Chapter 74: Acute Kidney Injury

INTRODUCTION

- *Acute kidney injury* (AKI) is a clinical syndrome generally defined by an abrupt reduction in kidney function as evidenced by changes in serum creatinine (Scr), blood urea nitrogen (BUN), and urine output.
- RIFLE (Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Renal Disease), AKIN (Acute Kidney Injury Network), and the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines are three criteria-based classification systems developed to define and stage AKI in different patient populations (**Table 74-1**).
- All three staging systems have been validated across different patient populations, and their staging correlates closely with hospital mortality, cost, and length of stay.
- Scr and urine output are the main diagnostic criteria for each staging system.

TABLE 74-1

RIFLE, AKIN, and KDIGO Classification Schemes for AKI[a]

RIFLE Category	Scr and GFR[b] Criteria	Urine Output Criteria
Risk	Scr increase to 1.5-fold or GFR decrease >25% from baseline	<0.5 mL/kg/hr for ≥6 hr
Injury	Scr increase to 2-fold or GFR decrease >50% from baseline	<0.5 mL/kg/hr for ≥12 hr
Failure	Scr increase to 3-fold or GFR decrease >75% from baseline, or Scr ≥4 mg/dL (354 µmol/L) with an acute increase of at least 0.5 mg/dL (44 µmol/L)	Anuria for ≥12 hr
Loss	Complete loss of function (RRT) for >4 weeks	
ESKD	RRT >3 months	
AKIN Criteria	**Scr Criteria**	**Urine Output Criteria**
Stage 1	Scr increase ≥0.3 mg/dL (27 µmol/L) or 1.5- to 2-fold from baseline	<0.5 mL/kg/hr for ≥6 hr
Stage 2	Scr increase >2- to 3-fold from baseline	<0.5 mL/kg/hr for ≥12 hr
Stage 3	Scr increase >3-fold from baseline, or Scr ≥4 mg/dL (354 µmol/L) with an acute increase of at least 0.5 mg/dL (44 µmol/L), or need for RRT	<0.3 mL/kg/hr for ≥24 hr or anuria for ≥12 hr
KDIGO Criteria	**Scr Criteria**	**Urine Output Criteria**
Stage 1	Scr increase ≥0.3 mg/dL (27 µmol/L) or 1.5–1.9 times from baseline	<0.5 mL/kg/hr for 6–12 hr
Stage 2	Scr increase 2–2.9 times from baseline	<0.5 mL/kg/hr for ≥12 hr
Stage 3	Scr increase three times from baseline, or Scr ≥4 mg/dL (354 µmol/L), or need for RRT, or eGFR[c] <35 mL/min/1.73 m^2 (0.34 mL/sec/m^2) in patients <18 years	Anuria for ≥12 hr

[a]For all staging systems, the criterion that leads to worst possible diagnosis should be used.

[b]GFR calculated using the Modification of Diet in Renal Disease (MDRD) equation.

[c]GFR calculated using the Schwartz formula.

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; h, hours; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease; RRT, renal replacement therapy; Scr, serum creatinine.

PATHOPHYSIOLOGY

- AKI can be categorized as prerenal (resulting from decreased renal perfusion in the setting of undamaged parenchymal tissue), intrinsic (resulting from structural damage to the kidney, most commonly the tubule from an ischemic or toxic insult), and postrenal (resulting from obstruction of urine flow downstream from the kidney) (**Figure 74-1**).

FIGURE 74-1

Classification of acute kidney injury (AKI) based on etiology.

(ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BPH, benign prostatic hyperplasia; GI, gastrointestinal; HPI, history of present illness; HTN, hypertension; HUS, hemolytic uremic syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs; PMH, past medical history; TTP, thrombotic thrombocytopenic purpura.)

image

CLINICAL PRESENTATION

- Patient presentation varies widely and depends on the underlying cause. Early recognition and cause identification are critical, as they directly affect the outcome of AKI. Outpatients often are not in acute distress; hospitalized patients may develop AKI after a catastrophic event.
- Symptoms in the outpatient setting include acute change in urinary habits, sudden weight gain, or severe abdominal or flank pain. Signs include edema, colored or foamy urine, and, in volume-depleted patients, postural hypotension, decreased jugular venous pressure, and dry mucous membranes.

DIAGNOSIS

- Thorough medical and medication histories, physical examination, assessment of laboratory values, and, if needed, imaging studies are important in the diagnosis of AKI.
- Scr cannot be used alone to diagnose AKI because it is insensitive to rapid changes in glomerular filtration rate (GFR). Scr lag behind the GFR's decline by 1-2 days, leading to a significant overestimation of GFR in the early stages of AKI and a potential delay in diagnosis of the syndrome. The use of BUN in AKI is very limited because urea production and renal clearance are heavily influenced by extrarenal factors such as critical illness, volume status, protein intake, and medications.
- Urine output measured over a specified period of time allows for short-term assessment of renal function, but its utility is limited to cases in which it is significantly decreased.
- In addition to BUN and Scr, selected blood and urine tests, and urinary sediment are used to differentiate the cause of AKI and guide patient management (**Tables 74-2** and **74-3**).
- Simultaneous measurement of urine and serum electrolytes and calculation of the fractional excretion of sodium (FE_{Na}) can help determine the etiology of AKI (see **Table 74-2**).
- The FE_{Na} is one of the better diagnostic parameters to differentiate the cause of AKI and is calculated as:

  $FE_{Na} = (U_{Na} \times Scr \times 100) / (U_{Cr} \times S_{Na})$

  where U_{Na} = urine sodium, Scr = serum creatinine, U_{Cr} = urine creatinine, and S_{Na} = serum sodium.
- A number of new serum and urinary biomarkers have been investigated to detect and predict the clinical outcomes of AKI, including tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7).

TABLE 74-2

Diagnostic Parameters for Differentiating Causes of AKI[a]

Laboratory Test	Prerenal AKI	Intrinsic AKI	Postrenal AKI
Urine sediment	Hyaline casts, may be normal	Granular casts, cellular debris	Cellular debris
Urinary RBC	None	2–4+	Variable
Urinary WBC	None	2–4+	1+
Urine Na (mEq/L or mmol/L)	<20	>40	>40
FE_{Na} (%)	<1	>2	Variable
Urine specific gravity	>1.018	<1.012	Variable

[a]Common laboratory tests are used to classify the cause of AKI. Functional AKI, which is not included in this table, would have laboratory values similar to those seen in prerenal AKI. The laboratory results listed under intrinsic AKI are those seen in acute tubular necrosis, the most common cause of intrinsic AKI.

AKI, acute kidney injury; FE_{Na}, fractional excretion of sodium; RBC, red blood cell; Scr, serum creatinine; WBC, white blood cell.

TABLE 74-3

Urinary Findings as a Guide to the Etiology of Acute Kidney Injury

Type of Urinary Evaluation	Presence of	Suggestive of
Urinalysis	Leukocyte esterases	Urinary tract infection
	Nitrites	Urinary tract infection
	Protein	
	Mild (<0.5 g/day)	Tubular damage
	Moderate (0.5–3 g/day)	Glomerulonephritis, pyelonephritis, tubular damage
	Large (>3 g/day)	Glomerulonephritis, nephrotic syndrome
	Hemoglobin	Glomerulonephritis, pyelonephritis, renal infarction, renal tumors, kidney stones
	Myoglobin	Rhabdomyolysis-associated tubular necrosis
	Urobilinogen	Hemolysis-associated tubular necrosis
Urine sediment	Microorganisms	Urinary tract infection
Cells	Red blood cells	Glomerulonephritis, urinary tract infection, renal infarction, papillary necrosis, renal tumors, kidney stones
	White blood cells	Urinary tract infection, interstitial nephritis
	Eosinophils	Drug-induced interstitial nephritis, renal transplant rejection
	Epithelial cells	Tubular necrosis
Casts	Granular casts	Tubular necrosis
	Hyaline casts	Prerenal azotemia
	White blood cell casts	Urinary tract infection, interstitial nephritis
	Red blood cell casts	Glomerulonephritis, renal infarct, lupus nephritis, vasculitis
Crystals	Urate	Postrenal obstruction
	Calcium phosphate	Postrenal obstruction

PREVENTION

- Goals of Prevention: The goals are to screen and identify patients at risk; monitor high-risk patients until the risk subsides; and implement prevention strategies when appropriate.

General Approach to Prevention

Nonpharmacologic Therapy

- Intravenous fluids are routinely used in the prevention of AKI. KDIGO guidelines recommend isotonic crystalloids over colloids for intravascular volume expansion. Balanced solutions may offer some benefit compared to normal saline solutions.
- Fluids are the mainstay of therapy for prevention of contrast-induced acute kidney injury (CI-AKI), a common cause of acute tubular necrosis in the inpatient setting.
- KDIGO guidelines recommend either sodium bicarbonate or isotonic saline infusions in high-risk individuals receiving radiocontrast media. A common sodium bicarbonate regimen is 154 mEq/L (mmol/L) infused at 3 mL/kg/hr for 1 hour before the procedure and at 1 mL/kg/hr for 6 hours after the procedure. One frequently cited normal saline regimen is 1 mL/kg/hr for 12 hours pre- and post-procedure.
- Oral ingestion of a specific amount of water pre- and post-procedure is best reserved for outpatients with either normal or mildly impaired renal function undergoing elective procedures.

Pharmacologic Therapy

- Inadequate evidence exists to support use of ascorbic acid, an antioxidant, in the treatment or prevention of CI-AKI. The landmark PRESERVE trial demonstrated no benefit of *N*-acetylcysteine in the prevention of CI-AKI.
- Both hyper- and hypoglycemia are associated with adverse patient outcomes. Guidelines from the American Diabetes Association and Surviving Sepsis Campaign recommend a glycemic target range of 140–180 mg/dL (7.8–10 mmol/L) and less than 180 mg/dL (10 mmol/L), respectively, in critically ill patients.

TREATMENT OF ACUTE KIDNEY INJURY

- Goals of Treatment: Short-term goals include minimizing the degree of insult to the kidney, reducing extrarenal complications, and expediting recovery of renal function. Restoration of renal function to pre-AKI baseline is the ultimate goal.

General Approach to Treatment

- There is no specific treatment that can reverse AKI or hasten its recovery. Supportive measures that focus on hemodynamics, fluid balance, acid–base balance, and electrolyte homeostasis are the mainstays of therapy.

Nonpharmacologic Therapy

- Fluid therapy is used to maintain or restore intravascular volume to assure adequate renal perfusion. Use IV fluids judiciously to prevent volume depletion and/or fluid overload which adversely affect kidney function and increase mortality.
- Serum electrolytes should be monitored daily. Hyperkalemia is the most common and serious electrolyte abnormality in AKI. Hypernatremia and fluid retention commonly occur, requiring calculation of daily sodium intake, including sodium contained in commonly administered antibiotics.
- Phosphorus and magnesium should be monitored, especially in patients with significant tissue destruction due to increased amounts of released phosphorus; neither is efficiently removed by dialysis.
- Nutritional management of critically ill patients with AKI is complex due to multiple mechanisms for metabolic derangements. Nutritional

requirements are altered by stress, inflammation, and injury that lead to hypermetabolic and hypercatabolic states.

- In severe AKI, renal replacement therapy (RRT), such as hemodialysis and peritoneal dialysis, is used to treat fluid overload, electrolyte disturbances (eg, hyperkalemia), acid–base imbalances, uremic complications, and pulmonary edema. See **Table 74-4** for indications for RRT in AKI. Intermittent and continuous (CRRT) options have different advantages (and disadvantages); the choice usually depends on physician preference and resources available. No difference in mortality or dialysis dependence has been shown; however, CRRT is generally preferred in hemodynamically unstable patients.

- Intermittent hemodialysis (IHD) is the most frequently used RRT and has the advantage of widespread availability and the convenience of lasting only 3–4 hours. Disadvantages include difficult venous dialysis access in hypotensive patients and hypotension due to rapid removal of large amounts of fluid.

- Several CRRT variants have been developed including continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF) which differ in fluid clearance and solute removal. CRRT gradually removes solute, resulting in better tolerability by critically ill patients. Disadvantages include limited availability of equipment, need for intensive nursing care, and the need to individualize IV replacement, dialysate fluids, and drug therapy adjustments.

- Circuit clotting and filter patency limit CRRT performance requiring anticoagulation. The KDIGO Work Group recommends regional citrate as the preferred anticoagulant. This requires infusion of parenteral calcium which may limit feasibility of regional citrate when the supply of parenteral calcium is limited. The specific approach to anticoagulation is patient specific; if the patient requires systemic anticoagulation for an underlying comorbidity (eg, atrial fibrillation, artificial heart valve) no additional anticoagulation for RRT is needed.

TABLE 74-4

Common Indications for Renal Replacement Therapy

Indication for RRT	Clinical Setting
A: *a*cid–base abnormalities	Metabolic acidosis (especially if pH <7.2)
E: *e*lectrolyte imbalance	Severe hyperkalemia and/or hypermagnesemia
I: *i*ntoxications	Salicylates, lithium, methanol, ethylene glycol, theophylline, phenobarbital
O: fluid *o*verload	Fluid overload (especially pulmonary edema unresponsive to diuretics)
U: *u*remia	Uremia or associated complications (neuropathy, encephalopathy, pericarditis)

Pharmacologic Therapy

- Loop diuretics effectively reduce fluid overload but can worsen AKI. Equipotent doses of loop diuretics (**furosemide, bumetanide, torsemide**, and **ethacrynic acid**) have similar efficacy. KDIGO guidelines recommend limiting the use of loop diuretics to the management of fluid overload and avoiding their use for the sole purpose of prevention or treatment of AKI. Continuous infusions of loop diuretics appear to overcome diuretic resistance and to have fewer adverse effects than intermittent boluses but require more extensive and frequent monitoring.

- Strategies are available to overcome diuretic resistance (**Table 74-5**). Combination therapy of loop diuretics plus a diuretic from a different pharmacologic class such as diuretics that work at the distal convoluted tubule **(thiazides)** or the collecting duct (**amiloride, triamterene**, and **spironolactone**) may have a synergistic effect. **Metolazone** is commonly used with a loop diuretic because, unlike other thiazides, it produces effective diuresis at GFR less than 20 mL/min (0.33 mL/sec).

TABLE 74-5

Common Causes of Diuretic Resistance in Patients with Acute Kidney Injury

Causes of Diuretic Resistance	Potential Therapeutic Solutions
Excessive sodium intake (sources may be dietary, IV fluids, and drugs)	Remove sodium from nutritional sources and medications
Inadequate diuretic dose or inappropriate regimen	Increase dose, increase frequency, use continuous infusion, or add thiazide
Reduced oral bioavailability (usually furosemide)	Use parenteral therapy, switch to oral torsemide or bumetanide
Nephrotic syndrome (loop diuretic protein binding in tubule lumen)	Increase dose, add thiazide
Reduced renal blood flow	
Drugs (NSAIDs, ACEIs, vasodilators)	Discontinue these drugs if possible
Intravascular depletion	Intravascular volume expansion
Increased sodium resorption	
Distal nephron hypertrophy	Add thiazide, sodium restriction
Postdiuretic sodium retention	Dietary sodium restriction, use continuous infusion
Heart failure	Assess effective circulatory volume, increase dose, increase frequency, use continuous infusion
Cirrhosis	Assess effective circulatory volume, consider paracentesis
Acute tubular necrosis	Increase diuretic dose, diuretic combination therapy

ACEIs, angiotensin-converting enzyme inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs.

Drug-Dosing Considerations

- Drug therapy optimization in AKI is a challenge. Confounding variables include residual drug clearance, fluid accumulation, and use of RRTs.
- Pharmacotherapy decisions should take into consideration the four distinct phases of AKI: initiation, extension, maintenance, and recovery phase. This requires frequent monitoring and adjustment of drug dosing to optimize therapy as kidney function stabilizes.
- Volume of distribution for water soluble drugs is significantly increased due to edema. Use of dosing guidelines for chronic kidney disease (CKD) does not reflect the clearance and volume of distribution in critically ill AKI patients.
- Patients with AKI may have a higher residual nonrenal clearance than those with CKD with similar creatinine clearances; this complicates drug therapy individualization, especially with RRTs.
- The mode of CRRT determines rate of drug removal, further complicating individualization of drug therapy. Rates of ultrafiltration, blood flow,

and dialysate flow influence drug clearance during CRRT.

EVALUATION OF THERAPEUTIC OUTCOMES

- Vigilant monitoring of patient status is essential (**Table 74-6**).
- Perform therapeutic drug monitoring for drugs that have a narrow therapeutic index if results can be obtained in a timely manner.

TABLE 74-6

Key Monitoring Parameters for Patients with Established Acute Kidney Injury

Parameter	Frequency
Fluid intake and output	Daily
Patient weight	Daily
Hemodynamics (eg, blood pressure, heart rate, mean arterial pressure.)	Hourly/Every shift
Blood chemistries	
Sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium	Daily
Blood urea nitrogen/serum creatinine	Daily
Drugs and their dosing regimens	Daily
Nutritional regimen	Daily
Blood glucose	Daily (minimum)
Therapeutic drug monitoring of renally cleared drugs (eg, vancomycin aminoglycosides)	Highly variable, about three times weekly
Times of administered doses	Daily
Doses relative to administration of renal replacement therapy	Daily
Urinalysis, urinary output	
Calculate measured creatinine clearance	Every time measured urine collection performed
Calculate fractional excretion of sodium	Every time measured urine collection performed
Plans for renal replacement therapy	Daily

See Chapter 60, Acute Kidney Injury, authored by Jenana Halilovic Maker, Lauren Roller, and William Dager, for a more detailed discussion of this topic.