Acute Renal Failure

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**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

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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
- Extraperireteral:
  - 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

Interstitium
• Causes:
  ▪ Bacterial pyelonephritis
  ▪ Drug-induced acute allergic interstitial nephritis (AIN):
    ▪ Antibiotics
    ▪ Antituberculosis drugs
    ▪ Diuretics
    ▪ NSAIDs
    ▪ Anticonvulsant drugs
    ▪ Allopurinol
    ▪ Many other drugs

Tubular
• Causes of acute tubular necrosis (ATN):
  ▪ Renal ischemia:
    ▪ Sepsis
    ▪ Shock
    ▪ Hemorrhage
    ▪ Trauma
    ▪ Pancreatitis
  ▪ 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 antegrade pyelography

**Renal Biopsy in ARF**

**Indications**
- ARF of unknown cause
- Suspicion of GN, systemic disease (e.g., 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