Chapter 8
Acute Kidney Injury After Cardiovascular Surgery in Children

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Objectives

- To understand the etiology and epidemiology of acute kidney injury after pediatric cardiovascular surgery.
- To learn the current methods used to diagnose acute kidney injury and their limitations, as well as potential biomarker diagnostic tools.
- To apply the current management and novel treatment strategies of acute kidney injury in the pediatric patient after cardiac surgery.

Introduction

Acute kidney injury (AKI) is a frequent and serious complication after pediatric cardiovascular surgery, affecting up to 60 % of patients [1, 2]. Multiple studies have demonstrated that even minor degrees of AKI are associated with worse clinical outcomes, including mortality [1–5]. Infants are particularly vulnerable to AKI given the immaturity of their nephron system and the complexity of their cardiac repairs, often necessitating long durations of cardiopulmonary bypass (CPB). Within the neonatal cohort, surgery for congenital heart disease comprises the leading cause of AKI and has been the subject of considerable research [6].

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Table 8.1 Pediatric-modified RIFLE (pRIFLE) criteria

	GFR criteria	Urine output criteria
Risk	eCCl decrease by 25 %	<0.5 ml/kg/h for 8 h
Injury	eCCl decrease by 50 %	<0.5 ml/kg/h for 16 h
Failure	eCCl decrease by 75 % or eCCl <35 ml/min/1.73 m^2	<0.3 ml/kg/h for 24 h or anuric for 12 h
Loss	Persistent failure >4 weeks	
End-stage	End-stage renal disease (persistent failure >3 months)	

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Abbreviations: *eCCl* estimated creatinine clearance using the Schwartz formula (eCCl = k*ht/Scr), *pRIFLE* pediatric risk, injury, failure, loss, and end-stage renal disease

The most commonly used definition for pediatric AKI is the pRIFLE criteria (pediatric risk, injury, failure, loss, and end-stage renal disease), which is a modification of the adult RIFLE system. This validated classification system differs by having decreased diagnostic thresholds to account for lower normal pediatric creatinine ranges and urine outputs (Table 8.1) [7]. The AKI Network (AKIN) created a similar definition with three numerical categories corresponding to risk, injury, and failure [8]. Both definitions use a lower creatinine threshold to define risk (1.5-fold increase or 0.3 mg/dl) and incorporate urine output.

Pathophysiology

The mechanism of AKI after CPB has many contributing factors, including renal ischemia and reperfusion injury, oxidative stress, a maladaptive inflammatory response, and microemboli (Table 8.2). In periods of low cardiac output, the renal medulla is at particularly high risk of ischemic injury. Despite being a small organ, the kidney depends on a large portion of the body's cardiac output, and the ion transport channels within the nephron require a significant amount of energy via ATP. Periods of decreased oxygen delivery can be detrimental to the kidney and cause generation of reactive oxidation molecules and increases in intracellular calcium levels, which are both deleterious processes [9]. The dependence of the kidney on oxygen delivery has been demonstrated in an adult study post-CPB which associated lower urinary partial pressure of oxygen (PO_2) levels with the development of AKI [10].

As with any other organ, the kidney has the ability to maintain consistent perfusion during a period of diminished blood flow through a process called autoregulation. With changes in cardiac output or increased metabolic demand, afferent and efferent arterioles within the nephron dilate or constrict to modify vascular resistance and ensure a relatively constant perfusion pressure. However, the ability to adapt for significant decreases in blood flow is not known, especially in pediatric and neonatal physiologies.

Table 8.2 Causes of AKI in the pediatric population

Pathophysiology of AKI
Ischemia and reperfusion injury (vasoconstriction and low cardiac output)
Inflammation
Oxidative stress
ATP depletion
Microemboli
Apoptosis

This table lists multiple factors involved in the complex pathophysiology involved in AKI after cardiopulmonary bypass in the pediatric setting

Inflammation is thought to have a major role in all ischemic and reperfusion renal injury and is exacerbated by extracorporeal circulation. The complex interactions between injured endothelial cells and inflammatory cells in the milieu of cytokine and chemokine upregulation likely worsen AKI. Inflammatory cascades implicit in renal injury include the proinflammatory cytokines of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and transforming growth factor β (TGF-β) which may ultimately serve as targets for diagnosis or treatment.

Lastly, CPB exposes blood cells to nonphysiologic surfaces and shear forces, leading to cell lysis and the release of plasma free hemoglobin into the circulation. This, and other microemboli that may occur with CPB, may contribute to further tubular damage.

Epidemiology and Risk Factors

AKI rates after CPB in children continue to be exceedingly high affecting up to 60 % of high-risk patients [1, 2]. Among children, palliative surgery for congenital heart disease is the most common cause for AKI [6] and associated with a worse outcome. Postoperative pediatric patients may have multiple risk factors contributing to the development of AKI. The TRIBE-AKI group, a large multicenter consortium sponsored by the National Institutes of Health/National Heart, Lung, and Blood Institute (NIH/NHLBI) designed to study AKI in adults and children after heart surgery, reported that 87 % of patients with AKI had intraoperative hypotension, 15 % were exposed to gentamicin, 56 % were exposed to nonsteroidal antiinflammatory drugs (NSAIDs), and 6 % experienced low cardiac output syndrome [1]. Unlike other models of kidney injury, sepsis and urinary tract obstruction are rare, presenting in less than 5 % of this population [1]. Unlike adult populations who often are exposed to multiple comorbidities including diabetes mellitus, tobacco use, and coronary artery disease, pediatric cohorts are generally without chronic kidney disease or factors which may predispose AKI [3].

Identified risk factors for development of AKI are generally unavoidable and relate to patient size and complexity of required repair. Smaller patients, both by age and body surface area, have been demonstrated to be more likely to develop AKI [1, 2, 4, 5, 11, 12], and children older than 2 years are 70 % less likely to develop AKI when compared to those younger than 2 [1]. Higher surgical complexity, by Risk Adjustment for Congenital Heart Surgery (RACHS-1) surgical severity score, has been demonstrated to be independently associated with AKI in multiple studies [1, 2, 4, 5, 11, 12]. The TRIBE-AKI group reported that when stratified by RACHS-1 score, AKI was present 0, 42, 43, and 75 % for categories 1–4, respectively. Surprisingly, preoperative lactate elevation and inotropic medication demands did not correlate with later AKI, although there was a correlation with elevated preoperative serum creatinine level [2].

The primary intraoperative risk factors for AKI development are the duration of CPB [1, 2, 4, 5, 11, 12] and use of deep hypothermic circulatory arrest [2, 11]. There is a suggestion that longer aortic cross-clamp time is associated with AKI [1, 2], although a statistical association has not been demonstrated. The TRIBE-AKI group compared the incidence of AKI to a standard duration of CPB less than 60 min and found that bypass of 90–120 min had an odds ratio of 2.5 (95 % CI: 1.08, 5.65) and >180 min had an odds ratio of 7.6 for the development of AKI (95 % CI: 2.62, 21.92) [1].

Outcomes After AKI

AKI after CPB is most commonly a self-limited state which typically occurs within the first 24–48 postoperative hours. In the TRIBE-AKI consortium, 47 % of patients met AKI diagnostic criteria for 1 day, and only 11 % of patients still met the AKI definition by the fourth postoperative day [1]. Only 2/130 patients studied required dialysis within the first week [1].

AKI-related morbidity is most commonly related to fluid overload and has been considered a biomarker for worse outcomes. As the degree of fluid overload increases, the likelihood of mortality increases, irrespective of illness severity scores [13, 14]. Fluid overload is associated with worsening oxygenation indices and prolonged durations of mechanical ventilation [15].

AKI is an independent risk factor for prolonged duration of mechanical ventilation [1, 2]. In the TRIBE-AKI consortium, 30 % of patients with AKI were mechanically ventilated after 48 h as opposed to 8 % of patients without AKI [1]. Intensive care unit stay and hospital stay were demonstrated to be longer for patients with AKI [1]. Mortality is higher in patients with AKI after CPB in adult studies, even with mild degrees of injury [3]. Mortality in pediatric heart surgery is low, and institutional volumes are relatively small, making an association between AKI and mortality difficult to discern. However, within a large Canadian cohort, patients with severe AKI were shown to have an increase in mortality and neonates who required postoperative dialysis were 6.4 times more likely to die in the hospital [2].

Postoperative AKI portends worse long-term outcomes, and there is growing evidence that after laboratory and functional markers of injury improve, patients

often suffer from subclinical kidney injury. Even when controlling for gestational age, age at surgery, surgical group, preoperative ventilation, the highest lactate value, and extracorporeal membrane oxygenation (ECMO) use, a Canadian group demonstrated that as AKI status worsened, 2-year follow-up weight percentile decreased and more specialists were seen, with more cardiac-related hospitalizations [2]. There is evidence that these children remain affected by subclinical kidney disease years after CPB. This was demonstrated in a cohort of children who had a persistent elevation of kidney injury biomarkers despite a lack of clinical evidence of chronic kidney disease 7 years after bypass [16]. It is as yet unknown if these children will go on to develop clinical signs of chronic kidney disease.

Diagnosis of AKI

One of the key challenges to management of AKI after CPB is the difficulty achieving prompt diagnosis. Laboratory evidence of AKI relies upon serum creatinine elevation which is insensitive for damage, because creatinine elevations are not seen until 50 % of kidney function is lost. AKI-related creatinine elevation is secondary to functional changes in glomerular filtration rate, which is delayed from the initial structural damage that occurs with the operative and postoperative renal injury [17]. Waiting for creatinine elevation for management decisions is analogous to waiting for cardiac output to decrease before treating a myocardial infarction.

The concept of "renal angina" is often used to illustrate the challenges associated with delayed diagnosis of AKI [18]. Unlike the chest pain and dyspnea experienced by a patient with a myocardial infarction, kidney injury is painless, with low urine output as the only symptom. At current time, unlike myocardial infarctions, there are no commercially available troponin-like biomarkers to diagnose AKI early enough to direct therapy. Fortunately, there are many promising novel biomarkers being investigated, with some likely to be commercially available soon. Infants with AKI after CPB are often chosen as the population to study these biomarkers because they have a planned, finite exposure of renal ischemia and lack comorbidities which affect other populations. The most promising candidate biomarkers are neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), liver-type fatty acid-binding protein (L-FABP), kidney injury molecule-1 (KIM-1), and cystatin C (CyC). For a full description of these biomarkers, see Chap. 3. A brief review of these biomarkers in the pediatric cardiac setting is included here.

NGAL may be the most promising biomarker of AKI in pediatric settings, reliably showing elevation as early as 2 h after bypass [4, 19], and has been shown to predict clinical outcomes such as hospital and intensive care unit (ICU) stay, duration of AKI, duration of mechanical ventilation, dialysis requirement, and mortality [19–21]. NGAL may also have AKI treatment applications for renal tubule survival and recovery through its role of iron transportation [22]. IL-18 is also a sensitive early (4–6 h post-bypass) biomarker for AKI and correlates well with severity of AKI and associated outcomes [23]. In limited pediatric studies, later elevation (12–24 h post-bypass) of KIM-1 has been shown to be predictive of worsening

degrees of AKI and associated sequelae [4]. Serum level of cystatin C is a commonly used clinical tool to estimate kidney function; however, pediatric studies have shown that urine cystatin can be used as a sensitive and specific predictor of the duration and severity of AKI, with an odds ratio of 17 of predicting AKI when compared to creatinine elevation [24, 25].

Pediatric models have shown these biomarkers have different temporal elevations and their individual specificity and sensitivity can be increased when used as part of biomarker "panels" [4]. They may help distinguish between various etiologies causing AKI and help direct optimal treatment. Many of these biomarkers are still in research phases, and large-scale post-clinical research will be helpful after they arrive to the market.

Prevention and Treatment of AKI During the Perioperative Period

Intraoperative Prevention

Since longer bypass times and the use of circulatory arrest are associated with higher incidence of AKI, both should be limited whenever possible. The use of modified ultrafiltration after separation from CPB has been shown to reduce the accumulation of total body water, decrease postoperative blood loss, decrease the need for postoperative blood product need, and improve postoperative ventricular systolic function and is often used in surgery for congenital heart disease [26–28].

Postoperative AKI Management

The natural history of postoperative AKI is generally self-limited, and therefore the management of AKI is typically directed toward managing the sequelae of AKI, namely, fluid overload. Fluid overload has been shown to be an independent predictor of hospital stay, and severity of fluid overload is associated with worsening outcomes in children [15, 29]. The quintessential step for limiting fluid overload is controlling the volume given to patients; however, nutritional demands, blood products, medications, and resuscitation fluids often exceed outputs, especially in the face of AKI-related oliguria.

Diuretics are the mainstay of treatment for postoperative oliguria, most commonly with loop diuretics, such as furosemide and bumetanide. These are often used in synergy with thiazide diuretics, such as chlorothiazide and metolazone.

The timing of initiation of renal replacement therapy (RRT) and specific indications for intervention is somewhat controversial with recent research arguing for earlier initiation. There are two commonly used modalities of RRT in children after cardiac surgery: continuous renal replacement therapy [30] and peritoneal dialysis

(PD) [11, 12, 31]. In the United States, PD is the most commonly used method [11, 12, 31, 32]. Although some centers insert PD catheters after they have developed AKI, many postulate that inserting PD catheters at the time of surgery is less likely to cause adverse events including bowel injury and peritonitis [31, 33]. The benefits of PD use in early AKI are demonstrated in a retrospective study which showed that initiation of PD within the first 24 h of surgery is associated with lower mortality [11]. The concept of prophylactic PD has also been proposed, with retrospective data demonstrating that this practice is associated with shorter time to extubation and negative fluid balance when compared to peritoneal drain [12]. Although center variation exists, a common PD prescription consists of 1.5 % dextrose diasylate with 10 ml/kg dwell volumes with continuous 1-h cycles [11, 12, 31].

There is a saying that the "best diuretic is a good cardiac output." Although often said in jest, without adequate renal perfusion, no treatment will be adequate. A case-control study of AKI post-CPB for patients receiving PD showed arterial hypotension and poor cardiac performance-related venous hypertension were independent risk factors for AKI development and stronger risk factors than preexisting renal failure [34]. In the postoperative period, inotropic and vasoactive medications are often essential for adequate renal perfusion and constitute primary prevention of AKI.

Novel Treatments

Rather than managing the effects of AKI, there has been recent research focused on preventative measures. Some of the most promising representatives are discussed below (Table 8.3):

Fenoldopam is a selective dopamine-1 receptor agonist which causes systemic vasodilation, increasing renal and splanchnic blood flow, thus augmenting tubular sodium excretion. It has been used for short-term management of adult hypertension and to increase renal perfusion as an adjunct to conventional diuretic therapy [35], although its use is limited by the potential complication of systemic hypotension. There has been recent interest in fenoldopam to prevent AKI, and a recent prospective randomized study among neonates demonstrated the addition of fenoldopam was associated with less need for diuretics, lower NGAL and CyC values, and trends toward less AKI [36]. Although individual studies have mixed data, a meta-analysis of 440 patients from 6 studies showed a pooled odds ratio of 0.41 for developing AKI in adult patients, suggesting reno-protective properties [37].

By a similar mechanism, it is thought that natriuretic peptides may help prevent AKI. Among other actions, natriuretic peptides are antagonists of the renin-angiotensin system and induce selective dilation of the afferent arterioles and constriction of efferent arterioles causing an increase in glomerular filtration rate (GFR). Nesiritide is a commercially available recombinant brain natriuretic peptide which is used for the diuresis of acutely decompensated adult congestive heart failure. Adult studies of the prophylactic use of nesiritide have demonstrated a decrease in AKI

Table 8.3 Novel therapies for AKI

Timing	Earlier	→						Later
Pathology of injury	Ischemia (vasoconstriction)	Ischemia (low cardiac output)	ATP depletion	Oxidative stress	Inflammatory response	Apoptosis	Ongoing injury	Regeneration
Mechanism of treatment	Vasodilation	Improving cardiac output	ATP donors	Antioxidants	Antiinflammatory	Antiapoptotic	Renal replacement therapy	Nephron repair
Potential therapies	Fenoldopam	Inotropic medications		N-acetylcysteine	Glucocorticoids		Peritoneal dialysis	Growth factor (NGAL)
	Nesiritide							
	Aminophylline			Rasburicase	Peritoneal dialysis		CRRT	Stem cells

This table lists various mechanisms of acute kidney injury and proposed mechanisms of intervention with potential candidate therapies, where available. Notably, a majority of these interventions are experimental and not used in clinical practice

incidence, but no change in hospital length of stay, mortality, or need for dialysis [38]. At present, there are no pediatric studies for CPB-related AKI, although there are limited data supporting its use in children with congestive heart failure [39].

Since the mechanism of AKI is multifactorial with some component of injury likely due to oxidative stress, there is a growing body of literature to investigate the use of N-acetylcysteine (NAC) to prevent AKI by free radical scavenging and prevention of oxidative stress. There are several large randomized adult studies which show no clear improvement in outcomes with NAC as prophylaxis for AKI after CPB [40]. However, NAC continues to be commonly used especially in patients with chronic kidney disease as it is generally considered a benign medication. A recent randomized trial among neonates undergoing the arterial switch operation demonstrated the use of perioperative NAC was associated with reduced AKI, reduced need for RRT, shorter ICU stays, and less time to negative fluid balance [41]. By a similar mechanism, there is growing literature that the antioxidant uric acid may have a detrimental association with AKI after CPB. Adult studies have demonstrated that elevated postoperative uric acid levels were associated with a 40-fold risk in AKI [42], while treatment with rasburicase to lower uric acid levels was associated with a decrease in NGAL levels [43].

A more thorough understanding of the mechanism of CPB-associated AKI, plus earlier diagnosis through the use of biomarkers, should allow continued investigation of potential therapies directed at the prevention of AKI.

Conclusion

AKI is a frequent and serious complication of cardiac surgery in children and is independently associated with negative outcomes. Currently, practitioners are challenged by delays in diagnosis and poor treatment options. However, a recent increase in research will likely expedite the advent of novel biomarkers to improve diagnosis and guide thoughtful management.

Key Messages

- Acute kidney injury (AKI) is a frequent and serious complication after pediatric cardiovascular surgery. Infants are particularly vulnerable to AKI.
- Even minor degrees of AKI are associated with worse clinical outcomes.
- Limitations of serum creatinine prevent timely diagnosis. New biomarkers in research development promise to facilitate earlier diagnosis with higher sensitivity and specificity.
- Current treatment strategies are focused on managing AKI-related fluid overload.
- Early renal replacement therapy, often with institution of peritoneal dialysis, is becoming increasingly common in these patients.

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