Prevention of Pediatric Acute Kidney Injury

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The incidence of acute kidney injury (AKI) in critically ill pediatric patients has been reported as increasing to 25 %, depending on population characteristics. The etiology of AKI has changed over the last 10-20 years from primary renal disease to the renal conditions associated with systemic illness. The AKI in pediatric population is associated with increased mortality and morbidity, and prevention is needed to reduce the consequence of AKI. It is known that the most important risk factors for AKI in critically ill pediatric patients are clinical conditions to be associated with decreased renal blood flow, direct renal injury, and illness severity. Renal hypoperfusion leads to neurohormonal activation including renin-angiotensin-aldosterone system, sympathetic nervous system, antidiuretic hormone, and prostaglandins. Prolonged renal hypoperfusion can result in acute tubular necrosis. The direct renal injury can be predisposed under the condition of renal hypoperfusion, and appropriate treatment of volume depletion is important to prevent AKI. The preventable causes of AKI include contrast-induced nephropathy, hemodynamic instability, inappropriate medication use, and multiple nephrotoxic insults. Given the evidence of preventable factors for AKI, several actions such as the use of protocol for prevention of contrast-induced nephropathy, appropriate treatment of volume depletion, vigorous treatment of sepsis, avoidance of combinations of nephrotoxic medications, and monitoring of levels of drugs should be recommended.

Key words: Acute kidney injury, Biomarker, Children

Introduction

The definitions and characterization of acute kidney injury (AKI) in children have advanced significantly over the past 2 decades. Acute kidney injury is common in critically ill children and is associated with increased morbidity and mortality¹⁾. Acute kidney injury in association with sepsis, multiple organ involvement, and fluid overload carries heightened risk¹⁾. Gene probes and urinary biomarkers represent intriguing tools for predicting and monitoring pediatric AKI.

To prevent AKI, the step-by-step approach such as coronary angiography is needed. First step is risk factor and symptom assessment¹⁾. Risk factor for coronary angiography such as smoking or hypercholesterolemia has been known and the patients usually manifest the typical symptom such as chest pain. However, AKI does not hurt. It means that there is no typical symptom in

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Table 1. Causes of pediatric acute kidney injury

Renal origin	Systemic illness associated conditions
Renal hypoperfusion	
<i>Low intravascular volume</i>	
Urinary losses, diuretics	Hemorrhage/bleeding
	Third-space loss: sepsis and capillary leak
<i>Decreased effective circulating volume</i>	
Renal-artery obstruction	Cardiac dysfunction
	Sepsis-associated vasodilation
Intrinsic	
<i>Glomerular</i>	
Glomerulonephritis	
<i>Vascular</i>	
Hemolytic uremic syndrome	Disseminated intravascular coagulation
<i>Interstitial</i>	
Acute interstitial nephritis: drug-induced	
<i>Tubular</i>	
Acute tubular necrosis: ischemic, drug-induced	Tumor lysis syndrome
Obstruction of urinary tract	
Congenital anomalies	Mass, stones

AKI. In AKI, the risk factor evaluation is more important. Second step is to measure biomarker such as troponin I and assess AKI¹⁾. In the past, serum creatinine (Cr) has been used as a biomarker of AKI. It has been known that even as small elevation of serum Cr may reflect significant kidney damage and be associated with poor outcome¹⁾. It means that serum Cr is a late marker of AKI. The numerous biomarkers have been addressed as an early marker of AKI. Third step is intervention such as thrombolysis in coronary angina. It is difficult to prevent AKI because AKI does not show typical symptoms and there was little data for the earlier biomarker of AKI. In the past decade, research has been expanded to discover risk factor, biomarkers and intervention in AKI. In the literature, the etiology, risk factors, assessment modalities, and prevention in pediatric AKI patients will be addressed.

Etiology of AKI

The etiology of AKI has changed over the last 10-20 years from primary renal disease (hemolytic uremic syndrome, glomerulonephritis) to the renal complications of systemic illness or associated treatment (sepsis, cardiac disease,

oncologic disease). Common causes of AKI in critically ill pediatric patients were renal ischemia, nephrotoxic medication and sepsis, and these conditions lead to acute tubular necrosis. The etiology of AKI is classified to prerenal, renal (intrinsic), or postrenal disease (Table 1). Causes of pre-renal azotemia are absolute loss of effective blood volume such as hemorrhage and relative loss due to capillary leak in sepsis. Extra-corporeal membrane oxygenation and heart failure can be prerenal causes. Pharmacologic agents such as indomethacin, tolazoline, angiotensin-converting-enzyme inhibitor, and angiotensin receptor blockers can cause AKI by decreasing renal perfusion. When renal blood flow decreases, renal autoregulation preserves glomerular filtration rate (GFR) by increasing renal sympathetic tone, activation of the renin-angiotensin-aldosterone system, and increased activation of hormones such as vasopressin and endothelin. If tubular function is intact, sodium and urinary urea reabsorption can increase in response to decreased renal blood flow. These renal hemodynamic changes maintain systemic volume expansion and blood pressure. This situation is reflected by low urine sodium concentrations, low urine urea concentration and increased blood urea to creatinine ratio. This period of renal hypoperfusion, so called "renal angina" is critical to recognize and

treat to prevent cellular damage. Prompt recognition and correction for the cause of renal hypoperfusion can restore GFR.

In contrast to pre-renal AKI, renal function abnormalities in intrinsic AKI have been supposed not to be immediately reversible. The severity of intrinsic AKI ranges from mild tubular dysfunction to acute tubular necrosis and corticomedullary necrosis with irreversible renal damage. The intrinsic kidney injury can be divided into glomerular, vascular, tubular, and interstitial disease. Glomerulonephritis/vascular diseases should be suspected when children present with AKI without an identifiable cause. The examination of the urine sediment can differentiate glomerular from tubular injury, and the laboratory evaluation for autoimmune antibodies and a diagnostic kidney biopsy may be helpful to differentiate the cause. Pharmacologic agents are one of the most common causes of nephrotoxic AKI, and these toxins can cause AKI by decreasing renal perfusion (non-steroidal anti-inflammatory drug, diuretics, angiotensin-converting-enzyme inhibitor), by direct tubular injury (aminglycocides, cephalosporins, amphotericin B, rifampin, vancomycin, non-steroidal anti-inflammatory drug, contrast media, myoglobin/hemoglobin), by interstitial nephritis, or tubular obstruction (acyclovir, uric acid).

The common causes of postrenal AKI are congenital malformations including imperforate prepuce, urethral stricture, prune-belly syndrome, and posterior urethral valves.

Other causes of acute obstruction include neurogenic bladder, extrinsic compression, and intrinsic obstruction from renal calculi or fungal balls. Depending on the cause and associated damage to the kidneys, the relief of the obstruction is essential to restore renal function.

In pediatric AKI series, the incidence of sepsis-associated AKI has ranged from 9% to 34%, and sepsis-associated AKI is also associated with lower survival.

The pathogenic mechanism of AKI in sepsis is complex and multifactorial, and has been known to be related to combination of blood flow alterations and cytokine-mediated injury.

The “peak concentration hypothesis” has been proposed that the elevations and imbalances of both pro-inflammatory and anti-inflammatory mediators coupled with endo-

thelial dysfunction and altered coagulation cascade can synergistically induce AKI.

AKI frequently occurs with other organ failure in critically ill children. The complex pathophysiologic interaction of heart and kidney dysfunction is described as cardio-renal syndrome. Type 1 cardio-renal syndrome is primarily caused by acute cardiac disease with secondary acute renal impact, and common in the perioperative setting with acute decompensated heart failure. The interaction of liver and kidney known as hepatorenal syndrome is well recognized, but the pathophysiologic mechanisms remain unknown. AKI can occur in undergoing surgery for congenital heart disease, and the mechanisms are multifactorial. The ischemia results in ATP depletion and tubular cell death. The contact of RBC with the bypass circuit during cardiopulmonary bypass causes hemolysis, and in the presence of free radicals, the free iron participates in oxygen radical reactions. Loss of brush borders and disruption of cell polarity and cytoskeleton extend to apoptosis, and the desquamation of tubule cells into the lumen leads to the cast obstruction.

Risk factor assessment

In critically ill adult patients, multiple risk factors for AKI such as old age, diabetes, liver cirrhosis, congestive heart failure, chronic kidney disease, or cardiopulmonary bypass have been identified¹⁾. However, children typically do not have the comorbid conditions noted for adult patients¹⁾. There is a little data to evaluate the risk factor for AKI in children. Bailey D et al. reported the risk factors of AKI in critically ill children in a single-center, prospective observational study over 1 year²⁾. The enrolled patients were the pediatric intensive care unit population with 3 days to 18 years of age²⁾. Acute kidney injury was defined as doubling of baseline serum creatinine²⁾. In chronic kidney disease patients, AKI was defined as 25% increase in serum Cr²⁾. The incidence rate of AKI was 4.5%²⁾. Significant risk factors for AKI were thrombocytopenia, age > 12 years, hypoxemia, hypotension, and coagulopathy²⁾. A few studies for risk factors for developing AKI in children were performed and the risk factors included invasive mechanical ventilation, vasoactive medications, nephrotoxic medica-

Table 2. Pediatric-modified RIFLE (pRIFLE) criteria

	Estimated CCI	Urine output
Risk	eCCI decrease by 25%	< 0.5 ml/kg/hour for 8 hours
Injury	eCCI decrease by 50%	< 0.5 ml/kg/hour for 16 hours
Failure	eCCI decrease by 75% or eCCI < 35ml/min/1.73m ²	< 0.3 ml/kg/hour for 24 hours or anuria for 12 hours
Loss	Persistent failure > 4 weeks	
End stage	End stage renal disease (persistent failure > 3 months)	

eCCI, estimated creatinine clearance; pRIFLE, pediatric risk, injury, failure, loss and end-stage renal disease.

Table 3. Kidney Disease Improving Global Outcome (KDIGO) criteria

Stage	Serum creatinine criteria	Urine output criteria
1	Increase > 0.3mg/dL in 48 hours or 1.5-1.9 times	< 0.5ml/kg/hour for 6-12 hours
2	Increase 2-2.99 times	< 0.5ml/kg/hour for 12 hours
3	>3.0 Increase or > 4.0 mg/dL or If <18 years of age then eCCI <35 mL/min/1.73m ²	< 0.5ml/kg/hour for 24 hours or < 0.3mL/kg/hour for 12 hours

eCCI, estimated creatinine clearance

tions, sepsis, multiple organ failure, volume depletion, thrombocytopenia, hypoxemia, neurologic dysfunction, and stem cell transplantation¹⁾. It is recommended that all children with any of these risk factors should be monitored for the development of AKI.

Acute kidney injury assessment

1. Definition of Acute kidney injury

It has been known that children with small changes in serum Cr or with high degree of fluid overload are at risk for poor outcomes¹⁾. The widely used AKI criteria in children were based on the change of serum Cr, and AKI can be assessed by criteria. In 2004, the Acute Dialysis Quality Initiative group developed the first consensus multidimensional AKI definition, termed the RIFLE criteria. In 2007, Aclan-Arkan developed and validated a pediatric modified version of the RIFLE criteria (pRIFLE) in critically ill children (Table 2)³⁾. RIFLE has 3 AKI staging strata, Risk, Injury, Failure, and 2 outcome criteria, Loss and End-Stage Kidney Disease³⁾. AKI development by RIFLE (RIFLE-R) is defined as a 50% rise in serum Cr (or 25% decrease in estimated Cr clearance) over baseline or by urine output of less than 0.5 mL/kg/hour for 6 hours³⁾. RIFLE-I and RIFLE-F are each defined by greater changes in Cr or

urine output³⁾. And the RIFLE was modified by the Acute Kidney Injury Network (AKIN) in 2007 to include a 0.3 mg/dL serum Cr rise in less than 48 hours for the AKI definition⁴⁾. In 2012, an international guideline was developed by the Kidney Disease Improving Global Outcomes (KDIGO) (Table 3)⁵⁾. Acute Kidney Injury Work Group harmonized RIFLE, AKIN, and pRIFLE into a single standardized definition⁵⁾. The KDIGO AKI definition and staging criteria should be used at the current time unless further modifications are warranted by prospective study.

2. Fluid overload

Acute kidney injury can be assessed by fluid overload. Decreased renal function and oliguria in AKI result in fluid overload^{1,6)}. However, fluid overload itself may contribute to AKI^{1,6)}. In patients with AKI, outcomes progressively worsened with increasing degree of fluid overload^{1,6)}. Fluid balance was an independent risk factor for mortality, and the early institution of renal replacement therapy was associated with better outcome^{1,6)}. Therefore, the aggressive use of diuretics and early initiation of hemofiltration is suggested. Goldstein SL et al. reported that lesser percent fluid overload at continuous veno-veno hemofiltration (CVVH) initiation was associated with improved outcome when sample was adjusted for severity of illness⁶⁾. Foland et al. reported that percent fluid overload was significantly

Table 4. Pediatric acute kidney injury biomarkers

Biomarker	Sample	Clinical setting	Author	Year
NGAL	S/U	CIN	Hirsch et al. ¹¹⁾	2007
NGAL	U	Critically ill patients	Zappitelli et al. ¹²⁾	2007
NGAL	U	Post-cardiac surgery	Parikh et al. ¹³⁾	2011
IL-18	U	Critically ill patients	Washburn et al. ¹⁴⁾	2008
IL-18	U	Emergency department	Du et al. ¹⁵⁾	2011
IL-18	U	Post-cardiac surgery	Parikh et al. ¹³⁾	2011
IL-6	U	Post-cardiac surgery	Dennen et al. ¹⁶⁾	2010
IL-8	S	Post-cardiac surgery	Liu et al. ¹⁷⁾	2009
KIM-1	U	Emergency department	Du et al. ¹⁵⁾	2011
β2-MG	U	Emergency department	Du et al. ¹⁵⁾	2011
Cystatin-C	S	Post-cardiac surgery	Krawczeski et al. ¹⁸⁾	2010
LFABP	U	Post-cardiac surgery	Portilla et al. ¹⁹⁾	2008

NGAL, neutrophil gelatinase-associated lipocalin; S, serum; U, urine; CIN, contrast-induced nephropathy; IL-18, interleukin-18; IL-6, interleukin-6; IL-8, interleukin-8; KIM-1, kidney injury molecule-1; β2-MG, β2-microglobulin; LFABP, Liver-type fatty acid-binding protein.

lower in survivors compared with non-survivors in children with multiple organ dysfunction syndrome and percent fluid overload was independently associated with survival when severity of illness is adjusted⁷⁾. Gillespie R et al. reported that pediatric continuous renal replacement therapy (CRRT) survival outcomes progressively worsened with increasing percent fluid overload and children with high fluid overload (>10%) at CVVH initiation were at 3 times greater risk of mortality⁸⁾.

3. Biomarker

Acute kidney injury can be assessed by biomarker, but serum Cr has a few limitations. Because, serum Cr is a late functional marker of AKI, serum Cr may not change until loss of 25-50% kidney function^{1,9,10)}. It may take days after an injury before a rise in serum Cr. At lower glomerular filtration rate, serum Cr will overestimate renal function^{1,9,10)}. Serum Cr varies by muscle mass, hydration status, sex, age, and method of measurement^{1,9,10)}. Novel biomarker to detect development and severity of kidney injury earlier than serum Cr in AKI is needed and the utilities of biomarkers are as follow⁹⁾: (1) Early diagnosis, (2) Define severity of injury, monitor AKI course, (3) Define AKI subtypes & etiology (pre-renal, septic, nephrotoxic), (4) Monitor response to AKI interventions, (5) Risk stratify for poor outcomes (dialysis need, CKD, mortality), (6) Identify location of renal tubular injury. The ideal qualities of a biomarker are as follow¹⁰⁾: (1) Accurate, reliable, (2)

Relatively non-invasive/acceptable to patients, (3) Rapidly measurable, standardized assay, (4) Sensitive/specific with reproducible cutoff values.

Urine neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), interleukin 18 (IL-18), interleukin 6 (IL-6), interleukin 8 (IL-8), β2-microglobulin, Cystatin-C, and Liver-type fatty acid-binding protein (LFABP) are urinary and serum biomarkers for the diagnosis of AKI in pediatric patients (Table 4)¹¹⁻¹⁹⁾. NGAL is expressed in proximal and distal nephron and binds and transports iron-carrying molecules^{10,11)}. NGAL plays an important role in injury and repair and rises very early (hours) after injury in animals, confirmed in children with cardiopulmonary bypass, critically ill children, and children with contrast-induced nephropathy¹¹⁻¹³⁾. In a prospective cohort study of critically ill children, mean and peak urine NGAL concentrations increased with worsening pRIFLE status, and urine NGAL concentrations rose in AKI, 2 days before and after a 50% or greater rise in serum creatinine, without change in control urine NGAL¹²⁾. This study suggested that urine NGAL might be a useful early AKI marker that predicted development of severe AKI in a heterogeneous group of patients with unknown timing of kidney injury. IL-18 plays a role in inflammation, activating macrophages and mediates ischemic renal injury¹³⁾. IL-18 antiserum to animals protects against ischemic AKI¹⁰⁾. Urinary IL-18 was reported to be an AKI biomarker in critically ill children, children with port-cardiac surgery,

and pediatric patients in emergency department¹³⁻¹⁵. Washburn K et al. reported that urine IL-18 might be used as a useful early AKI marker in critically ill children¹⁴. Urinary IL-6 and serum IL-8 was confirmed in children with port-cardiac surgery^{16,17}. KIM-1 is an epithelial transmembrane protein, and is involved in cell-cell interaction¹⁰. KIM-1 appears to have strong relationship with severity of renal injury¹⁰. Du Y et al. reported that KIM-1 and β 2-microglobulin could be used as urinary biomarkers to detect AKI in pediatric emergency center¹⁵. Serum cystatin C and urinary LFABP was reported as a biomarker of AKI after pediatric cardiac surgery [18, 19]. In the pediatric setting, many studies were conducted post-cardiac surgery, and the collaborations among pediatric nephrology, cardiology, emergency medicine, and critical care medicine are needed for the research of AKI biomarkers.

Therapeutic intervention

In the time-course of AKI, initiation of AKI can involve hemodynamic changes in glomerular filtration rate, sub-clinical tubular injury or both processes occurring simultaneously. A short time window may exist where specific therapy might reverse AKI. Established AKI requires days to weeks for recovery, and during this period supportive therapy and the avoidance of secondary renal injury is very important. Secondary injury may result in non-recovery of renal function or chronic kidney disease and end-stage renal disease.

Intervention of AKI is composed of diagnostic evaluation to uncover the underlying etiology, optimization of hemodynamics, minimize exposure to nephrotoxic medications, conservative fluid management after an initial resuscitation, and maximize nutrition.

1. Fluid management

Attention to the patient's volume status is essential throughout the hospital stay. Intake and output measurement does not take into account insensible losses. Therefore, obtaining daily weight measurement on the same scale is very important and, in combination with vital signs, heart rate, and blood pressure, it will give the clinician a better sense of the patient's volume status.

2. Avoidance of further renal injury

1) Drug dosing in AKI

Toxicity of drugs can be avoided by careful monitoring and adjusting the dose in accordance with the patient's changing renal function status. Antibiotics such as aminoglycosides or vancomycin can be used safely in patients with AKI with careful attention to serum drug levels. Antibacterials usually need a high peak and lower trough level, and have to be given with longer dosing intervals²⁰. Antiviral such as acyclovir might induce crystal nephropathy and acute tubular necrosis, and adequate hydration is necessary to prevent renal injury. Amphotericin B can cause renal vasoconstriction associated AKI and toxic effect to distal tubular epithelium. To prevent these adverse effects, sodium and volume loading prior to administration of amphotericin-B is needed. In the use of oral voriconazole, dosage adjustment in AKI is not necessary. Histamine antagonist can induce thrombocytopenia in AKI and dosage adjustment is needed. Proton pump inhibitor can be given with no dosage adjustment in AKI patients. Sucralfate is supposed to have a risk of aluminum accumulation in AKI. Phenytoin and levetiracetam can be used with dosage adjustment in AKI.

2) Contrast-induced nephropathy

Contrast-induced nephropathy has been known to be the third most common cause of hospital-acquired AKI in adults. The pathophysiology has been supposed to be renal vasoconstriction through endothelin-1 or inhibition of nitric oxide and toxic effect to the renal tubular epithelium¹¹. Prevention include the fluid volume loading with sodium bicarbonate, avoiding nephrotoxic drug prior to contrast, the use of lower osmolarity contrast agent, and N-acetylcystein¹¹.

3. Specific intervention

1) Diuretics

Diuretics can be used to augment urine output but will not enhance solute clearance. Accordingly, increased urine output does not correlate with improvement of renal function or with improvement of solute clearance. Comparison of loop diuretics given as an intermittent bolus or by continuous infusion shows that the use of continuous infusion involves less exposure to these potentially toxic agents with

the same amount of urine output²¹). Thiazide-like diuretics (e.g., oral metolazone or intravenous chlorothiazide) can be given to enhance the effectiveness of loop diuretics.

2) Potential therapies

There is no evidence to support the use of renal dose-dopamine. However, fenoldopam, a selective dopaminergic-1 Rc agonist has been reported to reduce the risk of AKI in critically ill adults and improve urine output in critically ill neonates following cardiopulmonary bypass²²). N-acetylcystein has been known to be effective in the prevention of contrast-induced nephropathy, but there is no evidence for prevention of AKI in critically ill patients²³). It has been reported that human natriuretic peptide nesiritide might be favorable for renal hemodynamic effects and increase urine output after cardiac surgery²⁴). Additionally, growth factor, erythropoietin, or free-radical scavengers have been tried as a potential therapy in AKI²⁵⁻²⁷).

4. Nutrition

Nutrition is important in patients with AKI as part of ongoing care. Specialized formulas to maximize nutrition and minimize both solute and fluid excess can be delivered to patients with AKI^{28,29}). Enteral nutrition has an advantage over parenteral nutrition and these formulas can be given either orally or by feeding tube to provide adequate caloric intake^{28,29}). These formulas deliver 2 cal/mL, with either no or low electrolytes (specifically, potassium and phosphorus)^{28,29}).

Conclusion

The AKI in pediatric population is associated with increased mortality and morbidity, and prevention is needed to reduce the consequence of AKI. To prevent AKI, the close monitoring of the pediatric patients with risk factor and the AKI assessment by AKI definition, fluid overload, and biomarker are necessary. Intervention should include the use of protocol for prevention of contrast-induced nephropathy, appropriate treatment of volume depletion, vigorous treatment of sepsis, avoidance of combinations of nephrotoxic medications, and monitoring of levels of drugs. Critically ill children tend to be medically complex patients

with multiple organ dysfunction, and the comprehensive team approach for early recognition of AKI and appropriate interventions are necessary to promote renal recovery and overall survival. The collaborative research should be conducted to find more accurate diagnostic methods such as biomarkers to detect AKI in pediatric patients under the complex situations such as intensive care unit, emergency department, preterm birth, post-cardiac surgery, and trauma.

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