Acute Renal Failure
Belda Dursun, MD, and Charles L. Edelstein, MD, PhD

EPIDEMIOLOGY

- Incidence:
  - Community: Less than 1%
  - Hospital: 2% to 7%
  - Intensive care unit (ICU)/postoperative: 4% to 25%
- Risk factors for postoperative renal failure:
  - Age >70 years
  - Insulin-dependent diabetes mellitus
  - Chronic renal failure
  - Left ventricular dysfunction
- Significant associated mortality in ICU: 43% to 88%
- Independent predictor of mortality
- Factors increasing mortality:
  - Multiorgan failure
  - Respiratory failure
  - Cardiovascular dysfunction
  - Significantly longer length of hospital stay
  - Formidable health care costs

PATHOPHYSIOLOGY OF ACUTE TUBULAR NECROSIS

Vascular Factors
- Alterations in regional blood flow
- Increased sensitivity to vasoconstrictor stimuli
- Increased sensitivity to renal nerve stimuli
- Impaired autoregulation
- Endothelial injury
- Decreased nitric oxide derived from endothelial nitric oxide synthase
- Increased endothelin
- Decreased prostaglandins
- Leukocyte adhesion to endothelium

Sublethal Reversible Proximal Tubular Injury
- Cytoskeletal disruption
- Loss of polarity
- Tubular obstruction
- Abnormal gene expression

Tubular Factors

Proximal tubular necrosis
- Calcium influx
- Metalloproteases
- Oxygen radicals
- Lipid peroxidation
- Nitric oxide derived from inducible nitric oxide synthase
- Defective heat shock protein response
- Phospholipase A₂
- Calpain
- Caspase-1
- Neutrophils
- T cells

Proximal tubular apoptosis
- Caspase-3
- Endonucleases
- Insulin-like growth factor (IGF) deficiency

Inflammatory Response
- Endothelial injury and leukocyte infiltration:
  - Neutrophils
  - T lymphocytes
  - Monocyte/macrophages
- Activation of leukocytes by inflammatory mediators

Sepsis and Acute Renal Failure
- Renal vasoconstriction with intact tubular function
- Tumor necrosis factor
- Reactive oxygen species
Inducible nitric oxide synthase
Cytokines
Glomerular and vascular microthrombosis
Translation of above experimental results to patients warrants caution

MAKING THE DIAGNOSIS

Characteristic Signs
- Decrease in glomerular filtration rate (GFR) over a period of hours to days
- Failure to excrete nitrogenous waste products
- Failure to maintain fluid and electrolyte homeostasis

Clinical Diagnosis
- Increase in blood urea nitrogen only (prerenal acute renal failure [ARF])
- Increase in blood urea nitrogen and serum creatinine
- Decrease in GFR:
  - Calculated GFR:
    - Cockcroft-Gault formula (accurate only if renal function is in a steady state)
  - Measured GFR:
    - Creatinine clearance
    - Urea clearance
    - Inulin clearance (research tool)
    - Iodothalamate clearance (gold standard, expensive)
- Oliguria, <400 mL urine per day
- Serum markers of renal function (future):
  - Cystatin C
- Urine biomarkers of tubular injury (future):
  - Interleukin 18
  - Kidney injury molecule 1
  - Neutrophil gelatinase-associated lipocalin

ETIOLOGY

Prerenal Azotemia

Definition
- Acute rise in blood urea nitrogen, serum creatinine, or both
- Renal hypoperfusion
- Bland urine sediment
- Fractional excretion of sodium <1%
- Return of renal function to normal within 24 to 72 hours of correction of the hypoperfused state

Causes
- Intravascular volume depletion:
  - Hemorrhage
  - Renal fluid loss
  - Gastrointestinal losses
  - Skin loss of sweat
  - Third-space losses
- Reduced cardiac output:
  - Congestive heart failure
  - Cardiogenic shock
  - Pericardial effusion with tamponad
  - Massive pulmonary embolism
- Increased renal vascular resistance:
  - Anesthesia
  - Hepatorenal syndrome
  - Prostaglandin inhibitors
  - Aspirin
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Vasoconstricting drugs:
  - Cyclosporine
  - Tacrolimus
  - Radiocontrast
- Decreased intraglomerular pressure
  - Angiotensin-converting enzyme inhibitors
  - Angiotensin II receptor blockers

Postrenal Azotemia

Common denominator in this setting is obstruction to the flow of urine.

Bilateral ureteral obstruction or unilateral obstruction in a solitary kidney:
- Intraureteral:
  - Stones
  - Blood clots
  - Papillary necrosis
- Extraureteral:
  - Bladder
  - Prostatic cancer
  - Cervical cancer
  - Retroperitoneal fibrosis

Bladder neck obstruction
- Prostatic hypertrophy
- Prostatic cancer
Bladder cancer
Autonomic neuropathy
Ganglionic blocking agents: urethral obstruction
Valves
Strictures

Intrarenal or Intrinsic ARF

Vascular
- Bilateral renal artery:
  - Stenosis
  - Thrombosis
  - Embolism
  - Operative arterial cross clamping
- Bilateral renal vein
  - Thrombosis
- Small vessel
  - Atheroembolic disease
  - Thrombotic microangiopathy
    - Hemolytic uremic syndrome/thrombotic thrombocytopenic purpura
    - Scleroderma renal crisis
    - Malignant hypertension
    - Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome
    - Postpartum ARF

Glomerular
- When ARF develops in glomerulonephritis (GN) setting, rapidly progressive GN (RPGN) should be excluded
- Histologically a RPGN manifests as a crescentic GN on kidney histology
- Causes of RPGN are classified according to immunofluorescence staining on kidney biopsy:
  - Linear immune complex deposition:
    - Goodpasture’s syndrome
  - Granular immune complex deposition:
    - Postinfectious
    - Infective endocarditis
    - Lupus nephritis
    - Immunoglobulin A (IgA) nephropathy
    - Henoch-Schönlein purpura
    - Membranoproliferative GN
  - No immune deposits:
    - Wegener’s granulomatosis
    - Polyarteritis nodosa
    - Churg Strauss
- Idiopathic crescentic GN

Interstitial
- Causes:
  - Bacterial pyelonephritis
  - Drug-induced acute allergic interstitial nephritis (AIN):
    - Antibiotics
    - Antituberculosis drugs
    - Diuretics
    - NSAIDs
    - Anticonvulsant drugs
    - Allopurinol
    - Many other drugs
  - Exogenous toxins and nephrotoxic drugs:
    - Aminoglycosides
    - Cisplatin
    - Radiocontrast
    - Ethylene glycol
  - Endogenous toxins:
    - Myoglobin (rhabdomyolysis)
    - Hemoglobin (incompatible blood transfusion, acute falciparum malaria)
    - Uric acid (acute uric acid nephropathy)

EVALUATION OF PATIENT

First Steps in Diagnosis and Treatment

Careful data tabulation and recording
- Past and current laboratory data
- Vital signs
- Daily weights
- Intake and output
- Fluid and medication review
- Did ARF develop outside hospital, in hospital but not ICU, or in ICU?
- Thorough history and physical examination

Urine Sediment
- Prerenal
- Postrenal
GN/vasculitis
• AIN
• ATN
• Ethylene glycol intoxication
• Acute uric acid nephropathy
• Obstructive uropathy due to sulfadiazine
• Rhabdomyolysis

Urine Chemistry
• Specific gravity
• Sodium
• Creatinine
• Urea nitrogen
• Osmolality

Radiology
• Renal ultrasonography (procedure most widely used)
• Isotope renography
• Computed tomography
• Cystoscopy and retrograde or anterograde pyelography

Renal Biopsy in ARF
Indications
• ARF of unknown cause
• Suspicion of GN, systemic disease (eg, vasculitis), or AIN
• ATN not recovering after 4 to 6 weeks of dialysis with no more recurrent insults

Pathology
• Not much true necrosis of tubular cells
• Tubular swelling and vacuolization
• Tubular loss of brush border
• Apical blebbing of tubular cytoplasm
• Tubular cell loss manifest as gaps in tubular epithelium
• Lack of histological findings that predict clinical outcome

Know the Clinical Features of Common Causes of ARF
• Hepatorenal syndrome
• Vasomotor ARF due to NSAIDs, cyclosporine, tacrolimus, angiotensin-converting enzyme inhibitors
• Radiographic contrast nephropathy
• Atheroembolic disease
• Thrombotic microangiopathies
• Aminoglycoside nephrotoxicity
• Rhabdomyolysis
• Acute uric acid nephropathy
• ARF in patients with acquired immunodeficiency syndrome
• ARF in bone marrow transplant patients

MANAGEMENT

General
• Management of the complications of ARF is important
• Dialysis is the only Food and Drug Administration–approved treatment
• No specific treatments of established ARF

Prerenal Azotemia
• Correct underlying disorder
• Monitor response to therapy:
  • Daily weight
  • Clinical examination of volume status
  • Central venous catheter
  • Swan-Ganz catheter

Renal or Intrinsic ARF

Conservative treatment
• Avoidance of renal-dose dopamine
• Use of diuretics to convert oliguric to nonoliguric ARF is controversial
• Avoidance of nephrotoxic drugs
• Adjustment of drug dosages based on measured or best estimate of GFR, not merely on serum creatinine
• Nutrition (enteral nutrition preferred)

Dialysis therapy
• Indications to start dialysis in ARF:
  • Not specific
  • Absolute indications:
    • Pulmonary edema unresponsive to conservative therapy
    • Hyperkalemia unresponsive to conservative therapy
    • Metabolic acidosis unresponsive to conservative therapy
    • Symptomatic uremia: encephalopathy, pericarditis
  • Individualized by nephrologic consultation
Timing of initiation of dialysis (recent studies):
- “Prophylactic” hemodialysis (HD) in chronic kidney disease patients prior to coronary artery bypass graft may have survival benefit
- “Prophylactic” continuous venovenous hemofiltration (CVVH) in high-risk patients may prevent contrast nephropathy

Dose of dialysis:
- Alternate-day HD
- Daily HD
- Continuous

Main modalities of dialysis:
- Intermittent HD (IHD)
- Continuous renal replacement therapy (CRRT):
  - CVVH
  - Continuous venovenous HD (CVVHD)
  - Continuous venovenous hemodiafiltration (CVVHDF)
  - Sustained low-efficiency daily dialysis (SLEDD)
  - Acute peritoneal dialysis (PD)
- IHD and CRRT regarded as equivalent methods for ARF treatment
- CRRT may be modality of choice in critically ill, hypotensive patients
- IHD may be used in mobile, less ill patients without hypotension
- Dialysis modality may depend on facility-specific issues:
  - Experience
  - Nursing resources
  - Cost
  - Technical proficiency
- In summary, choice of IHD versus CRRT should be individualized at nephrology consultation

Type of dialysis membrane:
- Bioincompatible:
  - Cellulose
  - Cuprophane
  - Hemophane
- Biocompatible (most widely used):
  - Polyamides
  - Polycarbonate
  - Polysulfone

Temporary vascular access:
- Internal jugular vein:
  - For longer duration
  - Lower infection risk
  - Technically more difficult to insert
  - Lower failure rate
- Femoral vein:
  - For shorter duration
  - Higher infection risk
  - Technically easier to insert
  - Higher failure rate
- Subclavian vein
  - Avoid if possible

ADDITIONAL READING