Annals of Internal Medicine®

In the Clinic®

Acute Kidney Injury

Acute kidney injury is a heterogeneous group of conditions characterized by a sudden decrease in glomerular filtration rate, manifested by an increase in serum creatinine concentration or oliguria, and classified by stage and cause. This type of injury occurs in approximately 20% of hospitalized patients, with major complications including volume overload, electrolyte disorders, uremic complications, and drug toxicity. Management includes specific treatments according to the underlying cause and supportive treatment to prevent and manage complications. Kidney replacement therapy is used when complications cannot be managed with medical therapy alone. Despite advances in care, the mortality rate in patients requiring kidney replacement therapy remains approximately 50%.

Screening and Prevention

Diagnosis

Treatment

CME/MOC activity available at Annals.org.

Physician Writers
Andrew S. Levey, MD
Matthew T. James, MD
From Tufts Medical Center, Boston, Massachusetts; and the University of Calgary, Calgary, Alberta.

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Acute kidney injry (AKI) is not a single disease entity. It is a heterogeneous group of conditions characterized by a sudden decrease in glomerular filtration rate (GFR) followed by an increase in serum creatinine concentration (SCC) or oliguria. AKI generally occurs in the setting of acute or chronic illness. It affects approximately 20% of hospitalized patients, of whom 10% require kidney replacement therapy (KRT). Recent clinical guidelines from Kidney Disease Improving Global Outcomes (KDIGO) define AKI as a subgroup of acute kidney diseases and disorders (AKD), and classify AKI according to severity (stages) and cause, which influence prognosis and management (1). Major complications include volume overload, electrolyte disorders, uremic complications, and drug toxicity. Despite advances in prevention and treatment, the mortality in patients requiring KRT remains approximately 50%. AKI may occur in patients with or without underlying chronic kidney disease (CKD). Incomplete recovery may lead to new onset or worsening of CKD. Evaluation and management of AKI proceed in parallel rather than sequentially. The goals are to apply specific treatments according to the underlying cause and provide supportive care to prevent and treat complications. KRT is used when complications of kidney failure cannot be managed with medical therapy alone. The need for nephrologist consultation or comanagement depends on the stage, cause, and severity of complications. This review focuses on general features of AKI in adults in developed countries, not including pregnant women or kidney transplant recipients. AKI is a more serious problem in developing countries due to risk factors related to underdevelopment and lack of availability of KRT (2).

Screening and Prevention

Which patients are at increased risk for AKI, and how should clinicians identify them?

AKI generally occurs in the setting of acute and chronic illness, and is common among hospitalized patients.

A systematic review of large cohort studies, primarily among hospitalized patients, conducted between 2004 and 2012, showed significant heterogeneity in estimates among studies, countries, and clinical settings, and between adults and children (3). In studies of adults that identified AKI according to the KDIGO criteria and staging system, the pooled incidence rate of AKI was 21.6% (95% CI, 19.3%–24.1%). Approximately 10% required dialysis. The highest pooled AKI rate was observed in critical care settings (32%). In other studies, among hospitalized patients approximately two thirds of AKI episodes were community-acquired–the remaining one third were hospital-acquired (4, 5).

In 1 population-based study (6), the rate of adults with AKI but not CKD who required hospital admission was 0.1% per year. Approximately 10% required dialysis. Rates were substantially higher for patients with CKD. Decreased GFR and proteinuria were independent risk factors. Adjusted rate ratios were 2.5–4.4 for patients with GFR >60 mL/min/1.73 m^2 (CKD stages 1–2); 2.3–8.2 for GFR 45–59 mL/min/1.73 m^2 (CKD stage 3a); 5.6–13 for GFR 30-44 mL/min/1.73 m^2 (CKD stage 3b); and 13–19 for GFR 15–29 mL/min/1.73 m^2 (CKD stage 4).

The Box shows risk factors for AKI. Acute illness, complications of medications, and medical procedures are the most common. Older age and preexisting CKD are the main susceptibility factors. Risk prediction instruments are available for some high-risk settings, such as percutaneous coronary intervention, cardiac surgery, liver surgery, and vascular surgery (7–11).

AKI is generally asymptomatic, so screening is usually required for detection. The U.S. Preventive Services Task Force does not have recommendations regarding

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screening for AKI. KDIGO recommends screening based on stratification by risk according to exposures and susceptibility. Because there are few risk prediction instruments, we suggest the following approach guided by the clinical setting. For outpatients with acute illness, measure SCC and calculate estimated GFR (eGFR) and compare to previous ("baseline") values (12). Remeasure if SCC or eGFR are abnormal or worse than previous values. The urgency of repeated measurement depends on the severity of illness and the level of SCC and eGFR; hospitalization should be considered. For hospitalized patients, SCC and eGFR are generally measured on admission and should be measured daily or every other day. For patients with critical illness, SCC and eGFR, as well as urine output, should be measured at least daily. In our experience, accurate measurement of urine output is difficult, unless the patient is in an intensive care unit (ICU). In all settings, urinalysis should be done for detection of AKD and CKD.

Increased SCC and oliguria may not occur for several hours after the onset of an acute decline in GFR. Novel biomarkers are under investigation to determine whether they may enable earlier detection of decreased GFR and complications of AKI (13, 14).

Which measures are useful for preventing AKI, and when should they be used?

We recommend general measures to reduce exposures and susceptibility when possible—for example, correcting volume depletion by increasing oral salt and fluid intake or intravenous (IV) isotonic saline. Other examples are avoiding diuretics and angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) during acute illness to prevent volume depletion and hypotension, and avoiding nephrotoxic drugs in patients with CKD, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and iodinated radiocontrast media (contrast-induced AKI) (15–17).

Risk for contrast-induced AKI seems to be greater after arterial than venous administration of contrast media. For patients at increased risk for this disorder, KDIGO recommends using either an iso-osmolal or a low-osmolal medium (osmolality 2–3 times that of plasma) rather than a high-osmolal contrast medium (osmolality >4 times that of plasma). IV volume expansion with either an isotonic sodium chloride or a sodium bicarbonate solution should be done rather than no IV volume expansion. Several protocols are available for intra-arterial contrast administration, and these can be used for high-risk patients receiving IV contrast administration (18–22). Tailoring administration to left ventricular filling pressure can safely facilitate more volume expansion and reduce the incidence of contrast-induced AKI during cardiac catheterization (23, 24). A recent comparative effectiveness review compares other strategies for preventing this complication (25, 26).

We also recommend volume expansion with isotonic sodium chloride for other high-risk conditions, such as cardiac surgery; hemolysis; rhabdomyolysis; tumor lysis; and administration of cisplatinum, carboplatin, ifosphamide, and amphotericin B. Caution is warranted in patients with volume overload, and IV fluids should be discontinued if symptoms of volume overload develop (see below).

Monitoring therapeutic levels of nephrotoxic drugs, such as vancomycin, aminoglycosides, and calcineurin inhibitors, can reduce risk for AKI. KDIGO suggests additional measures to reduce the risk for nephrotoxicity of aminoglycosides and amphotericin B.

Risk Factors for Acute Kidney Injury

Exposures

- Critical illness
- Sepsis
- Circulatory shock
- Burns
- Trauma
- Cardiac surgery (especially with cardiopulmonary bypass)
- Major noncardiac surgery
- Nephrotoxic drugs
- Iodinated radiocontrast agents
- Poisonous plants and animals

Susceptibility factors

- Volume depletion
- Older age
- Female sex
- Black race
- Chronic kidney disease
- Other chronic diseases (heart, lung, liver)
- Diabetes mellitus
- Cancer
- Anemia

From reference 1.

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Screening and Prevention... AKI generally occurs in the setting of acute and chronic illness and is common among hospitalized patients. Older age and CKD are the main susceptibility factors. Measurement of SCC and eGFR and monitoring during hospitalization are essential to detect AKI. Urine output should be monitored in patients with critical illness. Urinalysis is helpful to detect AKD and CKD. General measures to reduce risk include prevention and treatment of volume depletion and avoidance of nephrotoxic drugs. IV isotonic fluids before, during, and after intra-arterial administration of iodinated radiocontrast media can reduce risk for contrast-induced AKI.

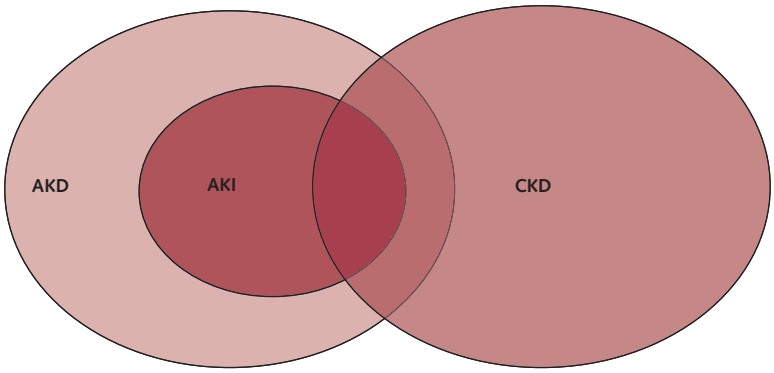
CLINICAL BOTTOM LINE

Diagnosis

What criteria should clinicians use to define and classify AKI?

AKI is a heterogeneous group of conditions, with a common definition (**Figure 1**) and classification based on severity (stages) and cause (**Figure 2**). KDIGO definition and staging are based on the Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE) and AKI Network (AKIN) criteria and studies on risk relationships. The rationale for defining AKI separately from other acute kidney diseases and disorders was to provide a more rigorous basis for research studies, clinical practice guidelines, and public health efforts.

Figure 1. **Relationships and definitions of kidney diseases and disorders.**

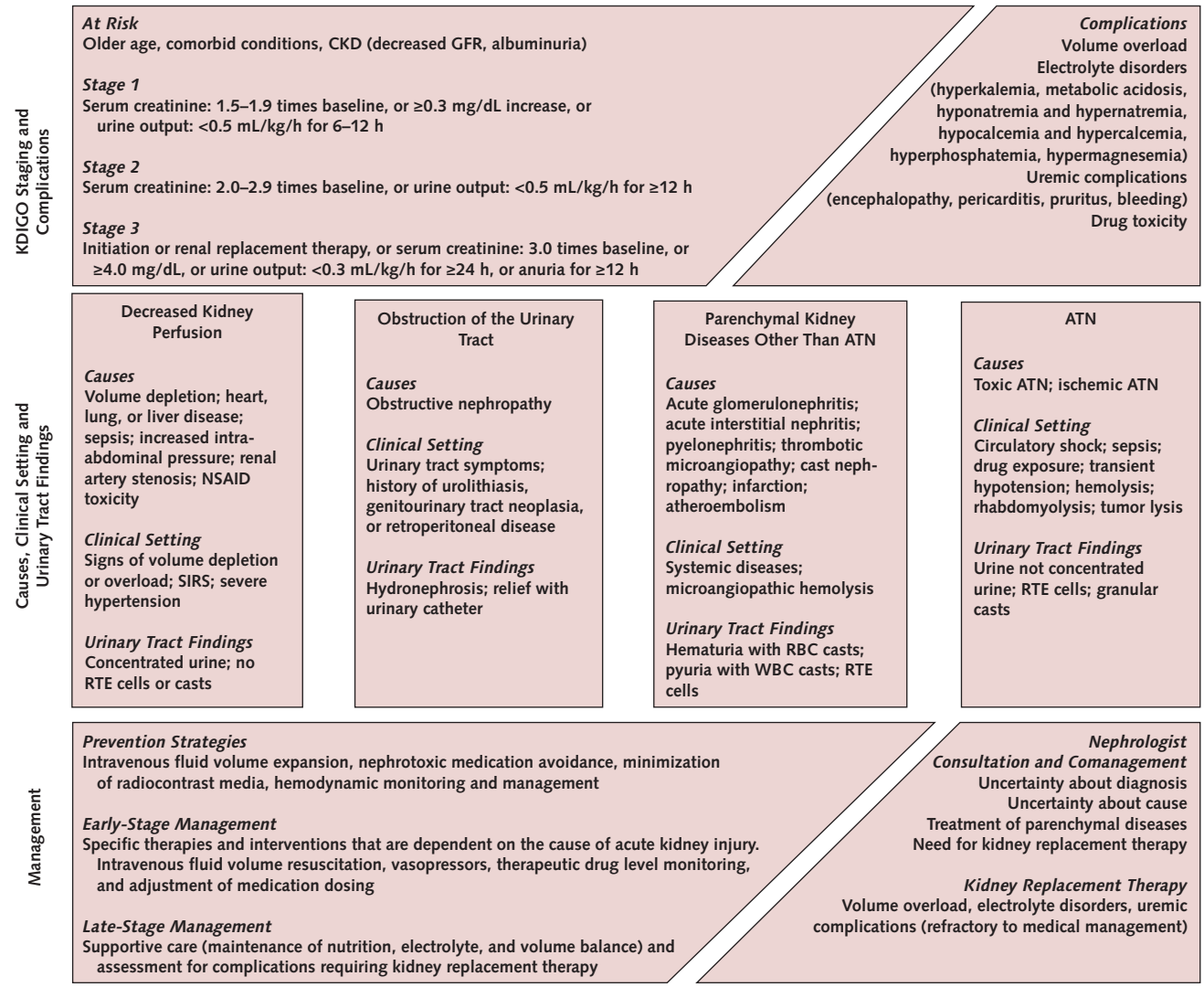


Variable	AKI	AKD	CKD	NKD*
Duration	Within 7 d	≤3 mo	>3 mo	
Functional criteria	Increase in serum creatinine concentration by ≥50% within 7 d OR Increase in serum creatinine concentration by ≥0.3 mg/dL within 2 d OR Oliguria for ≥6 h	AKI OR GFR <60 mL/min/1.73 m² OR Decrease in GFR by ≥35% times baseline OR Increase in serum creatinine concentration by ≥50% times baseline	GFR <60 mL/min/1.73 m²	GFR ≥60 mL/min/1.73 m²
Structural criteria	Not defined	Marker of kidney damage (albuminuria, hematuria, or pyuria is most common)	Marker of kidney damage for >3 mo (albuminuria is most common)	No marker of kidney damage

AKI = acute kidney injury; AKD = acute kidney diseases and disorders; CKD = chronic kidney disease; GFR = glomerular filtration rate; NKD = no kidney disease.
* Implies no functional or structural criteria according to the definitions for AKI, AKD, or CKD. Clinical judgment required for individual patient decision making.

The KDIGO definition of AKI includes a change in SCC within 2–7 days and oliguria for 6 or more hours. The stage is defined by the peak rise in SCC compared with previous values and nadir in urine output and is related to risk for complications and prognosis (**Figure 2**). eGFR is preferred to SCC for assessing GFR in the steady state (i.e., when GFR is stable) because the coefficients for age, sex, and race in the estimating equation take into account variation in creatinine generation by muscle, independent of GFR (12). A 1.5-, 2.0-, and 3.0-fold increase in SCC during steady-state conditions reflect a 39%, 57%, and 74% decrease in eGFR, respectively. However, during AKI, SCC may be in the nonsteady state, so changes in SCC and eGFR lag

Figure 2. **Overview of acute kidney injury.**



ATN = acute tubular necrosis; CKD = chronic kidney disease; GFR = glomerular filtration rate; NSAID = nonsteroidal anti-inflammatory drug; RBC = red blood cell; RTE = renal tubular epithelial; SIRS = systemic inflammatory response syndrome; WBC = white blood cell.

behind changes in GFR, and eGFR may be a less accurate estimate of measured GFR. Nonetheless, reporting eGFR in AKI may be useful because changes in eGFR show the direction and estimate the magnitude of changes in GFR.

The causes of AKI, which are categorized according to underlying pathophysiology, are decreased kidney perfusion, obstruction of the urinary tract, parenchymal kidney diseases other than acute tubular necrosis (ATN), and ATN (**Figure 2**). AKI often has more than 1 cause. Identifying causes other than ATN is important because specific treatment of other causes can reverse the decline in GFR, whereas treatment for ATN is supportive. The **Box** discusses features that distinguish decreased kidney perfusion from ATN.

Complications of AKI result from impaired excretory, endocrine, and metabolic kidney functions. Decreased GFR and tubular function lead to retained water and solutes, manifested by volume overload, hyperkalemia, high an-

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Features Distinguishing Decreased Kidney Perfusion From ATN

Extracellular fluid volume depletion or circulatory disorders associated with volume expansion are common in decreased kidney perfusion, whereas recent exposure to radiographic contrast or nephrotoxic drugs or hypotension is more prominent in ATN.

Decreased kidney perfusion improves rapidly after measures to increase kidney perfusion (e.g., intravenous fluid in volume depletion), but no such response is observed in ATN.

Decreased kidney perfusion usually has concentrated urine and no RTE cells or granular casts in urine; ATN usually has nonconcentrated urine, RTE cells, and granular casts.

ATN = acute tubular necrosis; RTE = renal tubular epithelial.

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ion gap metabolic acidosis, hyponatremia, hyperphosphatemia, hypermagnesemia, encephalopathy, pericarditis, pruritus, and bleeding due to platelet dysfunction. Deficiencies of erythropoietin and decreased synthesis of active vitamin D lead to anemia and hypocalcemia. During recovery from AKI, persistent impairment in tubular function despite increasing GFR may give rise to excessive water and solute loss, leading to volume depletion, hypernatremia, hypokalemia, non–anion gap metabolic acidosis, hypophosphatemia, hypomagnesemia, and hypercalcemia in some cases. Drug toxicity is common because of altered pharmacokinetics and pharmacodynamics. Complications may occur in other organ systems throughout the course of disease; multiple organ failure is associated with the highest mortality.

What clinical manifestations should clinicians look for?

AKI is generally asymptomatic until the onset of kidney failure, emphasizing the importance of monitoring SCC and eGFR and urine output in patients at increased risk. However, clinical manifestations are useful to determine the cause of AKI and detect its complications. After detection, whether rapid evaluation is necessary depends on the clinical setting and severity of AKI. We recommend a combined diagnostic and therapeutic approach (see the **Box**). If AKI is severe, treatment must begin concurrently with evaluation.

Evaluating Causes

Decreased kidney perfusion is the most common cause of community-acquired AKI, whereas ATN is the most common cause of hospital-acquired AKI.

Causes of community-acquired AKI were described in a large survey of hospital discharges in China. Of 4136 patients, 49% of AKI cases were due to decreased kidney perfusion, 12% were due to obstruction, 27% had "intrinsic kidney diseases" (parenchymal diseases, including ATN), and 12% were not classified (5). Causes of hospital-acquired AKI in patients were described in patients admitted to general medical or surgical services of an urban teaching hospital. Of 380 episodes, 39% were due to decreased kidney perfusion, 2% to obstruction, 3% to parenchymal kidney diseases other than ATN, and 55% to causes associated with ATN; 3% were not classified (27).

Decreased kidney perfusion decreases GFR and increases tubular reabsorption of sodium, chloride, urea, and water, leading to urine concentration. Volume depletion as the cause of decreased kidney perfusion should be considered in patients with a history of decreased oral intake, vomiting, diarrhea, increased ostomy output, excessive sweating, percutaneous fluid drainage, bleeding, dizziness, light-headedness, fainting, or recent weight loss, especially in the setting of dietary

Combined Diagnostic and Therapeutic Approach to AKI

Assess volume status; administer intravenous fluid if volume depleted or volume status is uncertain

Assess for indications for urgent kidney replacement therapy (volume overload, uremic complications, electrolyte disorders, drug toxicity)

Conduct urine studies

Consider additional laboratory tests and imaging

In all cases, thoroughly review the history of present illness, medical history, medications and exposure to radiocontrast media, recent surgery and other procedures, recent travel or exposure to infectious diseases, fluid intake and output, and laboratory tests and imaging and conduct a careful physical examination. In particular, assessment for complications should be done promptly to determine the need for urgent therapy.

AKI = acute kidney injury.

salt restriction or diuretic therapy. Increased GFR within hours of volume repletion with oral or IV fluids confirms the diagnosis. Decreased kidney perfusion due to exacerbations of chronic heart, lung, or liver disease manifests as weight gain and edema (cardiorenal and hepatorenal syndromes), often with low blood pressure. Sepsis may also be associated with low blood pressure and other features of the systemic inflammatory response syndrome. Intra-abdominal pressure may increase in critically ill patients with abdominal or pelvic disorders (trauma, hemoperitoneum, pancreatitis, surgery, radiologic procedures) or in conditions that do not originate in that region (fluid resuscitation, sepsis, burns). Bilateral renal artery stenosis may occur in patients with aortic aneurysm or diffuse atherosclerotic cardiovascular disease and causes severe hypertension. Use of NSAIDs can decrease kidney perfusion, even without volume or blood pressure abnormalities. ACEIs and ARBs reduce GFR in patients with acute and chronic kidney disease and may cause severe AKI in the setting of decreased kidney perfusion.

Obstruction of both kidneys or obstruction of a solitary kidney may cause AKI. Obstruction may be acute or chronic, complete or partial, due to upper or lower urinary tract disease, and due to lesions within or outside the urinary tract. Flank pain or a history of urolithiasis, genitourinary tract neoplasia, or retroperitoneal disease should raise suspicion for obstruction (28). Symptoms of lower urinary tract disease include dysuria, suprapubic pain, slow urine stream, and increased frequency of urination. Bladder distention may be detectable by physical examination. Gross hematuria (with blood clots) suggests lesions in the urinary tract. Complete obstruction causes anuria, but partial obstruction may cause polyuria due to impairment of tubular function. Immediate improvement in GFR is expected after relief of acute obstruction, but improvement after relief of chronic obstruction may be slow or incomplete.

Parenchymal kidney diseases other than ATN are frequent causes of AKI. Many of these diseases occur in the setting of systemic disorders (infections; vasculitis; inflammatory, myeloproliferative, or lymphoproliferative diseases; or drug toxicity) and may be associated with fever, night sweats, arthralgias, mononeuropathy, or skin rash. Glomerulonephritis may cause gross hematuria (without clots). Acute interstitial nephritis is generally due to an allergic or toxic drug reaction (see the **Box**). Bacterial pyelonephritis must be severe and bilateral to cause AKI and often causes flank pain with high fever. Urinary symptoms are prominent when pyelonephritis is caused by ascending infection from the lower urinary tract but may be absent in the presence of hematogeneous dissemination of bacteremia. Thrombotic microangiopathy is accompanied by mircoangiopathic hemolysis and thrombocytopenia with schistocytes. Cast nephropathy in myeloma is typically associated with a high tumor burden and large amounts of paraprotein in the urine and frequently with hypercalcemia. Renal infarction is associated with flank pain and abrupt onset of severe hypertension. Atheroembolism may occur after percutaneous intra-arterial procedures or surgery involving the aorta or initiation of anticoagulation.

The pathology of ATN is characterized by necrosis of tubular epithelial cells diffusely or local-

Drugs That Contribute to Acute Kidney Injury and the Pathophysiologic Mechanism of Injury*

- Iodinated radiocontrast media (acute tubular necrosis)
- Nonsteroidal anti-inflammatory drugs (decreased kidney perfusion and tubular toxicity)
- Aminoglycosides (acute tubular necrosis)
- Amphotericin B (acute tubular necrosis)
- β-Lactam antibiotics (interstitial nephritis)
- Sulfonamides (interstitial nephrtitis)
- Vancomycin (acute tubular necrosis)
- Acyclovir (crystal nephropathy)
- Tenofovir (tubular toxicity)
- Methotrexate (crystal nephropathy)
- Cisplatinum and carboplatin (acute tubular necrosis)
- Ifosphamide (acute tubular necrosis)
- Vascular endothelial growth factor inhibitors (thrombotic microangiopathy)
- Calcineurin inhibitors (e.g., cyclosporine, tacrolimus) (decreased kidney perfusion and tubular toxicity)
- Herbal and dietary supplements (e.g., aristolochic acid; creatine; vitamins A, C, and D; germanium; star fruit) (interstitial nephritis)
- Proton-pump inhibitors (interstitial nephritis)
- Angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, direct renin inhibitors (decreased kidney perfusion)

* Many drugs have several pathyphysiologic mechanisms.

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ized to nephron segments, without involvement of the glomeruli, accompanied by variable interstitial inflammation. However, clinical pathologic correlations are imprecise, and renal biopsy is rarely done in AKI. As a result, the diagnosis of ATN in AKI is generally presumed in patients with a typical clinical history and urinary tract findings (as described below) after exclusion of other causes of AKI. Despite this uncertainty, we will retain use of the term ATN as a cause of AKI because it remains a useful clinical concept in diagnosis and treatment. Circulatory shock and sepsis are the most common causes of ATN. Other common causes include recent exposure to nephrotoxic drugs (see the **Box**) or radiocontrast media, transient hypotension after surgery or a procedure, and rapid cell necrosis (hemolysis, rhabdomyolysis, and tumor lysis). Pigment-associated ATN may cause urine discoloration. Tumor lysis can occur before or after chemotherapy.

It is essential to review the history and medical record to determine whether the patient has had CKD or past episodes of AKD. Comparison of current values of SCC and eGFR to previous levels is helpful for early detection of AKI. Past urinalyses, measures of albuminuria (albumin-to-creatinine ratio, protein-to-creatinine ratio), and imaging studies of the kidneys (abdominal ultrasonography, computed tomography, magnetic resonance imaging, and angiography) may also be used. AKI superimposed on CKD may be due to an exacerbation of the underlying disease, which is common in chronic diseases causing decreased kidney perfusion, or onset of a new condition. A history of AKD may provide a clue to the cause of a current episode, such as a flare of autoimmune disease or nephrotoxicity of intermittently administered medication.

Evaluating Complications

Irrespective of cause, the stage (severity) of AKI is related to the risk for complications.

The frequency of AKI-related complications was studied in 18 410 patients in ICUs in 4 hospitals (29). The risk for volume overload increased from 41% in patients without AKI to 58% for stage 1, 77% for stage 2, and 83% for stage 3 AKI. Other comparisons found respective increases in hyperkalemia from 3% to 9%, 17%, and 32%; in metabolic acidosis from 59% to 74%, 86%, and 91%; in hyponatremia from 19% to 30%, 46%, and 60%; and azotemia (blood urea nitrogen >60 mg/dL) from 1% to 10%, 20%, and 49%.

Physical examination can detect volume overload (dyspnea, jugular venous distention, rales, ascites, lower extremity edema), uremic encephalopathy (lethargy, asterixis, hyperreflexia, and myoclonus), and pericarditis (pericardial friction rub), which require urgent therapy. Detection of other complications requires laboratory testing.

What laboratory tests and imaging should clinicians use?

The need for laboratory tests and imaging depends on the clinical setting. No further evaluation may be necessary for outpatients with AKI and decreased kidney perfusion due to volume depletion and rapid resolution of AKI after oral or IV volume repletion. If volume status is not clear, we recommend an early therapeutic trial of withholding diuretics and administering an IV fluid bolus of 500 mL isotonic saline over 4–6 hours with assessment of volume status, urine output, and SCC and eGFR within 8–12 hours. Improved urine output, SCC, and eGFR suggests AKI due to volume depletion, whereas no improvement suggests some other cause.

In patients with AKI from some other cause, urine appearance, dipstick, sediment, and chemis-

tries (osmolality, sodium, urea nitrogen, creatinine, albumin, and total protein) must be assessed to ascertain concentration; albuminuria and total proteinuria; and the presence or absence of hematuria, pyuria, renal tubular epithelial cells, and granular and cellular casts (**Appendix Table 1**, available at Annals.org). If obstruction is suspected, ultrasonography of the kidneys is warranted, with a postvoiding image of the bladder if symptoms occur during urination (**Appendix Table 1**) (28). We generally obtain a urine culture, since urinary tract infection can be a cause of AKI (pyelonephritis or ATN associated with sepsis) or may complicate other causes. Additional tests are required to assess complications, systemic diseases or diseases in other organ systems, and hemodynamic status in critically ill patients.

Tests of urine concentration were initially proposed for the evaluation of oliguric AKI to distinguish decreased kidney perfusion from ATN (14, 30). They are also useful in nonoliguric AKI due to these and other causes. The glomerular filtrate is isotonic with plasma; concentration of the urine requires intact tubular function. Concentration of the urine in the setting of AKI indicates decreased kidney perfusion and preserved tubular function. Absence of urine concentration indicates impaired tubular function. The fractional excretion of sodium and urea (FENa and FEurea) can be computed easily from simultaneous serum and spot urine samples (**Appendix Table 1**). Diuretic therapy impairs sodium reabsorption more than urea reabsorption, so a low FEurea may be a more reliable test for distinguishing decreased kidney perfusion from ATN than a low FENa in patients with recent diuretic therapy. Exacerbations of heart, lung, or liver disease may be associated with preserved urine concentration, despite the presence of urine sediment findings suggestive of ATN.

Tests for albumin rather than total protein are preferred for evaluation of kidney disease in adults (12), but both may be helpful in the evaluation of AKI. Loss of albumin in the urine is a marker of glomerular damage and occurs in most parenchymal kidney diseases other than ATN. Total proteinuria in the absence of albuminuria is a marker of increased production or impaired tubular reabsorption of low-molecular-weight serum proteins (light-chain proteinuria or tubular proteinuria, respectively). The urine dipstick is more sensitive to albumin than other serum proteins; the albumin-to-creatinine ratio and protein-to-creatinine ratio provide a quantitative assessment, but urine creatinine excretion decreases when SCC increases, which may cause a falsely elevated albumin-to-creatinine or protein-to-creatinine ratio.

Red blood cells and white blood cells may be detected in unspun urine with a dipstick (heme or leukocyte esterase reagent pads, respectively) and quantified with a manual or automated cell counter. We do not recommend routine testing for urine eosinophils (31). Detection of renal tubular epithelial cells and granular and cellular casts requires microscopic examination of urine sediment. Increased red or white blood cells in the urine indicates a urinary tract lesion, but the presence of renal tubular epithelial cells or granular or cellular casts in the sediment localizes the lesion to the kidney. The diagnostic accuracy of these findings has not been well-studied (32, 33). Our interpretation is that the presence of renal tubular epithelial cells and granular and cel-

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lular casts for the conditions in **Appendix Table 2** (available at Annals.org) is more specific than sensitive—in other words, parenchymal kidney disease is more likely when these findings are present but is not ruled out when they are absent. Kidney biopsy may be performed when suspicion for a parenchymal disease other than ATN is high.

Imaging studies are usually done to assess hydronephrosis, defined as dilatation of the renal collecting system due to obstruction. However, they may also be performed to assess kidney shape and size in patients with AKI superimposed on CKD or in patients who have not had previous imaging studies. Renal ultrasonography is preferred because it has >90% sensitivity for detecting hydronephrosis and is not associated with radiation exposure or contrast administration. Causes of obstruction of the urinary tract without hydronephrosis include massive bleeding into the urinary tract or extensive retroperitoneal fibrosis. Dilatation of the urinary tract in the absence of obstruction may be observed after relief of obstruction in vesicoureteral reflux, during massive diuresis, and in pregnancy. A combination of clinical characteristics can identify patients in which ultrasonography could be omitted (28).

Other tests are required to assess causes and complications of AKI. Serum urea nitrogen and electrolyte (sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium) levels should be measured. Venous or arterial blood gasses may be required for interpretation of acid–base disorders. Complete blood count; liver function tests; muscle enzymes; and imaging for heart, lung, and liver diseases should be obtained. Blood and body fluid cultures and serologic tests for infectious diseases, autoantibodies, complement components, and inflammatory markers may be indicated.

Hemodynamic monitoring (jugular venous pressure or pulmonary capillary wedge pressure) may be required to assess cardiac filling and guide volume management in patients with hypotension. Dynamic variables, such as pulse–pressure variation, inferior vena cava filling on ultrasonography, and echocardiography may be useful. Intra-abdominal pressure can be assessed by measuring bladder pressure. Subclavian vein catheters should be avoided in patients with CKD stages 4–5 (GFR <30 mL/min/1.73 m^2) to avoid venous stenosis that may preclude later vascular access for hemodialysis.

What other diagnoses should clinicians consider in patients with possible AKI?

Decreased GFR is classified as CKD, AKD, or AKI, depending on severity and duration; AKD and AKI can be superimposed on CKD (**Figure 1**). Distinguishing among these conditions is important for determining the cause of kidney disease and for determining the urgency of evaluation and treatment. Many causes of kidney disease may have an acute or chronic presentation, although the most common causes of CKD (diabetic glomerulosclerosis and hypertension nephrosclerosis) do not have an acute presentation, and ATN does not have a chronic presentation. Due to the non-steady state, changes in SCC and eGFR lag behind those in GFR, causing delayed recognition of AKI. The rise in SCC (and decrease in eGFR) may be slower in patients with low muscle mass or volume overload and faster in patients with high muscle mass or volume depletion. When baseline GFR is low, minor fluctuations in GFR can cause a rise in SCC by 0.3 mg/dL in the absence of acute kidney disease. Adher-

ence to the time requirement for diagnosis of AKI (48 hours) can minimize overdiagnosis. An increase in SCC (and decrease in eGFR) in the absence of decline in GFR may occur after a medication is started that inhibits creatinine secretion (trimethoprim or cimetidine) or interferes with the assay for creatinine (flucytosine for the creatinine iminohydrolase assay). Serum ketones interfere with the widely used colorimetric assay for creatinine. GFR, measured using clearance of an exogenous filtration marker, or creatinine clearance, can be assessed to identify misleading alterations in SCC or eGFR. If GFR is less than 20 mL/min/1.73 m^2, it can be assessed as the mean of urine clearance of urea and creatinine during a timed urine collection.

When should clinicians consider consulting a specialist?

Consultation with a nephrologist is often unnecessary for detecting AKI. However, it should usually be requested for identifying the cause of AKI resulting from something other than volume depletion that resolves promptly with volume repletion (**Figure 2**). Consultation may also be helpful for identifying the cause of CKD.

Diagnosis... Decreased GFR may be due to AKI, AKD, or CKD. KDIGO guidelines define AKI as an increase in SCC by ≥50% within 7 days or ≥0.3 mg/dL (26.5 μmol/L) within 2 days, or oliguria for ≥6 hours. The stage (severity) is defined by the peak increase in SCC compared with previous values and the nadir in urine output, and is related to the risk for complications and the prognosis. The causes of AKI—decreased kidney perfusion, obstruction of the urinary tract, parenchymal kidney diseases other than ATN, and ATN—are grouped according to underlying pathophysiology and are the basis for specific therapy. The clinical setting, including response to IV fluid, and urinary tract findings are helpful in determining the cause of AKI.

CLINICAL BOTTOM LINE

Treatment

The goals of management of AKI include use of specific treatments according to the underlying cause and providing supportive care to prevent and manage complications. KRT is used when complications develop that cannot be managed with medical therapy alone (**Figure 2**).

When should patients be hospitalized?

For outpatients with new-onset or worsening GFR decline, early follow-up is required to distinguish AKI from AKD and CKD (1, 34). Although evidence to support specific criteria for hospitalization is not available, hospitalization is generally recommended if further diagnostic evaluation is required, if AKI is severe or not rapidly reversible, or when complications are present. Management in the ICU should be considered for patients with AKI and serious illness (35).

What pharmacologic therapies should be used?

The use of pharmacologic therapies in the setting of AKI is specific to the underlying cause (**Appendix Table 2**). IV fluids are recommended to correct volume depletion. Afterload reducing agents are appropriate in cases of acute heart failure (36), whereas midodrine, octreotide, and albumin can be used in

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cases of liver failure (37). IV fluid and early antibiotic therapy is important for treating infections (38). Withdrawal of NSAIDs, ACEIs, and ARBs is recommended. Immunosuppressive therapies are recommended for many causes of acute glomerulonephritis (39). Although high-quality evidence is lacking, many experts recommend corticosteroids to treat acute interstitial nephritis when AKI is severe or in cases of drug-induced interstitial nephritis if AKI does not resolve after the causative medication is discontinued (40). Plasma exchange is recommended for some causes of thrombotic microangiopathy. High-dose chemotherapy is used in multiple myeloma. There are currently no effective pharmacotherapies for treating ATN. The KIDGO guidelines recommend against diuretics to treat AKI except for management of volume overload. However, a furosemide "stress test" (administration of 1 mg/kg of IV furosemide with 1:1 replacement of urine output with saline) can be used to assess prognosis: Patients with <200 mL of urine output over the subsequent 2 hours are at greater risk for progression to a higher AKI stage or to the need for KRT (41, 42). Although high-dose loop diuretics can increase urine output in AKI, they do not seem to reduce mortality or the need for dialysis.

A systematic review of 6 moderate- to low-quality randomized controlled trials of furosemide to treat AKI reported that it did not reduce in-hospital mortality, requirement for dialysis, or the number of dialysis treatments required until recovery of kidney function. In addition, higher doses were associated with increased toxicity (43).

In a moderate-quality randomized trial of 338 patients from ICUs and nephrology wards who had AKI requiring KRT, patients who were randomly assigned to daily furosemide 25 mg/kg IV or 35 mg/kg orally more rapidly achieved urine output >2 L per day (5.7 days with furosemide vs. 7.8 days with placebo). However, no significant differences in mortality, time receiving dialysis, or time to achieve a serum creatinine level < 200 umol/L was noted (44).

KDIGO guidelines recommend using vasopressors (e.g., norepinephrine or vasopressin) in conjunction with fluids in patients with vasomotor shock accompanying AKI (1). Low-quality evidence suggests using a protocol-based approach to achieve specific mean arterial pressure and other physiologic targets (1). On the basis of moderate-quality evidence, KDIGO guidelines recommend against dopamine, fenoldopam, atrial natriuretic peptides, insulin-like growth factor, or N-acetylcysteine to treat AKI (1).

How should clinicians manage volume problems?

AKI may develop in the setting of volume depletion or overload, and either condition may occur during the course of AKI. Volume overload is more likely to occur in the setting of oliguria, is associated with poor outcomes in AKI, and should be avoided to prevent life-threatening pulmonary edema. Volume depletion should also be avoided because it can delay recovery of AKI due to other conditions. Frequent monitoring of fluid intake and output, body weight, and volume status and administering or restricting fluid depending on the results are important.

IV fluids are recommended for correcting AKI with volume depletion and for intravascular volume expansion in AKI with sepsis (1). Isotonic crystalloids (e.g., normal saline, Ringer lactate, or other balanced crystalloid solutions) are recommended rather than colloids (albumin or starches) as initial management on the basis of moderate-quality evidence (45–47). Colloids may be used for patients with liver failure or burns. Treatment of volume overload in patients with AKI can sometimes be accom-

plished using high doses of IV loop diuretics, given as multiple doses throughout the day or as an infusion and often in conjunction with IV thiazide diuretics.

How should clinicians manage electrolyte problems?

Initial management of electrolyte abnormalities should start with medical management and proceed to KRT when medical management is no longer satisfactory. Dietary potassium should be restricted, and medications that cause hyperkalemia should be used cautiously. Treatment of severe hyperkalemia (serum potassium > 6.5 mmol/L or with electrocardiographic changes) includes administration of calcium gluconate to reduce the risk for arrhythmia, followed by insulin plus dextrose, β-agonists, or sodium bicarbonate to shift potassium from the extracellular to the intracellular compartment. These treatments are temporary and must be accompanied by measures to remove potassium from the body. For patients without oliguria, high-dose loop diuretics can be used to increase urine output and potassium excretion. For patients with oliguria, sorbitol with sodium polystyrene sulfonate or calcium polystyrene sulfonate resins can be used to induce osmotic diarrhea and fecal potassium losses. Most experts suggest using supplemental sodium bicarbonate when metabolic acidosis is severe, although there is no high-quality evidence (48). Hypernatremia may be encountered in AKI with dehydration, after normal saline resuscitation, or when access to water is restricted. It can usually be corrected by providing water via enteral routes or IV hyponatric solutions. The management of hyponatremia in the setting of AKI depends on its cause. In states of volume depletion, administration of isotonic IV fluids is generally appropriate. In the presence of volume overload, water restriction and loop diuretics should be used. Hypercalcemia may be encountered in AKI accompanying multiple myeloma and can be corrected by volume expansion and loop diuretics in patients who are not oliguric or by promoting bone uptake with administration of an IV bisphosphate. Hyperphosphatemia can be managed by dietary phosphate restriction and oral phosphate binders. Hypermagnesemia may occur after magnesium infusion and can be managed by discontinuing the infusion and administering loop diuretics.

How should clinicians manage nutrition, drug dosing, and anticoagulation?

Nutrition should provide adequate calories with restricted potassium and phosphate. KDIGO guidelines for patients with AKI recommend a total energy intake of 20–30 kcal/kg per day, preferably provided via the enteral route (49). Minimal nitrogenous waste production is desirable in AKI; however, protein restriction is not suggested as a means to avoid KRT. On the basis of low-quality evidence, KDIGO guidelines recommend protein goals of 0.8–1.0 g/kg per day in noncatabolic patients, 1.1–1.5 g/kg per day in patients receiving renal replacement therapy, and a maximum 1.7 g/kg per day in hypercatabolic patients or those requiring continuous KRT (1, 50). In critically ill patients, KDIGO guidelines suggest insulin therapy targeting plasma glucose 110–149 mg/dL.

Patients with AKI require special drug dosing due to buildup from decreased excretion and metabolism by the kidney as well as the effects of kidney failure on other routes of drug excretion and metabolism (51, 52). Estimated GFR is less accurate to guide dosing in the nonsteady state than in the

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steady state. Expert consensus recommends closely monitoring drug response in patients with known nephrotoxicity or other toxicities, using therapeutic drug monitoring when clinically useful assays are available, and being cognizant of residual effects of medicines that are excreted by the kidney even after they have been discontinued (e.g., oral hypoglycemic agents and opioids) (52, 53). The assistance of a pharmacist may be helpful, particularly in determining dosing and dosing intervals in patients receiving dialysis and those requiring antibiotics for AKI accompanying sepsis.

Certain anticoagulants should be used with caution in patients with AKI due to the increased bleeding risk attributed to uremic platelet dysfunction and to decreased excretion of low-molecular-weight heparins and direct oral anticoagulants. Although some manufacturers provide altered dosing schedules based on creatinine clearance for some low-molecular-weight heparins (e.g., enoxaparin) and direct oral anticoagulants (e.g., dabigatran), determining safe dosing schedules when GFR is changing, especially during dialysis, is difficult. Although low-molecular-weight heparins are used intermittently in patients receiving long-term dialysis and some organizations have suggested monitoring anti-factor X activity with continuous use, many experts prefer to use unfractionated heparin in severe AKI. For patients with active bleeding in the presence of uremia, desmopressin (0.3 mcg/kg IV, subcutaneous, or intranasal) and cryoprecipitate can be used to rapidly diminish bleeding time, whereas conjugated estrogens and dialysis (without systemic anticoagulation) can be used for more prolonged bleeding control.

What is the role of KRT?

KRT is used to manage the complications of severe AKI. Common indications include life-threatening changes in fluid, electrolyte, and acid–base balance that require emergent correction (**Figure 2**). KRT may be started before these complications develop, although evidence conflicts about whether preemptive initiation at an earlier stage of AKI is more beneficial than when complications occur (54–56). KRT should be discontinued as soon as it is no longer required, either because kidney function has recovered enough to meet the patient's needs or life-sustaining therapy is no longer the goal of the patient's care.

Several types of KRT can be used, and the type varies by location of care and available equipment and expertise (**Appendix Table 3**, available at Annals.org). Peritoneal dialysis is rarely used for KRT in adults with AKI in North America, although it is more commonly used in areas with limited resources. Continuous KRT is a slow, continuous form of therapy delivered 24 hours a day in ICUs and is usually used to treat hemodynamically unstable patients (57). Conventional intermittent hemodialysis is used in AKI for hemodynamically stable patients; it is similar to the in-center long-term hemodialysis used for end-stage kidney disease (58). More frequent sessions may be required to manage fluid and electrolyte abnormalities for some patients with AKI. Prolonged intermittent KRT uses the same equipment as conventional dialysis but provides dialysis using lower blood flow rates over longer sessions (usually ≥6 hours/session). Several randomized trials have compared outcomes with continuous KRT versus intermittent hemodialysis in critically ill patients (59). Significant differences between the 2 methods in terms of mortality, length of hospitalization, and long-term requirements for dialysis have not been found (59, 60).

What is the prognosis?

AKI is associated with high mortality rates that range from 16%–50% according to stage (**Appendix Figure**, available at Annals.org) and vary according to the cause, coexisting conditions, and availability of KRT (3). Survivors of AKI are at increased risk for hypertension and progressive CKD, including end-stage kidney disease (61–65). KDIGO guidelines thus recommend evaluating patients after AKI for recovery of kidney function, new onset, or worsening of preexisting CKD. Older age, lower baseline eGFR, higher baseline albuminuria, and AKI severity (KDIGO stage) are predictors of CKD after AKI and should prompt postdischarge follow-up (6, 66, 67). Referral to community nephrology services may be appropriate for patients who do not recover kidney function given the associated long-term risks of kidney failure, cardiovascular events, and mortality for several years after hospital discharge (62, 68).

*In a systematic review, the pooled mortality rate was 23.0% overall and 49.4% in patients needing dialysis (**Appendix Figure**) (3). The pooled unadjusted odds of death were 3.4-fold higher for patients with KDIGO stage 1 AKI, 7.5-fold higher for stage 2, 13.2-fold higher for stage 3, and 24-fold higher in patients needing dialysis compared with patients without AKI. The AKI-associated mortality rate declined over 8 years and was inversely related to the percentage of a country's gross domestic product spent on total health expenditure.*

When should clinicians consider consulting a specialist?

Because AKI is a common complication of many medical and surgical illnesses, most patients

with AKI are cared for by general internists, hospitalists, surgeons, and critical care and primary care physicians. These clinicians should consult a nephrologist or critical care specialist for patients who have AKI with any indication for KRT (69). Nephrology referral and comanagement is also appropriate if the cause of AKI is uncertain, particularly when decreased kidney perfusion and urinary tract obstruction have been excluded or corrected. Clinicians should discuss management with a nephrologist if a diagnosis that may need specific treatments is suspected (e.g., parenchymal kidney diseases other than ATN), response to treatment has been inadequate, there are associated complications, AKI is severe (KDIGO stage 3), or it is superimposed on CKD stages 4–5 (baseline GFR < 30 mL/min/1.73 m^2) (70).

Treatment... The main goals of managing AKI are specific pharmacologic therapy addressing underlying causes and providing supportive care to prevent and manage complications. Supportive care includes maintenance of hemodynamic stability and kidney perfusion using IV crystalloids when volume expansion is needed and the use of diuretics in states of volume overload, medical management of electrolyte disorders, provision of adequate nutrition and glycemic control, and cautious use of medications to avoid adverse drug events. When AKI is severe, KRT may be required to manage complications. Survivors of AKI should be assessed for recovery of kidney function and receive subsequent follow-up to identify and subsequently manage CKD.

CLINICAL BOTTOM LINE

In the Clinic
Tool Kit

Acute Kidney Injury

Clinical Guidelines

www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO%20AKI%20Guideline.pdf
Guidelines published by the International Society of Nephrology.

www.clinicalguidelines.gov.au/portal/2481/clinical-practice-guideline-acute-kidney-injury
2014 guideline from the National Health and Medical Research Council of Australia.

www.nice.org.uk/guidance/cg169
Guidance from the National Institute for Health and Care Excellence.

Patient Information

www.kidney.org/atoz/content/AcuteKidneyInjury
Information presented by the National Kidney foundation for both patients and caregivers.

www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2015/11/BKPA-RCGP-A4-Printout-Leaflet_v4.pdf
Printable leaflet of the British Kidney Patient Association.

www.ncbi.nlm.nih.gov/pubmedhealth/PMH0071507/
Information for patients and caregivers from PubMed Health.

www.nhs.uk/conditions/acute-kidney-injury/Pages/Introduction.aspx
Information from the National Health Service.

In the Clinic

WHAT YOU SHOULD KNOW ABOUT ACUTE KIDNEY INJURY

In the Clinic
Annals of Internal Medicine

What Is Acute Kidney Injury?

Doctors diagnose acute kidney injury (AKI) when your kidneys stop working properly and the change happens over a few hours or a few days. It can cause a buildup of waste products in your blood and make it hard for your kidneys to balance the fluids in your body. It can lead to serious health problems, such as permanent kidney damage and even death.

AKI usually happens to people who are sick, especially when they are in the hospital. AKI can be a complication of the following conditions:

- Sepsis (a type of infection)
- Shock
- Accidents
- Burns
- Heart attack or other heart disease
- Blockage of the urinary tract
- Infection of the urinary tract
- Surgery
- Dyes for x-rays
- Certain over-the-counter and prescription medicines
- Contact with a poisonous plant or animal
- Severe allergic reaction

What Are the Risk Factors?

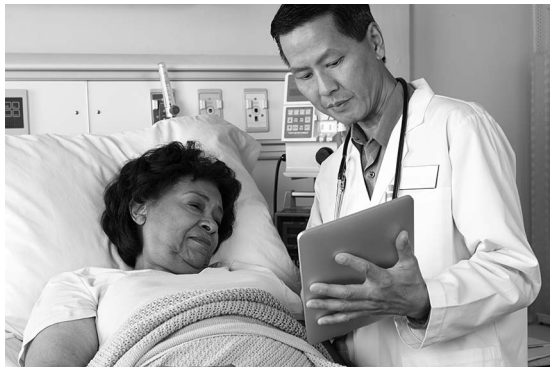
You are more susceptible to AKI if you:

- Are an older adult
- Are female
- Are African American
- Have chronic kidney disease
- Have chronic heart, lung, or liver disease
- Have diabetes
- Have cancer
- Are anemic

What Are the Symptoms?

AKI usually has no symptoms until your kidneys start to fail. Kidney failure means that your kidneys can no longer properly remove waste from your body. These symptoms may occur if you have kidney failure:

- Feeling sleepy
- Feeling sick to your stomach



- Swelling or retaining fluid
- Shortness of breath
- Feeling dizzy or lightheaded

How Is It Diagnosed?

- Your doctor will ask you questions about your health history and take blood and urine samples.
- If there is something wrong with your kidneys, you may have an imaging test. This could include an ultrasound.

How Is It Treated?

- Patients with AKI are usually treated in a hospital. Your health care provider will give you intravenous fluids to bring your levels back to normal. You may also take medicines to help balance your fluid levels.
- In more serious cases, you may need dialysis while your kidneys recover. Dialysis filters the waste in your body, just as healthy kidneys do.

Questions for My Doctor

- What caused my AKI?
- Will I need dialysis?
- Will I have permanent damage?
- If I recover, what are the chances I'll get it again in the future?
- Should I eat a special diet?
- Should I avoid any medications?

For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

National Kidney Foundation
www.kidney.org/atoz/content/AcuteKidneyInjury
Medline Plus
https://medlineplus.gov/ency/article/000501.htm

Patient Information

Appendix Table 1. **Findings of Urine Testing in Acute Kidney Injury**

Variable	*Normal*	*Decreased Kidney Perfusion*	*Obstruction of the Urinary Tract*	*Parenchymal Kidney Diseases Other Than ATN*	*ATN*
Concentration*	Varies, depending on water intake	Concentrated, possibly not if recent diuretic administration	Concentrated, not if chronic	Not concentrated, may be concentrated in glomerulonephritis	Not concentrated; may be concentrated in heart failure or liver failure
Albumin/total protein levels†	Normal to mildly increased	Normal to mildly increased	Normal to mildly increased (unless chronic)	Increased albumin and total protein in glomerular disease; normal albumin and increased total protein in cast nephropathy (immunoglobulin light chains) and in tubular diseases (β_2-microglobulin)	Normal to mildly increased
Hematuria (RBCs)‡	No	No	Yes, with instrinsic disease	Yes, with dysmorphic RBCs and RBC casts in glomerulonephritis; yes, without RBC casts in thrombotic microangiopathy	No, heme-positive dipstick in hemolysis and rhabdomyolysis
Pyuria (WBCs)‡	No	No	Yes, if superimposed urinary tract infection	Yes, with WBC casts in interstitial nephritis	No
Renal tubular epithelial cells and granular casts	No	No (may contain hyaline casts)	No (except if chronic)	Yes	Yes
Hydronephrosis, kidney shape and size§	No hydronephrosis, normal size, symmetrical	No hydronephrosis, normal size, symmetrical, may be asymmetrical if renal artery stenosis	Hydronephrosis, enlarged, may be small if chronic, may be asymmetrical if unilateral, nephrolithiasis may be present	No hydronephrosis, normal size, may be large in infiltrative diseases, symmetrical, may be small if chronic	No hydronephrosis, normal size

RBC = red blood cell; HPF = high-power field; WBC = white blood cell.
** Urine concentration assessed from urine specific gravity (concentrated > 1.020); osmolality (concentrated >500 mosm/kg); fractional excretion of sodium (FENa) (concentrated <1%); fractional excretion of urea (FEurea) (concentrated <35%); ratio of SUN to serum creatinine concentration (Scr) >20:1. FENa is calculated from UNa x Scr/SNa x Ucr. FEurea is calculated from UUN x Scr/SUN x Ucr.*
† Albumin and total protein assessed from dipstick (more sensitive to albumin than other proteins); albumin-to-creatinine ratio (ACR), moderately increased 30–300 mg/g, severely increased >300 mg/g (nephrotic range >2200 mg/g); and total protein-to-creatinine ratio (PCR), moderately increased 150–500 mg/g, severely increased >500 mg/g (nephrotic range >3500 mg/g). Ranges for ACR and PCR are defined for steady-state conditions; values may be higher in acute kidney injury because urine creatinine excretion decreases with increased Scr.
‡ Normal urine contains <5 RBC/HPF and <5 WBC/HPF.
§ Renal ultrasonography is the preferred method for evaluating hydronephrosis. Hydronephrosis may be absent in cases of massive bleeding into the urinary tract or extensive retroperitoneal fibrosis.

Appendix Table 2. **Treatment According to Specific Causes of AKI Other Than Acute Tubular Necrosis**

Cause of AKI	*Treatment/Intervention*	*Comment*
Decreased kidney perfusion		
Volume depletion	Intravenous fluid	Isotonic crystalloids (normal saline, Ringer lactate, or balanced crystalloid solutions) are recommended rather than colloids as initial management for intravascular volume expansion; improvement in Scr and eGFR and urine output after intravenous fluid administration confirms the diagnosis of decreased kidney perfusion due to volume depletion
Heart failure, left- or right-sided (with lung disease) (cardiorenal syndrome)	Afterload reduction and diuretics if volume overloaded	Cardiac output may be improved with ACE/ARB, hydralazine or nitrates; diuresis can improve GFR when left ventricular filling pressure exceeds that for optimum cardiac output or when systemic venous pressure is elevated so as to reduce the afferent versus efferent arteriolar pressure gradient across the glomerulus
Liver failure (hepatorenal syndrome)	Albumin, midodrine, and octreotide	Volume may be expanded with albumin, especially in setting of bacterial peritonitis or paracentesis; midodrine and octreotide are used to raise blood pressure and promote splanchnic vasoconstriction; terlipressin may improve outcomes (but is not currently available in the United States or Canada); kidney failure can be an indication for liver transplant in eligible patients
Sepsis	Intravenous fluid and antibiotics	Intravenous volume expansion and early broad-spectrum antibiotics, subsequently tailored to culture and sensitivity results
Increased intra-abdominal pressure	Intra-abdominal decompression	Nasogastric and rectal drainage, and evacuation of intra-abdominal space-occupying lesions (e.g., ascites, fluid collections, hematomas); may require surgical decompression (open abdomen) when intra-abdominal pressure is ≥20 mm Hg
Renovascular disease	Antihypertensive therapy; revascularization	Angioplasty with or without stenting or surgical bypass of the renal artery can be considered in select situations of AKI (e.g., bilateral renal artery stenosis or stenosis to a solitary kidney)
Nonsteroidal anti-inflammatory drugs	Withdrawal of medications	Isotonic crystalloid is a useful adjunct
ACE inhibitors and ARBs	Temporary medication withdrawal	Consider educating patients about tablet holidays (withholding ACE inhibitors or ARBs, especially when combined with diuretics); during periods of potential volume depletion from acute illness, to avoid recurrent AKI episodes
Urinary tract obstruction		
Obstructive nephropathy	Nephrostomy tube or urinary catheter	Percutaneous nephrostomy tubes or ureteric stenting for relief of upper tract obstruction or Foley catheter or definitive surgical intervention for lower tract obstruction
Parenchymal kidney disease		
Acute glomerulonephritis	Immunosuppressive therapy	Dependent on histopathologic findings on kidney biopsy and underlying cause; crescentic glomerulonephritis (e.g., anti-neutrophil cytoplasmic antibody and anti-GBM disease) is usually treated with induction therapy using steroids and cyclophosphamide; proliferative lupus nephritis is treated with steroids and cyclophosphamide or mycophenolate mofetil for induction therapy; corticosteroids or other immunosuppressive regimens may be used to treat IgA nephropathy; when glomerulonephritis is due to an infection or cancer, these secondary causes should be treated

Continued on following page

Appendix Table 2–Continued

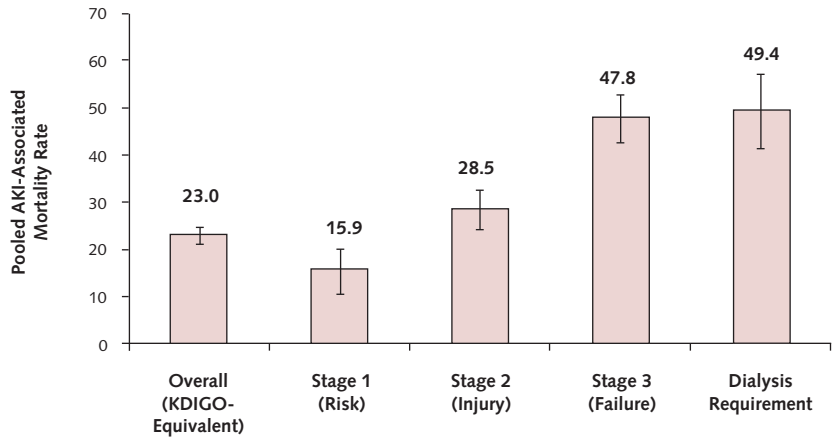
Cause of AKI	*Treatment/Intervention*	*Comment*
Acute interstitial nephritis	Withdrawal of culprit medication and corticosteroids	Stop culprit drug when medication-related; may consider corticosteroids if AKI is severe or patient is not recovering
Acute pyelonephritis	Antibiotics	Intravenous antibiotics when accompanied by AKI; consider investigations for anatomical urinary tract abnormalities, obstruction or stones, or sources of hematogenous dissemination
Thrombotic microangiopathy	Plasma exchange	Used for thrombotic thromobocytopenia purpura and some secondary (immune-mediated) causes of thrombotic microangiopathy.
Cast nephropathy (multiple myeloma)	Chemotherapy	High-dose chemotherapy provided through consultation with a hematologist, which may include steroids, cyclophosphamide, immunomodulatory drugs (e.g., lenolidamide, or proteasome inhibitors (e.g., bortezemab) for initial treatement, followed by autologous hematopoietic cell transplantation for eligible patients
Renal infarction	Revascularization or anticoagulation	Consider revascularization for arterial fibromuscular dysplasia of the renal arteries or anticoagulation for arterial embolism or venous thrombosis to prevent recurrence; not indicated for treatment of acute events
Atheroembolism	Avoidance of intra-arterial procedures	Avoidance of intra-arterial procedures to prevent recurrence; consider withdrawal of anticoagulation (if recently initiated) and atheroembolism is spontaneous (not following intra-arterial procedures)

ACE = angiotensin-converting enzyme; AKI = acute kidney injury; ARB = angiotensin-receptor blocker; eGFR = estimated glomerular filration rate; GBM = glomerular basement membrane; GFR = glomerular filration rate; Scr = serum creatinine.

Appendix Table 3. **Kidney Replacement Therapies for Hemodialysis and Hemofiltration in Acute Kidney Injury**

Example	*Solute Removal*	*Blood Flow Rate*	*Duration*	*Recommended Dose*
Continuous kidney replacement therapies				
Continuous venovenous hemofiltration	Convective	150–250 mL/min	Daily for 24 h/d (minus interruptions)	To deliver an effluent volume (replacement for fluid removed by ultrafiltration) of 20–25 mL/kg per h
Continuous venovenous hemodialysis	Diffusive			
Continuous venovenous hemodiafiltration	Diffusive and convective			
Intermittent kidney replacement therapies				
Intermittent hemodialysis	Diffusive	200–350 mL/min	Typically 3–4 times/wk, 4 h/session	To deliver a weekly Kt/V (a measure of urea clearance) of 3.9
Prolonged intermittent kidney replacement therapies				
Sustained low efficiency dialysis	Diffusive	100–300 mL/min	Typically daily for ≥6 h	To deliver a weekly Kt/V (a measure of urea clearance) of 3.9
Sustained low efficiency diafiltration	Diffusive and convective			
Sustained continuous ultrafiltration	Convective			

Appendix Figure. **Pooled AKI-associated mortality rate from studies based on KDIGO creatinine-based staging.**



	Overall (KDIGO-Equivalent)	Stage 1 (Risk)	Stage 2 (Injury)	Stage 3 (Failure)	Dialysis Requirement
Studies, *n*	110	26	25	25	31
Patients With AKI, *n*	429 535	8226	42 354	42 354	6534

Error bars represent 95% CIs. AKI = acute kidney injury; KDIGO = Kidney Disease Improving Global Outcomes.

Correction: In the Clinic–Acute Kidney Injury

In 3 places in Figure 1 and the footnote adjacent to the asterisk in Appendix Table 1 (1), "serum creatinine clearance" should be "serum creatinine concentration."

This has been corrected.

Reference

1. Levey AS, James MT. In the Clinic: acute kidney injury. Ann Intern Med. 2017;167:ITC66-80. [PMID: 29114754] doi: 10.7326/AITC201711070