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Risk factors for recurrent acute kidney injury in children who undergo multiple cardiac surgeries: A retrospective analysis

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Abstract

Objective: Determine the risk factors for repeated episodes of acute kidney injury (AKI) in children who undergo multiple cardiac surgical procedures

Design: Single center retrospective chart review

Setting: Cardiac intensive care unit at a quaternary pediatric care center

Patients: Birth to 18 years who underwent at least 2 cardiac surgical procedures with cardiopulmonary bypass.

Interventions: None

Measurements and Main Results: 180 patients underwent 2 cardiac surgical procedures and 89 underwent 3. AKI was defined by the Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine criteria. AKI incidence was 26% (n = 46) after surgery 1, 20% (n = 36) after surgery 2, and 24% (n = 21) after surgery 3, with most AKI occurring on post-operative days 1 and 2. The proportion of patients with severe AKI increased from surgery 1 to surgery 3. Patients with AKI had a significantly longer duration of ventilation and length of stay after each surgery. The odds of AKI after surgery 3 was 2.40 times greater if AKI was present after surgery 1 or 2 (95% CI: 1.26 to 4.56, p = 0.008) after adjusting for confounders. The time between surgeries was not significantly associated with AKI (p = 0.85).

Conclusions: In a heterogeneous population of pediatric patients with congenital heart disease undergoing multiple cardiopulmonary bypass surgeries, odds of AKI after a third surgery was

increased by the presence of AKI after prior procedures. Time between surgery did not play a role in increasing odds of AKI. Further studies in a larger multi-center investigation are necessary to confirm these findings.

Keywords

acute kidney injury; cardiac surgery; cardiopulmonary bypass; children; recurrent kidney injury

Introduction

Acute Kidney Injury (AKI) is a common complication of cardiac surgery in children with critical congenital or acquired heart disease. AKI rates from single center retrospective studies range from 11–68% (1–5). Several well described risk factors for AKI include younger age at surgery, single ventricle physiology, surgical complexity, and cardiopulmonary bypass (CPB) duration (1, 2, 4, 6). CPB-associated AKI, irrespective of the cause, is associated with increased morbidity, including post-operative infection (7, 8), increased duration of mechanical ventilation, hospital length of stay, and increased mortality (1, 3, 4, 6, 9–13). These all lead to increased hospital costs (14).

With improved outcomes after congenital heart surgery, children are surviving to adulthood and often need additional cardiac surgical procedures. In a recent study, 14% of patients developed AKI after an initial cardiac surgery, but 52% developed AKI after reoperation (3). Interestingly, nearly 75% of patients with AKI after the first cardiac operation in their cohort developed AKI after reoperation (3). In contrast, Watkins et al found no association between reoperation and repeated AKI episodes (12). In a study of patients undergoing a 3-staged palliative repair for single ventricle heart disease, severe AKI (stage 2 or 3) after the first surgery was independently associated with AKI after the second surgery (15). Importantly, none of these studies assessed for the impact of mild AKI after one or more surgical procedures.

The purpose of this study was to determine the risk factors for AKI among a heterogeneous cohort of children undergoing multiple cardiac surgical procedures. We hypothesized the following: 1) AKI after the initial cardiac surgery will be associated with AKI after a subsequent cardiac surgery, 2) specific intra- and post-operative characteristics will be associated with single and multiple episodes of AKI, and 3) less time between surgeries will increase the risk for recurrent AKI.

Materials and Methods:

We performed a single-center retrospective cohort study of pediatric patients (birth-18 years) who underwent more than one cardiac surgery with CPB at Children's Hospital Colorado from January 1, 2007 – August 31, 2017. We excluded patients with known significant renal abnormalities that were documented on a renal ultrasound. The study was approved by the Institutional Review Board with waiver of informed consent.

AKI was defined as the highest serum creatinine during the first 7 post-operative days using the KDIGO serum creatinine criteria. Baseline serum creatinine was defined as the serum

creatinine most proximate to surgery, which was almost always at a pre-operative visit or on the morning of surgery. This was not always the lowest creatinine available in the electronic health record.

Demographic, clinical, and surgical data were abstracted from the electronic health record. Surgical complexity was determined using the Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery (STAT) score (16), and categorized into 2 groups, < 3 and ≥ 3. Postoperative variables specific to intensive care unit management were collected immediately after surgery and at 7am on post-operative days (POD) 1–3. The vasoactive inotrope score (VIS) was calculated on arrival to the intensive care unit and on POD 1–3 as previously described (17).

Statistical Analysis

The primary outcome was AKI after each cardiac surgery. Data are summarized as frequencies (%) for categorical variables and means ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables. Categorical variables were compared using Chi-Square or Fisher's Exact tests as appropriate. Continuous variables were compared using unpaired t-tests or Wilcoxon rank sum tests as appropriate.

In order to identify risk factors for recurrent AKI, a stepwise multivariable model selection process identified associations with AKI incidence at each surgery. An *a priori* list of potential covariates were chosen based on risk factors identified in prior studies and included: age at surgery, weight for age z-score, post-operative platelet count, VIS on admission, VIS on POD 1, CPB duration, cross clamp duration, use of circulatory arrest, STAT score, single ventricle status, and highest post-operative lactate. Univariate models identified potential model covariates by significance at an alpha 0.10 level. For the outcome of AKI at each surgery, associations for all potential covariates were estimated in a multivariable model. Development of previous AKI after either surgery was included as a covariate in models with AKI as the outcome at surgery 2 and 3. All post hoc models were adjusted for pre-operative serum creatinine and PD drain placement.

Due to the correlated nature of repeated observations on participants, an additional longitudinal data analysis using a generalized linear model was conducted, with response following a binomial distribution and loglink function. The model included time since previous surgery in days and all covariates previously mentioned. Associations were estimated in SAS statistical software (PROC GENMOD), including repeated subject statement with an independent working correlation matrix. Sensitivity of the results to the definition of AKI was evaluated by modifying the outcome of AKI to mild AKI and severe AKI and repeating all analyses. Statistical significance level for identifying a potential risk factor was set at alpha < 0.05 level. All data analyses were performed using SAS software 9.4, Cary, NC, USA, and JMP. Copyright © 2002–2012 SAS Institute Inc.

Results:

Demographics.

A total of 180 patients underwent at least 2 cardiac surgical procedures with the use of CPB, with 89 patients going on to require a third surgery. A schematic of patient procedures is summarized in Figure 1. The median patient age was 7 days (IQR: 4–97 days) for the first surgical procedure, 168 days (IQR: 134–520 days) for the second, and 990 days (IQR: 773–1242 days) for the third. There was a slight preponderance of males undergoing multiple cardiac surgical procedures (61% for surgeries 1 and 2 and 55% for surgery 3). More than half of the patients (56%) had single ventricle heart disease and were palliated with a 3-staged approach.

The incidence of AKI after the first surgery was 26% (n = 46), 20% (n = 36) after the second and 24% (n = 21) after the third. At surgery 1, 78% (n=36) patients experienced mild AKI (KDIGO stage 1) and 22% (n=10) severe AKI (KDIGO stage 2 or 3). At surgery 2, 64% (n=23) patients experienced mild AKI and 36% (n=13) severe AKI. At surgery 3, 71% (n=15) patients experienced mild AKI and 29% (n=6) severe AKI. The percentage of patients with severe AKI (stage 3) increased from surgery 1 to surgery 3. A summary of the percentage of patients with each stage of AKI is summarized in Figure 2. A summary of the number of patients with AKI on each post-operative day is summarized in Figure 3. A summary of the demographics, operative, post-operative characteristics and outcomes after each surgery are summarized in supplemental table 1.

Surgery 1.

CPB time and cross clamp duration were not significantly different in patients with and without AKI; however, a greater proportion of patients with AKI underwent circulatory arrest compared to those without AKI ($p = 0.02$). VIS on POD 1–3 and the highest post-operative lactate were significantly higher among patients with AKI compared to those without. Patients with AKI also more frequently required invasive mechanical ventilation on or after POD 1 ($p=0.04$). They also had a lower nadir in post-operative platelet count ($p = 0.003$). Duration of mechanical ventilation, intensive care unit (ICU) length of stay, and hospital length of stay were all significantly longer among patients with AKI compared to those without AKI ($p < 0.001$). A summary of the demographic, operative, and post-operative characteristics after surgery 1 are summarized in Supplemental Table 1. The univariate associations after surgery 1 are summarized in supplemental table 2. In the multivariable logistic regression, lower pre-operative serum creatinine (OR 0.07, 95% CI 0.01–0.99, $p=0.049$), post-operative lactate (OR: 1.14, 95% CI 1.02 – 1.28, $p = 0.02$), and VIS on post-operative day 1 (OR: 1.12, 95% CI 1.01 – 1.21, $p=0.007$) remained independently associated with AKI after adjusting for covariates (Table 1).

Surgery 2.

Patients with AKI after surgery 2 had both longer CPB duration (161 minutes vs 131 minutes, $p=0.01$) and cross clamp duration (69 minutes vs 45 minutes, $p=0.036$). VIS on POD 1–3, post-operative lactate, and the need for invasive mechanical ventilation on or after POD 1 were significantly higher among patients with AKI. Duration of mechanical

ventilation, ICU length of stay, and hospital length of stay were all significantly longer among patients with AKI ($p=0.001$, $p < 0.001$ and $p < 0.001$, respectively). A greater proportion of patients with AKI after surgery 1 had AKI after surgery 2 (33% vs 15%; $p=0.01$). A summary of the demographic, operative, and post-operative characteristics after surgery 2 are summarized in Supplemental Table 1. The univariate associations after surgery 2 are summarized in supplemental table 2. In the multivariable logistic regression, the odds of having AKI after surgery 2 were 2.89 times greater if AKI was incurred after surgery 1, after adjusting for covariates (95% CI: 1.15 – 7.21; $p = 0.02$) (Table 1).

Surgery 3.

Similar to surgeries 1 and 2, VIS on POD 1–3 and post-operative lactate were significantly higher among patients with AKI. Duration of mechanical ventilation, ICU length of stay, and hospital length of stay were all significantly longer among patients with AKI ($p=0.02$, $p < 0.001$, $p < 0.001$, respectively). A summary of the demographic, operative, and post-operative characteristics after surgery 3 are summarized in Supplemental Table 1. The univariate associations after surgery 3 are summarized in supplemental table 2. In the multivariable logistic regression, only post-operative lactate was independently associated with AKI (OR: 1.73, 95% CI 1.02 – 2.92, $p = 0.04$) after adjusting for covariates (Table 1).

Of the 46 patients with AKI at the first surgery, 7 (15.2%) went on to experience AKI at surgery 2 alone. Three (6.5%) went on to experience AKI at both surgery 2 and 3. The relative risk of AKI at surgery 2 alone after having had AKI at surgery 1 is 1.9 (95% CI: 0.7 to 4.5). For the 134 patients who did not experience AKI at the first surgery, 11 (8.2%) went on to experience AKI at surgery 2 alone. One (0.7%) went on to experience AKI at both surgery 2 and 3. The relative risk of AKI at surgery 2 and 3 after having had AKI at surgery 1 is 8.7 (95% CI: 1.8 to 41.8).

In the longitudinal model, any prior AKI was independently associated with the development of AKI after a subsequent surgery (OR 2.40, 95% CI: 1.26 – 4.56, $p = 0.008$). Post-operative lactate (OR 1.10, 95% CI: 1.01–1.20, $p=0.03$) and VIS on post-operative day 1 (OR 1.07, 95% CI: 1.02–1.13, $p=0.009$) also remained independently associated with AKI (Table 2). Time between surgeries was not associated with AKI ($p=0.85$). In the longitudinal linear regression analysis for factors associated with mild (stage 1) AKI, only VIS on post-operative day 1 remained independently associated with development of AKI after a subsequent surgery (OR 1.1, 95% CI 1.01–1.19, $p = 0.03$) (Supplemental Table 3).

Discussion:

To our knowledge, this is the first study that includes a heterogeneous cohort of children with and without single ventricle heart disease undergoing a variety of cardiac procedures with the use of CPB, evaluating risk factors for recurrent AKI. In this study, AKI was common after each surgery with rates ranging from 20–26%. Similar to other studies, AKI was associated with worse outcomes, including longer duration of mechanical ventilation, and longer ICU and hospital length of stay. We demonstrated that inclusion of all cases of AKI (approximately 70% with KDIGO stage 1) after surgery 1 or 2 was independently

associated with AKI after surgery 3. Interestingly, the time between each surgery was not associated with increased AKI risk for a subsequent surgery.

Risk for recurrent AKI after subsequent CPB surgeries has been reported in 3 prior pediatric studies (3, 12, 15). In each of these studies, patients with mild AKI were excluded. In a homogenous group of patients who underwent a 3-staged palliation procedure for single ventricle heart disease, severe AKI (KDIGO stage 2 or 3) at surgery 1 was independently associated with severe AKI after surgery 2. In this cohort, rates of mild AKI ranged from 58–75% and severe AKI ranged from 10–21% after each surgery. In our study, the majority of patients had mild AKI that occurred most frequently on post-operative days 1 or 2. Our data suggest that any AKI was associated with worse outcomes, including increased odds of recurrent AKI after reoperation. When the analysis was conducted on multiple repeated outcomes with the categories of none, mild or severe AKI, statistical significance of the association with previous AKI was lost, although the magnitude and direction of our associations remained, suggesting that a larger cohort of patients with mild AKI need be studied to determine association between mild AKI and worse outcomes. In addition, the relative risk of AKI at surgery 2 alone after having had AKI at surgery 1 and the relative risk of AKI at surgery 2 or 3 after having had AKI at surgery 1 were both greater than 1. These data suggest that the risk of AKI on surgery 2 or 3 is greater in the group who first experienced AKI at surgery 1.

Little is known about the consequences of recurrent AKI in children, as there are few populations outside of children with congenital heart disease who incur multiple discrete insults. One of the first studies to assess recurrent AKI was in a rat model with a heme-oxidase mechanism of injury. AKI after a first episode of injury was evident by a marked and prompt fall in glomerular filtration rate (GFR) along with histopathologic evidence of necrosis. However, subsequent episodes of injury (incurred every 7–9 days) over the next 3 months showed a very blunted fall in GFR, with less necrosis and apoptosis of renal tubular epithelial cells, suggesting renal resistance to injury. It wasn't until greater than 3 months after initial injury that GFR steadily fell and histopathology showed tubulointerstitial injury (18). In a more recent diphtheria toxin-induced mouse model of AKI, histopathology after a single episode of sublethal kidney injury in mice returned to normal if no further injury was incurred, whereas pathologic specimens in mice who had 3 weekly injuries demonstrated interstitial fibrosis and tubular atrophy, with some showing focal segmental glomerulosclerosis and advanced tubulointerstitial scarring. Those animals with advanced damage also exhibited a rise in serum creatinine and albuminuria (19). Both the rat and mouse models demonstrated a time-dependent response to recurrent injury. It is possible that children who undergo multiple surgeries activate profibrotic pathways that lead to maladaptive renal repair that increases risk from repeat AKI episodes. Although we did not find time between surgeries to associate with development of AKI, it is possible that patients were still in a state of resistance to injury, which could be protective in the short-term but may be more detrimental and portend an increased risk for future AKI and chronic kidney disease (CKD) in the long-term.

It has been shown that a single episode of AKI is associated with a higher risk for later CKD in critically ill children (20, 21), and even an increased risk of end stage renal disease

(ESRD) in adulthood (22). In a population-based historical cohort of children with congenital anomalies of the kidney or urinary tract, pyelonephritis, or glomerular disease who had normalized their renal function by adolescence, there was a 4 times greater risk of dialysis-dependent ESRD as adults, and ESRD occurred on average 7 years earlier than the general population (41 ± 10 years in those with childhood kidney injury versus 48 ± 10 years in healthy controls). Likewise, a cohort of adults with acyanotic congenital heart disease had a prevalence of renal dysfunction that was 18 times higher than the general population (23). In this study, CKD was also not seen until later ages: 39 years for those with GFR 60–90 mL/min/m² and 50 years for those with GFR < 60 mL/min/m². Both of these cohorts show that an average of 30 years of time elapses between the original renal insult and subsequent ESRD. Thus, although the results of the TRIBE-AKI (24) and FRAIL-AKI (21) studies may have called into question the role of CPB-AKI on the progression to CKD, it is likely that insufficient follow-up time and cohort size limited detection of this association. The FRAIL-AKI cohort did however find changes in novel kidney injury biomarkers to suggest either ongoing renal injury past the initial renal insult or subclinical CKD when using standard currently available markers (21).

This study identified several known risk factors associated with AKI, including higher VIS scores, higher post-operative lactate, and lower post-operative platelets. Interestingly, an association between duration of CPB or cross clamp and AKI was found only after surgery 2. Many earlier studies reported that longer CPB duration was a major risk factor for AKI, conferring up to 7 times greater odds if CPB duration was greater than 180 minutes (4, 11). Contrarily, a lack of association between CPB duration and AKI has been found by several other groups (15, 25, 26). The association seen only in 1 of the 3 surgeries could be because of cross-clamp time, as CPB duration was only significant in the setting of longer cross clamp times. It is also possible it may be related to center specific surgical practices as well as the possibility that CPB may in fact be a surrogate for an inflammatory response and activation of reactive oxygen species that then lead to differences in other illness severity markers among patients with AKI.

We did not find an association between AKI and younger age at surgery or surrogates for failure to thrive, such as weight-for-age z-score, which had previously shown association with increased AKI risk. It is possible this is because these known risks are optimized and incorporated into pre-operative decisions regarding approach and timing of these high-risk surgeries. Additionally, accounting for these variables in our multivariable and longitudinal regression analyses did not change our results. We did find a higher serum creatinine before surgery 1 to be protective against AKI. Although this could be because a patient would need a higher numerical rise to achieve the 1.5x increase in serum creatinine amount, this could also be because these higher numbers are reflective of maternal creatinine, and the pre-operative value was before the neonate's serum creatinine nadir. This is supported by the fact that the average age at surgery 1 was 7 days, with the lowest quartile being 4 days old at surgery. If this were the case, we could be underestimating the decline in GFR incurred during surgery, and thus underestimating the magnitude and frequency of AKI after surgery 1. This underestimation of diagnosis of AKI at surgery 1 may impact the associations found at surgery 2 and 3 in our longitudinal models. Future studies that include alternate methods

for AKI diagnosis, or refined AKI definitions as was recently reported for AKI in neonates of varying gestational ages should be used to enhance diagnostic precision (27).

The association between AKI and higher VIS in the early post-operative period is likely a marker of illness severity (26, 28). Garcia et al evaluated a cohort of adolescents and found that VIS was a predictor of worse outcomes (composite of death, cardiopulmonary resuscitation, mechanical circulatory support, arrhythmias, infection, acute neurologic injury and stage 3 AKI), but they did not specifically evaluate the association between AKI and higher VIS (29). Kumar et al sought to associate VIS with a broad range of short-term postoperative complications including AKI, sepsis, hematologic complications and hepatic dysfunction. In this study, VIS was not an independent predictor of hospital length of stay, AKI or mortality, suggesting that VIS is a marker of poor cardiac physiology in the immediate post-operative period that may lead to prolonged therapy and more frequent complications.

Although we are able to conclude that prior episodes of AKI increase the risk of future AKI after CPB, we can only speculate as to why. There are many reasons for these patients to incur injury at each surgery—ischemia reperfusion injury, concurrent exposure to nephrotoxic medications, post-operative volume overload worsened by poor cardiac function and oxidant exposure from red blood cell lysis during CPB. There were a few patients who incurred AKI at surgery 1, not at surgery 2, and again at surgery 3. It is possible that these patients may have experienced subclinical AKI at surgery 2 that worsened renal reserve and increased the odds of AKI at surgery 3. There is also the aforementioned hypothesis of maladaptive hyperfiltration that occurs after recurrent AKI, which could manifest as higher GFR after surgery 2 but then lower GFR after subsequent episodes of injury. Future studies addressing long-term follow-up, as well as use of biomarkers are necessary to better define the impact of recurrent AKI on lasting morbidity, specifically progression to CKD, in this vulnerable patient population.

This study has several strengths and limitations. The major strength of this study is the heterogeneity of the population with regards to the patients' anatomy and the procedures being performed. Our follow-up allowed for the assessment of a larger cohort who underwent at least 2 surgeries. As with any single center retrospective study, there is limited generalizability, decreased ability to detect power given smaller sample size, and only postulation of association rather than causality. Our main study limitation comes in the imprecise nature of serum creatinine as a marker of renal dysfunction. This is particularly important in the neonatal patients, in which identification of AKI can be particularly challenging as described above. In addition, patients may also have significant fluid overload and without correcting creatinine for fluid balance, AKI may have also been missed (25, 26). In an attempt to correct fluid overload, some patients had prophylactic PD catheters placed in the operating room, almost exclusively after surgery 1, and mainly for drainage purposes. Interesting, in our data, a greater proportion of patients with PD drains developed AKI (37% vs 19%, $p=0.03$). This may in fact not be due to the PD drain but rather the dilutional effect of creatinine measure is mitigated by fluid removal from the peritoneal drain. Other factors such as low muscle mass and poor nutrition may also impair creatinine rise in older patients thereby masking AKI. We did not use urine output criteria to define AKI in this cohort as

diuretics are typically initiated within the first few hours of surgery. Another large limitation is the low incidence of moderate-severe AKI, and thus the inability to assess the impact of higher grade AKI on outcomes including risk for recurrent severe AKI.

Conclusion:

AKI is common in children undergoing cardiac surgery, and it is associated with worse short-term outcomes, including longer duration of mechanical ventilation and hospital length of stay. Higher VIS and post-operative lactate, both markers of increased illness severity, are associated with AKI after a first surgery. AKI incurred at an initial surgery, is independently associated with AKI after subsequent surgeries. We did not find time between surgeries to be a risk factor for AKI. Large, multicenter studies are necessary to confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Summary of patients with and without AKI after each cardiac surgery.
n = number, AKI = acute kidney injury.

Figure 2. Acute Kidney Injury Stage by Surgery.

Percentage of patients who developed each stage acute kidney injury after each surgery defined by the Kidney Disease: Improving Global Outcomes serum creatinine criteria. AKI = acute kidney injury.

Figure 3. Day of acute kidney injury occurrence.

Number of patients who developed acute kidney injury after each surgery on each postoperative day. AKI = acute kidney injury.

Table 1.

Multivariable regression analysis for factors associated with acute kidney injury.

Variable	Odds Ratio (95% Confidence Interval)	P Value
Surgery 1 *		
VIS POD 1	1.12 (1.03, 1.21)	0.007
Post-operative lactate	1.14 (1.02, 1.28)	0.022
Pre-operative Serum Creatinine	0.07 (0.01, 0.99)	0.049
Surgery 2 **		
AKI after Surgery 1	2.89 (1.15, 7.21)	0.023
Surgery 3 ***		
Lactate	1.73 (1.02, 2.92)	0.042

* Indicates model adjusted for age at surgery, weight for age z-score, indication of peritoneal drain, post-operative platelet count, VIS on admission, CPB duration, cross clamp duration, circulatory arrest, STAT score, single ventricle, post-operative lactate and VIS on POD 1.

** Model adjusted all variables in the first model with the addition of AKI after surgery 1.

*** Model adjusted for all variables in the second model except pre-surgery creatinine, PD drain and ECMO status, with the addition of AKI after surgery 1 or 2. VIS = vasoactive inotrope score, POD = post-operative day.

Table 2:

Longitudinal linear regression analysis for factors associated with acute kidney injury.

Variable	Odds Ratio (95% Confidence Interval)	P value
Previous AKI	2.40 (1.26, 4.56)	0.008
VIS POD 1	1.07 (1.02, 1.13)	0.009
Post-operative lactate	1.10 (1.01, 1.20)	0.028

Longitudinal model adjusted for time since previous surgery (days), weight for age z-score, any indication of any previous AKI at the time of surgery, post-operative platelet count, VIS on admission, CPB duration, STAT score, single ventricle, post-operative lactate, VIS on POD 1 and indication of PD drain. VIS = vasoactive inotrope score, POD = post-operative day.