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Editorial

Progress Towards Understanding Cardiac Surgery Associated Kidney Injury in Children

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Cardiac surgery–associated acute kidney injury (CS-AKI) is a common complication after surgery for congenital heart disease (CHD) in children with a reported incidence of up to 42%.[1] The scope of the problem presented by CS-AKI includes not only the high prevalence but also the impact that it has on both short- and long-term morbidity in paediatric patients after surgery for CHD. Not only is CS-AKI associated with increased length of intensive care unit and hospital stay, prolonged ventilation, and mortality, but the risk of long-term morbidity due to chronic kidney disease (CKD) has been described to be up to 28% after 5 years of follow-up according to long-term follow-up of the Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) cohort.[2] Despite the known prevalence and clinical significance of acute and CKD in this population, the perioperative factors that can differentiate between patients who will have a rapid reversal of CS-AKI vs a patient who will have a clinical course with persistent renal dysfunction progressing to CKD remain elusive. The paper by Gritti et al.[3] entitled "Factors associated with acute kidney injury after cardiopulmonary bypass in children," in this issue of *CJCPC*, re-emphasizes the problem of CS-AKI in paediatrics and takes positive steps towards a better understanding of the mechanism of this problem and explores novel territory to improve our means of identifying paediatric patients with CHD at risk of significant renal dysfunction.

Investigations on this matter have led to the identification of perioperative and patient-related factors associated with CS-AKI; however, there has not been any success in identifying any key modifiable procedure or patient-related risk factors that can serve to prevent CS-AKI or identify patients at risk of developing a persistent AKI or CKD. The duration of cardiopulmonary bypass (CPB), cross-clamp time, surgical complexity, patient age, preoperative ventilation, and intraoperative hypotension are some of the risk factors for CS-AKI that have been identified in previous literature.[4] Investigations on the influence of preoperative exposure to diuretics have shown to increase the risk of CS-AKI in adults but not in an infant population.[5-7] Exposure to nephrotoxic agents such as nonsteroidal anti-inflammatory drugs has also shown an association with CS-AKI in some studies.[4] Intravenous contrast agents, however, have been investigated specifically with data suggesting that preoperative catheterization requiring contrast does not influence the baseline incidence of CS-AKI after CPB.[8]

With the hypothesis that the etiology of CS-AKI is related to the inflammatory response and oxidative stress injury resulting from CPB, more specific markers of renal tubular injury and inflammation have been investigated with encouraging results. An elevation of cytokines interleukin (IL)-6, IL-8, and IL-10 preoperatively has been shown to be associated with CS-AKI in the early postoperative period.[9] Other plasma markers of note are endothelial microparticles that have been documented to increase hours to days after CPB.[10] Specific renal tubule markers of kidney function such as liver-type fatty acid binding protein have shown the ability to discriminate between patients susceptible to progress to develop AKI.[11] These emerging candidates to provide more sensitivity to identify significant CS-AKI with a likelihood of progressing to a persistent AKI or CKD are encouraging and provide a new foundation for further investigation.

The paper by Gritti et al.[3] has taken a step in the right direction to better understand the potential utility of these novel markers of renal injury by providing further investigation of previously suspected risk factors for CS-AKI. Multivariable analysis reaffirmed the known association between CS-AKI and duration of CPB.[3] Univariate analysis also provided additional potential risk factors for CS-AKI including preoperative use of diuretics, steroids, and prostaglandin; previous cardiac catheterization procedures; and cyanotic CHD. They also provide a thorough investigation into the association of a series of vascular endothelial and inflammatory markers with CS-AKI in a large paediatric cohort of children after CPB. Analysis of these markers at multiple time points both pre- and postoperatively did not demonstrate any association with postoperative CS-AKI. Even when the severity of CS-AKI was taken into consideration, a correlation was not identified. The neutral result from this study remains important as it may serve as a stepping stone for further

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investigations into additional biomarkers or longer-term investigations on the biomarkers in question in a prospective manner to evaluate any association with persistent AKI or CKD in paediatric cohorts.

Because of the high incidence of CS-AKI, it is not feasible for all patients to enter a long-term renal surveillance protocol. A more targeted pathway based on sensitive markers of renal dysfunction or well-established risk factors is a priority in the future management of paediatric patients after congenital heart surgery. The TRIBE-AKI study illustrated the importance of improving our approach to be more targeted as it demonstrated that even if all patients with CS-AKI were monitored long-term, a large proportion of patients who develop CKD would be missed as there was no difference in the incidence of CKD between patients diagnosed with early postoperative CS-AKI vs those who were not.[2] This investigation was based on classifying CS-AKI using conventional criteria. This illustrates one important reason why exploring new biomarkers of renal function and renal injury has been a subject of several recent publications along with the study featured in this issue that focuses specifically on a paediatric population. A novel marker more specific to the mechanism of renal insult associated with CPB may circumvent the apparent limitations of conventional definitions of AKI and serve to reliably recognize patients at risk of clinically significant renal dysfunction. This was the intention of the authors of the paper despite not identifying any significant association with the markers of inflammation or vascular injury that were studied. As suggested by the authors, shifting to evaluate for evidence of renal ischemia as opposed to inflammation may be of higher yield by being more specific to the haemodynamic insult from CPB.

Further to seeking novel markers of renal injury, an additional consideration for future investigations may be to reconsider the time frame over which patients are monitored to evaluate the incidence of both AKI and AKD. AKD is a definition of renal dysfunction that bridges the gap between AKI and CKD based on the presence of renal dysfunction that is persistent between 7 days and 3 months after insult.[12] Guidelines for monitoring patients with AKD have been established as it has been identified that all patients who do not have a rapid reversal of AKI within 48 hours are at an increased risk of CKD.[12] Even patients who no longer satisfy the Kidney Disease: Improving Global Outcomes (KDIGO) definition of AKI but maintain a creatinine above their baseline satisfy the definition of AKD and are considered at risk. Most investigations of CS-AKI have focused on either the very early postoperative period or long-term follow-up to assess for CKD. More scrutiny of renal function using traditional definitions along with novel biomarkers beyond the first 48 hours and over the first 3 months postoperatively may serve to identify those at highest risk of CKD and provide a more manageable subset of patients who can be monitored long-term from a renal perspective.

Although we are without an evidence-based approach for surveillance and management of CS-AKI in paediatric patients with CHD, there is compelling evidence based on its prevalence and the associated risk of CKD that it needs to be an important consideration during routine follow-up after cardiac surgery. This is especially true for those with known preoperative or operative risk factors. As many cases of CS-AKI are subclinical, we must be diligent to diagnose all stages of CS-AKI by recognizing a significant change in serum creatinine values or urine output during the early postoperative period. The general recommendations from the KDIGO guidelines are to re-evaluate all patients with an AKI within 3 months to ensure complete resolution and recognize those in need of consultation by a nephrologist.[12] Ongoing investigations such as the one by Gritti et al. in this issue raise optimism that a more sensitive means to recognize patients at highest risk of persistent AKI and CKD will eventually be a reality in the future. Until then we must exercise clinical vigilance and approach patients with a broad scope to recognize the potential for multiorgan dysfunction that is known to be associated with the interventions required to manage patients with CHD.

Ethics Statement

This editorial has adhered to the relevant ethical guidelines.

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References

1. Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. *Nat Rev Nephrol*. 2017;13:697–711.

2. Menez S, Moledina DG, Garg AX, et al. Results from the TRIBE-AKI study found associations between post-operative blood biomarkers and risk of chronic kidney disease after cardiac surgery. *Kidney Int*. 2021;99:716–724.

3. Gritti MN, Farid P, Manlhiot C, Noone D, et al. Factors associated with acute kidney injury after cardiopulmonary bypass in children. *CJC Pediat Cong Heart Dis*. 2023;2:20–29.

4. Kwiatkowski DM, Krawczeski CD. Acute kidney injury and fluid overload in infants and children after cardiac surgery. *Pediatr Nephrol*. 2017;32:1509–1517.

5. Rathgber SL, Chakrabarti A, Kapravelou E, et al. Association of preoperative diuretic use with early acute kidney injury in infants with biventricular hearts following cardiac surgery. *J Am Heart Assoc*. 2021;10:e020519.

6. Bandeali SJ, Kayani WT, Lee VV, et al. Association between preoperative diuretic use and in-hospital outcome after cardiac surgery. *Cardiovasc Ther*. 2013;31:291–297.

7. Zheng H, Liu L, Fan G, et al. Preoperative use of furosemide may increase the incidence of acute kidney injury after coronary artery bypass grafting: a propensity score-matched study. *Gen Thorac Cardiovasc Surg*. 2021;69:1392–1399.

8. Guo S, Bai L, Tong Y, et al. Contrast media exposure in the perioperative period confers no additional risk of acute kidney injury in infants and young children undergoing cardiac surgery with cardiopulmonary bypass. *Pediatr Nephrol*. 2021;36:2485–2491.

9. Greenberg JH, Whitlock R, Zhang WR, et al. Interleukin-6 and interleukin-10 as acute kidney injury biomarkers in pediatric cardiac surgery. *Pediatr Nephrol*. 2015;30:1519−1527.

10. Ma J, Yuan H, Chen Y, et al. Circulating endothelial microparticles: a promising biomarker of acute kidney injury after cardiac surgery with cardiopulmonary bypass. *Ann Transl Med*. 2021;9:786.

11. Greenberg JH, Zappitelli M, Jia Y, et al. Biomarkers of AKI progression after pediatric cardiac surgery. *J Am Soc Nephrol*. 2018;29:1549−1556.

12. Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality inititative (ADQI) 16 Workgroup. *Nat Rev Nephrol*. 2017;13:241−257.