Acute Renal Failure

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ACUTE RENAL FAILURE (ARF) remains a common and critical clinical entity affecting 5% to 7% of all hospitalized patients.1,2 It is associated with various medical problems, treatments, and procedures. Despite advances in medical care, ARF still carries a significant morbidity and a 20% to 70% mortality rate. Unfortunately, this has not improved during the past 50 years because of a sicker and older population.

Epidemiology

Acute renal failure is characterized by an abrupt decline in renal function resulting in an inability to excrete metabolic wastes and maintain proper fluid and electrolyte balance. Although there is no universal laboratory definition, it is reasonable to define ARF as an increase in serum creatinine for 2 weeks or less of 0.5 mg/dL (44.2 µmol/L) if the baseline is less than 2.5 mg/dL (221 µmol/L) or an increase in serum creatinine by more than 20% if the baseline is more than 2.5 mg/dL (221 µmol/L).

The incidence of ARF during hospitalization has remained stable over the last 20 years.1,2 This is due not only to the higher acuity of illnesses and aggressive treatment of an aging population, but also to the impact of newer nephrotoxic medications, treatments, diagnostic testing, and procedures.

When mild cases are included, the overall outcome of ARF leads to a 20% mortality rate.3 Patients with more severe renal insufficiency (an increase of serum creatinine >3.0 mg/dL [265 µmol/L]) and those requiring renal replacement therapy have mortality rates approaching 40% to 50%.3 In the intensive care unit (ICU), patients with ARF carry the highest mortality rate of 50% to 70%. This rate has remained unchanged during the past 50 years, because patients in the ICU have more complicated ARF and may be elderly with multiple comorbidities.2 The subset of patients who develop ARF during the first 24 hours after cardiogenic shock from a myocardial infarction have a mortality rate of 87% vs 53% in those patients who did not develop ARF.4 The development of ARF increases the mortality associated with any primary disease.

Presentation

Most patients are asymptomatic and are diagnosed with renal failure based on laboratory data. Patients may present with malaise, hematuria, flank pain, dyspnea, edema, hypertension, or encephalopathy. Acute renal failure is either oliguric (<400 mL of urine/d) or nonoliguric. Oliguria indicates a more severe insult to the kidney compared with nonoliguria. Affected patients with contrast nephropathy and aminoglycoside toxicity commonly present with nonoliguric ARF. Anuria is defined as less than 100 mL of urine/d. Only a few conditions lead to complete anuria, including vascular lesions, total obstruction, severe acute tubular necrosis (ATN), or severe glomerulonephritis.

As toxins accumulate, patients become lethargic, nauseated, confused, and then comatose. Seizures and death may ensue. Salt and water excess can lead to vascular congestion, pulmonary edema, and hypoxia. Hyperkalemia may cause life-threatening arrhythmias. Acidosis can compromise cardiac contractility and cellular enzyme function.

Causes

The etiology of ARF is best divided into prerenal, intrarenal, and postrenal causes (TABLE 1).1,2,5,6 Prerenal azotemia describes any condition leading to decreased renal perfusion, including intravascular volume depletion, relative hypotension, compromised cardiac output, or hepatorenal syndrome. Intra-renal diseases affect structures of the nephron such as the glomeruli, tubules, vessels, or interstitium. The most common condition is ATN induced by ischemia or toxins; ATN occurs when the reduction in renal blood flow is severe or prolonged enough to lead to cell death. Prerenal azotemia and ischemic tubular necrosis occur on a continuum of the same pathophysiologic process. These 2 conditions account for 75% of the cases of ARF.2 Postrenal disease signifies obstruction of urinary flow anywhere from the renal pelvis to the urethra and accounts for 5% of all cases of ARF in the hospital.2

Patients who present with ARF in the outpatient setting typically have drug toxicity (angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs), acute interstitial nephritis, volume depletion, obstruction, glomerulonephritis, vasculitis, or sepsis. Inpatients tend to experience volume depletion, drug toxicity, contrast nephropathy, hypotension, and sepsis. Multiple etiologies frequently contribute to the development of ARF.

Diagnosis

The history and physical examination remain invaluable tools in the workup of ARF. A history of nephrotoxic medications, intravenous contrast, or hypo-
tension from rigorous chart review (including intraoperative flowsheets) can be found. Examination can show evidence of orthostasis, edema, congestive heart failure, bladder distension, livedo reticularis, petechiae, or palpable purpura (Table 2).

A blood urea nitrogen/creatinine ratio of more than 15:1 to 20:1 suggests hypoperfusion of the kidney leading to increased reabsorption of urea by the renal tubules. Patients with cirrhosis or other protein deficient states may have renal hypoperfusion with a blood urea nitrogen/creatinine ratio of only 10:1. If glomerular filtration falls to less than 10 mL/min, serum creatinine should increase by 0.5 to 1.5 mg/dL (44-133 µmol/L) per day depending on age, muscle mass, and muscle injury. Blood urea nitrogen should increase by 10 to 20 mg/dL (3.6-7.1 mmol/L) per day but can be higher in hypercatabolic states like sepsis, gastrointestinal bleeding, or with corticosteroid use.

A urinalysis examined immediately after voiding is essential in the workup of ARF (Table 3). A bland sediment without casts and protein suggests an underperfused state or obstructive uropathy. Once ATN has developed, brownish granular casts with renal tubular epithelial cells may be present. In the setting of glomerulonephritis and vasculitis, proteinuria, dysmorphic red blood cells, and red blood cell casts may be observed. Red urine in the absence of red blood cells suggests rhabdomyolysis or hemolysis.

The urinalysis also measures specific gravity, which estimates urine osmolality. A urine osmolality of more than 400 mOsm/kg is frequently associated with prerenal azotemia or glomerulonephritis. A specific gravity of 1.010 indicates the percentage of filtered sodium that is excreted in the urine. In the setting of glomerulonephritis and vasculitis, proteinuria, dysmorphic red blood cells, and red blood cell casts may be observed. Red urine in the absence of red blood cells suggests rhabdomyolysis or hemolysis.

Urine electrolytes are helpful in differentiating prerenal azotemia from ATN. The urine sodium concentration is usually less than 20 mEq/L with renal hypoperfusion and more than 30 to 40 mEq/L with ATN (Table 3). The fractional excretion of sodium (FENa) is the percentage of filtered sodium that is excreted in the urine. In the setting of oliguria, a FENa of less than 1% suggests hypoperfusion while a value of more than 1% is usually due to intrinsic renal disease. However, an elevated FENa may be misleading if diuretics or intravenous fluids were given before the urine collection. Other causes of a low FENa include glomerulonephritis, contrast nephropathy, myoglobinuria, hemoglobinuria, and early ATN.

### Table 1. Causes of Acute Renal Failure

<table>
<thead>
<tr>
<th>Causes</th>
<th>Inpatient</th>
<th>Outpatient</th>
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<tbody>
<tr>
<td>Prerenal (renal hypoperfusion)</td>
<td>35-40</td>
<td>70</td>
</tr>
<tr>
<td>Hypertension; sepsis; anesthesia and medication-induced; hepatorenal syndrome; relative hypotension below patient’s autoregulatory level</td>
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<tr>
<td>Pharmacologic: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors</td>
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<td>Large vessel: thrombosis, embolus, dissection</td>
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<tr>
<td>Intrarenal</td>
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<tr>
<td>Small vessel: atheroembolism, malignant hypertension, scleroderma, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome, disseminated intravascular coagulation</td>
<td>55-60</td>
<td>11</td>
</tr>
<tr>
<td>Glomeruli: acute or rapidly progressive glomerulonephritis, vasculitis</td>
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<td></td>
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<tr>
<td>Tubules</td>
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<td></td>
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<tr>
<td>Acute tubular necrosis</td>
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<tr>
<td>Ischemic; hypovolemia, hypotension, sepsis</td>
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<tr>
<td>Toxic (eg, intravenous contrast, aminoglycosides, amphotericin B, cisplatin, myoglobin, hemoglobin)</td>
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<tr>
<td>Obstruction (uric acid, calcium oxalate, acyclovir, indinavir, light chains)</td>
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<tr>
<td>Intertitial: acute interstitial nephritis, infection (bilateral pyelonephritis), infiltration (lymphoma, sarcoidosis), aristolochic acid (Chinese herb)</td>
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<tr>
<td>Postrenal</td>
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<tr>
<td>Ureteral: tumors, calculi, clot, sloughed papillae, retroperitoneal fibrosis, lymphadenopathy</td>
<td>2.5</td>
<td>17</td>
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<tr>
<td>Bladder neck: tumors, thromboemboli, calculi, prostatic hypertrophy or carcinoma, neurogenic</td>
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<tr>
<td>Urethral: strictures, tumors, obstructed indwelling catheters</td>
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### Table 2. History and Physical Examination in Acute Renal Failure

<table>
<thead>
<tr>
<th>History</th>
<th>Physical Examination</th>
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<tbody>
<tr>
<td>Prerenal</td>
<td>Orthostatic hypotension, poor skin turgor, dry buccal mucosa, congestive heart failure, edema (these signs can also be seen in acute tubular necrosis resulting from severe prerenal azotemia), signs of liver disease</td>
</tr>
<tr>
<td>Intrarenal</td>
<td>Edema, livedo reticularis, petechiae, palpable purpura, muscle tenderness</td>
</tr>
<tr>
<td>Postrenal</td>
<td>Decreased urinary stream, nocturia, anuria, frequency, dribbling, flank pain</td>
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<tr>
<td></td>
<td>Distended bladder, enlarged prostate, abdominal or pelvic masses</td>
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(transition from prerenal azotemia to ischemic tubular necrosis).

Other laboratory studies may also be helpful in the workup of ARF. A complete blood cell count with coagulation studies may reveal evidence of platelet consumption, red blood cell membrane damage, or both, indicating thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome, or disseminated intravascular coagulation. Eosinophilia may suggest acute interstitial nephritis or atheroembolic disease. Eosinophiluria (>1%) can be seen in some forms of acute interstitial nephritis but has poor sensitivity and specificity. An elevated creatine phosphokinase may suggest rhabdomyolysis.

Ultrasonography is the safe, readily available radiologic procedure for assessing obstruction, kidney size, and echogenicity. Unless a clear inciting factor is found, a renal ultrasound should be performed early in the evaluation of ARF. Small kidneys with increased cortical echogenicity imply chronic medical disease, but a component of acute renal deterioration may also be present. Renal Doppler blood flows are helpful if renovascular compromise is suspected clinically. Kidney biopsy is used in the evaluation of ARF if a nephritic or nephrotic syndrome, or unexplained recent onset of renal failure exists.

**Treatment**

Once renal failure occurs, the physician should attempt to reverse the underlying cause. The intravascular volume and mean arterial pressure (MAP) should be returned to baseline, and electrolyte abnormalities should be corrected. Further damage should be prevented by avoiding nephrotoxic agents. The ICU mortality rate has been shown to be increased when renal consultation was delayed for more than 48 hours; thus, the nephrologist should become involved early in the course of ARF.

Hyperkalemia can be treated medically. Inhaled β-agonists, insulin/glucose (5-10 U intravenously followed by 1 ampule 50% dextrose), and sodium bicarbonate (to neutralize acids) shift potassium intracellularly but will not lower total body potassium. Sodium polystyrene sulfonate (SPS), a potassium-binding resin, can be used to decrease total body potassium through gastrointestinal potassium transporters. As most of these transporters lie in the rectosigmoid colon, rectal administration of SPS can result in immediate potassium reduction. Sorbitol has been used to hasten kaexalate delivery. Due to recent reports of gastrointestinal ulcers with its use, SPS may be mixed with ginger ale for oral administration or suspended in dextrose with water or saline for rectal administration. A diet low in potassium is also recommended.

Some physicians still use renal-dose dopamine (0.5-2.0 µg/kg per minute) for prophylaxis or treatment of ARF. In healthy patients, dopamine improves renal blood flow, glomerular filtration rate (GFR), and sodium excretion. However, recent studies and a meta-analysis have shown no benefit in the prevention or early treatment of ARF. Furthermore, dopamine may be harmful by shifting oxygen consumption to the renal medulla from deep cortical structures and by suppressing anterior pituitary hormone concentrations.

Renal replacement therapy is initiated for hyperkalemia, volume overload, or metabolic acidosis refractory to medical therapy. It is also started for uremic complications such as pericarditis or encephalopathy. Intensive daily dialysis leading to decreased mortality and faster recovery of renal function has been recently described. However, because lower surface area dialyzers were used and desired dialysis clearances were not achieved, further data need to be acquired before daily dialysis can be recommended. Continuous renal replacement therapy is initiated in patients with hemodynamic instability and has not been shown to be superior to conventional hemodialysis.

Patients recovering from oliguric ARF may have an increase in urine output before stabilization or improvement of serum chemistries is noted. The GFR may have improved slightly but insufficiently to clear metabolic wastes. Continued renal replacement therapy may be necessary despite resumption of urinary output.
Conversion of oliguric to nonoliguric ARF with the use of high-dose diuretics has not been shown to improve mortality or lessen the need for hemodialysis.17,18 Recently, a cohort study of ICU patients with ARF suggested that patients treated with diuretics had an increased risk of death and nonrecovery of renal function.19 Despite adjustment for age, comorbidities, and urine output, the group who received diuretics still appeared to have a poorer prognosis. An age- and comorbidity-matched prospective trial is probably the best way to determine whether these variables influenced the study’s results. If these truly were negative effects of diuretics, they could have occurred because of a direct toxic effect or because of a delay in obtaining nephrology consultation and dialysis while awaiting a potential salutary effect of the diuretics, or perhaps other factors not yet elucidated. Nonetheless, it appears that diuretics rarely have a beneficial effect on established ARF and may be harmful. Nephrologic consultation should be obtained as soon as possible.

In ARF, medications need to be adjusted for a GFR of less than 10 mL/min to avoid overdosing, regardless of the serum creatinine. Any formula used to calculate GFR is accurate only in the presence of stable renal function.

Prevention

Because of the high morbidity, mortality, and costs associated with ARF, prevention of ARF is most important. Endothelin antagonists, atrial natriuretic peptides, prostaglandins, nitric oxide inhibitors, thyroxine, and human insulin-like growth factor 1 have been studied for the prophylaxis and treatment of ATN without clinical benefit.20-23

The prevention or immediate correction of hypotension and stabilization of the MAP may preclude ARF. This requires volume replacement with isotonic saline. Elderly patients have a diminished ability to autoregulate renal blood flow in the face of low blood pressure. Although an MAP of 70 mm Hg may be tolerated in a younger patient, it can lead to azotemia in an older patient. This is especially important in the intraoperative setting under general anesthesia.

Identifying patients who are at increased risk for developing ARF is crucial. Increased age, chronic renal insufficiency (CRI), diabetes mellitus, obesity, and jaundice are important risk factors. In patients with stable baseline renal function, the creatinine clearance, an estimate of GFR, can be calculated using the Cockcroft-Gault formula24: creatinine clearance = (140 – age) × ideal weight (kg) (× 0.85 for women)/72 × serum creatinine (mg/dL).

Older individuals and those with low muscle mass (eg, patients with end-stage liver disease) may have compromised renal function despite normal or near-normal serum creatinine levels. Acute renal failure can be prevented by appropriate dosing of medications and the use of prophylactic measures for contrast nephropathy in patients with known CRI.

Radiographic contrast still accounts for 10% of hospital-acquired ARF. Recently, several groups have studied the combination of acetylcysteine and 0.45% saline in preventing ARF in high-risk patients. Two trials using an oral acetylcysteine regimen with 0.45% saline reduced the incidence of contrast nephropathy in patients with CRI (serum creatinine, 1.6-2.4 mg/dL [141-212 µmol/L]) undergoing computed tomography scans (90% risk reduction; 21% to 2% incidence)25 and coronary angiograms (82% risk reduction; 45% to 8% incidence).26 Another study27 of patients with CRI (serum creatinine >1.2 mg/dL; >106 µmol/L) or creatinine clearance <60 mL/min [<1.0 mL/s] undergoing coronary angiography showed that fenoldopam with 0.45% saline was superior to 0.45% saline alone in preventing contrast nephropathy (50% risk reduction; 41% to 21% incidence).28 These results are promising and larger multicenter trials are currently taking place.

Medications that frequently cause ARF, especially in patients with hemodynamic compromise, include amphotericin B, aminoglycosides, and nonsteroidal anti-inflammatory drugs. Risk factors leading to amphotericin B nephrotoxicity include male sex, CRI, daily dose of more than 35 mg, total cumulative dose, duration of therapy, and concurrent use of cyclosporine or aminoglycosides.34,35 Therefore, amphotericin B should be dosed at 0.6 mg/kg per day and, if tolerated, isotonic saline given prior to each dose.
Aminoglycoside toxicity usually occurs after 1 week of therapy but can present as early as 1 to 2 days after starting therapy if another renal insult coexists. Renal dysfunction can occur even with close monitoring of levels due to continued accumulation in the proximal tubular cells. The risk is higher in patients with elevated drug levels, longer duration of therapy, divided doses, jaundice, and obesity but can be reduced with single daily dosing (79% risk reduction; 24% to 5% incidence). Dosage of all potentially nephrotoxic medications should always be adjusted for renal function.

**Conclusion**

Although ARF remains a significant problem, many episodes can be prevented by recognizing those individuals at risk and minimizing factors that predispose to renal failure. For those episodes that are not preventable, attempts to reverse the underlying pathophysiology should be made. Restoration of adequate renal perfusion by rapid correction and maintenance of intravascular volume and MAP is crucial. Avoidance of nephrotoxic agents and providing treatment of hyperkalemia, volume overload, and acidosis are a daily responsibility. Renal replacement therapy can be life-saving if renal function has not recovered before an indication for dialysis arises.

**REFERENCES**