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Acute Kidney Injury in Pediatric Patients: Diagnosis and Management in the Emergency Department

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Abstract

Pediatric acute kidney injury is a condition that is underdiagnosed among children seen in the emergency department, and it has been associated with significant morbidity and mortality, including increased risk for chronic kidney disease. The most common etiologies in pediatric patients are now known to be due to hypovolemia, sepsis, shock, and cardiac dysfunction. This issue compares 3 classification systems for the diagnosis and staging of acute kidney injury and reviews the etiologies that lead to kidney injury in children. The management of pediatric acute kidney injury focuses on identifying patients at high risk, monitoring intravascular volume status, avoiding nephrotoxic medication exposure, and involving a pediatric nephrologist once acute kidney injury is diagnosed.

Case Presentations

An otherwise-healthy 3-year-old girl presents to the ED. According to the child's mother, her daughter has been vomiting after meals for 3 days and has had 5 episodes of nonbloody, liquid diarrhea today. The mother also states that the girl drank only 4 oz of juice and 4 oz of water yesterday and would only drink half as much today. The girl has urinated only once today. She is afebrile, with a heart rate of 145 beats/min and a blood pressure of 80/30 mm Hg. On examination, the girl appears tired, has dry mucous membranes, and a capillary refill time of 3 seconds. She has diffuse abdominal tenderness but no costovertebral angle tenderness and no rash.

In the next room, a 16-year-old adolescent boy who was diagnosed with osteosarcoma 4 months ago and recently underwent treatment with cisplatin has presented with 1 day of diffuse abdominal and back pain associated with nausea, vomiting, and a decrease in oral intake and urine output.

Which historical or physical examination findings in these patients would warrant an evaluation for acute kidney injury? Which laboratory tests or imaging would be most useful in the diagnosis of these patients? How should the risk of kidney injury affect your medical management of these patients?

Introduction

Acute kidney injury (AKI) refers to a sudden loss of kidney function resulting in a decline in the glomerular filtration rate (GFR) and a reduced capacity to excrete nitrogenous waste and regulate extracellular volume and electrolytes. AKI is an increasing problem in children as the medical care being administered becomes increasingly complex. An initial report of hospitalization data revealed an AKI diagnosis in 3.9 per 1000 hospitalized patients; however, the true incidence may be higher, as most diagnostic criteria rely on knowledge of a patient's baseline creatinine level.[1-4] While the incidence of AKI is higher among children who are hospitalized or in the intensive care unit (ICU), the incidence among children presenting to the emergency department (ED) is unclear.[5] In one surveillance study, only 18.5% of pediatric patients who had AKI during hospitalization were diagnosed in the ED, with the majority developing AKI after admission.[6]

The true incidence of pediatric AKI (pAKI) is partly unknown due to the lack of consensus regarding the definition of pAKI and the lack of prospective data. However, available studies suggest that pAKI is slightly more prevalent among boys than girls (1.3:1) and among black patients as compared with other races.[1] Previously, the most common causes of pAKI in hospitalized patients were thought to be hemolytic uremic syndrome, glomerulonephritis, and primary renal pathology. More recent data have identified sepsis, surgery for congenital heart disease involving cardiopulmonary bypass, nephrotoxic drug exposure, and oncologic illness as having the highest association with pAKI.[7] With these other associated disease processes, pAKI diagnosis and management may be overlooked in the ED setting.

Beyond the potentially worsening acute clinical processes taking place, pAKI may also be a risk factor for chronic kidney disease (CKD),[3] which affects 26 million Americans and is responsible for over $40 billion of Medicare payments annually.[8] Previously, AKI was thought to be a transient and reversible process; however, animal studies have shown that episodes of AKI can cause a permanent reduction in peritubular capillaries, predisposing a patient to further renal hypoxia, inflammation, and eventually fibrosis.[9] In a retrospective meta-analysis of 346 pediatric patients, Greenberg et al demonstrated a high rate of proteinuria, hypertension, decreased GFR, and mortality after pAKI; however, the primary studies in this systemic review were small and lacked control groups.[4] Pediatric emergency clinicians may have an opportunity to provide immediate treatment for pAKI, and, in doing so, may mitigate potential long-term effects.

This issue of *Pediatric Emergency Medicine Practice* focuses on the recently constructed definitions of AKI, the array of diagnoses that are associated with its development, and the management of these patients in the ED setting.

Critical Appraisal of the Literature

The available literature on pAKI and its management was reviewed in PubMed using the search terms a*cute kidney injury, acute kidney injury management, acute renal failure, kidney failure, renal insufficiency, renal vein thrombosis, prerenal failure,* and *obstructive renal failure.* The search was limited to studies of patients from birth to age 18. Abstracts were reviewed for relevance to the topic, and cited articles within the search results were also considered. Articles that primarily focused on neonatal intensive care or cardiac surgery patient populations were excluded.

The current literature on pAKI includes few

high-powered prospective controlled trials, with a greater volume of retrospective data, case reports, and adult studies. Many of the existing pediatric studies are limited by small sample size and a primary focus on ICU patients or those requiring dialysis.[10] The greatest limitation is the lack of a single unified classification system; prior to 2004, over 30 definitions of AKI existed in the literature, making cohort analyses virtually impossible.[11]

Classification of the Stages of Acute Kidney Injury

The term *acute kidney injury* has replaced the previously used term, *acute renal failure*. AKI better represents the spectrum of disease between normal renal function and the absence of renal function, which includes early renal injury that precedes changes in urine output and metabolic derangements. AKI represents a continuum of renal disease that can lead to a progressive loss of renal function.

Currently, there are numerous published definitions of AKI in the literature, and consensus has yet to be reached about which classification to use in the clinical setting. A universally accepted definition and categorization of the disease would be helpful for research and for making recommendations on this topic. Furthermore, consensus on this topic could help to identify children at risk for CKD.

RIFLE/pRIFLE Criteria

First proposed in 2004, the RIFLE criteria were one of the first accepted means of standardized staging of patients with AKI. RIFLE is an acronym for the stages of AKI: Risk, Injury, Failure, Loss, and End-stage renal disease.[12] Studies in adults have verified the RIFLE criteria, showing a clear association of the stages of disease severity in this definition of AKI with increased morbidity and mortality.[13] In 2007, these criteria were modified for use in the pediatric population, based on data from 150 critically ill children.[11] These pediatric RIFLE (pRIFLE) criteria were independently verified in critically ill pediatric patients by Plotz et al in 2008 and again by Palmieri et al in 2009.[14,15] The pRIFLE criteria primarily classify disease severity based on estimated creatinine clearance (eCCl) as well as duration of oliguria. **(See Table 1.)** eCCl is calculated using the Schwartz formula, which accounts for serum creatinine (SCr) and height. The pRIFLE Risk stage is particularly relevant in the emergency setting and may be the most amenable to reversal of the disease process via preventative or therapeutic interventions. Because children have the greatest incidence of AKI within the first 3 days of admission to an ICU, early identification is crucial.[11,16]

AKIN and KDIGO Criteria

In 2005, experts in both adult and pediatric critical care and nephrology met at the Acute Kidney Injury

Table 1. Comparison of the Current Classification Systems for Acute Kidney Injury

Classification/ Criteria	Urine Output Over Time (mL/kg/hr)			Estimated Creatinine Clearance Decrease		
pRIFLE[11]	**Risk**	**Injury**	**Failure**	**Risk**	**Injury**	**Failure**
	Oliguria (< 0.5) for 8 hr	Oliguria (< 0.5) for 16 hr	Oliguria (< 0.3) for 24 hr or Anuria for 12 hr	25%	50%	75% or eGFR < 35 mL/ min/1.73 m^2
AKIN[17]	**Urine Output Over Time (mL/kg/hr)**			**Serum Creatinine Increase**		
	Stage 1	**Stage 2**	**Stage 3**	**Stage 1**	**Stage 2**	**Stage 3**
	Oliguria (< 0.5) for > 6 hr	Oliguria (< 0.5) for > 12 hr	Oliguria (< 0.3) for 24 hr or Anuria for 12 hr	0.3 mg/dL or > 1.5- to 2-fold from baseline	> 2- to 3-fold from baseline	> 3-fold from baseline
KDIGO[18]	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 1**	**Stage 2**	**Stage 3**
	Oliguria (< 0.5) for 6-12 hr	Oliguria (< 0.5) for ≥ 12 hr	Oliguria (< 0.3) for ≥ 24 hr or Anuria for ≥ 12 hr	0.3 mg/dL or 1.5 to 1.9 times baseline	2.0 to 2.9 times baseline	3.0 times baseline or eGFR < 35 mL/min/ 1.73 m^2 (if age < 18 years)

Abbreviations: AKIN, American Kidney Injury Network; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; pRIFLE, pediatric Risk, Injury, Failure, Loss, and End-stage renal disease.

Network (AKIN) conference and later published a classification of AKI to "accommodate variation in clinical presentation over age groups, locations, and clinical situations."[17] The AKIN criteria consist of 3 stages and allow for the diagnosis of AKI based on SCr or urine output. **(See Table 1, page 3.)** This classification system is a modified version of the RIFLE criteria; however, it was based on both adult and pediatric data and clinical expertise.[17] In 2012, a nonprofit foundation, Kidney Disease: Improving Global Outcomes (KDIGO), published the first international clinical practice guidelines on AKI. These guidelines combined some of the criteria from pRIFLE and AKIN and have been used in several recent prospective studies.[5,18] **(See Table 1, page 3.)**

Comparison of the Classification Systems

Although there are similarities between these classification systems, there are also important differences. The pRIFLE criteria utilize an eCCl, rather than SCr measures; however, the rapid calculation of creatinine clearance by the Schwartz formula incorporates SCr in addition to a patient's height. There are 3 notable differences in these criteria/classification systems: (1) the duration of oliguria is shorter in both the AKIN and KDIGO criteria compared to the pRIFLE criteria; (2) the AKIN and KDIGO criteria use an absolute increase in creatinine level of > 0.3 mg/dL as a qualifying condition, whereas pRIFLE lacks this criterion; and (3) the pRIFLE Risk stage criterion of a 25% decrease in eCCl may occur with only a 33% relative increase in SCr values, less than the 50% increase to qualify for both AKIN and KDIGO stage 1.

A study that compared the pRIFLE, AKIN, and KDIGO classification systems showed that their application to the same clinical population resulted in differences in AKI incidence and staging. In this retrospective single-center study of 14,795 hospitalized patients, the pRIFLE, AKIN, and KDIGO criteria identified AKI incidences of 51.1%, 37.3%, and 40.3%, respectively. This study was limited by its exclusion of patients who did not have a follow-up creatinine level measured, thereby removing most otherwise-healthy hospitalized children who may not have had repeat blood work obtained. Nevertheless, the discrepancies identified in this study illustrate the dilemma of comparing different studies that use different definitions of pAKI.[19]

Etiology and Pathophysiology

AKI can be subdivided into prerenal, intrinsic, and postrenal causes; however, in some cases, these divisions may overlap. **(See Table 2.)** For example, prerenal dysfunction may predispose and exacerbate the intrinsic injury caused by nephrotoxic medications or, if prolonged, cause acute tubular necrosis. Previously, the most common etiologies of pAKI were thought to be intrinsic, such as glomerulonephritis and hemolytic uremic syndrome. While these etiologies continue to contribute to the overall incidence of AKI, the most common etiologies in pediatric patients are now known to be due to hypovolemia, sepsis, shock, and cardiac dysfunction.[7]

Prerenal Acute Kidney Injury

Prerenal AKI is caused by renal hypoperfusion; this can be due to a decline in circulating blood volume from hypovolemia as well as from poor cardiac function. The kidneys are particularly susceptible to the ischemic effects of inadequate perfusion, such as in hypotension, sepsis, surgery, and cardiac arrest. The epithelial cells of the medullary portions of the proximal tubule and of the thick ascending limb of the loop of Henle are particularly susceptible to ischemic damage from prolonged hypoperfusion.[20,21] In cardiac patients undergoing surgical repair, ischemic injury results from alterations in renal blood flow and autoregulation.[22-24]

Sepsis causes AKI via several mechanisms, including hypotension with decreased renal perfu-

Table 2. Etiology and Pathophysiology of Acute Kidney Injury

Prerenal Acute Kidney Injury
• Hypotension • Sepsis • Severe burns • Abdominal compartment syndrome • Nephrotic syndrome • Hypovolemia (from acute gastrointestinal losses) • Hemorrhage • Distributive shock from anaphylaxis • Nonsteroidal anti-inflammatory drugs • Angiotensin-converting enzyme (ACE) inhibitors
Intrinsic Acute Kidney Injury
• Transition from prerenal acute kidney injury ◦ Prolonged renal hypoperfusion, occurring through acute tubular necrosis • Nephrotoxin exposure • Vascular damage ◦ Hemolytic uremic syndrome (most common primary renal disease that causes acute kidney injury in children) ◦ Rhabdomyolysis • Glomerular damage ◦ Antiglomerular basement membrane disease (Goodpasture syndrome) ◦ Poststreptococcal acute glomerulonephritis • Tubular damage • Interstitial damage
Postrenal Acute Kidney Injury
• Nephrolithiasis • Anatomical obstruction • Urinary retention • Renal vein thrombosis

sion. Animal studies suggest that sepsis may cause a decrease in creatinine clearance despite renal artery vasodilation and increased renal blood flow, thereby suggesting a novel secondary mechanism for sepsis-induced AKI.[25] In a retrospective cohort study of 4532 adult patients with septic shock, 64% of patients developed AKI within 24 hours of the onset of hypotension, and the development of AKI was associated with an increased risk of death in both ICU-hospitalized and non-ICU-hospitalized patients, particularly in patients who had a delayed initiation of appropriate antimicrobial therapy.[26] Gram-negative sepsis has an additional mechanism by which it causes AKI, via a direct interaction between endotoxin and renal Toll-like receptor 4, which induces tumor necrosis factor release, further renal hypoperfusion, and injury of renal endothelial and epithelial cells.[27]

Pediatric patients with severe burns are highly susceptible to AKI. In a prospective study of 123 pediatric patients at a single burn center, the incidence of AKI (as determined by pRIFLE criteria) was 45.5%. The mechanism of injury might have been related to hypovolemia, sepsis, or abdominal compartment syndrome.[15]

Other conditions that can lead to prerenal AKI include nephrotic syndrome, hypovolemia from acute gastrointestinal losses, hemorrhage, and distributive shock from anaphylaxis. Nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors may cause or exacerbate prerenal injury. (For further discussion on nephrotoxic agents, see the following section on "Intrinsic Acute Kidney Injury.") Neonates are more susceptible to hypovolemia and prerenal AKI due to their poor ability to concentrate urine and increased insensible losses.

Intrinsic Acute Kidney Injury

Intrinsic AKI refers to direct damage to the renal parenchyma, and it can be subdivided into nephrotoxin exposure; vascular damage; and glomerular, tubular, or interstitial damage. While it is helpful to categorize intrinsic AKI as a separate entity from prerenal AKI, it is important to remember that with prolonged renal hypoperfusion, prerenal AKI may transition to intrinsic AKI and cause acute tubular necrosis. Tubular damage can occur secondary to prerenal AKI and can also be secondary to nephrotoxin exposure, thus blurring the lines between these categories.

Intrinsic Acute Kidney Injury Caused by Nephrotoxin Exposure

Nephrotoxic medication exposure is an increasingly common etiology of AKI in the pediatric population. There are many commonly used nephrotoxic agents, including NSAIDs, antimicrobials, diuretics, antihypertensive medications, radiologic contrast, and chemotherapeutic agents.[28] **(See Table 3.)** Additionally, recent cases of AKI caused by "designer" drugs (synthetic psychoactive substances such as synthetic cannabinoids and opioids) have been described.[29] In a case-controlled study of 1660 non–critically ill pediatric patients, > 80% of patients received a potentially nephrotoxic agent and 33.8% of patients developed AKI, as determined by pRIFLE criteria. Patients who received 1 or more nephrotoxic agents were significantly more likely to develop AKI.[30]

Nephrotoxic agents can cause AKI through a variety of mechanisms, including direct tubular injury (antimicrobials) and interstitial nephritis (antibiotics and NSAIDs).[20] Designer drugs may cause AKI via pigment nephropathy, acute tubular necrosis, and obstructive nephropathy. Nephrotoxin-induced AKI may not be associated with oliguria; therefore, urine output may not be a sensitive diagnostic tool. In a prospective study of 726 hospitalized children who were treated with nephrotoxic agents, 25% of patients developed AKI (by pRIFLE criteria of change in creatinine clearance alone).[31] In this study, Goldstein et al demonstrated the utility of an AKI surveillance algorithm for patients exposed to nephrotoxic agents, proving an association between exposure and injury.

Nonsteroidal Anti-inflammatory Drugs

Commonly used NSAIDs can result in nephrotoxicity and pAKI, even with short-term treatment.[32] Ibuprofen, commonly prescribed in the ED for the control of fever and pain, has been shown to be potentially nephrotoxic at standard dosing, particularly in the setting of volume depletion or pre-existing kidney injury. NSAIDs, such as ibuprofen and

Table 3. Commonly Used Medications With Potential for Nephrotoxicity

Antipyretics
- Ibuprofen
- Acetaminophen
- Ketorolac

Antimicrobials
- Aminoglycosides
- Amphotericin B
- Beta-lactams (eg, ceftazidime, nafcillin, piperacillin/tazobactam)
- Ticarcillin/clavulanic acid (not available in the United States)
- Acyclovir (antiviral)
- Vancomycin

Diuretics
- Furosemide

Antihypertensive agents
- Captopril
- Enalapril
- Lisinopril

Chemotherapeutic agents
- Ifosfamide
- Cisplatin
- Carboplatin
- Interferons
- Nitrosoureas (eg, carmustine, lomustine)
- Rituximab
- Methotrexate

Neuropsychiatric agents
- Lithium

Other
- Tacrolimus

ketorolac, inhibit prostaglandin synthesis. Although prostaglandin synthesis typically plays a minimal role in maintaining GFR with normal intravascular volume, in the hypovolemic state it may be required as a compensatory mechanism to counteract the vasoconstrictive effects of autologous epinephrine and angiotensin II production.[33]

When dehydration is accompanied by complaints of pain (such as in the case of acute gastroenteritis), analgesia may be required. Children being treated for acute gastroenteritis in the ED may be at particular risk for AKI due to both prerenal injury and intrinsic renal injury from hypovolemia, as well as further renal injury due to NSAID exposure. In addition, acute tubular necrosis is associated with prolonged renal hypoperfusion from decreased intravascular volume. In a retrospective single-center study of pediatric patients with AKI (as diagnosed by pRIFLE criteria), 27 of 1015 (2.7%) cases had evidence of being caused by NSAID use; notably, 15 of the 20 patients for whom dosing data were available received the recommended NSAID dosing.[34] In another prospective, single-center, case-controlled study of 105 pediatric patients with acute gastroenteritis and dehydration, ibuprofen use was identified as a significant independent risk factor for AKI.[35] After controlling for the degree of dehydration and ibuprofen exposure, there was a 2-fold increased risk of AKI in this setting. Therefore, ibuprofen, though efficacious in the treatment of pain and fever, should be used cautiously in a child with acute gastroenteritis or other illnesses that may predispose them to hypovolemia, and it should not be considered to be a universally benign intervention.

Acetaminophen

Acetaminophen has also been associated with pAKI.[36] Acetaminophen is well known to cause liver and kidney damage in supratherapeutic doses and in patients with pre-existing hepatorenal disease. However, even therapeutic doses of acetaminophen have been shown to cause a slight, but significant, level of apoptosis in cultured tubular cells, and may cause some degree of injury in previously healthy children.[37] In a retrospective analysis of 47,803 pediatric patients, Yue et al identified an increased risk of AKI with the use of ibuprofen, but the highest risk, while modest, was seen in patients taking both ibuprofen and acetaminophen concomitantly.[38] However, this study did not control for the degree of dehydration, exposure to other nephrotoxic agents, the appropriateness of dosage, or the frequency of dosing. Although ibuprofen and acetaminophen each have good safety profiles, further evaluation of the nephrotoxic potential of the concomitant use of these medications is warranted.

Contrast-Induced Nephropathy

Contrast-induced nephropathy following the administration of iodinated contrast agents is the third leading cause of AKI in adult hospitalized patients and is an important cause of nephrotoxin-induced AKI, which is more prevalent among adults with a history of CKD and diabetes.[39,40] There are no studies on the incidence of contrast-induced nephropathy in children.[39] Adult studies have shown the highest risk in patients with CKD or diabetes, as well as in patients who received contrast agents that were not iso-osmolar or those who received a higher volume of contrast agent.[39] Most studies on contrast-induced nephropathy involve adults undergoing cardiac catheterization or angiography, which typically requires a larger volume of contrast than a computed tomography (CT) scan. Volumes of contrast > 100 mL have been associated with an increased risk of contrast-induced nephropathy. The pathophysiology of contrast-induced nephropathy is unclear, but is likely multifactorial. Proposed mechanisms include vasoconstriction and shunting of blood away from the medulla to the cortex, causing medullary ischemia, direct nephrotoxicity to the tubular epithelial cells, increased blood viscosity causing stasis, and production of reactive oxygen species and subsequent tubular damage.[39]

Intrinsic Acute Kidney Injury Caused by Vascular Damage

Hemolytic Uremic Syndrome

Vascular etiologies of intrinsic AKI include microangiopathic processes. Among intrinsic AKI etiologies, hemolytic uremic syndrome is the most common primary renal disease that causes AKI in children.[41] Hemolytic uremic syndrome is characterized by the triad of thrombocytopenia, microangiopathic anemia, and AKI. It is most commonly caused by infection with Shiga toxin-producing bacteria and is classically preceded by gastrointestinal infection. Hemolytic uremic syndrome can also occur secondary to infections caused by pneumococcus, *Mycoplasma pneumoniae*, histoplasmosis, human immunodeficiency virus, or coxsackievirus, as well as medications, systemic disease, or, as in most cases of familial atypical hemolytic uremic syndrome, a complement pathway abnormality.[42]

The pathophysiology of hemolytic uremic syndrome, either the classic form induced by Shiga toxin or an atypical form, involves vascular endothelial injury and an ensuing prothrombotic condition, causing increased thrombin and platelet-activating factor levels, consumption of platelets, shearing of red cells by the thrombus, and increased inflammatory cytokines.[43] Multiple factors involved in the pathogenesis of hemolytic uremic syndrome may lead to renal microvascular occlusion, causing AKI. This process may be modifiable with early volume

expansion. No other therapy for Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome has been proven to reduce the need for dialysis, shorten the course of disease, or improve long-term outcomes. As such, treatment recommendations have, until now, focused on supportive care and the management of fluid and electrolyte balance, anemia, and hypertension. Overall prognosis with hemolytic uremic syndrome depends on its cause, as pediatric patients with Shiga toxin-producing *E coli* hemolytic uremic syndrome have a reported mortality rate of < 5%; however, up to 25% of affected children may develop sequelae of CKD, including proteinuria, hypertension, or reduced GFR.[41] In the setting of pneumococcal hemolytic uremic syndrome, up to 80% of patients may require dialysis, which is much higher than the 50% of patients with Shiga toxin-producing *E coli* hemolytic uremic syndrome.[43]

Rhabdomyolysis

Rhabdomyolysis, another notable cause of pAKI, is characterized by destruction of striated muscle leading to release of intracellular materials (eg, creatinine kinase and myoglobin) into the bloodstream. AKI can occur in up to 50% of patients with rhabdomyolysis,[44] particularly in the setting of hypovolemia or decreased renal perfusion. Symptoms of muscle pain and fever are common, and in children, there are often associated viral-like symptoms. Rhabdomyolysis has numerous causes, with the 3 most common in children being: (1) viral myositis (hence the associated viral symptoms), (2) traumatic or crush injuries, and (3) connective tissue disorders. Other etiologies include exertion, metabolic defects, electrolyte disorders, and drug toxicity. Pediatric cases tend to be less severe than those in adults, with 1 study showing 5% of affected children exhibiting evidence of AKI (defined here as creatinine above 97.5% for age and sex[45]), whereas affected adults have an 8% incidence of end-stage renal failure or death.[46] In a study of adult ED patients presenting with rhabdomyolysis, 56% of patients presented with signs of AKI and only 2% of the patients with no signs of AKI went on to develop renal injury.[47]

Crush injuries causing rhabdomyolysis have a particularly high association with AKI. In a retrospective analysis of 521 pediatric trauma patients at a single center, Talving et al found that AKI occurred in 13.4% of children with traumatic rhabdomyolysis.[48] Myoglobin can cause both direct and indirect tubular damage via tubular obstruction and the release of free radicals, causing cellular injury. Renal vasoconstriction is also a key mechanism in rhabdomyolysis-associated nephrotoxicity and is a result of myoglobin-induced pH changes.

Intrinsic Acute Kidney Injury Caused by Glomerular Damage

Glomerulonephritides can predispose a child to develop AKI because the chronic injury of the kidneys causes a loss of renal reserve over time, but the child may initially present with AKI. Antiglomerular basement membrane antibody disease (previously called Goodpasture syndrome) is caused by circulating antibodies against a component of type-4 collagen in the glomerular and alveolar basement membrane. Antineutrophil cytoplasm antibodies in granulomatosis with polyangiitis and microscopic polyangiitis may also present with acute glomerulonephritis and AKI.

Poststreptococcal acute glomerulonephritis (PSAGN) is an important cause of pAKI. PSAGN occurs within 3 to 33 days following a streptococcal infection, and most commonly occurs in school-aged children. Affected children classically present with the acute onset of hematuria, hypertension, and edema, with a history of pharyngitis 2 to 3 weeks earlier or skin infection 4 to 6 weeks earlier. Hematuria occurs in nearly all patients, though often the patient does not give a history of visible hematuria (classic tea-colored or cola-colored urine). Hypertension is also common, occurring in 80% to 90% of patients. Associated laboratory findings are a low C3 level with normal C4 level. The fractional excretion of sodium in PSAGN can be < 1%, similar to what may be found with prerenal causes, whereas a fractional excretion of sodium > 2% may indicate acute tubular necrosis or other types of glomerulonephritis.

Pyelonephritis has been described as a rare cause of AKI in both children and adults; the mechanism is thought to relate to dehydration, interstitial edema, inflammation, tubular obstruction by cellular debris, and intrarenal vasoconstriction.[49]

Postrenal Acute Kidney Injury

Etiologies of postrenal AKI include obstructive uropathy, such as those caused by nephrolithiasis or anatomic obstruction, certain forms of urinary retention, and renal vein thrombosis.

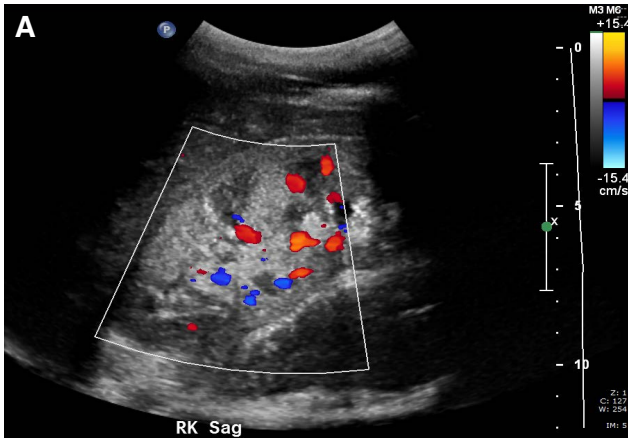
In most—but not all—affected children, nephrolithiasis presents with mild-to-severe pain, often localized to the flank or abdomen. Other associated symptoms include hematuria in 30% to 55% of patients, while dysuria and urgency are present in only 10%, with or without an associated urinary tract infection.[50-53] The majority of pediatric kidney stones are composed of calcium with either oxalate or phosphate, while struvite, uric acid, and cysteine stones may also be seen.[51] Sixteen percent of affected children have a first-degree relative with a history of nephrolithiasis. Seventy-five percent of cases of pediatric nephrolithiasis occur in children with at least 1 predisposing risk factor, such as immobility; metabolic disorders (eg, hypercalciuria, cystinuria); urinary

tract infection, particularly with urease-producing bacteria such as *Proteus* or *Klebsiella* species; inflammatory bowel disease; or hematologic malignancy. In a retrospective study of 2095 pediatric patients undergoing treatment for acute lymphoblastic leukemia, urolithiasis was identified in 0.9% of patients, a much higher rate than the general pediatric population.[54] Although none of the children in that particular study developed AKI, patients at higher risk of developing nephrolithiasis should also raise suspicion for the development of AKI secondary to obstructive injury. Due to the large degree of reserve function, AKI will typically only develop with bilateral ureteral obstruction or obstruction of a solitary kidney.

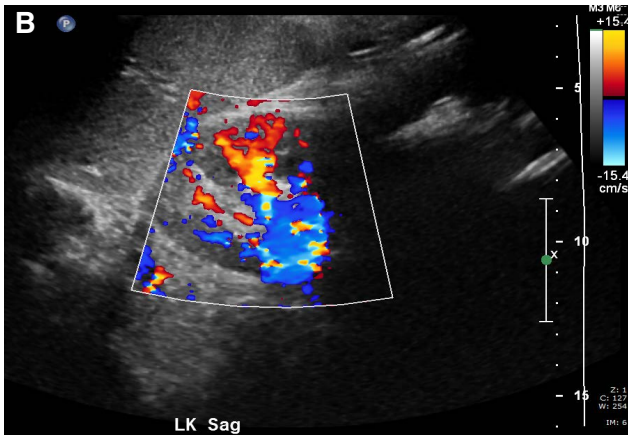
Posterior urethral valves are the most common cause of urinary tract obstruction in newborn boys, and, if not identified prenatally, may present in infancy or later. Affected infants may present with poor growth, urosepsis, grunting with urination, and AKI.[55] Older boys may present with urinary tract infection, enuresis, and other symptoms of urinary dysfunction.[55] Renal and bladder ultrasound may be helpful in identifying hydronephrosis or bladder wall thickening, but the gold standard of diagnosis is by voiding cystourethrogram. Even after the initial diagnosis, these patients may continue to have poor bladder emptying from neurogenic causes, and can develop AKI from increased bladder pressure and ureteral distention.

Renal vein thrombosis is a known complication of nephrotic syndrome and may occur in up to 25% of affected children.[56,57] **(See Figure 1.)** AKI due to renal vein thrombosis may present acutely with flank pain, microscopic hematuria, and AKI, though it may also be asymptomatic.[57] Renal vein thrombosis has also been observed with amyloidosis, abdominal trauma,[58] dehydration, systemic lupus erythematosus,[59] sickle cell anemia, renal neoplasm, homocystinuria, antithrombin III deficiency,[60] oral contraceptive use, and steroid administration.[61] Treatment of renal vein thrombosis may include anticoagulation or thrombolytic therapy.[57,62]

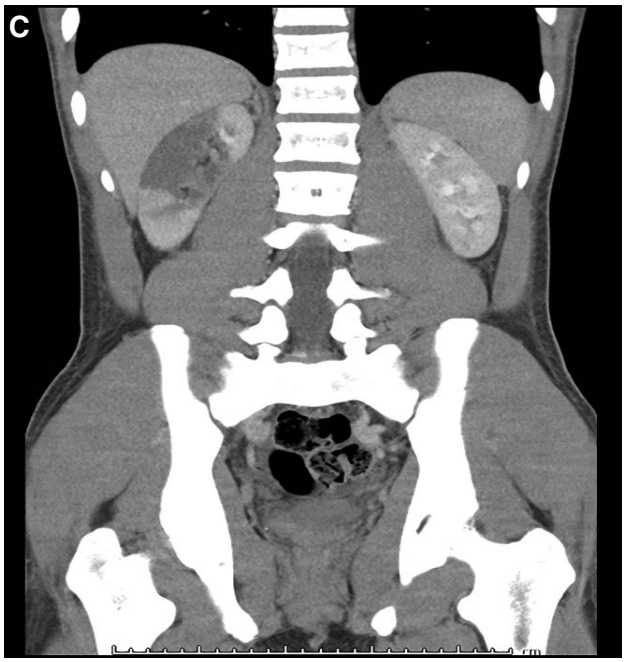
Figure 1. Analysis of Kidney Perfusion



View A: Decreased perfusion in right kidney on Doppler ultrasound.



View B: Normal perfusion in left kidney on Doppler ultrasound.



View C: Corresponding area of infarction on computed tomography scan.

Images courtesy of Melissa Langhan, MD, MHS.

To view a full-color version of these figures and other figures in this issue, scan the QR code below with a smartphone or tablet or go to: https://www.ebmedicine.net/AcuteKidneyInjuryFigures

Differential Diagnosis

An important factor to consider when seeing a patient with an elevated SCr level is whether this is an acute process or simply the initial presentation of CKD. Several findings may help to differentiate between these diagnoses. A history of poor growth or chronic hypertension may support a diagnosis of CKD, whereas patients with AKI should have normal growth and normal preceding blood pressure values. Anemia may be present with either diagnosis; however, more severe anemia may be seen with CKD but is rare with AKI. While a single set of laboratory data may be collected and reviewed in the ED setting, a progressive rise in blood urea nitrogen (BUN) and creatinine over the course of several hours or a few days suggests an acute injury process, as opposed to the progression seen over weeks to months in worsening CKD. A history of fractures or bone demineralization may suggest renal osteodystrophy in the setting of CKD, whereas AKI should have no immediate effect on bone mineralization.[63] An elevated parathyroid hormone level may also indicate a more chronic kidney condition. Ultrasound may reveal small, shrunken kidneys with some etiologies of CKD, primarily congenital etiologies that would not be seen in AKI. (See the "Imaging Studies" section, pages 11 and 12.) Finally, in AKI, normal renal function should resume within days to weeks, whereas dysfunction caused by CKD may persist for months to years.

Prehospital Care

When decreased systemic perfusion is suspected based on initial vital signs and physical examination findings, particularly in the setting of hypotension, intravenous (IV) access should be obtained and IV isotonic fluids should be given before arrival to the hospital. Tachycardia or hypotension may be an important first clue that kidney injury has occurred. A thorough medical history and list of medication exposures should also be obtained to identify other potential risk factors for AKI.

In critically ill children, hypoxemia, hypotension, age > 12 years, coagulopathy, and thrombocytopenia were each found to be independent risk factors for AKI.[16] In the setting of a crush injury, IV isotonic fluid administration should be initiated at the scene of the injury to increase GFR and dilute myoglobin. Kidney injury from rhabdomyolysis may be progressive, but can be reversed with early intervention; as such, there should be no delay in presentation to the ED.

Emergency Department Evaluation

History

A high degree of suspicion is often needed to identify patients with or at risk for AKI. It is important to identify risk factors for AKI, such as hypovolemic status, pre-existing kidney or cardiac disease, recent infection, or exposure to nephrotoxic medications. A review of systems should include questions about gastrointestinal symptoms, the presence of swelling, estimated fluid intake and urine output, as well as urinary symptoms such as dysuria and change in urine appearance. The past medical history should address whether the patient has any previous cardiac, urologic, or oncologic diagnoses that may place them at higher risk. When inquiring about medications, the emergency clinician should ask about prescribed and over-the-counter agents. Assessing family history for kidney disease, nephrolithiasis, or autoimmune disease may not identify children at risk but can assist in narrowing an otherwise broad differential if pAKI is present.

Physical Examination

Vital sign abnormalities such as tachycardia or hypotension suggest a hypovolemic state, whereas hypertension can be a symptom of either AKI or CKD. Physical examination may provide subtle hints in identifying the cause of AKI; however, normal findings do not rule out AKI. Hydration assessment, including the status of mucous membranes, skin turgor, and capillary refill time may guide fluid administration. If a prior weight is available for comparison, this may provide the best evidence for dehydration or fluid overload. Rash, uveitis, joint swelling, and fever may be found in rheumatologic conditions associated with nephritic syndromes. Alternatively, a palpable bladder may suggest an obstructive uropathy. When kidney injury is associated with nephrotic range proteinuria, edema may be notable on examination. If uremia is fairly advanced, the child may have altered mental status or signs of excess bleeding.

Once diagnosed, determining whether AKI is oliguric or nonoliguric—specifically, whether urine output is < 0.5 mL/kg/hr or > 0.5 mL/kg/hr over 6 hours—can help direct fluid management. It is important to quantify all fluid intake and urine output of patients suspected of having AKI. Placement of a Foley catheter may be considered in the critically ill patient.

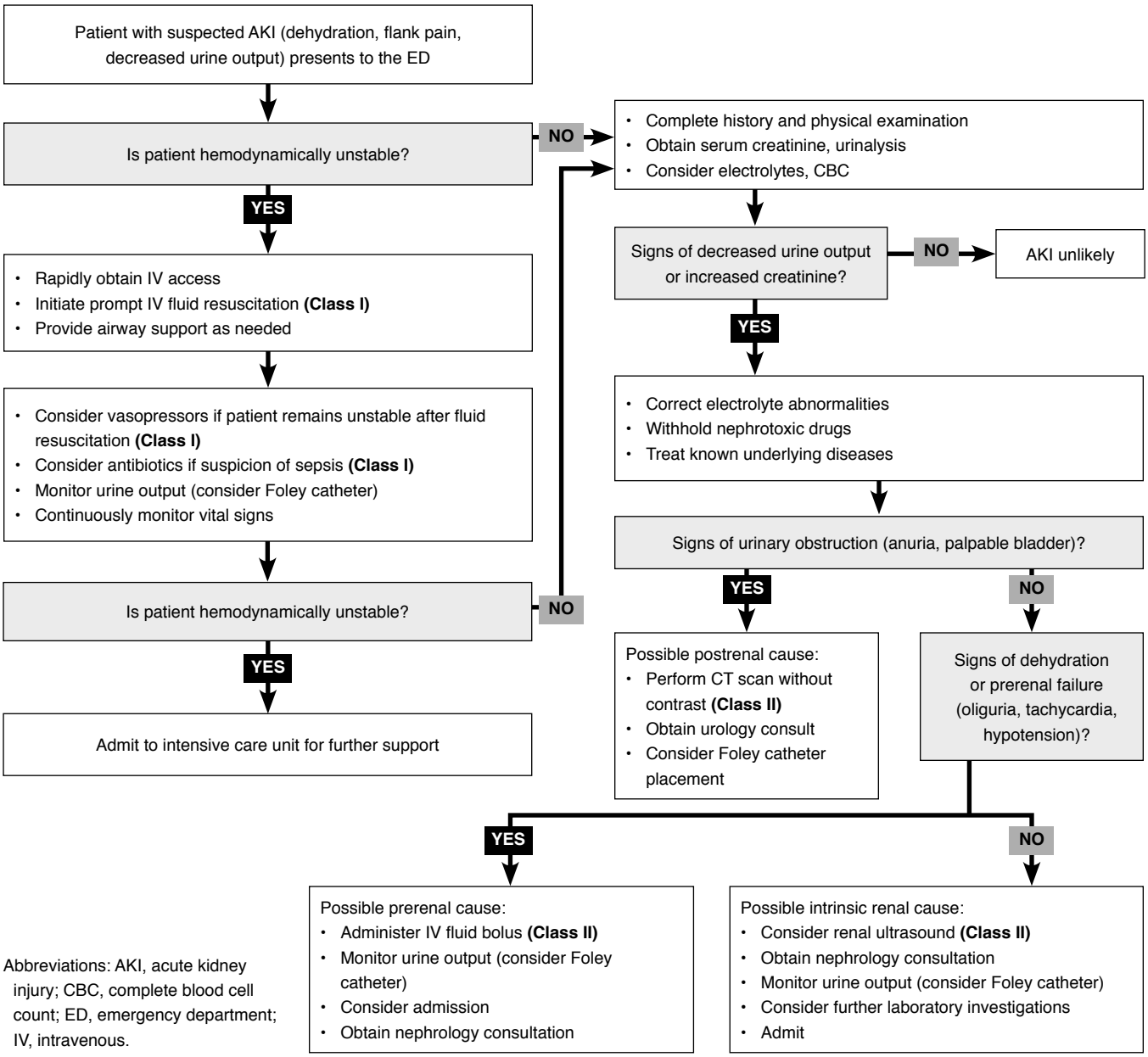
Diagnostic Studies

Laboratory Studies

Serum Creatinine

Given the potential progression of AKI in critically ill children, early identification is crucial.[5,23] An increase in SCr is currently the gold-standard biomarker of AKI, as a rise in SCr is associated with a decreased GFR. However, SCr has shortcomings as a biomarker, particularly in the pediatric population in which baseline creatinine may be unknown or may be low enough such that a rise in value may remain within

Clinical Pathway for Management of Pediatric Patients With Suspected Acute Kidney Injury



Abbreviations: AKI, acute kidney injury; CBC, complete blood cell count; ED, emergency department; IV, intravenous.

Class Of Evidence Definitions

Each action in the clinical pathways section of *Pediatric Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

the normal range for age. Additionally, creatinine testing is not sensitive in the early phase of AKI; creatinine may not rise for up to 48 hours after initial insult or until up to 50% of kidney function has been lost,[64] as kidney reserve function must first be overwhelmed before a rise in SCr occurs. Creatinine is also sensitive to differences in muscle mass, gender, hydration status, and age.[65] **(See Table 4.)** Moreover, as a spot value in the acute setting, SCr measurement may provide false reassurance, as there may not be a baseline value for comparison. For example, if a 3-year-old boy has an undocumented baseline SCr level of 0.3 mg/dL, then an acute rise by 100% would remain within the reference range for age.

In a 2017 prospective study of nearly 5000 patients, it was shown that using a rise in creatinine alone would have missed 28% of AKI cases among children in the ICU who were diagnosed with AKI based on low urine output. Low urine output was associated with higher mortality when compared to children with normal urine output.[5] SCr and measured urine output are both helpful in establishing a diagnosis of AKI by current criteria; however, more specific and sensitive biomarkers are needed.

Metabolic Panel and Additional Serum Testing

Initial laboratory evaluation should be focused on traditional markers of kidney injury and the potential abnormalities associated with AKI. A basic metabolic panel can demonstrate metabolic acidosis, which can occur in AKI due to insufficient excretion of endogenous acids,[67] and the development of an anion gap. This panel also would identify hyperkalemia, one of the more significant morbidities seen with renal injury. Additional serum testing should include bone and mineral markers, as elevated serum phosphate and low serum calcium levels may be associated with AKI.

Urinalysis

Urinalysis can be helpful in identifying patients at risk for AKI, specifically when certain risk conditions are suspected, such as rhabdomyolysis, glomerulonephritis, infection, or nephrotic syndrome.

Table 4. Reference Values for Creatinine Based on Age[66]

Age	mg/dL	mcmol/L
Cord	0.6-1.2	53-106
Newborn	0.3-1.0	27-88
Infant	0.2-0.4	18-35
Child	0.3-0.7	27-62
Adolescent	0.5-1.0	44-88
Adult man	0.7-1.3	62-115
Adult woman	0.6-1.1	53-97

Reference values may vary by laboratory.

Among hospitalized adults, only 4% of patients with AKI were noted to have a normal urinalysis, with the most common etiology being hypertension.[68] The presence of red or white blood cells; renal epithelial cells; epithelial, hyaline, or granular casts; and higher levels of protein in the urine are all associated with AKI.[69]

In rhabdomyolysis, urinalysis results for hemoglobin may be useful in ruling out AKI, but may also be useful in assessing the evolution and recovery of injury. In a retrospective analysis of 1821 patients hospitalized following the 2003 Bam, Iran earthquake, Alavi-Moghaddam et al found that urine dipstick testing had a sensitivity of 83% and specificity of 56% in identifying patients at high risk for AKI due to crush-induced rhabdomyolysis.[70] Furthermore, hematuria measuring < 2+ is much less likely to be caused by rhabdomyolysis.[45] Another effective urinary biomarker is the presence of urinary casts, which may be a specific, but insensitive, finding of intrinsic renal injury. While red blood cell casts are pathognomonic of glomerulonephritis, granular casts can be seen with acute tubular necrosis. However, for most patients with AKI not from these specified conditions, urinalysis findings may not have as great of a predictive value for AKI risk.[71]

Urine testing for specific gravity, urine sodium, urine osmolality, fractional excretion of sodium, and fraction of excreted urea can also be helpful in identifying AKI and establishing whether the renal insult was prerenal or intrinsic. Prerenal AKI is supported by elevated urine specific gravity or osmolality and a decrease in urine sodium, fractional excretion of sodium, or fraction of excreted urea. Conversely, intrinsic AKI is suspected in the setting of low urine specific gravity or osmolality, or an increase in urine sodium, fractional excretion of sodium, or fraction of excreted urea, which suggests an impairment in the concentrating ability of the nephrons.

Other Laboratory Studies

In addition to serum and urinary biomarkers of kidney injury, other laboratory testing may be helpful in uncovering the etiology of the renal insult. Additional testing, if necessary, should be guided by the findings of a thorough history and physical examination. This may include a complete blood cell count, blood or stool culture, complement levels, coagulation studies, creatinine phosphokinase, and specific immunologic titers (eg, antinuclear antibodies, antineutrophil cytoplasmic antibodies, antiglomerular basement membrane antibody).

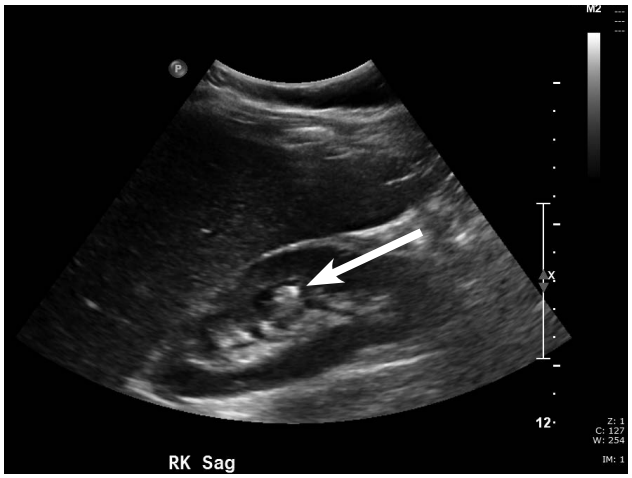
Imaging Studies

Radiologic evaluation is not as helpful in determining whether AKI is present, but may aid greatly in determining the etiology of AKI. Ultrasound is the most useful radiologic test in the evaluation of AKI,

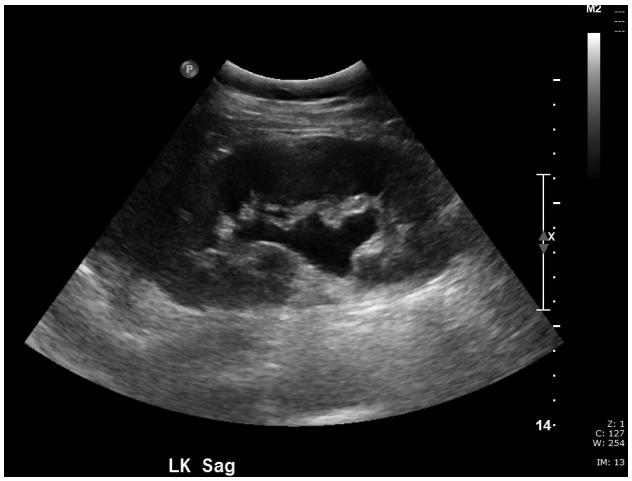
as recommended by the American College of Radiology,[71] as it may assess for the presence of renal enlargement, increased echogenicity, or urinary tract obstruction, such as hydronephrosis. **(See Figure 2.)** Renal size can help differentiate AKI versus CKD. Small, echogenic kidneys may represent either congenital conditions or a chronic process that has led to parenchymal atrophy, whereas increased echogenicity may indicate intrinsic renal disease.[71] Renal length is an imperfect substitute for total size because it includes the kidney's central sinus fat, but it is a practical substitute for renal volume (measurement of which may be more dependent on the technician's skill). Ultrasound with Doppler flow can be useful if renal vein thrombosis is a concern. **(See Figure 1, page 8.)** The use of bedside ultrasound by emergency clinicians also may be helpful in noting the presence of hydronephrosis and intravascular volume status through measurements of the inferior vena cava and aorta.[72]

If obstructive uropathy is suspected as the cause of AKI, then CT or magnetic resonance imaging may be warranted to determine the cause of obstruction. Noncontrast abdominal CT is the most sensitive imaging in the diagnosis of nephrolithiasis; however, because of the associated radiation exposure, initial investigation with x-ray and ultrasound should be considered. CT or magnetic resonance imaging may also be used for assessing other anatomical abnormalities of the urinary tract, but they have a low yield for most other conditions that cause AKI.

Figure 2. Ultrasound Imaging of Kidneys



Right kidney without evidence of hydronephrosis. Arrow indicates a small renal stone.



Left kidney with evidence of hydronephrosis.
Images courtesy of Melissa Langhan, MD, MHS.

Prevention and Treatment

The mainstays of AKI prevention and treatment include maintenance of renal perfusion by preservation of intravascular volume, avoidance of hypotension, and the careful consideration of nephrotoxic agent administration. There are no effective pharmaceutical agents to treat AKI itself.

Fluid Resuscitation

When prerenal AKI is suspected, early fluid resuscitation by oral or IV hydration is considered the most critical aspect of therapy; however, well-powered data in pediatric patients is lacking. Notably, aggressive IV fluid resuscitation could be detrimental to patients with cardiac dysfunction. In a randomized controlled study of 224 adult ICU patients with sepsis, early fluid administration was shown to decrease the risk of AKI from 55% to 39% ($P = .015$).[73] After a patient has been hemodynamically stabilized, the underlying etiology of renal injury should be quickly identified and treated accordingly.

Oral rehydration therapy is recommended as first-line therapy for mild-to-moderate dehydration,[74] but it is less useful in the setting of severe dehydration or if there is suspicion of AKI. In the hypovolemic child requiring IV fluid administration, an initial normal saline (0.9%) bolus of 20 mL/kg infused over ≤ 15 minutes can improve renal perfusion and prevent worsening intrinsic kidney injury. In situations of severe volume depletion, up to 60 mL/kg of fluid resuscitation may be warranted. When cardiac disease is known or suspected, initial fluid boluses may be smaller (10 mL/kg) and, overall, fluid should be administered at slower rates.[75] In all cases of fluid resuscitation, treatment should be modified based on a child's presentation, medical history, and individual requirements, as fluid overload can have high morbidity, particularly in a patient with heart failure or a predisposition to fluid overload.

In addition to treatment of sepsis and hypovolemia, fluid administration has renal benefit in patients with hemoglobinuria, myoglobinuria, neph-

rotoxic agent exposure, or tumor lysis syndrome.[76] In these settings, increasing the GFR allows for both renal protection and the expedited excretion of the offending agents. However, specific guideline recommendations for the amount and duration of fluid resuscitation for the prevention and management of pAKI are lacking.

Vasopressors and Inotropes

If fluid resuscitation is insufficient in correcting hypotension and improving renal perfusion, the use of vasopressors or inotropes such as norepinephrine, dobutamine, or dopamine may be indicated. Low-dose dopamine, (< 5 mcg/kg/min) has been considered to be a potential agent in the prevention and treatment of kidney injury.[41] The theory behind its use is that low-dose infusions allow dopaminergic and beta-adrenergic effects to predominate over the alpha-adrenergic effects. In other words, low-dose dopamine can stimulate renal dopamine receptors, causing renal vasodilation and increased renal blood flow without causing a change in blood pressure. However, no studies have shown that use of low-dose dopamine to improve renal function actually leads to improvement in clinical outcomes.[41] In a multicenter randomized placebo-controlled trial of 328 ICU patients receiving either continuous low-dose dopamine or placebo, there was no significant difference in peak creatinine concentration, length of stay, or need for renal replacement therapy.[77] Given the lack of evidence in its support and the potential adverse effects, which include cardiac dysrhythmia, myocardial ischemia, decreased intestinal blood flow, hypopituitarism, and T cell suppression, dopamine infusion should not be used first-line to treat or prevent pAKI.

Mannitol and Loop Diuretics

Mannitol has been used to correct an oliguric state; however, it has not been shown to prevent AKI and may instead induce or exacerbate nephropathy.[18] Mannitol is an osmotic diuretic that is filtered at the glomerulus, undergoes minimal reabsorption by the renal tubules, and causes a shift of fluid into the extracellular space. In animal models, mannitol has been shown to mitigate the reduction in GFR associated with acute tubular necrosis when given before the induction of renal ischemia or exposure to nephrotoxic agents. This may be due to the removal of obstructing tubular casts, dilution of nephrotoxic substances, or prevention of tubular cell swelling via osmotic forces. However, there are insufficient data to justify its use in human subjects. In a randomized prospective study of 78 patients with mild-to-moderate renal insufficiency, Solomon et al found that hydration with saline plus either mannitol or furosemide prior to angiography was associated with increased renal injury compared to pretreatment with 0.9% saline alone.[78] In another retrospective analysis of 24 ICU patients with rhabdomyolysis, Homsi et al found that adding mannitol to the hydration protocol had no effect on SCr levels.[79] Although mannitol has been used in the setting of rhabdomyolysis in order to attenuate or prevent renal injury, this off-label use is not supported by high-powered, prospective, randomized clinical trials, and mannitol is never indicated in the prevention or management of pAKI.

Loop diuretics are also not recommended for the treatment of AKI despite their potential to resolve an oliguric state.[18] They have no clinical benefit[18] and may have adverse effects, including allergic interstitial nephritis[80] or decreased renal perfusion secondary to overdiuresis.[81]

Alkali Therapy

In the treatment of rhabdomyolysis, urine alkalinization via sodium bicarbonate infusion has been proposed to be a renoprotective mechanism by decreasing the precipitation of heme protein and free iron from myoglobin, thereby decreasing cast formation and renal vasoconstriction. However, the data supporting this treatment are derived from uncontrolled case series, as no randomized controlled trials exist to suggest that alkaline diuresis is more effective than diuresis with normal saline in preventing AKI with rhabdomyolysis. The potential risks of plasma alkalinization include deposition of calcium phosphate and amplification of the effects of hypocalcemia, including tetany, seizures, and cardiac arrhythmias. Patients with hypocalcemia, alkalosis, or serum bicarbonate levels > 30 mEq/L should not be considered for alkali therapy.

Intravenous Fluids

Prevention of Contrast-Induced Nephropathy

The majority of studies assessing prevention strategies for contrast-induced nephropathy focus on adult patients with CKD who are typically undergoing angiography with higher volumes of contrast delivered intra-arterially; thus, recommendations in otherwise-healthy pediatric patients are limited. Administration of isotonic IV fluids in the periprocedural period has been shown to have a protective effect against the development of contrast-induced nephropathy; however, the type of fluid and volume of fluid have yet to be clearly established.[39] Individual studies using sodium bicarbonate have mixed results, but meta-analyses show no benefit.[39,40,82,83] N-acetylcysteine may offer benefit in preventing contrast-induced nephropathy when low-osmolar contrast is used or when contrast is administered intra-arterially.[83] Among adult ED patients undergoing contrast-enhanced CT scans, the addition of N-acetylcysteine to IV fluid administration was not shown to provide any benefit in preventing contrast-induced nephropathy.[84] More research on the use of

preventative agents in pediatric patients receiving IV contrast is warranted before recommendations can be made on its use.

Treatment of Electrolyte Derangements

Electrolyte derangement can be a life-threatening, but treatable, complication of AKI. Hyperkalemia, hyperphosphatemia, and hypocalcemia may all be seen with AKI, so it is important to adjust the additives to IV fluids (specifically to withhold potassium and phosphate) and to be mindful of the effects of medications on these serum levels. Additionally, in the setting of oliguria and fluid overload, total fluid intake should be minimized to compensate only for insensible losses. Hyperkalemia can be life-threatening and should be managed expeditiously. Continuous cardiac monitoring is warranted and electrocardiogram evaluation can identify deleterious effects on cardiac function. Administration of a beta agonist (eg, albuterol) as well as a combination of regular insulin IV and IV dextrose can help to shift potassium intracellularly. IV calcium administration has cardioprotective effects and also should be used when hypocalcemia or hyperkalemia with electrocardiogram changes is present. Excess potassium can be removed with sodium polystyrene sulfonate, loop diuretics, or via hemodialysis.[44]

Renal Replacement Therapy

The time at which to initiate renal replacement therapy is still a matter of debate, as there is a lack of strong evidence in the literature. Renal replacement therapy use has been documented in up 16% of critically ill children and is associated with higher mortality.[1,16,85] Current indications for renal replacement therapy include hyperkalemia resistant to treatment, fluid overload with pulmonary edema, resistant metabolic acidosis, anuria, and progressively worsening renal function or uremia with encephalopathy.[13,85]

Nephrology Consultation

In most cases of pAKI, consultation with a nephrologist is warranted, though it is not always needed in the emergent setting. If a child is suffering from potentially life-threatening complications of AKI or is at risk for progressing to renal failure, early and emergent consultation with a nephrologist is needed to determine whether renal replacement therapy should be initiated and what mode to use, if warranted.[85] However, patients with milder AKI, especially those having repeated episodes of injury, are at risk for developing long-term derangements in kidney function and merit ongoing monitoring with the goal of prevention or expeditious detection of the development of CKD.[18]

Special Circumstances

Trauma

Trauma can result in direct or indirect kidney injury. Crush injuries should always raise suspicion for rhabdomyolysis and warrant immediate IV fluid administration.[48] Blunt abdominal trauma can result in renal laceration, renal contusion, and renovascular injury.[58] In a study of 48 children sustaining renal injuries, the degree of hematuria did not correlate with the degree of injury, and some patients suffered substantial injury without associated hematuria.[86] The authors of that study concluded that CT scan of the abdomen was justified in any patient with blunt abdominal trauma and any degree of hematuria.

Children With Special Needs

Another population to be particularly sensitive to the risk of AKI is in medically complex or special-needs pediatric patients. These patients are particularly susceptible to prerenal injury when acutely ill, as fever and tachypnea may increase their fluid requirements, but they may be unable to act on their thirst mechanism if they are nonverbal or physically restricted. These patients also may be prescribed many medications and may be exposed to 1 or more nephrotoxic agents, the effects of which may be more pronounced in a dehydrated state. Immobile patients are at increased risk of nephrolithiasis secondary to increased bone resorption. Flank pain can go unrecognized in the nonverbal patient. Additionally, hematuria may be falsely attributed to traumatic catheterization in patients regularly requiring such procedures. Finally, patients with certain genetic disorders may have underlying CKD or a decreased number of functioning nephrons, putting them at greater risk for the development of AKI.[87]

Children With Solitary Functioning Kidneys

A child with a solitary functioning kidney is at risk of developing both AKI and CKD. In a multicenter retrospective longitudinal cohort study of 407 children with a solitary functioning kidney, Westland et al found that 37% had signs of chronic renal injury such as hypertension, proteinuria, impaired GFR, or the need for use of a renoprotective medication. In this study, renal length was inversely associated with risk of developing renal injury, suggesting a benefit of renal hypertrophy in the setting of a solitary functioning kidney.[87] Therefore, in any child with a solitary functioning kidney or known CKD who presents to the ED, the possibility of AKI should always be considered.

Patients Who Have Had a Kidney Transplant

Although the data primarily focus on adults, patients who have had a kidney transplant or have a history of CKD are also at much higher risk of AKI than

otherwise-healthy patients.[88] Baseline GFR has been inversely correlated with risk for AKI.[88] Common etiologies among these patient include infections, medication toxicity, and graft failure.[89,90] Among patients who have had a kidney transplant, the development of AKI is associated with graft failure.[90]

Controversies and Cutting Edge

Biomarkers for Diagnosis of Acute Kidney Injury

Much of the current clinical investigation regarding AKI has focused on the use of novel biomarkers for the prompt diagnosis of AKI. Biomarkers under investigation include neutrophil gelatinase associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), cystatin C (CysC), tissue inhibitor of metalloproteinases-2 (TIMP-2), insulin-like growth factor-binding protein 7 (IGFBP7), and liver fatty acid-binding protein (L-FABP).[64] The promise in these biomarkers is that they may identify AKI earlier in the course of renal injury than SCr elevation, allowing more timely diagnosis and intervention. Urinary biomarkers have shown limited ability to detect pAKI at the pRIFLE Risk stage, but greater promise in identifying patients at the pRIFLE Injury stage in the emergency setting.[91]

NGAL is secreted from kidney tubular cells within hours of tubular injury.[92] Because of its small size (25 kDa), it is easily filtered at the glomeruli but is reabsorbed by undamaged proximal tubules.[93] If injured, the proximal tubule has decreased reabsorption capability, resulting in increased excretion and elevated urinary NGAL levels.[94] A prospective study of pediatric cardiac surgery patients found that children who developed a 50% increase in SCr (ie, those with AKI) would first have a 20-fold increase in NGAL concentrations in their urine and serum within 2 hours of cardiopulmonary bypass as compared to a 2-fold increase in patients without AKI.[95] Urine NGAL levels have diagnostic and prognostic utility as a biomarker of intrinsic kidney damage;[92] however, lack of currently defined cutoff levels and immediate clinical availability has limited its clinical utility in the ED setting.

IL-18 is a proinflammatory cytokine that is upregulated by renal tubules in response to ischemic injury, and its presence in urine is associated with AKI. In a multicenter cohort study of 311 children undergoing surgery for congenital cardiac defects, Parikh et al found that elevated urine levels of IL-18 and NGAL were associated with greater risk of severe AKI.[96] In a prospective multicenter cohort study of 91 adult kidney transplant patients, a rise in IL-18 was a more sensitive marker than creatinine for predicting dialysis requirement.[97]

KIM-1 is a membrane protein expressed in proximal tubule cells, the transcription and expression of which are increased in the setting of ischemic injury.[98] Although its function is not well understood, it is helpful in identifying kidney damage in humans before the onset of functional damage, as indicated by an increase in SCr. However, the low positive predictive value of KIM-1 has made it less helpful as a clinical tool.[99]

CysC is a cationic cysteine protease inhibitor that is released by all nucleated cells. It is freely filtered at the glomerulus and completely reabsorbed by the proximal tubule. These characteristics make it a useful predictor of GFR and an early biomarker of proximal renal tubule damage and AKI.[64,100] An increase in serum CysC levels may detect renal dysfunction 24 to 48 hours earlier than SCr. Unlike SCr, serum CysC level is independent of a patient's muscle mass,[100] and it may be more useful in pediatric patients, especially those with compromised neuromuscular status.

TIMP-2 and IGFPB7, both measured from the urine, are considered cell cycle arrest markers and, in most studies, have been found to have superior test characteristics when compared to other biomarkers for AKI.[101] Unlike the other biomarkers discussed here, TIMP-2 and IGFPB7 levels have not been shown to rise due to other comorbid conditions, and are thus more specific for AKI. While the United States Food and Drug Administration has approved a test for TIMP-2/IGFPB7, it is indicated for critically ill hospitalized patients at risk for moderate-to-severe AKI; reference ranges for children have not yet been established.[102]

Novel Therapies for Acute Kidney Injury

In addition to biomarkers, current research is investigating novel therapies for the prevention and treatment of pAKI. Fenoldopam is a potent and short-acting dopamine alpha-1 receptor agonist that was shown to increase urine output and reduce BUN in a retrospective study of 13 critically ill children.[103] In a prospective randomized controlled trial of 80 infants undergoing cardiac bypass, fenoldopam administration led to decreased urinary NGAL and CysC levels and reduced the use of diuretics and vasodilators compared with placebo.[104] In a trial of adults who had cardiac surgery and evidence of AKI, fenoldopam did not significantly reduce mortality or the need for renal replacement therapy, but did result in a higher rate of hypotension.[105] Fenoldopam, therefore, has the potential to increase renal perfusion in critically ill patients, but at this point, there are insufficient data to recommend its use in children with AKI.

Natriuretic peptide analogues are effective in the treatment of heart failure in adults and have been considered as therapy for pAKI that is associated with cardiac disease. In an observational cohort study of 63 children with heart failure, administration of nesiritide, a recombinant beta-type natriuretic

peptide, effectively increased urine output and decreased SCr.[106] Among adults with CKD, nesiritide was shown to reduce the rates of contrast-induced nephropathy.[107] Nesiritide promotes natriuresis and diuresis, but there are currently insufficient data to support its use in pAKI.

With better biomarkers that are able to accurately diagnose AKI earlier than before, previously investigated therapies may also be revisited for efficacy in AKI if instituted earlier, as previous failures may have been due to their institution late in the course rather than a true lack of efficacy.

Disposition

AKI is an independent risk factor for morbidity and mortality, and its identification should be considered, along with the underlying etiology, when planning a patient's disposition. In a study of 150 critically ill children, Akcan-Arikan et al found that

Risk Management Pitfalls in Pediatric Patients With Acute Kidney Injury

(Continued on page 17)

1. **"The rise in creatinine was minimal and the patient was classified in the Risk category of AKI. There was no need to consult nephrology, since this category does not lead to any long-term consequences."**
   AKI is not a static process, but can progress throughout the course of a patient's illness based on the etiology and the management they receive. Thus, AKI in a patient who is in the Risk stage that is not caught early could continue to progress to worsening stages, particularly if the patient has a serious illness, such as sepsis. When AKI is identified, a nephrology consult should be considered, as all patients may be at risk for long-term consequences and should have follow-up even when "recovered."

2. **"I checked that patient's creatinine, and the result was within the normal range, so I ruled out AKI."**
   While the creatinine level is typically used as a screening tool to diagnose AKI, it is not always a reliable indicator in children. This is due to the relatively low levels of creatinine in children as compared to adults, and the wide range of normal values for different age groups. Since many children do not have baseline values of creatinine available as a reference point, it is difficult to assess the degree of change based on a measurement at a single point in time.

3. **"Muscle aches associated with viral infections are a benign symptom and are not associated with AKI."**
   While myalgias are a common complaint associated with viral infections, emergency clinicians should consider viral myositis in their differential as well. In this case, muscle breakdown could lead to rhabdomyolysis and cause AKI. Other causes of rhabdomyolysis include exertion and traumatic crush injuries.

4. **"Mannitol is an osmotic diuretic. It improves a patient's urine output, and, thus, renal function. That's why it is the best treatment option for AKI."**
   While osmotic diuresis facilitated by mannitol can correct a patient's oliguria, there is no evidence to support the use of mannitol in the prevention or management of AKI. In fact, the administration of mannitol may worsen AKI by causing or worsening nephropathy. This is also true of other diuretics, which should only be used in the setting of volume overload.

5. **"Since I didn't have a baseline creatinine value to compare to my current creatinine level, I ordered a renal ultrasound to determine whether AKI is present."**
   Renal ultrasonography is considered the first diagnostic imaging modality of choice for AKI; however, it cannot identify whether AKI is present. In patients with CKD, small kidney size may be noted on ultrasound and may be an indication that the elevated creatinine is not from an acute process. Similarly, in postrenal AKI, the ultrasound may demonstrate hydronephrosis as a cause of elevated creatinine. However, in patients with intrinsic renal disease, the ultrasound may be normal or show enlarged, echogenic kidneys, but this does not distinguish between acute and chronic disease.

6. **"The patient's creatinine did not increase much compared to a prior value in her medical record, so she cannot have AKI."**
   Although a rise in creatinine is used in all of the classification systems to define AKI, it is not the most sensitive or reliable test. Creatinine may not rise until up to 50% of the patient's glomerular filtration is lost, and may not increase during the first 24 to 48 hours of disease, thus delaying the ability of this test to identify patients with AKI.

children with AKI (as defined by pRIFLE classification) had significantly longer pediatric ICU and hospital admissions compared to those without AKI; however, the authors of that study did not identify a significantly higher mortality rate in either group, which may be attributable to the relatively small sample size.[11] Sutherland et al found 46% of children with AKI admissions were classified as having an extreme likelihood of dying as compared to only 1% of children with non-AKI admissions.[1] However, the actual mortality rate among AKI admissions in this sample was 15.3%, compared with 0.6% of non-AKI admissions. Pediatric ICU patients who have AKI have a higher mortality compared to patients without AKI, with risk varying by severity of AKI.[5,23]

Indications for hospital admission include the requirement for continued IV administration of fluids or antibiotics, correction of electrolyte disturbances, an underlying etiology of injury requiring immediate surgical intervention, or another medical

Risk Management Pitfalls in Pediatric Patients With Acute Kidney Injury

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7. **"The patient with AKI was tolerating oral fluids, so I did not consider the need for expedited volume repletion with IV fluids."**
While oral rehydration is often the first-line choice for management of mild dehydration in children, it may be insufficient in the setting of AKI. Moderate-to-severe dehydration, elevated creatinine levels, and decreased urine output should prompt the provider to consider IV fluid replacement therapy. Prompt administration of IV isotonic fluids may improve renal perfusion and lessen further kidney damage. Urine output should be monitored carefully in this setting.

8. **"Ibuprofen is a benign medication, and its use in patients is always appropriate."**
Ibuprofen is a commonly administered medication to address pain and/or fever. However, ibuprofen can also cause AKI. The history should include questions regarding a patient's previous use of ibuprofen, as this is an identifiable risk factor for AKI. The use of ibuprofen should be avoided if it is unnecessary, particularly in a dehydrated patient. After controlling for the degree of dehydration, ibuprofen exposure increased the risk of AKI more than 2-fold in this setting, and concomitant use of ibuprofen and acetaminophen further increased the risk of developing AKI. Therefore, ibuprofen use should be avoided in any child suffering from acute gastroenteritis or other illnesses that may predispose them to hypovolemia.

9. **"The urinalysis was negative, so there was no evidence of kidney injury."**
Similar to creatinine, a urinalysis may provide helpful information about the kidneys and their function; however, it is not a useful screening test for AKI. Nonetheless, positive findings on urinalysis may be helpful in the differential diagnosis. The presence of leukocyte esterase or nitrites may indicate a urinary tract infection. The presence of hematuria may indicate nephritis, urolithiasis, trauma, viral cystitis, or myoglobinuria from rhabdomyolysis. The presence of red cell casts is diagnostic of glomerulonephritis. Persistent proteinuria may be an indicator of nephrotic syndrome, tubulointerstitial disease, or glomerular disease, whereas transient proteinuria may have a more benign etiology. The combination of hematuria and proteinuria should suggest a renal disease such as Alport syndrome, membranoproliferative glomerulonephritis, or IgA nephropathy.

10. **"There was no evidence of kidney involvement because there was no abdominal pain, back pain, or costovertebral angle tenderness on examination."**
A high degree of suspicion is needed to diagnose AKI in children. There may be no indication from the history or physical examination that a renal problem is present. Pain is often not a presenting sign. Emergency clinicians must consider the risk of AKI when managing other acute problems in children such as dehydration, infection, trauma, drug intoxication, and medication administration.

issue requiring prolonged medical care or observation. Admission to the ICU may be warranted in many presenting cases of AKI, but should be based on hemodynamic stability and the intensity of interventions required. AKI may be an independent reason for admission; however, if a mild rise in creatinine can be corrected after interventions in the ED, outpatient follow-up may be appropriate. Because CKD is a known complication of AKI, it is important that follow-up with a pediatric nephrologist as an outpatient be considered in any child diagnosed with AKI.

Time- and Cost-Effective Strategies

- In cases of AKI, early consultation with a nephrologist may be warranted. Many patients with AKI may have long-term derangements in kidney function and will require ongoing monitoring and medical care. Follow-up should be arranged prior to discharge from the ED.
- Early consideration of AKI and measures to prevent progression are critical in the management of this process.
- Ultrasound is a quick, noninvasive, and inexpensive test (compared to other imaging), and can be used to assess the kidneys when AKI is confirmed.
- Early fluid resuscitation may reduce the risk of AKI in patients with sepsis.

Summary

AKI can cause significant morbidity and has been associated with increased mortality in children, although reported mortality rates associated with AKI vary greatly.[85] Often requiring a high degree of suspicion, AKI is likely underdiagnosed in the ED setting. The lack of a unified classification system and the need for more sensitive and specific biomarkers at the time of renal injury are 2 barriers to research and improved identification of at-risk patients. The 3 major classification systems currently used for diagnosis of AKI in children are pRIFLE, AKIN, and KDIGO, which rely upon SCr and urine output parameters to define AKI.[11] Future research should focus on defining a single verified classification system. However, the burden of this task is amplified by the lack of a biomarker that is capable of identifying kidney injury at its earliest stage, which would allow for earlier interventions.

An increase in SCr is currently the gold standard for clinical diagnosis by all major diagnostic criteria. However, an increase in SCr may be delayed up to 48 hours after injury, and values may vary based on age, sex, and degree of muscle mass. Additionally, single values without a known baseline, as often may occur in the ED setting, can make the diagnosis of AKI difficult. The wide range of normal SCr values in children as well as the comparatively small increases that are associated with increased morbidity and mortality increases false-negative results and potentially false reassurance regarding kidney health.[91] Furthermore, a single elevated creatinine level cannot differentiate between AKI and CKD.[108]

New biomarkers that are sensitive and specific and could provide rapid, noninvasive, and low-cost evidence of early AKI would improve research and allow earlier intervention and potential prevention of complications. Novel promising biomarkers of kidney injury include NGAL, CysC, IL-18, and KIM-1, but none have yet proven to be of practical use in the ED setting.

Current assessment tools, including laboratory and imaging studies, are neither sensitive nor specific enough to rely on for a timely diagnosis. However, once the diagnosis is made, the patient may be at risk for CKD, and follow-up with a nephrologist may be needed. Currently, the most effective management tool for pAKI is prevention, which can be accomplished by identifying at-risk patients, being mindful of a patient's intravascular volume status, and avoiding potentially nephrotoxic medications, when possible. Some of the most commonly used medications in the pediatric population (such as NSAIDs and certain antibiotics) may pose a risk to kidney function, and these agents should be avoided whenever possible when treating a patient with or at risk of developing AKI.

Case Conclusions

In the case of the 3-year-old girl with increased GI losses and poor oral feeding, you were concerned that the patient was moderately dehydrated, which was supported by your physical examination findings of dry mucous membranes and prolonged capillary refill. You realized that she was at risk of developing AKI. You asked a nurse to obtain IV access and to send an electrolyte panel with renal function testing. The nurse asked if you would like to order ibuprofen for the girl's mild, generalized abdominal pain. You told the nurse to avoid the use of NSAIDs, which are potentially nephrotoxic. While waiting for the lab results, you encouraged the patient to drink, but she only tolerated 10 mL. You initiated a 20-mL/kg bolus of normal saline. The lab results showed normal electrolytes with a creatinine of 0.6 mg/dL and a BUN/creatinine ratio of 25:1. You reviewed the pRIFLE criteria and were frustrated that you did not have a baseline creatinine; you wished there was a more sensitive biomarker of AKI available to you in the ED. However, given the patient's risk for AKI and her inability to tolerate sufficient oral rehydration, you continued IV fluids and admitted her to the floor for management of dehydration. You recommended that another creatinine and electrolyte panel be obtained prior to discharge and that the patient have a pediatric nephrology

follow-up if the diagnosis of AKI is made.

The 16-year-old adolescent boy with history of osteosarcoma and recent exposure to a nephrotoxic chemotherapeutic agent was worrisome. You realized that he had multiple risk factors for AKI and that he may have prerenal AKI in the setting of dehydration, as well as intrinsic AKI caused by cisplatin and prolonged hypovolemia. You asked the nurse to obtain IV access and send labs; in addition to a CBC, you obtained an electrolyte panel with kidney function testing, which revealed hyperkalemia at 5.8 mEq/L and a serum creatinine of 1.4 mg/dL. The CBC revealed a white count < 1 x 10^9 WBC/L with an ANC of 200/mcL. While you were calling the pediatric oncology fellow, you asked the nurse to administer a normal saline bolus. The nurse notified you that the boy now had a fever, and together you drew blood cultures and initiated cefepime for febrile neutropenia. You remembered that accurate urine output data are important in the setting of AKI, but you deferred Foley catheter placement because of the patient's neutropenia. After discussing the case with the oncology fellow, you admitted the patient to the floor for management of febrile neutropenia and AKI. Prior to sending him upstairs, you requested a consult from the pediatric nephrology fellow.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study is included in bold type following the references, where available. The most informative references cited in this paper, as determined by the authors, are noted by an asterisk (*) next to the number of the reference.

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Coming Soon in *Pediatric Emergency Medicine Practice*

Vascular Access in the Pediatric Emergency Department: Choices and Complications

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The ability to obtain and manage vascular access is a staple of emergency medical care. While peripheral intravenous access is the most common form of access in the emergency department, intraosseous needles, central venous catheters, and venous cutdown may be necessary in patients who are critically ill when peripheral access is difficult to obtain. The ease by which peripheral intravenous access is obtained may be predicted by both patient and staff factors. This issue reviews the indications and contraindications, devices and insertion techniques (including ultrasound), optimal fluid choices, and possible complications of peripheral access, intraosseous access, central venous access, and arterial access. New technologies, such as infrared illumination and transillumination, are available to help assist emergency department staff to locate vessels that may be suitable for access. Because all forms of venous and arterial access are painful and invasive procedures, pain control and nonpharmacologic assistance should be considered to improve the comfort of patients during these procedures and improve the likelihood of first-attempt placement success. All forms of access should be monitored for rare, but serious complications including extravasation of caustic medications and thrombophlebitis.

CME Questions

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1. **A 5-year-old boy presents with vomiting and diarrhea for 5 days. His physical examination is concerning for moderate dehydration and his parents report decreased urine output for the last 12 hours. His creatinine level is 0.8 mg/dL. A prior creatinine level was noted in his chart as 0.3 mg/dL. When you consult the pediatric nephrologist, you describe his AKI as:**
   a. pRIFLE Risk
   b. pRIFLE Failure
   c. AKIN stage 2
   d. KDIGO stage 3

2. **What is the difference between the current classification schemes of pRIFLE, KDIGO, and AKIN?**
   a. pRIFLE uses estimated creatinine clearance.
   b. The criteria for duration of oliguria in AKIN is longer than in KDIGO.
   c. The Schwartz formula is used for KDIGO.
   d. pRIFLE requires urinalysis results.

3. **Which of the following is the most common cause of pAKI in the community?**
   a. Hemolytic uremic syndrome
   b. Sepsis
   c. Congenital cystic kidney
   d. Ureteropelvic junction obstruction

4. **A pRIFLE classification of Risk or Injury caused by hemolytic uremic syndrome is best treated with which of the following options?**
   a. Intravenous antibiotics
   b. Volume expansion
   c. Renal replacement therapy
   d. Red blood cell transfusion

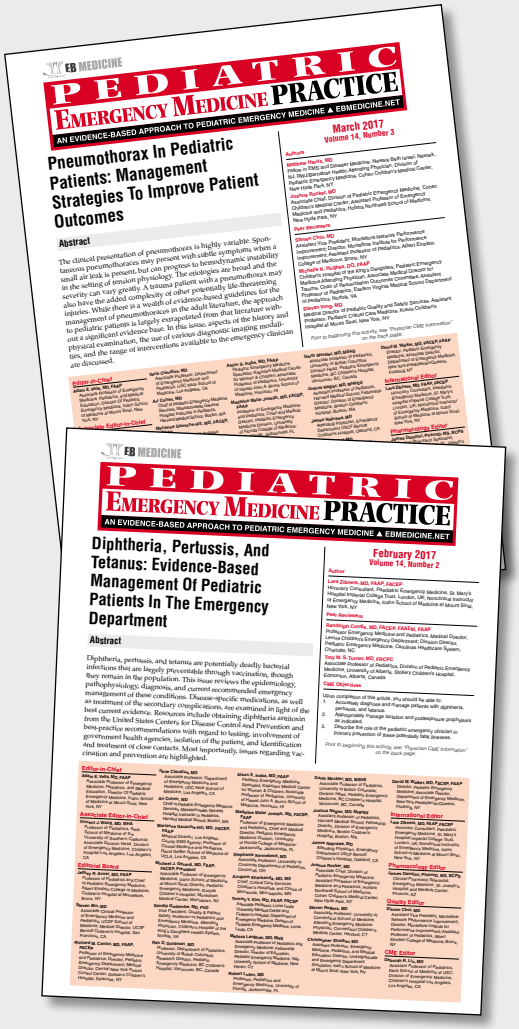
5. **A 14-year-old boy is brought to the ED complaining of muscle aches and dark-colored urine after a vigorous run today. Regarding this condition and AKI, which of the following is TRUE?**
   a. This condition typically causes AKI in 10% of patients.
   b. Pediatric patients typically have a more severe course than adults.
   c. Fluid resuscitation should be limited in AKI associated with this condition.
   d. Renal vasoconstriction is a key mechanism in nephrotoxicity associated with this condition.

6. **A 6-year-old girl presents to the ED with nausea and decreased oral intake. Her blood pressure was 130/70 mm Hg at triage, and a spot urine test shows microscopic blood. She has no significant past medical history, and you do not have access to her last weight or growth chart. One finding that may better differentiate between CKD and AKI is the presence of:**
   a. Elevated parathyroid hormone
   b. Elevated BUN
   c. Hypertension
   d. Elevated creatinine

7. **Which of the following is the most useful diagnostic imaging method of the kidneys for the workup of AKI?**
   a. Ultrasound
   b. Computed tomography
   c. Magnetic resonance imaging
   d. Intravenous pyelography

8. **You are discussing the management of a 12-year-old girl with dehydration and AKI prior to admission with the floor team. Which IV fluid choice is most appropriate for this patient?**
   a. Hypertonic saline
   b. Normal saline
   c. Potassium-containing fluid
   d. Lactated Ringer's

9. **You are treating a child who shows evidence of AKI. Which of the following may be an indication for renal replacement therapy?**
   a. Fever
   b. Hyperkalemia
   c. Hypertension
   d. Moderate dehydration



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- Vascular Access
- Nonaccidental Trauma
- Orthopedic Emergencies

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Needs Assessment: The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

CME Objectives: Upon completion of this article, you should be able to: (1) summarize the 3 current classification systems for AKI; (2) recognize the most common etiologies of AKI in children; (3) describe biomarkers that may be useful in the identification of AKI; and (4) plan for appropriate management and disposition of children presenting to the emergency department with AKI.

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