Acute Kidney Injury

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Author Disclosure
Drs Selewski and Symons have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational Gap

The term *acute kidney injury* has replaced *acute renal failure* and represents a spectrum of clinically meaningful kidney damage.

Objectives

After completing this article, readers should be able to:

1. **Recognize and define the spectrum of acute kidney injury (AKI).**
2. **Understand the diagnostic approach and be able to differentiate the main causes of AKI.**
3. **Understand the complications of AKI and the treatment of a child with AKI.**

Introduction

Acute kidney injury (AKI), formerly called acute renal failure, is characterized by multiple abnormalities, including increases in serum creatinine and blood urea nitrogen, electrolyte abnormalities, acidosis, and difficulties with fluid management. We have come to realize that what was previously thought to be relatively minor damage to the kidney can have significant short-term effects on morbidity and mortality and potential long-term implications for the development of chronic kidney disease. Thus, the term *acute kidney injury* has replaced *acute renal failure*, suggesting the spectrum of kidney damage that can occur.

Definition

AKI is classically defined as an acute decrease in glomerular filtration rate, which results in an increase in serum creatinine. It is important to recognize the limitations of creatinine as a marker of AKI because an increase in creatinine can be delayed by as much as 48 hours after damage to the kidney has occurred. Despite this limitation, change in creatinine remains the gold standard for the diagnosis of AKI. An evolution in the definition of AKI to better understand, characterize, and study the disease spectrum, has occurred, which has sought to capture the clinical importance of even small variations in kidney function. In addition, previous definitions used in the literature were widely disparate; this lack of standardization made the understanding of AKI challenging. These circumstances have led to the development of 2 systems to define pediatric AKI that rely on changes in creatinine, estimated creatinine clearance, or urine output. The first of these definitions is the pediatric Risk, Injury, Failure, Loss, and End-stage (RIFLE) criteria, (1) which are modified from similar adult criteria. (2) The second is the Acute Kidney Injury Network (AKIN) definition, which relies on an increase in creatinine from a previous trough level. (3) The Kidney Disease: Improving Global Outcomes (KDIGO) consortium has put forth modifications to reconcile subtle differences in the adult AKIN and RIFLE criteria. (4) KDIGO is an international initiative composed of experts who, based on systematic review of evidence, develop and standardize clinical practice guidelines for children and adults with a variety of kidney diseases (including AKI). At

Abbreviations

ACE: angiotensin-converting enzyme
AKI: acute kidney injury
AKIN: Acute Kidney Injury Network
ANCA: antineutrophil cytoplasmic antibody
ATN: acute tubular necrosis
ECG: electrocardiogram
FE_{urea}: fractional excretion of urea
FE_{Na}: fractional excretion of sodium
KDIGO: Kidney Disease: Improving Global Outcomes
NSAID: nonsteroidal anti-inflammatory drug
RIFLE: Risk, Injury, Failure, Loss, and End-stage

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this time, in practice and research, the pediatric RIFLE and modified AKIN criteria are most frequently used to define AKI in children (Table 1).

Normal Renal Physiology

A basic knowledge of renal development and normal renal physiology is necessary to better understand the pathophysiologic mechanisms of AKI. The kidney is immature at birth and continues to develop early in life. Term neonates are born with a full complement of nephrons but have only approximately 25% of their adult glomerular filtration rates. The renal function of a healthy child progressively increases, reaching a mature glomerular filtration rate by age 2 years. Neonates have immature compensatory mechanisms to handle changes in renal blood flow and are not able to fully concentrate their urine.

Renal blood flow helps to drive a number of physiologic processes, including glomerular filtration, oxygen delivery to the kidneys, and solute or water reabsorption. Renal blood flow is under intricate control by a combination of hormones and reflex mechanisms. The afferent and efferent arterioles control renal blood flow to and from the glomerulus, respectively. The stretch of these arterioles (myogenic feedback) and delivery of sodium chloride sensed by the juxtaglomerular apparatus (tubuloglomerular feedback) drive a number of local and systemic hormone responses to low renal blood flow. In decreased renal perfusion, afferent arteriolar vasodilation occurs in response to prostaglandins (progtaglandins E and I), nitric oxide, and bradykinins to maintain glomerular filtration and renal blood flow. At the same time, the efferent arteriole is reflexively constricted by sympathetic nerve activation, endothelin, and activation of the renin-

Table 1. Schema for Defining Acute Kidney Injury

Stage	Change in Serum Creatinine[a]	Change in GFR	Urine Output
	RIFLE (2)		
At Risk of kidney injury	Increase 150%–200%	Decrease by 25%	<0.5 mL/kg/h for 8 hours
Injury to the kidney	Increase ≥200%–300%	Decrease by 50%	<0.5 mL/kg/h for 16 hours
Failure of the kidney	Increase ≥300%, serum creatinine ≥4 mg/dL (≥354 μmol/L) or dialysis	Decrease by 75%	<0.5 mL/kg/h for 24 hours or anuria for 12 hours
Loss of kidney function	Failure for >4 weeks		
End stage kidney disease	Failure for >3 months		
	Pediatric RIFLE (1)		
Stage	Change in estimated Creatinine Clearance[b]		Urine Output
At Risk of kidney injury	Decrease by 25%		<0.5 mL/kg/h for 8 hours
Injury to the kidney	Decrease by 50%		<0.5 mL/kg/h for 12 hours
Failure of the kidney	Decrease by 75% or <35 mL/min/1.73 m^2		<0.5 mL/kg/h for 24 hours or anuria for 12 hours
Loss of kidney function	Failure for >4 weeks		
End stage kidney disease	Failure for >3 months		
	KDIGO modifications of the Acute Kidney Injury Network (4)		
Stage	Change in Serum Creatinine[a]		Urine Output
I	Increase 0.3 mg/dL (27 μmol/L) during 48 hours[c] or increased 150%–200%		<0.5 mL/kg/hr for 8 hours
II	Increase ≥200%–300%		<0.5 mL/kg/hr for 16 hours
III	Increase ≥300%, serum creatinine ≥4 mg/dL (≥354 μmol/L) or dialysis or estimated GFR <35 mL/min/1.73 m^2 for those <18 years old		<0.5 mL/kg/h for 24 hours or anuria for 12 hours

GFR=glomerular filtration rate; KDIGO=Kidney Disease: Improving Global Outcomes; RIFLE=Risk, Injury, Failure, Loss, and End-stage.
[a]From previous trough creatinine.
[b]For the pediatric RIFLE, change in serum creatinine is the change in estimated creatinine clearance based on the Schwartz equation.
[c]The remainder of creatinine changes occur during 7 days.

angiotensin system, leading to the production of angiotensin II. These mechanisms work in concert to maintain glomerular filtration and renal blood flow. Disease states and certain medical interventions may interfere with these mechanisms, leading to negative effects on glomerular filtration. Further, some of these compensatory mechanisms, when stressed beyond normal parameters, may themselves lead to diminished urinary output and clinical findings one would associate with AKI.

With decreased renal perfusion, a number of these compensatory mechanisms also drive sodium and water reabsorption to increase extracellular volume. Increased activity of the renin-angiotensin system and production of angiotensin II (active in the proximal tubule) leads to increased secretion of aldosterone (active in the distal tubule), resulting in increased sodium reabsorption. Increased sympathetic nerve activity also drives sodium reabsorption. The reabsorption of urea and water is driven by antidiuretic hormone. The activity of these reflex mechanisms explains a number of the changes in urine electrolyte concentrations and clinical findings that help to differentiate the causes of AKI. The immaturity of these mechanisms in the neonate also explains why the diagnosis and evaluation of the cause of AKI in the neonate differs from that in older children.

Epidemiology

The epidemiology of AKI has evolved over the years and reflects the patient population under study. In developing countries the most common causes of AKI continue to be volume depletion, infection, and primary renal diseases (hemolytic uremic syndrome, glomerulonephritis). In developed countries, volume depletion and primary renal disease remain common causes of AKI in previously healthy children. In hospitalized children in developed countries, particularly in tertiary care centers, there has been a shift in the etiology of AKI from primary renal disease to secondary causes of AKI that are often multifactorial in nature and often complicate another diagnosis or its treatment (eg, heart disease, sepsis, and nephrotoxic drug exposure). (5) Despite this shift in epidemiology, an ordered approach to the diagnosis of AKI divides the potential origins into prerenal, intrinsic, and postrenal causes.

Pathophysiology of AKI

Prerenal AKI

Prerenal AKI results from a decrease in renal blood flow, leading to hypoperfusion (Table 2). The underlying pathophysiologic states may be due to a decrease in effective circulating volume, loss of vascular tone, or decreased cardiac output or blood delivery to the kidneys. Renal losses, gastrointestinal tract losses, or hemorrhage can lead to direct reduction in volume and decreased renal perfusion. Alternatively, a redistribution of fluid may occur from either reduced oncotic pressure within the blood (low albumin from liver disease, nephrotic syndrome, or protein losing enteropathy) or increased leak from vessels (systemic inflammatory response syndrome or sepsis), leading to suboptimal renal perfusion. Systemic vasodilation or poor vascular tone complicates a number of illnesses in critically ill children and may result in hypoperfusion of the kidneys. Finally, there may be a decrease in the delivery of blood to the kidneys because of an overall decrease in cardiac output (underlying heart disease or myocarditis) or increased resistance to flow (abdominal compartment syndrome or renal artery stenosis). In practice, previously healthy children frequently present with a decreased effective circulating volume from a single cause, whereas chronically ill or hospitalized children may have multifactorial processes.

As noted above, low renal blood flow stimulates compensatory mechanisms, including increased sympathetic tone, activation of the renin-angiotensin system, release of antidiuretic hormone, and local paracrine activities (prostaglandin release). In the prerenal state, the afferent arterioles vasodilate in response to the local effects of prostaglandins in an effort to maintain renal blood flow and glomerular filtration. Consequently, nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, in volume-depleted children may worsen AKI by preventing this compensatory afferent arteriolar vasodilation. At the same time, angiotensin II causes efferent arteriolar constriction. Interruption of this compensatory mechanism by angiotensin-converting enzyme (ACE) inhibitors predisposes patients to prerenal AKI. The effects of renin-angiotensin system activation and antidiuretic hormone release result in increased sodium and urea reabsorption, respectively. The reabsorption of sodium, urea, and water leads to oliguria and the characteristic urine findings in prerenal AKI (Table 3).

Neonates are a special group when considering prerenal AKI. Neonates have increased insensible losses because of a high body surface area to mass ratio, which can be exacerbated by the use of radiant warmers for critically ill newborns. Neonates are further at risk for prerenal AKI due to immature compensatory mechanisms, including poor urine concentrating abilities. This inability to concentrate urine explains why AKI in neonates is often nonoliguric, making its recognition more difficult.

Patients with sickle cell disease are predisposed to prerenal AKI because of a number of pathophysiologic

Table 2. Causes of Prerenal Acute Kidney Injury

- Decreased effective circulating volume
  - Reduction in blood volume
    - Gastrointestinal losses (eg, gastroenteritis)
    - Renal losses (eg, diabetes insipidus and diuretic exposure)
    - Hemorrhage (eg, gastrointestinal bleed and trauma)
    - Increased losses through the skin (eg, burn patients)
  - Redistribution of blood volume
    - Decreased oncotic pressure
      - Cirrhosis or liver disease
      - Nephrotic syndrome
      - Malnutrition
      - Protein-losing enteropathy
    - Increased leak from vessels (systemic inflammatory response syndrome/sepsis)
- Loss of vascular tone (systemic vasodilation)
  - Sepsis
  - Anaphylaxis
- Decreased blood delivery to the kidneys
  - Decreased cardiac output
    - Heart disease (congenital heart disease, heart failure)
- Increased resistance to flow
  - Renal artery stenosis
  - Abdominal compartment syndrome

mechanisms inherent to the disease that may affect the kidney. The renal medulla represents an area of the kidney at risk in sickle cell disease because of a low oxygen concentration and high tonicity; this predisposes patients to sickling. Repeated episodes of sickling in the renal medulla result in vascular congestion and the loss of vasa recta of the juxtaglomerular nephrons, which can lead to chronic interstitial fibrosis and urine concentrating defects. In early childhood, the urinary concentrating defects frequently are reversible with treatment of the sickle cell disease but can progress to chronic concentrating defects over time.

Intrinsic AKI

Intrinsic AKI refers to direct renal parenchymal damage or dysfunction. Categories include AKI associated with tubular, interstitial, glomerular, or vascular damage and nephrotoxin exposure (Table 4).

The most common cause of intrinsic AKI in tertiary care centers is transformation of prerenal AKI to acute tubular necrosis (ATN) after prolonged hypoperfusion. The areas of the kidney that are most susceptible to damage with prolonged renal hypoperfusion include the third segment of the proximal tubule (high energy requirement) and the region of the thick ascending limb of the loop of Henle located within the medulla (low oxygen tension in the medulla). The damage seen from prolonged hypoperfusion can range from mild tubular injury to cell death. As cellular necrosis occurs, debris may build up in the tubules and further block tubular flow. Tubular dysfunction, a frequent hallmark of ATN, will not be evident during periods of oliguria but may become apparent during the recovery phase.

In previously healthy children, glomerular and vascular causes of intrinsic AKI are more common. Where there is concern for glomerulonephritis, the clinical presentation and timing often suggest the origin, including isolated glomerulonephritides (eg, postinfectious glomerulonephritis) and multisystem immune complex–mediated processes that involve the kidney (eg, systemic lupus erythematosus). Vascular causes of intrinsic AKI include microangiopathic processes (hemolytic uremic syndrome and thrombotic thrombocytopenic purpura) and systemic vasculitides that involve larger vessels.

Acute interstitial nephritis occurs after exposure to an offending agent, such as certain medications, including antibiotics, proton pump inhibitors, NSAIDs, and diuretics. Signs and symptoms may develop 3 to 5 days after a second exposure to as long as weeks to months after an initial exposure. Drugs can cause AKI in ways other than acute interstitial nephritis. Nephrotoxin

Table 3. Comparison of Laboratory Findings in AKI

Test	Prerenal AKI	Intrinsic AKI
Urine specific gravity	>1.020	≤1.010
Urine sodium, mEq/L	<20	>40
Fractional excretion of sodium	<1% (neonates <2%)	>2% (neonates >2.5%)
Fractional excretion of urea	<35%	>50%
Urine osmolality, mOsm/kg	>500	<350
Urea nitrogen–creatinine ratio	>20	10–15

AKI=acute kidney injury.

exposure is an increasingly common cause of intrinsic AKI, particularly in hospitalized patients. As previously mentioned, drugs such as NSAIDs and ACE inhibitors can contribute to AKI by inhibiting renal vascular autoregulation. Other common drugs implicated in AKI include aminoglycosides, amphotericin, chemotherapeutic agents (cisplatin, ifosfamide, and methotrexate), and calcineurin inhibitors (cyclosporine and tacrolimus). Radiocontrast agents are a significant cause of nephrotoxin-related AKI; newer iso-osmolar agents are somewhat less nephrotoxic, but the risk remains. In instances of massive hemolysis or rhabdomyolysis, endogenous elements, such as myoglobin and hemoglobin, can obstruct tubules and/or cause direct toxic effects to the kidney.

Postrenal AKI

Postrenal AKI results from obstructive processes that block urine flow. Acquired causes of urinary tract obstruction include those that result from local mass effect (bilateral ureteral obstruction by a tumor), renal calculi, or clots within the bladder.

The Renal Angina Concept and Early Identification of AKI

An important developing paradigm in the study and treatment of AKI is the idea of *renal angina*, a term used to describe a high-risk state that occurs before AKI. (6) Earlier recognition of a prerenal state defines a period before significant parenchymal damage (eg, the development of ATN) where AKI can be reversed. Furthermore, patients who are identified as being at risk may have nephrotoxic medications held or dosages adjusted to potentially prevent the development of intrinsic AKI. Research using renal angina scoring systems is an active area that aims to identify patients at risk for AKI. Concurrently, investigation is under way to study novel biomarkers (urine neutrophil gelatinase–associated lipocalin and urine kidney injury molecule 1) that will allow for the earlier identification of kidney injury in critically ill children (often up to 48 hours before an increase in creatinine) to allow prevention and potentially earlier intervention.

Diagnosis of AKI

A detailed history and physical examination are invaluable for children who develop AKI. Quantifying the urine output during the previous several days may provide insight to the cause and severity of the episode of AKI and serves to categorize the event as oliguric (defined as urine output <1 mL/kg/h) or nonoliguric. Systematic

Table 4. Causes of Intrinsic AKI

- Tubular injury
  - Acute tubular necrosis
    - Urine microscopy: muddy brown granular casts
    - Commonly from transformation of prerenal AKI
    - Drugs associated with acute tubular necrosis: aminoglycosides, calcineurin inhibitors, amphotericin, chemotherapeutic agents (platinum based), methotrexate, intravenous contrast
    - Toxin mediated: myoglobinuria, hemoglobinuria, heavy metals
- Glomerulonephritis
  - Hematuria, proteinuria, red blood cell casts on urinalysis
  - Postinfectious glomerulonephritis
    - Classically 2–3 weeks after upper respiratory tract infection, 4–6 weeks after skin infection
    - Low C3, normal C4
    - Dark brown or "smoky" urine
  - IgA nephropathy
    - Gross hematuria soon after (1–3 days) an upper respiratory tract infection
    - Normal C3, C4
  - Systemic lupus erythematosus
    - Anti–double-stranded DNA associated with renal disease; antinuclear antibody positive
    - Low C3 and low C4
    - Associated systemic symptoms (eg, arthritis, discoid rash, malar rash, photosensitivity, serositis)
  - Membranoproliferative glomerulonephritis
    - Low C3; normal or low C4
    - Uncommon pediatric condition
  - Goodpasture syndrome
    - Hemoptysis
    - Anti–glomerular basement membrane antibody
  - Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
    - Respiratory tract involvement including upper airway (sinus) and lungs
    - Cytoplasmic antineutrophil cytoplasmic antibody
  - Microscopic polyangiitis
    - Lung involvement
    - Perinuclear antineutrophil cytoplasmic antibody
  - Eosinophilic granulomatosis (formerly Churg-Strauss syndrome)
    - Associated with sinusitis, asthma, and skin findings
    - Peripheral eosinophilia
    - Perinuclear antineutrophil cytoplasmic antibody
  - Rapidly progressive glomerulonephritis
    - Progressive loss of renal function over short period of time
    - Medical emergency warranting renal biopsy
    - Typified by crescents on renal biopsy
    - Potentially caused by any of the glomerulonephritides

Continued

Table 4. (Continued)

Interstitial nephritis
Allergic interstitial nephritis
Frequently drug induced (classically antibiotics; proton pump inhibitors an increasing cause)
Classic triad (fever, eosinophilia, and rash) in only 15%
Urinalysis may reveal eosinophils, white blood cell casts, or red blood cell casts or may be bland
May also result from systemic disease capable of causing acute interstitial nephritis, including sarcoidosis, Sjögren disease, infections, and renal transplant rejection
Hemolytic uremic syndrome
Microangiopathic hemolytic anemia (schistocytes on peripheral smear), thrombocytopenia, elevated lactate dehydrogenase
Diarrhea-positive, classic, Shiga toxin–producing *Escherichia coli* hemolytic uremic syndrome
Occurs within several days after infection with toxin-producing organism
Colitis or bloody diarrhea
Usually self-resolves
Diarrhea-negative hemolytic uremic syndrome
Nonintestinal infections (*Streptococcus pneumoniae* and human immunodeficiency virus)
Medication or therapy related (calcineurin inhibitors, radiation therapy, and stem cell transplantation)
Disorders of complement regulation (deficiencies of factor H, factor I, and membrane cofactor protein)

AKI=acute kidney injury.

evaluation of potential prerenal, intrinsic, and postrenal causes is key to diagnosing the origin of AKI. Frequently, the history will provide insight into causes or risk factors for prerenal AKI, including decreased circulatory volume (gastroenteritis and hemorrhage), redistribution of circulatory volume (edematous states, nephrotic syndrome, and sepsis), decreased cardiac output (heart disease), or increased resistance to blood flow (abdominal compartment syndrome and renal artery stenosis). In previously healthy children, the history and physical examination may offer clues (Table 4) to the underlying intrinsic renal origin, including volume depletion, recent viral illness or sore throat (possibly consistent with acute glomerulonephritis), rashes, swollen joints (suggesting systemic disorders such as lupus), hematuria, or medication exposures. In newborns with a suspected obstruction, a good prenatal history is important. For example, abnormalities on fetal ultrasonogram, including enlarged bladder, hydronephrosis, or decreased amniotic fluid, may suggest posterior urethral valves in a male infant. When evaluating AKI, it is important to remember that an increase in creatinine typically occurs up to 48 hours after renal injury and may reflect events that occurred 2 to 3 days earlier. Therefore, it is important to review episodes of hypotension, hypoxia, sepsis, surgery, contrast exposures, and drug exposures that occur 48 to 72 hours before the episode of AKI becomes apparent.

As part of the initial evaluation for AKI, patients should have the following tests performed: basic electrolyte panel, serum creatinine measurement, urinalysis, urine sodium measurement, urine urea measurement, urine creatine measurement, urinalysis, and a renal ultrasound study. Frequently, urine studies will allow differentiation between prerenal AKI and intrinsic AKI (eg, ATN). Typical laboratory findings for prerenal AKI include a normal urinalysis result, concentrated urine (osmolality >500 mOsm/kg [>500 mmol/kg]), fractional excretion of sodium (FE_{Na}) less than 1% (<2% in neonates), fractional excretion of urea (FE_{urea}) less than 35%, urine sodium less than 20 mEq/L (<20 mmol/L), and urea nitrogen to creatinine ratio greater than 20 (Table 3). A loss of urine concentrating ability is classically seen in ATN and results in the characteristic urine studies that differentiate it from prerenal AKI (Table 3). Urinalysis with accompanying urine microscopy can be illuminating and point toward particular diagnostic categories. Muddy granular casts on microscopy suggest ATN; red blood cell casts suggest glomerulonephritis. A urinalysis positive for blood on dipstick evaluation without evidence of red blood cells on microscopy should raise concerns for hemoglobinuria (hemolysis) or myoglobinuria (rhabdomyolysis).

The presence of hematuria, proteinuria, and/or red blood cell casts in the right clinical scenario should raise concern for possible glomerulonephritis. In the context of a recent upper respiratory tract infection, one should consider the diagnosis of postinfectious glomerulonephritis (classically with pharyngitis 2-3 weeks earlier or skin infections 4-6 weeks earlier) and should evaluate serum complements (low C3 and normal C4). In patients with a more recent upper respiratory tract infection (2-3 days) with gross hematuria on urinalysis, one must consider IgA nephropathy (normal complement levels). A urinalysis consistent with glomerulonephritis in the context of the appropriate systemic symptoms (eg, rash and arthritis) may point toward systemic lupus erythematosus (low C3 and low C4) and may warrant further antibody testing (antinuclear and anti–double-stranded DNA antibodies). If there is involvement of the pulmonary system

(cough, infiltrate on radiographs, and hemoptysis) and evidence of active glomerulonephritis, the pulmonary renal syndromes should be considered. These syndromes include granulomatosis with polyangiitis (formerly Wegener granulomatosis and cytoplasmic antineutrophil cytoplasmic antibody [ANCA]), microscopic polyangiitis (perinuclear ANCA), eosinophilic granulomatosis (formerly Churg-Strauss Syndrome and perinuclear ANCA), and Goodpasture syndrome (anti–glomerular basement membrane antibody). A more detailed description of glomerulonephritides is beyond the scope of this review. In the setting of a classic clinical and laboratory presentation of postinfectious glomerulonephritis, a renal biopsy is not warranted, but to confirm the diagnosis and guide treatment of the remaining glomerulonephritides, a biopsy is necessary. Each of the glomerulonephritides is capable of causing rapidly progressive glomerulonephritis, which is defined by rapidly increasing blood urea nitrogen and creatine levels. In this scenario, a renal biopsy and treatment are immediately warranted because irreversible renal injury may develop without prompt intervention.

The classic triad for allergic interstitial nephritis of fever, rash, and eosinophilia is not often seen in the modern era and is observed in less than 15% of patients. This is due to a change over time in the most common offending agents. In patients with suspected interstitial nephritis, there is frequently bland urine sediment that does not have red blood cell casts but may have white blood cell casts present. The classic finding is urine eosinophils, although this is not universal. There can be varying degrees of proteinuria; NSAID-associated interstitial nephritis is capable of causing nephrotic range proteinuria. A renal biopsy is necessary to confirm the diagnosis.

If a patient has a recent history of diarrheal illness, low platelet counts, and hemolytic anemia with AKI, one should consider hemolytic uremic syndrome. In the appropriate setting, a peripheral blood smear with schistocytes is confirmatory. In recent years there has been an increase in the recognition of atypical hemolytic uremic syndrome caused by nondiarrheal infections (eg, *Streptococcus pneumonia* or human immunodeficiency virus) or genetic abnormalities in complement regulatory components (eg, factor H or factor I); a high index of suspicion is necessary, and specialty consultation is warranted.

Imaging plays a small role in the diagnosis of intrinsic renal disease. Kidney size, measured by renal ultrasonography, can provide information about the duration of the disease. Larger kidneys point toward an acute process that involves active inflammation. Kidneys that are particularly small for age may suggest a more chronic process. Often the kidneys will demonstrate increased echogenicity in the setting of AKI, which is a nonspecific finding. A Doppler evaluation of the renal vasculature is an important initial step if there are concerns of renal artery stenosis, but if the result of the evaluation is negative and concern of renal artery stenosis remains, further studies should be considered in consultation with a pediatric nephrologist. Imaging by renal ultrasonography to demonstrate hydronephrosis is the most important initial step in the diagnosis of an obstructive process and may provide clues to the anatomical location of the obstruction. For example, bilateral hydronephrosis suggests a more distal obstruction. If an obstructive process is diagnosed, one should relieve the obstruction immediately.

Management of AKI

The most important management principle for children with AKI is prevention. In both the outpatient settings and the hospital this can be achieved by identifying children who are at risk for developing AKI. In outpatient pediatrics it is important to ensure adequate hydration and be mindful of medications children may take in the short term (NSAIDs) or long term (diuretics and ACE inhibitors) that increase the risk of AKI. In hospitalized patients, it is also important to be mindful of daily volume status, nephrotoxic medications, or nephrotoxic exposures. For patients at risk for developing AKI, it is important that the team evaluates all potentially nephrotoxic medications, reviews prescribed doses, actively considers alternatives, and monitors levels of medications such as gentamicin and vancomycin.

Fluid and Electrolyte Management

The initial step in the treatment of children who present with oliguria, hypotension, or instability is to restore intravascular volume. An initial 20-mL/kg bolus of isotonic fluids should be given rapidly (in minutes if necessary in the setting of shock). Isotonic fluids that may be used for short-term volume expansion include normal saline, lactated Ringer solution, albumin, and packed red blood cells. The choice of fluid depends on the clinical scenario, but normal saline is most commonly used. This treatment should be repeated according to the Pediatric Advanced Life Support algorithms. (7) In children with underlying or suspected cardiac disease, smaller initial fluid boluses (10 mL/kg) may be given repeatedly, as indicated, for longer periods; this will permit appropriate resuscitation while reducing the risk of unintentional volume overload, which could be problematic in the setting of heart disease. During the fluid resuscitation process, repeated reevaluation is necessary for all children to monitor for signs of fluid

overload (pulmonary or peripheral edema) and response (improved vital signs and urine output).

After adequate fluid resuscitation, early initiation of vasopressor support may be indicated; vasopressor support may be required sooner for a child who presents with obvious fluid overload. Studies in adults evaluating low renal dose dopamine have found no benefit; dopamine at these low doses does not increase or preserve urine output or improve the outcome of AKI. Vasopressor support should be provided to ensure adequate renal perfusion with the choice of vasopressor based on the clinical scenario. Once the patient has been adequately fluid resuscitated, one may consider a trial of diuretics (furosemide) if the patient remains oliguric. The literature reports mixed results for diuretics in patients with oliguria. The literature surrounding the use of mannitol is inconclusive, and this medication may be associated with serious adverse effects (increased serum osmolarity, pulmonary edema, and AKI). The use of mannitol to ensure urine output is not recommended.

In children who remain oliguric after intravascular volume resuscitation, conservative fluid management may be necessary. In these children, one may restrict fluid to insensible fluid losses (300-500 mL/m^2/d). Individuals with AKI are subject to a number of electrolyte disturbances, including dysnatremias, hyperkalemia, acidosis, and hyperphosphatemia. Typical sodium requirements in healthy children are 2 to 3 mEq/kg/d, but management should be individualized in children with AKI, with adjustments made based on frequent monitoring. Excessive sodium input should be avoided to prevent hypertension and other complications of sodium overload. Potassium and phosphorous should be withheld from fluids in these patients to avoid the risks of iatrogenic overload. Potassium and phosphorous will need to be replaced intermittently as necessary because low levels of potassium (cardiac conduction abnormalities) and phosphorous (poor muscle contraction) can have detrimental implications in critically ill children. Inability to maintain biochemical or fluid balance in AKI patients represents an indication for renal replacement therapy.

Hyperkalemia remains one of the most recognized complications of AKI. The presenting symptoms of hyperkalemia are frequently nonspecific, including fatigue, weakness, tingling, nausea, and even paralysis. For this reason, limiting potassium intake and diligent monitoring of laboratory test results in children with AKI are important. The most serious manifestation of hyperkalemia is cardiac conduction abnormalities and arrhythmias. Electrocardiographic (ECG) changes may be noted when potassium levels are 6.5 to 7 mEq/L (6.5-7 mmol/L), but there can be significant variability, depending on the clinical circumstances. In pathophysiologic states of increased potassium release from cells (tumor lysis syndrome and rhabdomyolysis), ECG changes may occur at lower levels. The potassium levels that result in ECG changes fluctuate with the underlying pathophysiologic mechanisms, acuity, and associated electrolyte abnormalities (hypocalcemia). The ECG changes are typified first by peaked T waves. Other ECG changes may include widened QRS, flattened p waves, and prolonged PR interval. Untreated hyperkalemia may lead to life-threatening arrhythmias.

In patients with potassium levels greater than 6 mEq/L (>6 mmol/L), one should obtain an ECG. If potassium levels are 5.5 to 6.5 mEq/L (5.5-6.5 mmol/L) and the patient has an appropriate urine output without any abnormalities on ECG, one may consider treatment with a resin that binds potassium in the gut (sodium polystyrene sulfonate) or a saline bolus with furosemide to reverse any upward trend and slowly bring the potassium back to a more normal range. If there are changes on ECG, a potassium level greater than 7 mEq/L (>7 mmol/L), or a rapidly increasing potassium level in a child with high cell turnover states (eg, tumor lysis and rhabdomyolysis), hyperkalemia should be viewed as life threatening and treated accordingly. Initial rapid treatment measures include calcium gluconate, which acts to stabilize the cardiac membrane potential and limit the risk of arrhythmia but does not lower potassium levels. This may be followed by the administration of sodium bicarbonate, β_2-agonists, and/or insulin with glucose, all of which cause intracellular movement of potassium and subsequent reduction of blood levels, but these do not remove potassium from the body. Sodium bicarbonate may be considered if there is an acidosis associated with the hyperkalemia. Recent trials evaluating sodium bicarbonate therapy in adults with hyperkalemia have not reported efficacy, but this has not been studied in children. Although sodium bicarbonate may be given as part of treatment for hyperkalemia, it should not be the sole therapy. Sodium bicarbonate theoretically acts by shifting potassium intracellularly as it is exchanged for hydrogen ions. β_2-agonists, such as albuterol, can be given via nebulizer. This therapy has been reported to lower potassium by 1 mEq/L (1 mmol/L) and is well tolerated but may need to be avoided in children with cardiac issues because tachycardia is a common adverse effect of β_2-agonist therapy. Insulin given with glucose drives potassium into cells by increasing sodium and potassium adenosine triphosphatase activity. In conjunction with these various methods, efforts should be made to remove potassium from the body, including loop diuretics with fluid bolus and

sodium polystyrene sulfonate. Sodium polystyrene sulfonate should be avoided in neonates or children with underlying bowel disease. If these measures fail, renal replacement therapy should be considered.

The acidosis seen in AKI is characterized by an elevated anion gap, which reflects an inability of the kidneys to excrete acid or reabsorb bicarbonate. With the exception of the treatment of hyperkalemia, use of bicarbonate should be reserved for severe acidosis and administered with great care. Correction of acidosis with bicarbonate can lead to a lowering of ionized calcium (functional hypocalcemia) as hydrogen ions are exchanged on plasma proteins for calcium, which can result in tetany.

Because of a suboptimal glomerular filtration rate in the setting of AKI, hyperphosphatemia can develop, particularly with increased cell turnover (tumor lysis syndrome and rhabdomyolysis). In most circumstances, hyperphosphatemia can be managed conservatively by limiting intake. In patients with hyperphosphatemia, it is important to diligently monitor calcium and ionized calcium levels because ionized hypocalcemia may occur as a result of intravascular binding to excess phosphorus.

Medications

In children with AKI drug clearance may be reduced; daily evaluation of patient medication lists is imperative to avoid iatrogenic drug overdose. Once the kidney function decreases to 50% of normal, most renally excreted drugs will require dose adjustment. Early in episodes of evolving AKI, bedside estimates of kidney function can lead to overestimation of the glomerular filtration rate; careful clinical judgment is required. One should evaluate the appropriateness of administering nephrotoxic medications on a daily basis, consider alternatives, and closely monitor drug levels as able when nephrotoxic medications are unavoidable. When children begin renal replacement therapy, many medication doses must be adjusted further (particularly antibiotics). During episodes of AKI, it is important to manage medication adjustments in a team-based approach that involves pediatric nephrologists and specialized pharmacists.

Nutrition

Typically, AKI is marked by a catabolic state, particularly in critically ill children. The protein requirements in these children may be as high as 3 g/kg/d of amino acids with an accompanying caloric need of 125% to 150% that of healthy children and infants. One should not limit protein delivery as a method to control blood urea nitrogen levels; to ensure adequate protein intake, one may accept a blood urea nitrogen level of 40 to 80 mg/dL (14.3-28.6 mmol/L). If adequate nutrition and metabolic balance cannot be obtained through conservative measures, this may be an indication for renal replacement therapy.

Renal Replacement Therapy

Renal replacement therapy is considered when conservative measures to manage AKI have failed or are unlikely to be sufficient. Indications for renal replacement therapy include volume overload (10%-20% fluid excess), severe acidosis, hyperkalemia, uremia (typically blood urea nitrogen >100 mg/dL [>35.7 mmol/L] or symptomatic), or an inability to provide adequate nutrition in patients with renal dysfunction. In recent years the importance of volume overload in critically ill children has become apparent, and the degree of fluid overload at the initiation of renal replacement therapy has been found to be associated with increased mortality. (8)(9)

Modalities of renal replacement therapy include peritoneal dialysis, hemodialysis, and continuous renal replacement therapy. The correct choice of modality is a reflection of center-specific expertise, patient characteristics, and clinical situation. Peritoneal dialysis is well tolerated in critically ill children and relatively easy to perform but does not provide the same rate of clearance or ability to manage volume as other modalities. Intermittent hemodialysis performed during 3 to 4 hours provides better clearance but is generally not as well tolerated in critically ill children or children with unstable disease; total daily fluid removal during a short intermittent session can be challenging in these patients. There has been a shift toward continuous renal replacement as the modality of choice in critically ill children. This mode allows for continuous volume and metabolic control spread during 24 hours. Benefits include increased tolerance of fluid removal and improved ability to provide nutrition. Intermittent hemodialysis and peritoneal dialysis remain viable options for those patients who require renal replacement but are not critically ill.

Progression to Chronic Kidney Disease and Follow-up

Recent literature has indicated that critically ill children who are discharged after an episode of AKI are at increased risk of chronic kidney disease later in life. (10)(11) Long-term follow-up of these patients is important. The optimal follow-up plan for these children is not clear. In more severe cases of AKI that require renal replacement therapy, follow-up should initially be with specialists. In milder cases, one may consider yearly blood pressure checks and urinalysis.

Summary

- On the basis of research evidence and consensus, the term *acute kidney injury* (AKI) has replaced *acute renal failure*, suggesting the spectrum of kidney damage that can occur (Table 1). (1)(2)(3)(4)
- On the basis of research evidence, in developing countries the most common causes of AKI continue to be volume depletion, infections, and primary renal diseases.
- On the basis of research evidence and expert opinion, in developed countries volume depletion and primary renal disease remain common causes of AKI in previously healthy children.
- On the basis of research evidence, in hospitalized children, particularly in tertiary care centers, there has been a shift in the etiology of AKI from primary renal disease to secondary causes of AKI that are often multifactorial in nature and often complicate another diagnosis or its treatment (heart disease, sepsis, and nephrotoxic drug exposure). (1)(5)
- On the basis of expert opinion, an ordered approach to the diagnosis of AKI divides the potential origins into prerenal, intrinsic renal, and postrenal causes.
- On the basis of research evidence, expert opinion, and consensus, patients with AKI are subject to a number of fluid and electrolyte disturbances, including hypervolemia, dysnatremias, hyperkalemia, acidosis, and hyperphosphatemia.
- On the basis of research evidence, expert opinion, and consensus, indications for renal replacement therapy include volume overload (10%–20% fluid excess), acidosis, hyperkalemia, uremia (typically blood urea nitrogen >100 mg/dL [>35.7 mmol/L] or symptomatic), or an inability to provide adequate nutrition in patients with renal dysfunction. (8)(9)
- On the basis of research evidence and expert opinion, recent literature has reported that critically ill children who are discharged after an episode of AKI are at increased risk for chronic kidney disease later in life. Long-term follow-up of these patients is important, but the optimal follow-up plan remains unclear. (10)(11)

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PIR Quiz Requirements

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1. An 8-month-old, 8-kg infant is brought in by his parents to the emergency department because of reduced urine output after viral gastroenteritis. On examination, the patient is mildly tachycardic and has dry mucous membranes but normal capillary refill. You prescribe oral rehydration but admit the patient for observation and monitor urine output for 12 hours. Of the following, which criterion would be sufficient to diagnose acute kidney injury in this infant?

   A. Serum creatinine level of 0.4 mg/dL (35 μmol/L) on baseline assessment.
   B. Urine output of 150 mL in 12 hours.
   C. Blood urea nitrogen level of 12 mg/dL (4.3 mmol/L) after 12 hours of observation.
   D. Urine output of 40 mL in 12 hours.
   E. Blood urea nitrogen level of 15 mg/dL (5.4 mmol/L) at baseline assessment.

2. You are evaluating a male newborn in the nursery. The neonatal nurse notes reduced urine output in the first 12 hours of life. On reviewing the medical record, you note that child had a prenatal ultrasonogram that demonstrated an enlarged bladder. Of the following, which diagnosis best explains the findings above?

   A. Infantile nephrotic syndrome.
   B. Juvenile nephronophthisis.
   C. Posterior urethral valves.
   D. Renal artery stenosis.
   E. Ureteropelvic junction obstruction.

3. A patient with cystic fibrosis is transferred to the intensive care unit with pneumonia and respiratory distress. Previously, the patient had received ketorolac and tobramycin. In the intensive care unit, you document a markedly reduced urine output. Of the following, which finding is more consistent with intrinsic acute kidney injury as opposed to prerenal azotemia?

   A. Blood urea nitrogen to creatinine ratio of 25.
   B. Fractional excretion of sodium of 0.5%.
   C. Urine osmolality of 800 mOsm/kg (800 mmol/kg).
   D. Urine sodium of 60 mEq/L (60 mmol/L).
   E. Urine specific gravity of 1.030.

4. A 12-year-old boy has been admitted to the ward for abdominal pain and a creatinine level of 2.0 mg/dL (177 μmol/L). He underwent a liver transplantation 1 year ago and since that time has had multiple admissions for infection and rejection. He is taking several medications. On examination, he is in no acute distress, although he has mild jaundice. Laboratory studies demonstrate the following: creatinine, 2.0 mg/dL (177 μmol/L); blood urea nitrogen, 20 mg/dL (7.1 mmol/L); alanine aminotransferase, 80 U/mL; hematocrit, 37% (0.37); and white blood count, 8,900/μL (8.9×10^9/L). His urine sodium level is 60 mEq/L (60 mmol/L), and urine microscopy reveals granular casts. Of the following, which medication is most likely to cause the presentation above?

   A. Azathioprine.
   B. Cyclosporine.
   C. Fluconazole.
   D. Furosemide.
   E. Prednisone.

5. An 8-year-old girl presents with headache and reddish urine. On further questioning, you note she had a respiratory infection and sore throat 3 weeks ago, but the symptoms resolved and she never came in for evaluation. On examination of the urine, you note gross hematuria. Microscopic examination demonstrates red

blood cell casts. Of the following tests, which would be the most consistent with a diagnosis of poststreptococcal glomerulonephritis?

A. Low blood urea nitrogen level.
B. Low C3 level.
C. Low C4 level.
D. Low urine sodium level.
E. Low serum IgA level.