. In ATN, the urine sediment consists of dirty-brown, granular casts and both free renal tubular epithelial cells and epithelial cell casts. A "benign" urine sediment containing few formed elements should alert the physician to the possibility that obstruction is present. In ARF associated with intratubular oxalate (e.g., methoxyflurane anesthesia) or uric acid deposition (associated with acute hyperuricemia after chemotherapy of neoplastic disease), the sediment contains abundant oxalate or uric acid crystals, respectively.

Distinguishing between Prerenal Azotemia and Acute Tubular Necrosis

Urinary indices are often used to differentiate prerenal azotemia from ATN. The rationale for the use of these indices is as follows: 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, owing to the reduction in the amount of glomerular filtrate entering each nephron and to 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 4]. In contrast, in ARF associated with 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}). Interpretations of

Table 4 Urinary Diagnostic Indices

Indices	Prerenal Azotemia	Acute Tubular Necrosis
Urinary sodium (U_{Na}) (mEq/L)	< 20	> 40
Urine osmolarity (U_{osm}) (mOsm/kg H_2O)	> 500	< 450
Fractional excretion of sodium ($U_{Na}P_{Cr}/P_{Na}U_{Cr}$) (100)	< 1%	> 1%
BUN-to-creatinine ratio	> 20:1	—
Urine creatinine-plasma creatinine [U_{Cr} (mg/dl)/ P_{Cr} (mg/dl)]	> 40	< 20

BUN—blood urea nitrogen P_{Cr} —plasma creatinine P_{Na} —plasma sodium

these tests, however, 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, may present with all the clinical characteristics of ATN but with rates of FE_{Na} of less than 1%.

OTHER DIAGNOSTIC TESTS AND RENAL BIOPSY

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

Radionuclide methods are available for assessing renal blood flow and excretory (secretory) function. Blood flow studies can be used to easily determine whether renal blood flow is occurring and, if so, whether the blood flow to the two kidneys is symmetrical; such tests are less accurate in quantitating absolute rates of flow.

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

Community-Acquired Acute Renal Failure

ETIOLOGY

Azotemia that first occurs outside the hospital may be either acute or chronic. Useful points in determining whether the renal failure is acute or chronic are summarized [see Table 5]. The majority of patients who present with advanced azotemia have chronic renal failure.

The preponderance of cases of ARF occur in the elderly; this is possibly related to the anatomic and physiologic changes of aging. In a study evaluating 748 patients presenting with ARF, 36% were older than 70 years.⁶ Frequent causes of community-acquired ARF are hypovolemia, ingestion of over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) and prescription medications, and obstruction. Before a detailed evaluation is carried out, priority should be given to identifying complications of renal failure that may be lethal unless treated promptly. Some of

these, such as marked fluid overload and pericardial tamponade, may be detected on clinical examination. However, life-threatening complications, such as severe hyperkalemia or extreme metabolic acidosis, require laboratory evaluation. The electrocardiogram is valuable in assessing the effects of hyperkalemia on the heart [see Complications, *below*]. Even before the underlying disease that is causing the azotemia is known, often a decision to initiate dialysis has to be made. Dialysis should be instituted promptly in patients with severe hyperkalemia, acidosis, marked fluid overload, or signs or symptoms of uremia. Many manifestations of uremia are nonspecific. However, a pericardial rub or neurologic manifestations, such as asterixis or confusion, are indications for prompt dialysis.

After serious electrolyte and acid-base imbalances have been addressed, other clinical information important in the evaluation can be ascertained.

DIAGNOSIS

Clinical Presentation

A patient presenting with ARF 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, symptoms may include changes in mental status and seizures. The recent introduction of new medications may suggest drug-related renal injury. A history of nausea, vomiting, diarrhea, or other volume losses suggests ARF resulting from a prerenal condition. A history of recent trauma with muscle injury suggests rhabdomyolysis as the cause of ARF. Fever, skin rash, and joint pains raise the possibility of a rheumatic disease, such as systemic lupus erythematosus, vasculitis, endocarditis, or drug allergy with acute interstitial nephritis. A history of shortness of breath or pulmonary hemorrhage suggests a pulmonary renal syndrome, such as Goodpasture syndrome, Wegener granulomatosis, Churg-Strauss edema, or pulmonary edema associated

with acute glomerulonephritis. 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.

Urinalysis and Urine Sediment

In an outpatient setting in which prerenal and postrenal causes have been excluded, ARF is more often caused by other renal parenchymal diseases. Examination of the urine for blood and protein and of the urine sediment can give valuable information that often helps narrow considerably the diagnostic possibilities and to suggest further appropriate laboratory evaluation.

The following is a list of findings on urinalysis, including urine sediment analysis, and their implications for renal failure.

1. In prerenal failure, a moderate number of hyaline and finely granular casts may be seen, but coarsely granular and cellular casts are infrequent.
2. In ATN, the sediment is usually quite characteristic and is found in 70% to 80% of patients; it consists of dirty-brown, granular casts and both free renal tubular epithelial cells and epithelial cell casts.
3. A "benign" urine sediment containing few formed elements should alert the physician to the possibility that obstruction is present.
4. Findings of 3+ to 4+ protein, 2+ to 3+ blood, and active sediment, defined as sediment containing red blood cells (RBCs) and RBC casts, are characteristic of proliferative glomerulonephritis. 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 either urine that is strongly heme positive or supernatant that is heme positive (after having removed the RBCs by

Table 5 Features That Help Differentiate between Acute and Chronic Renal Failure

	<i>Acute Renal Failure</i>	<i>Chronic Renal Failure</i>
Previous laboratory assay	Normal renal function	Abnormal renal function is documented on old laboratory studies
Medical history	None	Longstanding and poorly controlled diabetes, hypertension, and severe vascular disease are risk factors
Renal ultrasonography	Normal	Small, echogenic kidneys; patients with diabetes, HIV, multiple myeloma/amyloidosis, and polycystic kidney disease may have large kidneys
Bone films	Normal	Possible evidence of renal osteodystrophy with osteitis fibrosa, osteomalacia, mixed and adynamic bone lesions, and dialysis-related amyloidosis; subperiosteal erosions of the phalanges and tuft; bone cysts with amyloidosis
Hemoglobin/hematocrit	Anemia is possible, but a normal hemoglobin level in a patient with advanced azotemia is presumptive evidence of acute renal failure	Anemia is common

centrifugation) usually indicate myoglobinuria or hemoglobinuria. Patients with rhabdomyolysis have a marked increase in the level of muscle enzyme, such as creatinine phosphokinase. The urine sediment in patients with myoglobinuria may show RBCs, pigmented casts, granular casts, and numerous uric acid crystals.

6. The presence of leukocytes with white blood cells (WBCs) in clumps and in cast, in the absence of evidence of bacteria, suggests AIN. This can be associated with microscopic hematuria and RBC cast.

Renal Ultrasound

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 acute rather than chronic renal failure; however, several important causes of chronic renal failure, including diabetes mellitus, HIV, multiple myeloma, and amyloidosis, may be associated with normal-sized kidneys. The renal ultrasound examination is also helpful in diagnosing or ruling out obstruction; making a diagnosis of polycystic kidney disease; determining whether one or two kidneys are present; and localizing the kidney for renal biopsy.

Specific Causes of Acute Renal Failure

EXOGENOUS NEPHROTOXINS

Radiocontrast

Radiocontrast is a common cause of hospital-acquired ARF.⁷ In patients with normal renal function who have no other risk factors for ARF, the incidence of contrast-induced renal injury is low (< 1%). The most important risk factor is preexisting renal insufficiency; other risk factors include diabetes,⁸⁻¹³ volume depletion, and concomitant exposure to other nephrotoxins. A meta-analysis of 31 controlled, randomized 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.¹⁴ 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 ARF, because these agents are associated with less nephrotoxicity. Preliminary research has suggested that iso-osmolar contrast agents may be even less nephrotoxic than low-osmolar agents.

Extracellular fluid volume expansion, through use of sodium chloride, plays a key role in the prevention of contrast-induced ARF.^{12,15-17} High-risk patients should be kept well hydrated by administration of half-normal saline at the rate of 1 ml/kg/hr for 8 to 12 hours before and after the procedure. The addition of diuretics and mannitol to accelerate diuresis has not been shown to provide any benefit over volume expansion alone, and it may be harmful. However, if needed, diuretics may be useful for fluid management in patients with volume overload or low cardiac output. For patients at high risk for contrast-induced ARF, 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 the evaluation of the high-risk patient, con-

sideration should be given to the use of diagnostic procedures that do not require contrast.

Fenoldopam, a selective D₁ dopamine receptor agonist that causes both systemic and renal arteriolar vasodilatation, is being investigated for the prevention of radiocontrast nephropathy in high-risk patients.¹⁸

Nephrotoxic Drugs

Aminoglycosides For the aminoglycosides (e.g., tobramycin, gentamicin, amikacin), the most important manifestation of nephrotoxicity is ARF secondary to ATN, which occurs in about 10% to 20% of patients receiving aminoglycosides.^{19,20} Maintaining blood levels in the therapeutic range reduces but does not eliminate the risk of nephrotoxicity. Aminoglycoside-associated ARF 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.¹⁹ Several clinical factors or conditions can potentiate the effect of aminoglycosides on the kidney and can thus potentiate nephrotoxicity; these include renal ischemia induced by hypotension or volume depletion^{21,22}; the dosing schedule and the serum levels of aminoglycosides^{23,24}; sepsis; administration of other nephrotoxins; and liver disease.^{20,25} It has been shown that once-daily dosing of aminoglycosides is as effective in controlling infection as more frequent dosing, with less nephrotoxic effect; there is no difference in the incidence of ototoxicity between once-daily dosing and more frequent dosing.^{23,26-29} Therefore, when aminoglycosides are indicated, once-daily dosing is recommended.

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

Nonsteroidal anti-inflammatory drugs NSAIDs are potent inhibitors of prostaglandin synthesis, a property that contributes to their nephrotoxic potential in certain high-risk patients who require the use of prostaglandins for renal vasodilatation. The most frequent pattern of injury that is related to the use of NSAIDs is prerenal azotemia; this is particularly the case for patients who are either experiencing volume depletion or who have a reduced effective circulating volume. Susceptible persons include those with congestive heart failure, cirrhosis, diabetes, chronic renal disease, nephrotic syndrome, and septic shock, as well as those of advanced age or who require use of a diuretic.³⁰ 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, often associated with renal insufficiency and marked proteinuria.³¹ This complication appears to be an idiosyncratic reaction and is particularly associated with the use of propionic acid derivatives, such as ibuprofen, naproxen, and fenoprofen.³² In contrast to AIN associated with other drugs, in AIN associated with NSAIDs, there is a low incidence of symptoms of hypersensitivity and of eosinophilia.

This disorder usually resolves with discontinuance of the offending agent.³³ High-risk patients should be educated about the risk of using NSAIDs, and they should be advised to avoid these medications if possible.

Cisplatin Renal injury is a well-recognized complication of the use of cisplatin for the management of many carcinomas. 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 increases, 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 isotonic saline (200 to 250 ml/hr) before administration of cisplatin³⁴; known nephrotoxins should be avoided whenever possible. The usual lesion is that of ATN, but with severe damage or recurrent administration of the drug, chronic interstitial disease may ensue.

Angiotensin-converting enzyme inhibitors ARF that is associated with the use of angiotensin-converting enzyme (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 30% increase from baseline in serum creatinine levels is acceptable when ACE inhibitors are initiated.³⁵ 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, discontinuance of the medication should allow renal function to return to baseline if no other insults have occurred.

Ethylene Glycol Toxicity

Ethylene glycol is a colorless, odorless, sweet 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:

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

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

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. This difference was thought to be the result of the use of automated laboratory analysis techniques that use ion-selective electrodes.³⁶

The osmolar gap is calculated on the basis of the difference between the measured and calculated osmolality. The calculated osmolar gap is derived by use of the serum sodium, glucose, and urea levels, which are routinely measured in clinical care. 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.³⁷ The key clinical findings in patients who have ingested ethylene glycol are initial disorientation and agitation, with pro-

gression to central nervous system depression, renal failure, metabolic acidosis, respiratory failure, and circulatory insufficiency.³⁸ 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. ARF generally manifests after 48 to 72 hours.

Aggressive intervention should be initiated at the time of diagnosis. Intervention should consist of use of intravenous sodium bicarbonate to enhance renal clearance of glycolate through ion trapping; intravenous ethanol or fomepizole (Antizol) to block the metabolism of ethylene glycol; and hemodialysis for the removal of ethylene glycol and glycolate.³⁹ Regular monitoring of the osmolar gap (corrected for ethanol level if I.V. ethanol is being used during treatment) and the anion gap will help guide therapy during hemodialysis.³⁷

ENDOGENOUS NEPHROTOXINS

Rhabdomyolysis

Since the first description of the causative association between rhabdomyolysis and ARF with regard to the crush injuries of World War II, the spectrum of 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; and infections.⁴⁰ Some important metabolic derangements that can cause rhabdomyolysis include hypokalemia and hypophosphatemia; 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 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors in the treatment of hypercholesterolemia also contribute to or cause rhabdomyolysis. Muscle pain and dark-brown orthotoluidine-positive urine in which RBCs are absent are important diagnostic clues, but the diagnosis must be confirmed by findings of elevated creatine phosphokinase and myoglobin levels. About one third of patients with rhabdomyolysis develop ARF; in these patients, ARF is frequently associated with hyperkalemia, hyperuricemia, hyperphosphatemia, early hypocalcemia, and a reduced BUN-to-creatinine ratio because of excessive creatinine release from muscle. Late hypercalcemia is also a typical feature of the disease. Early recognition of rhabdomyolysis and initiation of treatment are the keys to minimizing ARF. These patients commonly develop hypovolemic shock, particularly when the injury is associated with trauma and massive muscle crushing.

The most important aspect of management is rapid volume repletion. When patients are encountered in the field, treatment with intravenous normal saline, 200 to 300 ml/hr, should be initiated. If urine output increases in 4 to 6 hours, the solution should be continued to match the urine output until the rhabdomyolysis resolves. However, if the patient continues to be oliguric (i.e., the patient's urine output is less than 400 ml/day), the infusion should be discontinued and the patient treated conservatively for ARF. Experience from recent disasters has shown that early aggressive hydration and alkalization are capable of preventing myoglobinuric ARF by protecting the kidney from the nephrotoxicity of myoglobin and urate.⁴¹ Therapy consists of the administration of sodium bicarbonate and 5% dextrose in water (D5W) in a ratio of three ampules of sodium bicarbonate to 1 L of D5W at

a rate of 250 ml/hr. The metabolic alkalosis induced will help protect the patient from hyperkalemia, which can be a lethal complication of rhabdomyolysis. Urinary alkalization is considered by some investigators to be controversial because such an approach is not superior to saline diuresis and because it may contribute to intratubular calcium and phosphate deposition.⁴²

A clinical presentation that is similar to that of rhabdomyolysis occurs after the release of heme pigments after intravascular hemolysis.

Hyperuricemic Acute Renal Failure

ARF may occur in patients with malignancies that are associated with a high rate of tumor cell turnover. Such turnover may occur either spontaneously or after chemotherapy has been initiated; high cell turnover is particularly associated with poorly differentiated lymphomas and acute lymphoblastic leukemia. There may be an increase in uric acid production and hyperuricosuria, causing uric acid nephropathy. In addition, during massive cell lysis, phosphate and potassium are released in large amounts, resulting in hyperphosphatemia and hyperkalemia. In some patients, the precipitation of calcium and phosphate in the renal tubules can induce ARF independently of and in addition to uric acid deposition. The peak uric acid level is often greater than 20 mg/dl, and a ratio of uric acid to creatinine concentrations greater than 1 to 1 suggests the diagnosis of acute uric acid nephropathy.

Prevention of ARF involves establishing a urinary output of greater than 3 to 5 L/24 hr and initiating treatment with allopurinol before institution of cytotoxic therapy. By establishing a high urinary output, high intratubular pressure is achieved. This in turn leads to the prevention of intratubular obstruction. Allopurinol is a xanthine oxidase inhibitor; it thus blocks the synthesis of uric acid. It should be administered in doses of 300 to 600 mg/day; therapy should begin 3 days before initiation of chemotherapy. In patients with initial hyperuricemia, allopurinol should be initiated and chemotherapy delayed until the serum uric acid concentration has become normal. Urinary alkalization increases the solubility of xanthine and enhances its excretion. Urinary alkalization can be achieved by the infusion of sodium bicarbonate in amounts sufficient to keep the urinary pH above 7. Acetazolamide inhibits the reabsorption of sodium bicarbonate in the proximal tubule, thereby making the tubular fluid and the urine alkaline. Acetazolamide can be added to the interventions described above.

The development of oliguria with hyperuricemia may be an indication for dialysis even before severe renal impairment or uremic manifestations are present.

Hepatorenal Syndrome

The hepatorenal syndrome 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. It closely resembles prerenal failure except that it does not respond to conventional volume replacement. It is thought that the underlying etiology is related to significant reductions in renal perfusion associated with splanchnic vasodilatation.⁴³ In the United States and Europe, the great majority of cases of hepatorenal syndrome occur in patients with advanced alcoholic cirrhosis. Hepatorenal syndrome may begin insidiously over a period of weeks to months or may appear suddenly and cause severe azotemia within days. The common precipitating causes are deterioration of liver function; sepsis; the use of nephrotoxic antibiotics or NSAIDs; overzealous use of di-

uretics; diarrhea; or GI bleeding. Hepatorenal syndrome 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. An important step in management is to exclude reversible prerenal azotemia. Because hepatorenal syndrome and prerenal azotemia have similar urinary diagnostic indices, one must often use a functional approach, such as the administration of volume expanders, to differentiate between these two entities. Once a diagnosis of hepatorenal syndrome is established, there is no specific treatment; management is conservative. If the patient is hypotensive, steps to improve the blood pressure may lead to improvement in renal perfusion and thus stabilization of renal function.

In patients at risk for hepatorenal syndrome, the probability of developing this syndrome is 18% at 1 year and 39% at 5 years.⁴⁴ Without liver transplantation, the mortality is 80% to 95%.

ACUTE RENAL FAILURE RELATED TO PREGNANCY

In industrialized nations, ARF rarely occurs in association with pregnancy. The incidence is approximately one in 20,000 deliveries.⁴⁵ The low incidence is directly related to legalization of abortion in many countries.⁴⁵

ARF associated with infection that occurs after an abortion may be precipitated by hypotension, hemorrhage, sepsis, and disseminated intravascular coagulopathy. Although many organisms can be involved, the most serious and common infection associated with ARF is that caused by *Clostridium* species. The clinical picture may be associated with hemolysis resulting from the production of a toxin. Aggressive management with broad-spectrum antibiotics and dialysis are the mainstays of therapy for these patients.

Pyelonephritis or urinary tract infections are among the most common medical complications of pregnancy. Approximately 25% of pregnant patients with pyelonephritis develop a transient decline in GFR.⁴⁶ These patients should be treated initially with intravenous antibiotics, followed by up to 2 weeks of therapy with oral antibiotics.

In the third trimester, ARF is associated with and secondary to complications of pregnancy; such complications include preeclampsia, postpartum hemorrhage, amniotic fluid embolism, placental abruption, and retained fetal/placental parts. A renal failure pattern similar to that of ATN is seen in patients suffering from preeclampsia and peripartum hemorrhage. Bilateral cortical necrosis may occur in association with any type of ischemic injury; the incidence seems disproportionately higher in pregnant patients than in nonpregnant adult patients. Although abruptio placentae can also cause ATN, renal cortical necrosis is the most common cause of ATN. The HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome has been associated with ARF in up to 7.7% of patients.

Postpartum ARF, also known as postpartum hemolytic-uremic syndrome (HUS), is characterized by hypertension and microangiopathic hemolytic anemia. It can occur anytime from postpartum day 1 to several months after delivery, the most common period being from postpartum week 2 to week 5. Glomerular lesions resemble those found in adult HUS; lesions are characterized by fibrin deposition, thickened capillary walls,

and subendothelial swelling associated with large granular subendothelial deposits. The mainstay of treatment is plasma exchange; current maternal survival rates are from 70% to 80% (before the advent of plasma exchange therapy, mortality was 90%).^{47,48} Pregnancy-associated HUS has been documented in sisters, and there is an increased incidence of recurrence in a person who has suffered a previous episode. Pregnancy-associated HUS is associated with elevations in the lactate dehydrogenase (LDH) level; the HELLP syndrome, in contrast, is associated with elevations in transaminase levels. This difference is useful in distinguishing between these two syndromes.

Other underlying renal disorders may be present 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 occur in patients with a history of lupus nephritis or extrarenal lupus. Complement levels are typically elevated during pregnancy; thus, it may be helpful to include assessment of complement levels in the serologic evaluation. 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 ARF can be present in the pregnant patient and should be considered. After the 20th week of gestation, ARF in a patient with hypertension is most likely the result of preeclampsia.

ACUTE INTERSTITIAL NEPHRITIS

Although AIN is an uncommon cause of ARF, the diagnosis should not be overlooked, because it requires specific intervention. AIN has been shown in some cases to be an immunologically induced hypersensitivity reaction to an antigen, usually a drug. AIN is detected in 2% to 3% of all renal biopsies that are performed, but it is detected in up to 25% of renal biopsies that are performed specifically in the setting of drug-induced ARF. The most common drugs involved in the induction of AIN are NSAIDs and antibiotics [see 10:VIII *Tubulointerstitial Diseases and Table 2*].⁴⁹

The diagnosis of 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 cast 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.

The definitive diagnosis is made by renal biopsy. Noninvasive techniques suggestive of AIN, which may include an increased urine eosinophil count (using Hansel stain) and a positive gallium scan, are not specific.

Management of Acute Renal Failure

The signs and symptoms of ARF 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 HCO₃⁻ decreases to a steady-state level of 17 to 18 mEq/L. The serum potassium concentration ([K⁺]) need not rise appreciably unless there is a hypercatabolic state, GI bleeding, or extensive tissue trauma.

EMERGENT INTERVENTION

Hyperkalemia is a life-threatening complication of ARF that often necessitates urgent intervention. The electromechanical effects of hyperkalemia on the heart are potentiated by hypocalcemia, acidosis, and hyponatremia. Thus, the ECG, which measures the summation of these effects, is a better guide to therapy than a single determination of [K⁺]. It must be emphasized that the most common biochemical abnormality responsible for death in patients with ATN is hyperkalemia. 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

Because ATN is inherently a catabolic disorder, patients with ATN 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/kg of protein a day. The use of hyperalimentation with 50% dextrose and essential amino acids has had little effect on minimizing mortality and morbidity in patients with ATN, except in patients who also have significant burns.

DIALYSIS

Indications for initiating dialysis are (1) severe hyperkalemia, acidosis that is not easily controlled by medical treatment, or both and (2) fluid overload that is not responsive to fluid restriction, diuretics, or both. In the absence of any of these indications, most nephrologists advocate dialysis when BUN 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 at less than 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 ARF. Monitoring of blood concentrations of drugs is an important adjunct to effective treatment.

In a patient who receives appropriate therapy with early dialysis, many of the uremic manifestations associated with ARF 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

There are no clinical data to support the use of low-dose dopamine for the protection or improvement of renal function in patients with ATN or ARF. In a multicenter study comparing dopamine with placebo, dopamine was not found to improve survival or eliminate the need for dialysis.⁵⁰ In both animal and human studies, use of low-dose dopamine was found to be associated with an increase in renal blood flow and natriuresis in the context of euolemia and normal renal function.

Complications

VOLUME OVERLOAD

Volume overload is one of the first manifestations of ARF caused by salt and water retention secondary to a decrease in

GFR. In an aggressive attempt to reverse ARF or to treat oliguria, intravenous fluids may be given; however, they will subsequently contribute to volume overload. It is important that patients with ARF be evaluated daily for volume status. This evaluation includes assessment of weight, blood pressure, and heart rate, and a physical examination should be conducted. The physical examination should be directed specifically toward the detection of skin turgor, peripheral edema, and pulmonary edema; a cardiac examination should be undertaken to detect a third heart sound. In the patient evaluation, it is beneficial to review the records of daily intake and output of fluids, but insensible fluid losses as well as weight loss resulting from a high catabolic state^{51,52} must be taken into consideration. The typical patient loses about 200 to 300 g of body weight a day as a result of catabolism, and the average 70 kg patient has insensible losses of around 850 to 1,000 ml/day. In determining the patient's weight, it is beneficial to use the same scale every day; it should be borne in mind that the daily records of fluid intake and output can be very inaccurate.

The most useful therapy for volume overload is loop diuretics.^{53,55} Furosemide can be given intravenously as a bolus or by continuous infusion [see Table 6]. If started in the early stages of ARF, this intervention along with fluid restriction can be very beneficial in preventing or minimizing volume overload. The main risk of using high doses of furosemide is deafness, which can be transient or permanent.^{53,56} This risk is increased if the serum albumin level is low and if other ototoxic medications are being used simultaneously with furosemide.⁵⁷ If volume overload cannot be prevented and the patient remains oliguric, early intervention with dialysis should be considered.

There is no good evidence that the use of diuretics alters the course of ATN; however, in patients with fluid overload, diuretics may be useful in increasing urine output and preventing the need for dialysis.

HYPONATREMIA

In patients who have ARF that is related to a decrease in GFR and impaired tubular function, hyponatremia is a common problem. Usually, such hyponatremia is associated with hypervolemia.

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; too aggressive correction of a low serum sodium level can lead to central pontine myelinolysis (CPM) if the duration of electrolyte imbalance has been longer than 48 hours. The initial approach in a patient who is experiencing volume overload and who has hyponatremia is to administer loop diuretics and restrict free water. If symptoms of hyponatremia occur in a patient with ARF that is unresponsive to diuretic therapy or saline replacement therapy, the removal of free water may be warranted as the initial step in renal replacement therapy. Caution should be used when correcting hyponatremia. The sodium level should not be corrected too rapidly; the targeted rate of change of sodium level should be 1 to 2 mEq/L/hr until symptoms resolve or until the serum sodium level approaches 130 mEq/L. Therefore, continuous monitoring of the patient's condition and serum electrolyte panel on a 1- to 2-hour basis is warranted.

HYPERKALEMIA

Hyperkalemia is commonly encountered in patients with

Table 6 Furosemide Dosing

Bolus dosing	Initially, 20 mg I.V.; if no response in 30 min to 1 hr, the dose should be doubled to 40 mg If no response, the dose can be increased slowly until a response is achieved Dosing should be repeated every 8 to 12 hr to maintain diuresis Single bolus doses should not exceed 240 mg
Continuous infusion	Safer and more effective than bolus dosing in patients with refractory disease Initial I.V. bolus of 0.1 mg/kg (or a bolus dose previously determined to initiate diuresis) Continuous infusion of 0.1 mg/kg/hr; double every 2 hr to a maximum of 0.4 mg/kg/hr <i>or</i> After an initial bolus of furosemide, continuous infusion of 20 mg/hr If a diuresis is not sustained, a second, higher bolus is given, and the infusion rate is increased to 40 mg/hr Risk of toxicity increases with continuous infusion rates above 80 mg/hr
For refractory cases	Consider the addition of an intravenous thiazide diuretic Consider fluid removal via hemofiltration (dialysis)

ARF; causal factors include a decrease in GFR, a low rate of urinary flow to the collecting duct, distal tubular damage, and concomitant conditions that contributed to or are associated with ARF, such as rhabdomyolysis, acidosis, and the hypercatabolic state. ACE inhibitors 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 that is about 38-fold higher than the extracellular compartment. Thus, any process that leads to cellular destruction can contribute to hyperkalemia, especially in patients with ARF.

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; these findings call for prompt treatment. Other symptoms consistent with hyperkalemia include paresthesias, muscular weakness, and depressed deep tendon reflexes. These symptoms can progress to flaccid paralysis and acute respiratory failure. Severe hyperkalemia is life threatening and should be considered a medical emergency.

ACIDOSIS

A healthy adult produces 1 mEq/kg/day of hydrogen ions; this production is influenced to a large degree by dietary intake. The kidney plays a major role in acid-base balance through the excretion of nonvolatile acids and by the reabsorption and regeneration of bicarbonate.

Clinical manifestations of acidosis are partially related to the rapidity with which the acidosis develops. Patients with ARF who experience the rapid development of metabolic acidosis may present with Kussmaul respiration, which is characterized by deep inspiration and an increased respiratory rate. Other clinical manifestations 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 ARF should be treated more aggressively with intravenous sodium bicarbonate, renal replacement therapy, or both; continuous renal replacement therapy is the preferred approach. There are many risks associated with intravenous sodium bicarbonate replacement; thus, the critically ill patient should be monitored closely. 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.

OTHER ELECTROLYTE IMBALANCES

Hypocalcemia is a common finding in patients with ARF, but it rarely requires intervention. In patients with ARF, 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. The use of blood products that have been stored in citrate and the use of sodium bicarbonate infusions can contribute to a decrease in the serum calcium level. Calcium supplementation should be carried out with caution and should be undertaken only if it is clinically indicated.

Hypercalcemia is rare in patients with ARF and may be indicative of other underlying medical conditions. The most common underlying disorders are malignancies, particularly multiple myeloma. Hypercalcemia can occur in about 30% of patients during the recovery phase of ARF-associated rhabdomyolysis.

Hyperphosphatemia is common in patients with ARF. The primary mechanism underlying an elevation in the phosphate level is a decrease in renal excretion; tissue destruction and shifts from the intracellular to 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, including calcium salts (calcium carbonate or calcium acetate), aluminum hydroxide, or sevelamer, which is a cationic polymer that binds phosphate through ion exchange. These medications act by binding the phosphorus in the food while the food is still in the gut, thus preventing absorption into the bloodstream. Attempts should especially be made to lower the phosphate level if the calcium-phosphorus product is greater than 70, so that metastatic calcification in soft tissues can be minimized.

ANEMIA

Anemia occurs in 65% to 95% of patients with ARF. The anemia that is associated with ARF is of the normochromic-normocytic type. Patients with this type of anemia have normal levels of iron; results of bone marrow examination may be normal or show hypercellularity. In patients with ARF, 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. The most important cause of ARF-associated anemia is inadequate production of erythropoietin,⁵⁸ but in critically ill patients, a decrease in erythropoietin responsiveness also plays a role. Because of the risk of significant complications related to anemia in the critically ill patient, it is recommended that hemoglobin levels be maintained at a level greater than 10 g/L. Sever-

al measures can be initiated to minimize blood loss or further reductions in hemoglobin levels. Intravenous or subcutaneous therapy with erythropoietin is increasingly being used in the acute setting to improve the anemic state and to help minimize the need for blood transfusions.

Prognosis of Patients with Acute Renal Failure

Mortality can be as high as 50% to 80% in patients who have ARF in association with sepsis, hypotension, and respiratory failure.⁵⁹ The prognosis for hospitalized patients with ARF depends largely on the site (ward or ICU); the presence of comorbidities; the underlying cause of the renal failure; the severity of the renal failure; early diagnosis; and the rapid initiation of treatment. In hospitalized patients with ARF caused by ATN, the oliguric phase of ATN typically lasts for 1 to 2 weeks, but it can persist for 4 to 6 weeks. It is followed by the diuretic phase. It is important to remember that about one fourth to one third of the 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 the ATN. Infection is also a common cause of death in patients with ATN-related ARF.

In patients who survive the acute episode, renal function essentially returns to normal. Early in the recovery phase, 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.

Cost of Care

The estimated cost of dialysis and aggressive care of a critically ill patient with ARF is approximately \$128,000 per quality-adjusted life-year saved. With the accepted upper limit of cost-effective care being \$50,000, ARF places an overwhelming burden on the health care system.⁶⁰ Thus, prevention is the cornerstone in patient care.

Prevention

Approximately 25% of all hospital-acquired cases of ARF are related to the use of one or more nephrotoxic agents.^{3,5,59,61,62} Thus, the best strategy for prevention is the avoidance of drug-related nephrotoxicity and other high-risk situations. The first principle of good management is prophylaxis. This requires recognition of the clinical settings in which ATN normally occurs (e.g., cardiac or aortic surgery) and recognition of those patients who are particularly susceptible to ATN. The serum creatinine level is a poor marker of actual renal function, especially in the elderly population. To estimate creatinine clearance, especially in elderly patients, so as to properly manage the drug levels of all potential nephrotoxic agents, it is necessary to use the Cockcroft-Gault formula:

$$\text{Creatinine clearance (ml/min)} = [(140 - \text{age}) \times \text{weight (kg)}] \div (\text{serum creatinine [mg/dl]} \times 72)$$

For women, the quotient is multiplied by 0.85 because women have less muscle mass than men. Correcting fluid deficiencies before surgery and providing adequate hydration for patients who are particularly at risk before use of radiocontrast studies are some useful measures. Nephrotoxic drugs should be used

only when essential and, then, only with careful monitoring of the patient. Pretreatment with allopurinol before chemotherapy of massive tumors diminishes uric acid excretion and thus the potential for nephrotoxicity.

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