Diagnosis of Acute Renal Failure

Although acute renal failure (ARF) is relatively uncommon, its mortality rate is potentially so high that it is important to recognize this condition in children. Rapid deterioration of renal function is caused by numerous insults and results in typical findings, including extracellular volume expansion, hyperkalemia, hypertension, metabolic acidosis, and azotemia. It usually is reversible, with the majority of patients recovering completely. However, ARF can lead to residual impairment of renal function and progress to end-stage renal disease and death. Conservative medical treatment often is life-saving.

Definition

ARF represents the rapidly progressive (within several hours or days) cessation of renal function, which results in the inability of the kidney to control body homeostasis, manifesting in retention of nitrogenous waste products (azotemia) and fluid and electrolyte imbalance. On the basis of pathophysiologic process, ARF has been divided broadly into three diagnostic categories: prerenal, intrarenal (organic-intrinsic), and postrenal failure (Table 1). Prerenal and early postrenal failures are renal functional disorders and responses of a structurally intact kidney to extrarenal processes. These forms of renal dysfunction recover rapidly as soon as the cause is reversed. However, if these two disorders are not recognized in time, persist too long, or are treated inadequately, they can result in intrinsic renal failure. Intrinsic or organic renal failure is caused by structural changes within the kidney. It is potentially reversible but requires an extended period of recovery.

Etiology

Prerenal failure is the most common form of ARF in children. The main process in the development of prerenal failure is hypoperfusion of the kidney, secondary to reduced effective plasma volume or heart failure. Numerous underlying conditions can lead to prerenal failure (Table 1). In children, the most common causes are hypovolemia secondary to gastrointestinal losses, the state of shock, and postoperative conditions. For example, ARF may occur after heart surgery when the aorta is cross-clamped or following prolonged cardiopulmonary bypass time.

A variety of renal disorders and insulting events can contribute to the development of
intrinsic renal failure (Table 1). Among these are acute glomerulonephritis and vasculitis of childhood, acute tubular necrosis, and acute interstitial nephritis.

Acute tubular necrosis (ATN) is the most common cause of intrinsic renal failure. It is associated with necrosis of the tubular epithelium following hypoxic or nephrotoxic injury. Various substances, including ethylene glycol, heavy metals, hydrocarbons, and certain antibiotics, including cephalosporins, aminoglycosides, sulfonamides, methicillin, and colistin, are potent nephrotoxins. Aminoglycoside-induced acute renal failure occurs typically 5 days after drug administration and represents a dose-dependent phenomenon.

Radiologic contrast material of the ionic type can cause ARF, usually within 24 hours after exposure, especially in individuals who are dehydrated, have diabetes mellitus, or have preexisting renal insufficiency. Primary diseases of the glomeruli and small blood vessels of the kidney may present with rapidly progressive ARF (Table 1). Large vessel diseases (renal artery thrombosis or embolism, renal vein thrombosis) are uncommon. Acute interstitial nephritis usually results from immune-mediated drug sensitivity or infection.

Postrenal failure is a less frequent cause of ARF in children. It presents as an abrupt decline in glomerular filtration rate (GFR) secondary to lower tract obstruction or bilateral upper tract obstructions, unless the patient has a single kidney. Obstruction can be secondary to structural, congenital, or acquired anomalies of the urinary tract, including posterior urethral valve, ectopic ureter, aberrant vessels, or stones, or may result from functional abnormalities such as neurogenic bladder. Uric acid, the end product of purine metabolism, is insoluble at high concentrations in an acidic medium; during rapid cellular lysis before or after chemotherapy it often will precipitate in a distal nephron and cause renal obstruction. Depending on localization, obstruction can be extrinsic or intrinsic, at the level of the collecting duct, pelvis, ureter, bladder, urethra, or meatus (Table 1).

Pathophysiology

Prerenal dysfunction can lead to development of renal failure and is characterized by a decline in renal blood flow (RBF), GFR, and urine flow. After an acute reduction in effective intravascular volume, compensatory mechanisms of both the organism and the kidney will operate to counteract the volume loss and restore renal perfusion. Central activation of several neural and humoral responses occurs, including increased activity of the sympathetic system and the renin-angiotensin II-aldosterone system and enhanced release of antidiuretic hormone. Hemodynamic alterations within the kidney develop. An initial, short response of maximum
dilatation of afferent arteriole is replaced by vasoconstriction. Blood flow is redistributed away from the renal cortex to juxtamedullary nephrons, which results in extensive tubular reabsorption of sodium, water, and urea.

With intense vasoconstriction, the kidney, acting as a blood reservoir, will shunt additional volumes of blood to the most vital organs (brain and heart); this response actually may be lifesaving in states of shock, blood loss, or severe dehydration. When the kidney has used these compensatory mechanisms fully, and the delivery of oxygen to the kidney remains critically impaired, acute necrosis of tubular cells occurs.

Injury due to ischemia or toxins is manifested by alterations in cellular metabolism. Cell detachment, desquamation, necrosis, and generation of intratubular debris and cast formations develop. The backward leak of tubular fluid across the injured tubular membrane and tubular obstruction results in further hemodynamic changes. Finally, decreased filtration rate leads to oliguria or anuria, defined as follows:

- **Oliguria**—urine output less than 0.5 mL/kg per hour in infants or less than 500 mL/1.73 m² per day) in older children
- **Anuria**—total cessation of urinary output

Although intrinsic renal failures generally present as oliguria or anuria, the entity of nonoliguric ARF (sometimes called nonoliguric vasomotor nephropathy) is being increasingly recognized. Nonoliguric renal failure typically consists of azotemia in the face of a normal urine output (> 1 mL/kg per hour). It occurs primarily as a result of exposure to a nephrotoxic drug, especially an aminoglycoside.

Postrenal failure is a result of a total or partial obstruction of the urinary tract that affects the flow of normally produced urine. In the case of partial obstruction, the patient usually is nonoliguric and may even be polyuric. With the development of an obstruction, pressure proximal to the site of obstruction rises, which results in increased intratubular pressure and dilatation of the collecting system (hydronephrosis). Vasodilatation occurs only in the first 1 to 3 hours after obstruction and is followed by a period of intense vasoconstriction that leads to the ultimate damage of the tubular cells.
Diagnostic Approach to ARF

Azotemia (a rise in blood urea nitrogen [BUN] and serum creatinine) or changes in the urine excretory pattern such as oliguria or anuria should alert the physician to the presence of ARF. Anuria usually indicates a complete obstruction, cortical necrosis, or severe glomerulonephritis. To diagnose intrinsic renal failure, one must exclude prerenal and postrenal causes. A history of renal problems, poor growth and development, and signs of renal osteodystrophy may help to establish the diagnosis of chronic renal failure presenting as an acute condition (Table 2).

An elevated BUN can be evident as a result of steroid therapy, parenteral nutrition, upper gastrointestinal bleeding, or a hypercatabolic state, such as sepsis. An elevated serum creatinine level (Scr) can result from the increased release of stored creatinine (rhabdomyolysis), the use of drugs (trimethoprim-sulfamethoxasole, cimetidine) that interfere with creatinine secretion at the level of tubule, or the presence of chromogenic substances in blood (acetone, cephalosporins) that interfere with the Jaffe reaction for creatinine determination. Nonrenal causes of azotemia must be assessed; serial laboratory determination of BUN or Scr may be necessary to establish that a patient has ARF.

A physical examination always is indicated to assess the fluid status, cardiovascular status, hemodynamic parameters, patency of the urinary tract, and signs of other organ involvement. Initial laboratory studies would include a complete blood cell count, blood smear, serum electrolytes, creatinine and blood nitrogen urea, uric acid, and serum proteins. A fresh urine sample should be examined for evidence of proteinuria, hematuria, casts, crystals, red blood cells, or eosinophils. Eosinophils often are found in ARF due to interstitial nephritis. The demonstration of eosinophils in the urine can best be documented by the use of Hansel stain.

If the patient is nonoliguric, a timed urine collection for creatinine and total protein levels should be obtained to quantify residual renal function and urine protein loss.

Urinalysis, urinary sodium, creatinine, osmolality, urea, and urinary indices such as urine/plasma osmolality ratio, urine/plasma creatinine ratio, urine/plasma urea ratio, and fractional excretion of sodium (if urine is present) will reflect pathophysiologic events and may help differentiate prerenal from intrinsic renal failure; however, findings also may overlap. Only values that are clearly high or low are diagnostic. The fractional excretion of sodium (FENa), discussed in Table 3 and Table 4, is the most useful urinary index. If possible, urine samples for the untimed spot urine determination should be obtained simultaneously with blood samples before the therapeutic or diagnostic maneuvers are begun. Use of diuretics (furosemide) within 12 hours will invalidate the interpretation of data obtained.
Additional laboratory studies may be indicated in specific clinical situations, such as determination of the creatine phosphokinase level for rhabdomyolysis; the complement level (C3, C4), anti-streptolysin-O titer, streptozymes, and antideoxyribonuclease-B (anti DNA-ase-B) for acute poststreptococcal glomerulonephritis; antinuclear antibodies for lupus nephritis; or antineutrophil cytoplasmatic antibodies in the case of suspected vasculitis.

Imaging studies may include a chest radiograph, plain abdominal radiograph, renal ultrasonography with doppler flow studies, and renal scan, depending on probable diagnosis or findings in patients. Renal ultrasonography with doppler flow studies is the least invasive and should be routine in all patients who have renal failure, regardless of cause. It assists in assessing kidney size, shape, and number; the adequacy of renal blood flow; and whether any obstruction is present. Renal nuclear scans estimate renal perfusion and function. Occasionally, computed tomography without contrast, voiding cystourethrogram, magnetic resonance imaging, echocardiogram, or electrocardiogram also may be needed.

A renal biopsy may be valuable for making a diagnosis, confirming a clinical impression, assessing prognosis, or providing a basis for specific treatment (Table 5).

**DIAGNOSIS OF PRERENAL FAILURE**

The patient who has prerenal failure will evidence the signs and symptoms of decreased effective blood volume or perfusion. There may be a history of vomiting, diarrhea, recent febrile illness, surgery, imbalance between input and output, heart problems, thirst, weight loss, or decrease in urine output. Signs of moderate or severe dehydration (hypotension, tachycardia, decreased skin turgor, dry mucous membrane, oliguria/ anuria) or of congestive heart failure (hepatomegaly, pulmonary edema, peripheral edema, gallop) may be present.

Laboratory studies will demonstrate hemoconcentration with an increase in hematocrit, uric acid, and total protein and a markedly elevated BUN. The BUN/SCr ratio usually is more than 20. Urinalysis will show a trace to + 1 protein, and sediment usually is normal, but hyaline and fine granular casts may be present as well. Urinary indices will reflect a maximally concentrated urine (specific gravity >1.016 to 1.030, urine osmolality >400 mOsm per kg H2O), preserved tubular integrity (urine/ plasma osmolality ratio > 1.5, urine/ plasma creatinine ratio >40, urine/ plasma urea ratio >20), and salt conservation (urine sodium <720 mEq/L, FENA <1%) (Table 3). In the case of metabolic alkalosis, a spot urine chloride of less than 20 mEq/L usually indicates preserved tubular function.

The chest radiograph may evidence signs of heart failure. Findings on renal ultrasonography usually are non specific, and kidney size is normal.
DIAGNOSIS OF POSTRENAL FAILURE

Clearly, the pediatrician must be alert to the possibility of renal obstruction. When a child presents with the signs of azotemia and a sudden decrease in urine output, the history and physical examination can help determine the location and cause of obstruction. The patient may have had frequent urinary tract infections, hematuria, trauma, underlying lesions, an alteration in the urinary pattern (decrease in urine stream, dribbling), and presence of lower abdominal or flank pain secondary to renal enlargement and dilatation of the collecting system. The physical examination may reveal a palpable suprapubic mass, such as in male newborns who have posterior urethral valves. This is the most common cause of postrenal failure in boys.

Rectal and gynecologic examinations should be done to exclude extrinsic causes of renal obstruction. The patency of the urinary tract must be established first in every patient who has ARF. Thus, in patients who have ARF, assessment by renal ultrasonography must include evaluation of the lower urinary tract and bladder.

Urinalysis can reveal microscopic or macroscopic hematuria with eumorphic (normal-appearing) red blood cells, pyuria in case of infection, crystals such as calcium oxalate in nephrolithiasis, or ethylene glycol intoxication. A plain abdominal radiograph can demonstrate radiopaque stones or an ileus secondary to colic, suggest abdominal masses, and provide data about bony structures. Renal ultrasonography can detect the pattern of hydronephrosis and sometimes the site of obstruction.

DIAGNOSIS OF INTRINSIC RENAL FAILURE

During acute intrinsic renal failure, three clinical phases can be distinguished. The initial phase of injury is the period between the onset of insult and established renal failure. This phase can last several hours or, rarely, days. The second phase is that of established renal failure or the maintenance phase, characterized by reduction of the GFR and azotemia. This phase usually lasts several days to weeks. Oliguria that lasts more than 90 days often indicates the possibility of residual structural impairment.

The third or recovery phase results in a gradual increase in GFR and diuresis. An increase in urine output will improve the fluid and electrolyte imbalance. Glomerular filtration recovers more rapidly than tubular function, and the patient may demonstrate a lengthy period of tubular dysfunction, such as an inability to concentrate urine and increased salt losses. Recovery may extend over several weeks to months; the usual time of renal recovery is about 30
A history may help in establishing the etiology of intrinsic renal failure. Edema, skin infection, or smoky urine suggests postinfection glomerulonephritis; purpuric rash, abdominal pain, and diarrhea suggest vasculitis; and urticarial rash, use of drugs, fever, and arthralgia may indicate acute interstitial nephritis. Once the kidney has developed intrinsic renal failure, the signs and symptoms usually are independent of the etiology. Nonspecific generalized symptoms (lethargy, anorexia, vomiting, abdominal pain) can be present. Signs of fluid retention (peripheral and pulmonary edema, hypertension) and changes in urine pattern (oliguria, anuria, or polyuria) are prominent. The hallmark of intrinsic renal failure is the worsening of azotemia, with a daily rise in serum creatinine (0.5 to 1.5 mg/dL) and in BUN (10 to 20 mg/dL).

Hyponatremia frequently is dilutional, secondary to fluid retention and/or to the administration of hypotonic solutions. Hyperkalemia develops primarily as the result of decreased GFR and cellular catabolism. Metabolic acidosis results from the reduced capacity of the kidneys to regulate acid base homeostasis and lactic acid accumulation. Hyperphosphatemia develop secondary to decreased filtration as well as cell destruction. Low serum calcium is secondary to hyperphosphatemia, resistance to parathyroid hormone, and abnormalities in vitamin D metabolism. Usually, hypocalcemia is asymptomatic, but can lead to tetany, convulsions, or hypotension. The uric acid level may become markedly elevated during the oliguric phase.

Anemia is a result of the dilution, decreased erythropoiesis, hemolysis, and blood loss. Leukopenia or leukocytosis can be evident. Microangiopathic hemolytic anemia (Coombs negative) with fragmented erythrocytes on the peripheral smear and thrombocytopenia are characteristics of hemolytic-uremic syndrome. Coagulation abnormalities accompanied by an increase in bleeding time secondary to the platelet dysfunction are found in severe uremia.

Proteinuria of more than 1 g/d, numerous dysmorphic red blood cells, and red blood cell and granular casts are seen in glomerulonephritis and vasculitis. In the case of acute interstitial nephritis, pyuria, eosinophiluria, scant casts (mainly white blood cell casts), and tubular cells are present. Myoglobinuria or hemoglobinuria should be suspected whenever there exists a urine sample that has blood on the dipstick and only 1 to 2 red blood cells in the sediment. Urinary sediment with numerous coarse granular or pigmented casts and/or tubular cells are characteristic of ATN. Urinary indices will reflect tubular dysfunction and injury and will document the inability of the kidney to concentrate urine and conserve sodium (a urine osmolality <350 mOsm/kg H2O, urine Na >40 mEq/L, FENa >2.5%) (Table 3).

Renal ultrasonography usually shows enlarged kidneys with a uniform increased cortical echogenicity; a renal scan shows poor uptake and excretion of radioisotope.