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Review

Early detection of acute kidney injury after pediatric cardiac surgery

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ABSTRACT

Acute kidney injury (AKI) is increasingly recognized as a common problem in children undergoing cardiac surgery, with well documented increases in morbidity and mortality in both the short and the long term. Traditional approaches to the identification of AKI such as changes in serum creatinine have revealed a large incidence in this population with significant negative impact on clinical outcomes. However, the traditional diagnostic approaches to AKI diagnosis have inherent limitations that may lead to under-diagnosis of this pathologic process. There is a dearth of randomized controlled trials for the prevention and treatment of AKI associated with cardiac surgery, at least in part due to the paucity of early predictive biomarkers. Novel non-invasive biomarkers have ushered in a new era that allows for earlier detection of AKI. With these new diagnostic tools, a more consistent approach can be employed across centers that may facilitate a more accurate representation of the actual prevalence of AKI and more importantly, clinical investigation that may minimize the occurrence of AKI following pediatric cardiac surgery. A thoughtful management approach is necessary to mitigate the effects of AKI after cardiac surgery, which is best accomplished in close collaboration with pediatric nephrologists. Long-term surveillance for improvement in kidney function and potential development of chronic kidney disease should also be a part of the comprehensive management strategy.

1. Introduction

Acute kidney injury (AKI) is common following pediatric cardiac surgery and occurs in ~40–50% of cases [1]. This is likely an underestimate and offers an important target for improved clinical care. The occurrence of AKI has been consistently reported as a risk factor for morbidity and mortality in this vulnerable population and is related to prolonged length of stay, post-operative ventilator duration, fluid disturbances, electrolyte derangements, and abnormal drug metabolism [1–3]. AKI in adults undergoing cardiac surgery has been more extensively studied and is associated with increased hospital cost and in-hospital mortality, increased need for hemodialysis after discharge, increased incidence of chronic kidney disease (CKD), and decreased survival [4–7]. However, many patients regardless of age fail to be diagnosed with AKI. There are many potential reasons that AKI is underappreciated, including a lack of awareness by clinicians and limitations in the current diagnostic approach to AKI. Herein, we report the current definitions, epidemiology, mechanisms, clinical approach, and the development of novel diagnostic strategies for AKI after pediatric cardiac surgery.

2. Definition of AKI

Prior to the development of the RIFLE (Risk, Injury, Failure, Loss, and End-Stage) criteria in 2004, the reported incidence of AKI varied widely and resulted in many patients with AKI not being recognized [8]. The RIFLE criteria consists of three graded levels of injury (Risk, Injury, and Failure) based upon either the fold increase in serum creatinine (1.5-, 2-, or 3-fold respectively) or reduction in urine output. A modification termed as the Acute Kidney Injury Network (AKIN) criteria was developed which defined AKI as a ≥0.3 mg/dl increase in serum creatinine within a restrictive 48-hour period. However, the AKIN criteria have not been adequately validated for use in children, and the restricted diagnostic timeframe of 48 h for a rise in serum creatinine may limit its utility. Recently, the criteria for diagnosis of AKI have been further refined by the Kidney Disease Improving Global Outcomes (KDIGO) group and are now widely accepted for children and adults (Table 1) [9]. These criteria still rely heavily on a rise in serum creatinine (SCr) and changes in urine output. The degree of SCr increase is also still used to define AKI severity using a 3-level staging system with stage 1 being the least severe and stage 3 being most severe. However, the use of SCr in the diagnosis and staging of AKI has many inherent limitations. Even normal SCr can vary widely with age, gender, diet, muscle mass, nutrition status, medications, and hydration status. An increase in SCr does not differentiate the nature, type and timing of the renal insult. Dialysis readily clears serum creatinine, rendering this marker useless in the assessment of renal function once dialysis has begun. In

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Table 1
The Kidney Disease Improving Global Outcomes (KDIGO) AKI criteria.
Adapted from reference [9].

Stage	Serum creatinine	Urine output
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 h
2	1.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3.0 times baseline, OR SCr ≥4.0 mg/dl (≥353.6 μmol/l), OR Initiation of renal replacement therapy, OR eGFR <35 ml/min per 1.73 m^2 (<18 years)	<0.3 ml/kg/h for ≥24 h, OR Anuria for ≥12 h

SCr, serum creatinine; eGFR, estimated glomerular filtration rate.

the acute setting, it is estimated that more than 50% of kidney function must be lost before SCr even begins to rise. Changes in SCr often lag behind changes in renal function due to an acute insult until a steady state has been reached, which can take several days. This leads to delayed diagnosis of AKI and greatly limits opportunity for timely clinical intervention. Even with these recognized limitations, changes in either serum creatinine or urine output do offer powerful diagnostic and prognostic capacity. If both worsening serum creatinine and decreased urine output occur, the severity of disease is worse with associated higher mortality. The duration of AKI also offers important prognostic information and depending on AKI stage, can alter outcome. Kellum et al. recently evaluated a cohort of over 23,000 patients that developed AKI as classified by the KDIGO criteria [10]. In patients meeting stage 3 AKI diagnosis by one criteria, hospital mortality and need for renal replacement therapy (RRT) were <18% and <3.5%, respectively. There was a dramatic change in these outcomes when stage 3 AKI was diagnosed by both criteria, with need for RRT increasing to 55% and mortality increasing to 51%. They also documented that the duration of AKI was a strong predictor of death or end stage renal disease regardless of AKI stage. Additionally, data from this report suggest that changes in SCr for those with higher baseline values may be more important clinically than a change of similar magnitude in patients with low baseline SCr values.

3. Incidence and Etiology of Cardiac Surgery-associated Acute Kidney Injury

In recent years, improvements in surgical techniques have expanded the complexity of congenital heart lesions that are correctible, but with an associated increase in the incidence of cardiac surgery-associated AKI (CS-AKI) [11]. Recent reports of AKI using current definitions in large pediatric populations undergoing congenital heart disease surgery have revealed an incidence of 40–50% [1,3,12–14], with an even higher incidence of 64% among neonates [15]. More importantly, pediatric CS-AKI has been consistently associated with a number of complications including increased morbidity and mortality in this population. In the short term, after adjustment for covariates, pediatric CS-AKI is independently associated with longer duration of ventilation, longer intensive care unit and hospital stay, increased inotropic support, increased occurrence of low cardiac output syndrome, and increased mortality [1,3,12–19]. In the long term, severe pediatric CS-AKI is independently associated with increased mortality [3,15], lower z-score for height [15], as well as evidence for chronic kidney disease [20]. The short- and long-term implications of AKI in this setting clearly underscore the importance of a better understanding of the pathogenesis and risk factors, the significance of making an early diagnosis in the post-operative period, and the need for long-term follow up.

Historically, it had been thought that AKI in the setting of cardiac disease was secondary to low cardiac output and/or impaired arterial perfusion of the kidneys. Current data would suggest that the more pertinent contributory mechanisms include venous congestion along with an upregulation of inflammatory cytokines [21,22]. The pathogenesis of CS-AKI is complex, incompletely understood, and based largely on animal models. Primary mechanisms include ischemia, ischemia–reperfusion injury, mechanical blood trauma, oxidative stress, nephrotoxins, and activation of inflammatory cascades [11,23,24]. Reduced mean arterial pressure and non-pulsatile renal blood flow during cardiopulmonary bypass (CPB) leads to renal ischemia and hypoxia, with resultant activation of apoptotic and necrotic pathways of tubule and endothelial cell death [25,26]. Direct and convincing evidence for low renal oxygenation during pediatric CPB has been obtained using near-infrared spectroscopy [27–29]. Not surprisingly, the duration of CPB has been the single most consistently identified risk factor for pediatric CS-AKI [1]. It has been directly demonstrated that human kidneys can safely tolerate 30–60 min of controlled clamp ischemia with only mild structural changes and no acute functional loss [30]. Reperfusion following release of aortic cross-clamps results in activation of oxidative pathways that further exacerbate tubular and microvascular injury [25,26]. Mechanical trauma to red blood cells in the CPB circuit causes hemolysis and the release of free hemoglobin and iron, which exacerbate oxidant-mediated injury. Injured tubule and endothelial cells initiate a local inflammatory response. In addition, a systemic inflammatory response is induced by CPB, triggered by contact between blood and the artificial surfaces of the CPB circuit. Activation of neutrophils, platelets, and other pro-inflammatory cascades further exacerbates the damage to renal tubule and endothelial cells. While inflammation is prominent in animal models of AKI, its role in humans undergoing CPB is not fully known. During the post-operative period, the use of nephrotoxic agents such as non-steroidal anti-inflammatory agents, antibiotics, and contrast agents can worsen the kidney injury. These multiple mechanisms of injury are likely to be activated at different time points with varying intensities and may act synergistically.

Numerous risk factors have been identified for the development of pediatric CS-AKI, in the pre-operative, intra-operative, and post-operative phases [31,32]. The most consistently identified independent risk factors for pediatric CS-AKI include younger age, longer duration of CPB, higher surgical complexity (as reflected by the risk-adjusted classification for congenital heart surgery [RACHS-1] score), preoperative ventilator support, and lower preoperative serum creatinine [1,12,15]. Many pre-operative risk factors such as lower age and genetic predisposition are not modifiable but should be considered in decision making if known. Other potentially modifiable pre-operative risk factors include diabetes mellitus, lower preoperative serum creatinine, preoperative ventilator support, history of congestive heart failure, and hypertension. Although these may not be fully correctible, optimal management should be targeted. In addition, screening to assess for other pre-operative risk factors such as renal dysfunction or reduced left ventricular ejection fraction (LVEF) should be completed. Appropriate assessment for causes of these conditions and subsequent treatment could result in an improvement in kidney and/or systolic function. There are also recognized intra-operative risk factors, including low blood pressure and low hemoglobin concentrations, both of which can be optimized to improve oxygen delivery during CPB. Some intra-operative risks, such as use of deep hypothermic circulatory arrest and longer duration of bypass, may be modified but often will be dependent on the surgical approach in particular centers [32]. However, some risks are unavoidable such as need for emergent surgical intervention or need for thoracic aortic surgery. Post-operative factors that increase the risk of AKI include volume status, use of renal replacement therapy, kidney perfusion pressure, kidney function immediately following surgery, prior existing chronic kidney disease, and use of mechanical circulatory support [32,33]. Appropriate control of blood pressure and volume status in the post-operative period offers clinicians potential strategies to mitigate or avoid AKI.

4. Novel Diagnostic Strategies in AKI

There are inherent limitations to relying on changes in SCr and urine output as diagnostic vehicles for AKI. To assist clinicians in the diagnosis