Acute Kidney Injury

Chapter 321 | Part 9: Disorders of the Kidney and Urinary Tract | Part 9 – Renal & Urinary Tract Disorders | DETAILED EDITION

KEY CLINICAL POINTS

1. AKI is defined by KDIGO as an increase in serum creatinine (SCr) of ≥0.3 mg/dL within 48 h or ≥1.5 times baseline over 7 days, or urine output <0.5 mL/kg/h for >6 h.
2. AKI is a clinical diagnosis, not a structural one; it can occur with or without parenchymal injury.
3. AKI complicates 5–7% of acute-care hospital admissions and up to 30% of ICU admissions.
4. Prerenal azotemia is the most common form, resulting from inadequate renal perfusion (hypovolemia, heart failure, medications).
5. Intrinsic AKI causes include sepsis, ischemia, and nephrotoxins (contrast, antibiotics, chemotherapy).
6. Postrenal AKI is caused by obstruction of urinary flow from the renal pelvis to the urethra.
7. The renal medulla is the most hypoxic region and is particularly vulnerable to ischemic damage.
8. SGLT-2 inhibitors do not appear to increase AKI risk and may have a protective effect.
9. Hepatorenal syndrome is a diagnosis of exclusion with a particularly poor prognosis in type 1.
10. CKD is defined by eGFR <60 mL/min/1.73 m2 or ACR >30 mg/g for ≥3 months.

FIGURES IN THIS CHAPTER

1. DEFINITION & OVERVIEW

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 retention 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.

1.1 KDIGO Definition

Harrison's defines this as: *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 retention 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.

1.2 Clinical vs Structural Diagnosis

- AKI is a clinical diagnosis and not a structural one.
- A patient may have AKI with or without injury to the kidney parenchyma.
- The term AKI is a misnomer when parenchymal injury is absent.
- 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.

2. 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 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 medications, 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.

2.1 Incidence and Trends

- Incidence has grown by more than fourfold in the United States since 1988.
- Estimated yearly incidence is 500 per 100,000 population.
- Incidence is higher than the yearly incidence of stroke.
- Morbidity of AKI in those admitted to the ICU exceeds 50% in many studies.

2.2 Long-term Implications

- AKI increases the risk for the development or worsening of chronic kidney disease (CKD).
- AKI increases the risk of future cardiovascular disease.
- AKI may also occur in the community.

3. ETIOLOGY & 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 (from "azo," meaning nitrogen, and "-emia," meaning in the blood), the most common form of AKI, results from inadequate renal perfusion. 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, however, prerenal azotemia may coexist with other forms of intrinsic AKI associated with processes acting directly on the renal parenchyma. Prolonged 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 compensatory 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. 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 these counterregulatory mechanisms to maintain GFR in the face of systemic hypotension. Even in healthy adults, renal autoregulation usually fails once the systolic blood pressure falls below 80 mmHg. A number of factors determine the robustness of the autoregulatory 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 intrarenal arterioles and impaired capacity for renal afferent vasodilation. In CKD, renal afferent vasodilation may be operating at maximal capacity 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) inhibitors and angiotensin receptor blockers (ARBs) limit renal efferent vasoconstriction; this effect is particularly pronounced in patients 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.

Table 1 **Table 321-1 Staging of Acute Kidney Injury Severity**

STAGE	SERUM CREATININE	URINE OUTPUT
1	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	2.0–2.9 times baseline	<0.5 mL/kg per h for ≥12 h
3	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

3.1 Prerenal Azotemia

• Prerenal azotemia results from inadequate renal perfusion.

• Common clinical conditions associated with prerenal azotemia are hypovolemia, decreased cardiac output, and medications that interfere with renal autoregulatory vascular responses such as nonsteroidal anti-inflammatory drugs (NSAIDs) and inhibitors of the renin-angiotensin system.

• Sodium-glucose 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 pressure and inducing natriuresis; in fact, recent studies have suggested a protective effect of these agents in preventing AKI.

• Hepatorenal syndrome is a cause of AKI in individuals with multiorgan 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. Systemic vascular resistance is markedly reduced due to primary arterial vasodilation in the splanchnic circulation, resulting ultimately in activation of vasoconstrictor responses similar to those seen in hypovolemia. AKI is a common complication in this setting, and it can be triggered by volume depletion and spontaneous bacterial peritonitis.

3.2 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 important 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 other causes of intrinsic AKI can be catalogued anatomically according to the major site of renal parenchymal damage: glomeruli, tubulointerstitium, and vessels, although there is frequently overlap in tissue compartment involvement.

• 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.

3.3 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 inflammation, mitochondrial dysfunction, and interstitial edema, contribute to the pathophysiology of sepsis-induced AKI.

• The hemodynamic effects of sepsis—arising from generalized arterial vasodilation, mediated in part by cytokines that upregulate the expression of inducible NO synthase in the vasculature—can lead to a reduction in GFR.

• 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.

3.4 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 during 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 vasoconstriction may be a common underlying cause of the reduction in GFR seen in AKI; implicated factors for vasoconstriction include activation 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 vasoconstrictive agents, and decreased vasodilator 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).

• Glomerular vasoconstriction in response to endothelin, adenosine, angiotensin II, thromboxane A2, leukotrienes, sympathetic nerve activity, Mitochondrial injury, Cytoskeletal breakdown, Loss of polarity, Apoptosis and necrosis, Inflammatory and Endothelial and vascular smooth muscle cell structural damage and necrotic cells, Desquamation of viable tubular cells, Tubular obstruction, Leukocyte-endothelial adhesion, vascular obstruction, leukocyte activation, and inflammation, Backleak.

3.5 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 nephrotoxicity include older age, CKD, and prerenal azotemia.

• Hypoalbuminemia 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. 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 common 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 solutions 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 standard 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 combination 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 therapeutic 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, pentamidine, 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 accumulated 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, hypokalemia, 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 pembrolizumab 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 predisposing risk factors for AKI secondary to immune checkpoint inhibitors. 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 intratubular 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.

• Endogenous Toxins: AKI may be caused by a number of endogenous 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). Pathogenic 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 ascending 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 hyperphosphatemia. 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 inhibitors and NSAIDs are commonly used drugs that have been associated with acute tubulointerstitial nephritis. AKI may also be caused by severe infections and infiltrative malignant or nonmalignant (e.g., sarcoidosis) diseases with tubulointerstitial disease.

• Anticoagulant-Related Nephropathy: Excessive anticoagulation with warfarin or other classes of anticoagulants has been reported to cause AKI through glomerular hemorrhage resulting in the formation of obstructing red blood cell casts within the kidney tubule and tubular injury.

3.6 Postrenal AKI

• Postrenal AKI occurs when the normally unidirectional 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 for a healthy kidney 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 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 pathophysiology 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 glomeruli and, possibly, changes in the glomerular ultrafiltration coefficient.

4. CLINICAL FEATURES

• AKI is a clinical diagnosis and not a structural one.

• 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.

• Clinically, AKI more commonly 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 subset of nephrons or in response to a perceived need to enhance excretion, 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.

4.1 Symptoms and Signs

• AKI is often asymptomatic in early stages.

• Signs may include oliguria, edema, and hypertension.

• Severe AKI may present with anuria.

4.2 Complications

• AKI increases the risk for the development or worsening of chronic kidney disease (CKD).

• AKI increases the risk of future cardiovascular disease.

• AKI also has longer term implications even if the patient survives the hospitalization.

5. DIFFERENTIAL DIAGNOSIS

• 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 suggestive 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 superimposed on CKD.

• Serial blood tests showing a continued substantial rise of SCr represent clear evidence of AKI.

• Once the diagnosis 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 processes, as described previously.

5.1 Prerenal vs Intrinsic vs Postrenal

• Prerenal azotemia: Inadequate renal perfusion, no parenchymal damage, rapidly reversible.

• Intrinsic AKI: Parenchymal damage (tubules, glomeruli, vessels, interstitium), often irreversible without treatment.

• Postrenal AKI: Obstruction of urinary flow, reversible with relief of obstruction.

6. INVESTIGATIONS & DIAGNOSIS

• 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.

• Some patients with AKI will not have tubular or glomerular damage (e.g., prerenal azotemia).

• 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.

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• Once the diagnosis 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 processes, as described previously.

• Increasingly, 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.

6.1 Laboratory Evaluation

- Serum creatinine (SCr) increase ≥0.3 mg/dL within 48 h or ≥1.5 times baseline over 7 days.
- Urine output <0.5 mL/kg per h for >6 h.
- Serum cystatin C for GFR estimation.
- Urine sediment analysis for casts (e.g., muddy brown casts for ATN).

6.2 Imaging

- Renal ultrasound to assess kidney size and obstruction.
- Small, shrunken kidneys with cortical thinning suggest CKD.
- Doppler ultrasound for vascular assessment.

7. MANAGEMENT & TREATMENT

- 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, diuretic use, or decreased oral intake.
- Management focuses on treating the underlying cause.
- Volume resuscitation for prerenal azotemia.
- Stop nephrotoxic medications.
- Relieve obstruction for postrenal AKI.
- Immunosuppressive agents or therapeutic plasma exchange for glomerulonephritis.
- Dialysis for severe AKI (AEIOU: Acidosis, Electrolytes, Intoxication, Overload, Uremia).

7.1 Prerenal Management

- Volume resuscitation.
- Discontinue offending medications (NSAIDs, ACE-I/ARBs in high risk).

7.2 Intrinsic Management

- Sepsis: Antibiotics, source control, hemodynamic support.
- Ischemia: Restore perfusion.
- Nephrotoxins: Discontinue offending agents, hydration (e.g., cisplatin).

7.3 Postrenal Management

- Relieve obstruction (catheterization, stenting, surgery).

7.4 Dialysis Indications

- Acidosis.
- Electrolytes (hyperkalemia).
- Intoxication.
- Overload.
- Uremia.

8. PROGNOSIS & COMPLICATIONS

- AKI increases the risk for the development or worsening of chronic kidney disease (CKD).

• AKI increases the risk of future cardiovascular disease.

• AKI also has longer term implications even if the patient survives the hospitalization.

• AKI may also occur in the community.

• Common causes of community-acquired AKI include volume depletion, heart failure, adverse effects of medications, 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.

8.1 Long-term Outcomes

• Progression to CKD.

• Cardiovascular events.

• Mortality in ICU.

9. SPECIAL CONSIDERATIONS

• 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 countries, resources to diagnose and manage AKI are often limited.

• Hepatorenal syndrome is a cause of AKI in individuals with multiorgan 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. Systemic vascular resistance is markedly reduced due to primary arterial vasodilation in the splanchnic circulation, resulting ultimately in activation of vasoconstrictor responses similar to those seen in hypovolemia. 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 administration and withholding of diuretics. Type 2 hepatorenal syndrome is a less severe form characterized mainly by refractory ascites.

9.1 Developing World

• Epidemiology differs from developed countries.

• Region-specific etiologies: envenomations, malaria, leptospirosis, crush injuries.

• Limited resources for diagnosis and management.

9.2 Hepatorenal Syndrome

• Diagnosis of exclusion.

• Type 1: Poor prognosis, AKI persists despite volume.

• Type 2: Less severe, refractory ascites.

10. KEY PEARLS & CLINICAL TRAPS

• AKI is a clinical diagnosis and not a structural one.

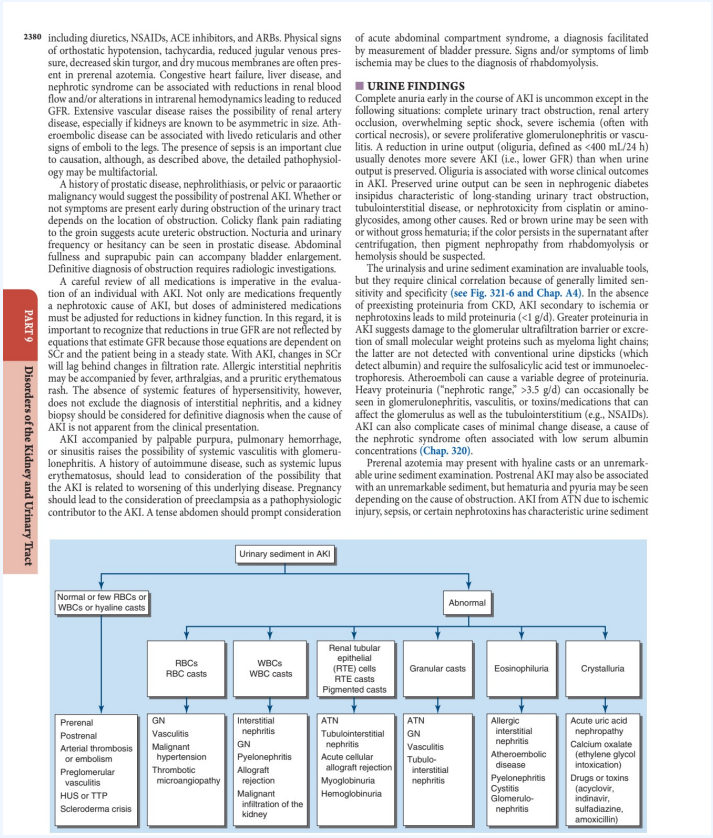
• AKI can range in severity from asymptomatic and transient changes in laboratory parameters of glomerular filtration rate (GFR) to overwhelming and rapidly fatal derangements in the ability of the kidney to maintain effective circulating volume regulation, excrete nitrogenous wastes and metabolic toxins, and maintain electrolyte and acid-base composition of the plasma.

• The combined use of NSAIDs with ACE inhibitors or ARBs poses a particularly high risk for developing prerenal azotemia.

• Hepatorenal syndrome is a diagnosis of exclusion.

• No set of tests, however, can rule out AKI superimposed on CKD.

FIGURES & ILLUSTRATIONS — FROM HARRISON'S



2380 including diuretics, NSAIDs, ACE inhibitors, and ARBs. Physical signs of orthostatic hypotension, tachycardia, reduced jugular venous pressure, decreased skin turgor, and dry mucous membranes are often present 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. Atheroembolic 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 pathophysiology 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 evaluation 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.

AKI accompanied by palpable purpura, pulmonary hemorrhage, or sinusitis raises the possibility of systemic vasculitis with glomerulonephritis. 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 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 vasculitis. 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 aminoglycosides, 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 sensitivity 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 excretion 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 immunoelectrophoresis. 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 unremarkable 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

PART 9 Disorders of the Kidney and Urinary Tract

Harrison's 22e · Figure 1

FIGURE 321-6 Interpretation of urinary sediment findings in acute kidney injury syndrome; RBCs, red blood cells; RTE, renal tubular epithelial; TTP, thrombotic Diagnosis and clinical evaluation of acute kidney injury. In Comprehensive Nephrology, — Figure 321-1: Classification of the major causes of acute kidney injury, categorizing etiologies into prerenal (hypovolemia, decreased cardiac output), intrinsic (glomerulonephritis, vasculitis, ATN, interstitial nephritis), and postrenal (obstruction) causes.

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 medications, 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 commonly 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 subset of nephrons or in response to a perceived need to enhance excretion, 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 countries, resources to diagnose and manage AKI are often limited.

ETIOLOGY AND PATHOPHYSIOLOGY

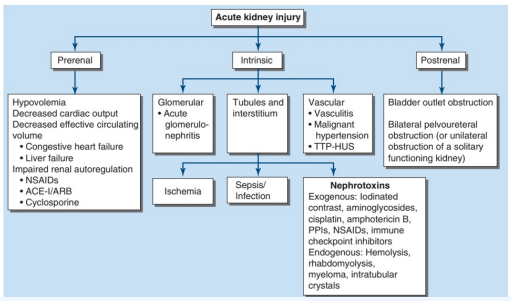
The causes of AKI have traditionally been divided into three broad categories: prerenal azotemia, intrinsic renal parenchymal disease, and postrenal obstruction (Fig. 321-1).

PRERENAL AZOTEMIA

Prerenal azotemia (from "azo," meaning nitrogen, and "-emia," meaning in the blood), the most common form of AKI, results from inadequate 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 vascular responses such as nonsteroidal anti-inflammatory drugs (NSAIDs) and inhibitors of the renin-angiotensin system (Fig. 321-2). Sodium-glucose 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 pressure and inducing natriuresis; in fact, recent studies have suggested a protective effect of these agents in preventing AKI.

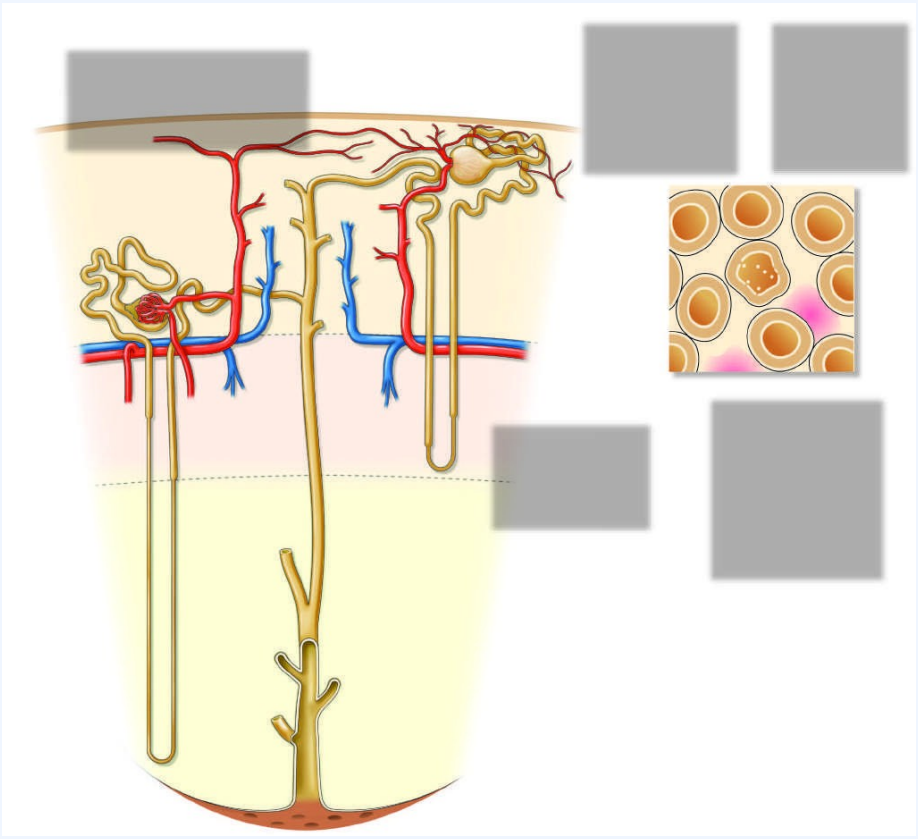
By definition, prerenal azotemia involves no parenchymal damage to the kidney and is rapidly reversible once parenchymal blood flow and intraglomerular hemodynamics are restored. In many cases, however, prerenal azotemia may coexist with other forms of intrinsic AKI associated with processes acting directly on the renal parenchyma. Prolonged 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 compensatory 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 (prostacyclin, prostaglandin E_2), 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



Harrison's 22e · Figure 2

FIGURE 321-1 Classification of the major causes of acute kidney injury. ACE-I, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors; TTP-HUS, thrombotic — Figure 321-2 Panel A: Normal glomerular filtration rate (GFR) maintained by afferent vasodilatation and efferent vasoconstriction under normal perfusion pressure.

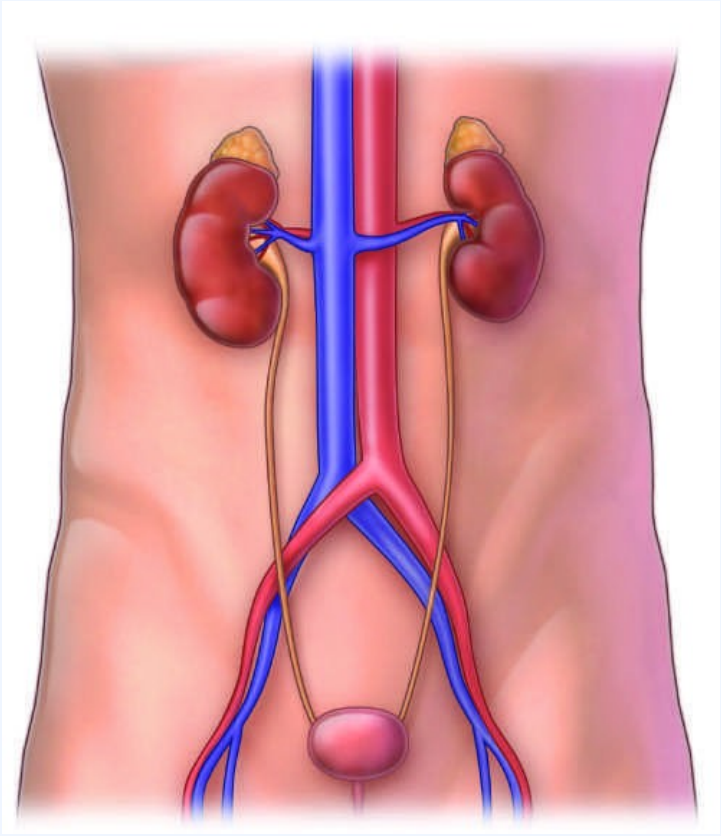


Harrison's 22e · Figure 3

FIGURE 321-3 Major causes of intrinsic acute kidney injury. ATN, acute tubular necrosis; PPI, proton pump inhibitors; TINU, tubulointerstitial nephritis-uveitis; TTP/HUS, — Figure 321-2 Panel B: Reduced perfusion pressure within the autoregulatory range, where normal GFR is maintained by afferent vasodilatation and efferent vasoconstriction mediated by angiotensin II.

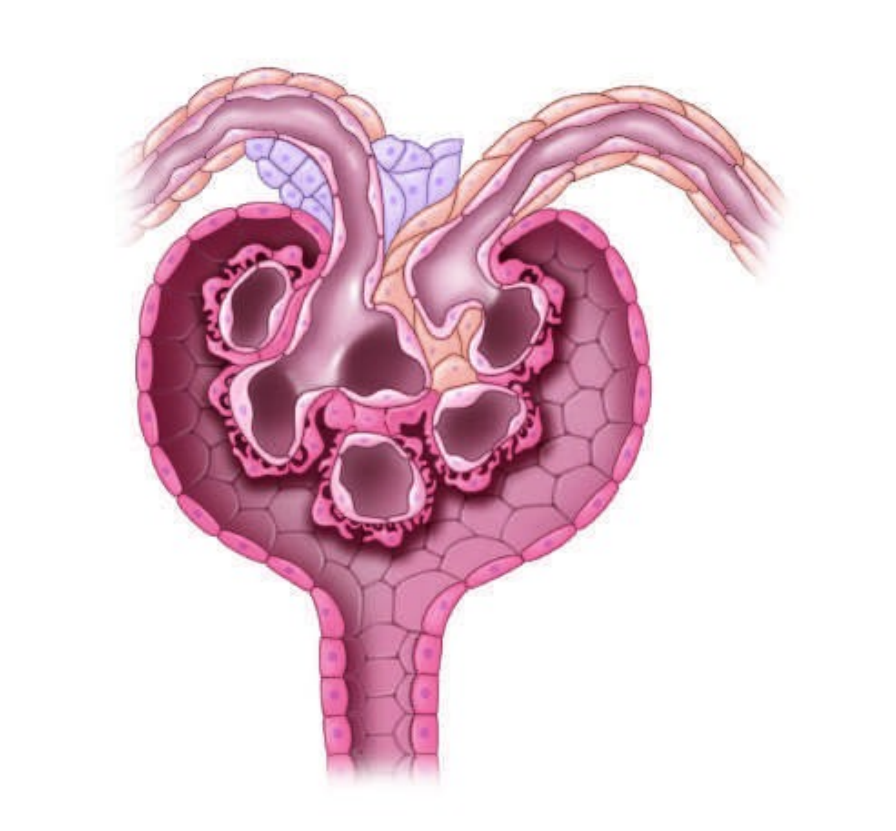
Harrison's 22e · Figure 4

to FIGURE 321-4 Interacting microvascular and tubular events contributing to the kidney injury. PGE, prostaglandin E. (Reproduced with permission from JV Nephrol. 14:2199, 20 2 03.) 2 — Figure 321-2 Panel C: Reduced perfusion pressure with a nonsteroidal anti-inflammatory drug (NSAID), where loss of vasodilatory prostaglandins increases afferent resistance and decreases GFR.



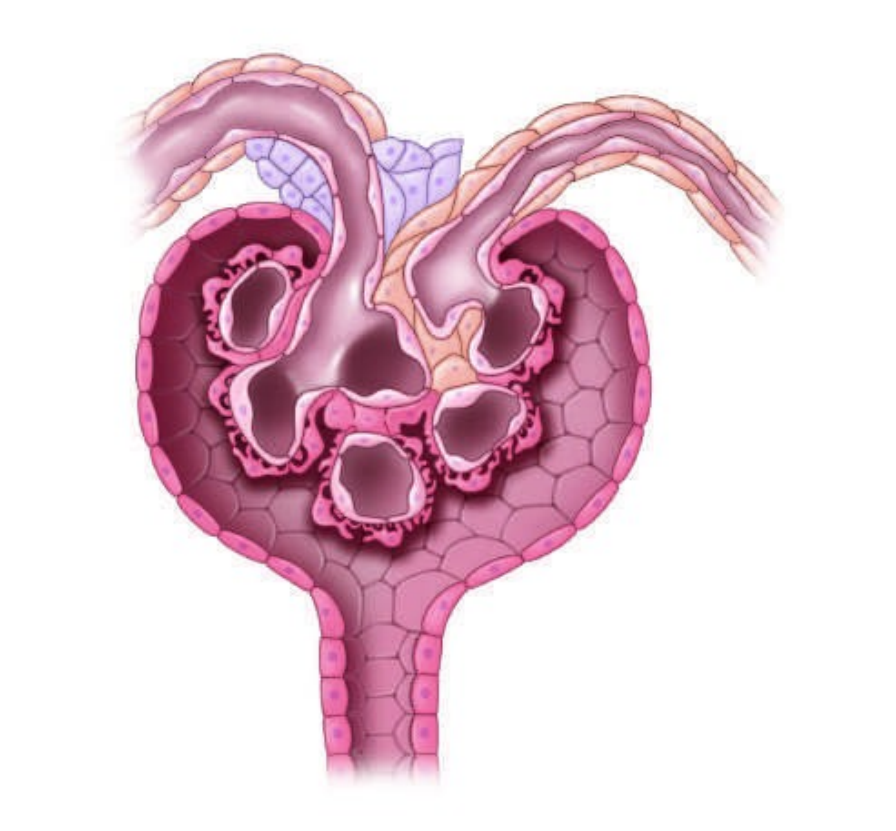
Harrison's 22e · Figure 5

FIGURE 321-5 Anatomic sites and causes of obstruction leading to postrenal acute — Figure 321-2 Panel D: Reduced perfusion pressure with an ACE inhibitor (ACE-I) or angiotensin receptor blocker (ARB), where loss of angiotensin II action reduces efferent resistance and decreases GFR.



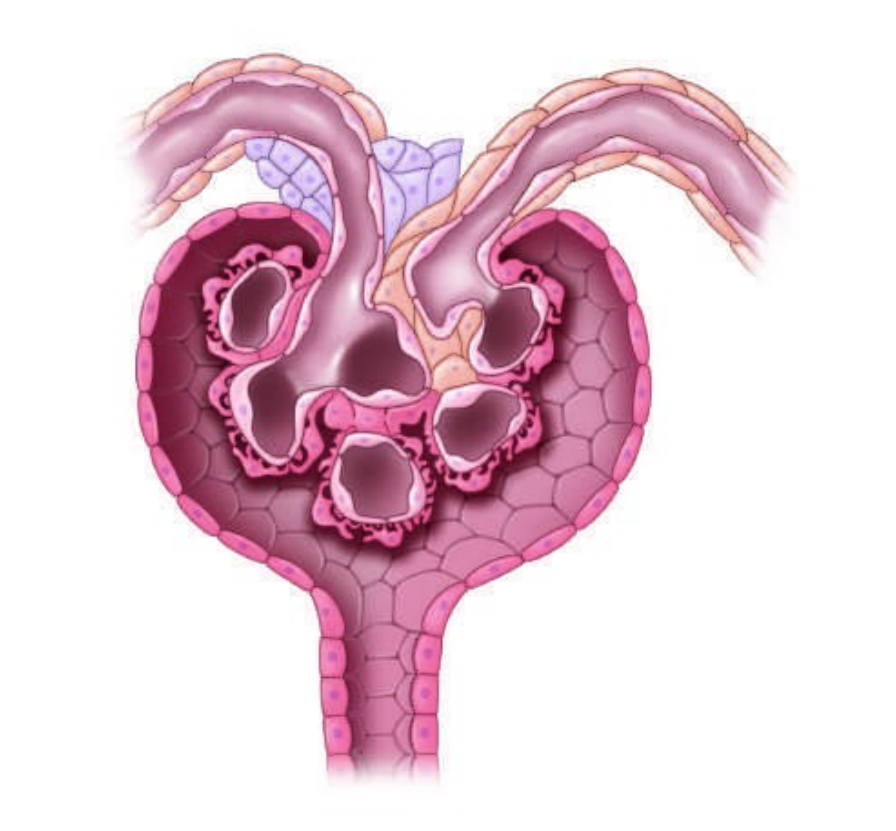
Harrison's 22e · Figure 6

FIGURE 321-2 Intrarenal mechanisms for autoregulation of the glomerular filtration A. Normal conditions and a normal GFR. B. Reduced perfusion pressure within the vasodilatation and efferent vasoconstriction. Angiotensin constricts afferent arteriolar resistance. C. Reduced perfusion pressure with a nonsteroidal this causes the glomerular capillary pressure to drop below normal values and the GFR to inhibitor (ACE-I) or an angiotensin receptor blocker (ARB). Loss of angiotensin II action below normal values and the GFR to decrease. (From JG Abuelo: Normotensive ischemic Medical Society. Reprinted with permission from Massachusetts Medical Society.) — Figure 321-3: Major causes of intrinsic acute kidney injury, categorized by site of parenchymal damage including glomeruli (glomerulonephritis), tubules (ATN, toxic ATN), interstitium (infection, infiltration), and vessels (vasculitis, thrombosis).



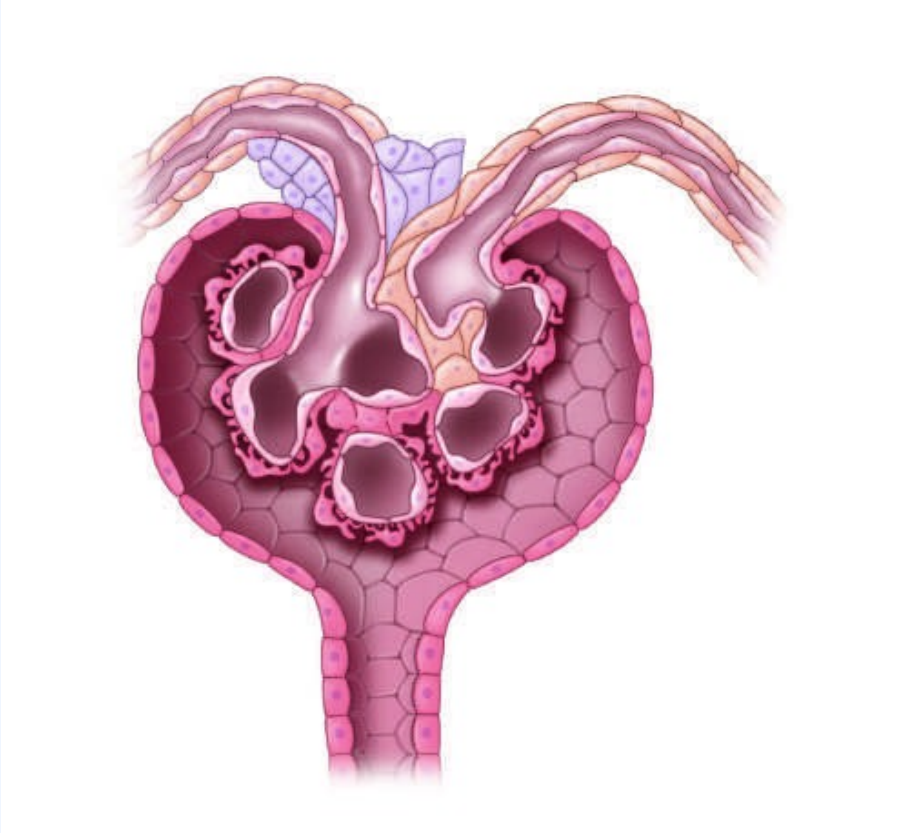
Harrison's 22e · Figure 7

FIGURE 321-2 Intrarenal mechanisms for autoregulation of the glomerular filtration A. Normal conditions and a normal GFR. B. Reduced perfusion pressure within the vasodilatation and efferent vasoconstriction. Angiotensin constricts afferent arteriolar resistance. C. Reduced perfusion pressure with a nonsteroidal this causes the glomerular capillary pressure to drop below normal values and the GFR to inhibitor (ACE-I) or an angiotensin receptor blocker (ARB). Loss of angiotensin II action below normal values and the GFR to decrease. (From JG Abuelo: Normotensive ischemic Medical Society. Reprinted with permission from Massachusetts Medical Society.) — Figure 321-4: Interacting microvascular and tubular events contributing to the pathophysiology of ischemic acute kidney injury, showing vasoconstriction, mitochondrial injury, apoptosis, and tubular obstruction.



Harrison's 22e · Figure 8

FIGURE 321-2 Intrarenal mechanisms for autoregulation of the glomerular filtration A. Normal conditions and a normal GFR. B. Reduced perfusion pressure within the vasodilatation and efferent vasoconstriction. Angiotensin constricts afferent arteriolar resistance. C. Reduced perfusion pressure with a nonsteroidal this causes the glomerular capillary pressure to drop below normal values and the GFR to inhibitor (ACE-I) or an angiotensin receptor blocker (ARB). Loss of angiotensin II action below normal values and the GFR to decrease. (From JG Abuelo: Normotensive ischemic Medical Society. Reprinted with permission from Massachusetts Medical Society.) — Figure 321-5: Causes of postrenal AKI, illustrating sites of obstruction from the renal pelvis to the urethra including stones, blood clots, tumors, prostatic enlargement, and strictures.



Harrison's 22e · Figure 9

FIGURE 321-2 Intrarenal mechanisms for autoregulation of the glomerular filtration A. Normal conditions and a normal GFR. B. Reduced perfusion pressure within the vasodilatation and efferent vasoconstriction. Angiotensin constricts afferent arteriolar resistance. C. Reduced perfusion pressure with a nonsteroidal this causes the glomerular capillary pressure to drop below normal values and the GFR to inhibitor (ACE-I) or an angiotensin receptor blocker (ARB). Loss of angiotensin II action below normal values and the GFR to decrease. (From JG Abuelo: Normotensive ischemic Medical Society. Reprinted with permission from Massachusetts Medical Society.) — Table 321-1: Staging of Acute Kidney Injury Severity, detailing serum creatinine thresholds (1.5–1.9 times baseline, 2.0–2.9 times baseline, ≥3.0 times baseline or ≥4.0 mg/dL) and urine output criteria for each stage.