Acute Kidney Injury

Definition

Acute kidney injury (AKI) is characterized by a sudden decrease in kidney function commonly accompanied by decreased urine output, fluid retention, metabolic acidosis, hyperkalemia, and hyperphosphatemia. The Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group definitions for AKI are described in **Table 25**.

Table 25. Open in New Window

KDIGO Definition of Acute Kidney Injury[a]

Stage[b]	Serum Creatinine Criteria	Urine Output Criteria
1	Increase in S_{Cr} to 1.5 to 1.9 times baseline within 7 days or ≥0.3 mg/dL (26.5 µmol/L) within 48 h	<0.5 mL/kg/h for 6 to 12 h
2	Increase in S_{Cr} to 2 to 2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	Increase in S_{Cr} to 3 times baseline or ≥4.0 mg/dL (353.6 µmol/L) or initiation of RRT or, in patients <18 years, a decrease in eGFR to <35 mL/min/1.73 m^2	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

eGFR = estimated glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes; RRT = renal replacement therapy; S_{Cr} = serum creatinine.

[a]The KDIGO definition is based on the RIFLE (Risk, Injury, Failure, Loss, and ESKD) and AKIN (Acute Kidney Injury Network) criteria.

[b]The definition of acute kidney injury in any stage can be met by fulfilling either the serum creatinine criteria or the urine output criteria. Classification follows correction of volume status and relief of obstruction.

Multiple studies have shown a correlation between more severe stages of AKI and higher mortality and health care utilization. Patients with AKI have an increased risk for developing chronic kidney disease (CKD) and end-stage kidney disease (ESKD). Likewise, patients with preexisting CKD are at an increased risk for developing AKI, a condition known as acute-on-chronic kidney disease.

Key Point

- The Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group defines acute kidney injury by any of the following: increase in serum creatinine by ≥0.3 mg/dL (26.5 µmol/L) within 48 hours; an increase in serum creatinine to ≥1.5 times baseline over 7 days; or a urine volume <0.5 mL/kg/h for 6 hours.

Epidemiology and Pathophysiology

The incidence of AKI is estimated to be about 20% of all hospital admissions, of which approximately 10% require dialysis support. AKI affects >50% of patients in the ICU. Mortality varies depending on the severity of AKI, underlying cause, and patient population. Critically ill patients with AKI in the context of multiorgan failure have been reported to have mortality rates >50% when dialysis therapy is required.

AKI can be divided into prerenal, intrinsic, and postrenal causes and can be due to pharmacologic and nonpharmacologic causes (**Table 26** and **Table 27**). Prerenal AKI (prerenal azotemia) is caused by decreased renal perfusion. The integrity of renal tissue is preserved, and tubular and glomerular function remains normal. Intrinsic AKI is caused by structural damage to the renal parenchyma. Postrenal AKI refers to AKI caused by urinary tract obstruction. Prerenal AKI and acute tubular necrosis (ATN) account for approximately 65% to 75% of AKI cases in hospitalized patients.

Table 26. Open in New Window

Pharmacologic Causes of Acute Kidney Injury

Cause	Examples

Prerenal	
Volume depletion	SGLT2 inhibitors, diuretics
Intrarenal/afferent arteriolar vasoconstriction	NSAIDs (including COX-2 inhibitors); amphotericin B; calcineurin inhibitors; iodinated radiocontrast agents
Efferent arteriolar vasodilation	Renin inhibitors; ACE inhibitors; ARBs
Intrinsic	
Acute tubular necrosis	Aminoglycosides; vancomycin, particularly in combination with piperacillin-tazobactam; polymyxins; lithium; amphotericin B; pentamidine; cisplatin; foscarnet; tenofovir; cidofovir; carboplatin; ifosfamide; zoledronate; contrast agents; sucrose; immune globulins; mannitol; hydroxyethyl starch; dextran; synthetic cannabinoids; amphetamines
Acute interstitial nephritis	Etiologies of acute interstitial nephritis are similar to those for chronic tubulointerstitial nephritis. Acute interstitial nephritis may lead to chronic tubulointerstitial nephritis with protracted exposure (see Table 19)
Acute glomerulonephritis	ANCA-associated drugs, such as minocycline and levamisole (veterinary antihelmintic used in some cocaine preparations)
Acute vascular syndromes	Drug-induced TMA: quinine; cancer therapies (gemcitabine, mitomycin, bortezomib, sunitinib); calcineurin inhibitors (cyclosporine, tacrolimus); drugs of abuse (cocaine, ecstasy, intravenous extended-release oxymorphone); clopidogrel; anti-angiogenesis drugs; interferon; mTOR inhibitors
Intratubular obstruction	Crystals: sulfonamides; triamterene; ciprofloxacin; ethylene glycol; acyclovir; indinavir; atazanavir; methotrexate; orlistat; large doses of vitamin C; sodium phosphate purgatives

AKI = acute kidney injury; ARB = angiotensin receptor blocker; COX = cyclooxygenase; mTOR = mammalian target of rapamycin; SGLT2 = sodium-glucose cotransporter 2; TMA = thrombotic microangiopathy.

Table 27. Open in New Window

Nonpharmacologic Causes of Acute Kidney Injury

Cause	Examples
Prerenal	
Volume depletion	Renal losses; GI fluid losses; hemorrhage; burns
Decreased cardiac output	Heart failure; massive pulmonary embolus; acute coronary syndrome
Systemic vasodilation	Sepsis; cirrhosis; anaphylaxis; anesthesia
Intrinsic	
Acute tubular necrosis	Ischemic: prolonged prerenal AKI from hypovolemia, sepsis, or other causes of hypoperfusion Pigment: rhabdomyolysis; intravascular hemolysis
Acute interstitial nephritis	Etiologies of acute interstitial nephritis are similar to those for chronic tubulointerstitial nephritis. Acute interstitial nephritis may lead to chronic tubulointerstitial nephritis with protracted exposure (see Table 20)
Acute	Infection-related glomerulonephritis; cryoglobulinemia; IgA; lupus nephritis; renal vasculitis, including

glomerulonephritis	ANCA-associated; anti–GBM antibody disease
Acute vascular syndromes	Macrovascular: renal artery occlusion; renal vein thrombosis; polyarteritis nodosa Microvascular: Disease-associated TMA: HUS; atypical HUS; TTP; HELLP; scleroderma renal crisis; hypertensive emergency Atheroembolic disease
Intratubular obstruction	Paraprotein: myeloma; TLS
Postrenal	
Upper tract obstruction	Nephrolithiasis; blood clots; external compression
Lower tract obstruction	BPH; neurogenic bladder; blood clots; cancer; urethral stricture

AKI = acute kidney injury; ANCA = antineutrophil cytoplasmic antibody; BPH = benign prostatic hyperplasia; GBM = glomerular basement membrane; GI = gastrointestinal; HELLP = hemolysis, elevated liver enzymes, and low platelets; HUS = hemolytic uremic syndrome; TLS = tumor lysis syndrome; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura.

Key Point

- Prerenal acute kidney injury and acute tubular necrosis account for approximately 65% to 75% of acute kidney injury cases in hospitalized patients.

Clinical Manifestations

Patients with AKI can be asymptomatic until extreme loss of kidney function occurs, and patients with mild to moderate AKI are often diagnosed by laboratory studies only. Patients with AKI can also present with oliguria (urine output <500 mL/d or <0.3 mL/kg/h) or anuria (urine output <50 mL/d). Severe AKI can lead to symptoms from volume overload, electrolyte abnormalities, and uremia. Acute uremic symptoms include nausea, vomiting, anorexia, fatigue, muscle cramps, restless legs, confusion, and pruritus. Physical signs may include asterixis. Other manifestations may be bleeding (due to platelet dysfunction), pericarditis, and seizures. Drug or metabolite accumulation and toxicity may complicate the course.

Key Point

- Patients with acute kidney injury (AKI) can be asymptomatic until extreme loss of kidney function occurs; severe AKI can lead to symptoms from volume overload, electrolyte abnormalities, and uremia.

Diagnosis

The diagnosis of AKI is based on increased levels of serum creatinine. The most reliable way to distinguish AKI from CKD is knowledge of previous serum creatinine levels; documentation of similarly elevated creatinine levels for ≥3 months suggests that the kidney failure is chronic. However, serum creatinine concentration can be increased by multiple factors independent of kidney function, limiting its specificity for diagnosis of AKI. Serum creatinine is not a sensitive marker of kidney injury in patients with sepsis, liver disease, muscle wasting, or fluid overload and does not provide any information regarding the cause of AKI. Moreover, the rise in serum creatinine is delayed 24 to 36 hours after the onset of injury and decline in glomerular filtration rate (GFR).

The history focuses on identifying vasoactive and potential nephrotoxic medications (including over-the-counter medications, herbal products, and recreational drugs); recent exposure to iodinated contrast agents; other predisposing conditions for AKI; and urinary obstructive symptoms (see **Table 26** and **Table 27**). Physical examination focuses on blood pressure, heart rate, signs of volume

status such as jugular venous pressure level and skin turgor, and bladder percussion/palpation. Laboratory evaluation includes blood urea nitrogen (BUN) and creatinine concentrations, electrolytes, complete blood count, and assessment of the urine (urine indices, urinalysis, and microscopic evaluation of the urine sediment) (**Table 28** and **Table 29**).

In patients with oliguria, the fractional excretion of sodium (FE_{Na}) or urea (FE_{Urea}) can help distinguish between prerenal AKI and ATN, with some caveats (see **Table 28**).

Ultrasonography of the kidneys (**Video 1**) and bladder should be obtained to exclude urinary tract obstruction and when the underlying cause of AKI is unclear. Kidney size may help distinguish between AKI and CKD, because diminished kidney size with increased cortical echogenicity and/or thinning suggests CKD. Kidney size can be normal in patients with CKD from infiltrative disorders such as diabetes mellitus, HIV-associated nephropathy, amyloidosis, or multiple myeloma. Kidney biopsy should be considered in patients with AKI from no apparent cause, suspected glomerulonephritis, or unexplained systemic disease.

Key Points

- In patients with suspected acute kidney injury, physical examination focuses on blood pressure, heart rate, signs of volume status, and bladder percussion/palpation.
- Ultrasonography of the kidneys and bladder should be obtained for suspected urinary tract obstruction or when the underlying cause of acute kidney injury is unclear.

Causes

AKI can be divided into prerenal, intrinsic, and postrenal causes.

Prerenal Acute Kidney Injury

See **Table 26** and **Table 27** for the causes of prerenal AKI.

Prerenal AKI (prerenal azotemia) is caused by underperfusion of the kidney with a subsequent decrease in GFR, which is reversible with appropriate therapy. Renal hypoperfusion can occur due to intravascular volume depletion, decreased effective arterial circulation, renal vasoconstriction, and/or medications. Patients may have a history of acute hemorrhage, loss of gastrointestinal fluids, heart failure, decompensated liver disease, sepsis, or recent diuretic or NSAID use. Physical signs of hypovolemia include hypotension, tachycardia, orthostasis, and decreased skin turgor. Patients with heart failure or cirrhosis have physical examination findings supporting these conditions.

In prerenal AKI, the kidney responds by reabsorbing urea, sodium, and water. Laboratory values that support a diagnosis of prerenal AKI are listed in **Table 28**. Prerenal AKI due to hypovolemia can be distinguished from ATN by the response to a volume challenge. Improvement in urine output (if oliguric) and serum creatinine support the diagnosis of a prerenal etiology.

Drug-induced prerenal AKI typically results from decreased blood flow to the kidney or intraglomerular hemodynamic alterations. Sodium-glucose cotransporter-2 inhibitors or diuretics can cause prerenal AKI from volume depletion. Drugs impairing vasodilatation of the afferent arterioles (such as NSAIDs) or vasoconstriction of the efferent arterioles (such as ACE inhibitors or angiotensin receptor blockers) can cause prerenal AKI, especially in the setting of volume depletion, decreased effective arterial circulation, or preexisting CKD. Calcineurin inhibitors such as cyclosporine and tacrolimus can cause prerenal AKI from afferent arteriolar vasoconstriction.

Management of prerenal AKI includes discontinuing nephrotoxins and increasing renal perfusion by treating the underlying cause, such as correcting volume deficits. If prerenal AKI is not recognized and treated in a timely fashion, prolonged renal hypoperfusion can result in ATN and progressive intrinsic kidney failure.

Key Points

- Prerenal acute kidney injury is caused by underperfusion of the kidney with a subsequent decrease in glomerular filtration rate, which is reversible with discontinuing nephrotoxins and treating the underlying cause.
- Renal hypoperfusion can occur due to intravascular volume depletion, decreased effective arterial circulation, or renal vasoconstriction.

Intrinsic Kidney Diseases

Intrinsic AKI occurs from structural damage to the renal tubules, interstitium, glomerulus, or vascular structures, or from intratubular obstruction (see **Table 26** and **Table 27**).

Acute Tubular Necrosis

ATN due to ischemia, nephrotoxins, and/or sepsis is the most common cause of AKI in hospitalized patients. A history of sepsis, documented protracted hypotension, or nephrotoxin exposure along with assessment of hemodynamics and volume status can aid in the diagnosis. Laboratory values suggestive of ATN are described in **Table 28**. Urine sediment may be bland but is usually notable for the presence of tubular epithelial cells and coarse granular (muddy brown) casts (**Figure 18**).

Table 28. Open in New Window

Diagnostic Findings Differentiating Prerenal Acute Kidney Injury From Acute Tubular Necrosis

Condition	BUN-Creatinine Ratio	Urine Osmolality (mOsm/kg H_2O)	Urine Sodium (mEq/L [mmol/L])	FE_{Na}[a]	FE_{Urea}[b]	Urinalysis and Microscopy
Prerenal	>20:1	>500	<20	<1%[c]	<35%	Specific gravity >1.020; normal or hyaline casts
Acute tubular necrosis	10-15:1	~300	>40	>2%[d]	>35%	Specific gravity ~1.010; pigmented granular (muddy brown) casts and tubular epithelial cells

BUN = blood urea nitrogen; FE_{Na} = fractional excretion of sodium; FE_{Urea} = fractional excretion of urea.

[a] FE_{Na} = (Urine sodium concentration × Plasma creatinine concentration)/(Urine creatinine concentration × Plasma sodium concentration) × 100.

[b] FE_{Urea} = (Urine urea concentration × Plasma creatinine concentration)/(Urine creatinine concentration × Plasma urea concentration) × 100

[c] FE_{Na} can be high in prerenal states with diuretic use, adrenal insufficiency, or metabolic alkalosis.

[d] FE_{Na} can be low in acute tubular necrosis due to contrast-associated nephropathy, pigment nephropathy, glomerulonephritis, or early obstruction.

Unlike prerenal AKI, ATN does not rapidly improve with restoration of intravascular volume and blood flow to the kidneys. Treatment is supportive because no efficacious pharmacologic therapies exist. Complete or partial renal recovery can take days to weeks. Nonoliguric ATN portends a better renal prognosis than oliguric ATN. Patients with advanced CKD are less likely to recover kidney function compared with patients with baseline normal kidney function or early CKD. Patients with severe ATN who require acute dialysis often recover kidney function but may progress to dialysis-dependent ESKD.

Ischemic Acute Tubular Necrosis

Severe ischemia due to prolonged hypotension, protracted prerenal state, or sepsis can cause ATN (see **Table 27**). The ischemic injury leads to cytokine release, oxygen-free radical and enzyme production, endothelial activation and leukocyte adhesion, activation of coagulation, and apoptosis. GFR declines because of renal vasoconstriction, tubular back leak of filtrate into the bloodstream, and tubular obstruction from sloughed cellular debris.

Normotensive ischemic ATN can occur without overt hypotension in conditions with impaired renal autoregulation. These conditions include older age, hypertension, atherosclerotic or renovascular disease, and CKD. Patients with hypertension can develop normotensive ischemic ATN if their blood pressure is decreased to a value lower than what they are accustomed to but within normal range. Management involves treating any volume deficits and decreasing antihypertensive medications to allow the blood pressure to increase to baseline levels.

Drug-Induced Acute Tubular Necrosis

Drug-induced ATN can be a consequence of prolonged hemodynamic alterations or direct tubular injury (see **Table 26**). The drugs associated with prerenal AKI can cause ATN from prolonged hypoperfusion. Early

Related Question

recognition and prompt discontinuation of the drug are essential for renal recovery. The risk of drug-induced ATN increases in older persons and in patients with decreased effective arterial circulation, CKD, or concomitant nephrotoxin exposure. Hypomagnesemia, hypokalemia, hypophosphatemia, hypocalcemia, and metabolic acidosis may reflect underlying tubular injury.

Question 43

Osmotic nephrosis is a form of tubular injury due to hyperosmolar substances such as sucrose-containing intravenous immunoglobulin, mannitol, hydroxyethyl starch, dextran, and contrast media. It is characterized by vacuolization and swelling of the renal proximal tubular cells with resultant tubular obstruction and damage.

Contrast agents can cause nonoliguric ATN primarily through renal vasoconstriction and oxygen-free, radical-associated injury. The serum creatinine increases within 24 to 48 hours after contrast administration. Aminoglycosides cause nonoliguric ATN through direct tubular toxicity with an increase in serum creatinine occurring 5 to 7 days after initiation of therapy. Cisplatin causes ATN through direct tubular toxicity, renal vasoconstriction, and inflammation. Amphotericin B causes dose-related AKI through both renal vasoconstriction and direct tubular toxicity and may be associated with arginine vasopressin resistance in addition to the aforementioned tubular defects. Lipid-based preparations decrease the risk for nephrotoxicity. Vancomycin nephrotoxicity occurs in the setting of high trough levels (>15 mg/L), high vancomycin dose (≥4 g/d), prolonged duration of therapy, and/or concomitant nephrotoxic drugs, most notably an aminoglycoside or piperacillin-tazobactam. Certain types of synthetic cannabinoids used as recreational drugs have been associated with ATN.

Pigment Nephropathy

Heme pigment released from myoglobin or hemoglobin can cause AKI through intravascular volume depletion (seen in rhabdomyolysis), renal vasoconstriction, direct proximal tubular injury, and tubular obstruction. Urine heme pigment from myoglobin or hemoglobin causes a positive urine dipstick for blood with the absence of erythrocytes on sediment examination.

Related Questions

Question 51

Question 77

In rhabdomyolysis, myoglobin is released in the circulation from damaged skeletal muscle. Major causes of rhabdomyolysis include trauma, drugs and toxins, seizures, metabolic and electrolyte disorders, endocrinopathies (diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, hypothyroidism), and intense exercise, particularly in poorly conditioned individuals. Rhabdomyolysis-induced AKI is more likely to occur with serum creatine kinase levels >5000 U/L. In addition to elevated serum creatine kinase and serum creatinine levels, hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia, metabolic acidosis, increased lactate dehydrogenase (LDH) concentration, and increased aspartate and alanine aminotransferase levels can occur. Urinary findings include FE_{Na} <1% (due to renal vasoconstriction), myoglobinuria, and pigmented (red) granular casts.

In addition to correcting the underlying cause, prevention and management of AKI involve aggressive intravenous isotonic fluid resuscitation aimed at maintaining urine output >200 to 300 mL/h. Although limited studies suggest that alkalinization of the urine with intravenous bicarbonate to increase the urine pH >6.5 may prevent tubular cast formation, there is no evidence that such alkaline diuresis either prevents rhabdomyolysis-related AKI or hastens its recovery. If urine alkalinization is used, it should be closely monitored and discontinued if the patient develops symptomatic hypocalcemia or arterial pH >7.5, or if urine pH does not increase to >6.5 after several hours. Dialysis may be necessary for severe electrolyte and acid-base abnormalities. Most patients have partial or complete renal recovery.

Heme pigment nephropathy is less common and occurs when large amounts of heme pigment are released into circulation due to intravascular hemolysis. Causes include glucose-6-phosphate dehydrogenase (G6PD) deficiency, drug reactions, cardiopulmonary bypass circuits, incompatible blood transfusion, paroxysmal nocturnal hemoglobinuria, malaria, certain poisonings, and snakebites. In addition to elevated serum creatinine concentration, other laboratory abnormalities include anemia, increased LDH, and decreased haptoglobin. Urinary findings include FE_{Na} <1%, hemoglobinuria, and pigmented granular casts. Treatment of hemoglobinuria involves treating the underlying cause as well as volume repletion with intravenous fluids.

Key Point

- Acute tubular necrosis due to ischemia, nephrotoxins, and/or sepsis is the most common cause of acute kidney injury in hospitalized patients; a history of sepsis, documented protracted hypotension, or nephrotoxin exposure along with hemodynamic and volume status assessment can aid in the diagnosis.

Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) is a common cause of AKI and is characterized by inflammation and edema of the interstitium. The classic clinical presentation of fever, rash, and peripheral eosinophilia occurs in only 10% to 30% of patients with AIN. Urinary findings can include leukocytes, erythrocytes, and leukocyte casts (see **Table 29**; see **Figure 2**). Urine eosinophils are neither sensitive nor specific for AIN, and testing is no longer recommended for diagnosis.

Related Question

Question 19

Table 29. Open in New Window

Urinalysis and Microscopy in Acute Kidney Injury

Condition	Findings
Acute interstitial nephritis	Mild proteinuria; leukocytes; erythrocytes; leukocyte casts
Acute glomerulonephritis	Proteinuria; dysmorphic erythrocytes; erythrocyte casts
Intratubular obstruction	Crystalluria or Bence-Jones proteinuria[a]
Acute vascular syndromes	Variable hematuria; sometimes mimics acute glomerulonephritis
Postrenal	Variable; bland

[a]Detected by urine immunofixation.

Drug-induced AIN, especially due to antibiotics, proton pump inhibitors, or NSAIDS, is the most common cause of AIN and should be considered in any patient with AKI, a characteristic urinalysis, and history of any drug exposure (see **Table 19**). Other causes include infections, toxin exposure, and systemic diseases such as autoimmune disorders (see **Table 20**). Typically, the serum creatinine gradually increases 7 to 10 days after drug exposure but can increase much sooner following repeat exposure of the drug.

Drug-induced AIN from NSAIDs, including selective cyclooxygenase-2 inhibitors, is usually not associated with fever, rash, or eosinophilia and develops 6 to 12 months after drug exposure. AIN from NSAIDs can be associated with the nephrotic syndrome due to minimal change glomerulopathy or membranous nephropathy. The onset of proton pump inhibitor–induced AIN is variable but typically occurs 10 to 13 weeks after exposure. Proton pump inhibitors are thought to be a risk factor for the development of CKD. Chemotherapeutic agents, including ifosfamide, immune checkpoint inhibitors, and pemetrexed, are an underrecognized cause of AIN.

Renal recovery from drug-induced AIN is usually complete if the drug is stopped immediately after the onset of kidney injury but may take weeks to several months. Irreversible interstitial fibrosis (chronic tubulointerstitial nephritis) can develop after 2 weeks of continued exposure. Kidney biopsy should be considered if there is no improvement in kidney function after 5 to 7 days of drug discontinuation. Early glucocorticoid administration may limit damage associated with drug-induced AIN.

Key Points

- Urine eosinophils are neither sensitive nor specific in the diagnosis of acute interstitial nephritis, and testing should not be obtained.
- Drug-induced acute interstitial nephritis is associated with a gradual increase in serum creatinine 7 to 10 days after drug exposure; renal recovery is usually complete if the drug is stopped immediately after the onset of kidney injury.

Acute Glomerulonephritis

Acute glomerulonephritis with AKI results from immune-mediated damage to glomeruli. Urinary findings include proteinuria, dysmorphic erythrocytes, and erythrocyte casts (see **Table 29**; see **Figure 2**). Constitutional signs and symptoms are often present. Serologic assays and kidney biopsy identify most causes. Early recognition is extremely important because, without treatment, it can be fatal and result in irreversible kidney damage. See Glomerular Diseases for more information.

Acute Vascular Syndromes

Macrovascular (large and medium vessel) or microvascular (small vessel) disease can cause AKI (see **Table 27**).

Related Questions

Question 9

Question 85

Acute renal arterial occlusion, most often embolic due to atrial fibrillation or atherosclerotic aortic disease, and acute renal vein thrombosis can cause acute renal infarction and present as abdominal or flank pain, elevated serum LDH levels, and hematuria. A notable risk of renal vein thrombosis accompanies the nephrotic syndrome, particularly with membranous nephropathy. Diagnosis may be made by kidney ultrasonography with Doppler. Treatment usually consists of anticoagulation and supportive care.

Patients with atherosclerotic disease who undergo an invasive vascular procedure such as vascular surgery or angiography are at increased risk for atheroembolic-induced AKI (cholesterol emboli). Atheroembolic events can occur spontaneously or several days to weeks after manipulation of the aorta. Plaque rupture causes cholesterol embolization to distal small- and medium-sized arteries, resulting in ischemia with end-organ damage. In addition to the kidneys, atheroemboli can affect the arteries in the skin, muscle, gastrointestinal tract, liver, eyes, and central nervous system. Physical examination findings may include livedo reticularis (lacy network of bluish red vessels, usually seen on legs) (see MKSAP 19 Rheumatology), Hollenhorst plaques on funduscopic examination (yellow refractile body within arteriole) (**Figure 19**), ulcerations, and blue toes from ischemia (**Figure 20**). Laboratory findings can include low serum complements, peripheral eosinophilia, and eosinophiluria; urinalysis may be unremarkable or can have proteinuria, microscopic hematuria, or erythrocyte casts. Treatment of atheroemboli is supportive and consists of risk factor reduction with aspirin, statins, and management of hypertension. Renal prognosis is poor.

AKI can also occur from polyarteritis nodosa. It causes microaneurysms of medium size and occasionally small arteries that subsequently rupture, resulting in hemorrhage, thrombosis, and organ ischemia and infarction, including AKI. See MKSAP 19 Rheumatology for more information.

AKI from microvascular disease can present as thrombotic microangiopathy (TMA) with microangiopathic hemolytic anemia, thrombocytopenia, and glomerular capillary thrombosis (see **Table 27**). See MKSAP 19 Hematology for more information. Urine may show hematuria, erythrocyte casts, and/or proteinuria. Treatment of TMA is based on the underlying cause.

Key Points

- In atheroemboli-induced acute kidney injury (AKI), plaque rupture, especially following a vascular procedure, causes cholesterol embolization resulting in ischemia with AKI and multisystem involvement; treatment is supportive.
- Physical findings of atheroembolic disease include livedo reticularis, digital gangrene, and yellow refractile bodies (Hollenhorst plaques) on funduscopic examination.
- Acute kidney injury from thrombotic microangiopathy (TMA) occurs in thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, preeclampsia, the HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome, hypertensive emergency, scleroderma renal crisis, and complement-mediated TMA (atypical hemolytic uremic syndrome).

Intratubular Obstruction

Intratubular obstruction can cause AKI through precipitation of either protein or crystals within the tubular lumen. Examples include monoclonal light chain deposition in multiple myeloma, calcium oxalate deposition from ethylene glycol ingestion, crystals from drugs, and uric acid from tumor lysis syndrome (see **Table 27**).

Related Question

Question 105

In multiple myeloma, AKI from light chain cast nephropathy is the most common type of kidney disease. Cast nephropathy is due to direct tubular toxicity and obstruction from the precipitation of filtered free light chains. See Kidney Manifestations of Deposition Diseases for more information.

Ethylene glycol intoxication causes AKI from intratubular precipitation of calcium oxalate crystals, which can be seen on urine

microscopy. Ethylene glycol should be suspected in a patient with a history of ingestion and whose laboratory studies demonstrate an increased anion gap metabolic acidosis and osmolal gap. Treatment consists of supportive care, the alcohol dehydrogenase inhibitor fomepizole, and hemodialysis if needed. Orlistat, a gastrointestinal lipase inhibitor used to induce clinically significant weight loss by fat malabsorption, has also been associated with intratubular calcium oxalate deposition and AKI. High doses of vitamin C, which is metabolized to oxalate, can also lead to AKI from calcium oxalate precipitation in the tubules.

Drugs associated with crystal-induced AKI are listed in **Table 26**. Urinary findings include hematuria, pyuria, and crystals. AKI is usually reversed after discontinuation of the drug. Predisposing factors include volume depletion, CKD, and changes in urine pH. Correction of volume depletion with intravenous fluids is critical for both the prevention and treatment of crystal-induced AKI. High-dose intravenous acyclovir can cause acyclovir crystal deposition in the tubules, which can be prevented by prior intravenous fluid administration and slow rate of drug infusion. Because crystals from sulfonamide antibiotics and methotrexate are more likely to form in acidic urine, urinary alkalinization can prevent crystal deposition. Crystals from protease inhibitors can cause AKI from both crystal deposition and nephrolithiasis.

Acute phosphate nephropathy is a potentially irreversible cause of AKI due to phosphate-containing bowel preparations. Although many of these agents have been removed from the U.S. market, acute phosphate nephropathy is occasionally seen in patients, particularly those with preexisting CKD, who have taken sodium phosphate retention enemas. A transient severe increase in serum phosphate in the setting of volume depletion causes acute and chronic tubular injury from tubular and interstitial precipitation of calcium phosphate crystals. AKI can present days to months after exposure. Predisposing factors include volume depletion, CKD, older age, NSAID use, and hypertension treated with ACE inhibitors, angiotensin receptor blockers, or diuretics.

Key Point

- Intratubular obstruction causes of acute kidney injury include monoclonal light chain deposition in multiple myeloma; calcium oxalate deposition from ethylene glycol ingestion, orlistat, and high doses of vitamin C; crystals from drugs; and uric acid or calcium phosphate crystal deposition from tumor lysis syndrome.

Postrenal Disease

Related Question

Question 35

Postrenal AKI can occur from obstruction anywhere from the renal pelvis to the external urethral meatus (see **Table 27**). Upper urinary tract obstruction (at the level of the ureters or renal pelvis) must be bilateral or affect a single functioning kidney to cause AKI. Obstruction of urinary flow leads to hydronephrosis and eventual renal parenchymal damage. If postrenal AKI is not treated promptly, the obstruction can predispose the patient to urinary tract infections and urosepsis, and it can also lead to CKD and ESKD.

Postrenal AKI should be suspected in patients with a history of benign prostatic hyperplasia, diabetes, nephrolithiasis, pelvic malignancies, previous retroperitoneal radiation therapy, abdominal or pelvic surgeries, or retroperitoneal adenopathy. Patients can present with anuria, oliguria, polyuria, or normal urine output. Symptoms of lower tract obstruction include abdominal fullness or pain, urinary frequency, urgency, hesitancy, nocturia, overflow incontinence, and incomplete voiding. Acute nephrolithiasis may present with flank pain and hematuria. Presenting signs of obstructive nephropathy may include hypertension. A distended palpable bladder may be evident in bladder outlet obstruction. Serum creatinine is typically elevated at presentation and is sometimes asymptomatic. Hyperkalemia and features of distal renal tubular acidosis may also be evident.

Lower urinary tract obstruction can be diagnosed by an elevated post-void bladder residual volume on ultrasound. Hydronephrosis on kidney ultrasound is present in most causes of obstruction, but false-negative results may occur in the early stages or from encasement of the ureter or kidney, as seen in retroperitoneal disease. Noncontrast CT is indicated for suspected nephrolithiasis. Although less sensitive than CT, kidney ultrasonography is less expensive, has no radiation exposure, and can be used in pregnant patients or when CT is unavailable. Treatment focuses on reversing the cause of the obstruction. Renal prognosis depends upon the severity and duration of the obstruction. Renal recovery is generally good if the obstruction is relieved within 1 to 2 weeks.

Key Points

- Postrenal acute kidney injury can occur from obstruction anywhere from the renal pelvis to the external urethral meatus; diagnosis can be made via ultrasonography or noncontrast CT, with generally good renal recovery if the obstruction is relieved within 1 to 2 weeks.

- In patients with postrenal acute kidney injury, the presence of normal urine output or polyuria do not exclude the possibility of obstructive uropathy.

Specific Clinical Settings

Contrast-Associated Nephropathy

Related Question

Question 2

Contrast-associated nephropathy (CAN), defined as an increase in serum creatinine levels within 24 to 48 hours of contrast exposure, is a common cause of reversible AKI in the hospital setting. Contrast-induced nephropathy (CIN) includes that subset of CAN in which the kidney injury can be more definitively linked to the contrast. Multiple risk factors have been associated with CAN, but a baseline reduction in estimated GFR (eGFR) appears most important, especially in patients with AKI as well as in patients with CKD and an eGFR <30 mL/min/1.73 m^2.

The AKI tends to be nonoliguric, with an FE_{Na} <1%. The urine sediment may be bland or show classic ATN findings. In addition to advanced CKD, risk factors include diabetic kidney disease, conditions of decreased renal perfusion, high contrast dose, hyperosmolar contrast, and intra-arterial contrast administration. The risk for CAN is lower than previously thought. Use of contrast without a suitable alternative should not be avoided solely on the basis of CAN risk.

Preventive strategies for patients at high risk for CAN include minimizing the amount of contrast and prophylactically administering intravenous isotonic saline. Prophylactic saline should be administered to all patients with an eGFR <30 mL/min/1.73 m^2 and should be considered for patients with an eGFR of 30 to 44 mL/min/1.73 m^2 who have other risk factors for AKI. There is no role for prophylactic intravenous sodium bicarbonate nor hemodialysis or hemofiltration following contrast exposure. Treatment of CAN is supportive.

Cardiorenal Syndrome

Cardiorenal syndrome (CRS) is a disorder of the heart and kidneys whereby acute or long-term dysfunction in one organ induces acute or long-term dysfunction in the other. CRS is characterized by the triad of concomitant decreased kidney function, diuretic-resistant heart failure with congestion, and worsening kidney function during heart failure therapy. It is seen primarily in heart failure with reduced ejection fraction. The decreased kidney function in CRS is thought to be due to neurohumoral activation, venous congestion and increased renal venous pressure, reduced renal perfusion, and right ventricular dysfunction.

Management is challenging because treatment directed toward improving cardiac function (diuretics, ACE inhibitor/angiotensin receptor blocker, vasodilators, and inotropes) can worsen kidney function. Current evidence does not support the use of ultrafiltration over intensive diuretic management. Decreased kidney function in patients with heart failure is an independent risk factor for all-cause mortality.

Hepatorenal Syndrome

Related Question

Question 25

Hepatorenal syndrome (HRS) is a potentially reversible functional kidney impairment that occurs in the setting of portal hypertension due to liver cirrhosis, severe alcoholic hepatitis, or acute liver failure. HRS is characterized by increased renal vasoconstriction and peripheral and splanchnic arterial vasodilation. Tubular function is preserved with the absence of significant hematuria and proteinuria, as well as lack of renal histological changes. Urine sodium concentration is typically <10 mEq/L (10 mmol/L).

Type 1 HRS is a clinical diagnosis made after exclusion of other causes of kidney dysfunction. It is characterized by a rise in serum creatinine of at least 0.3 mg/dL (26.5 µmol/L) and/or ≥50% from baseline within 48 hours, bland urinalysis, and normal findings on kidney ultrasound. Patients are often oliguric. Lack of improvement in kidney function after withdrawal of diuretics and 2 days of volume expansion with intravenous albumin supports the diagnosis. Type 2 HRS is defined as a more gradual decline in kidney function associated with refractory ascites.

Patients with HRS have an overall poor prognosis without liver transplantation. General management includes discontinuing diuretics, restricting sodium, restricting water in hyponatremic patients, and searching for precipitating factors. Therapeutic interventions include treatment with vasoconstrictors such as terlipressin (preferred), norepinephrine, or midodrine and octreotide, in combination with albumin infusion. Additional interventions may include placement of a transjugular intrahepatic portosystemic shunt in select patients, renal replacement therapy, and liver transplantation. Renal replacement therapy is usually reserved for

patients with severe AKI who are liver transplant candidates. See MKSAP 19 Gastroenterology and Hepatology for more information.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is characterized by the rapid lysis of malignant cells leading to hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and AKI. TLS typically occurs after initiation of chemotherapy in hematologic malignancies with high cell turnover rate, rapid growth rate, or high tumor bulk (acute leukemia or Burkitt lymphoma); however, it can also occur independent of chemotherapy. AKI occurs from deposition of uric acid and/or calcium phosphate crystals in the renal tubules.

Related Question

Question 70

Management of TLS requires the initiation of preventive measures in high-risk patients before cytotoxic therapy, as well as the timely initiation of supportive care for patients who develop TLS. Treatment of established TLS includes intravenous volume expansion, urate-lowering therapy, management of hyperkalemia and hyperphosphatemia, and renal replacement therapy in refractory cases. Patients at risk for or presenting with TLS require aggressive volume expansion to achieve a urine output of at least 80 to 100 mL/h. Urinary alkalinization is no longer recommended because the high urine pH can cause an increase in calcium phosphate crystal deposition. Allopurinol or febuxostat, inhibitors of xanthine oxidase, prevent the formation of new uric acid and are recommended as prophylaxis for patients at intermediate risk for TLS (those with highly chemotherapy-sensitive solid tumors); it has no effect on existing serum urate levels. Rasburicase, a recombinant urate oxidase that makes uric acid more soluble in urine with rapid reduction in serum urate levels, is given to patients at high risk for or with TLS. Rasburicase is contraindicated in patients with G6PD deficiency.

Abdominal Compartment Syndrome

Abdominal compartment syndrome (ACS) is defined as a sustained elevated intra-abdominal pressure (IAP) associated with new organ dysfunction. IAP >20 mm Hg is commonly associated with ACS, although the absolute pressure measurement is not a sufficient criterion. ACS occurs in the setting of abdominal surgery, trauma, hemoperitoneum, retroperitoneal bleed, ascites, bowel obstruction, ileus, and pancreatitis. It can also occur from capillary leak with concurrent massive fluid resuscitation. Increasing IAP causes hypoperfusion and ischemia of the intestines and other peritoneal and retroperitoneal structures, leading to hemodynamic, respiratory, neurologic, and kidney impairment. Renal vein compression and renal artery vasoconstriction can cause oliguric AKI.

Related Question

Question 59

ACS is diagnosed by measuring IAP; measurement of bladder pressure with an indwelling catheter is the standard methodology. Management includes supportive therapy, abdominal compartment decompression, and correction of positive fluid balance.

Key Points

- Preventive strategies for patients at high risk for contrast-associated nephropathy include minimizing the amount of contrast and expanding volume with intravenous isotonic saline.
- Cardiorenal syndrome is characterized by the triad of concomitant decreased kidney function, diuretic-resistant heart failure with congestion, and worsening kidney function during heart failure therapy.
- General management of hepatorenal syndrome includes discontinuing diuretics, restricting sodium, and treatment with vasoconstrictors in combination with albumin infusion.
- Treatment of established tumor lysis syndrome includes intravenous volume expansion, rasburicase, management of hyperkalemia and hyperphosphatemia, and renal replacement therapy in refractory cases.
- Abdominal compartment syndrome is diagnosed by measurement of bladder pressure with an indwelling catheter.

Management

General Considerations

In most cases of AKI, treatment of the underlying medical condition and discontinuation of nephrotoxic medications lead to improvement in kidney function. No specific pharmacologic therapy is effective in established ATN. Supportive measures include optimizing hemodynamics and renal perfusion, preventing further kidney injury, treating AKI complications, and providing

appropriate nutrition. Diuretics can be used for volume overload. Bicarbonate can be administered to correct metabolic acidosis. Dietary potassium, magnesium, and phosphate should be restricted. Phosphate binders may be required to prevent severe hyperphosphatemia. Medication dose adjustments for diminished GFR are necessary to avoid toxicities. An episode of AKI increases the risk for new or worsening CKD. Patients with AKI should be monitored during follow-up for complete recovery of function and/or emergence of CKD, and patients who had preexisting CKD should be evaluated for worsening function.

Renal Replacement Therapy

In some patients with severe AKI, initiation of renal replacement therapy (RRT) may be necessary to manage urgent complications, including hyperkalemia, metabolic acidosis, volume overload refractory to diuretics, uremic manifestations, and dialyzable toxins. Options for RRT for AKI include intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), "hybrid" therapies such as prolonged intermittent renal replacement therapy (PIRRT), and peritoneal dialysis (PD). IHD, CRRT, and PIRRT are extracorporeal therapies that require vascular access in the form of a large-bore, double-lumen central venous catheter; PD requires the placement of an intra-abdominal dialysis catheter and is utilized less frequently for AKI than for ESKD.

Related Questions

Question 16

Question 67

IHD, typically delivered 3 to 6 times a week for 3 to 5 hours per session, allows for rapid correction of electrolyte disturbances and rapid removal of drugs or toxins. The main disadvantage of IHD is the risk for hypotension caused by the rapid solute and volume removal. CRRT represents a variety of dialysis modalities developed specifically to manage critically ill patients with AKI who cannot tolerate IHD due to hemodynamic instability. CRRT is administered 24 hours daily and removes solutes and fluid much more slowly than IHD, resulting in better hemodynamic tolerance. PIRRT removes solutes and fluid more slowly than IHD but more quickly than CRRT and is administered 8 to 12 hours daily. Acute PD is not as effective as the other forms of RRT but may be useful when the other types of RRT are unavailable or vascular access cannot be obtained.

Randomized clinical trials have not shown a survival benefit of CRRT over IHD or PIRRT for critically ill AKI patients. CRRT or PIRRT is chosen for patients who are hemodynamically unstable. CRRT is also preferred in patients with cerebral edema because IHD may worsen neurologic status by compromising cerebral perfusion pressure. IHD is favored in patients who need rapid solute removal, such as those with severe hyperkalemia or drug intoxications. Transitions in therapy are common depending on the changing needs of the patient.

Studies of the timing of RRT initiation in critically ill patients and those with sepsis demonstrate no mortality benefit to early introduction of RRT compared with based on usual clinical criteria. In fact, the latter strategy was sometimes associated with avoiding the need for RRT.

Key Points

- In most cases of acute kidney injury, treatment of the underlying medical condition and discontinuation of nephrotoxic medications lead to improvement in kidney function.
- Patients with acute kidney injury should be evaluated in follow-up to monitor for complete recovery of function and/or emergence or worsening of chronic kidney disease.
- Renal replacement therapy is used to manage the urgent complications of severe acute kidney injury, including hyperkalemia, metabolic acidosis, volume overload refractory to diuretics, uremic manifestations, and dialyzable toxins.
- There is no proven benefit to early administration of renal replacement therapy versus timing based on usual clinical criteria in critically ill patients or those with sepsis.