Acute kidney injury (AKI) is a frequent problem in the pediatric intensive care unit (PICU), but an accurate incidence is difficult to establish due to the ongoing evolution of a clear definition of renal failure. The classic definition was a 50% reduction of glomerular filtration rate (GFR) accompanied by a 50% increase in creatinine. A RIFLE classification of renal injury to allow earlier appreciation of renal dysfunction is now utilized in adults and a modification of this system (pRIFLE) can also be applied to children.1-3

Early detection of renal dysfunction by biomarkers is needed, to allow a more timely awareness of injury and, thereby, modifications to alleviate the renal stress. Recent investigations in this area, although early in their development, postulate a panel approach (plasma panel of neutrophil gelatinase-associated lipocalin [NGAL] and cystatin C or a urine panel of NGAL, interleukin 18, and kidney injury molecule-1 [KIM-1]) may be of help in the future to provide more sensitive and specific detection of early AKI.4-6

Acute Kidney Injury Pathophysiology

Physiology of Glomerular Filtration

GFR is the product of the filtration rate of the individual nephron and the number of functioning nephrons.7 A single nephron glomerular filtration rate (SNGFR), is defined by the Starling forces of the glomerular capillaries and the properties of the glomerular capillary wall.

\[ \text{SNGFR} = Kf(\Delta P - \Delta \pi) = Kf P_{uf} \]

where \( Kf \) is a capillary wall property known as the ultrafiltration coefficient and is the product of the surface area available for filtration and the hydraulic conductivity of the membrane. The Starling forces (or pressures) that affect filtration are the hydraulic pressure in the glomerular capillary (\( P_{gc} \)), the hydraulic pressure in Bowman’s space (\( P_{bs} \)), the oncotic pressure of the glomerular capillary (\( \pi_{gc} \)), and the oncotic pressure in Bowman’s space (\( \pi_{bs} \)), which is usually zero because the ultrafiltrate is essentially protein-free.8 \( P_{gc} \) favors filtration; \( P_{bs} \) and \( \pi_{gc} \) are opposing forces to filtration. The mean ultrafiltration pressure (\( P_{uf} \)) is the difference between the net change in hydraulic pressure and the net change in the oncotic pressure. Thus SNGFR may be modified by alterations in the glomerular capillary pressures, glomerular membrane characteristics, or the surface area available for filtration.

The kidneys are responsible for plasma water and electrolyte balance through filtration at the glomerular membrane and then reabsorption of this filtrate from the renal tubular epithelium. The loss of filtration and tubular reabsorption in AKI is the result of renal adaptive changes that initially function to preserve renal perfusion and glomerular filtration; however, when these are exhausted, the kidney’s compensatory mechanisms fail and renal dysfunction ensues.

Glomerular filtration depends on adequate renal perfusion; the kidneys receive approximately 25% of total cardiac output. The fraction of cardiac output perfusing the kidneys is related to the ratio of renal vascular resistance (RVR) and systemic vascular resistance.9 Renal blood flow (RBF) is determined by systemic blood pressure (SBP) and RVR, expressed by the formula \( \text{RBF} = \text{SBP}/\text{RVR} \).9 Kidney autoregulation, which maintains a constant renal perfusion pressure, occurs through alterations in RVR in response to changes in systemic
vascular resistance or intravascular volume. When SBP is within the normal physiological or autoregulatory range, the kidney can maintain constant blood flow and GFR by dilation of the preglomerular or afferent arteriole, which reduces RVR and increases RBF. This afferent arteriolar dilation is accomplished by two known mechanisms, smooth muscle relaxation of the afferent arteriole in response to sensing a transmural pressure drop (the myogenic reflex) and the tubuloglomerular feedback system. The tubuloglomerular feedback system is operational following a reduction of plasma flow. When solute and water delivery to the macula densa are reduced, the juxtaglomerular apparatus responds by relaxing the smooth muscle of the adjacent afferent arteriole. Thus a reduction in cardiac output or effective renal plasma flow is accompanied by vasodilation at the preglomerular arteriole, which in turn reduces RVR, thereby restoring RBF.

During states of reduced cardiac output or intravascular volume depletion, the systemic vasoconstrictors, angiotensin II and vasopressin, are released to help preserve vascular tone. The kidney counteracts the renal vasoconstrictor activity of angiotensin II and increased sympathetic tone through the intrarenal production of vasodilator prostaglandins such as prostaglandin I2. These locally produced substances may attenuate renal vasoconstrictive forces and help preserve renal perfusion. Animal model data of congestive heart failure have provided evidence that enhanced prostaglandin synthesis is required for preservation of renal perfusion and GFR. Patients receiving prostaglandin synthetase inhibitors such as nonsteroidal antiinflammatory drugs (NSAIDs) have potentiation of renal ischemia because of an increase in renal vasoconstriction not antagonized by intrarenal prostaglandin synthesis. Endothelium-derived relaxation factors (EDRFs), which are vasodilatory, and the potent vasoconstrictor endothelin, produced by the endothelium, may also affect the regional vascular tone.

Constriction of the postglomerular capillary sphincter, the efferent arteriole, in the face of reduced RBF serves to increase the filtration fraction and preserve GFR, although this occurs at the expense of renal plasma flow, which may be further reduced. Vasoconstriction at the efferent arteriole is mediated by angiotensin II and, to a lesser extent, by the action of the adrenergic system by epinephrine. Elevation in postglomerular arteriolar resistance may be blocked by the angiotensin-converting enzyme inhibitors. When converting enzyme inhibitors are administered to the patient who requires efferent arteriolar constriction rather than vasodilation by endogenous or exogenous circulating catecholamines such as dopamine or norepinephrine. Thus the administration of these vasoactive-inotropic agents may actually compromise the kidney’s adaptive mechanisms. Excessive vasoconstriction eventually results in diminished filtration rate and oxygen delivery to the kidney.

Pharmacological agents may alter renal perfusion by changing SBP through an action on systemic vasculature or by direct effects on renal vasculature (Box 71-1). Vasodilators, such as hydralazine, lower SBP without changing renal perfusion pressure, because the decrease in SBP is accompanied by decreased RVR. Conversely, epinephrine increases SBP but decreases RBF by its vasoconstrictor effect on intrarenal blood vessels.

**Morphologic Changes in Renal Injury**

Morphologic changes seen in acute renal injury, especially those in the tubules, depends on the duration of injury as well the eliciting mechanism.

The kidney’s complex structure, with heterogeneous segments within the kidney receiving differential regional perfusion and thereby oxygenation, sets up a common form of renal failure, that of the tubulointerstitium. This region is at greatest risk for ischemia because of its gradient of regional perfusion and oxygenation. In addition, vascular disease, including

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**Box 71–1 Vasoactive Substances in the Kidney Vasculature**

1. Kidney vascular resistance/F kidney blood flow
   - Epinephrine
   - Norepinephrine
   - Angiotensin II
   - Arachidonic acid
   - Thromboxane A2
2. Kidney vascular resistance/F kidney blood flow
   - Prostaglandin E1
   - Prostaglandin E2
   - Dopamine
   - Furosemide
   - Angiotensin-converting enzyme inhibitors
   - Bradykinin
   - Isoproterenol
   - Acetylcholine

glomerular disease, often occurs in children and results in AKI, but there are studies that suggest the extent of damage to the tubulointerstitium has the greatest prognostic implication to the degree of final renal recovery.16

Initial structural changes in tubular cells are seen as apical and basal surface changes of simplification, with microvilli of the brush border shortening and disappearing by either detachment from the apical surface or being internalized within the tubular cells.17

In this scenario, enzymes of the brush border (alkaline phosphatase and gammaglutamyl transpeptidase), may be found in the urine and may be used as markers of early tubular injury.18

The loss of microvilli surface area leads to loss of enzymes and transport sites for transcellular absorption and apical uptake. Additionally, loss at the basolateral interdigitating infoldings of the tubular cells then results in further reduction of surface area for transport and loss of the Na-K-adenosine triphosphatase (ATPase) that is localized to this membrane and involved in many transport processes.19

Morphologic changes in distal tubules and outer medulla also occur and may be found even when proximal tubular injury is not readily identified on biopsy. Experimentally, the outer medulla has been identified as sensitive to hypoxia, including that induced by toxins such as radiocontrast agents and cyclosporine.20

Injury at this outer medulla region may be missed on biopsy since this site often is not sampled. Tubular cell detachment with exposed, denuded regions of the basement membrane can be found on biopsies, as a result of altered cell-matrix attachments.21

Renal tubular sensitivity to ischemic injury is primarily influenced by the individual renal cell’s energy requirements, its glycolytic capacity, and the extent of hypoxic stress upon the cell. Glycolysis and oxidative phosphorylation both supply the ATP required by the cell to drive its metabolism, and it follows that cells with a greater capacity for glycolysis (distal tubular cells) are less sensitive to oxygen deprivation than the cells that rely mainly on mitochondrial derived energy, (proximal tubular cells).22

In vivo and in vitro studies may be discordant in identifying susceptibility to hypoxia. Medullary straight portions of the distal tubule have a higher glycolytic capacity than the cortical segments of the proximal tubule but, due to the regional distribution of perfusion within the kidney, the medullary portions operate in a lower oxygen-tension environment and therefore are more susceptible to hypoxia/ischemic injury.23

The individual cell’s energy requirements to conduct its transport activities further influences its risk to hypoxic injury. The outer medullary proximal tubular cell (pars recta), due to the high energy requirements for its transport functions, has a greater injury risk than the deep inner medullary tubular cell with its low-oxygen environment, but also a low energy requirement to maintain its transport function.24

When energy stores are rapidly depleted, the normal Na-K ATPase pump begins to fail and the most basic of cell function, membrane integrity, is jeopardized, with resultant accumulation of Na, Cl, and water within the cell; this cell swelling (oncrosis) is a hallmark feature of necrosis.25 Not all cells that fail to maintain their energy requirements die through necrosis; apoptosis, which appears morphologically as cell shrinkage, is also a result of inadequate energy support. Apoptosis is an asynchronous cell death triggered over hours to days, with the earliest cellular element involving mitochondrial changes including loss of transmembrane potential and release of mitochondrial cytochrome c into the cytosol.26 It is mitochondrial function/dysfunction that primarily determines the fate of the cell for recovery and survival or death, and by what form: apoptosis or necrosis.

**Pathogenesis of Reduced Glomerular Filtration Rate in Acute Kidney Injury**

The mechanisms responsible for GFR reduction in acute renal injury have been studied extensively with experimental models of AKI. Multiple mechanisms are often operational in mediating hypofiltration. Whereas one factor may have greater importance in the initiation of injury and decreased filtration, others are involved in the sustained reduction in GFR during the maintenance phase of AKI. Four major mechanisms result in reduced GFR during AKI: reduced blood flow, decreased Kf, tubular obstruction, and backleakage of tubular fluid.27 Each factor is discussed regarding its role in both the initiation and maintenance phases of AKI.

A reduction in RBF can be demonstrated during the initiation phase of many forms of AKI and seems to play a predominant role in ischemic injury and rhabdomyolysis.28 Proposed theories for the reduction of RBF include (1) a proportional increase in the afferent and efferent arteriolar resistances in response to activation of the renin-angiotensin system; (2) vascular endothelial cell swelling and damage with release of vasoactive peptides such as endothelin; and (3) hyperemic congestion of the medullary peritubular capillaries.

Kf may be reduced in both nephrotoxic and ischemic forms of renal failure. Endothelial or mesangial cell swelling reduces the surface area available for filtration; altered permeability induced by humoral factors such as angiotensin II and vasopressin may also decrease Kf. Circulating levels of both hormones are increased during AKI.

Renal tubular cells are the primary site of injury in both ischemia and nephrotoxin-induced renal injury. Tubular cell injury may be sublethal or lethal and result in cell necrosis or apoptosis. Once this injury occurs, cells detach from the supporting basement membrane and obstruct the tubule lumen. In addition, even with sublethal injury, tight junctions may be disrupted, and the intact layer may be lost. The loss of epithelial integrity allows backleakage of ultrafiltrate, which contains creatinine and urea, through paracellular pathways into the renal interstitium, creating further diminution of excretory function and reduced urine formation. Necrosis of a selected region of the renal tubule is accompanied by tubular obstruction and eventual filtration failure by that entire unit or nephron.

Intratubular obstruction occurs in most forms of acute renal injury, either as a contributing factor in the initiation phase or during the maintenance phase.29 Tubular obstruction with cellular debris and precipitated protein is a prominent finding in both the initiation and maintenance phases of ischemic injury. In the case of nephrotoxic injury, the degree of injury may determine the extent of tubular obstruction. In an experimental model of gentamicin nephrotoxicity, the drug dose was positively correlated with the contribution of tubular obstruction to reduced GFR.30 Tubular obstruction and loss of epithelial integrity caused by tubular cell injury result in the backleakage of tubular fluid and solutes. Excretion of solute...
Mechanisms of Renal Cell Injury

The renal tubular cell expends energy in the form of ATP to maintain a high intracellular concentration of potassium and a low intracellular concentration of sodium. This concentration gradient depends on the continuous activity of the Na⁺/K⁺-ATPase and is the driving force for the reabsorption of sodium. Active reabsorption of sodium is the primary driving force for water reabsorption and the coupled transport of amino acids, carbohydrates, organic acids, and other compounds. Thus all transport functions, as well as many other vital cell functions, depend on normal activity of the Na⁺/K⁺ pump, which, in turn, depends on an adequate supply of energy. In addition, membrane fluidity or integrity is important to transport functions in tubular cells. Processes that result in alterations in the membrane or in the supply of energy are common final pathways for renal tubular cell death.

A decrease in the cellular ATP content occurs in many forms of renal injury, possibly as the result of primary alterations in the cell’s ability to perform oxidative phosphorylation or as the end result of other perturbations. Heterogeneity exists in the susceptibility of nephron segments to oxygen deprivation with more distal segments being relatively resistant. This is related to the greater glycolytic capacity of the distal tubule compared with the proximal tubule, which relies on oxygen-consuming pathways for ATP generation. Therefore the net result of renal injury is usually a depletion of energy in the form of ATP, with the inability of the cell to perform vital functions, including transport and maintenance of cell integrity.

Cellular injury may be modified by the requirements made on its energy stores. If more transport is required of the cell, more energy is consumed, and less energy is left for cell maintenance. Evidence exists to support this theory. If transport requirements are reduced by the administration of diuretics or by the stimulation of the glomerulotubular feedback mechanism, then further injury may be attenuated. The feedback mechanism, whereby there is reduction of GFR in the face of reduced reabsorption by the proximal tubule, is a protective signal that conserves cell energy by reducing metabolic demands made on the cell.

Heat shock proteins (HSPs) are a family of proteins that appear to protect cells from injury as a result of hyperthermia, ischemia, or toxins. The HSP induction by sublethal thermal stress has been found to attenuate subsequent injury in the kidney.34 Renal transplants from animals that underwent short-term hyperthermia had better initial function and subsequent survival. Furthermore, in cultured inner medullary collecting duct cells, induction of HSP-1 by preconditioning hyperthermia attenuated the alterations in mitochondrial function and glycolysis that were observed after cells were exposed to high temperatures. Investigations into potential mechanisms to use this natural cell defense mechanism are under way.

The ability of renal tubular epithelial cells to undergo regeneration determines in large part the degree of renal recovery. Therefore much work has recently been done to study ways that cells regenerate and mechanisms that might enhance recovery. Early in ischemic injury there is induction of early response genes such as c-fos and Egr-1.35 By 2 days after ischemia, the proliferating cell nuclear antigen is detected, followed by expression of other dedifferentiated cell markers, which seem to be a sign of early recovery. Other cells appear to undergo apoptosis or cell death. Postischemic regeneration seems to be a recapitulation of early renal tubular cell development. Growth factors such as insulin-like growth factor-1 (IGF-1) and epidermal growth factor 1 (EGF-1) have been associated with enhanced recovery as well. Renal levels of hepatocyte growth factor (HGF) increase after two models of renal failure, postnephrectomy, and following CCL4 (chemokine [C-C motif] ligand 4) injection, and this increase supports a role for HGF in renal repair.36 Exogenous EGF has been shown to enhance renal tubular cell regeneration and to lessen the severity and duration of hypoxia and toxin-induced renal failure. EGF receptor levels increase within hours of ischemic injury in the rat. Elevation of soluble EGF occurs along with morphological evidence of tubular injury within 12 hours of ischemia, which is followed by cell proliferation and a decrease in soluble EGF by 24 to 48 hours after ischemia.

Alterations in Cell Membranes

Membrane phospholipids have a structural function and affect membrane permeability, as well as the activity of membrane transport systems.37 These compounds are regulated in part by
the activity of phospholipases, which release free fatty acids from phospholipids. Several mechanisms related to acute cell injury may alter phospholipase activity and thereby change membrane phospholipids and membrane integrity: altered intracellular calcium homeostasis, depletion of ATP, and lipid peroxidation. Increased phospholipase activity has been associated with an abnormal increase in permeability of the inner mitochondrial membrane, which ultimately results in disruption of mitochondria and loss of the ability to produce adequate energy.

**Cellular Calcium Homeostasis**

Increased intracellular calcium is commonly found in cell injury. It is not, however, a consistent finding in all models of renal injury. Techniques to study changes in the subcellular distribution of calcium have allowed time-related changes to be assessed. In the rat proximal tubule, steady-state hypoxia is accompanied by a prompt increase in cytosolic free calcium that precedes the appearance of membrane damage. The increase in calcium is reversed with reoxygenation. Increased cellular calcium may activate phospholipases, as previously mentioned; alter the cytoskeleton and cause injury by allowing cell swelling; or affect membrane permeability at the plasma membrane, the mitochondrial membrane, or the endoplasmic reticulum. Alterations in mitochondrial function that occur as a result of calcium loading of this organelle have been extensively studied. Excess mitochondrial calcium is associated with changes in the permeability of the inner mitochondrial membrane with loss of the electrochemical gradient and the capacity for oxidative phosphorylation. In addition, changes in enzyme activity and mitochondrial levels of nucleotides may exist.

**Production of Free Radicals**

Renal cell damage induced by inflammation or oxygen deprivation may be mediated, in part, by oxygen free-radicals that are generated by several cell processes, including accumulation of long chain acyl CoA as a result of mitochondrial dysfunction. The net result is increased intracellular calcium and ultimately, changes in membrane-related functions.

**Tubular Cell Energy Metabolism**

After exposure to a variety of nephrotoxins or ischemia, renal cortical ATP levels are reduced even before changes in membrane integrity and cell death occur. In ischemic injury, alterations in renal perfusion may result in decreased oxygen delivery to tubular epithelium. Direct mitochondrial damage has been postulated to be the primary event in many forms of nephrotoxic injury. Other nephrotoxins interfere with energy production by the inhibition of enzymes along the citric acid cycle. In this way, toxins impair energy production. ATP levels decrease immediately after ischemia, with concomitant increases in ATP hydrolysis products. Reflow is associated with a gradual increase in cell ATP levels.

**Classification of Acute Glomerulotubular Dysfunction**

**Hemodynamically Mediated Acute Kidney Injury**

Renal hypoperfusion with ischemia is a common form of acute renal damage, especially in the setting of the ICU. This form of renal injury is often accompanied by oliguria and results from alterations in renal perfusion after a period of hypoxia, hypotension, cardiac dysfunction, or any condition that promotes hemodynamic instability, decreased effective plasma volume, or both states. This condition is commonly referred to as acute tubular necrosis because it is characterized by necrosis of tubule cells; however, this is a nonspecific term that may also define nephrotoxic injury. A preferred term is vasomotor nephropathy or hemodynamically-mediated renal failure. The same physiological alterations that initiate renal injury in this form of nephropathy may potentiate renal failure in conditions whose primary inciting event may not have been vascular.

Vasomotor nephropathy commonly follows a period of renal compensatory changes that may be termed prerenal failure, which are discussed in the preceding section on physiology. When the kidney has fully used normal compensatory mechanisms, renal oxygen delivery is critically impaired, and this impairment results in cell damage or tubular cell necrosis. Thus it is apparent that acute tubular necrosis is the end result of a continuum of renal adaptive mechanisms. Acute cortical necrosis is an exaggerated and more advanced form of renal ischemia.

When vascular or hemodynamic abnormalities persist or are profound, renal compensatory mechanisms are unable to preserve RBF and maintain sufficient oxygen delivery and GFR. At a mean renal perfusion pressure of 80 mm Hg, afferent, arteriolar dilation is maximal, and below these systemic pressures, RBF dramatically declines. In addition, loss of the ability to autoregulate as a result of ischemia may cause further damage. Renal cell injury develops as the result of deficient oxygen delivery, depletion of cellular energy, loss of membrane integrity, and release of reactive oxygen species. Without sufficient oxygen, the kidney cannot support cell functions that maintain architectural integrity and complex transport functions.

Although total RBF is decreased in vasomotor nephropathy, outer cortical blood flow is preferentially reduced. The medulla is not spared, however, because of its increased susceptibility to alterations in renal perfusion. Oxygen delivery to this segment of the kidney is precarious. Medullary partial pressure of oxygen (PO2) is approximately 10 mm Hg in the rat and dog. This oxygen level approaches the critical minimum level required to support oxidative phosphorylation and ATP synthesis for cell function. In general, however, the proximal tubule sustains the greatest injury. The renal arteriogram of human subjects with vasomotor nephropathy reveals marked narrowing of the arcuate arteries and absence of peripheral vasculature, providing further evidence for the marked vascular resistance enhancement.

The primary event in vasomotor nephropathy is injury of the renal tubule. The initiation of this injury, however, is microvascular in origin. Maximal renal compensation with marked efferent and afferent arteriolar vasoconstriction reduces glomerular plasma flow with resulting hypofiltration and compromises postglomerular blood supply to the renal tubule. Tubular cell necrosis with sloughing of tubular cells into the lumen results in obstruction of flow and backleakage of filtrate through the injured epithelium. Alterations in tubular cell function in cells receiving sublethal or lethal injury increase fluid and salt delivery distally, and this increase signals the glomerulotubular feedback system to cause vasoconstriction of the afferent arteriole and limit the fraction of plasma filtered at the glomerulus. Although the initial reduction in
GFR is the result of decreased RBF and tubular factors such as obstruction and backleakage, continued hypofiltration during the maintenance phase is related primarily to continued vasocnstriction and renal hypoperfusion. Recovery from post-ischemic AKI is biphasic. Initially, an increase in GFR occurs with relief of tubular obstruction and subsequently, improved filtration in association with renal vasodilation.

Oliguria in the presence of renal hypoperfusion has been referred to as acute renal success by investigators who propose that the response of an intelligent organ to a perceived reduction in blood flow is to reduce fluid and electrolyte losses by vasconstriction to reduce the fraction of plasma filtered and by maximal reabsorption of fluid and salt to restore the circulation. In addition, increased distal delivery of water and solutes because of tubular cell necrosis reflects failure of the renal tubule to absorb what is filtered. The appropriate response of an intact nephron is to reduce filtration by release of angiotensin II into the interstitium. Angiotensin II mediates arteriolar vasoconstriction, which decreases glomerular plasma flow, and retraction of the glomerular tuft, which reduces Kf, the net effect being decreased glomerular filtration.

The classic form of hemodynamically-mediated AKI was oliguric, by definition; however, nonoliguric acute vasomotor nephropathy is increasingly recognized. This form of less severe disease has been referred to as attenuated acute tubular dysfunction and has allowed the recognition of three stages of AKI that actually represent a continuum of worsening disease: first, abbreviated renal insufficiency occurs after a single event of renal hypoperfusion, such as aortic cross-clamping, in the face of adequate volume repletion and SBP. This syndrome is characterized by an acute drop in the GFR with gradual return to normal within a few days. The inability to concentrate the urine or to conserve sodium provides evidence of tubular injury. The second phase or form is referred to as overt renal failure. An example of this situation is aortic cross-clamping followed by continued renal hypoperfusion because of poor cardiac function. A more prolonged period of hypofiltration lasts for several days to weeks with a gradual return of the GFR. If recovery of renal perfusion is impaired by repeated episodes of ischemia/hypotension, sepsis, or hypoxia, the third pattern may be observed in which a protracted course may be observed of renal perfusion is impaired by repeated episodes of ischemia/hypotension, sepsis, or hypoxia, the third pattern may be observed in which a protracted course may be observed and chances for recovery may be doubtful. One situation in which the last example could exist is aggressive hemodialysis (ultrafiltration) with hypovolemia and, consequently, renal hypoperfusion in the recovering phase of renal failure. Clinical experience has supported this theory. Patients with multiple renal insults have a more protracted course and increased morbidity.

Using the Schwartz formula for estimate of creatinine clearance (GFR) in infants and children, a modified RIFLE classification (pRIFLE) has been developed.

Schwartz Formula: eGFR = eCrCl = K x Height (cm)/serum creatinine (mg/dL) [K value of premature infants (0.33), infants (0.45) and children > 1 year of age of 0.53]

The pRIFLE classification is defined by the percent reduction in eCrCl and/or the amount of diminishing urine output (Table 71-1).

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<th>Table 71–1 pRIFLE Classification</th>
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<td>pRIFLE</td>
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<td>End-stage renal disease</td>
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Treatment of Acute Kidney Injury

Prevention/Attenuation of Acute Renal Failure

Prevention or attenuation of ARF has been the subject of numerous studies, as most agree that protection of the kidney from damage or enhancing recovery after damage would be preferable to the currently available supportive therapies. Primary prevention of AKI in the ICU is limited to those conditions in which the timing of injury is predictable, such as exposure to radiocontrast dye, cardiopulmonary bypass, nephrotoxic medications, or chemotherapy. In contrast to most cases of community-acquired AKI, nearly all cases of ICU-associated AKI result from more than a single insult. Protective agents have been studied extensively with animal models of acute renal injury. Some of these agents have ultimately been used in clinical situations with variable success. In general, methods to reduce renal injury have been aimed at manipulation of RVR or alteration of the metabolic processes of the renal tubular cell.

Dopamine

Dopamine, when infused in low intravenous doses, increases RBF, increases GFR, and increases sodium excretion. In the past, clinicians frequently used “renal dose” dopamine in the hopes that such a maneuver might attenuate renal injury and improve survival. In addition, clinicians often interpret an increase in urinary output as proof that these two assumptions are valid. Dopamine stimulates both dopaminergic and adrenergic receptors. As such, dopamine may affect renal blood flow by direct vasoconstriction (dopamine receptors), by increasing cardiac output (β-receptors), or by increasing perfusion pressure. Of particular interest are its action on Dopamine 1 (D1) receptors, which are abundantly distributed throughout the renal vasculature. Stimulation of D1 receptors results in vasoconstriction by means of receptor coupling with cyclic adenosine monophosphate (cAMP) and calcium flux generated by protein kinase A. In addition, D1 receptors are also found within the brush border and basolateral membranes of the proximal tubule; medullary ascending limb of the loop of Henle; distal tubule; and cortical collecting ducts where agonist induces decreases in sodium, phosphate, and bicarbonate absorption. D1 receptors have also been localized to the macula densa where they may modify renin production. Dopamine inhibits the Na/K-ATPase along the nephron. Interestingly, this action would be expected to decrease
the oxygen consumption of the renal tubule; thus it would be less susceptible to ischemic or hypoxic injury. Dopamine 2 (D2) receptors are present along the renal tubule. In the inner medulla, a subclass, D2k is coupled to prostaglandin E2 and attenuates the action of antidiuretic hormone (ADH) in this segment.

Dopamine in the dosage range of 0.5 to 2 μg/kg/min increases RBF by 20% to 40%. The GFR increases by 5% to 20%, an effect related to enhanced glomerular ultrafiltration by a preferential vasodilation at the afferent arteriole. This is thought to be related to a dopamine-induced increase in local angiotensin production, which attenuates the dopamine-induced vasodilation at the efferent but not the afferent arteriole. The increase in medullary blood flow observed with dopamine results in a decrease in the urea concentration within the medullary interstitium and contributes to the limited concentrating ability of the dopamine-stimulated renal tubule.

The observed increase in urinary flow is thought to be related primarily to the tubular actions rather than the vascular actions of dopamine. At higher doses, dopamine stimulation of receptors results in decreased sodium and fluid excretion, as well as renal vasoconstriction. Dopamine clearance is decreased in the presence of renal or liver dysfunction.

However, dopamine does have noncardiac effects that complicate its use and should make clinicians rethink its previous role as a vasoactive agent. The group that formulated the 2008 International Guidelines for Management of Severe Sepsis and Septic Shock does not recommend the use of low-dose dopamine as a renal agent, based on available data. They also noted that dopamine may inhibit thyrotropin hormone release from the hypothalamus and have immunosuppressive effects through its inhibition of release of the lymphotrophic factor prolactin. Dopamine should be used cautiously in neonates because the renal vascular response to dopamine is age dependent, although administration of dopamine (0.5 to 2 μg/kg/min) to premature neonates with respiratory distress syndrome and renal insufficiency was reported to result in improved creatinine clearance without major side effects.

Diuretics

Intravenous diuretics have been frequently used in the intensive care unit to ameliorate fluid overload by increasing urine output. This widespread use of loop diuretics in the face of impending renal failure has been ascribed to a combination of animal and human data. Loop diuretics decrease renal vascular resistance and increase renal blood flow. In addition, loop diuretics inhibit the sodium/potassium chloride cotransporter system (NKCC2), thereby reducing active oxygen transport and potentially reducing oxygen consumption, and thus limiting ischemic injury to the outer medullary tubules. Indeed, furosemide has been shown to decrease renal oxygen consumption in critically ill patients.

Mannitol may attenuate renal failure if it is given before the insult or immediately afterward. Loop diuretics, such as furosemide, if given along with a potentially nephrotoxic agent, may increase the renal excretion of the agent and reduce associated nephrotoxicity. Mannitol has been shown to ameliorate nephrotoxicity related to gentamicin, amphotericin B, cisplatin, and myoglobin. A specific beneficial effect is doubtful, however, because acute saline loading alone provides similar protection. When tubular obstruction plays a major role, mannitol may increase tubular flow enough to wash obstructing debris downstream. It seems reasonable to use mannitol and potentially furosemide in the initial phases of oliguria when AKI may not be established; however, these agents provide little benefit and may increase toxicity in sustained oliguria as a result of tubular necrosis.

Calcium Entry Blockers

These agents may prevent renal insufficiency through their vasodilatory action on renal vasculature, as well as inhibition of calcium entry. The calcium channel blockers verapamil, nitrendipine, diltiazem, and nisoldipine have been administered to various animal models of ischemic injury with some success in the prevention or attenuation of renal failure. Minimal protection is observed, however, if they are administered after ischemia. Calcium entry blockers had a beneficial effect in endotoxin-mediated AKI. This effect was postulated to be a result of an antagonism of platelet-activating factor. The perfusion of cadaveric renal grafts before transplantation with diltiazem was associated with improved graft survival compared with control subjects. Preoperative administration of calcium channel blockers to adults undergoing cardiac surgical procedures did not provide any obvious protection from the development of AKI.

Prostaglandins

Vasoconstrictive forces in the renal vasculature may result from the action of vasoconstrictor prostaglandins and are counteracted by the vasodilatory substances. Infusion or stimulation of the vasodilatory prostaglandins or inhibition of the vasoconstrictor prostaglandins seems to be a reasonable approach. Prostacyclin provided protection during ischemia in a rat model. Administration of the thromboxane synthetase inhibitor OKY-046 partially ameliorated hypofiltration in a rat model of ischemic renal failure. In addition, the administration of the free radical scavenger’s dimethylthiourea and superoxide dismutase attenuated renal insufficiency and reduced thromboxane levels.

Renin-Angiotensin Antagonists

Administration of saralasin, an angiotensin II receptor antagonist, either before or after ischemia was not beneficial in the rat model. Blockade of angiotensin production by the conversion of enzyme inhibition with enalapril or captopril was not successful in preventing AKI. Although captopril did prevent a fall in RBF, in one study the GFR actually dropped.

Adenosine and Adenosine Triphosphate

Renal ischemia results in the depletion of cellular adenosine nucleotides and increased levels of adenosine, an agent implicated as a mediator of local renal vasoconstriction. Adenosine may also have protective tubular effects during ischemia because it inhibits solute reabsorption in the medullary thick ascending limb of the loop of Henle. Theophylline, a competitive inhibitor of adenosine receptors, partially prevents the hypofiltration following ischemia in the rat.

Infusion of ATP-magnesium chloride (ATP-MgCl₂) after renal ischemia promotes more rapid cellular recovery and attenuates renal injury. In animal models exogenous ATP, adenosine diphosphate (ADP), adenosine monophosphate
Acute Kidney Injury: Clinical Impact

Severe deterioration of kidney function can have a profound effect on body fluid homeostasis and on blood pressure. The nature of these alterations often requires intensive care management regardless of the precise underlying diagnosis. A wide variety of kidney diseases may result in AKI. The most urgent aspects of AKI are (1) hyperkalemia, (2) severe hypertension, (3) severe plasma and extracellular volume expansion leading to heart failure and pulmonary edema, (4) unremitting metabolic acidosis, (5) hypocalcemia/hyperphosphatemia. Each of these can be viewed as an indication for intensive care and consideration of dialysis. Additionally, over the past decade, the presence and degree of fluid overload (FO) has been shown to be a predictor of survival at the initiation of renal replacement therapy (RRT), and is now considered as an important indication for intervention.

Hyperkalemia

The major reason for the development of hyperkalemia (serum potassium concentration more than 6 mEq/L) is the release (or infusion, or both) of potassium into the extracellular space at a rate greater than the kidney’s ability to excrete potassium. Further the intracellular potassium is in the concentration range of 140 to 150 mEq/L, adding to the total source of potassium. The fact that AKI and oliguria have developed does not mean that hyperkalemia will develop. By the same token, hyperkalemia may develop rapidly in situations of extensive tissue destruction even without oliguria and “full-blown” AKI. Thus in the clinical situation of a crush injury or the tumor lysis syndrome, hyperkalemia should be anticipated and careful anticipatory monitoring begun.

Severe Hypertension

Hypertension is frequently associated with kidney disease. The two main mechanisms by which kidney disease leads to hypertension, especially accelerated hypertension, are (1) plasma volume expansion caused by the failure to excrete sodium chloride and water and (2) hyperreninemia associated with decreased kidney perfusion.

Plasma and Extracellular Volume Expansion

Plasma and extracellular volume expansion are associated with kidney failure. With an abrupt decline in GFR, even “normal” amounts of sodium and water intake expand the extracellular and plasma volumes. Depending on the cardiac status of the patient, the serum albumin level, and the degree of capillary permeability, this extracellular and plasma volume expansion may be manifest as peripheral edema, hypertension, or congestive heart failure and pulmonary edema. In situations of hypertension or congestive heart failure, the treatment involves two principles. The first is to reduce to as low a level as possible the amount of sodium and fluid the patient receives. This requires attention to diet, intravenous or hyperalimentation solutions, and drugs. The second principle is to remove extracellular fluid. If the patient’s kidney...
function permits (glomerular filtration of approximately 15 mL/min or higher), then diuretics, especially loop diuretics such as furosemide, bumetanide, or ethacrynic acid, will help to stimulate a diuresis that should improve the blood pressure or the congestive heart failure. The addition of thiazide diuretics prior to the use of loop diuretics may potentiate the effectiveness of loop diuretics allowing for a greater diuresis. In children with more severe kidney disease, diuretic therapy does not result in diuresis, and dialysis will be necessary.

Severe Metabolic Acidosis

The kidney is responsible for the excretion of hydrogen ion and the regeneration of bicarbonate. When kidney function rapidly deteriorates, then the extracellular concentration of hydrogen ion increases, and this increase leads to acidosis and low serum bicarbonate concentrations. This problem is exacerbated by conditions that increase the production of hydrogen ion and its release into the extracellular fluid. Conditions such as sepsis, severe trauma, burns, extensive abdominal disease or surgery, high chloride-containing intravenous fluids, and hemolysis are all examples in which hypoxia, high hydrogen ion production and/or release into the extracellular space, and a decline in RBF and the GFR are combined. The result is severe metabolic acidosis.

Hypocalcemia/Hyperphosphatemia

Hypocalcemia arises from hyperphosphatemia as a result of dietary load, cellular breakdown, and reduced kidney phosphate excretion; reduced synthesis of calcitriol; downregulation of skeletal cell receptors for PTH; and acidosis.

Hyperphosphatemia may not be recognized, for the plasma phosphorus level is not contained on any of the classic “lab panels” as directed by Medicare; it therefore needs to be thought of and sought out for identification.

Uremia

The symptoms of uremia are frequently vague and difficult to quantitate. They include central nervous system (CNS) manifestations such as lethargy, confusion, seizures, and obtundation and also gastrointestinal manifestations such as anorexia, nausea, and vomiting. These symptoms plus metabolic derangements often lead to the initiation of dialysis.

Renal Disposition of Endogenous and Exogenous Compounds

An important consideration in AKI is the role of the kidney in the metabolism, elimination, and detoxification of endogenous and exogenous materials. Any drugs given must be reviewed because the dosing interval or the dose of drug may need to be altered in AKI. Endogenous substances generally are more slowly metabolized or excreted. For example, the hormone gastrin is metabolized by the proximal tubule after being filtered by the glomerulus. The resultant persistent high circulating levels of gastrin may explain the higher incidence of gastritis and ulcer disease seen in patients with kidney failure.

Specific Kidney Diseases that May Lead to Acute Kidney Injury

Hemolytic-Uremic Syndrome

Hemolytic uremic syndrome (HUS) is considered to be the most common cause of AKI in children in the world. Whereas this may be correct, it should be recognized that within “westernized” medical systems, AKI due to sepsis and cardiac disease as well as in children with other comorbid and chronic underlying conditions are more likely the cause of AKI.

HUS is characterized by thrombotic microangiopathy with platelet aggregation and fibrin deposition in small vessels in the kidney, gut, CNS, and elsewhere. The hemolytic anemia is related predominantly to shearing of red blood cells as they pass through involved vessels. In the typical form of the disease, a triggering infectious agent has frequently been reported. The syndrome is defined by the presence of anemia (hemolysis), thrombocytopenia, and impaired kidney function. Escherichia coli (0157:H7) has been implicated in a large number of cases of typical (epidemic) forms of HUS. It should be understood that there exist a myriad of causes of HUS and that in the absence of verotoxin-secreting E. Coli, HUS can still occur.

Clinical Signs

Typical HUS usually presents in “epidemics” and is characterized by a prodrome of bloody diarrhea. Children with HUS are older than 1 year and younger than 10 years (typically, 18 months to 3 years). The important presenting features of bloody diarrhea, fever, lethargy, decreased urine output, and paleness should lead to a suspicion of HUS. Laboratory evaluation will verify the diagnosis.

The development of HUS has been associated with bacterial and viral infections, oral contraceptives, cyclosporin A, and complement abnormalities. The final common pathway, regardless of the initiating agent, is endothelial cell injury.

Once the endothelium is injured and the subendothelial region is exposed, a sequence of events is set into motion that serves to amplify the initial endothelial damage. Platelets adhere to the subendothelial space, and a release reaction follows that activates additional platelets and initiates fibrin deposition. Both endothelial cell and platelet factors are involved in the propagation of intraglomerular fibrin deposition and coagulation. Direct injury of the endothelial cell may initiate coagulation by release of tissue factor or exposure of the basement membrane. Evidence suggests that the endothelial cells in patients with HUS have reduced ability to produce prostacyclin (PGI₂), a potent vasodilator and inhibitor of platelet aggregation. Some patients with HUS lack a plasma factor that stimulates PGI₂ production. In addition, there is decreased glomerular fibrinolytic activity because of a circulating inhibitor of plasminogen activator. Interestingly, this fibrinolysis inhibitor is removed from the circulation by dialysis. Platelet count and survival time is decreased in patients with HUS, and occasionally there is evidence of platelet activation.

HUS is a heterogeneous group of disorders that have a common result. As a means of differentiating the pathogenesis and
clinical outcome, the following classification scheme has been proposed:

1. The classic form presents in infants or small children after a prodrome of bloody diarrhea that may involve the verotoxin-producing strain of bacteria such as *E. coli*.
2. The postinfectious form is associated with an identified infectious agent such as *Shigella* or *Salmonella* or with endotoxemia.
3. Hereditary forms have been recognized that have both autosomal dominant and recessive modes of inheritance. These patients probably lack a plasma factor necessary for PG12 production or have a prostacyclin inhibitor.
4. An immunologically mediated form is characterized by low plasma C3 and activation of the alternative complement pathway. This form may also be familial.
5. A so-called secondary form is related to known predisposing conditions such as lupus, scleroderma, chemotherapy, malignant hypertension, and kidney irradiation.
6. A form related to pregnancy or use of oral contraceptives is characterized by arterial microangiopathy.

Hemolysis may be brisk and may require transfusions on a daily basis. The aim of transfusions during the period of hemolysis should be to prevent heart failure and not to return the hematocrit value to normal. Thrombocytopenia may be severe but only rarely results in significant bleeding, and therefore platelets should not be given unless clearly needed to stop bleeding or in anticipation of invasive (especially vascular) procedures. Some have suggested that platelets play an important role in the pathophysiology of this disorder. It is further suggested that infusing platelets may actually prolong or worsen the intravascular deposition characteristic of HUS.

**Complications**

Other organ system involvement may lead to serious complications. CNS involvement may reflect the metabolic effects of uremia and can be manifested by lethargy, somnolence, stupor, coma, or seizures. Seizures, paresis, and even CNS hemorrhages can result from vascular damage and CNS vessel occlusion. Gastrointestinal involvement has also been well documented.79 Liver enzyme elevations; abdominal pain, intestinal obstruction, and bowel perforation have all been reported. These possibilities must be considered and evaluated when appropriate. In some instances, the diagnosis of HUS has been made after abdominal exploration.

**Therapy**

In recent years therapy has been conservative, aimed at preventing deterioration and carefully managing such complications as AKI, anemia, and CNS and abdominal symptoms. Furthermore, any therapy would have to show a dramatic benefit to improve on a complete recovery rate of more than 90%.

Comprehensive supportive care has clearly resulted in a dramatic decline in the mortality from HUS (40% in the 1950s to 5% to 10% in the 1980s).77 Nevertheless, therapy specifically aimed at HUS has been attempted because vascular platelet plugging and fibrin deposition in arterioles is part of the pathophysiology.

Heparin, fibrinolytics, and antiplatelet drugs (aspirin, dipyridamole) have all been attempted. In general, reports demonstrate lack of benefit and, in the cases of heparin and fibrinolytics, increased harm from increased bleeding. Fresh-frozen plasma infusion was suggested because of the finding that serum from some patients with HUS cannot generate normal amounts of prostaglandin or does not demonstrate normal antithrombotic and antiplatelet function.80 All these defects could account for the thrombotic microangiopathy of HUS. Fresh-frozen plasma might provide the missing factors that could ultimately reduce microangiopathy. Unfortunately, studies in patients did not demonstrate a beneficial effect. Plasmapheresis has not been tested as carefully as fresh-frozen plasma infusion in patients with typical HUS.81

Vitamin E therapy has been proposed after findings of abnormal lipid peroxidation and low vitamin E activity in patients with HUS. Anecdotal studies suggested some benefit, but controlled, albeit small, studies have not shown benefit.82

Further, intravenous immunoglobulin G (IgG) infusions have received attention on the basis of studies in adults that showed IgG can inhibit platelet aggregation.83 This presumably would diminish thrombotic microangiopathy and reduce the period of time of thrombocytopenia. Controlled studies have not been completed. The preliminary data suggest a shorter period of thrombocytopenia but, as yet, little information on reductions in other morbidities of HUS.

**Prognosis**

The prognosis for the “typical” form of HUS is good. Most series report 3% to 5% mortality rates and an additional 3% to 5% with chronic changes such as chronic kidney disease, persistent hematuria/proteinuria, and chronic hypertension. Thus more than 90% of children with the typical form of HUS recover completely.

In the face of AKI, many of the therapies (RBC, platelet infusion, fresh frozen plasma) result in volume to the children, potentially increasing the risk of fluid overload. Further, the plasma components of PRBCs are hyperkalemic, acidotic, and hypocalcemic. Therefore, transfusing PRBCs to a patient with AKI may induce not only fluid overload but also significant and even lethal electrolyte disbranches. The use of RRT may be needed to offset these potential risks.

**Acute Glomerulonephritis**

Nearly every form of glomerulonephritis has been reported to present as AKI (Box 71-2). In some instances the kidney insufficiency may be the result of an immunological process leading to acute inflammation (e.g., acute postinfectious glomerulonephritis). In others, intravascular volume depletion may play a prominent role in AKI (e.g., minimal change nephrotic syndrome).

In general, glomerulonephritis is initiated by immunological events within the glomerulus followed by mechanisms that result in damage to the glomerulus.84 Glomerular disease results from the deposition of immune complexes composed of (1) antibodies to nonkidney antigens that localize within the glomeruli and form in situ immune complexes; (2) circulating soluble immune complexes that are trapped within the mesangium or subendothelial space; or (3) antibody to antigens within the glomerulus, either as normal glomerular antigens or as neoantigens induced by inflammation or infection.
Antibody deposits promote injury by activation of inflammatory cells or by their direct interaction with glomerular cells. The result is mesangial cell proliferation, capillary wall and basement membrane injury, and extracapillary proliferation of epithelial cells, a process known as crescent formation.

Immune complexes mediate glomerular injury in two ways: through direct membrane damage by the membranolytic membrane attack complex (involving complement components, C5b-9) or by stimulation of glomerular localized inflammatory cells.

Salt and water retention commonly observed with acute glomerulonephritis is the result of a decreased GFR, not increased tubular reabsorption, as once proposed. The renin-angiotensin system is thought not to play a role in the positive salt and water balance. In general, the presentation of glomerulonephritis as AKI implies a virulent form of disease known as rapidly progressive or crescentic glomerulonephritis. Although rapidly progressive refers to a clinical characteristic and crescentic to a pathological feature, the two are commonly coincidental in the presentation of AKI. A classification of rapidly progressive glomerulonephritis is presented in Box 71–3. Four prototypical conditions serve as examples of acute kidney disease that may result in the need for intensive care.

**Acute Postinfectious (Streptococcal) Glomerulonephritis**

This condition is well known to pediatricians. An association between glomerulonephritis and scarlet fever was known in the eighteenth century. In the early twentieth century, however, a clear connection between streptococcal infections and glomerulonephritis was established. The disease most frequent occurs between the ages of 2 and 12 years. It is seen as a sporadic event or in epidemics. It appears that only certain strains of streptococci lead to glomerulonephritis, thus the term nephritogenic streptococcus. Over the past decade the more recent term has moved to postinfectious glomerulonephritis (PIGN) due to the fact that no longer does Streptococcus cause the majority of the cases of PIGN.

The mechanism(s) by which nephritogenic streptococci cause glomerular injury is similar to that seen with “shunt nephritis.” It is generally accepted that immune complexes, with the participation of complement and other inflammatory mediators, cause glomerular inflammation. The precise nature of the bacterial antigen and its site of formation (circulation compared with in situ in the glomerulus) remain areas of study.

**Clinical Signs.** The usual sites of infection are the upper respiratory tract, skin, or both. A longstanding observation is that the latent period is 7 to 14 days if the infection is in the upper respiratory tract and 21 to 40 days if the infection is on the skin. Subclinical cases may be common; they are estimated to be 2 to 19 times as frequent as clinical cases. Symptomatic cases usually present with an acute nephritic syndrome: edema, hypertension, hematuria, and oliguria. Other important clinical features include proteinuria, red cell casts, and abnormal urinary red cell morphological findings, all markers of glomerular injury. Pulmonary edema may also be present, especially if significant salt and water retention are present and if hypertension is severe. Nonspecific findings include malaise, anorexia, abdominal pain, nausea, and vomiting. (This presentation is seen with other forms of acute glomerulonephritis.) Patients may have AKI.

**Laboratory Findings.** Laboratory findings at the time of presentation or early in the course include high serum IgG levels and low serum complement levels, especially C3 and CH50. In general, the alternate pathway of complement is the mechanism of complement activation, although on occasion C2 and C4 may be depressed as well. Complement levels return to normal in 4 to 6 weeks. Therefore if complement levels remain depressed for 6 to 8 weeks after the onset of acute glomerulonephritis, another diagnosis should be strongly entertained (systemic lupus erythematosus or membranoproliferative glomerulonephritis). The definitive diagnosis is based upon renal biopsy that can be performed easily adding clarity to the diagnosis.

**Treatment.** Treatment is based on the patient’s symptoms and is directed at preventing or reducing salt and water retention and hypertension. All patients should have salt and water restriction unless dehydration is obvious (an unusual situation). Approximately 50% to 60% of patients require treatment for hypertension. Diuretics, angiotensin-converting enzyme inhibitors, and potent vasodilators should be considered. Five percent of patients may require dialysis for congestive heart failure, hypervolemia, or encephalopathy.

**Prognosis.** The long-term prognosis in acute postinfectious glomerulonephritis is a matter of debate. The mortality rate

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**Box 71–2 Glomerular Disease Associated with AKI**

<table>
<thead>
<tr>
<th>Hypocomplementemic (low C3)</th>
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<tbody>
<tr>
<td>• Acute postinfectious glomerulonephritis</td>
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<tr>
<td>• Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>• Systemic lupus erythematosus</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Normocomplementemic (normal C3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Henoch-Schönlein purpura</td>
</tr>
<tr>
<td>• Immunoglobulin A nephropathy</td>
</tr>
<tr>
<td>• Wegener granulomatosis</td>
</tr>
<tr>
<td>• Goodpasture syndrome</td>
</tr>
<tr>
<td>• Membranous nephropathy</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemolytic-uremic syndrome</th>
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<tbody>
<tr>
<td>Minimal-change nephrotic syndrome</td>
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</tbody>
</table>

**Box 71–3 Classification of Rapidly Progressive Crescentic Glomerulonephritis**

<table>
<thead>
<tr>
<th>Pulmonary renal syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Antiglomerular basement membrane antibody-mediated (Goodpasture syndrome)</td>
</tr>
<tr>
<td>• Systemic lupus erythematosus</td>
</tr>
<tr>
<td>• Polyarteritis nodosa</td>
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<tr>
<td>• Wegener granulomatosis</td>
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<tr>
<td>• Churg-Strauss syndrome</td>
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</table>

<table>
<thead>
<tr>
<th>Postinfectious</th>
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</thead>
<tbody>
<tr>
<td>Henoch-Schönlein purpura</td>
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<tr>
<td>Immunoglobulin A nephropathy</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
</tr>
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</table>
Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a protean illness affecting many organ systems. In some instances, intensive care is needed for such aspects of SLE as nephritis, cerebritis, carditis, serositis, or sepsis.

Even within a relatively narrow aspect of SLE such as nephritis, great heterogeneity exists. Glomerulonephritis develops in approximately 75% of patients with SLE. This may range from mild hematuria and proteinuria to nephrotic syndrome and rarely to rapidly progressive kidney failure. The patterns of lesions in lupus nephritis are varied. The World Health Organization (WHO) has classified lupus nephritis based upon light microscopy into five categories: (1) minimal disease; (2) mesangial disease; (3) focal proliferative glomerulonephritis; (4) diffuse proliferative glomerulonephritis; and (5) membranous nephropathy. These five categories have been further subdivided to reflect activity (e.g., cellular proliferation, crescents, thrombi, presence of tubulointerstitial disease) and chronicity (e.g., sclerosis, fibrosis, tubular atrophy). Combining these pathological categories with a small number of clinical predictors of poor outcome such as age younger than 24 years, male gender, and decreased kidney function on presentation has permitted a more careful assessment of therapeutic interventions.

Clinical Signs. The broad variation in clinical manifestations may reflect individual expression of similar immunopathological mechanisms or different immunopathological mechanisms presenting as a similar constellation of clinical manifestations. It is clear that SLE represents the overproduction of antibodies against multiple “self”-antigens. Patients with lupus have high titers of antinuclear antibodies and in particular antinuclear antibodies, which are often seen in SLE nephritis. Recent work by the author’s group demonstrates a high presence of antiphospholipid antibodies in plasma. These antibodies are associated with increased risk for thrombosis and other complications. The role of antiphospholipid antibodies in the pathogenesis of lupus nephritis remains to be elucidated.

Treatment. In the intensive care setting, treatment directed at rapidly progressive or diffuse proliferative SLE nephritis consists of high-dose bolus corticosteroid (usually methylprednisolone) at a dosage of 10 to 20 mg/kg intravenously (IV) given 3 to 5 times in a daily or every-other-day regimen. This therapy is associated with hypertension. Other treatments may include plasmapheresis; antiplatelet drugs such as dipyridamole; and immunosuppressives including azathioprine, cyclophosphamide, mycophenolate mofetil or other alkylating agents, and methotrexate. Recent data from the National Institutes of Health and others have suggested significant benefit from cyclophosphamide or mycophenolate mofetil in maintaining kidney function.

Prognosis. The long-term prognosis for children with SLE nephritis is unclear. Regardless, patients and families must expect persistent evidence of kidney injury such as hematuria, proteinuria, hypertension, and even reduced kidney function such as a diminished GFR. Further, patients may have relapsing episodes of nephrotic syndrome or acute glomerulonephritis.

Other Glomerulonephritides

Two other forms of glomerulonephritis may result in the need for intensive care therapy. These are antiglomerular basement membrane (anti-GBM) antibody disease (Goodpasture syndrome) and Wegener granulomatosis. Although rare in children, both conditions can result in AKI. Therapy should be directed at the general condition of AKI as discussed previously in addition to specific therapy.

In the case of anti-GBM antibody disease, patients may have both kidney disease and pulmonary disease, often pulmonary hemorrhage. Treatment includes corticosteroids, plasmapheresis, and immunosuppressives, mainly alkylating agents. Despite therapy, end-stage kidney disease develops in some patients. Recurrences of anti-GBM antibody disease in kidney allografts have also been reported. Vasculitic syndromes associated with kidney disease include Wegener granulomatosis and so-called antineutrophil cytoplasm antibody (ANCA) associated diseases. ANCA is an autoantibody that is found in one of two patterns in many forms of vasculitis and which serves as a potentially useful diagnostic tool. Wegener granulomatosis is characterized by granulomatous vasculitis that attacks the lungs, the respiratory tract including sinuses and trachea, and the kidneys. This condition may be difficult to diagnose, and biopsy may be the only means of determining the diagnosis if the plasma ANCA is negative. Five children with ANCA-associated glomerulonephritis and AKI have been described. Nonspecific systemic illness commonly preceded the presentation of AKI. In two of the five, kidney...
function recovered; the other three required long-term dialysis. Cyclophosphamide has been shown to be beneficial in the treatment of the kidney disease of Wegener granulomatosis, and plasmapheresis is also of potential benefit in crescentic forms, although it is not widely used because of frequent complications.

**Nephrotic Syndrome and Acute Kidney Failure**

AKI is an uncommon complication of primary nephrotic syndrome in children but may occur as a result of intravascular volume depletion, bilateral kidney venous thrombosis, or drug-induced kidney toxicity.95

The clinical scenario is one in which the child has a low serum albumin level and edema (increased extracellular volume). These patients have stable and often normal plasma volumes despite low oncotic pressure. Should an acute illness (e.g., gastroenteritis) occur, however, intravascular volume depletion and AKI may develop rapidly. Patients with nephrotic syndrome who have fluid losses or are unable to take in fluids should be admitted to the hospital, and intravenous administration of albumin plus maintenance and replacement fluids should be considered. The use of intravenous albumin helps to maintain the intravascular volume and reduces the edema that might develop during fluid therapy. In some children with nephrosis and AKI, no cause for reduced GFR can be found. In a recent report of four children with idiopathic AKI associated with primary nephrotic syndrome, three had evidence of peritonitis at presentation, two had minimal-change nephrotic syndrome, and two had focal segmental glomerulosclerosis. All four children required dialysis for treatment of marked anasarca. Kidney biopsies performed during AKI in three of the four children showed tubular ischemic injury. Removal of fluid with diuretics or dialysis/hemofiltration was associated with recovery of function. Placing a vascular access for dialysis in a child with nephrotic syndrome is not without risk. In general, children with nephrotic syndrome have a high risk of clotting, independent of vascular access. The large bore vascular access commonly used for dialysis may potentiate this risk. Use of heparin for thrombosis prevention should be considered in certain high-risk situations.

**Tubulointerstitial Disease**

**Acute Tubulointerstitial Nephritis**

Acute tubulointerstitial nephritis (ATIN) is a clinical syndrome characterized by inflammation of the kidney interstitium accompanied by interstitial edema and kidney tubular injury. ATIN may be caused by numerous drugs, infectious agents, and systemic illnesses.96 A partial list of causes can be found in Box 71-4.

In most cases, ATIN is immunological in origin. Most of understanding of the pathogenesis has been obtained from animal models. Three phases have been described for ATIN. The initial phase involves recognition of a nephritogenic antigen located in the interstitium. The antigen may be a normal component of the interstitium, a modified constituent, drug-induced, or infection-induced. Loss of host tolerance is thought to be required for the initial phase to occur. The immune regulatory phase is characterized by the activation of T-helper lymphocytes, which induce differentiation of T and B cells that directly injure the interstitium. The inability of the host to counteract this response with T-suppressor cells permits T- and B-cell activation to go unabated. In the effector phase, both humoral and cell-mediated components contribute to tissue injury. Antibodies to tissue antigens promote injury by activation of the complement cascade, chemotaxis, and cell-mediated cytolysis. IgE is also produced, that may recruit eosinophils or mast cells. Mononuclear cell infiltration produces tissue injury by release of proteases and lymphokines. Eosinophils also damage surrounding tissue by release of proteases, leukotrienes, and toxic oxygen species.

Several theories have been proposed to explain the reduced GFR: (1) the “clogged drain,” (2) the capillary bed, and (3) vascular tone hypotheses. The clogged drain theory proposes that tubular obstruction caused by luminal debris and interstitial edema results in increased pressure in Bowman’s space and decreased pressure favoring filtration. Interstitial inflammation results in injury to the blood supply of the tubules (capillary bed hypothesis). Because these vessels are postglomerular, the increased resistance and reduced surface area associated with vessel injury result in an increase in efferent arteriolar pressure and a reduction in the pressure gradient across the glomerulus with a resultant drop in the GFR. Decreased sodium reabsorption by injured proximal tubular epithelial cells reduces the medullary interstitial osmolality, and impairs the ability to concentrate the urine. Thus an increased volume of filtrate is delivered distally, stimulating the juxtaglomerular apparatus to increase angiotensin II production (vascular tone hypothesis). The net result is vasoconstriction and a diminished GFR.

Pathologically, diffuse or patchy infiltration of the kidney interstitium by lymphocytes, plasma cells, and eosinophils, and edema of the interstitial space is observed. Eosinophils are usually indicative of an acute phase, whereas epithelioid granulomas with giant cells and fibroblasts or fibrosis indicate chronic disease. Tubules may have mild structural alterations or marked necrosis with loss of brush border. Drug-induced interstitial nephritis is the most common form of ATIN in adults and children. Eight of 13 pediatric patients described in one series96 and 38 of 57 in another series of children97 with interstitial nephritis had drug-related causes of ATIN. Numerous drugs have been associated with ATIN. The β-lactam antibiotics are the most frequently associated with

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*Box 71-4 Primary Causes of Acute Tubulointerstitial Nephritis*

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Infections</th>
<th>Septicemia</th>
<th>Leptospirosis</th>
<th>Candidiasis</th>
<th>Malignant infiltration</th>
<th>Lymphoma</th>
<th>Leukemia</th>
<th>Systemic diseases</th>
<th>Systemic lupus erythematosus</th>
<th>Sarcoidosis</th>
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<td>Cyclosporine</td>
<td>Vaccines</td>
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<td>Rutoside</td>
<td>Drug-induced</td>
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<td>Mycophenolate sodium</td>
<td>Drug-induced</td>
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<td>Tacrolimus</td>
<td>Drug-induced</td>
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<td>Azathioprine</td>
<td>Drug-induced</td>
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<tr>
<td>Prednisone</td>
<td>Drug-induced</td>
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<tr>
<td>Methylprednisolone</td>
<td>Drug-induced</td>
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ATIN with methicillin being the prototype, although ampicillin is the most common offending drug in pediatric series. NSAIDs are increasingly recognized as a cause of acute kidney dysfunction.

Clinically apparent disease usually develops days to weeks after exposure to the inciting drug or agent but may be immediate. Drug-induced tubulointerstitial disease is localized predominantly to the cortex, whereas infectious or infiltrative disorders more commonly localize to the medulla. The functional abnormality often indicates the primary site of tubular injury. Damage involving mainly the proximal tubule results in the wasting of bicarbonate, phosphate, glucose, amino acids, and uric acid. Distal tubular involvement may be manifest as hyperkalemic kidney tubular acidosis as a result of impaired secretion of both $K^+$ and $H^+$. Nephrogenic diabetes insipidus can result with medullary involvement.

Although ATIN is primarily a disease of the kidney interstitium and tubule with lack of glomerular structural alterations, the GRF may also be reduced. Of 13 children described by Ellis et al. and Andreoli, 12 had a creatinine clearance of less than 50 mL/min/1.73 m$^2$. AKI resulting from ATIN may be oliguric. Other clinical signs of ATIN are fever and rash. ATIN usually resolves with removal of the offending agent, although occasionally chronic kidney insufficiency may result.

**Cardiorenal Syndrome**

Renal insufficiency occurs commonly in adult and pediatric patients with heart failure. Although the mechanisms are not fully understood, diminished cardiac function coupled with renal dysfunction, or the cardiorenal syndrome, has been observed in both the acute and chronic care settings. The phenomenon remains better characterized in adult medicine. Decreased urine output and resultant fluid retention can aggravate heart failure symptoms and contribute to clinical deterioration. Even a modest increase in serum creatinine (i.e., >0.2 mg/dL) can predict mortality in adult patients hospitalized for heart failure. The relationship of renal function and heart failure in children has not been well examined. Retrospective data analysis have shown a high incidence of cardiac disease among children who exhibit renal insufficiency while hospitalized, and clinical experience suggests that as in adults, worsening renal function is associated with worse outcomes among children with heart failure.

**Basis for Deteriorating Renal Function**

The physiologic interaction of the heart and kidney is complex and not well understood, although it is recognized that disease of one organ system frequently complicates the other. Some have termed this combined cardiac and renal dysfunction the cardiorenal syndrome. Renal insufficiency occurring in heart failure patients is usually attributed to a “prerenal state” resulting from diminished cardiac output and renal perfusion. It is hypothesized that deteriorating cardiac output and decreasing renal blood flow trigger neurohormonal activities that lead to fluid retention and increased systemic vascular resistance, causing further progression of ventricular dysfunction. Data from animal studies show that isolated renal ischemia leads to increased pulmonary vascular permeability, suggesting a bidirectional pathophysiologic interaction between the renal and cardiopulmonary systems. Other mechanisms may also contribute to a decline in a renal function, including medications being used to support cardiovascular function, such as vasoactive drugs. A study by Price et al. reported worsening renal function with the use of dopamine and nesiritide.

There is evidence that right ventricular dysfunction may be associated with the renal venous congestion. Using echocardiographically derived measurements, Testani et al. showed that in 151 patients, RV dysfunction remained a significant predictor of change in glomerular filtration rate after controlling for heart rate, hemoglobin, admission serum urea nitrogen, B-type natriuretic peptide level, diuretic dose, length of stay, ejection fraction, cardiac output, tricuspid regurgitation severity, and inferior vena cava inspiratory collapse.

**Cardiac Surgery–Related Acute Kidney Injury**

AKI is not uncommon following cardiac surgery, and its presence portends a worse prognosis. In a survey of 542 patients who underwent cardiopulmonary bypass to fix their congenital cardiac disease, the rate of acute kidney injury after congenital cardiac surgery was shown to be about 11%. Other studies have found mortality rates to be four times higher in patients with renal failure compared to those without. Studies have shown that a small rise (less than 50%) in creatinine in the first 48 hours could predict a greater than 50% increase in serum creatinine in the next 48 hours. Significant independent risk factors for AKI were bypass time and longer vasoressor use; there was a tendency toward younger age as a risk factor. Cardiac surgery-related AKI has been characterized and described in adult medicine; however, at this time it remains difficult to characterize the exact nature of the injury in the pediatric population. Cardiac surgery-associated acute kidney injury (CSA-AKI) is a significant clinical problem. It results from the interactions between the complicated interventions required in the process of congenital cardiac surgery such as bypass surgery, use of blood products, the anatomical variability of the congenital cardiac abnormality such as single ventricles, and the surgical correction/palliation of the lesion. It likely involves at least six major mechanisms: exogenous toxins and cytokines, metabolic factors, ischemia and reperfusion, neurohormonal activation, inflammation, and oxidative stress. These mechanisms of injury are likely to be active at different times with different intensity, and probably act synergistically. There are also some data that suggest that at least some of the injury may be pigment-related, but this is yet to be substantiated. There have also been attempts at ameliorating the injury with interventions such as N-acetyl cysteine, but this has resulted in an increase in bleeding with any benefit yet to be established.

There are, however, newer markers of renal injury such as plasma neutrophil gelatinase-associated lipocalin (NGAL) that are more sensitive than serum creatinine in predicting acute kidney injury. In fact, plasma NGAL at 2 hours after cardiopulmonary bypass (CPB) was the most powerful independent predictor of AKI in patients post-CPB. Serum creatinine is an inadequate marker because nearly 50% of renal function has to be lost before its levels are elevated, and serum creatinine does not accurately depict kidney function until a steady state has been reached, which may require
several days. Biomarkers such as plasma NGAL may provide for earlier clinical intervention, thereby preventing significant mortality or morbidity. The renal histological changes in cardiac surgery-related AKI are yet to be well characterized.

Porcine data utilizing experimental cardiopulmonary bypass revealed higher tubular injury scores in kidneys post-CPB relative to controls (median score 1.0 [IQR 1.0-1.0], P = .019). AKI was associated with endothelial injury and activation, as demonstrated by reduced DBA (*Dolichos biflorus* agglutinin) lectin and increased endothelin-1 and vascular cell adhesion molecule (VCAM) staining.112

**Tumor Lysis Syndrome**

Tumor lysis syndrome (TLS) is an oncologic emergency that is usually seen when tumor cells undergo rapid decomposition spontaneously or, more often, in response to cytoreductive therapy with the release of large amounts of potassium, phosphate, and nucleic acids into the systemic circulation. Catabolism of the nucleic acids to uric acid leads to hyperuricemia, and a marked increase in uric acid excretion can result in the precipitation of uric acid in the renal tubules and mediate acute renal failure. Despite advances in risk stratification, prophylaxis, and active interventions to reduce the incidence of TLS, up to 6% of at-risk pediatric and adult patients undergoing chemotherapy are believed to develop AKI.113 Even mild AKI that does not require renal replacement therapy has been associated with increased long-term risk for renal failure and mortality. The levels of phosphorus in malignant cells can be up to four times the levels found in normal cells, and rapid release of these stores can result in hyperphosphatemia, with an increase in serum levels by as much as 2.1 mmol/L in children.114 Initially, the kidneys respond by increasing urinary excretion and decreasing tubular resorption. However, tubular transport mechanisms eventually become saturated, leading to increasing serum phosphorus levels. Acute renal insufficiency caused by uric acid or other complications may further exacerbate the development of hyperphosphatemia. In 2008, a group of researchers published evidence-based guidelines for the prevention and treatment of tumor lysis syndrome.115 Their recommendations were based on the type of tumor at the initiation of chemotherapy as discussed in the following section.

**Management**

Vigorous IV hydration with diuresis has long been the cornerstone to prevention and treatment of tumor lysis syndrome (to achieve urine output of 80 to 100 mL/m²/h). Increasing intravascular volume and urine output increases the renal excretion of uric acid and phosphate. Alkalization of the urine is no longer recommended, due to the lack of supporting evidence and the potential for enhancing the precipitation of xanthine in the urine.116 Allopurinol works to lower serum uric acid levels by reducing the production of uric acid from purine precursors by inhibiting xanthine oxidase. Because it does not alter the uric acid already formed, it works best when initiated at least 48 hours prior to chemotherapy.117 It is generally well tolerated, and can be given orally or intravenously; the dose needs adjustment for preexisting renal impairment.

**Rasburicase.** Recombinant urate oxidase exerts its pharmacologic activity by enzymatic oxidation of uric acid into allantoin.118 It works rapidly, often dropping the uric acid level to levels less than normal within hours. Although contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, it is overall well tolerated. The traditional recommended dosage is 0.15 to 0.20 mg/kg per dose IV daily for up to 7 days. Investigators recommend the use of rasburicase as the first line intervention for high-risk patients (see Box 71-1) and as backup therapy for moderate-risk therapy for those patients who go on to develop hyperuricemia despite allopurinol and hydration (Table 71-2).115

Rasburicase is remarkably well tolerated. The rare, but serious, adverse events that require prompt and permanent discontinuation of rasburicase are methemoglobinemia and hemolysis.118 Glucose-6-phosphate dehydrogenase (G6PD) deficiency is regarded as the main predisposing factor for hemolysis and remains a contraindication to its use (the mechanism is related to oxidative stress from the hydrogen peroxide [H₂O₂] produced as uric acid is converted to allantoin), justifying, when possible, the screening for patients at high risk for G6PD deficiency (e.g., African or Mediterranean ancestry).

Recent work by the author’s group eliminated reversible AKI in infants associated with elevated uric acid when treated with rasburicase.119

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**Table 71–2 Patient Stratification by Risk**

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHL, Burkitt lymphoblastic, B-ALL</td>
<td>DLBCL</td>
<td>Indolent NHL</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>WBC ≥100,000</td>
<td>WBC 50,000–100,000</td>
<td>WBC ≤50,000</td>
</tr>
<tr>
<td>AML</td>
<td>WBC ≥50,000, monoblastic</td>
<td>WBC 10,000–50,000</td>
<td>WBC ≤10,000</td>
</tr>
<tr>
<td>CLL</td>
<td>WBC 10,000–100,000 Tx w/fludarabine</td>
<td>WBC ≤10,000</td>
<td></td>
</tr>
<tr>
<td>Other hematologic malignancies (including CML and multiple myeloma) and solid tumors</td>
<td>Rapid proliferation with expected rapid response to therapy</td>
<td>Remainder of patients</td>
<td></td>
</tr>
</tbody>
</table>

Role of Renal Replacement Therapy. The understanding of the optimal start time, method, and dosage of renal replacement therapies (RRT) has evolved. Early intervention is favored, because most AKI survivors leave the hospital with independent kidney function. Once the process of cell turnover is uncoupled, the rapid release of intracellular contents into the bloodstream, including anions, cations, proteins, and nucleic acids occurs. In this clinical paradigm, the early institution of renal replacement interrupts the cascade before the occurrence of tumor lysis-related AKI with life-threatening complications. Therefore, the group recommended that for pediatric patients at high risk of TLS, cytotoxic chemotherapy should only be administered in a facility with ready access to dialysis. Although dialysis usage has been reduced since the introduction of rasburicase, as many as 3% of patients (1.5% of pediatric patients and 5% of adult patients) still require RRT. In line with this, the panel recommends that renal consultation be obtained immediately if urine output is low, if there are persistently elevated phosphate levels, or in the case of hypocalcemia.

Pigment Nephropathy
Rhabdomyolysis is a dissolution of skeletal muscles that produces a nonspecific clinical syndrome that causes extrusion of toxic intracellular contents from myocytes into the circulatory system. The possible causes of rhabdomyolysis are myriad; with direct muscle injury remaining the most common cause of muscle injury, additional causes include hereditary enzyme disorders, drugs, toxins, endocrinopathies, malignant hyperthermia, neuroleptic malignant syndrome, heatstroke, hypothermia, electrolyte alterations, diabetic ketoacidosis and nonketotic hyperosmolar coma, severe hypothyroidism or hyperthyroidism, and bacterial or viral infections. Most of the data remains adult-based. In a study of 210 pediatric patients, the most common causes of rhabdomyolysis were viral myositis (38%), trauma (26%), and connective tissue disease (5%). Higher initial creatine kinase levels (>6000 IU/dL) and higher fluid administration rates were associated with higher maximal creatinine levels.

Pathophysiology
Rhabdomyolysis, which literally means “dissolution of striped [skeletal] muscle,” is the final pathway of many different processes. Regardless of the underlying mechanism, myocyte dissolution triggers a cascade of events that lead to the rapid release of calcium ions into muscle cells resulting in a pathological interaction between actin and myosin and activation of cell protease, with subsequent myocyte necrosis of muscle fibers, release of potassium, phosphates, myoglobin, creatine kinase (CK), and urates into the extracellular space and into the bloodstream. As such, myoglobin can precipitate in the glomerular filtrate, particularly in an acidic environment, causing tubular occlusion and severe kidney damage. Pigmented myoglobin casts, which characterize the rhabdomyolysis syndrome, are the result of the interaction between myoglobin and Tamm-Horsfall protein in an acid environment. Additional mechanisms causing renal damage include (1) a direct cytoprotective effect of myoglobin on renal cells; (2) urate precipitation, leading to intraluminal casts, increased intratubular pressure, and subsequent decreased glomerular filtration rate; (3) renal vasoconstriction and ischemia due to the toxic group of myoglobin causing activation of the cytokine cascade; and (4) oxidant injury through heme-induced reactive oxygen species such as superoxide anion, hydrogen peroxide, or hydroxyl radicals causing direct oxidative damage.

The classic triad of symptoms of rhabdomyolysis includes myalgia, weakness, and dark urine, although these findings may be inconsistent. The definitive diagnosis of rhabdomyolysis requires an elevation of CK levels to greater than five times normal in the absence of significant elevations of brain or cardiac CK fractions. The most dangerous sequela of rhabdomyolysis is AKI, the exact mechanisms of which are unclear but may be attributable to vasoconstriction/hypoperfusion, renal tubular dysfunction/cast formation, and/or myoglobin-induced tubular cytotoxicity. The mainstay of treatment for rhabdomyolysis, directed at preventing AKI, is fluid therapy. Many clinicians advocate alkalinization of urine with sodium bicarbonate (sometimes with concomitant forced diuresis with mannitol). There are no data that suggest that this strategy prevents AKI in children with rhabdomyolysis.

Once the patient has reached the hospital, fluid infusion should be continued, with the goal of maintaining a brisk urinary flow and a urine pH above 6.5 and plasma pH below 7.50. The rate of infusion should be at 150% of maintenance rate, with hemodynamic parameters and urine output monitored closely. Some authors also suggest administering mannitol. This is done to induce osmotic diuresis and to remove liquids from the damaged muscular interstitium, thus relaxing the compartments involved. To force diuresis, some clinicians also recommend the addition of furosemide.

There is little clinical evidence to support the use of bicarbonate, mannitol, and furosemide. It is important to understand that the treatment benchmark is aggressive forced hydration with saline and glucose solutions. Studies in humans show that alkalinization and osmotic and diuretic treatment add little to the beneficial effect of hydration. Forced hydration should be continued until the disappearance of myoglobinuria, which typically occurs after the third day. Hyperkalemia must be managed using the usual techniques, considering that treatment with glucose and insulin may prove to be ineffective in this context due to the damaged muscle’s inability to capture potassium from the extracellular space. It is often necessary to treat severe hyperkalemia with renal replacement therapy.

Hypocalcemia
Secondary sequestration of calcium into damaged muscle cells must be viewed critically. Administration of intravenous calcium (either chloride or gluconate) should be used only to treat life-threatening electrocardiographic alterations, secondary to hyperkalemia or extreme hypocalcemia.

Drug-Induced Nephrotoxicity
Many different drugs and agents may cause AKI in children. In the ICU, factors such as age, pharmacogenetics, underlying disease, the dosage of the toxin and concomitant medication all interact and influence the severity of nephrotoxic insults. Pediatric retrospective studies have reported incidences of AKI in PICUs of between 8% and 30%. It is widely recognized that neonates have higher rates of AKI, especially following cardiac surgery, severe asphyxia, or premature birth. While...
in most cases the etiology of AKI in the ICU is multifactorial (e.g., sepsis, ischemia/hypoperfusion), several recent large epidemiologic studies have shown that nephrotoxic drugs were contributing factors in 19% to 25% of cases of severe acute renal failure in critically ill adult patients.\textsuperscript{128}

NSAIDs, antibiotics, amphotericin B, antiviral agents, angiotensin-converting enzyme (ACE) inhibitors, calcineurin inhibitors, radiocontrast media, and cytostatics are the most important drugs implicated in the etiology of AKI in children. The mechanisms of nephrotoxicity include constriction of intrarenal vessels, acute tubular necrosis, acute interstitial nephritis, and, more infrequently, tubular obstruction.\textsuperscript{127}

### Aminoglycoside Nephrotoxicity

Aminoglycosides (AGs) are non–protein-bound drugs that are primarily excreted unmetabolized by glomerular filtration. Their cationic nature facilitates binding to the tubulooepithelial membrane in the proximal tubule, resulting in rapid intracellular transport.\textsuperscript{129} The molecular number of cationic groups determines the facility with which these drugs are transported across cell membranes and is an important determinant of toxicity.\textsuperscript{130,131} Neomycin is associated with the most nephrotoxicity; gentamicin, tobramycin, and amikacin are intermediate, and streptomycin is the least nephrotoxic.\textsuperscript{132} Several hypotheses have been proposed to explain the nephrotoxic effects of aminoglycosides. Intracellular accumulation of AG within lysosomes is thought to interfere with normal cellular function such as protein synthesis and mitochondrial function, eventually leading to cell death.\textsuperscript{133} Aminoglycosides also are known to stimulate the calcium-sensing receptor on the apical membrane thereby inducing cell signaling and eventual cell death.\textsuperscript{134}

Risk factors for aminoglycoside nephrotoxicity include the type of AG, high peak serum levels, cumulative dose, the duration and frequency of administration, and patient-related factors such as age, preexisting renal dysfunction, hypoalbuminemia, liver dysfunction, decreased renal perfusion, and the concomitant use of nephrotoxic drugs.\textsuperscript{132}

Several approaches have been evaluated in both animals and humans as potential treatments to attenuate the nephrotoxicity of aminoglycosides. Investigators have demonstrated that calcium supplementation reduces the nephrotoxic effect, likely through competitive inhibition of calcium channels in the proximal tubule.\textsuperscript{135} Similarly, calcium channel blockers also have been shown to attenuate AG nephrotoxicity.\textsuperscript{136} Also the protective effect of concomitant use of β-lactam antibiotics has been recognized for several years, although the mechanism by which this may occur is somewhat unclear.\textsuperscript{137,138} More recent investigations have evaluated a possible role for antioxidants in renoprotection.\textsuperscript{139} Once-daily dosing of aminoglycosides is the only clinical approach that is commonly used to reduce nephrotoxicity.\textsuperscript{140} The rationale for the efficacy of consolidated AG dosing against gram-negative bacteria is based on two pharmacodynamic properties of aminoglycosides: (1) the bacteriocidal mechanism of action is concentration-dependent; and (2) prolonged postantibiotic effect.\textsuperscript{132}

Clinical evidence of AG-induced acute tubular necrosis is seen within a week of initiation of aminoglycoside treatment. AG-induced acute renal failure is generally nonoliguric, and may be associated with decreased urine-concentrating ability and urinary magnesium wasting. It is generally reversible after discontinuation of the drug; however, supportive renal replacement therapy may be required. The authors recommend that alternative antimicrobials should be considered when possible in patients at high risk for AG nephrotoxicity. If required and consolidated AG dosing is used, renal function should be assessed daily to monitor for changes in renal function, and trough levels should be followed to guide dosage.

### Amphotericin B

The use of antifungals has become more commonplace in intensive care units, as the prevalence of fungemia (specifically candidemia) has increased in critically ill patients. For decades, amphotericin B was the drug of choice because of its broad spectrum of activity and its wide availability; however, its use has been sharply curtailed in recent years because of its considerable side effects (specifically, nephrotoxicity) and the availability of newer, less-toxic agents.

Approximately 80% of patients who receive treatment with amphotericin B will experience some renal dysfunction.\textsuperscript{141} There are several mechanisms by which amphotericin B is thought to induce renal dysfunction: (1) by directly binding to tubular epithelial cells in the cortical collecting duct, resulting in altered cell permeability; (2) by causing sodium, potassium, and magnesium wasting; and (3) by directly causing afferent arteriolar (glomerular) vasoconstriction.\textsuperscript{142} Risk factors for amphotericin B nephrotoxicity include preexisting renal insufficiency, hypokalemia, volume depletion, the use of concomitant nephrotoxins, and large individual and cumulative dosages.\textsuperscript{143}

A number of strategies have been studied to minimize the associated nephrotoxicity, including sodium loading and longer infusion rates.\textsuperscript{144} While some have shown a reduction in nephrotoxicity, these studies are very small and typically enroll low-risk patients. Lipid-based formulations of amphotericin B also are available, which may produce less nephrotoxicity. However, these agents are considerably more expensive. The recent introduction of alternative antifungal agents such as itraconazole, voriconazole, and caspofungin has largely supplanted the use of amphotericin B in high-risk patients with renal impairment; however, it continues to be used widely in patients with normal renal function because of its relatively low cost and broad spectrum of activity.

Given the presence of many underlying risk factors for nephrotoxicity in critically ill patients, it is recommended that amphotericin B should be avoided in this patient population if alternative therapies are available. When it is used, sodium loading with intravenous hydration is recommended to attenuate vasoconstrictive effects, and longer infusion times should also be considered. Renal function and serum electrolytes (specifically potassium) should be monitored during treatment.

### Vancomycin

The use of vancomycin hydrochloride has increased considerably over the last decade as it has become the standard therapy for treatment of methicillin-resistant Staphylococcus aureus infections. Recent data from the 2004 Centers for Disease Control and Prevention, National Nosocomial Infections Surveillance System indicate that the prevalence of methicillin-resistant S. aureus exceeds 50% in U.S. hospitals. The synergistic nephrotoxicity of combination therapy involving vancomycin and aminoglycosides is well established,
with a reported frequency of acute renal failure in the range of 20% to 30%. However, the nephrotoxicity of vancomycin alone increasingly is being recognized as high-dose therapy has become more common for the treatment of methicillin-resistant S. aureus.\textsuperscript{146}

Vancomycin is excreted by glomerular filtration, 80% to 90% in an unaltered form.\textsuperscript{147} It is hard to determine the exact rates of vancomycin-related toxicity because most reported cases have had additional risk factors for acute renal failure, which makes it difficult to determine the true risk of treatment. The mechanism by which it exerts its nephrotoxicity is unknown. Independent risk factors for nephrotoxicity include the use of concomitant nephrotoxic agents, age, duration of therapy, and drug levels achieved.\textsuperscript{147} Trough levels higher than 15 μg/mL are associated with increased risk of nephrotoxicity, and peak levels also have been associated with increased nephrotoxicity. The dosing of vancomycin requires careful consideration of renal function and estimated glomerular filtration rate. Trough levels should be monitored frequently in patients with fluctuating renal function.

Calcineurin Inhibitors

The introduction of calcineurin inhibitors (CNIs) has led to dramatic improvement in both allograft and patient survival. The clinical use of CNIs often is limited by their nephrotoxic effect, which can present as two distinct and well-characterized forms: acute and chronic nephrotoxicity. Calcineurin inhibitor-induced AKI may occur as early as a few weeks or months after initiation of therapy. The clinical manifestations of CNI-induced renal dysfunction include reduction of GFR, hyperkalemia, hypertension, renal tubular acidosis, increased resorption of sodium, and oliguria. The acute adverse effects of calcineurin inhibitors on renal hemodynamics are thought to be directly related to the cyclosporine (CsA) or tacrolimus dosage and blood concentration and can be managed by dose reduction. This is in contrast to calcineurin inhibitor-induced chronic nephropathy, which is largely irreversible and can occur independently of acute renal dysfunction, CNI dosage, or blood concentration.

Although the exact mechanism of nephrotoxicity is not fully understood, several factors have been implicated in the pathogenesis of CNI nephrotoxicity.\textsuperscript{148} Experimental models of acute CsA toxicity revealed that CsA administration is associated with afferent and efferent arteriolar vasoconstriction, which results in a significant reduction of renal plasma flow and GFR.\textsuperscript{149,150} The precise mechanism by which CsA induces renal vasoconstriction has not been established clearly. Results from several studies indicate that vascular dysfunction induced by CsA results from an increase in vasoconstrictor factors that include endothelin, thromboxane, and angiotensin II, as well as a reduction of vasodilator factors such as prostacyclin and nitric oxide.\textsuperscript{150,151} Cyclosporine and tacrolimus differ with respect to side effects; however, the available data comparing nephrotoxicity are conflicting. While some studies have suggested that tacrolimus may be associated with a decreased severity of renal dysfunction in comparison to CsA,\textsuperscript{132} other investigators have demonstrated no difference between the two CNIs.\textsuperscript{152}

Studies have been conflicting on the protective effect of calcium channel blockers on the preservation of renal function for patients receiving CNIs. In a multicenter, prospective, randomized, placebo-controlled study in 118 cadaveric renal transplant recipients receiving CsA, the use of a calcium channel blocker resulted in a significantly better allograft function at 2 years and demonstrated an improvement in graft function, as assessed by serum creatinine and GFR, that was independent of lowered blood pressure.\textsuperscript{153} Currently, more research is being done with goals of improving the safety profile of CNIs and identifying safer alternatives.

Sirolimus

Sirolimus is an mTOR (mammalian target of rapamycin) inhibitor that is becoming increasingly used in allograft preservation. Its target protein, mTOR, is a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription in transplantation.\textsuperscript{154} As its use in transplant medicine is increasing, it was hoped that its lack of nephrotoxicity in animal models would be translated in humans to improve immunosuppression with minimal effect on renal function. Unfortunately, several recent studies suggest that sirolimus has inherent nephrotoxicity, such as development of proteinuria and delay in recovery from ischemia-reperfusion injury. In addition, several studies have shown that the nephrotoxicity associated with CNIs is exacerbated when used in combination with sirolimus.\textsuperscript{155}

Nonsteroidal Antiinflammatory Drugs

In most circumstances, NSAIDs do not pose a significant risk to patients with normal renal function. However, in situations in which renal perfusion is compromised (which are relatively common with critically ill patients), the inhibition of prostaglandin-induced vasodilation with the use of NSAIDs may further compromise renal blood flow and exacerbate ischemia.\textsuperscript{156} The renal effects of NSAIDs do seem to be dependent on the type, dose, and duration of treatment.\textsuperscript{156} Indomethacin is thought to be the most likely drug to impair renal function, and aspirin the least likely.\textsuperscript{156} Patients at high risk of NSAID-induced nephrotoxicity include patients with preexisting renal dysfunction, severe cardiovascular or hepatic failure, or the concomitant use of other potentially nephrotoxic medications, such as aminoglycosides, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.\textsuperscript{156}

Contrast-Induced Nephropathy

Contrast-induced nephropathy (CIN) acute kidney injury is an important complication in the use of iodinated contrast media that accounts for a significant number of cases of hospital-acquired AKI. The occurrence of AKI as a result of contrast will continue to increase, as there is growing use of imaging and interventional procedures in pediatric intensive care patients.\textsuperscript{157} At the same time, many patients in intensive and critical care units have compromised renal function, representing the most important risk factor for contrast-induced AKI.

Three core elements are intertwined in the pathophysiology of CIN: (1) direct toxicity of iodinated contrast to nephrons; (2) microshowers of atheroemboli to the kidneys; and (3) contrast- and atheroemboli-induced intrarenal vasoconstriction.\textsuperscript{158} Direct toxicity to nephrons with iodinated contrast has been demonstrated and seems to be related to the osmolality of the contrast.\textsuperscript{159} Hence, low-ionic or nonionic,
and low-osmolar or iso-osmolar contrast agents were shown to be less nephrotoxic in vitro. Microshower of cholesterol emboli are believed to occur in up to 50% of percutaneous interventions where a guiding catheter is passed through the aorta. Most of these showers are clinically silent; however, in approximately 1% of high-risk cases, acute cholesterol emboli syndrome (CES) can develop, which is manifested by AKI, mesenteric ischemia, decreased microcirculation to the extremities, and in some cases, embolic stroke.\(^\text{160}\) Finally, intrarenal vasoconstriction as a pathologic vascular response to contrast media, and perhaps an organ response to cholesterol emboli, is a final hypoxic/ischemic injury to the kidney.\(^\text{161}\) Hypoxia triggers activation of the renal sympathetic nervous system and results in a reduction in renal blood flow, especially in the outer medulla.\(^\text{160}\) There is disagreement about the direct vasoconstrictor or vasodilator effects in the kidney of contrast agents when given to animals.\(^\text{162}\) It is likely that in completely normal human renal blood vessels, contrast agents provoke a vasodilation and an osmotic diuresis. When there is vascular disease, endothelial dysfunction, and glomerular injury, however, contrast and the multifactorial insult of renal hypoxia provoke a vasoconstrictive response, and hence mediate, in part, an ischemic injury.\(^\text{162}\) The most important predictor of CIN is underlying renal dysfunction. The "remnant nephron" theory postulates that after sufficient chronic kidney damage has occurred, the remaining nephrons assume the remaining filtration load, require increased oxygen demands, and are more susceptible to ischemic and oxidative injury. Understanding the pathophysiology of CIN is key to devising a preventive strategy.

**Role of Renal Replacement Therapy.** Contrast media is removed by dialysis, but there is no clinical evidence that prophylactic dialysis reduces the risk of AKI, even when carried out within 1 hour or simultaneously with administration. Hemofiltration performed before and after contrast administration deserves further investigation given reports of reduced mortality and need for hemodialysis but the high cost and need for prolonged ICU care will also limit the utility of this prophylactic approach.\(^\text{163}\)

There are no currently approved pharmacologic agents for the prevention of CIN AKI. With iodinated contrast, the pharmacologic agents tested in small trials that deserve further evaluation include theophylline, statins, ascorbic acid, and prostaglandin E\(_2\).\(^\text{164}\) Although popular, N-acetylcysteine has not been consistently shown to be effective. Nine published meta-analyses document significant heterogeneity between studies and pooled odds ratios for N-acetylcysteine approaching unity.\(^\text{165}\) Importantly, only in those trials in which N-acetylcysteine reduced serum creatinine below baseline values because of decreased skeletal muscle production did renal injury rates seem to be reduced. Thus N-acetylcysteine seems to falsely lower creatinine and not fundamentally protect the kidney against injury. However, a recent study suggested that the use of volume supplementation with sodium bicarbonate together with N-acetylcysteine was more effective than N-acetylcysteine alone in reducing the risk of CIN. Furosemide, mannitol, and an endothelin-receptor antagonist are potentially detrimental.\(^\text{165}\)

### Acute Renal Failure After Stem Cell Transplantation

One of the most frequent complications of bone marrow transplant (BMT) is renal failure, with 5% to 15% of all BMT patients developing AKI and 5% to 20% of the survivors developing chronic renal failure (CRF).\(^\text{166}\) Hematopoietic stem cell transplantation is a common procedure for the treatment of malignancies and some nonmalignant hematologic disorders. The process of stem cell transfusion predisposes these patients to renal failure because of prior chemotherapy, irradiation, sepsis, and exposure to nephrotoxic agents. Complicating outcomes are newer conditioning regimens which allow for reduced intensity and nonmyeloablative regimens, thereby allowing patients with significant comorbidities to undergo transplantation with reduced morbidity and mortality. These have led to challenges in the ICU management of these patients, because they already have residual organ injury. A recent study of 29 pediatric patients who required CRRT in the ICU showed an almost 100% mortality at 6 months post-ICU admission due to transplant-related illness. This study demonstrated the management and ethical difficulties being posed by hematopoietic stem cell transplant patients becoming critically ill and requiring organ support at tertiary care centers. In contrast with the improving survival rates following stem cell transplantation, there are a greater numbers of children surviving and progressing to end-stage renal disease (ESRD). Some of these patients are being treated with renal transplantation.\(^\text{167}\)

A better understanding of the underlying histopathologic changes in renal morphology would perhaps lead to a better control of the renal insults that occur during the process of stem cell transfection. Some histopathology-based studies have shown a variety of findings in patients post-stem cell transplantation, including features of tubulitis and peritubular vasculitis. These studies also show that kidneys from adult patients who had grade III-IV GVHD were more likely to have tubulitis and peritubular capillaritis.\(^\text{168}\) Other studies have shown membranous glomerulonephritis and thrombotic microangiopathy to be common histologic features post-stem cell transplantation.\(^\text{169}\) However, there still remains a paucity of pediatric studies examining renal histopathology in patients posttransplantation.

### Urinary Tract Obstruction

Obstruction of urine flow may result in AKI, although unilateral obstruction rarely causes AKI unless there is a single kidney or disease in the other kidney. Both unilateral and bilateral ureteral obstruction is accompanied by an initial increase in RBF caused by afferent arteriolar vasodilation.\(^\text{170}\) Relaxation of the preglomerular capillary sphincter is mediated by the local release of vasodilatory prostaglandins.\(^\text{171}\) Administration of indomethacin, a cyclooxygenase inhibitor, results in a marked reduction in the GFR after a decrease in glomerular plasma flow and an increase in both afferent and efferent arteriolar resistances. This indicates an important role of vasodilatory prostaglandins in the maintenance of the GFR.

If the obstruction persists, RBF progressively decreases as afferent arteriolar resistance increases because of the overriding action of angiotensin II and thromboxane. This vasoconstriction may actually protect the kidney from damage during
the period of obstruction. Intratubular pressure rises after ureteral obstruction; this pressure is translated to the glomerulus as increased pressure in Bowman’s space. The contribution of this increased force opposing filtration to the decrease in the GFR is probably inconsequential because the intratubular pressure rise is transient. In addition, the elevation in Bowman’s space pressure is negated by an increase in the glomerular capillary pressure that increases the GFR. RBF is redistributed from the outer to the inner cortex and results in relative ischemia of the kidney medulla.

Various clinical causes of urinary tract obstruction are listed in Table 71–3. The most important factors determining recovery of kidney and tubular function are the degree and severity of the obstruction. Treatment consists of decompression of the urinary collecting system by removal of the obstruction or by urinary diversion. Relief of obstruction is accompanied by a marked diuresis resulting from increased RBF and abnormal tubular function. The increase in urine volume is related to a concentrating defect caused by loss of the medullary gradient and unresponsiveness of the kidney tubule to vasopressin. Hydrogen ion and potassium secretion may also be impaired, and the result is a distal type of kidney tubular acidosis with hyperkalemia.

This chapter has reviewed the major factors that contribute to the development of AKI, both in its oliguric and nonoliguric forms. Also indicated are the clinical settings in which AKI may occur. In addition, treatment modalities have been discussed. Clearly, the challenge in AKI is the development of novel therapeutic strategies that will more directly intervene in the disease process and which can have an impact on the cellular and metabolic mechanisms that contribute to kidney cell injury. Certain current investigations were discussed because they may lead to clinical trials during the next 10 years. Included among these agents are calcium channel blockers, adenine nucleotides, thyroid hormone, and oxyradical scavengers because they may modulate the full expression of kidney cell injury. Only with understanding of the pathophysiological mechanisms in AKI can these potential therapeutics be applied in a clinical setting to the care of pediatric patients.

References are available online at http://www.expertconsult.com.

### Table 71–3 Management of Electrolyte Abnormalities

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Management Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPERPHOSPHATEMIA</td>
<td></td>
</tr>
<tr>
<td>Moderate (≥2.1 mmol/L)</td>
<td>Avoid IV phosphate administration Administration of phosphate binder</td>
</tr>
<tr>
<td>Severe</td>
<td>Dialysis, CAVH, CVVH, CAVHD, or CVVHD</td>
</tr>
<tr>
<td>Hypocalcemia (≤1.75 mmol/L)</td>
<td>No therapy</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Calcium gluconate 50–100 mg/kg IV administered slowly with ECG monitoring</td>
</tr>
<tr>
<td>HYPERKALEMIA</td>
<td></td>
</tr>
<tr>
<td>Moderate and asymptomatic (≥6.0 mmol/L)</td>
<td>Avoid IV and oral potassium ECG and cardiac rhythm monitoring Sodium polystyrene sulphonate</td>
</tr>
<tr>
<td>Severe (&gt;7.0 mmol/L) and/or symptomatic</td>
<td>Same as above, plus: Calcium gluconate 100–200 mg/kg by slow IV infusion for life-threatening arrhythmias Regular insulin (0.1 U/kg IV) + D25 (2 mL/kg) IV Sodium bicarbonate (1–2 mEq/kg IV push) can be given to induce influx of potassium into cells. However, sodium bicarbonate and calcium should not be administered through the same line. Dialysis</td>
</tr>
<tr>
<td>Renal dysfunction (uremia)</td>
<td>Fluid and electrolyte management Uric acid and phosphate management Adjust renally excreted drug doses Dialysis (hemodialysis or peritoneal) Hemofiltration (CAVH, CVVH, CAVHD, or CVVHD)</td>
</tr>
</tbody>
</table>