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321 Acute Kidney Injury

■ ■SODIUM BALANCE The perception of extracellular blood volume is determined, in part, by the integration of arterial tone, cardiac stroke volume, heart rate, and the water and solute content of extracellular fluid. Na+ and accompanying anions are the most abundant extracellular effective osmoles and together support a blood volume around which pres sure is generated. Under normal conditions, this volume is regulated by sodium balance (Fig. 320-4B), and the balance between daily Na+ intake and excretion is under the influence of baroreceptors in regional blood vessels and vascular hormone sensors modulated by atrial natriuretic peptides, the renin-angiotensin-aldosterone sys tem, Ca2+ signaling, adenosine, vasopressin, and the neural adrener gic axis. If Na+ intake exceeds Na+ excretion (positive Na+ balance), then a rising blood volume will trigger a proportional increase in urinary Na+ excretion. Conversely, when Na+ intake is less than urinary excretion (negative Na+ balance), blood volume will fall and trigger enhanced renal Na+ reabsorption, leading to decreased urinary Na+ excretion.

The renin-angiotensin-aldosterone system is the best-understood hormonal system modulating renal Na+ excretion. Renin is syn thesized and secreted by granular cells in the wall of the afferent arteriole. Its secretion is controlled by several factors, including β1-adrenergic stimulation to the afferent arteriole, input from the macula densa, and prostaglandins. Renin and ACE activity eventually produce angiotensin II that directly and indirectly promotes renal Na+ and water reabsorption. Stimulation of proximal tubular Na+/ H+ exchange by angiotensin II directly increases Na+ reabsorption. Angiotensin II also promotes Na+ reabsorption along the collect ing duct by stimulating aldosterone secretion by the adrenal cortex. Constriction of the efferent glomerular arteriole by angiotensin II indirectly boosts the filtration fraction and raises peritubular capil lary oncotic pressure to promote tubular Na+ reabsorption. Finally, angiotensin II inhibits renin secretion through a negative feedback loop. Alternative metabolism of angiotensin by ACE2 generates the vasodilatory peptide angiotensin 1-7 that acts through Mas receptors to counterbalance several actions of angiotensin II on blood pressure and renal function (Fig. 320-2C). PART 9 Disorders of the Kidney and Urinary Tract Aldosterone is synthesized and secreted by granulosa cells in the adrenal cortex. It binds to cytoplasmic mineralocorticoid receptors in the collecting duct principal cells and boosts the activ ity of ENaC, apical membrane K+ channel, and basolateral Na+/ K+-ATPase. These effects are mediated in part by aldosteronestimulated transcription of the gene encoding serum/glucocorti coid-induced kinase 1 (SGK1). The activity of ENaC is increased by SGK1-mediated phosphorylation of the ubiquitin-protein ligase Nedd4-2 that promotes ubiquitination and recycling of the Na+ channel from the plasma membrane. Phosphorylated Nedd4-2 has impaired interactions with ENaC, leading to higher channel density at the plasma membrane and greater capacity for Na+ reabsorption by the collecting duct. Chronic

exposure to aldosterone is associated with lower urinary Na+ excretion lasting only a few days, after which Na+ excretion returns to previous levels. This phenomenon, called aldosterone escape, is explained by lower proximal tubular Na+ reabsorption following blood volume expansion. Excess Na+ that is not reabsorbed by the proximal tubule overwhelms the reabsorptive capacity of more distal nephron segments. This escape may be facilitated by atrial natriuretic peptides that lose their effectiveness in the clinical settings of heart failure, nephrotic syndrome, and cirrhosis, leading to severe Na+ retention and volume overload. ■ ■FURTHER READING Avraham S: The mesangial cell: The glomerular stromal cell. Nature Rev Nephrol 17:855, 2021. Carrisoza-Gaytan R: PIEZO1 is a distal nephron mechanosen sory and is required for flow-induced K+ secretion. J Clin Invest 134:E174806, 2024. De Baaij JHF: Magnesium reabsorption in the kidney. Am J Physiol Renal Physiol 324:F227, 2023.

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Acute Kidney Injury Acute kidney injury (AKI) is defined by the impairment of kidney filtration and excretory function over days to weeks (generally known or expected to have occurred within 7 days), resulting in the reten tion of nitrogenous and other waste products normally cleared by the kidneys. The generally accepted Kidney Disease: Improving Global Outcomes (KDIGO) definition of AKI is an increase in serum creatinine (SCr) of ≥0.3 mg/dL within 48 h or an increase in SCr ≥1.5 times from baseline over 7 days or urine output <0.5 mL/kg per h for >6 h. AKI is not a single disease but rather a designation for a heterogeneous group of conditions that share common diagnostic features: specifically, an increase in filtration markers (SCr or cystatin C) often associated with a reduction in urine volume. It is important to recognize that AKI is a clinical diagnosis and not a structural one. A patient may have AKI with or without injury to the kidney parenchyma making the term a misnomer. AKI can range in severity from asymptomatic and transient changes in laboratory parameters of glomerular filtration rate (GFR), to overwhelming and rapidly fatal derangements in the ability of the kidney to maintain effective circulating volume regulation, excrete nitrogenous wastes and metabolic toxins, and maintain electrolyte and acid-base composition of the plasma. EPIDEMIOLOGY AKI complicates 5–7% of acute-care hospital admissions and up to 30% of admissions to the intensive care unit (ICU). AKI severity is staged based on the magnitude of the rise in SCr and severity and duration of oliguria (Table 321-1). The incidence of AKI has grown by more than fourfold in the United States since 1988 and is estimated to have a yearly incidence of 500 per 100,000 population, higher than the yearly incidence of stroke. Morbidity of AKI in those admitted to the ICU exceeds 50% in many studies. AKI also has longer term implications even if the patient survives the hospitalization. AKI increases the risk TABLE 321-1 Staging of Acute Kidney Injury Severity STAGE SERUM CREATININE URINE OUTPUT

1.5–1.9 times baseline OR ≥0.3 mg/dL (≥26.5 μmol/L) increase <0.5 mL/kg per h for 6–12 h

2.0–2.9 times baseline <0.5 mL/kg per h for ≥12 h

3.0 times baseline OR increase in serum creatinine to ≥4.0 mg/dL (≥353.6 μmol/L) OR initiation of renal replacement therapy OR, in patients <18 years of age, decrease in eGFR to <35 mL/min per 1.73 m2 <0.3 mL/kg per h for ≥24 h OR Anuria for ≥12 h Abbreviation: eGFR, estimated glomerular filtration rate.

for the development or worsening of chronic kidney disease (CKD) and also increases the risk of future cardiovascular disease. AKI may also occur in the community. Common causes of community-acquired AKI include volume depletion, heart failure, adverse effects of medi cations, obstruction of the urinary tract, or malignancy. The most common clinical settings for hospital-acquired AKI are sepsis, major surgical procedures, critical illness involving heart or liver failure, and nephrotoxic medication administration. Clinically, AKI more com monly develops when ischemia or other insults occur in the context of limited renal functional reserve. The healthy kidney has the ability to increase its regional or overall function in response to damage to a sub set of nephrons or in response to a perceived need to enhance excre tion, such as in response to a protein load. With normal aging, there is reduction in this capacity, which is also reduced in individuals with CKD or coexisting insults such as sepsis, vasoactive or nephrotoxic drugs, rhabdomyolysis, or the systemic inflammatory states associated with burns and pancreatitis. When there is reduced renal reserve, any additional impairment in GFR is likely to be reflected by a change in SCr or cystatin C and hence a more likely diagnosis of AKI. ■ ■AKI IN THE DEVELOPING WORLD AKI is also a major medical complication in the developing world, where the epidemiology differs from that in developed countries due to differences in demographics, economics, environmental factors, and comorbid disease burden. While certain features of AKI are common in developed and developing countries—particularly because urban centers of some developing countries increasingly resemble those in the developed world—many etiologies for AKI are region-specific, such as envenomations from snakes, spiders, caterpillars, and bees; infectious causes such as malaria and leptospirosis; and crush injuries and resultant rhabdomyolysis from earthquakes. In developing coun tries, resources to diagnose and manage AKI are often limited. ETIOLOGY AND PATHOPHYSIOLOGY The causes of AKI have traditionally been divided into three broad categories: prerenal azotemia, intrinsic renal parenchymal disease, and postrenal obstruction (Fig. 321-1). ■ ■PRERENAL AZOTEMIA Prerenal azotemia (from “azo,” meaning nitrogen, and “-emia,” meaning in the blood), the most common form of AKI, results from inadequate Prerenal Postrenal Intrinsic Glomerular • Acute glomerulo- nephritis Hypovolemia Decreased cardiac output Decreased effective circulating volume • Congestive heart failure • Liver failure Impaired renal autoregulation • NSAIDs • ACE-I/ARB • Cyclosporine Ischemia FIGURE 321-1 Classification of the major causes of acute kidney injury. ACE-I, angiotensin-converting enzyme inhibitor-I; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors; TTP-HUS, thrombotic thrombocytopenic purpura–hemolytic-uremic syndrome.

renal plasma flow and intraglomerular hydrostatic pressure to support normal glomerular filtration. The most common clinical conditions associated with prerenal azotemia are hypovolemia, decreased cardiac output, and medications that interfere with renal autoregulatory vascu lar responses such as nonsteroidal anti-inflammatory drugs (NSAIDs) and inhibitors of the renin-angiotensin system (Fig. 321-2). Sodiumglucose cotransporter 2 (SGLT-2) inhibitors used for the treatment of diabetes mellitus and related complications do not appear to increase the risk of AKI despite their effects on lowering intraglomerular pres sure and inducing natriuresis; in fact, recent

studies have suggested a protective effect of these agents in preventing AKI.

By definition, prerenal azotemia involves no parenchymal damage to the kidney and is rapidly reversible once parenchymal blood flow and intraglomerular hemodynamics are restored. In many cases, how ever, prerenal azotemia may coexist with other forms of intrinsic AKI associated with processes acting directly on the renal parenchyma. Pro longed periods of prerenal azotemia may lead to ischemic injury to the tubular cells with necrosis, hence termed acute tubular necrosis (ATN). Normal GFR is maintained in part by renal blood flow and the relative resistances of the afferent and efferent renal arterioles, which determine the glomerular plasma flow rate and the transcapillary hydraulic pressure gradient that drive glomerular ultrafiltration. Mild degrees of hypovolemia and reductions in cardiac output elicit com pensatory renal vasoconstriction and enhanced reabsorption of salt and water to maintain blood pressure and increase intravascular volume to sustain perfusion to the cerebral and coronary vessels. Mediators of this response include angiotensin II, norepinephrine, and vasopressin (also termed antidiuretic hormone). Glomerular filtration can be maintained despite reduced renal blood flow by angiotensin II–mediated renal efferent arteriolar vasoconstriction. In addition, a myogenic reflex within the afferent arteriole leads to dilation in the setting of low perfusion pressure, thereby maintaining glomerular perfusion. Intrarenal biosynthesis of vasodilator prostaglandins (pros tacyclin, prostaglandin E2), kallikrein and kinins, and possibly nitric oxide (NO) also increases in response to low renal perfusion pressure. Autoregulation is also accomplished by tubuloglomerular feedback, in which decreases in solute delivery to the macula densa (specialized cells within the distal tubule) elicit dilation of the juxtaposed afferent arteriole in order to maintain glomerular perfusion, a mechanism mediated, in part, by NO. There is a limit, however, to the ability of CHAPTER 321 Acute Kidney Injury Acute kidney injury Tubules and interstitium Vascular • Vasculitis • Malignant hypertension • TTP-HUS Bladder outlet obstruction Bilateral pelvoureteral obstruction (or unilateral obstruction of a solitary functioning kidney) Sepsis/ Infection Nephrotoxins Exogenous: Iodinated contrast, aminoglycosides, cisplatin, amphotericin B, PPIs, NSAIDs, immune checkpoint inhibitors Endogenous: Hemolysis, rhabdomyolysis, myeloma, intratubular crystals

Normal perfusion pressure Arteriolar resistances Afferent arteriole Efferent arteriole Increased vasodilatory prostaglandins Increased angiotensin II Glomerulus Tubule A B Normal GFR Normal GFR maintained PART 9 Disorders of the Kidney and Urinary Tract Decreased perfusion pressure in the presence of NSAIDs Decreased vasodilatory prostaglandins Increased angiotensin II C D Low GFR FIGURE 321-2 Intrarenal mechanisms for autoregulation of the glomerular filtration rate (GFR) under decreased perfusion pressure and reduction of the GFR by drugs. A. Normal conditions and a normal GFR. B. Reduced perfusion pressure within the autoregulatory range. Normal glomerular capillary pressure is maintained by afferent vasodilatation and efferent vasoconstriction. Angiotensin constricts afferent (preglomerular) and efferent (postglomerular) arterioles but preferentially increases efferent arteriolar resistance. C. Reduced perfusion pressure with a nonsteroidal anti-inflammatory drug (NSAID). Loss of vasodilatory prostaglandins increases afferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease. D. Reduced perfusion pressure with an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB). Loss of angiotensin II action reduces efferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease. (From JG Abuelo: Normotensive ischemic acute renal failure. N Engl J Med 357:797, 2007. Copyright © 2007, Massachusetts Medical Society. Reprinted with permission from

Massachusetts Medical Society.) these counterregulatory mechanisms to maintain GFR in the face of systemic hypotension. Even in healthy adults, renal autoregulation usu ally fails once the systolic blood pressure falls below 80 mmHg. A number of factors determine the robustness of the autoregula tory response and the risk of prerenal azotemia. Atherosclerosis, long-standing hypertension, and older age can lead to hyalinosis and myointimal hyperplasia, causing structural narrowing of the intrare nal arterioles and impaired capacity for renal afferent vasodilation. In CKD, renal afferent vasodilation may be operating at maximal capac ity in order to maximize GFR in response to reduced functional renal mass. Drugs can affect the compensatory changes evoked to maintain GFR. NSAIDs inhibit renal prostaglandin production, limiting renal afferent vasodilation. Angiotensin-converting enzyme (ACE) inhibi tors and angiotensin receptor blockers (ARBs) limit renal efferent vasoconstriction; this effect is particularly pronounced in patients

Decreased perfusion pressure Decreased perfusion pressure in the presence of ACE-I or ARB Slightly increased vasodilatory prostaglandins Decreased angiotensin II Low GFR with bilateral renal artery stenosis or unilateral renal artery stenosis (in the case of a solitary functioning kidney) because, as indicated above, efferent arteriolar vasoconstriction is needed to maintain GFR due to low renal perfusion. The combined use of NSAIDs with ACE inhibitors or ARBs poses a particularly high risk for developing prerenal azotemia. Hepatorenal syndrome is a cause of AKI in individuals with multi organ pathobiology affecting kidney and liver. Many individuals with advanced liver disease exhibit a hemodynamic profile that resembles prerenal azotemia in the setting of total-body volume overload. Sys temic vascular resistance is markedly reduced due to primary arte rial vasodilation in the splanchnic circulation, resulting ultimately in activation of vasoconstrictor responses similar to those seen in hypo volemia. AKI is a common complication in this setting, and it can be triggered by volume depletion and spontaneous bacterial peritonitis.

The hepatorenal syndrome, which represents the advanced stage of impaired perfusion to the kidneys secondary to advanced liver disease, is difficult to distinguish from prerenal azotemia and is a diagnosis of exclusion. A particularly poor prognosis is seen in the case of type 1 hepatorenal syndrome, in which AKI persists despite volume adminis tration and withholding of diuretics. Type 2 hepatorenal syndrome is a less severe form characterized mainly by refractory ascites. ■ ■INTRINSIC AKI The most common causes of intrinsic AKI are sepsis, ischemia, and nephrotoxins, both endogenous and exogenous (Fig. 321-3). As mentioned previously, in many cases, prerenal azotemia advances to tubular injury. Although often the AKI is attributed to “acute tubular necrosis,” human biopsy confirmation of tubular necrosis is, in general, often lacking in cases of sepsis and ischemia; indeed, processes such as inflammation, apoptosis, and altered regional perfusion may be impor tant contributors pathophysiologically without frank necrosis. There are other potential causes of AKI in settings such as sepsis, including drug-induced interstitial nephritis or glomerulonephritis. These and other causes of intrinsic AKI can be catalogued anatomically according to the major site of renal parenchymal damage: glomeruli, tubuloin terstitium, and vessels, although there is frequently overlap in tissue Intrinsic Renal Failure Small vessels • Glomerulonephritis • Vasculitis • TTP/HUS • DIC • Atheroemboli • Malignant HTN • Calcineurin inhibitors • Sepsis Juxtamedullary glomerulus Distal convoluted tubule Cortex Medulla Proximal convoluted tubule Outer Inner Pars recta Loop of Henle Thick ascending limb Loop of Henle Collecting duct Thin descending limb FIGURE 321-3 Major causes of intrinsic acute kidney injury. ATN, acute tubular necrosis; DIC, disseminated intravascular coagulation; HTN, hypertension; PCN, penicillin; PPI, proton pump inhibitors; TINU, tubulointerstitial nephritis-uveitis; TTP/HUS, thrombotic

thrombocytopenic purpura/hemolytic-uremic syndrome.

compartment involvement. For example, glomerulonephritis can alter efferent arteriolar blood flow, which then reduces capillary perfusion to a region of the nephron leading to cell death, obstruction of the lumen with cellular debris, and impaired tubular function.

■ ■SEPSIS-ASSOCIATED AKI In the United States, >1 million cases of sepsis occur each year. AKI complicates >50% of cases of severe sepsis and greatly increases the risk of death. Sepsis is also a very important cause of AKI in the developing world. AKI also predisposes to sepsis. Decreases in GFR with sepsis can occur even in the absence of overt hypotension, although many cases of severe AKI typically occur in the setting of hemodynamic compromise requiring vasopressor support. Reduced urine output is common in sepsis-induced AKI. While there can be tubular injury associated with AKI in sepsis as manifest by the presence of tubular debris and casts in the urine, postmortem examinations of kidneys from individuals with severe sepsis suggest that other factors, perhaps related to inflamma tion, mitochondrial dysfunction, and interstitial edema, contribute to the pathophysiology of sepsis-induced AKI. The hemodynamic effects of sepsis—arising from generalized arte rial vasodilation, mediated in part by cytokines that upregulate the expression of inducible NO synthase in the vasculature—can lead to a CHAPTER 321 Tubules • Toxic ATN • Endogenous (rhabdomyolysis, hemolysis) • Exogenous (contrast, cisplatin, gentamicin) • Ischemic ATN • Sepsis Intratubular • Endogenous • Myeloma proteins • Uric acid (tumor lysis syndrome) • Cellular debris • Exogenous • Acyclovir, methotrexate

Acute Kidney Injury Proximal convoluted tubule Outer cortical glomerulus Distal convoluted tubule Thick ascending limb Pars recta Interstitium • Allergic (PCN, PPIs, NSAIDs, rifampin, etc.) • Infection (severe pyelonephritis, Legionella, sepsis) • Infiltration (lymphoma, leukemia) • Inflammatory (Sjogren’s, tubulointerstitial nephritis uveitis), sepsis Large vessels • Renal artery embolus, dissection, vasculitis • Renal vein thrombosis • Abdominal compartment syndrome

reduction in GFR. The operative mechanisms may be excessive efferent arteriole vasodilation, particularly early in the course of sepsis, or renal vasoconstriction from activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, or increased levels of vaso pressin or endothelin. Sepsis may lead to endothelial damage, which results in increased microvascular leukocyte adhesion and migration, thrombosis, permeability, increased interstitial pressure, reduction in local flow to tubules, and activation of reactive oxygen species, all of which may injure renal tubular cells.

AKI can be an important complication of viral infections, such as hantavirus, dengue virus, or SARS-CoV-2. The pathophysiology of AKI due to viral infections remains incompletely understood. As an example, some have reported infection of the kidney with SARSCoV-2, whereas others have found less direct involvement. SARSCoV-2 is associated with a large release of cytokines into the circulation (“cytokine storm”), which may cause diffuse intrarenal vasoconstric tion. Finally, there is a generalized hypercoagulable state associated with SARS-CoV-2 that may contribute to the impairment of intrarenal blood flow. ■ ■ISCHEMIA-ASSOCIATED AKI Healthy kidneys receive 20% of the cardiac output and account for 10% of resting oxygen consumption, despite constituting only 0.5% of the human body mass. The kidneys are also the site of one of the most hypoxic regions in the body, the renal medulla. The outer medulla is particularly vulnerable to ischemic damage

because of the architecture of the blood vessels that supply oxygen and nutrients to the tubules. In the outer medulla, enhanced leukocyte-endothelial interactions in the small vessels lead to inflammation and reduced local blood flow to the metabolically very active S3 segment of the proximal tubule, which depends on oxidative metabolism for survival. Mitochondrial dysfunction leads to impaired oxidative phosphorylation with less efficient adenosine triphosphate (ATP) generation and mitochondrial release of reactive oxygen species, both of which play a role in renal tubular injury. Transient ischemia alone in a normal kidney is usually not sufficient to cause severe AKI, as evidenced by the relatively low risk of severe AKI even after total interruption of renal blood flow dur ing suprarenal aortic clamping or cardiac arrest. Prerenal azotemia and ischemia-associated AKI represent a continuum of the manifestations of renal hypoperfusion leading to ATN. Persistent preglomerular vaso constriction may be a common underlying cause of the reduction in GFR seen in AKI; implicated factors for vasoconstriction include acti vation of tubuloglomerular feedback from enhanced delivery of solute to the macula densa following proximal tubule injury and reduced reabsorption, increased basal vascular tone and reactivity to vasocon strictive agents, and decreased vasodila tor responsiveness. Other contributors to low GFR include backleak of filtrate across damaged and denuded tubular epithelium and mechanical obstruction of tubules from necrotic debris (Fig. 321-4). Postoperative AKI Ischemia-asso ciated AKI is a serious complication in the postoperative period, especially after major operations involving significant blood loss and intraoperative hypoten sion. The procedures most commonly associated with AKI are cardiac surgery with cardiopulmonary bypass (particu larly for combined valve and bypass pro cedures), vascular procedures with aortic cross clamping, and intraperitoneal pro cedures. Severe AKI requiring dialysis occurs in ~1% of cardiac and vascular surgery procedures. The risk of severe AKI has been less well studied for major intraperitoneal procedures but appears to be of comparable magnitude. Common risk factors for postoperative AKI include PART 9 Disorders of the Kidney and Urinary Tract Pathophysiology of Ischemic Acute Kidney Injury MICROVASCULAR Glomerular Medullary Vasoconstriction in response to: endothelin, adenosine, angiotensin II, thromboxane A2, leukotrienes, sympathetic nerve activity Vasodilation in response to: nitric oxide, PGE2, acetylcholine,
bradykinin Endothelial and vascular smooth muscle cell structural damage Leukocyte-endothelial adhesion, vascular obstruction, leukocyte activation, and inflammation FIGURE 321-4 Interacting microvascular and tubular events contributing to the pathophysiology of ischemic acute kidney injury. PGE2, prostaglandin E2. (Reproduced with permission from JV Bonventre, JM Weinberg. J Am Soc Nephrol. 14:2199, 2003.)

underlying CKD, older age, diabetes mellitus, congestive heart failure, and emergency procedures. The pathophysiology of AKI following cardiac surgery is multifactorial. Major AKI risk factors are common in the population undergoing cardiac or vascular surgery. Over time, more of these surgical procedures are performed on older patients with comorbidities that predispose them to AKI and hasten progression of end-stage kidney disease (ESKD) if they develop AKI. Longer dura tion of cardiopulmonary bypass is a risk factor for AKI. In addition to ischemic injury from sustained hypoperfusion, cardiopulmonary bypass may cause AKI through a number of mechanisms including extracorporeal circuit activation of leukocytes and inflammatory pro cesses, hemolysis with resultant pigment nephropathy (see below), and aortic injury with resultant atheroemboli. AKI from atheroembolic disease, which can also occur following percutaneous catheterization of the aorta, or spontaneously, is due to cholesterol crystal emboliza tion resulting in partial or total occlusion of multiple small arteries within the kidney. Over time, a foreign body reaction can result in intimal

proliferation, giant cell formation, and further narrowing of the vascular lumen, accounting for the generally subacute (over a period of weeks rather than days) decline in renal function. Burns and Acute Pancreatitis Extensive fluid losses into the extravascular compartments of the body frequently accompany severe burns and acute pancreatitis. AKI is an ominous complication of burns, affecting 25% of individuals with >10% total body surface area involve ment. In addition to severe hypovolemia resulting in decreased cardiac output and increased neurohormonal activation, burns and acute pan creatitis both lead to dysregulated inflammation and an increased risk of sepsis and acute lung injury, all of which may facilitate the develop ment and progression of AKI. Individuals undergoing massive fluid resuscitation for trauma, burns, and acute pancreatitis can also develop abdominal compartment syndrome, where markedly elevated intraab dominal pressures, usually >20 mmHg, lead to renal vein compression and reduced GFR. Drug nephrotoxicity is also an important contribu tor to AKI. Mortality is much higher in patients who develop AKI. Diseases of the Vasculature Leading to Ischemia These dis eases can compromise oxygen and metabolic substrate delivery to the tubules and glomeruli. Microvascular causes of AKI include the throm botic microangiopathies (due to cocaine, certain chemotherapeutic agents, antiphospholipid antibody syndrome, radiation nephritis, malignant hypertensive nephrosclerosis, thrombotic thrombocytope nic purpura/hemolytic-uremic syndrome [TTP-HUS]), scleroderma, some chemotherapeutic agents, and atheroembolic disease. Largevessel diseases associated with AKI include renal artery dissection, O2 TUBULAR Cytoskeletal breakdown Mitochondrial injury Loss of polarity Apoptosis and necrosis Inflammatory and vasoactive mediators Desquamation of viable and necrotic cells Tubular obstruction Backleak

thromboembolism, or thrombosis, and renal vein compression or thrombosis. ■ ■NEPHROTOXIN-ASSOCIATED AKI The kidney has very high susceptibility to nephrotoxic agents due to extremely high blood perfusion and concentration of filtered substances along the nephron where filtrate water is reabsorbed. Nephrotoxic injury occurs in response to a number of pharmacologic compounds with diverse structures, endogenous substances, and environmental exposures. All structures of the kidney are vulnerable to toxic injury, including the tubules, interstitium, vasculature, and collecting system. As with other forms of AKI, risk factors for nephro toxicity include older age, CKD, and prerenal azotemia. Hypoalbumin emia may increase the risk of some forms of nephrotoxin-associated AKI due to increased free circulating drug concentrations. Contrast Agents Iodinated contrast agents used for cardiovascular and computed tomography (CT) imaging have been implicated as a cause of AKI. Many question whether AKI in response to contrast agents represents an important consequence of contrast studies. It is likely to have been diagnosed too frequently in the past, particularly in individuals who had many risk factors for AKI, making the cause difficult to identify. The terminology has changed so that the former “contrast nephropathy” has been replaced by “contrast-associated AKI” or “contrast-induced AKI” (CI-AKI), with the latter representing a smaller subgroup of the former. The occurrence of CI-AKI is negligible in those with normal renal function but increases in the setting of CKD, particularly in individuals with diabetic kidney disease. The most com mon clinical course of contrast nephropathy is characterized by a rise in SCr beginning 24–48 h following exposure, peaking within 3–5 days, and resolving within 1 week. More severe, dialysis-requiring AKI is uncommon except in the setting of significant preexisting CKD, often in association with congestive heart failure or other coexisting causes for ischemia-associated AKI. Patients with multiple myeloma and/or renal disease are particularly susceptible. Other diagnostic agents implicated as a cause of AKI are high-dose gadolinium used for magnetic resonance imaging (MRI) and oral sodium phosphate solu tions used as bowel

purgatives. Gadolinium has been associated with development of nephrogenic systemic fibrosis (NSF) in subjects with advanced kidney disease or AKI, but the majority of these cases were associated with group I gadolinium-based contrast media, which are rarely used now in the United States and have been withdrawn from the market in many other countries. The risk of AKI associated with stan dard doses of group II gadolinium-based contrast media is very low. Antibiotics Several antimicrobial agents are commonly associated with AKI. Vancomycin may be associated with AKI from tubular injury, particularly when trough levels are high and when used in combina tion with other nephrotoxic antibiotics. Vancomycin can also crystalize in tubules and cause intratubular obstruction. Aminoglycosides and amphotericin B both cause tubular necrosis. Nonoliguric AKI (i.e., with a urine volume >400 mL/d) accompanies 10–30% of courses of aminoglycoside antibiotics, even when plasma levels are in the thera peutic range. Aminoglycosides are freely filtered across the glomerulus and then accumulate within the renal cortex, where concentrations can greatly exceed those of the plasma. AKI typically manifests after 5–7 days of therapy and can present even after the drug has been discontinued. Hypomagnesemia is a common finding. Amphotericin B causes renal vasoconstriction from an increase in tubuloglomerular feedback as well as direct tubular toxicity mediated by reactive oxygen species. Nephrotoxicity from amphotericin B is dose and duration dependent. This drug binds to tubular membrane cholesterol and introduces pores. Clinical features of amphotericin B nephrotoxicity include polyuria, hypomagnesemia, hypocalcemia, and nongap metabolic acidosis. Acyclovir can precipitate in tubules and cause AKI by tubular obstruction, particularly when given as an intravenous bolus at high doses (500 mg/m2) or in the setting of hypovolemia. Foscarnet, pentam idine, tenofovir, and cidofovir are also frequently associated with AKI due to tubular toxicity. AKI secondary to acute interstitial nephritis

can occur as a consequence of exposure to many antibiotics, including penicillins, cephalosporins, quinolones, sulfonamides, and rifampin.

Chemotherapeutic Agents Cisplatin and carboplatin are accu mulated by proximal tubular cells and cause necrosis and apoptosis. Intensive hydration regimens have reduced the incidence of cisplatin nephrotoxicity, but it remains a dose-limiting toxicity. Ifosfamide may cause hemorrhagic cystitis and tubular toxicity, manifested as type II renal tubular acidosis (Fanconi syndrome), polyuria, hypoka lemia, and a modest decline in GFR. Antiangiogenesis agents, such as bevacizumab, can cause proteinuria and hypertension via injury to the glomerular microvasculature (thrombotic microangiopathy). Other antineoplastic agents such as mitomycin C and gemcitabine may cause thrombotic microangiopathy with resultant AKI. Immune checkpoint inhibitors, such as ipilimumab, tremelimumab, nivolumab, and pembro lizumab can cause immune-related adverse events, often manifesting in the kidney as acute interstitial nephritis. Lower GFR, proton pump inhibitor use, and extrarenal immune-related adverse events are pre disposing risk factors for AKI secondary to immune checkpoint inhibi tors. The checkpoint inhibitors result in hyperactivity of the immune system triggered by these agents. Toxic Ingestions Ethylene glycol, present in automobile antifreeze, is metabolized to oxalic acid, glycolaldehyde, and glyoxylate, which may cause AKI through direct tubular injury and tubular obstruction. Diethylene glycol is an industrial agent that has caused outbreaks of severe AKI around the world due to adulteration of pharmaceutical preparations. The metabolite 2-hydroxyethoxyacetic acid (HEAA) is thought to be responsible for tubular injury. Melamine contamination of foodstuffs has led to nephrolithiasis and AKI, either through intra tubular obstruction or possibly direct tubular toxicity. Aristolochic acid was found to

be the cause of “Chinese herb nephropathy” and “Balkan nephropathy” due to its contamination of medicinal herbs or farming. The list of environmental toxins is likely to grow and contribute to a better understanding of previously catalogued “idiopathic” chronic tubular interstitial disease, a common diagnosis in both the developed and developing world. CHAPTER 321 Acute Kidney Injury Endogenous Toxins AKI may be caused by a number of endog enous compounds, including myoglobin, hemoglobin, uric acid, and myeloma light chains. Myoglobin can be released by injured muscle cells, and hemoglobin can be released during massive hemolysis leading to pigment nephropathy. Rhabdomyolysis may result from traumatic crush injuries, muscle ischemia during vascular or orthopedic surgery, compression during coma or immobilization, prolonged seizure activity, excessive exercise, heat stroke or malignant hyperthermia, infections, metabolic disorders (e.g., hypophosphatemia, severe hypothyroidism), and myopathies (drug-induced, metabolic, or inflammatory). Patho genic factors contributing to AKI upon exposure to endogenous toxins include intrarenal vasoconstriction, direct proximal tubular toxicity, and mechanical obstruction of the distal nephron lumen when myoglobin or hemoglobin precipitates with Tamm-Horsfall protein (uromodulin, the most common protein in urine and produced in the thick ascend ing limb of the loop of Henle), a process favored by acidic urine. Tumor lysis syndrome may follow initiation of cytotoxic therapy in patients with high-grade lymphomas and acute lymphoblastic leukemia; massive release of uric acid (with serum levels often exceeding 15 mg/dL) leads to precipitation of uric acid in the renal tubules and AKI (Chap. 75). Other features of tumor lysis syndrome include hyperkalemia and hyper phosphatemia. The tumor lysis syndrome can also occasionally occur spontaneously or with treatment for solid tumors or multiple myeloma. Myeloma light chains can also cause AKI by glomerular damage and/or direct tubular toxicity and by binding to Tamm-Horsfall protein to form obstructing intratubular casts. Hypercalcemia, which can also be seen in multiple myeloma, may cause AKI by intense renal vasoconstriction and inhibition of sodium and water reabsorption in the nephron with resultant volume depletion. Other Causes of Acute Tubulointerstitial Disease Leading to AKI

While many drugs result in toxin-induced injury to the nephron with

subsequent inflammation, drugs can also lead to the development of an allergic response characterized by an inflammatory infiltrate, sometimes associated with blood and urinary eosinophilia. Proton pump inhibi tors and NSAIDs are commonly used drugs that have been associated with acute tubulointerstitial nephritis. AKI may be also caused by severe infections and infiltrative malignant or nonmalignant (e.g., sarcoidosis) diseases with tubulointerstitial disease.

Anticoagulant-Related Nephropathy Excessive anticoagula tion with warfarin or other classes of anticoagulants has been reported to cause AKI through glomerular hemorrhage resulting in the forma tion of obstructing red blood cell casts within the kidney tubule and tubular injury. Glomerulonephritis Diseases involving the glomerular podo cytes, mesangial, and/or endothelial cells can lead to AKI by com promising the filtration barrier and blood flow within the renal circulation. Although glomerulonephritis is a less common (~5%) cause of AKI, early recognition is particularly important because the diseases can respond to timely treatment with immunosuppressive agents or therapeutic plasma exchange, and the treatment may reverse the AKI and decrease subsequent longer term injury. ■ ■POSTRENAL AKI (See also Chap. 331.) Postrenal AKI occurs when the normally uni directional flow of urine is acutely blocked either partially or totally, leading to increased retrograde hydrostatic pressure and interference with

glomerular filtration. Obstruction to urinary flow may be caused by functional or structural derangements anywhere from the renal pelvis to the tip of the urethra (Fig. 321-5). Normal urinary flow rate does not rule out the presence of partial obstruction, because the GFR is normally two orders of magnitude higher than the urinary flow rate and hence a preservation of urine output may be misleading in hiding the postrenal partial obstruction. For moderate to severe AKI to occur in individuals with two healthy functional kidneys, obstruction must affect both kidneys in order to observe large increases in SCr, unless there is asymmetric kidney function with one chronically diseased. Unilateral obstruction may cause AKI in the setting of significant underlying CKD with loss of renal reserve or, in rare cases, from reflex vasospasm of the contralateral kidney. Bladder neck obstruction is a PART 9 Disorders of the Kidney and Urinary Tract Postrenal Kidney Ureter Bladder Sphincter Urethra FIGURE 321-5 Anatomic sites and causes of obstruction leading to postrenal acute kidney injury.

common cause of postrenal AKI. This can be due to prostate disease (benign prostatic hypertrophy or prostate cancer), neurogenic bladder, or therapy with anticholinergic drugs. Obstructed bladder catheters can cause postrenal AKI if not recognized. Other causes of lower tract obstruction are blood clots, calculi, and urethral strictures. Ureteric obstruction can occur from intraluminal obstruction (e.g., calculi, blood clots, sloughed renal papillae), infiltration of the ureteric wall (e.g., neoplasia), or external compression (e.g., retroperitoneal fibrosis, neoplasia, abscess, or inadvertent surgical damage). The pathophysi ology of postrenal AKI involves hemodynamic alterations triggered by an abrupt increase in intratubular pressures. An initial period of hyperemia from afferent arteriolar dilation is followed by intrarenal vasoconstriction from the generation of angiotensin II, thromboxane A2, and vasopressin, and a reduction in NO production. Secondary reductions in glomerular function are due to underperfusion of glom eruli and, possibly, changes in the glomerular ultrafiltration coefficient. DIAGNOSTIC EVALUATION (TABLE 321-2) As described previously, AKI is defined by an elevation in the SCr concentration from baseline of at least 0.3 mg/dL within 48 h or at least 50% within 1 week, or a reduction in urine output to <0.5 mL/kg per h for longer than 6 h. Serum cystatin C is increasingly being used to estimate GFR and may have a role in AKI diagnosis; both SCr and cystatin C have distinct non-GFR determinants that can influence their sensitivity and specificity. As indicated previously, some patients with AKI will not have tubular or glomerular damage (e.g., prerenal azote mia). The distinction between AKI and CKD is important for proper diagnosis and treatment. CKD is defined by an estimated GFR <60 mL/min per 1.73 m2 or an albumin-to-creatinine ratio (ACR) of >30 mg/g for a period of at least 3 months. If the diagnosis of AKI is made and renal dysfunction persists for more than a week but not yet 3 months, then some refer to this renal dysfunction as acute kidney disease. The distinction between AKI and CKD is straightforward when a recent baseline SCr concentration is available, but more difficult in the many instances in which the baseline is unknown. In such cases, clues sug gestive of CKD can come from radiologic studies (e.g., small, shrunken kidneys with cortical thinning on renal ultrasound) or laboratory tests such as normocytic anemia in the absence of blood loss or secondary hyperparathyroidism with hyperphosphatemia and hypocalcemia, consistent with CKD. No set of tests, however, can rule out AKI super imposed on CKD because AKI is a frequent complication in patients with CKD, further complicating the distinc tion. Serial blood tests showing a con tinued substantial rise of SCr represent clear evidence of AKI. Once the diag nosis of AKI is established, its cause needs to be determined because the elevation of SCr or reduction in urine output can be due to a large number of physiologic and pathophysiologic pro cesses, as described previously. Increas ingly, the electronic medical record is being utilized for

automated alerts to identify AKI and artificial intelligence approaches for AKI prediction. The role of automated alerts and artificial intelligence to predict and/or identify AKI is an area of active investigation. Stones, blood clots, external compression, tumor, retroperitoneal fibrosis, cancer ■ ■HISTORY AND PHYSICAL EXAMINATION The clinical context, careful history taking, and physical examination often narrow the differential diagnosis for the cause of AKI. Prerenal azotemia should be suspected in the setting of vomiting, diarrhea, glycosuria caus ing polyuria, and several medications Prostatic enlargement, blood clots, cancer Strictures Obstructed Foley catheter

TABLE 321-2 Major Causes, Clinical Features, and Diagnostic Studies for Prerenal and Intrinsic Acute Kidney Injury ETIOLOGY CLINICAL FEATURES LABORATORY FEATURES COMMENTS Prerenal azotemia History of poor fluid intake or fluid loss (hemorrhage, diarrhea, vomiting, sequestration into extravascular space); NSAID/ ACE-I/ARB; heart failure; evidence of volume depletion (tachycardia, absolute or postural hypotension, low jugular venous pressure, dry mucous membranes), decreased effective circulatory volume (cirrhosis, heart failure) Sepsis, sepsis syndrome, or septic shock; overt hypotension not always seen in mild to moderate AKI Sepsis-associated AKI Systemic hypotension, often superimposed upon sepsis and/or reasons for limited renal reserve such as older age, CKD Ischemiaassociated AKI Nephrotoxin-Associated AKI: Endogenous Rhabdomyolysis Traumatic crush injuries, seizures, immobilization Elevated myoglobin, creatine kinase; urine heme positive with few red blood cells Hemolysis Recent blood transfusion with transfusion reaction Anemia, elevated LDH, low haptoglobin Tumor lysis Recent chemotherapy Hyperphosphatemia, hypocalcemia, hyperuricemia Multiple myeloma Age >60 years, constitutional symptoms, bone pain Monoclonal spike in urine or serum electrophoresis; elevated serum free light chains, low anion gap; anemia Nephrotoxin-Associated AKI: Exogenous Contrast nephropathy Exposure to iodinated contrast Characteristic course is rise in SCr within 1–2 d, peak within 3–5 d, recovery within 7 d Tubular injury Aminoglycoside antibiotics, cisplatin, tenofovir, vancomycin, zoledronate, ethylene glycol, aristolochic acid, and melamine (to name a few) Other Causes of Intrinsic AKI Glomerulonephritis/ vasculitis Variable (Chap. 326) features include skin rash, arthralgias, sinusitis (AGBM disease), lung hemorrhage (AGBM, ANCA, lupus), recent skin infection or pharyngitis (poststreptococcal), thrombotic microangiopathies including those related to drugs, such as cocaine, anti-VEGF agents, genetic abnormalities of the complement pathways Tubulointerstitial nephritis Drugs are responsible for about 75% of the biopsy-proven acute interstitial nephritis, which involves tubules in most cases. Examples of causes include antibiotics, PPIs, immune checkpoint inhibitors. Non-drug-related causes include tubulointerstitial nephritis-uveitis (TINU) syndrome, lupus, viral infection (e.g., COVID, HIV, hantavirus), and Legionella infection. TTP/HUS Neurologic abnormalities and/or AKI; recent diarrheal illness; use of calcineurin inhibitors; pregnancy or postpartum; spontaneous Atheroembolic disease Recent manipulation of the aorta or other large vessels; may occur spontaneously or after anticoagulation; retinal plaques, palpable purpura, livedo reticularis, GI bleed Postrenal AKI History of kidney stones, prostate disease, obstructed bladder catheter, retroperitoneal or pelvic neoplasm Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor-I; AGBM, antiglomerular basement membrane; AKI, acute kidney injury; ANA, antinuclear antibody; ANCA, antineutrophilic cytoplasmic antibody; ARB, angiotensin receptor blocker; ASO, antistreptolysin O; BUN, blood urea nitrogen; CKD, chronic kidney disease; FeNa, fractional excretion of sodium; GI, gastrointestinal; LDH, lactate dehydrogenase; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitors; TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome.

BUN/creatinine ratio above 20, FeNa <1%, hyaline casts in urine sediment, urine specific gravity >1.018, urine osmolality >500 mOsm/kg Low FeNa, high specific gravity and osmolality may not be seen in the setting of CKD, diuretic use; BUN elevation out of proportion to creatinine may alternatively indicate upper GI bleed or increased catabolism. Response to restoration of hemodynamics is most diagnostic. Positive culture from normally sterile body fluid or other test confirming infection; urine sediment often contains granular casts, renal tubular epithelial cell casts FeNa may be low (<1%), particularly early in the course, but is usually >1% with osmolality <500 mOsm/kg Urine sediment often contains granular casts, renal tubular epithelial cell casts; FeNa typically >1% FeNa may be low (<1%) FeNa may be low (<1%); evaluation for transfusion reaction CHAPTER 321 Bone marrow or renal biopsy can be diagnostic Acute Kidney Injury FeNa may be low (<1%) Urine sediment often contains granular casts, renal tubular epithelial cell casts. FeNa typically >1%. Can be oliguric or nonoliguric ANA, ANCA, Anti-GBM antibody, hepatitis serologies, cryoglobulins, blood culture, complement abnormalities, ASO titer (abnormalities of these tests depending on etiology) Kidney biopsy may be necessary Eosinophilia, sterile pyuria; often nonoliguric Urine eosinophils have limited diagnostic accuracy; kidney biopsy may be necessary Schistocytes on peripheral blood smear, elevated LDH, anemia, thrombocytopenia “Typical HUS” refers to AKI with a diarrheal prodrome, often due to Shiga toxin released from Escherichia coli or other bacteria; “atypical HUS” is due to inherited or acquired complement dysregulation. Diagnosis may involve screening for ADAMTS13 activity, Shiga toxin–producing E. coli, genetic evaluation of complement regulatory proteins, and kidney biopsy. Hypocomplementemia, eosinophiluria (variable), variable amounts of proteinuria Skin or kidney biopsy can be diagnostic No specific findings other than AKI; may have pyuria or hematuria Imaging with computed tomography or ultrasound

including diuretics, NSAIDs, ACE inhibitors, and ARBs. Physical signs of orthostatic hypotension, tachycardia, reduced jugular venous pres sure, decreased skin turgor, and dry mucous membranes are often pres ent in prerenal azotemia. Congestive heart failure, liver disease, and nephrotic syndrome can be associated with reductions in renal blood flow and/or alterations in intrarenal hemodynamics leading to reduced GFR. Extensive vascular disease raises the possibility of renal artery disease, especially if kidneys are known to be asymmetric in size. Ath eroembolic disease can be associated with livedo reticularis and other signs of emboli to the legs. The presence of sepsis is an important clue to causation, although, as described above, the detailed pathophysiol ogy may be multifactorial.

A history of prostatic disease, nephrolithiasis, or pelvic or paraaortic malignancy would suggest the possibility of postrenal AKI. Whether or not symptoms are present early during obstruction of the urinary tract depends on the location of obstruction. Colicky flank pain radiating to the groin suggests acute ureteric obstruction. Nocturia and urinary frequency or hesitancy can be seen in prostatic disease. Abdominal fullness and suprapubic pain can accompany bladder enlargement. Definitive diagnosis of obstruction requires radiologic investigations. A careful review of all medications is imperative in the evalua tion of an individual with AKI. Not only are medications frequently a nephrotoxic cause of AKI, but doses of administered medications must be adjusted for reductions in kidney function. In this regard, it is important to recognize that reductions in true GFR are not reflected by equations that estimate GFR because those equations are dependent on SCr and the patient being in a steady state. With AKI, changes in SCr will lag behind changes in filtration rate. Allergic interstitial nephritis may be accompanied by fever, arthralgias, and a pruritic

erythematous rash. The absence of systemic features of hypersensitivity, however, does not exclude the diagnosis of interstitial nephritis, and a kidney biopsy should be considered for definitive diagnosis when the cause of AKI is not apparent from the clinical presentation. PART 9 Disorders of the Kidney and Urinary Tract AKI accompanied by palpable purpura, pulmonary hemorrhage, or sinusitis raises the possibility of systemic vasculitis with glomeru lonephritis. A history of autoimmune disease, such as systemic lupus erythematosus, should lead to consideration of the possibility that the AKI is related to worsening of this underlying disease. Pregnancy should lead to the consideration of preeclampsia as a pathophysiologic contributor to the AKI. A tense abdomen should prompt consideration Urinary sediment in AKI Normal or few RBCs or WBCs or hyaline casts RBCs RBC casts WBCs WBC casts GN Interstitial nephritis ATN Prerenal Vasculitis Tubulointerstitial nephritis Postrenal GN Malignant hypertension Arterial thrombosis or embolism Pyelonephritis Acute cellular allograft rejection Thrombotic microangiopathy Allograft rejection Preglomerular vasculitis Myoglobinuria Malignant infiltration of the kidney Hemoglobinuria HUS or TTP Scleroderma crisis FIGURE 321-6 Interpretation of urinary sediment findings in acute kidney injury (AKI). ATN, acute tubular necrosis; GN, glomerulonephritis; HUS, hemolytic-uremic syndrome; RBCs, red blood cells; RTE, renal tubular epithelial; TTP, thrombotic thrombocytopenic purpura; WBCs, white blood cells. (Adapted from L Yang, JV Bonventre: Diagnosis and clinical evaluation of acute kidney injury. In Comprehensive Nephrology, 4th ed. J Floege et al [eds]. Philadelphia, Elsevier, 2010.)

of acute abdominal compartment syndrome, a diagnosis facilitated by measurement of bladder pressure. Signs and/or symptoms of limb ischemia may be clues to the diagnosis of rhabdomyolysis. ■ ■URINE FINDINGS Complete anuria early in the course of AKI is uncommon except in the following situations: complete urinary tract obstruction, renal artery occlusion, overwhelming septic shock, severe ischemia (often with cortical necrosis), or severe proliferative glomerulonephritis or vascu litis. A reduction in urine output (oliguria, defined as <400 mL/24 h) usually denotes more severe AKI (i.e., lower GFR) than when urine output is preserved. Oliguria is associated with worse clinical outcomes in AKI. Preserved urine output can be seen in nephrogenic diabetes insipidus characteristic of long-standing urinary tract obstruction, tubulointerstitial disease, or nephrotoxicity from cisplatin or amino glycosides, among other causes. Red or brown urine may be seen with or without gross hematuria; if the color persists in the supernatant after centrifugation, then pigment nephropathy from rhabdomyolysis or hemolysis should be suspected. The urinalysis and urine sediment examination are invaluable tools, but they require clinical correlation because of generally limited sen sitivity and specificity (see Fig. 321-6 and Chap. A4). In the absence of preexisting proteinuria from CKD, AKI secondary to ischemia or nephrotoxins leads to mild proteinuria (<1 g/d). Greater proteinuria in AKI suggests damage to the glomerular ultrafiltration barrier or excre tion of small molecular weight proteins such as myeloma light chains; the latter are not detected with conventional urine dipsticks (which detect albumin) and require the sulfosalicylic acid test or immunoelec trophoresis. Atheroemboli can cause a variable degree of proteinuria. Heavy proteinuria (“nephrotic range,” >3.5 g/d) can occasionally be seen in glomerulonephritis, vasculitis, or toxins/medications that can affect the glomerulus as well as the tubulointerstitium (e.g., NSAIDs). AKI can also complicate cases of minimal change disease, a cause of the nephrotic syndrome often associated with low serum albumin concentrations (Chap. 320). Prerenal azotemia may present with hyaline casts or an unremark able urine sediment examination. Postrenal AKI may also be associated with an unremarkable sediment, but hematuria and pyuria may be seen depending on the cause of obstruction. AKI from ATN due to ischemic

injury, sepsis, or certain nephrotoxins has characteristic urine sediment Abnormal Renal tubular epithelial (RTE) cells RTE casts Pigmented casts Granular casts Eosinophiluria Crystalluria ATN Allergic interstitial nephritis Acute uric acid nephropathy GN Calcium oxalate (ethylene glycol intoxication) Vasculitis Atheroembolic disease Tubulo- interstitial nephritis Pyelonephritis Cystitis Glomerulo- nephritis Drugs or toxins (acyclovir, indinavir, sulfadiazine, amoxicillin)

findings: pigmented “muddy brown” granular casts and tubular epithe lial cell casts. These findings may be absent in >20% of cases, however. Glomerulonephritis may lead to dysmorphic red blood cells or red blood cell casts. Interstitial nephritis may lead to white blood cell casts. The urine sediment findings overlap somewhat in glomerulonephritis and interstitial nephritis, and a diagnosis is not always possible on the basis of the urine sediment alone. Urine eosinophils have a limited role in differential diagnosis; they can be seen in interstitial nephritis, pyelonephritis, cystitis, atheroembolic disease, or glomerulonephritis. Crystalluria may be important diagnostically. The finding of oxalate crystals in AKI should prompt an evaluation for ethylene glycol toxic ity. Abundant uric acid crystals may be seen in tumor lysis syndrome. ■ ■BLOOD LABORATORY FINDINGS Certain forms of AKI are associated with characteristic patterns in the rise and fall of SCr. Prerenal azotemia typically leads to modest rises in SCr that return to baseline with improvement in hemodynamic status. In comparison, atheroembolic disease usually manifests with more subacute rises in SCr, although severe AKI with rapid increases in SCr can occur in this setting. With many of the epithelial cell toxins such as aminoglycoside antibiotics and cisplatin, the rise in SCr is characteris tically delayed for 3–5 days to 2 weeks after initial exposure. A complete blood count may provide diagnostic clues. Anemia is common in AKI and is usually multifactorial in origin. It is not related to an effect of AKI solely on production of red blood cells because this effect in isolation takes longer to manifest. Myeloma can be diagnosed with serum immunoelectrophoresis or free light chain assay, and it can often be suspected if the blood anion gap is low due to unmeasured cationic proteins. Peripheral eosinophilia can accompany interstitial nephritis, atheroembolic disease, polyarteritis nodosa, and ChurgStrauss vasculitis. Severe anemia in the absence of bleeding may reflect hemolysis, multiple myeloma, or thrombotic microangiopathy (e.g., HUS or TTP). Other laboratory findings of thrombotic microangi opathy include thrombocytopenia, schistocytes on peripheral blood smear, elevated lactate dehydrogenase level, and low haptoglobin con tent. Evaluation of patients suspected of having TTP or HUS includes measurement of levels of the von Willebrand factor cleaving protease (ADAMTS13) and testing for Shiga toxin–producing Escherichia coli. “Atypical HUS” constitutes the majority of adult cases of HUS; genetic testing is important because it is estimated that 60–70% of atypical HUS patients have mutations in genes encoding proteins that regulate the alternative complement pathway. AKI often leads to hyperkalemia, hyperphosphatemia, and hypocal cemia. Marked hyperphosphatemia with accompanying hypocalcemia may suggest rhabdomyolysis or tumor lysis syndrome. Serum creatine kinase and uric acid levels are often elevated in rhabdomyolysis, while tumor lysis syndrome can be associated with normal or marginally ele vated creatine kinase and markedly elevated serum uric acid. The anion gap may be increased with any cause of uremia due to retention of anions such as phosphate, hippurate, sulfate, and urate. The co-occurrence of an increased anion gap and an osmolal gap may suggest ethylene glycol poi soning, which may also cause oxalate crystalluria and oxalate deposition in kidney tissue. As discussed previously, low anion gap may provide a clue to the diagnosis of multiple myeloma due to the presence of unmea sured cationic proteins. Laboratory blood tests helpful for the diagnosis of glomerulonephritis and vasculitis include depressed complement levels and high titers of antinuclear antibodies (ANAs),

antineutrophil cytoplasmic antibodies (ANCAs), antiglomerular basement membrane (anti-GBM) antibodies, and cryoglobulins. It is important to diagnose glomerulonephritis or myeloma early in the course of AKI since effective therapies (e.g., immunosuppression or chemotherapy) are now available for some of the causes. In general, however, the therapies are less effec tive when severe kidney injury has progressed. ■ ■RENAL FAILURE INDICES Several indices have been used to help differentiate prerenal azotemia from intrinsic AKI when the tubules are malfunctioning. The low tubular flow rate and increased renal medullary recycling of urea seen in prerenal azotemia may cause a disproportionate elevation of

the blood urea nitrogen (BUN) compared to creatinine. Other causes of disproportionate BUN elevation need to be kept in mind, how ever, including upper gastrointestinal bleeding, hyperalimentation, increased tissue catabolism, and glucocorticoid use.

The FeNa is the fraction of the filtered sodium load that is not reab sorbed by the tubules and is a measure of both the kidney's ability to reabsorb sodium as well as endogenously and exogenously administered factors that affect tubular reabsorption. As such, it depends on sodium intake, effective intravascular volume, GFR, diuretic intake, and intact tubular reabsorptive mechanisms. With prerenal azotemia, the FeNa may be <1%, suggesting avid tubular sodium reabsorption. In patients with CKD, a FeNa significantly >1% can be present due to tubular dys function in the reabsorption of sodium, despite a superimposed prerenal state. The FeNa may also be >1% despite hypovolemia due to treatment with diuretics. Low FeNa is often seen early in glomerulonephritis and other disorders and, hence, should not be taken as prima facie evidence of prerenal azotemia. Low FeNa is therefore suggestive of, but not syn onymous with, effective intravascular volume depletion, and should not be used as the sole guide for volume management. The response of urine output to crystalloid or colloid fluid administration may be both diagnostic and therapeutic in prerenal azotemia. In ischemic AKI, the FeNa is frequently >1% because of tubular injury and resultant impaired ability to reabsorb sodium. Several causes of ischemia-associated and nephrotoxin-associated AKI can present with FeNa <1%, however, including sepsis (often early in the course), rhabdomyolysis, and contrast nephropathy. FeNa has the most utility in oliguric patients who are not given diuretics and do not have CKD. CHAPTER 321 The ability of the kidney to produce a concentrated urine is dependent upon many factors and relies on good blood flow and tubular function in multiple regions of the kidney. In the patient not taking diuretics and with good baseline kidney function, urine osmolality may be >500 mOsm/kg in prerenal azotemia, consistent with an intact medullary concentration gradient and elevated serum vasopressin levels causing water reabsorp tion by passive diffusion from the collecting duct into a concentrated medullary interstitium, resulting in concentrated urine. In elderly patients and those with CKD, however, baseline concentrating defects may exist, making urinary osmolality unreliable in many instances. Concentrating ability may also be maintained early in the course of glomerular disease when the tubules are not yet affected. Loss of concentrating ability (<350 mOsm/kg) is common in most forms of AKI that affect the tubules and interstitium, but this finding is not specific. Acute Kidney Injury ■ ■RADIOLOGIC EVALUATION Postrenal AKI should always be considered in the differential diagnosis of AKI because treatment is usually successful if instituted early. Simple bladder catheterization can rule out urethral obstruction. Imaging of the urinary tract with renal ultrasound or CT scan should be under taken to investigate obstruction in individuals with AKI unless an alternate diagnosis is apparent. Findings of obstruction include dilation of the collecting system and hydroureteronephrosis. Obstruction can be present without radiologic abnormalities in the setting

of volume depletion, retroperitoneal fibrosis, encasement with tumor, and also early in the course of obstruction. If a high clinical index of suspicion for obstruction persists despite normal imaging, antegrade or retro grade pyelography should be performed. Imaging may also provide additional helpful information about kidney size and echogenicity to assist in the distinction between AKI versus CKD. In CKD, kidneys are usually smaller unless the patient has diabetic nephropathy, HIVassociated nephropathy, or infiltrative diseases. Normal-sized kidneys are expected in AKI. Enlarged kidneys in a patient with AKI suggest the possibility of acute interstitial nephritis or infiltrative diseases. Vascular imaging may be useful if venous or arterial obstruction is suspected. ■ ■KIDNEY BIOPSY If the cause of AKI is not apparent based on the clinical context, physi cal examination, laboratory studies, and radiologic evaluation, kidney biopsy should be considered. The kidney biopsy can provide definitive diagnostic and prognostic information about acute kidney disease and CKD. The procedure is most often used in AKI when prerenal azotemia,

postrenal AKI, and ischemic or nephrotoxic AKI have been deemed unlikely and other possible diagnoses are being considered such as glo merulonephritis, vasculitis, interstitial nephritis, myeloma kidney, HUS and TTP, and allograft dysfunction. Kidney biopsy is associated with a risk of bleeding, which can be severe and organ- or life-threatening in patients with thrombocytopenia or coagulopathy, but the diagnostic and prognostic information obtained can be invaluable.

■ ■NOVEL BIOMARKERS BUN, SCr, and cystatin C are functional biomarkers of glomerular filtration rather than tissue injury biomarkers and, therefore, may be suboptimal for the diagnosis of actual parenchymal kidney damage. Filtration markers are also relatively slow to rise after kidney injury. Several urine and blood biomarkers have been investigated and show promise for earlier and accurate diagnosis of AKI and for predict ing AKI prognosis. In cases of oliguric AKI, the urinary flow rate in response to bolus intravenous furosemide 1.0–1.5 mg/kg can be used as a prognostic test: urine output <200 mL over 2 h after intravenous furosemide may identify patients at higher risk of progression to more severe AKI and the need for renal replacement therapy. The severity or risk of progressive AKI may also be reflected in findings on urine microscopy. In one study involving review of fresh urine sediments by board-certified nephrologists, a greater number of renal tubular epi thelial cells and/or granular casts in the urine sediment was associated with both the severity and worsening of AKI. Protein biomarkers of kidney injury have also been identified in animal models of AKI and have been used in humans and found to be particularly useful in toxic ity identification. Kidney injury molecule-1 (KIM-1) is a type 1 trans membrane protein that is abundantly expressed in proximal tubular cells injured by ischemia or multiple, distinct nephrotoxins, such as cis platin. KIM-1 is not expressed in appreciable quantities in the absence of tubular injury or in extrarenal tissues. KIM-1 can be detected after ischemic or nephrotoxic injury in the urine and plasma. Neutrophil gelatinase associated lipocalin (NGAL, also known as lipocalin-2 or siderocalin) is another biomarker of AKI. NGAL was first discovered as a protein in granules of human neutrophils. NGAL can bind to iron siderophore complexes and may have tissue-protective effects in the proximal tubule. NGAL is highly upregulated after inflammation and kidney injury and can be detected in the plasma and urine within 2 h of cardiopulmonary bypass–associated AKI. Soluble urokinase plasmino gen activator receptor (suPAR) is a signaling glycoprotein expressed in multiple cell types and thought to be involved in the pathogenesis of certain kidney diseases; suPAR has been measured in the plasma and found to predict the subsequent development of AKI. In 2014, the U.S. Food and Drug Administration (FDA) approved the marketing of a test based on the combination of the urinary concentrations of two cellcycle arrest biomarkers, insulin-like growth

factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinase-2 (TIMP-2) as pre dictive biomarkers for higher risk of the development of moderate to severe AKI in critically ill patients. In 2023, the FDA also approved the use of NGAL for the early identification of AKI in pediatric patients. Biomarkers may also be helpful in distinguishing tubulointerstitial nephritis where interstitial inflammation plays a dominant role from other causes of AKI that primarily affect the glomeruli or the tubule where inflammation also exists but may be less dominant. One such marker, CXCL9, has recently been reported. The optimal use of AKI biomarkers in clinical settings is an area of ongoing investigation. PART 9 Disorders of the Kidney and Urinary Tract COMPLICATIONS OF AKI The kidney plays a central role in homeostatic control of volume status, blood pressure, plasma electrolyte composition, acid-base balance, and the excretion of nitrogenous and other waste products. Complications associated with AKI are, therefore, protean, and depend on the severity of AKI and other associated conditions. Mild to moderate AKI may be entirely asymptomatic, particularly early in the course. ■ ■UREMIA Buildup of nitrogenous waste products, manifested as an elevated BUN concentration, is a hallmark of AKI. BUN itself poses little direct

toxicity at levels <100 mg/dL. In more severe AKI or when, as is often the case, AKI is on the backdrop of CKD, mental status changes and bleeding complications can arise. Other toxins normally cleared by the kidney may be responsible for the symptom complex known as uremia, which literally means “urine in the blood.” Urea has direct and indirect toxic effects. There are increased blood levels of parathyroid hormone, advanced glycosylation end products, and many other “middle mole cules” that contribute to the uremic syndrome. Few of the many possible uremic toxins have been definitively identified. The correlation of filtra tion markers or BUN concentrations with uremic symptoms is extremely variable, due in part to differences in generation rates across individuals. ■ ■HYPERVOLEMIA AND HYPOVOLEMIA Expansion of extracellular fluid volume is a major complication of oliguric and anuric AKI, due to impaired salt and water excretion. The result can be weight gain, dependent edema, increased jugular venous pressure, and pulmonary edema. AKI may also induce or exacerbate acute lung injury characterized by increased vascular permeability and inflammatory cell infiltration in lung parenchyma. Recovery from AKI is often heralded by an increase in urine output. This “polyuric” phase of recovery may be due to an osmotic diuresis from retained urea and other waste products as well as delayed recovery of tubular reabsorptive functions. ■ ■HYPONATREMIA Abnormalities in plasma electrolyte composition can be mild or lifethreatening. The dysfunctional kidney has limited ability to regulate electrolyte balance. Administration of excessive hypotonic crystal loid or isotonic dextrose solutions can result in hypoosmolality and hyponatremia, which, if severe, can cause neurologic abnormalities, including seizures. ■ ■HYPERKALEMIA An important complication of AKI is hyperkalemia. Marked hyper kalemia is particularly common in rhabdomyolysis, hemolysis, and tumor lysis syndrome due to release of intracellular potassium from damaged cells. Muscle weakness may be a symptom of hyperkalemia. Potassium affects the cellular membrane potential of cardiac and neu romuscular tissues. The more serious complication of hyperkalemia is due to effects on cardiac conduction, leading to potentially fatal arrhythmias. ■ ■ACIDOSIS Metabolic acidosis, usually accompanied by an elevation in the anion gap, is common in AKI, and can further complicate acid-base and potassium balance in individuals with other causes of acidosis, includ ing sepsis, diabetic ketoacidosis, or respiratory acidosis. ■ ■HYPERPHOSPHATEMIA AND HYPOCALCEMIA AKI can lead to hyperphosphatemia, particularly in highly catabolic patients or those with AKI from rhabdomyolysis, hemolysis, and tumor lysis syndrome. Metastatic deposition of calcium phosphate can lead to hypocalcemia. AKI-associated hypocalcemia may also arise from

derangements in the vitamin D–parathyroid hormone– fibroblast growth factor-23 axis. Hypocalcemia is often asymptom atic but can lead to perioral paresthesias, muscle cramps, seizures, carpopedal spasms, and prolongation of the QT interval on electro cardiography. Calcium levels should be corrected for the degree of hypoalbuminemia, if present, or ionized calcium levels should be fol lowed. Mild, asymptomatic hypocalcemia does not require treatment. ■ ■BLEEDING Hematologic complications of AKI include anemia and bleeding, both of which are exacerbated by coexisting disease processes such as sepsis, liver disease, and disseminated intravascular coagulation. Direct hema tologic effects from AKI-related uremia include decreased erythropoi esis and platelet dysfunction. ■ ■INFECTIONS Infections are a common precipitant of AKI and also a dreaded com plication of AKI. Impaired host immunity has been described in ESKD and may be operative in severe AKI.

■ ■CARDIAC COMPLICATIONS The major cardiac complications of AKI are arrhythmias, pericarditis, and pericardial effusion. In addition, volume overload and uremia may lead to cardiac injury and impaired cardiac function. In animal studies, cellular apoptosis and capillary vascular congestion as well as mitochondrial dysfunction have been described in the heart after renal ischemia reperfusion. ■ ■MALNUTRITION AKI is often a severely hypercatabolic state, and therefore, malnutrition is a major complication. ■ ■PREVENTION AND TREATMENT OF AKI The management of individuals with and at risk for AKI varies according to the underlying cause (Table 321-3). Common to all are several principles. Optimization of hemodynamics, correction of fluid and electrolyte imbalances, discontinuation of nephrotoxic medications, and dose adjustment of administered medications are all critical. Common causes of AKI such as sepsis and ischemic ATN do not yet have specific therapies once injury is established, but meticulous clinical attention is needed to support the patient until (if) AKI resolves. The kidney possesses remarkable capacity to repair itself after even severe, dialysis-requiring AKI, when baseline renal function was previously intact. However, many patients with AKI, particularly when superimposed on preexisting CKD, undergo mal adaptive repair processes and do not recover fully and may remain dialysis dependent. It has become increasingly apparent that AKI pre disposes to accelerated progression of CKD, and CKD is an important risk factor for AKI. Prerenal Azotemia Prevention and treatment of prerenal azote mia require optimization of renal perfusion. In AKI, oliguria alone is not an indication for fluid administration. Intravascular hypovole mia should be the only indication. The composition of replacement fluids should be targeted to the type of fluid lost. Severe acute blood loss should be treated with packed red blood cells. Crystalloids are in general favored over colloid-containing solutions (e.g., hyperoncotic albumin-containing solutions, which are still commonly used for volume resuscitation in liver failure). The colloidal solution hydroxy ethyl starch is no longer available for hospitalized patients, due in part to concerns over increased risk of AKI. The most commonly used crystalloid solution is 0.9% saline. Other options are buffered crystalloid solutions (e.g., Ringer’s lactate, Hartmann’s solution, Plasma-Lyte). The choice between 0.9% saline or buffered crystal loid solutions can be based on serum electrolyte (e.g., some buffered crystalloid solutions are slightly hypotonic to plasma water and may be preferred for patients with hypernatremia; 0.9% saline can cause or exacerbate hyperchloremic metabolic acidosis and can be used in those with metabolic alkalosis; bicarbonate-containing solutions like dextrose water with 150 mEq sodium bicarbonate can be used in those with metabolic acidosis). Optimization of cardiac function in AKI may require use of ino tropic agents, preload- and afterload-reducing agents, antiarrhythmic drugs, and mechanical aids such as ventricular assist devices. Invasive hemodynamic monitoring to guide therapy may be necessary. Cirrhosis and Hepatorenal Syndrome

Fluid management in individuals with cirrhosis, ascites, and AKI is challenging because of the frequent difficulty in ascertaining intravascular volume status. Administration of intravenous fluids as a volume challenge may be required diagnostically as well as therapeutically. Excessive volume administration may, however, result in worsening ascites and pulmo nary compromise in the setting of hepatorenal syndrome or AKI due to superimposed spontaneous bacterial peritonitis. Peritonitis should be ruled out by inflammatory cell count and culture of ascitic fluid. Albumin may prevent AKI in those treated with antibiotics for sponta neous bacterial peritonitis. The definitive treatment of the hepatorenal syndrome is orthotopic liver transplantation. Bridge therapies that have shown promise include norepinephrine, terlipressin (a vasopres sin analogue), or combination therapy with octreotide (a somatostatin

TABLE 321-3 Management of Acute Kidney Injury General Issues

1. Optimization of systemic and renal hemodynamics through volume resuscitation and judicious use of vasopressors
2. Maintain mean arterial pressure >65 mmHg
3. Elimination of nephrotoxic agents (e.g., ACE inhibitors, ARBs, NSAIDs, aminoglycosides, chemotherapeutic agents, checkpoint inhibitors, antibiotics) if possible
4. Sufficient protein and calorie intake (20–30 kcal/kg per day) to avoid negative nitrogen balance. Nutrition should be provided by the enteral route if oral intake is not possible.
5. Initiation of renal replacement therapy when indicated Specific Issues
6. Nephrotoxin-specific a. Rhabdomyolysis: aggressive intravenous fluids; consider forced alkaline diuresis b. Tumor lysis syndrome: aggressive intravenous fluids and allopurinol or rasburicase
7. Volume overload a. Salt and water restriction b. Diuretics c. Ultrafiltration
8. Hyponatremia CHAPTER 321 a. Restriction of enteral free water intake, minimization of hypotonic intravenous solutions including those containing dextrose b. Hypertonic saline is rarely necessary in AKI. Vasopressin antagonists are generally not needed.
9. Hyperkalemia Acute Kidney Injury a. Restriction of dietary potassium intake b. Discontinuation of potassium-sparing diuretics, ACE inhibitors, ARBs, NSAIDs c. Loop diuretics to promote urinary potassium loss d. Potassium-binding molecules (sodium zirconium cyclosilicate) or ionexchange resins (patiromer, sodium or calcium polystyrene sulfonate) e. Insulin and glucose to promote entry of potassium intracellularly f. Inhaled beta-agonist therapy to promote entry of potassium intracellularly g. Calcium gluconate or calcium chloride (1 g) to stabilize the myocardium
10. Metabolic acidosis a. Sodium bicarbonate (if pH <7.2 to keep serum bicarbonate >15 mmol/L) b. Renal replacement therapy
11. Hyperphosphatemia a. Restriction of dietary phosphate intake b. Phosphate binding agents (calcium acetate, sevelamer hydrochloride, aluminum hydroxide—taken with meals)
12. Hypocalcemia a. Calcium carbonate or calcium gluconate if symptomatic
13. Hypermagnesemia a. Discontinue Mg2+-containing antacids
14. Hyperuricemia a. Acute treatment is usually not required except in the setting of tumor lysis syndrome (see above)
15. Drug dosing a. Careful attention to dosages and frequency of administration of drugs, adjustment for degree of renal failure b. Note that serum creatinine concentration may

overestimate renal function in the non-steady-state characteristic of patients with AKI Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney infection; ARBs, angiotensin receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs. analogue) and midodrine (an α1-adrenergic agonist), in combination with intravenous albumin (25–50 g, maximum 100 g/d). Intrinsic AKI Several agents have been tested and have failed to show benefit in the treatment of acute tubular injury. These include atrial natriuretic peptide, low-dose dopamine, endothelin antagonists, erythropoietin, prostaglandin analogues, antioxidants, antibodies against leukocyte adhesion molecules, growth factors,

intra-aortic mesenchymal stem cells, and small interfering RNAs to inhibit p53-mediated cell death, among many others. Most studies have used changes in SCr to identify AKI; kidney injury biomarkers described previously may provide an opportunity to test agents with greater sensitivity.

AKI due to acute glomerulonephritis or vasculitis may respond to immunosuppressive agents, anticomplement therapies, and/or plasmapheresis (Chap. 320). Allergic interstitial nephritis due to medications requires discontinuation of the offending agent. Glu cocorticoids have been used but not tested in randomized trials, in cases where AKI persists or worsens despite discontinuation of the suspected medication. AKI due to scleroderma (scleroderma renal crisis) should be treated with ACE inhibitors. Idiopathic TTP is a medical emergency and should be treated promptly with plasma exchange. Pharmacologic blockade of complement activation may be effective in atypical HUS. Early and aggressive volume repletion is mandatory in patients with rhabdomyolysis, who may initially require 10 L of fluid per day. Alka line fluids (e.g., 75 mmol/L sodium bicarbonate added to 0.45% saline) may be beneficial in preventing tubular injury and cast formation but carry the risk of worsening hypocalcemia. Diuretics may be used if fluid repletion is adequate but unsuccessful in achieving urinary flow rates of 200–300 mL/h. There is no specific therapy for established AKI in rhab domyolysis, other than dialysis in severe cases or general supportive care to maintain fluid and electrolyte balance and tissue perfusion. Careful attention must be focused on calcium and phosphate status because of precipitation in damaged tissue and release when the tissue heals. PART 9 Disorders of the Kidney and Urinary Tract Postrenal AKI Prompt recognition and relief of urinary tract obstruction can forestall the development of permanent structural damage induced by urinary stasis. The site of obstruction defines the treatment approach. Transurethral or suprapubic bladder cath eterization may be all that is needed initially for urethral strictures or functional bladder impairment. Ureteric obstruction may be treated by percutaneous nephrostomy tube placement or ureteral stent place ment. Relief of obstruction is usually followed by an appropriate diure sis for several days. In rare cases, severe polyuria persists due to tubular dysfunction and may require continued administration of intravenous fluids and electrolytes for a period of time. ■ ■SUPPORTIVE MEASURES FOR AKI Volume Management Hypervolemia in oliguric or anuric AKI may be life threatening due to acute pulmonary edema, especially because many patients have coexisting pulmonary disease, and AKI likely increases pulmonary vascular permeability. Fluid and sodium should be restricted, and diuretics may be used to increase the uri nary flow rate. There is no evidence that increasing urine output itself improves the natural history of AKI, but diuretics may help to avoid the need for dialysis in some cases. In severe cases of volume overload, furosemide may be given as a bolus (200 mg) followed by an intravenous drip (10–40 mg/h), with or without a thiazide diuretic. In decompensated heart failure, stepped diuretic therapy was found to be superior to ultrafiltration in preserving renal function. Dopamine in low doses may transiently

increase salt and water excretion by the kid ney in prerenal states, but clinical trials have failed to show any benefit in patients with intrinsic AKI. Because of the risk of arrhythmias and potential bowel ischemia, the risks of dopamine outweigh the benefits if used specifically for the treatment or prevention of AKI. Electrolyte and Acid-Base Abnormalities The treatment of dysnatremias and hyperkalemia is described in Chap. 56. Metabolic acidosis associated with AKI is generally not treated unless severe (pH <7.20 and serum bicarbonate <15 mmol/L). Acidosis can be treated with oral or intravenous sodium bicarbonate (Chap. 58), but overcorrec tion should be avoided because of the possibility of metabolic alkalosis, hypocalcemia, hypokalemia, and volume overload. Hyperphosphatemia is common in AKI and can usually be treated by limiting intestinal absorption of phosphate using phosphate binders (calcium carbon ate, calcium acetate, lanthanum, sevelamer, or aluminum hydroxide).

Symptomatic hypocalcemia should be treated with calcium gluconate or calcium chloride. Ionized calcium should be monitored rather than total calcium when hypoalbuminemia is present. Malnutrition Increased catabolism with protein energy wasting is common in severe AKI, particularly in the setting of multisystem organ failure. Inadequate nutrition may lead to starvation ketoacidosis and protein catabolism. Excessive nutrition may increase the generation of nitrogenous waste and lead to worsening azotemia. Total parenteral nutrition requires large volumes of fluid administration and may com plicate efforts at volume control. According to the KDIGO guidelines, patients with AKI should achieve a total energy intake of 20–30 kcal/ kg per day. Protein intake should vary depending on the severity of AKI: 0.8–1.0 g/kg per day in noncatabolic AKI without the need for dialysis; 1.0–1.5 g/kg per day in patients on dialysis; and up to a maxi mum of 1.7 g/kg per day if hypercatabolic and receiving continuous renal replacement therapy. Trace elements and water-soluble vitamins should also be supplemented in AKI patients treated with dialysis and continuous renal replacement therapy. Anemia The anemia seen in AKI is usually multifactorial and is not improved by erythropoiesis-stimulating agents, due to their delayed onset of action and the presence of bone marrow resistance in critically ill patients. Uremic bleeding may respond to desmopressin or estrogens but may require dialysis for treatment in the case of long-standing or severe uremia. Gastrointestinal prophylaxis with proton pump inhibi tors or histamine (H2) receptor blockers is required. It is important to recognize, however, that proton pump inhibitors have been associated with AKI due to interstitial nephritis, a relationship that is increasingly being recognized. Venous thromboembolism prophylaxis is important and should be tailored to the clinical setting; low-molecular-weight heparins and factor Xa inhibitors have unpredictable pharmacokinetics in severe AKI and should generally be avoided if possible. Dialysis Indications and Modalities (See also Chap. 323.)

Dialysis is indicated when medical management fails to control volume overload, hyperkalemia, or acidosis; in some toxic ingestions; and when there are severe complications of uremia (asterixis, pericardial rub or effusion, encephalopathy, uremic bleeding). Late initiation of dialysis carries the risk of avoidable volume, electrolyte, and metabolic complications of AKI. On the other hand, initiating dialysis too early may unnecessarily expose individuals to intravenous lines and invasive procedures, with the attendant risks of infection, bleeding, procedural complications, and hypotension. In randomized controlled trials, earlier versus later initiation of dialysis has not been demonstrated to improve survival and may increase the risk of adverse events. The initiation of dialysis should not, however, await the development of a life-threatening complication of renal failure. Many nephrologists initi ate dialysis for AKI empirically when the BUN exceeds a certain value (e.g., 100 mg/dL) in patients without clinical signs of recovery of kidney function. The

available modes for renal replacement therapy in AKI require either access to the peritoneal cavity (for peritoneal dialysis) or the large blood vessels (for hemodialysis, hemofiltration, and other hybrid procedures). Small solutes are removed across a semiperme able membrane down their concentration gradient (“diffusive” clear ance) and/or along with the movement of plasma water (“convective” clearance). Hemodialysis can be used intermittently or continuously and can be done through convective clearance, diffusive clearance, or a combination of the two. Vascular access is through the femoral, internal jugular, or subclavian veins. Hemodialysis is an intermittent procedure that removes solutes through diffusive and convective clear ance. Hemodialysis is typically performed 3–4 h per day, three to four times per week, and is the most common form of renal replacement therapy for AKI. One of the major complications of hemodialysis is hypotension, particularly in the critically ill, which can perpetuate AKI by causing ischemic injury to the recovering organ. Continuous intravascular procedures were developed in the early 1980s to treat hemodynamically unstable patients without inducing the rapid shifts of volume, osmolarity, and electrolytes characteristic of inter mittent hemodialysis. Continuous renal replacement therapy (CRRT)

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