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*Review*

# Cardiac Surgery-Associated Acute Kidney Injury in Children after Cardiopulmonary Bypass

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**Abstract:** Cardiac surgery-associated acute kidney injury (CSA-AKI) is a complication of cardiopulmonary bypass surgery that frequently occurs in children. The increased availability of pediatric cardiac surgery leads to yearly increases in congenital heart disease (CHD) procedures performed worldwide. The number of complications, including pediatric CSA-AKI, has also increased. Children with CSA-AKI have worse postoperative periods and require more complex post-op intensive care. Thus, the timely commencement of interventions to prevent and to treat kidney injury in CHD children are one of a leading goals of pediatric cardiac intensive care.

**Keywords:** acute kidney injury; cardiopulmonary bypass; congenital heart disease; children

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## 1. Introduction

CSA-AKI is a common complication of congenital heart disease procedures that are performed with a cardiopulmonary bypass (CPB) [1]. Improving the quality of global health care services, as well as its rising availability, has led to yearly increases in CHD procedures performed worldwide. Consequently, the number of perioperative complications, including pediatric CSA-AKI, has also increased. Children with CSA-AKI undergo [2] longer periods of mechanical ventilation, require more inotropes, and they are characterized by increased in-hospital morbidity and mortality rates. Severe AKI cases require peritoneal dialysis (PD) or renal replacement therapy (RRT). These factors lead to increased hospital and ICU length of stay and treatment costs [3]. CSA-AKI increases the risk of chronic kidney disease development [4], followed by a decreased quality of life and lifespan. Thus, early diagnostics and the timely commencement of CSA-AKI treatment, as well as the development of effective preventive measures, are among the main aims of pediatric cardiac intensive care.

## 2. Risk Factors

Recent studies [5,6] have revealed that an early age at the procedure, a lower weight, greater procedure complexity according to the RACHS-II scale, cyanotic congenital heart defects, pulmonary hypertension, inotrope and prostaglandin E1 use, mechanical ventilation, and ICU length of stay are the most significant preoperative risk factors. The most important intraoperative risk factors for kidney damage are longer procedures, CPB and aortic cross-clamp time, deep hypothermic circulatory arrest, mild hypothermia, packed red blood cell transfusion, and open chests.

## 3. Epidemiology of CSA-AKI in Children

There are several approaches to CHD repair in children, and they are determined both by the heart defect anatomy and the individual features of a child. Many congenital heart defects require preoperative computed tomography examination, and some heart defects may be repaired using endovascular techniques. Both procedures require intravenous

X-ray dye injections. Although these agents cause direct kidney damage, endovascular procedures have the smallest AKI rate in children compared with open heart surgery, which is estimated to be approximately 10% of cases [7].

Conversely, open heart procedures with CPB are characterized by the highest incidence of postoperative renal dysfunction in 30–50% of cases [8].

## 4. Pathology of CSA-AKI

Kidney damage in CHD children is a multifactorial process with many independent variables. The key cause of kidney damage is systemic inflammatory response syndrome, which occurs in all mechanical circulation procedures [9].

Before CPB initiation, all blood circulation lines, oxygenators, and filters must be thoroughly filled with a primary solution. In newborns and infants, packed red blood cells are necessarily added to the prime solution. On the one hand, this makes it possible to reduce the severity of hemodilution, which is a solely damage-based factor; on the other hand, it increases the total transfusion volume and propagates the immune response [10]. Hemodilution leads to an underestimation of serum creatinine (SCr) concentration, which delays AKI diagnostics [11].

Blood contact with the inner surface of the extracorporeal circulation lines and shear stress lead to neutrophil activation and a subsequent burst of pro-inflammatory cascades—a phenomenon known as post-CPB systemic inflammatory response syndrome that is characterized by vasoplegia and renal dysfunction [12].

Compensatory anti-inflammatory syndrome (CARS), which develops later, may increase postoperative infectious complications risks, and antibacterial drugs may have nephrotoxic effects. Sepsis also alters renal perfusion parameters. Thus, both SIRS and CARS [13] are independent factors for CSA-AKI development in children.

Every CPB procedure is accompanied by hemolysis [14], which also contributes to the development of CSA-AKI [15]. Released free hemoglobin is oxidized, reacts with endogenous nitric oxide (II), and forms methemoglobin. The results of these interactions are endothelial dysfunction and vasoconstriction due to the nitric oxide (II) consumption. In addition, methemoglobin causes direct tubular damage, which further decreases renal function [16].

Finally, blood passing through an oxygenator may become hyperoxic due to relative antioxidation system deficiency and mitochondrial dysfunction. Forming reactive oxygen species have a direct cytotoxic effect. Activated neutrophils damage the endothelial glycocalyx, leading to decreased superoxide dismutase activity and the impaired deactivation of reactive oxygen species [17,18]. Reactive oxygen species excess causes myocardial stunning [19], the dysregulation of vascular tone, and cell destruction, and these are followed by additional cytokine production. In the Bae J. et al. study on $PaO_2$ levels above 150 mmHg within an hour, it was found to significantly increase the incidence of CSA-AKI [20].

Thus, many of these simultaneously existing or sequentially replacing factors have a damaging effect on the renal parenchyma and lead to renal dysfunction of some degree, which can have clinical significance and seriously deteriorate the postoperative period and outcomes in children with CHD.

## 5. Diagnostics of CSA-AKI in Children

Scoring systems based on SCr and urine output are the only approved tools for AKI diagnostics. Currently, the neonatal and pediatric modifications of KDIGO scores are recommended for use, whereas RIFLE and AKIN scores are considered irrelevant. But there are data suggesting that pediatric RIFLE is a more sensitive score for mild kidney injury degrees, especially in infants [21]. KDIGO score also has a potential for evaluating renal replacement therapy (RRT) requirements and mortality rates [22]. At the same time, SCr concentration increases significantly after only a 50% drop in renal function, and in newborns there is the circulation of maternal creatinine. At least two of these points make it difficult to assess SCr concentration dynamics over time. Urine output may not reflect

the subclinical cases of AKI that are not followed by oliguria but still have extra-renal clinical symptoms. These factors predetermine the beginning of investigations that are aimed at finding early and sensitive laboratory or instrumental methods for renal function evaluation, and they also allow for timely preventive interventions and treatment.

One such instrumental method for renal perfusion assessment in children is near infrared spectroscopy (NIRS) [23]. This technique allows for continuously estimating the oxygen delivery and consumption relationship in underlying renal parenchyma; thus, it reflects the renal perfusion state. The advantages of NIRS are found in its non-invasiveness and its ability to detect and display renal hypoperfusion in real time, thereby providing opportunities to improve kidney blood flow in the shortest possible time period and reducing AKI development risk. Ultrasound renal blood flow assessment is another tool for real-time renal perfusion evaluation. This method has prognostic significance regarding kidney injury development; however, it is operator dependent and technically more complex [24]. Measuring partial oxygen pressure in urine, as an indirect indicator of the oxygen delivery to kidney tissues, also allows for continuous assessments of kidney perfusion by installing a fiberoptic probe into the bladder through a urethral catheter. Urine oxygen pressure can be measured by laboratory methods using a gas analyzer, which is a more accessible, simpler, and relatively cheaper alternative [25].

It is not only a rise in SCr concentration that is associated with AKI, but there are other laboratory findings that are also correlated with kidney damage, which include renal tubular epithelial cells and granular casts, as well as mixed-cast detection by urine sediment microscopy (which allows for relatively easier and earlier kidney injury diagnostics). The findings of Goldani et al. [26] show a specificity of 94.3% with only 22.8% sensitivity. Some researchers showed almost the same result with 89.9% specificity and 29.6% sensitivity [27], while another study did not reveal a significant diagnostic improvement by sediment microscopy [28]. Therefore, the absence of casts or epithelial cells in urine sediment microscopy is more likely to lead to a false negative AKI diagnostic test result, while the presence of them indicates AKI with high probability. The acidic preoperative urine pH state (pH $\leq$ 5.5) is a common finding in severe AKI, and it is followed by an increased incidence of morbidity and mortality after some cardiac surgery in adult patients [29]. The probable reason for this is the increased methemoglobin formation and subsequent tubular obstruction by casts in an acidic urine pH state.

It is known that damaged kidneys temporarily lose their ability to reabsorb proteins, and albuminuria is a common laboratory finding in chronic kidney disease. During AKI in children, urinary albumin measurement could be a useful diagnostic tool. Urine albumin corrected by urine creatinine has been shown to have an even higher sensitivity and specificity with an AUC of 0.57–0.76 [30]. Urine albumin usage in AKI diagnostics has several limitations; specifically, there are reference range differences depending on weight, age, race, and gender. Most likely, albumin could be used in a row with some other parameters for more precise AKI diagnostics.

The most actively studied laboratory tests for renal dysfunction are kidney injury biomarkers.

Neutrophil gelatinase-associated lipocalin (NGAL) is the most studied molecule for kidney damage. It is a protein synthesized by neutrophils and distal renal tubule epithelia in response to inflammation and ischemia. Considering the simultaneous existence of various NGAL synthesis sources, its blood concentration assessment may not precisely reflect the degree of kidney damage since up to 90% of plasma NGAL is represented by isoforms of neutrophil origin (45 kDa and 145 kDa) [31]. Thus, NGAL blood concentration change assessments must be adjusted for neutrophil activation severity in each specific case, which can be challenging due to additional lactoferrin concentration assessment necessity [32]. Several studies examining AKI in pediatric patients have shown that urinary NGAL concentrations changes can predict renal dysfunction development before SCr concentrations and GFR changes [33]. The timing of NGAL concentration measurements is also a considerable question. It is known that its concentration increases significantly 2 h

after the affect (CPB initiation), and this reaches a peak after 6–12 h and then has minimal or no changes for at least 48 h [34].

Another potential biomarker is kidney injury molecule 1 (KIM-1): a transmembrane protein that usually is almost undetectable in kidney tissue but is highly expressed in animal models of kidney injury and in human AKI studies [35]. KIM-1 concentration increase also indicates AKI development earlier than creatinine, can predict the RRT need, and is associated with increased mortality in children with kidney injury [36].

Along with the abovementioned advantages of biomarkers over creatinine, there are significant disadvantages, such as dependence on the age and gender of a child, the incompletely studied characteristics of concentration–time curves and reference intervals, as well as the relatively high cost of kits, which seriously limits their routine clinical use. Additionally, NGAL and KIM-1 concentrations vary depending on antibacterial drug use [37], which further complicates test results given the mandatory perioperative antibiotic prophylaxis prescribed to cardiac surgery patients.

Liver-type fatty acid binding protein (L-FABP) can also be used as a kidney injury biomarker. This protein is expressed in the renal tubular epithelium, and, since L-FABP has antioxidant properties, its synthesis is highly increased in response to renal parenchyma ischemia. Recent research data [38,39] show that its concentration in urine, which is measured between 4 and 6 h after the cardiopulmonary bypass initiation, is better than creatinine for kidney injury diagnostics. Increased L-FABP concentration is also associated with increased mechanical ventilation and hospital length of stay [40].

Cystatin-C (cystatin-C, CysC) is a protein that is synthesized by all human body nucleated cells, and it is characterized by a constant synthesis rate. The important features of cystatin-C are gender and the muscle mass independence of its concentration. Cystatin-C concentration remains almost unchanged during inflammatory processes. These properties allow CysC use as a creatinine alternative. A study by Hazle et al. demonstrated that urinary cystatin-C concentration significantly increases 24 h after cardiopulmonary bypass initiation, and it could be a predictor of negative outcomes (i.e., RRT requirement, increased mechanical ventilation time, hospital length of stay, and death) in children under 6 months [41]. At the same time, studies of serum cystatin concentrations have shown multidirectional changes in its concentration 6 and 12 h after surgery, which complicates the result comprehension [42].

Interleukin-18 (IL-18) is a pro-inflammatory cytokine synthesized by monocytes, macrophages, and kidney tissue. Its synthesis increases significantly in response to ischemia-reperfusion injury and leads to kidney parenchyma infiltration by neutrophils [43]. The concentration of IL-18 increases significantly 6–12 h after surgery both in plasma and urine; furthermore, it could indicate AKI development, and it is also associated with increased mechanical ventilation, RRT requirement, and mortality [44].

Tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP7) complex induce cell cycle arrest in the G1 phase, and they are secreted during the early stages of cellular damage, thereby preventing apoptosis and providing time for DNA repair. According to the study by Meerch et al. [45], an increased urine concentration of [TIMP-2] $\times$ [IGWBP7] is a specific and sensitive marker, and it predicts AKI in children well.

The problem of the incomplete definition of the reference range boundaries of biomarker concentrations appears when trying to investigate AKI in children. While each conducted study used a control group in their statistical analyses, which usually consisted of children who were exposed to kidney damage risk factors, the control groups did not develop signs of renal dysfunction. The results of a study by Bennett et al. [46], which included healthy children without risk factors of kidney injury and was conducted to determine reference biomarker values, are shown in Table 1.

Some studies of biomarker predictive abilities revealed no association between the changes in their concentrations and AKI development. When comparing them with other studies, it was found that the time of sampling was an important factor. Table 2 shows the

biomarkers, optimal sampling time, and concentration cutoff point with proper sensitivity and specificity across studies.

**Table 1.** The upper limit of urine biomarker concentration in children of different ages and sex.

| Biomarker | Upper Limit | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Age | | | | | | | | | |
| | 3–5 y.o. | | 5–10 y.o. | | 10–15 y.o. | | 15–18 y.o. | | On Average | |
| | M | F | M | F | M | F | M | F | M | F |
| NGAL, ng/mL | 26.1 | 52.2 | 10.9 | 139.5 | 25.5 | 72.3 | 50 | 138.6 | 28.3 | 73.1 |
| IL-18, pg/mL | 78.3 | 100.5 | 41.7 | 79 | 58.5 | 111.1 | 71.2 | 273.1 | 56.1 | 104.5 |
| KIM-1, pg/mL | 983.7 | 1291.7 | 1276.6 | 1212.9 | 1156.6 | 1103.5 | 1877.3 | 1934.5 | 1298.4 | 1444.7 |
| L-FABP, ng/mL | 49.4 | 41.4 | 15.5 | 13.5 | 13.7 | 13.3 | 10.5 | 6.7 | 15.5 | 18.6 |

Abbreviations: NGAL—neutrophil gelatinase-associated lipocalin, IL-18—interleukin-18, KIM-1—kidney injury molecule-1, L-FABP—liver-type fatty acid binding protein, M—male, and F—female.

**Table 2.** The optimal sampling time and cutoff values of biomarker concentrations.

| Biomarker | Substrate | Time after Surgery | Source | Cutoff Values | |
|---|---|---|---|---|---|
| | | | | Before 28 Days of Life | After 28 Days of Life |
| NGAL, ng/mL | Serum | 2 h | Krawczeski et al. [34] | 100 | 50 |
| | Urine | 2 h | Krawczeski et al. [34] | 185 | |
| | | 2 h | Greenberg et al. [47] | 185 | 50 |
| | | 2 h | Bennett et al. [48] | 100 | |
| | | 3 h | Alcaraz et al. [49] | 75 | |
| | | 2 h | Cantinotti et al. [50] | 50 | |
| | | | Mishra et al. [51] | | |
| | | 4 h | Zheng et al. [52] | 54 | |
| | | ICU admission | Yoneyama et al. [40] | 40 | |
| | | 4 h | Yoneyama et al. [40] | 70 | |
| | Serum | 2 h | Fadel et al. [53] | 100 | |
| | | 2 h | Dent et al. [54] | 150 | |
| IL-18, pg/mL | Urine | 4 h | Zheng et al. [52] | 49 | |
| | | 6 h | Greenberg et al. [47] | 362 | |
| | | 12 h | Parikh et al. [55] | 234 | |
| KIM-1, pg/mL | Urine | 6 h | Greenberg et al. [47] | 0.99 | |
| L-FABP, ng/mL | Urine | 6 h | Cavalcante et al. [43] | 69.1 | |
| | | ICU admission | Yoneyama et al. [40] | 90 | |
| | | 4 h | Yoneyama et al. [40] | 155 | |
| TIMP2x IGFBP7 | Urine | 4 h | Cavalcante et al. [43] | 0.47 | |

Abbreviations: NGAL—neutrophil gelatinase-associated lipocalin, IL-18—interleukin-18, KIM-1—kidney injury molecule-1, L-FABP—liver-type fatty acid binding protein, and TIMP-2x IGFBP7—tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein-7 complex.

There are also studies that investigated the biomarker levels and outcomes in children after cardiac surgery, such as in AKI cases that required dialysis and or resulted in death.

For instance, the meta-analysis of Haase et al. [56] revealed a value of 278 ng/mL for NGAL; another study on hemolytic uremic syndrome in children suggested a tighter boundary of 200 ng/mL [57].

Another important outcome to be predicted in a timely fashion is AKI progression. While stage 1 AKI has minimal impact on the postoperative health of children and is more likely to be self-limiting, it is the enhanced stages that lead to a prolonged ICU length of stay and dialysis requirement, and they are characterized by increased mortality. In a multicenter prospective cohort study by Greenberg et al. [44], plasma Il-8 and urine L-FABP were found to have the highest predictive ability for AKI progression, and NGAL demonstrated the worst ability in discriminating AKI progression, which corresponds to the prior findings of Zapitelli's study [58].

## 6. CSA-AKI Treatment in Children

To date, the acute liquid and electrolyte disturbances in children arising after cardiac surgery could be treated either by conservative methods (intravenous fluid limitation, diuretic therapy, etc.), by passive peritoneal drainage, or via dialysis techniques. The conservative therapy of AKI with different acting diuretics could remain ineffective for up to 72 h postoperatively due to drug resistance development [59]. This phenomenon could effectively be overcome by peritoneal dialysis [60]. Obviously, CRRT could also be applied.

Peritoneal dialysis advantages include the relative simplicity and inexpensiveness of the technique and the fact that no anticoagulants are needed; this, therefore, also means that there will be a reduced or lack of a hemorrhagic complication number and slight hemodynamic changes during procedure, and the possibility for it to be applied to premature infants with low body weight. The disadvantages, in turn, include a low clearance and a slower ultrafiltration rate, as well as a risk of dialysis peritonitis development and other infectious complications. Due to the few disadvantages, some authors [61] have suggested preventively installing peritoneal dialysis catheters and commencing the procedure in high-risk children without oliguria appearance. This allows one to achieve a negative liquid balance more quickly.

If possible, both veno-venous hemodialysis and veno-venous hemodiafiltration could be applied in children. However, a review by Liu et al. [62] showed no significant differences between peritoneal dialysis and CRRT in mortality, infectious complication, and quality of life values. The major advantage of CRRT is high procedure efficiency, while its disadvantages are in significant hemodynamic changes, additional red blood cell transfusion requirement when used in children below 8–10 kg, proper intravenous access challenges in children, and the need for systemic anticoagulant drugs. Table 3 shows the recommended values for the main parameters of CRRT in children.

**Table 3.** Recommended CRRT settings in children.

| Parameter | Flow | Source |
|---|---|---|
| Blood pump | 3–5 mL/kg/min | Cho et al. [9], John et al. [63] |
| Dialysis solution | 1.5–2 times blood flow | Sanderson et al. [64] |
| | 500 mL/kg/h | Cho et al. [9] |
| | 2000 mL/h/1.73 $m^2$ | Park et al. [65], John et al. [63] |
| | 2000–8000 mL/h/1.73 $m^2$ | Sanderson et al. [64] |
| | 20–60 mL/kg/h | Park et al. [65] |
| Substitute solution | 2000 mL/h/1.73 $m^2$ | Park et al. [65], John et al. [63] |
| | 20–60 mL/kg/h | Park et al. [65] |
| Ultrafiltration | No more than 0.2 mL/kg/min | Cho et al. [9] |
| | 0.5–2 mL/kg/h | John et al. [64] |

## 7. Prevention of CSA-AKI in Children

A recent study in adult patients after cardiac surgery showed that NO insufflation into the CBP circuit has an ability to prevent AKI [66], but current global data are inconsistent and require further investigation. Otherwise, the measures to prevent kidney damage during cardiac surgery in children are non-specific and boil down to reduced intraoperative damaging factor exposure. The primary direction of AKI prevention is the search of diagnostic and therapeutic algorithms aimed at timely detection and treatment of AKI in children, especially in risk groups. Thorough volemia status monitoring, ensuring adequate perfusion pressure, and limiting nephrotoxic drug use, including contrast media, are some of the basic components of the postoperative management of children who undergo cardiac surgery.

## 8. Conclusions

CSA-AKI is one of the most important problems in pediatric cardiac intensive care due to its significant impact on both the early postoperative period and long-term outcomes. Despite understanding some of the general mechanisms of kidney damage during CPB, there are still some pathogenesis issues that remain incompletely understood, which could potentially serve as both a new biomarker source and as a treatment target. The prevention and treatment of CSA-AKI are nonspecific and are carried out as part of the general approaches to treat acute kidney injury.

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