Acute Kidney Injury

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EDUCATIONAL GAP

The term acute kidney injury (AKI) has replaced the term acute renal failure and represents a spectrum of clinically meaningful kidney damage. AKI occurs commonly in hospitalized children and has been shown to adversely impact outcomes across populations. It is important for clinicians to understand the epidemiology, risk factors, pathophysiology, differential diagnosis, diagnostic evaluation, and treatment of the complications associated with AKI.

PRACTICE GAP

Acute kidney injury (AKI) remains underrecognized and underdiagnosed in hospitalized children. Nephrotoxic medications represent a modifiable risk factor for AKI. Adequate follow-up of children with AKI should be ensured because they are at risk for sequelae (including chronic kidney disease, hypertension, recurrent AKI, and proteinuria).

OBJECTIVES After completing this article, readers should be able to:

1. Recognize and define the spectrum of acute kidney injury (AKI).
2. Describe the etiologies of AKI and the evaluation of children with AKI.
3. Describe treatment of the common complications of AKI, including electrolyte derangements, fluid management, nutritional support, and kidney support therapy.

ABSTRACT

Acute kidney injury (AKI) has been shown to occur commonly in hospitalized children. AKI is associated with multiple complications, including elevated blood urea nitrogen level, electrolyte dyscrasias, acidosis, and fluid balance disorders. During the past 10 years, multiple multicenter studies have shown that AKI occurs commonly and is associated with adverse outcomes across a variety of populations in pediatrics. This state-of-the-art review provides a detailed overview and update on AKI, including definition, epidemiology, outcomes, differential diagnosis, diagnostics, and management of complications.

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ABBREVIATIONS

ADH antidiuretic hormone
AIN acute interstitial nephritis
AKI acute kidney injury
ANCA antineutrophilic cytoplasmic antibody
BUN blood urea nitrogen
CKD chronic kidney disease
CRS cardiorenal syndrome
ECG electrocardiography
EHR electronic health record
FE urea fractional excretion of urea
FE Na fractional excretion of sodium
GFR glomerular filtration rate
GN glomerulonephritis
HIC high-income country
KDIGO Kidney Disease: Improving Global Outcomes
KRT kidney replacement therapy
LMIC lower- and middle-income countries
NGAL neutrophil gelatinase-associated lipocalin
NSAID nonsteroidal anti-inflammatory drug
PIGN postinfectious glomerulonephritis
RAI renal angina index
RIFLE Risk, Injury, Failure, Loss, and End stage
SLE systemic lupus erythematosus
INTRODUCTION

Acute kidney injury (AKI) is the sudden decrease in kidney function, which results in decreased glomerular filtration and, ultimately, a rise in serum creatinine level. AKI may be associated with multiple complications, including azotemia (elevated blood urea nitrogen [BUN] level), electrolyte abnormalities (hyperkalemia, acidosis, hyperphosphatemia, etc), and fluid accumulation. During the past 10 years, the understanding of the epidemiology, risk factors, outcomes, and management of children with AKI has significantly expanded. This review provides an in-depth update of AKI with particular focus on definition, renal physiology, epidemiology, outcomes, diagnostics, and management.

DEFINITION

The advancement of our understanding of the epidemiology and impact of AKI in children has been driven by the development and use of consensus definitions of AKI. This evolution began with the RIFLE criteria (Risk, Injury, Failure, Loss, and End stage), (1) which was adapted to form the pediatric RIFLE criteria. (2) This was followed by the Acute Kidney Injury Network definition. (3) The Kidney Disease: Improving Global Outcomes (KDIGO) consortium has consolidated these criteria and put forth the current consensus definition of AKI. (4) The KDIGO AKI definition is based on an absolute rise in serum creatinine level or a change in urine output (Table 1). This definition captures the spectrum of AKI from mild to severe that is associated with adverse outcomes. At this time, in practice and research, the KDIGO definition should be used to define AKI in children. (5)

The KDIGO AKI definition is anchored to changes in serum creatinine level from a baseline (usually a stable value in the previous 3 months) and/or a decrease in urine output. The 2 common practices used if baseline serum creatinine level is unknown include using the high normal value based on laboratory standards or back-calculating creatinine level or a change in urine output. The KDIGO AKI criteria are the agreed on definition and classification of AKI for older populations there has been the development of a consensus neonatal AKI definition. The neonatal modified KDIGO AKI criteria are the agreed on definition for neonatal AKI, endorsed by multidisciplinary experts at the National Institute of Diabetes and Digestive and Kidney Diseases–sponsored neonatal AKI workshop in 2013. (8)(9)(10) This neonatal modified KDIGO AKI staging system relies on a rise in serum creatinine level from a previous trough (Table 2). This staging system was studied in single-center studies and validated in the international Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study. (11)

<table>
<thead>
<tr>
<th>STAGE</th>
<th>CHANGE IN SERUM CREATININE LEVEL a</th>
<th>URINE OUTPUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase of 0.3 mg/dL (26.52 µmol/L) over 48 h b or increased 1.5–1.9x baseline</td>
<td>&lt;0.5 mL/kg per hour for 6–12 h</td>
</tr>
<tr>
<td>2</td>
<td>Increase ≥2–2.9x</td>
<td>&lt;0.5 mL/kg per hour for ≥12 h</td>
</tr>
<tr>
<td>3</td>
<td>Increase ≥3x, ≥4 mg/dL (≥35.60 µmol/L) or initiation of kidney replacement therapy or estimated glomerular filtration rate &lt;35 mL/min/1.73 m² for those aged &lt;18 y</td>
<td>&lt;0.3 mL/kg per hour for ≥24 h or anuria for 12 h</td>
</tr>
</tbody>
</table>

*KDIGO=Kidney Disease: Improving Global Outcomes.
*bFrom baseline creatinine level.
*The remainder of creatinine level changes occur over 7 days.

Table 1. KDIGO Acute Kidney Injury Definition and Classification
Table 2. Neonatal Acute Kidney Injury Definition and Classification

<table>
<thead>
<tr>
<th>STAGE</th>
<th>CHANGE IN SERUM CREATININE LEVEL*</th>
<th>URINE OUTPUTb</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No change or rise &lt;0.3 mg/dL (&lt;26.5 µmol/L)</td>
<td>≥0.5 mL/kg per hour</td>
</tr>
<tr>
<td>1</td>
<td>Increase of ≥0.3 mg/dL (≥26.52 µmol/L) within 48 h or ≥1.5–1.9x reference value within 7 d</td>
<td>&lt;0.5 mL/kg per hour for 6–12 h</td>
</tr>
<tr>
<td>2</td>
<td>Rise ≥2.0–2.9x reference value within 7 d</td>
<td>&lt;0.5 mL/kg per hour for ≥12 h</td>
</tr>
<tr>
<td>3</td>
<td>≥3x reference value or &gt;2.5 mg/dL (≥221 µmol/L) or receipt of kidney replacement therapy</td>
<td>&lt;0.3 mL/kg per hour for ≥24 h or anuria for ≥12 h</td>
</tr>
</tbody>
</table>

*From reference creatinine level, defined as the previous trough value.

Urine output criteria have not been systematically interrogated in neonates. The AWAKEN (Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates) study evaluated urine output over 24-hour periods.

Differences between the neonatal acute kidney injury definition and Kidney Disease: Improving Global Outcomes definition include the following:

bReference value is defined as the lowest previous serum creatinine value.

cSerum creatinine value of 2.5 mg/dL (221 µmol/L) represents less than 10 mL/min/1.73 m².

dSerum creatinine value of 1.5–3.3 cases per 100,000 children. (14)

Epidemiology

Before the use of standardized definitions, there were limited data on the precise incidence and prevalence of pediatric AKI. Sutherland et al (12) used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes for AKI and reported an incidence of 3.9 per 1,000 pediatric admissions. Another study using retrospective data from the electronic health records (EHRs) estimated that AKI occurred in at least 5% of all noncritically ill hospitalized children. (13) A population-based study in Norway from 1999 to 2008 using the ICD-10-CM codes to identify AKI in children younger than 16 years found an incidence of 3.3 cases per 100,000 children. (14)

The multicenter, international, prospective AWARE study was a landmark epidemiological study of AKI in critically ill, hospitalized patients. (6) Kaddourah et al looked at 4,683 patients, aged 3 months to 25 years from 32 PICUs at participating centers. (6)(7) AKI occurred in 26.9% of patients (n = 1,261), and severe AKI (KDIGO stage 2 or 3) in 11.6% of participants (n = 543). In this study, severe AKI was associated with an incremental risk of death by day 28 and increased use of kidney replacement therapy (KRT) and mechanical ventilation.

Outside the ICU population, some of the more recent data are from various health systems using electronic alerts (e-alerts). A recent retrospective cross-sectional study that looked at the incidence of AKI using a serum creatinine–based e-alert algorithm across 6 hospitals in England reported an incidence of 10.8%, with most patients diagnosed as having AKI being younger than 6 years and having AKI stage 1. (15) A prospective national cohort study using the Welsh electronic AKI reporting system reported an incidence of 77.3 cases of AKI per 100,000 person-years, with 84% of all AKI being stage 1. (16) A large study of more than 1.5 million children cared for in the Kaiser Permanente Northern California health system between 2008-2016 showed an estimated incidence of community-based AKI of 0.7 cases per 1,000 person-years, with two-thirds of cases not associated with an ICU stay. (17)

There are limited data on the global burden of AKI, particularly from lower- and middle-income countries (LMICs). In the 0by25 Global Snapshot study, 80% of identified AKI cases occurred in the community in LMICs compared with 20% in high-income countries (HICs). (18) Children from HICs were younger and had AKI mostly due to hypotension, postsurgical complications, or dehydration. In LMICs the most common causes of AKI included infection, nephrotoxic medications, and primary kidney diseases. A systematic review and meta-analysis of large cohort studies from 2004 to 2012 by Susantitaphong et al (19) showed pooled incidence rates of AKI in children of 33.7% (95% confidence interval [CI], 26.9%–41.3%), with a pooled AKI-associated mortality rate of 13.8% (95% CI, 8.8%–21.0%). However, more than 80% of the studies included came from HICs.

Normal Kidney Physiology

Normal kidney function encompasses biochemical homeostasis, maintenance of fluid balance, blood pressure regulation, and endocrinological control of processes such as erythropoiesis and mineral bone balance. Kidney dysfunction can lead to disorders in any or all these areas. In the setting of AKI, clinical focus is generally on fluid/electrolyte balance and changes in kidney clearance, although other kidney function–related problems may also manifest.

The kidneys receive 20% to 25% of cardiac output, which distributes to the nephrons of the kidney, entering glomeruli through the afferent arterioles and leaving through the efferent arterioles. Transmembrane pressure across each glomerulus generates a cell-free glomerular filtrate, which then
traverses the renal tubule. During tubular transit, water and other molecules are reabsorbed and/or secreted into the tubular fluid, based on homeostatic needs, to generate the final urine, which leaves the kidneys for excretion.

Complex regulatory systems control the total filtration across all glomeruli (GFR), free water balance, and biochemical equilibrium. In low-volume states, urinary output drops under the influence of neurohumoral systems, including the renin-angiotensin-aldosterone axis, to limit further volume loss and maintain intravascular volume. In volume excess, the inverse occurs. Tubuloglomerular feedback adjusts GFR through variations in glomerular perfusion pressure based on renal tubular chloride flow. Urinary biochemical content varies depending on the interplay of active and passive transport systems in the renal tubule. Osmolar balance depends on cross talk that involves hypothalamic monitoring, pituitary excretion of antidiuretic hormone (ADH), and interface between specialized renal tubular epithelial cells and renal medullary interstitium. Normal urinary output and kidney function, therefore, comes from a complex balance of interactions between specialized epithelial and endothelial structures in the kidney, cellular transport mechanisms, macrovascular and microvascular blood flows, and neurohumoral monitoring and signaling systems designed to maintain homeostasis.

**PATHOPHYSIOLOGY OF AKI**

The traditional categorization of AKI into prerenal (ie, low perfusion), postrenal (ie, urinary obstruction), and intrinsic (ie, kidney-related) processes is a useful heuristic but oversimplifies the complex physiology seen in kidney dysfunction. In particular, the term *prerenal AKI* has fallen out of favor with preference for the newer term—*functional AKI*—which better supports the implication that low urinary output in some settings is appropriate and adaptive rather than being evidence of injury or dysfunction.

**Functional AKI**

Functional AKI results from reduced blood flow to the kidney. Reduced kidney perfusion may also be seen in states of volume depletion (hemorrhage, gastrointestinal tract losses, urinary losses). Redistribution of fluid leading to suboptimal kidney perfusion may occur from low oncotic pressure in the vascular compartment (eg, hypoalbuminemia from nephrotic syndrome, liver disease, protein-losing enteropathy) or increased capillary leak (eg, systemic inflammation, sepsis). Systemic vasodilation or poor vascular tone often seen in critical illness may have similar effect on kidney perfusion. Poor kidney perfusion may also be seen with low cardiac output due to an underlying cardiac condition or due to increased resistance to flow (abdominal compartment syndrome, renal artery stenosis). Previously healthy children with functional AKI may have a single cause for low effective circulating volume. On the other hand, AKI in hospitalized children may be multifactorial in origin.

Reduced kidney blood flow stimulates a cascade of compensatory mechanisms, including activation of the renin-angiotensin-aldosterone system, increased sympathetic tone, release of ADH, and prostaglandin release by the local paracrine system. The local effect of prostaglandin leads to afferent arteriolar vasodilation, which helps maintain blood flow and glomerular filtration in the underperfused kidney. The use of 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, and interruption of this mechanism by angiotensin-converting enzyme inhibitors predisposes these patients to functional AKI. Renin-angiotensin-aldosterone system activation and ADH release lead to increased sodium and urea reabsorption, respectively, which, along with water reabsorption, leads to oliguria and the characteristic urine findings in functional AKI (Table 3).

Functional AKI is often readily reversible with improved perfusion. This is seen with oliguria in volume depletion that rapidly corrects with volume expansion. Whether functional AKI abates with simple maneuvers may depend on the overall clinical condition of the patient and whether the underlying physiology is adaptive or maladaptive.

**Postrenal AKI**

Postrenal AKI is infrequent in pediatrics and results from processes that obstruct urine flow. These include those resulting from local mass effect (bilateral ureteral obstruction or urethral obstruction by a tumor), nephrolithiasis, or clots in the bladder.

**Intrinsic AKI**

Intrinsic AKI refers to direct renal parenchymal damage or dysfunction. This may be seen in conditions causing tubular, interstitial, glomerular, or vascular damage; exposure to nephrotoxins; and the AKI of critical illness associated with multiorgan dysfunction. AKI occurs frequently in tertiary care centers caring for patients with multisystem disease. Our understanding of the mechanisms that underlie intrinsic AKI continues to evolve.
AKI in Sepsis. Multiple factors interact in sepsis to cause AKI. Older concepts of kidney underperfusion leading to ischemic injury and “acute tubular necrosis” are not well supported by histologic studies that fail to show necrosis in kidneys of patients who died with septic AKI. Animal models of sepsis do not show universal reduction of renal blood flow, with some models indicating that renal blood flow may be increased in sepsis, not reduced, due to a hyperdynamic state with elevated cardiac output. Furthermore, other models of renal underperfusion, such as cardiac arrest and the process of kidney harvest for transplantation, do not universally result in significant AKI. Gene activation patterns in septic AKI seem to differ from those seen in functional AKI, suggesting different physiological pathways. AKI in sepsis is clearly more complicated than previously imagined.

Table 3. Causes of Acute Kidney Injury

<table>
<thead>
<tr>
<th>COMMON CAUSES</th>
<th>COMMON CLINICAL AND LABORATORY FINDINGS</th>
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<tbody>
<tr>
<td>Decreased kidney perfusion (functional AKI)</td>
<td>Urinalysis with high specific gravity (&gt;1.020)</td>
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<tr>
<td>Systemic vasodilation</td>
<td>Heart failure, cardiac tamponade</td>
</tr>
<tr>
<td>Reduced cardiac output</td>
<td>Urine sodium may be &lt;20 mEq/L (&lt;20 mmol/L)</td>
</tr>
<tr>
<td>Renal vasomodulation or shunting</td>
<td>FE_Na &lt;1%</td>
</tr>
<tr>
<td>Intrinsic kidney injury</td>
<td>FE_urea &lt;35%</td>
</tr>
</tbody>
</table>

Glomerular
- Postinfectious GN
- IgA nephropathy
- Systemic lupus erythematosus
- Membranoproliferative GN
- Antineutrophilic cytoplasmic antibody–associated vasculitis
- Rapidly progressive GN

Tubulointerstitial
- Acute interstitial nephritis
  - Frequently drug-induced
  - May result from systemic diseases, including sarcoidosis, Sjögren disease, infections

Acute tubular injury
- Functional AKI may progress into acute tubular injury
- May be caused by medications or toxins (myoglobinuria, hemoglobinuria)
- Other causes: ischemia, inflammation-shock, sepsis

Microvascular
- Thrombotic microangiopathies
  - Hemolytic uremic syndrome
  - May be Shiga toxin–producing *Escherichia coli*–associated
  - Atypical or diarrhea-negative hemolytic uremic syndrome may be caused by *Streptococcus pneumoniae* infection, related to medication/therapy (calcineurin inhibitors, radiotherapy, stem cell transplantation) or due to disorders of complement regulation (deficiencies of factor H, factor I, membrane cofactor protein)

Postrenal
- Bladder outlet obstruction (posterior urethral valves, neurogenic bladder)
- Bilateral obstruction (or unilateral with 1 kidney) due to stones, malignancy
- Papillary necrosis, stones

ACE=angiotensin-converting enzyme, AKI=acute kidney injury, ARB=angiotensin receptor blocker, FE_Na=fractional excretion of sodium, FE_urea=fractional excretion of urea, GN, glomerulonephritis, NSAID=nonsteroidal anti-inflammatory drug.
AKI in sepsis likely stems from an interplay between body responses and maladaptive mechanisms to illness. Systemic inflammation, including the elaboration of reactive oxygen and nitrogen species, causes local changes in renal blood flow and tubular injury. Alterations in microvascular flow patterns, possibly exacerbated by inflammation-associated microthrombus formation, reduces glomerular pressure, whereas changes in the renal tubules cause autoregulatory systems to drop glomerular perfusion. This interplay of mechanisms leads to lower GFR and oliguria. (25)

Several interacting processes have been proposed to cause this sequence of events. Receptors on neutrophils recognize pathogen-associated molecular patterns elaborated by infectious agents and damage-associated molecular patterns released from injured cells. This recognition leads neutrophils to produce reactive oxygen and nitrogen species, cytokines, and chemokines, which, along with pathogen-associated and damage-associated molecular patterns, can enter the renal microcirculation. In response, blood can be shunted away from glomeruli, leading to reduced glomerular perfusion and a drop in GFR. Activated neutrophils may also cause renal tubular cell injury (loss of polarity, changes in energy utilization, cell cycle arrest), further inhibiting normal kidney function. (26) Endothelium may experience direct injury with inflammation, leading to endothelial cell dysfunction, loss of protective glycocalyx (the gel-like layer covering the luminal surface of vascular endothelial cells), changes in vascular permeability, and release of more reactive molecules. (27)(28) Although further details remain to be clarified, the simple model of underperfusion leading to kidney cell injury and subsequent AKI is clearly insufficient to explain the complex interactions that underlie kidney dysfunction in sepsis. (29)

**AKI in Cardiac Disease.** Patients with significant cardiac dysfunction, such as heart failure, may develop kidney complications. Cardiorenal syndrome (CRS) was originally defined as kidney dysfunction that occurred in association with decompensated heart failure and its treatment. The CRS concept has been expanded to encompass a spectrum of heart and kidney disorders in acute or chronic settings characterized by mutual deterioration. (30) The acute subtypes of CRS start with primary cardiac dysfunction that leads to AKI (CRS type 1) or with AKI leading to cardiac decompensation (CRS type 3). CRS types 2 and 4 are analogous chronic disorders; in CRS type 2, chronic primary cardiac dysfunction leads to sustained reduction in renal function, and CRS type 4 is characterized by chronic kidney disease (CKD) leading to chronic cardiac dysfunction. CRS type 5 begins with a noncardiac, nonrenal systemic disorder that then leads to heart-kidney deterioration. Autoregulatory maladaptation and inflammation, as in sepsis, can occur in CRS with deleterious effects on the heart and kidney. Venous congestion is also a complicating factor, initiated either from heart failure or oliguria and exacerbating dysfunction of both organs.

**AKI in Other Settings.** Glomerular and vascular causes of intrinsic AKI are more common in previously healthy children. The timing and clinical presentation often suggest either isolated glomerulonephritis (GN) (eg, postinfectious GN [PIGN]) or multisystem autoimmune diseases that involve the kidney (eg, IgA vasculitis [formerly Henoch-Schönlein purpura] or systemic lupus erythematosus [SLE]). Vascular etiologies include microangiopathic conditions (hemolytic uremic syndrome, thrombotic microangiopathy, and thrombotic thrombocytopenic purpura) and systemic vasculitides affecting medium and larger vessels.

Acute interstitial nephritis (AIN) is most often due to exposure to medications, although it may also be caused by systemic autoimmune disorders (SLE, Sjögren syndrome, sarcoidosis) and infections; AIN also appears in tubulointerstitial nephritis with uveitis syndrome.

The timing is unpredictable with AIN and may develop within 3 to 5 days after being reexposed to an offending drug or can occur weeks to months after an exposure. Drugs can cause AKI in ways other than AIN. Nephrotoxin exposure is now recognized as a common cause of intrinsic AKI, particularly in hospitalized patients. Angiotensin-converting enzyme inhibitors and NSAIDs can cause AKI by blocking renal vascular autoregulation. Other drugs that may lead to AKI include aminoglycosides, amphotericin, calcineurin inhibitors (cyclosporine, tacrolimus), and chemotherapeutic agents (cisplatin, ifosfamide, methotrexate). Endogenous elements such as hemoglobin and myoglobin, seen in patients with massive hemolysis or rhabdomyolysis, can obstruct tubules and/or cause direct toxicity to the kidney.

**DIAGNOSIS OF AKI**

A thorough history and physical examination are key in making the diagnosis of AKI and ascertaining the underlying cause. A systematic approach to identify potential functional, intrinsic, and obstructive causes is important. Based on the history, one may be able to delineate risk factors for functional AKI. There may be a history of volume loss (gastroenteritis, hemorrhage), circulatory volume redistribution (nephrotic syndrome, sepsis), low cardiac output, or conditions causing increased resistance to renal blood flow (massive edema and abdominal compartment syndrome,
renal artery stenosis). Additional clues in the history and physical examination include recent illness/sore throat (PIGN), rashes, arthralgia/arthritis (SLE), gross hematuria, or exposure to a new or known nephrotoxic medication. Prenatal history in newborns with a suspected postrenal AKI may provide details about fetal ultrasonography abnormalities, such as a large bladder, hydronephrosis, or oligohydramnios, which in turn suggest bladder outlet obstruction or posterior urethral valves in a male infant. Accurate assessment of urine output over the previous several days may help categorize the patient as having oliguria (defined as urine output <1 mL/kg per hour) or not. This can also define AKI severity. As discussed earlier, creatinine level elevation can be delayed by as much as 48 hours after damage to the kidney has already occurred. Hence, one must consider episodes of hypotension, hypoxia, sepsis, surgery, and drug exposures that occurred in the previous 48 to 72 hours.

The initial laboratory evaluation of AKI should include an electrolyte panel, BUN, serum creatinine, urinalysis, urine sodium, urine urea nitrogen (UN), urine creatinine, and a renal ultrasonography. Urine studies may allow differentiation between functional AKI and intrinsic AKI. The fractional excretion of sodium (FE\textsubscript{Na}) and the fractional excretion of urea (FE\textsubscript{Urea}) may be calculated as follows:

\[
\text{FE}_{\text{Na}} = \left( \frac{\text{Urine Na} \times \text{Serum Creatinine}}{\text{Serum Na} \times \text{Urine Creatinine}} \right) \times 100\% \\
\text{FE}_{\text{Urea}} = \left( \frac{\text{Urine UN} \times \text{Serum Creatinine}}{\text{BUN} \times \text{Urine Creatinine}} \right) \times 100\%
\]

Typical laboratory findings for functional AKI include normal urinalysis, concentrated urine (osmolality >500 mOsm/kg), FE\textsubscript{Na} less than 1% (<2% in neonates), FE\textsubscript{Urea} less than 35%, urine sodium level less than 20 mEq/L (<20 mmol/L), and a BUN (mg/dL) to creatinine (mg/dL) ratio greater than 20. A loss of urine concentrating ability is classically seen in the tubular dysfunction of some forms of intrinsic AKI. A positive result for blood seen on urine dipstick without microscopy evidence of red blood cells merits further evaluation for hemoglobinuria (hemolysis) or myoglobinuria (rhabdomyolysis).

Urinalysis with microscopy may show findings associated with conditions such as acute tubular injury (“muddy” granular casts), or GN (red blood cell casts). GNs may have additional findings, including hematuria and proteinuria (Table 3). A history of a recent upper respiratory tract infection (typically pharyngitis 2–3 weeks previously) or skin infections 4 to 6 weeks previously with these urinary findings may suggest PIGN. Such patients should have serum complement levels evaluated and may show low C3 and normal C4 levels. IgA nephropathy may present with more recent upper respiratory tract infection (2–3 days previously) and gross hematuria (synpharyngitic GN) with normal complement levels. Presence of systemic signs and symptoms such as rash or arthritis and urinalysis consistent with GN is suggestive of SLE (low C3 and C4 levels) and necessitates additional antibody testing (antinuclear and anti–double-stranded DNA antibodies). Pulmonary renal syndrome presents with pulmonary signs and symptoms such as cough, hemoptysis, radiographic chest infiltrates, and active GN. The causes of pulmonary renal syndrome include often with the presence of anti–proteinase 3 antibodies), microscopic polyangiitis (perinuclear ANCA, often with the presence of antineutrophil cytoplasmic antibodies), eosinophilic granulomatosis (perinuclear ANCA), and anti–glomerular basement membrane antibody disease. Although a kidney biopsy may not be needed in classic PIGN, it is important to confirm the diagnosis and to guide treatment of the other GNs because the degree of renal involvement in a variety of these syndromes dictates extent of treatment. Rapidly progressive GN, defined by steadily increasing BUN and creatinine levels, may be seen in any of the GNs. Rapidly progressive GN warrants urgent evaluation, including a renal biopsy and prompt treatment to prevent irreversible progression of kidney disease.

Allergic interstitial nephritis may be associated with fever, rash, and eosinophilia. However, the classic triad is seen in fewer than 15% of patients. Patients often have a bland urine sediment with occasional white blood cell casts, but red blood cell casts are absent. Urinary eosinophils may be seen, but their presence lacks sensitivity and specificity for the diagnosis of interstitial nephritis. The degree of proteinuria may be variable; nephrotic-range proteinuria may be seen with NSAID-associated interstitial nephritis. The diagnosis of AIN can only be confirmed on a kidney biopsy.

Hemolytic uremic syndrome should be suspected in patients with AKI in the setting of a recent diarrheal illness, low platelet count, and hemolytic anemia. A peripheral blood smear with schistocytes may confirm hemolysis. Atypical hemolytic uremic syndrome caused by nondiarrheal infections (Streptococcus pneumoniae, Bordetella pertussis, Haemophilus influenzae, human immunodeficiency virus, cytomegalovirus, influenza H1N1) or genetic abnormalities in the complement system can be challenging to recognize and treat.

Kidney ultrasonography may provide limited information in intrinsic AKI. Kidney size can provide clues toward acuity or chronicity of kidney dysfunction, with larger kidneys suggesting active inflammation and small-for-age
Kidneys suggesting a chronic process. Ultrasonography may also show the nonspecific finding of increased echogenicity. Ultrasonography is critical to the diagnosis of obstructive AKI, where it may show unilateral or bilateral hydronephrosis. This may also provide hints to the site of obstruction, with bilateral hydronephrosis and/or hydrouretters suggesting distal obstruction. If an obstructive process is diagnosed, the obstruction should be relieved immediately.

**ADVANCES IN AKI DIAGNOSTICS**

**Renal Angina**

Renal angina is a risk stratification construct that combines patient risk factors and early signs of kidney injury (fluid overload and change in creatinine level) for prediction of severe (stage 2 or 3) ICU day 3 AKI. Renal angina is a conceptual framework to identify evolving AKI and does not suggest physical symptoms. It is assessed by calculating the renal angina index (RAI), which is usually performed 12 hours after admission to an ICU. Patients are given a risk score and an injury score, which are multiplied to calculate the RAI, with a score of 8 or more being positive for renal angina. An RAI less than 8 has high negative predictive value for severe AKI on day 3. In a single-center study, Menon et al (32) reported that 32.6% of patients were positive for renal angina on day 0 of ICU admission. Day 0 positive renal angina status was associated with an increased incidence of AKI on ICU day 3 (23.1% vs 2.9%; P < .001). In the AWARE study, the RAI demonstrated better prediction for severe AKI than serum creatinine level elevation from baseline (adjusted odds ratio, 3.21; 95% CI, 2.20–4.67). (33)

**Markers**

Traditionally, AKI biomarker research has sought to recapitulate the success of troponin in detecting myocardial infarction. However, unlike myocardial infarction, which represents primarily ischemic injury, AKI is a syndrome with multiple phenotypes and etiologies and is caused by multiple heterogeneous mechanisms. Hence, a single biomarker is unlikely to be appropriate for AKI. Although creatinine is the most used diagnostic marker for AKI, it is a marker of kidney function, not kidney injury. In the past few years, biomarkers of structural injury (eg, neutrophil gelatinase–associated lipocalin [NGAL]), tissue inhibitor of metalloproteinases-2, insulin-like growth factor–binding protein 7, and kidney injury molecule-1) have been studied for prediction, early detection, and diagnosis of subclinical AKI. NGAL is one of the most widely studied AKI biomarkers in children. In a cohort of 71 children after cardiopulmonary bypass, Mishra et al (35) showed that NGAL level checked 2 hours after cardiopulmonary bypass initiation was an independent predictor of AKI on multivariable analysis (area under the receiver operating characteristic curve, 0.99845). Other studies have shown the utility of NGAL in the early diagnosis of AKI, particularly after cardiac surgery. However, its performance has been less optimal in more heterogeneous populations because elevated levels of NGAL may be seen in multiple non-AKI–like conditions, including urinary tract infections, sepsis, and malignancy. A combined tissue inhibitor of metalloproteinases-2 and insulinlike growth factor–binding protein 7 assay is approved by the Food and Drug Administration (FDA) for use in adults and is available commercially.

Functional and damage biomarkers can be combined to identify different AKI phenotypes as proposed by the 10th and the 23rd Acute Disease Quality Initiative consensus conferences. (36,37) Using a combination of functional and damage biomarkers allows earlier diagnosis and better delineation of the AKI syndrome. It is important to understand that AKI as a syndrome is dynamic, and patients may transition between subtypes.

**Furosemide Stress Test**

A recent advancement in the early diagnosis and stratification of children at risk for severe AKI is the development of a test of kidney function that serves to identify patients at highest risk for severe progressive AKI. The furosemide stress test represents such a test and uses a single dose of furosemide in patients with stage 1 or 2 AKI followed by close monitoring of urine output for 6 hours. In adult studies, a urine output of less than 200 mL in the first 2 hours after furosemide has been shown to predict adverse outcomes (stage 3 AKI, need for kidney support therapy, increased mortality). (38,39) Small single-center series in children after cardiac surgery have suggested that the furosemide stress test can be used in children and neonates. (40,41) Further studies are necessary in children to define clinically relevant thresholds for the furosemide stress test in children. The Trial in AKI using NGAL and Fluid Overload to optimize CRRT Use (Taking FOCUS 2) is an ongoing trial evaluating the impact of sequentially mobilizing urinary biomarkers and the furosemide stress test to improve outcomes in children at risk for severe AKI. (42)

**Leveraging EHR Systems**

With the widespread use of EHRs, it has become feasible to use EHRs for clinical decision support systems. These include automated real-time alerts and diagnostic or therapeutic care...
bundies. (16)(43) AKI is well suited for electronic alerts because it has a consensus definition and is easily diagnosed from discrete, readily available data (creatinine level and urine output). These alerts may be used to identify patients with AKI or those at high risk for AKI. Although electronic alerts have been shown to improve the recognition and diagnosis of AKI, there are limited data on outcomes in pediatric patients. Electronic alerts may work better when paired with a standardized management care plan.

**MANAGEMENT OF AKI**

The first step in the management of children who present with oliguria, hemodynamic instability, or hypotension is intravascular volume restoration. An initial bolus of isotonic fluids (20 mL/kg) should be given rapidly and repeated according to pediatric advanced life support algorithms. Isotonic fluids are used for acute volume expansion (normal saline, lactated Ringer, and balanced electrolyte solutions; 5% albumin; packed red blood cells). The clinical scenario drives the choice of fluids. In recent years there has been increasing data to suggest a potential benefit from balanced electrolyte solutions compared with isotonic sodium chloride to improve renal function and decrease the incidence of AKI. (44)(45) Recent work in children has suggested that hyperchloremia related to intravenous fluids is an independent risk factor for the development of AKI in children with sepsis. (46) Children with underlying or suspected cardiac disease are usually given smaller initial fluid boluses (10 mL/kg) to decrease the risk of iatrogenic volume overload. During fluid resuscitation, it is critical to perform serial evaluations for signs of response (lower heart rate, improved blood pressure, improved capillary refill, urine output) and fluid overload (pulmonary or peripheral edema).

After fluid resuscitation, the initiation of vasopressor support should be considered; such support may be required sooner for those who have obvious fluid overload. Once the patient has been adequately fluid resuscitated, a time-limited diuretic (furosemide) trial may be considered if the patient remains oliguric. (4) In children who remain oliguric after intravascular volume resuscitation, one may use conservative fluid management by restricting fluids to insensible losses (300–500 mL/m² per day) plus output replacement to prevent subsequent volume overload.

Pediatricians have been leaders in medicine in recognizing the deleterious effect on outcomes of fluid accumulation and the development of the pathologic state of fluid overload in children with and without AKI. (47)(48)(49)(50) Classically in the literature, the term fluid overload has been used to denote a state of positive fluid balance, but this terminology is biased because it assumes that all fluid accumulation is pathologic. In 2022, the pediatric Acute Disease Quality Initiative consensus conference sought to standardize the terminology describing fluid balance; the terms *daily fluid balance*, *cumulative fluid balance*, and *percent cumulative fluid balance* have been put forth to describe fluid status in patients at risk for fluid overload (Table 4). (51) Fluid balance is an objective measure of fluid accumulation or loss that is based on cumulative input and output or changes in weight. Fluid overload represents a distinct pathologic state of positive fluid balance with clinically observable adverse consequences. No single threshold can be used to describe fluid overload; rather, it is unique to pathophysiology, population, and timing. To monitor for the development of fluid overload, it is important to track patient fluid balance and describe it daily as a vital sign in high-risk patients.

Individuals with AKI may show various electrolyte disturbances, including hyponatremia and hypernatremia, hyperkalemia, metabolic acidosis, and hyperphosphatemia. Excessive sodium input higher than the typical requirements in healthy children (2–3 mEq/kg per day) should be avoided to prevent elevated blood pressure and other complications of sodium overload. Potassium and phosphorous should be withheld from fluids and restricted in diets of children with AKI. Based on the serum levels, children with AKI may need intermittent replacement because low levels of potassium (cardiac conduction abnormalities) and phosphorous (poor muscle contraction) can have adverse effects.

Hyperkalemia is one of the most serious complications of AKI. It may present with nonspecific symptoms, including fatigue, nausea, tingling, weakness, and even paralysis. Cardiac conduction abnormalities and arrhythmias are the most serious manifestations of hyperkalemia. Electrocardiography (ECG) changes may occur when potassium levels are 6.5 to 7.0 mEq/L (6.5–7.0 mmol/L), but significant variability exists. The potassium levels that result in ECG changes fluctuate with acuity, associated electrolyte abnormalities (hypocalcemia, hypomagnesemia), and disease pathophysiology (tumor lysis syndrome, rhabdomyolysis). The typical initial ECG findings are peaked T waves. Other changes include a widened QRS complex, flattened P waves, and a prolonged PR interval. Untreated hyperkalemia may lead to life-threatening arrhythmias.

An ECG should be obtained in patients with potassium levels greater than 6 mEq/L (>6 mmol/L). In patients with potassium levels of 5.5 to 6.5 mEq/L (5.5–6.5 mmol/L) and appropriate urine output without ECG abnormalities, one may consider treatment with a potassium-binding resin in...
the gastrointestinal tract (sodium polystyrene sulfonate) or a saline bolus with furosemide (Table 5). If there are changes on ECG, a potassium level greater than 7.0 mEq/L (>7.0 mmol/L), or a rapidly rising potassium level, hyperkalemia should be viewed as life-threatening and treated more aggressively. Initial rapid treatment measures include intravenous 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 \( \beta_2 \)-agonists, sodium bicarbonate, and/or insulin with glucose. It is critical to understand that these agents do not remove potassium from the body but are simply temporizing measures that act by shifting potassium intracellularly. \( \beta_2 \)-Agonists, such as albuterol, can be given via nebulizer and have been shown to lower the potassium level by 1 mEq/L (1 mmol/L) (may need to avoid using in patients with underlying cardiac disease). Insulin given with glucose drives potassium into cells by increasing sodium/potassium ATPase activity. Sodium bicarbonate increases the extracellular pH, resulting in movement of hydrogen ions to the extracellular space with a shift of potassium ions intracellularly, and administration of sodium bicarbonate may be considered if there is an underlying acidosis. Trials evaluating sodium bicarbonate therapy in adults with hyperkalemia have not shown efficacy, but this remains to be studied in children.

In conjunction with these temporizing measures, efforts aimed at potassium removal from the body, including administering loop diuretics with fluid bolus and sodium polystyrene sulfonate, must be performed. Sodium polystyrene sulfonate should be avoided in neonates or children with underlying bowel pathology. If these measures fail, or in the case of severe life-threatening hyperkalemia, KRT should be considered.

### Table 4. Fluid Balance Terminology and Management

<table>
<thead>
<tr>
<th>Terminology</th>
<th>MEASUREMENT/EQUATION</th>
<th>DURATION</th>
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</thead>
<tbody>
<tr>
<td>Daily fluid balance</td>
<td>Fluid Intake (L) – Fluid Output (L)</td>
<td>&gt;24 h</td>
</tr>
<tr>
<td></td>
<td>or Current Weight (kg) – Weight from Previous Day (kg)</td>
<td></td>
</tr>
<tr>
<td>Cumulative fluid balance</td>
<td>( \Sigma ) Fluid Intake (L) – Fluid Output (L)</td>
<td>Over a defined period</td>
</tr>
<tr>
<td></td>
<td>or Current Weight (kg) – Anchor Weight (kg)</td>
<td></td>
</tr>
<tr>
<td>Percent cumulative fluid balance</td>
<td>( \Sigma ) \left( \frac{\text{Fluid Intake } [L] – \text{Fluid Output } [L]}{\text{Anchor Weight } [kg]} \right) \times 100%</td>
<td>Over a defined period</td>
</tr>
<tr>
<td></td>
<td>Or ( \frac{\text{Current Weight } [kg] – \text{Anchor Weight } [kg] \times 100%}{\text{Anchor Weight } [kg]} )</td>
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</tbody>
</table>
| Fluid overload                    | – Definition: A distinct pathologic state of positive fluid balance with clinically observable adverse consequences
|                                   | – No single threshold can be used to describe fluid overload, but instead is unique to pathophysiology, population, phase of illness, and timing |
| Fluid management strategy         |                                                                                      |            |

#### Fluid restriction
- Considered in children with a time-limited underlying disease and oliguria after volume resuscitation
- Classically includes insensible losses (300–500 mL/m² per day) and additional losses
- Consider escalation of care if:
  - Fluid overload
  - Electrolyte disturbances
  - Inability to provide adequate nutrition
  - Anticipation of prolonged duration of fluid restriction

#### Furosemide or diuretic challenge
- Kidney Disease: Improving Global Outcomes recommends time-limited trial of diuretics (single large dose followed by intermittent dosing or continuous infusion if successful)
- Furosemide stress test: Monitor the response to initial diuretic challenges and guide further therapy with rapid escalation of care in those who fail to respond
- Success defined as ability to achieve negative fluid balance while achieving metabolic control and nutrition
- Avoid prolonged diuretic therapy with inadequate response

**“Renal dose” dopamine** No benefit

**Mannitol** No benefit

*Anchor weight is classically ICU admission weight in older children but may differ by population (e.g., preoperative weight in congenital heart surgery, birthweight during the first postnatal week).
The acidosis associated with AKI classically is described as an anion gap acidosis. Except for the treatment of acidosis associated with hyperkalemia, use of bicarbonate is reserved for severe acidosis. The administration of bicarbonate in these circumstances requires diligent monitoring because this can lead to ionized hypocalcemia, as calcium is exchanged on plasma proteins for hydrogen ions. In severe cases, tetany may result from ionized hypocalcemia related to excessive bicarbonate supplementation.

Severe hyperphosphatemia can develop in AKI, particularly in disease states typified by high cell turnover (tumor lysis syndrome, rhabdomyolysis). Most commonly, the hyperphosphatemia associated with AKI can be prevented or managed conservatively by limiting intake. Calcium and ionized calcium levels should be closely monitored in cases of severe hyperphosphatemia because the intravascular binding of calcium to excess phosphorus may lead to ionized hypocalcemia.

Contrast Use

Radiocontrast agents have long been considered a cause of nephrotoxin-related AKI. However, the risk of AKI in patients exposed to intravenous iodinated contrast media has been overstated. Newer iso-osmolar agents seem to be less nephotoxic, and overall concern for AKI with radiocontrast has diminished. One may see both contrast-associated AKI (any AKI within 48 hours of contrast administration) and contrast-induced AKI (AKI caused by contrast administration). (52) True contrast-induced AKI is not common and may be seen in individuals with preexisting kidney dysfunction. Intravenous contrast should not be withheld from a patient owing to concern for AKI in situations where the information gained from the contrast study could have therapeutic implications.

Medications

Medications remain a common and increasingly recognized cause of AKI in children. Drug-associated AKI may occur secondary to tubular injury, tubular obstruction by crystals or casts containing drugs and their metabolites, and interstitial nephritis. Other reasons for an increase in creatinine level after medication exposure include drugs that may block tubular creatinine secretion (eg, cimetidine, trimethoprim, tyrosine kinase inhibitors), and drugs that cause hemodynamic changes in the glomerular blood flow (Table 6).

Drug dosing is also affected in the setting of AKI due to changes in drug clearance from alterations in glomerular and tubular kidney function, nonrenal drug metabolism, or change in drug pharmacokinetics from complications such as volume overload or metabolic acidosis. Dose adjustments in AKI may be difficult because of the challenges of assessing kidney function while it is rapidly changing. Drug selection and dosing in AKI requires periodic reassessment of kidney function and trajectory, clinical response, availability of alternative therapies, and therapeutic drug monitoring.

Nutrition

AKI is commonly characterized nutritionally by a catabolic state. The protein requirements in these children may be as high as 3 g/kg per day of amino acids with an accompanying caloric need of 125% to 150% that of healthy children and infants. To provide adequate protein, one will typically allow BUN levels of up to 40 to 80 mg/dL (14.28–28.56 mmol/L) in children with AKI. One may consider limiting protein delivery as a short-lived or temporizing measure to control BUN level, but this should not be used for extended periods. Recent literature has shown that critically ill children with AKI often do not

### Table 5. Management of Hyperkalemia

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>MEDICATION AND DOSE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stabilizes cardiac membrane potential</td>
<td>Calcium gluconate: 100 mg/kg IV over 5–10 min</td>
<td>Administered if ECG changes seen</td>
</tr>
<tr>
<td>Transcellular shift of potassium</td>
<td>Glucose (0.5 g/kg) and insulin (0.1 U/kg) IV over 30 min</td>
<td>When administering sodium bicarbonate, monitor serum calcium carefully because hypocalcemia may worsen</td>
</tr>
<tr>
<td>Sodium bicarbonate (1–2 mEq/kg) IV over 10–30 min if acidosis present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β2-adrenergic agonist, nebulized albuterol</td>
<td></td>
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</tr>
<tr>
<td>Eliminates potassium from the body</td>
<td>Cation exchange resins: Sodium polystyrene sulfonate (1 g/kg) orally or parenterally in sorbitol</td>
<td>Use exchange resins with caution with ileus/obstruction or in patients with dehydration; associated with risk of colonic necrosis</td>
</tr>
<tr>
<td>Sodium zirconium cyclosilicate and patiromer are approved for adults with chronic hyperkalemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide (1–2 mg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney replacement therapy if other interventions fail</td>
<td></td>
<td></td>
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</table>

ECG = electrocardiography, IV = intravenous.
receive adequate nutrition. (53) KRT is indicated if adequate nutrition or metabolic balance cannot be obtained using conservative measures. Children who receive KRT have amino acid requirements as high as 3 to 4 g/kg per day. (54)

**Kidney Replacement Therapy**

KRT is considered when conservative measures to manage AKI have failed or are unlikely to be sufficient. Indications for KRT in children with AKI include refractory acidosis, fluid overload, hyperkalemia, uremia (typically a BUN level >100 mg/dL [>35.70 mmol/L] or symptomatic), or an inability to provide adequate nutrition. In recent years, the association of fluid accumulation and the development of the pathologic state of fluid overload with adverse outcomes in critically ill children and neonates has become clear. In single-center and multicenter studies, fluid overload has been consistently shown to be the most common indication for KRT in children. (55) Multiple studies have shown that a higher degree of fluid overload at KRT initiation is associated with increased mortality. (47)(48)(56)(57)

Modalities of KRT include peritoneal dialysis, hemodialysis, and continuous KRT. The choice of modality depends on center-specific expertise and resources, patient characteristics, and indication. Peritoneal dialysis is generally well tolerated and easily performed but does not provide precise volume management or high rates of clearance. Intermittent hemodialysis (typically over 3–4 hours) provides the high clearance, but short intermittent sessions make fluid removal difficult in critically ill patients. In recent years, continuous KRT has become the most used modality in critically ill children when the resources are available. Continuous KRT provides advantages in that it allows for precise metabolic and volume control over a 24-hour period. The continuous nature of the therapy allows for improved nutritional support and more successful fluid removal. It is the most resource-intensive modality of kidney support therapy and requires significant nursing support and ICU-level care.

**PROGRESSION TO CKD AND FOLLOW-UP**

AKI has been independently associated with poor short- and long-term outcomes. It is linked with a higher risk of hospitalization, recurrent AKI, a lower quality of life, and CKD. (58)(59)(60) Studies have reported proteinuria, hypertension, and reduced GFR after AKI. (61)(62)(63) Although this association is well understood, it is less clear whether AKI causes CKD or whether it highlights a lack of renal reserve or preexisting kidney dysfunction.

The KDIGO guidelines recommended a 3-month follow-up for all patients who developed AKI to assess for presence of CKD. However, most long-term studies show rates of follow-up of less than 50%. Children who develop AKI need long-term observation and monitoring, with the intensity...
of post-AKI care depending on various factors, including the severity of AKI, recovery of kidney function, and other comorbidities.

CONCLUSIONS

Our understanding of AKI in children has advanced during the past decade. It has become obvious that AKI is not a single disease limited to the kidneys but a systemic syndrome that can affect multiple organs. The use of newer tools such as AKI risk stratification models, biomarkers, and electronic alerts allows us to consider a dynamic and multidimensional approach, which may further improve characterization and phenotyping of AKI. The management of AKI remains supportive, but these tools may also allow predictive enrichment and personalized pediatric AKI management in the future.

Summary

- The term acute kidney injury (AKI) is used instead of acute renal failure. The staging of AKI reflects the spectrum of kidney damage that can occur (Table 1). (Based on some research evidence as well as consensus) (1)(2)(3)
- The most common etiologies of AKI are volume depletion, infections, nephrotoxic medications, and primary renal diseases. (Based on research evidence, in lower- and middle-income countries) (18)
- In high-income countries, volume depletion and primary renal disease remain common causes of AKI in previously healthy children. (Based on research evidence and expert opinion)
- In hospitalized children or children with chronic medical conditions, “secondary” causes of AKI are more common than primary renal diseases. These are often multifactorial and often complicate another diagnosis or its treatment (heart disease, sepsis, nephrotoxic medications). (Based on research evidence) (2)(18)
- A systematic approach to the diagnosis of AKI divides the potential etiologies into prerenal (or functional), intrinsic renal, and postrenal causes. (Based on expert opinion)
- Patients with AKI may show a variety of electrolyte abnormalities, including hyponatremia and hypernatremia, hyperkalemia, metabolic acidosis, and hyperphosphatemia. (Based on research evidence as well as expert opinion and consensus)
- Indications for kidney replacement therapy include refractory acidosis, hyperkalemia, volume overload (>10%-20% fluid excess), uremia (typically a blood urea nitrogen level >100 mg/dL [>35.70 mmol/L] or symptomatic), or an inability to provide adequate nutrition in the face of oliguria and AKI. (Based on some research evidence as well as expert opinion and consensus) (47)(48)
- Critically ill children with a history of severe 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 frequency and duration remain unclear. (Based on some research evidence as well as expert opinion)

References and teaching slides for this article can be found at https://doi.org/10.1542/pir.2021-005438.
1. A previously healthy 12-year-old boy is hospitalized with acute kidney injury (AKI). He sustained an ankle sprain a few weeks ago playing soccer and was treated with rest and a nonsteroidal anti-inflammatory drug (NSAID). He is not taking any other medications. Intake of NSAIDs as the responsible cause for acute interstitial nephritis in this patient is mediated by which of the following pathophysiologic mechanisms?
   A. Blockage of renal vascular autoregulation.
   B. IgA-mediated vasculitis.
   C. Immune complex deposition at the glomerular basement membrane level.
   D. Renal tubular obstruction.
   E. Toxin-mediated tubular injury.

2. A 7-year-old girl with meningococcemia is admitted to the PICU. She is diagnosed as having acute kidney injury (AKI). Which of the following laboratory findings are consistent with a diagnosis of AKI (urine analysis, urine osmolality, fractional excretion of sodium, fractional excretion of urea, urine sodium, blood urea nitrogen to creatinine ratio)?
   A. Granular casts, 400 mOsm/kg, 0.8%, 37%, 25 mEq/L (25 mmol/L), 15.
   B. Granular casts, 520 mOsm/kg, 0.8%, 30%, 25 mEq/L (25 mmol/L), 25.
   C. Normal, 400 mOsm/kg, 0.8%, 37%, 25 mEq/L (25 mmol/L), 15.
   D. Normal, 520 mOsm/kg, 0.8%, 30%, 15 mEq/L (15 mmol/L), 25.
   E. Normal, 400 mOsm/kg, 1.5%, 45%, 30 mEq/L (30 mmol/L), 10.

3. A 10-year-old boy is brought to the emergency department by his parents because of fatigue, pallor, and bruising noted today. He has had a recent febrile diarrheal illness. Laboratory studies show a platelet count of 80,000 × 10^3/µL (80,000 × 10^9/L), a hemoglobin level of 7 g/dL (70 g/L), and a serum creatinine level of 1.8 mg/dL (159.12 µmol/L). A peripheral smear reveals schistocytes. Which of the following is the most likely diagnosis in this child?
   A. Allergic interstitial nephritis.
   B. Alport nephritis.
   C. Hemolytic uremic syndrome.
   D. IgA nephropathy.
   E. Poststreptococcal glomerulonephritis.
4. A 2-year-old girl is brought to the emergency department by her parents because of a 24-hour history of multiple episodes of profuse vomiting and diarrhea. The parents are unable to estimate the number of wet diapers because of her recurrent severe diarrheal episodes. They became concerned when their daughter was hard to arouse to drink fluids. Her physical examination is significant for tachycardia, lethargy, delayed capillary refill time, and clinical signs consistent with severe dehydration. She has no significant medical history. Intravenous (IV) access is secured. Which of the following is the most appropriate immediate next step in management of this patient?

A. 10 mL/kg of 5% dextrose in half normal saline bolus given IV.
B. 20 mL/kg of normal saline bolus given IV.
C. Serum electrolytes followed by IV hydration based on serum sodium level.
D. Vasopressor support followed by 10 mL/kg of normal saline given IV over the next 8 hours.
E. Vasopressor support followed by 20 mL/kg of 5% dextrose in half normal saline bolus given IV.

5. A 5-year-old boy is diagnosed as having severe dehydration after an episode of gastroenteritis. A basic metabolic panel shows a serum sodium level of 128 mEq/L (128 mmol/L); potassium level, 7.0 mEq/L (7.0 mmol/L); bicarbonate, 18 mEq/L (18 mmol/L); and creatinine level, 1.3 mg/dL (115 micromol/L). He is transferred to the PICU setting for close monitoring. His blood urea nitrogen and creatinine levels have remained consistently elevated. His recent electrocardiogram shows peaked T waves. Which of the following is the most appropriate immediate next step in management?

A. Administer IV calcium gluconate and insulin with glucose.
B. Administer IV sodium polystyrene sulfonate.
C. Give an IV bolus of normal saline followed by an IV furosemide dose.
D. Replace the IV fluids being administered with a solution without potassium and recheck serum potassium in 4 hours.
E. Start peritoneal dialysis.