PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B, Vol. 68 (2014), No. 5/6 (692/693), pp. 207–215.
DOI: 10.2478/prolas-2014-0025

Review

ACUTE KIDNEY INJURY — AN UNDERESTIMATED PROBLEM IN PEDIATRIC INTENSIVE CARE

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Communicated by Rafails Rozentāls

Acute kidney injury (AKI) frequently occurs in critically ill children and adults, with 5–20% of patients experiencing an episode during their stay in an intensive care unit. AKI rarely is an isolated event and is associated with a broader spectrum of diseases, including sepsis and respiratory insufficiency, and often progresses into multiorgan dysfunction syndrome. Despite recent advancements in renal replacement therapy (RRT), mortality among patients who sustain AKI complicated by multiorgan dysfunction appears to have remained unchanged and is estimated at approximately 50%. Recent clinical evidence suggests that AKI is not only an indicator for severity of illness, but that it also leads to earlier onset of multiorgan dysfunction with profound effects on mortality rates. The aim of this paper is to inform medical professionals involved in the paediatric intensive care of recent advances in AKI diagnosis and management. Studies were identified from MEDLINE (OVID), PubMed, and the Cochrane Library for topics relevant to AKI. There is limited evidence in paediatrics regarding effective therapy for acute kidney injury, a significant problem in the paediatric intensive care unit that extends length of stay, duration of mechanical ventilation, and overall mortality. Sublethal kidney injury may be contributing to overall morbidity. Prospective clinical trials are needed to evaluate specific diagnostic aids, such as biomarkers, and therapeutic strategies like early initiation of continuous RRT in children with fluid overload.

Key words: *paediatric acute kidney injury, AKI epidemiology, kidney biomarkers, fluid overload, renal replacement therapy.*

INTRODUCTION

Acute kidney injury (AKI) is increasingly recognised as a cause of increased morbidity in critically ill children and adults, and damage to the kidney, a central mediator of homeostasis in the body, and it affects patient survival (Andreoli, 2002; Hui-Stikle *et al.,* 2005). AKI is now known to be an independent risk factor for mortality,. The list of causes of AKI in pediatrics is long (Andreoli, 2009); however, the true etiology is likely multifactorial, related to a combination of several factors, such as ischemia and reperfusion injury, disruption of renal vasomotor homeostasis, hypoxic and oxidative stress, and cytokine-driven effects. The kidney is central to numerous homeostatic control mechanisms, including water balance, electrolyte handling, erythropoiesis, vascular tone, acid–base status, and regulation of normal glucose metabolism. The laboratory indicator, glomerular filtration rate (GFR), is the accepted reflection of nephron function. Calculations of GFR rely on serum creatinine (SCr) and are often unreliable because of variability within age groups, gender, metabolic state, body composition, and excretion by the kidney itself (Schwartz *et al.,* 2009). Definitions of oliguria, the bedside indicator for AKI diagnosis, also are varied. Although clinicians have shown that sick kidneys affect morbidity independently and synergistically with multi-organ disease, the study of the impact of kidney injury is limited by having to use these markers of failure. This review is focused on evidence-based AKI research, highlighting disturbing epidemiologic trends for paediatric AKI, novel detection strategies, the role of AKI as an independent causative agent of injury, and available evidence-based data regarding management and outcomes.

Children usually do not have comorbidities like diabetes, obesity, hypertension, cardiovascular disease that are typical for adult patients. However, the epidemiology of AKI in children has changed over the past decade, from primary kidney disease, such as HUS (hemolytic uremic syndrome), to diseases in which the kidneys are affected as a result of another systemic disease or its treatment (Vlasselaers *et al.,* 2009). Critically ill children with multiorgan dysfunction or who are exposed to nephrotoxic medications represent the most prevalent pediatric cohorts who develop AKI (Hui-Stickle *et al.,* 2005). The rates of AKI development in pediatric ICUs depend on the populations studied and the AKI definition used, ranging from 4.5% (all admitted patients with AKI defined as a doubling of SCr) (Bailey *et al.,* 2007) to 82% (only children receiving invasive mechanical ventilation and receiving one or more vasoactive medications, with AKI defined by a 25% decrease in estimated SCr). Mortality is higher for children with AKI, especially for

those with multiorgan failure (Gallego *et al.,* 2001). Therefore, all children with any of these risks factors should be monitored closely for the development of AKI. Early AKI detection is crucial, as even small increases in SCr may be associated with paediatric patient morbidity and mortality (Price *et al.,* 2009).

The aim of this paper is to inform medical professionals involved in the paediatric intensive care of recent advances in AKI diagnosis and management. This review will highlight recent studies on the diagnosis of AKI, the importance of cumulative fluid overload and provide key management strategies for the paediatric patient with AKI. A search was performed in 2013–2014 using the PubMed, Ovid, MEDLINE, and Cochrane databases for the following search terms: "Pediatric acute kidney injury", "AKI epidemiology", "renal replacement therapy (RRT)", and "outcomes of AKI". Inclusion criteria were paediatric articles from 2000 to 2014 in the English language. All retrospective paediatric AKI studies performed from 2000 to 2014 were included. Additionally, heavily cited adult articles within our search results were considered for inclusion.

ETIOLOGY OF ACUTE KIDNEY INJURY

Traditional AKI causes are stratified into location of injury relative to the kidney. The diseases that fit into "pre-renal" and "intrinsic renal" share the commonality that they alter the regional perfusion of, and subsequent oxygen delivery to, the kidney. "Post-renal" injury refers to antegrade urine flow disruption from the kidney. The pathophysiology of AKI in the intensive care unit, however, is much more complex and multifactorial.

Altered renal perfusion. Kidneys receive a high percentage (20 to 25%) of the cardiac output at any moment. Aberrations in the intricate regulatory mechanism in place to maintain renal perfusion pressure lead to injury, such as acute tubular necrosis (Just, 2007). Pediatric kidney transplant recipients of organs with increased ischemic times during harvest have increased rates of acute tubular necrosis (El-Husseini *et al.,* 2005), as do patients with long cross clamp times during cardiopulmonary bypass (CPB) (Boldt *et al.,* 2003). Direct effects on renal blood flow in the microvasculature of the vasa recta occur in sickle cell disease, rhabdomyolysis, HUS, and tumour lysis syndrome.

Vasomotor nephropathy. AKI occurs by stress-mediated glomerular endothelial release of vasoactive substances, proteases, reactive oxygen species, and nitric oxide. For example, the factor XII plasma contact system, coagulation cascades, and complement pathways are activated in renal endothelium during CPB (Moat *et al.,* 1993).

Sepsis and AKI. Sepsis causes AKI in up to 50% of cases (Warady and Bunchman, 2000). Although the precise mechanism remains unclear, a wide spectrum of cytokineses are implicated, as are circulating lymphocytes, T cells, and native kidney tubular epithelial and endothelial cells. Interestingly, septic AKI does not appear to be ischemia-dependent, because it can occur in hyperdynamic renal blood flow (Bellomo, 2008).

Aberrant oxygen homeostasis. A natural degradation in oxygen tension exists from the level of the renal artery to the counter-current mechanism in the vasa recta, making the kidney highly susceptible to both hypoxic and oxidative injury during ischemia-reperfusion. Experimental ischemia leads to renal dysoxia, a situation also seen in sepsis, in which renal cells are unable to utilise oxygen for energy, regardless of oxygen availability (Legrand *et al.,* 2008).

Nephrotoxins and AKI. Nephrotoxic medications in the intensive care unit contribute to nearly 25% of AKI cases. Common offenders include aminoglycoside antibiotics, nonsteroid alantiinflammatory agents, radiopaque contrast, and immunosuppressives, such as calcineurin inhibitors (Jones and Lee, 2008).

Associated syndromes. AKI is seen in conjunction with pulmonary, hepatic, and cardiac failure (Price *et al*., 2008). The increased mortality reported with these dual-axis syndromes underscores the kidney's centrality to host survival. Although exact mechanisms are unknown, they all are almost certainly linked to aberrations in blood flow distribution and to endothelial activation (Moore *et al.,* 2004).

EPIDEMIOLOGY OF ACUTE KIDNEY INJURY

One of the fundamental problems in interpreting studies in AKI has been the lack of a unified definition. There were discrepancies between the two more commonly used definitions (Bellomo *et al.,* 2004), leading to differences in incidence and outcomes of AKI. It was therefore essential to have an agreed definition for epidemiological studies, assessment of risk factors for AKI, evaluation of biomarkers predicting severity and recovery from AKI, and interventional trials. Paediatric AKI epidemiological study has intensified over the recent years, likely as a result of more widespread provision of acute RRT modalities to critically ill children (Warady *et al.,* 2004). AKI rates appear to have increased by over ninefold from the 1980s through 2004 due to increasing use of more invasive management and higher illness severity of critically ill children (Vachvanichsanong *et al.,* 2006). Single centre studies from the 1980s and 1990s reported HUS, other primary renal causes, sepsis, and burns as the most prevalent causes leading to AKI (Andreoli, 2002). More recent data (Williams *et al.,* 2002) reveal a dramatic shift in the epidemiology of AKI, with the most common causes being renal ischemia, nephrotoxin use, and sepsis. Thus, in the current era, AKI more often develops in hospitalised children as a result of a systemic illness or its treatment and not from primary kidney disease, which is similar to the situation in adults. Another limitation of the past AKI studies was the lack of a standardised definition. The incidence of the most severe forms of AKI, defined by dialysis requirement, ranges from 1 to 2% of all critically ill children (Bailey *et al.,* 2007). In children under-

going CPB surgery, the incidence of AKI is in the range of 10–50%, depending on the definition used (Boldt *et al.,* 2003). Even small increases in SCr, much less than would be considered indicative of the need for RRT, are now recognised to contribute to poor outcomes. Chertow and colleagues demonstrated that increases in SCr of 0.3 mg/dl were associated with increased adult patient mortality, even when outcome was controlled for significant patient comorbidity (Chertow *et al.,* 2005). Similar results were noted in paediatric patients with acute decompensated heart failure; patients with a >0.3 mg/dl rise in SCr demonstrated a sevenfold increased mortality risk (Price *et al.,* 2008). These studies highlight the need for more refined AKI definitions for both children and adults and for a focus on earlier detection of AKI before a patient requires RRT.

DEFINITION AND CLASSIFICATION OF ACUTE KIDNEY INJURY

Historically, a substantial rise in SCr and a drop in urine output have been used to determine if a child has AKI. Prior to 2004, over 30 definitions of AKI existed in the literature, which made comparison between studies very difficult. In 2004, the ADKI group proposed the RIFLE (Risk, Injury, Failure, Loss and End-Stage) classification definition of AKI (Bellomo *et al.,* 2004) (Table 1). The first three categories (Risk, Injury and Failure) staged the degree of AKI based on whether the amplitude of SCr increased (or decrease in estimated glomerular filtration rate, eGFR) and/or was a drop in urine output. The last two categories (Loss and End-stage) defined temporary or permanent loss of kidney function after AKI. In 2007, a similar definition (pRIFLE) (Table 2) was proposed for pediatric patients and has been used to describe several cohorts (Akcan-Arikan *et al.,* 2007; Zappitelli, 2008). The RIFLE definition was updated in 2007 by the Acute Kidney Injury Network (Mehta *et al.,* 2007), by many of the same experts who proposed RIFLE. The AKIN definition is similar to the first three stages of the RIFLE classification, but with some changes (Table 3). Recently, the Kidney Disease Improving Global Outcomes (KDIGO) (www.kdigo.org) group was formed of international experts from many different specialties to produce a definition and staging system, which will harmonise these recent definitions (Table 4). The first study that defined AKI using the pRIFLE criteria found that AKI occurred in 82% of critically ill children admitted to a ICU, who received invasive mechanical ventilation and at least one vasoactive medication (Akcan-Arikan *et al.,* 2007). That is opposite to 4.5% prevalence of AKI in all patients admitted to the PICU (Bailey *et al.,* 2007). Worsening AKI defined by the pRIFLE criteria was an independent risk factor for mortality and increased hospital length of stay. The critically ill patient receiving invasive mechanical ventilation and vasoactive medications should prompt early vigilance for AKI occurrence. A recent publication proposed the concept of a "renal angina" to prompt investigation into the presence and causes of AKI, such as chest pain and as-

Table 1

RIFLE CLASSIFICATION AND STAGING SYSTEM*

Stage	Serum creatinine criteria	Urine output criteria
Risk	Serum creatinine increase 1.5- fold OR GFR decrease >25% from baseline	<0.5 ml/kg/h for 6 hours
Injury	Serum creatinine increase 2- fold OR GFR decrease >50% from baseline	<0.5 ml/kg/h for 12 hours
Failure	Serum creatinine increase 3- fold OR GFR decrease >75% from baseline or serum creatinine ≥354 μmol/l (4 mg/dl) with an acute increase of at least 44 μmol/l (0,5 mg/dl)	Anuria for 12 hours

* Bellomo *et al.,* 2004

Table 2

pRIFLE CLASSIFICATION AND STAGING SYSTEM*

Stage	Serum creatinine criteria	Urine output criteria
Risk	eClCr decrease by 25%	< 0.5 ml/kg/h for 8 hours
Injury	eClCr decrease by 50%	< 0.5 ml/kg/h for 16 hours
Failure	eClCr decrease by 75% OR eClCr < 35 ml/min. per 1.73 m^2	< 0.3 ml/kg/h for 24 hours OR anuric for 12 hours

eClCr – estimated creatinine clearance

* Akcan-Arikan *et al.,* 2007

Table 3

AKIN CLASSIFICATION AND STAGING SYSTEM*

Stage	Serum creatinine criteria	Urine output criteria
1	Serum creatinine increase ≥23.5 μmol/l (≥0.3 mg/dl) OR increse to 1.5 to 2-fold from baseline	< 0.5 ml/kg/h for 6 hours
2	Serum creatinine increase 2-3 –fold from baseline	< 0.5 ml/kg/h for 12 hours
3	Serum creatinine increase > 3–fold from baseline or serum creatinine ≥354 μmol/l (4 mg/dl) with an acute increase of at least 44 μmol/l (0,5 mg/dl) OR need for RRT	< 0.3 ml/kg/h for 24 hours OR anuria for 12 hours or need for RRT

* Ricci *et al*., 2011; AKI, acute kidney injury; AKIN, AKI Network; GFR, glomerular filtration rate; RIFLE, Risk, Injury Failure, RRT, renal replacement therapy.

Table 4

KDIGO CLASSIFICATION AND STAGING SYSTEM*

Stage	Serum creatinine criteria	Urine output criteria
1	1.5–1.9 times baseline OR ≥0.3 mg/dl (≥26.5 μmol/l) increase	< 0.5 ml/kg/h for 6–12 hours
2	2-2.9 times baseline	< 0.5 ml/kg/h for ≥12 hours
3	3 times baseline OR increase in serum creatinine ≥354 μmol/l (4 mg/dl) with an acute increase of at least 44 μmol/l (0,5 mg/dl) OR Initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to #ml/min per 1.73 m^2	< 0.3 ml/kg/h for ≥24 hours OR anuria for ≥12 hours

* Anonymous, 2012; eClCr – estimated creatinine clearance

sociated signs and symptoms evaluation for acute coronary syndrome and myocardial infarction (Goldstein and Chawla, 2010). The goal was to develop a simple score (RAI, renal angina index) that is easily calculated and can be used at the bedside (Basu *et al.,* 2014).

ROLE OF FLUID BALANCE.

No consensus exists regarding the appropriate balance of fluids, diuresis, and dialysis to use in AKI. In response to hypoperfusion, many patients may receive total fluid doses to reach central venous pressure and mean arterial pressure targets, which results in total body water overload. The Prospective Pediatric Continuous Renal Replacement Therapy Registry Group (Prospective Pediatric CRRT), studying a sample of 116 children, retrospectively found increased fluid administration to be independently associated with mortality in children started on CRRT (Goldstein *et al.,* 2005). When Goldstein *et al.* (2001) first published results on the potential detrimental effects of cumulative fluid overload, there was a lot of resistance from the critical care community about their conclusions, as there was new data on the importance of aggressive goal-directed use of fluids in the early course of sepsis (de Oliveira *et al.,* 2008). In paediatrics, the percent fluid overload has been used as an initiating trigger and is calculated as follows: fluid overload = ((Fluids IN + fluids OUT) / admission weight) × 100. In a study of 113 children with multiple organ dysfunction syndrome started on CRRT, median percent fluid overload was significantly lower in survivors compared to nonsurvivors (7.8% vs. 15.1%), independent of severity of illness (Foland *et al.,* 2004). Even more recently, in 297 patients, percent fluid overload was again significantly lower in survivors vs. nonsurvivors (12.5% vs. 23.0%) (Sutherland *et al.,* 2010). Prospective Pediatric CRRT data suggest that 10 to 15% fluid overload is a signal for CRRT or peritoneal dialysis initiation.

RENAL REPLACEMENT THERAPY DOSE AND MODALITY

RRT modality choice for children with AKI is guided by many of the same principles used for adult patients. However, severe AKI is relatively rare in children compared to adults, and occur in less than 1% of hospitalised children and 4.5% of children admitted to an intensive care unit (Bailey *et al.,* 2007). As noted below, each modality of acute RRT can be successfully provided to paediatric patients of all sizes. Each programme should evaluate which modality is provided most optimally and feasibly in its particular setting. Given their small size and associated low blood volume, peritoneal dialysis (PD) may provide the least technically challenging option for infants and small children. However, technological advances aimed at providing accurate ultrafiltration with volumetric control incorporated into CRRT equipment, and disposable lines, circuits, and dialysers sized for the entire paediatric weight spectrum, have made CRRT safer and feasible for children of all ages and sizes (Symons *et al.,* 2003; 2007). Accurate ultrafiltration and blood flow rates are crucial for paediatric RRT, since the extracorporeal circuit volume can comprise more than 15% of a small paediatric patient's total blood volume, and small ultrafiltration inaccuracies may represent a large percentage of a small paediatric patient's total body water.

Peritoneal dialysis. PD can be efficacious in fluid overload and offers advantages for younger children, including simplicity, less invasiveness, and improved haemodynamic tolerance. PD is generally safe and effective in children after CPB, with some investigators utilising it as a prophylactic therapy as well (Pedersen *et al.,* 2008).

DIAGNOSTICS

Biomarkers. RIFLE, paediatric RIFLE, and Acute Kidney Injury Network (AKIN) criteria have limited real-time/pre-injury utility, because they rely on creatinine and urine output. Accordingly, the search is for a real-time markers of AKI, which would allow rapid and reliable diagnosis, theoretically providing a therapeutic advantage to intensivists, similarly as using troponins in myocardial infarction. Many candidate biomarkers of AKI have been identified (Parikh *et al.,* 2007). Serum Cystatin C levels show high correlation to established AKI and are used by some urologists as a marker of disease progression after kidney transplantation. Kidney injury molecule-1, interleukin-18, and liver fatty acid-binding protein have been shown to be associated with kidney ischemia (Parikh *et al.,* 2010). Clinical studies indicate urinea nd serum neutrophil gelatinase-associated lipocalin (NGAL) as highly sensitive, specific, and predictive of AKI in many different disease processes (Williams *et al.,* 2002). In paediatrics, NGAL has been studied after CPB, after nephrotoxin administration and contrast nephropathy, in sepsis, and in cardiorenal syndrome. Urine NGAL concentrations >50 ng/ml predict AKI with high sensitivity and specificity in children after CPB (Bennett *et al.,* 2008).

Diagnostic tools. Imaging modalities, such as blood oxygen level-dependent magnetic resonance imaging, have been used in adults to determine changes in renal parenchymal oxygenation (Han *et al.,* 2008). Adult urine PO_2 levels, assumed to mirror changes in renal oxygenation, have been correlated to AKI (Kainuma *et al.,* 1996).

MANAGEMENT OF ACUTE KIDNEY INJURY

Development of management parameters in AKI is limited by the multifactorial aetiology of the disease process and by the paucity of prospectively validated data.

Maintaining renal perfusion. To limit ischemic injury, attempts are made to modulate renal perfusion pressure and to optimise renal preload. The use of renal vasodilators to increase renal perfusion has not demonstrated improved outcomes. Adult studies of low-dose, or "renal-dose," dopamine have failed to show benefit and actually may even be

harmful (Bellomo *et al.,* 2000). Low-dose dopamine in children has not been effective at improving outcomes either (Andreoli, 2009). Fenoldopam, a selective dopamine agonist, increases renal blood flow and may reduce mortality and the need for RRT in adults, but has not significantly improved AKI outcomes in children (Ricci *et al.,* 2008). In the acute setting, the two most significant threats to renal perfusion pressure are systemic arterial hypotension and increased intra-abdominal pressure (including so-called abdominal compartment syndrome). Specific recommendations to maintain renal perfusion are difficult to make. First, vasopressor medications (e.g. norepinephrine) should be used only to treat arterial hypotension once intravascular volume has been restored. In practice, vasopressors are often started when volume loading is underway and discontinued if no longer required, once hypovolaemia has been reversed (Kellum and Pinsky, 2002). There is no evidence from clinical studies or appropriately designed animal experiments (Langenberg *et al.,* 2005) that norepinephrine is associated with increased risk of AKI when used to treat arterial hypotension. Indeed, a large observational study (Sakr *et al.,* 2006) suggested that other vasopressors, like dopamine, may be less efficacious and possibly associated with lower survival. Kidney is a highly adaptive organ designed to maintain renal perfusion and GFR over a wide range of blood pressures. Autoregulatory mechanisms are first line of defense, but might be significantly impaired as a consequence of: underlying kidney disease and as a consequence of AKI secondary to drug therapy. Maintaining an adequate filtration pressure gradient is key to maintaining GFR. Many clinicians and clinical protocols target a mean arterial pressure of 60–65 mmHg. However, patients with long-standing hypertension and/or renal vascular disease may require substantially higher pressures to maintain renal perfusion. These data are valid in adult patients and in children; according the PALS guidelines (Anonymous, 2000), *hypotension* is characterised by the following: for term neonates (0 to 28 days of age), SBP < 60 mm Hg, for infants from 1 month to 12 months, SBP < 70 mm Hg, for children >1 year to 10 years, SBP < 70 + (2 × age in years), beyond 10 years, hypotension is defined as an SBP < 90 mm Hg. Consensus among paediatric anaesthetists regarding the definition of intraoperative hypotension is still lacking (Naftiu *et al.,* 2007) and specific arterial pressure targets for titration of therapy to avoid renal hypoperfusion are not known. Renal dysfunction secondary to increased intraabdominal pressure (IAP) results from decrease in cardiac output, direct compression of renal vessels and parenchyma with decreased renal blood flow, increased renal vascular resistance, and redistribution of renal blood flow from the cortex to the medulla (Moore *et al.,* 2004). Experimental studies demonstrated that IAP 15–20 mm Hg was associated with decreased GFR and oliguria, which progressed to anuria when IAP values exceeded 30 mm Hg (Harman *et al.,* 2005). Decrease in cardiac output and renal plasma flow results in increased secretion of catecholamines, angiotensin II, and aldosterone, with subsequent renal vasoconstriction, which exacerbates the decrease in renal blood flow and GFR (Shear and Rosner, 2006). Intra-abdominal hypertension is associated with decreased renal perfusion and may result in AKI (Malbrain *et al.,* 2005). Prompt recognition, often guided by urinary bladder pressure measurement, and surgical treatment offer the best potential for recovery.

Crystalloid or colloid infusions. In the adult population, studies have compared albumin to saline (SAFE study) and hydroxyethylstarches to saline (SOAP study) (Finfer *et al.,* 2004) for resuscitation. Neither demonstrated clear benefit in colloid over crystalloid infusions. There was no survival difference in 7000 patients between recipients of albumin or saline (SAFE). However, in three randomised studies of children with severe malaria, albumin conferred a survival advantage when compared with both normal saline and gelatin (Maitland *et al.,* 2005; Akech *et al.,* 2006, 2010).

Diuretics. Diuretic treatment is widely used in ICU to resolve fluid overload or to treat (or prevent) AKI; furosemide is the most commonly prescribed drug, at least for AKI (Uchino *et al.,* 2004). Despite the wide use of furosemide and the fact that continuous infusion intuitively seems superior to bolus injections, evidence on this topic is still lacking. Meta-analysis showed that continuous infusion and bolus administration were associated with similar amounts of administered furosemide (Andoni *et al.,* 2012). Reducing fluid overload with diuresis can limit the use of RRT, but has not been proven to improve outcomes of AKI. Data regarding augmentation of urine output in paediatric AKI using diuretics are limited to bone marrow transplantation and after bypass (Michael *et al.,* 2004). The use of natriuretic peptides has been attempted in patients with AKI and cardiorenal syndrome (Price *et al.,* 2008). Intravenous infusion of theophylline, given to severely asphyxiated neonates within the first hour of birth, was associated with improved fluid balance, creatinine clearance, and reduced SCr levels, and had no effects on neurological and respiratory complications (Jenik *et al.,* 2008). Aminophylline is converted to theophylline in the human body, which in turn vasodilates the renal afferent arterioles through competitive inhibition of adenosine on the adenosine A1 receptor. Thereby aminophylline improves renal blood flow and glomerular perfusion pressure and filtration (Rudnick *et al.,* 2006). Recent studies show that aminophylline therapy may be associated with significantly improved renal excretory function and may augment urine output in children who experience oliguric acute kidney injury after CPB-assisted surgery ICU (Axelrod *et al.,* 2014).

Oxidative and inflammatory homeostasis. The kidney has derangements in oxygen homeostasis during AKI. Although prospective study of CPB patients demonstrated that anaemia is independently associated with AKI, the risks of increased volume and blood viscosity must be balanced against the presumed benefit of increased oxygen-carrying capacity. Studies of N-acetylcysteine and dexamethasonet therapies to limit oxidative and inflammatory damage in AKI after CPB have shown conflicting results (Rosner and Okusa, 2006). The use of nephrotoxins, such as aminoglycoside antimicrobials, nonsteroidal anti-inflammatory drugs, radiocontrast media, antifungal agents, and immuno-

suppressive drugs are associated with high rates of AKI and must be diligently constrained (Patzer, 2008).

Nutritional support. Optimising nutrition in pediatric AKI patients can be challenging, and Bunchman (2008) recommends using a metabolic cart to determine the amount of nutrition necessary. CRRT may reduce fluid concerns when optimal nutrition, using renoprotective and anabolic formulas, is desired. A prospective paediatric study demonstrated morbidity improvements in children receiving intensive insulin therapy, but no effects on outcomes with AKI or dialysis were seen (Ympa *et al.,* 2005).

OUTCOME

It has been thought that AKI due to hypoxic/ischemic and nephrotoxic insults were reversible, with a return of renal function to normal. However, recent studies have demonstrated that hypoxic/ischemic and nephrotoxic insults can lead to physiologic and morphologic alterations in the kidney that may lead to kidney disease at a later time (Zager, 1996). Since nephrogenesis is not complete until approximately 34 weeks gestation, AKI during this interval might lead to a decreased number of nephrons, and, indeed studies have suggested that AKI during nephrogenesis results in decreased numbers of nephrons and subsequent glomerulomegaly (Rodriguez *et al.,* 2005). AKI in the full-term neonate is also associated with later kidney disease (Polito *et al.,* 1998). Studies on older children have also shown that AKI leads to CKD in a higher percentage of children than was previously appreciated (Askenazi *et al.,* 2006). In a prospective study of renal insufficiency in children undergoing bone marrow transplantation, the incidence of acute renal insufficiency was high and was predictive of chronic renal insufficiency. Of those who survived, 11% developed CKD, and AKI was the sole predictor of CKD (Kist-van Holthe *et al.,* 2002). In the recent study (Cooper *et al.,* 2014), it was shown that a novel biomarker L-FABP remained elevated even five years after the CPB-associated AKI. Thus, children with a history of AKI from any cause need long-term follow-up.

CONCLUSIONS

The management of AKI in paediatrics is complex and challenging. Our understanding and ability to detect renal distress are in their infancy. Biomarkers may improve our management if early detection actually affects outcomes. To date, therapy of AKI revolves around optimising renal perfusion pressure and oxygenation through a combination of judicious fluid prescription, inotropy, and RRT while attending to proper nutrition and avoidance of additional nephrotoxins. However, paediatric intensivists have limited consensus or best-practice parameters to follow, as little prospective evidence is available. Kidney injury is likely incremental, more temporally proximal than fluid overload and anuric failure, and likely causes more significant distal harm than previously appreciated. The impact of AKI on critically ill children is significant and demands prospective study if we are to find effective therapies and improve outcomes.

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23 August 2014

AKŪTS NIERU BOJĀJUMS — NENOVĒRTĒTA PROBLĒMA BĒRNU INTENSĪVAJĀ TERAPIJĀ

Akūts nieru bojājums (ANB) sastopams gan bērniem, gan pieaugušajiem kritiskā stāvoklī. To novēro 5–20% gadījumu pacientiem, ārstējoties intensīvās terapijas nodaļā. Reti ANB ir izolēts sindroms, bieži tas saistīts ar sepsi, elpošanas mazspēju un nereti noved pie multiplu orgānu disfunkcijas. Neraugoties uz progresu, kas pēdējā laikā sasniegts, lietojot nieru aizstājējterapiju (NAT), letalitāte no ANB, saistībā ar multiplu orgānu disfunkciju, saglabājas nemainīgi augsta un sasniedz apmēram 50%. Pētījumi liecina, ka ANB ir ne vien klīniskās gaitas smaguma indikators, bet arī veicina agrīnu multiplu orgānu disfunkciju un palielina letalitāti. Raksta mērķis ir informēt speciālistus par jaunākajiem pētījumiem un atziņām ANB diagnostikā un terapijā. Informācija, kas satur ar ANB saistītus avotus, tika meklēta *Medline, Pubmed, Ovid* un *Cochrane library* datu bāzēs. Secinājumi: ANB ir nozīmīga problēma intensīvajā terapijā pediatrijā, kas pagarina ārstēšanas ilgumu, mākslīgās ventilācijas laiku un kopējo letalitāti. Vajadzīgi prospektīvi pētījumi, lai izvērtētu biomarķieru un ārstnieciskās stratēģijas efektivitāti, tādas kā agrīnas NAT izmantošanu pacientiem ar šķidruma pārslodzi.