

# CORE CURRICULUM IN NEPHROLOGY

## Acute Renal Failure

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### EPIDEMIOLOGY

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- 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

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### PATHOPHYSIOLOGY OF ACUTE TUBULAR NECROSIS

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#### Vascular Factors

- Alterations in regional blood flow
- Increased sensitivity to vasoconstrictor stimuli
- Increased sensitivity to renal nerve stimuli
- Impaired autoregulation
- Endothelial injury

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- 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 A<sub>2</sub>
- 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

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### MAKING THE DIAGNOSIS

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#### 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

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### ETIOLOGY

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#### 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 tamponade
  - 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

#### 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)

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## EVALUATION OF PATIENT

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### 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 antero-grade 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

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### MANAGEMENT

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#### 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

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