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Renal replacement therapy in children

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ABSTRACT

Acute kidney injury (AKI) affects 3.9/1000 at-risk children in the United States, a number that has been increasing as critically ill and injured children have access to improved care and the diagnosis of AKI is being made more accurately. Children with AKI have a higher mortality and hospital length of stay as compared to children without AKI. Renal replacement therapy can improve outcomes in these patients. This article reviews the pathophysiology of AKI and the modalities, indications, and outcomes of renal replacement for children with AKI.

Acute kidney injury

Renal failure is the inability of the kidneys to maintain fluid, electrolyte, and acid–base homeostasis. Sudden deterioration of renal function, also known as *acute renal failure* (ARF), is due to a direct insult to the kidney (primary renal disease), or the result of a systemic disease process that affects renal perfusion or injures the renal interstitium (secondary failure). The term ARF was recently changed to *acute kidney injury* (AKI). AKI describes more accurately the pathophysiology behind ARF, reflecting its potentially reversible course.

Common causes of AKI include hypovolemic states leading to shock, toxins causing interstitial or tubular damage, and acute obstruction of the urinary outflow. These three mechanisms are universally known as pre-renal, renal/intrinsic, and post-renal AKI.

AKI is manifested clinically by a decline in urine output (UO) and a simultaneous elevation of serum creatinine (Cr). These two clinical parameters, however, are unreliable. A low UO does not necessarily correlate with the severity of renal dysfunction as seen in non-oliguric renal failure or in those patients receiving diuretics. Similarly, minor changes in Cr may not accurately reflect the ongoing kidney injury, since nearly a 50% loss in functioning renal mass is needed to affect the serum Cr. Concomitant fluid overload in critically ill children with AKI will dilute and falsely affect the serum Cr.

Chronic kidney disease is defined as the persistence of renal dysfunction beyond the period of resolution of the causative injury and is associated with a progressive decline in the glomerular filtration rate (GFR).

End-stage kidney disease refers to chronic kidney disease requiring dialysis or kidney transplant.

The AKI criteria

The Acute Dialysis Quality Initiative (ADQI) Group—a multicenter disciplinary group working on developing evidence-based guidelines for the treatment of ARF—identified specific characteristics of AKI to help define and measure outcomes.[1] According to the ADQI guidelines, the acute deterioration of kidney function follows a series of stages to reach permanent cessation of renal function. The RIFLE criteria for acute renal dysfunction are characterized by a progressive decline of UO and GFR and increasing plasma Cr.

R = Risk of renal dysfunction
I = Injury to the kidney
F = Failure of kidney function
L = Loss of kidney function—indicates persistent loss requiring RRT for more than 4 weeks
E = End-stage kidney disease—indicates need for renal replacement therapy (RRT) for more than 3 months

The initiation of RRT in early stages or "less severe" renal failure (RIFLE-*R* and RIFLE-*I*) is associated with improved outcomes and decreased 30-day mortality. In contrast, when RRT was initiated in more severe stages (RIFLE-*F* and RIFLE-*L*), the 30-day mortality approached almost 50%.[2]

A pediatric version of the RIFLE criteria was developed in 2007. The pediatric RIFLE or pRIFLE criteria have a few variations

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compared to the adult criteria, considering only UO and GFR but not serum Cr. However, a recent review demonstrated that the pRIFLE criteria were inconsistent when used to determine the morbidity and the mortality outcomes in children with renal failure.[3]

Most recently, the Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group delineated an international guideline to define and stage AKI in adults and children.[4] Stages I–III include increase in Cr and decline in UO as given in the Table.

In children with an established AKI, the estimation of baseline serum Cr may be difficult. The creatinine level and GFR can be estimated using the "modification of diet in renal disease" (MDRD) formula, which normalizes the GFR to the body surface area based on age, sex, and race. Unfortunately, this formula can only be used in children over 12 years of age, and estimations are inaccurate when the patient is not in a steady state of creatinine balance as in small infants and patients with restricted creatinine secretion due to chemotherapy, cimetidine, or AIDS therapy.[5]

Recently, several plasma and urinary biomarkers released by the kidney under stress or ischemia have been described. These are undergoing intensive research before they are accepted for the prediction and prognosis of AKI. Some of these biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP), and interleukin (IL)-18.[6]

Causes of AKI

In developed countries, only 10% of AKI are due to primary kidney disease. The majority are secondary to systemic illnesses, cardiac surgery for congenital heart disease, sepsis, and nephrotoxic medications.[6–9] Hemolytic uremic syndrome is still the main cause of renal failure in children in developing countries.

Pre-renal AKI

In pre-renal AKI, kidney injury occurs from hypoperfusion. The most common cause of hypoperfusion is hypovolemia due to severe dehydration, bleeding, gastrointestinal losses, or major burns. Diminished renal perfusion can also occur with normal or elevated extracellular volume in conditions such as congestive heart failure, hepatorenal syndrome, or sepsis. Hypoperfusion activates the juxtaglomerular complex (renin–angiotensin–aldosterone axis), promoting avid reabsorption of sodium and water in an attempt to replenish the intravascular volume. Non-steroidal anti-inflammatory medications inhibit cyclooxygenase-1 and cyclooxygenase-2 enzyme activity, diminishing prostaglandin formation that serves as a renal vasodilator. This physiologic response can worsen renal insufficiency in states of hypoperfusion.

Table
Kidney Disease Improving Global Outcomes Acute Kidney Injury Work Group International Stages of acute kidney injury in adults and children.[4]

Stage I	Stage II	Stage III
SCr increase $\geq$ 0.3 mg/dL in 48 h or 1.5–1.9 times UO $<$ 0.5 mL/kg/h for 6–12 h	SCr increase 2.0–2.9 times UO $<$ 0.5 mL/kg/h for 12 h	SCr = 3 $\times$ baseline or SCr $>$ 4.0 mg/dL or RRT initiation or if $<$ 18 y of age, then eGFR $<$ 35 mL/min/1.73 UO $<$ 0.5 mL/kg/h for 24 h or UO $<$ 0.3 mL/kg/h for 12 h

SCr = serum creatinine; UO = urine output; RRT = renal replacement therapy; eGFR = estimated glomerular filtration rate.

Upon activation of the mentioned axis, the release of angiotensin causes vasoconstriction of the glomerular efferent arteriole (closing the exit "valve"), increasing intracapillary pressure and improving transglomerular filtration. The administration of angiotensin-converting enzyme (ACE) inhibitors to patients with renovascular disease is deleterious since it inhibits this compensatory mechanism by dilating the efferent arteriole (thus decreasing ultrafiltration pressure).

Mechanical ventilation and conditions that increase the intrathoracic pressure and reduce the pre-load (pneumothorax and cardiac tamponade) may lead to renal hypoperfusion and renal failure. This is particularly true during states of inadequate cardiac filling volumes.

Renal or intrinsic AKI

Parenchymal damage prevents the kidney from absorbing water and electrolytes and prevents elimination of by-products of catabolism (creatinine and urea). Tubular casts precipitate from urinary stasis, low pH, and greater urinary concentration and "plug" the fine tubular system, causing acute tubular obstruction, back-leak into the interstitium, loss of epithelial integrity, and epithelial damage, a phenomenon known as *acute tubular necrosis* or ATN. Direct toxicity of myoglobin occurs when the epithelial cells are exposed to free oxygen radicals originating from the oxidation of ferrous oxide to ferric oxide.

Acute interstitial nephritis (AIN), an inflammatory infiltration of extraglomerular structures (tubules and interstitium), leads to acute epithelial injury and renal dysfunction due to the activation of pro-inflammatory cytokines. This process is usually secondary to the use of nephrotoxic medications (aminoglycosides and anphotericine among others). AIN is usually self-limited and rarely progresses to permanent renal injury.

Radiocontrast dyes impose a high solute load to the tubular system, which in turn imposes high energy demands to the renal medulla (increased tubular activity). Since the renal medulla is an area of limited blood flow, the enormous metabolic demand easily leads to interstitial hypoxia and subsequent renal injury. Kidney injury from contrast dye is known as *contrast-induced nephropathy* or CIN.[10]

Other causes of interstitial nephritis include bacterial and viral infections, systemic lupus, and acute transplant rejection.

Post-renal AKI

In post-renal AKI, obstruction of the urinary outflow leads to decreased ultrafiltration pressure and acute tubular injury. The obstruction leads to retrograde or "backflow" of urine, causing tubular hypertension. Hydronephrosis or dilatation of the collecting system occurs with prolonged obstruction usually over days.

Common causes of post-renal AKI include papillary necrosis, posterior urethral valves, urethral strictures, or acute neurogenic bladder seen in trauma or the presence of a pelvic mass.

AKI and sepsis

Sepsis-related AKI accounts for one-third of cases of renal injury in children.[11] Injury mechanisms include systemic hypoperfusion, release of pro-inflammatory mediators, decrease in anti-inflammatory mediators, and activation of the coagulation cascade, leading to intra-renal microthrombosis.[12] Recent evidence suggests that upregulation of metalloproteinase-8 and elastase-2e may play a role in sepsis-related AKI.[13] Whether these biomarkers are causative of AKI or simply a consequence of an increased pro-inflammatory state is unknown.