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Review

The importance of renal function for the management of the sick newborn with congenital heart disease

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ABSTRACT

Acute kidney injury (AKI) is increasingly recognized as a cause of increased morbidity and mortality in neonates and infants with congenital heart disease. The list of putative causes of AKI in this population is long, however, the true etiology is multifactorial. Some of the possible factors related to AKI in neonates with heart disease could be neonatal adaptation to extrauterine life (immature kidneys, low glomerular filtration rate, high renal vascular resistance, high plasma renin activity), or perioperative factors affecting renal blood flow (ischemia, reperfusion injury, use of cardiopulmonary bypass, peri-operative hemodynamics), or renal injury due to hormonal, biochemical and cytokine related factors. There is lack of consensus definition for AKI in neonates with congenital heart disease. Use of novel biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule (KIM-1), cystatin C, and interleukin-18 (IL-18) has emerged as a possible alternative to diagnose early AKI. The challenge with all these biomarkers is the lack of good reference intervals by post-conceptual age. Neonates with congenital heart disease may have varying degrees of renal impairment with multiple alternatives for treatment. The therapy of AKI revolves around optimizing renal perfusion pressure and oxygenation through judicious management of fluid balance, electrolyte status, acid–base balance, nutrition, and initiation of renal replacement therapy when appropriate. The focus of this review is to evaluate the prevalence of renal impairment in patients with congenital heart disease before and after surgery, to explore the impact of several risk factors for AKI in this population, to evaluate potential variables for early detection and to review the available treatment options for AKI with renal failure.

1. Introduction

The interdependence between the heart and the kidney is a well-known phenomenon that is frequently observed and must be considered in the management of neonates with congenital heart disease. Acute kidney injury (AKI) is the primary manifestation of renal dysfunction encountered in this population and can have a profound effect of morbidity and mortality [1–4].

In newborns patients, AKI importance and dilemmas are even more pronounced. Neonatal kidneys are more susceptible to hypoperfusion, have low glomerular filtration rate, high renal vascular resistance, high plasma renin activity, decreased intercortical perfusion, and decreased reabsorption of sodium in the proximal tubules [5]. The true etiology of AKI is multifactorial and includes a host of factors, including ischemia, reperfusion injury, disruption of renal vascular homeostasis, cytokine-driven effects, hypoxic and oxidative stress (Table 1).

A huge limitation in management of AKI is the heavy reliance on downstream data collection variables such as oliguria/anuria, serum creatinine and decreased glomerular filtration rate (GFR), which are usually delayed in demonstrating a significant injury, secondary to the exceptional reserve capacity of the kidneys [4]. Early detection and management of congenital heart patients with a risk of developing renal dysfunction can alter morbidity and mortality in this population, thereby affecting outcomes. Therefore, the focus of this review is to evaluate the prevalence of renal impairment in neonates with congenital heart disease before and after surgery, to explore the impact of several risk factors for AKI in this population, to evaluate potential variables for early detection and to review the available treatment options for AKI with renal failure.

Abbreviations: AKI, Acute kidney injury; GFR, Glomerular filtration rate; CRS, Cardiorenal syndrome; CHF, Congestive heart failure; NGAL, Neutrophil gelatinase-associated lipocalin; KIM-1, Kidney injury molecule; IL-18, Interleukin-18; ECMO, Extracorporeal membrane oxygenation; VAD, Ventricular assist device; RIFLE, Risk, Injury, Failure, Loss and End stage classification; AKIN, Acute Kidney Injury Network classification; KDIGO, Kidney Disease, Improving Global Outcomes; RRT, Renal replacement therapy; RBF, Renal blood flow; ESRD, End stage renal disease; CPB, Cardiopulmonary bypass.

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Table 1
Factors related to renal dysfunction in neonates with heart disease.

Patient Factors
Prematurity or low birth weight
Low 5-min Apgar scores
Perinatal asphyxia
Prolonged premature rupture of membranes
Pregnancy induced hypertension
Heart failure
Cyanotic heart disease
Single ventricle palliation
Pulmonary hypertension
Previous cardiac operation
Chronic diuretic therapy
Hypertension
Diabetes mellitus
Hypertrophic cardiomyopathy
Renal vascular thrombosis
Congenital diaphragmatic hernia
Use of umbilical arterial catheter
Factors related to heart disease/operation
Use of cardiopulmonary bypass
Deep hypothermic circulatory arrest
Use of mechanical cardiac support (ECMO or VAD)
Fluid shifts in perioperative period
High complexity operation
Perioperative hemodynamic instability
Excessive diuresis
Excessive bleeding
Right heart dysfunction
Sepsis or infection
Low cardiac output syndrome
Use of indwelling catheters
Disseminated intravascular coagulation
High mean airway pressures
Hemolysis or thrombosis
Reperfusion injury to kidneys
Pharmacological interventions
Inotropes
Calcineurin inhibitors
Aminoglycoside antibiotics
Non-steroidal anti-inflammatory drugs
Vancomycin
Radiographic contrast
Intravenous immunoglobulins (IVIG)
Ganciclovir/Valganciclovir
Corticosteroids
Ranitidine

1.1. Classification of Acute Kidney Injury

In the available literature, there are dozens of definitions for AKI. This hinders progress in assessing preventive and therapeutic strategies to prevent AKI among neonates with critical illness [6]. The first effort to standardize the definition of AKI was made by Quality Initiative group that proposed the 'RIFLE criteria' for use in critically ill adult patients. The RIFLE (acronym for Risk for renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease, ESRD) stratifies patients based on changes in baseline serum creatinine with/without an associated decrease in urine output [6–7]. In 2007, the RIFLE system was modified for the pediatric population (pRIFLE) to more accurately evaluate pediatric patients by replacing the change in serum creatinine with a change in estimated creatinine clearance [7]. In recent literature, some authors have proposed neonatal RIFLE score to estimate AKI in neonates with critical illness [8] (Table 2).

Another important system used to assess the degree of AKI is the Acute Kidney Injury Network's (AKIN) 3-tiered staging system [9] (Table 2). The AKIN system uses a fold change in creatinine concentration to determine the stage of AKI. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) group put forth recommendations for an update consensus on the definition of AKI to reconcile the differences between AKIN, RIFLE and pRIFLE thereby utilizing KDIGO as the standard definition for pediatric AKI [10–11] (Table 2). The debate regarding the superiority of each classification system incited comparative research to study outcomes associated with AKI in children with critical illness [12–18]. There was no consensus on the superiority of one system over the other in any of these studies [12–18]. KDIGO appears to yield the lowest incidence of AKI with a range of 15%–16%, however, there are fewer studies utilizing the KDIGO criteria to date [19–20].

1.2. Cardiorenal Syndrome

Cardiac and kidney function are strongly interconnected and the communication between the two organs occurs through a variety of pathways, including perfusion, filling pressures and neurohormonal activity [21–22]. This interconnection is classified as the cardiorenal syndrome (CRS) and the definition includes five subtypes reflecting the possibility of transition of patients between each subgroups [21–23]. The most common subtype, CRS type 1, occurs in approximately 27%–40% of patients admitted with acute decompensated heart failure, and is secondary to the abrupt worsening of cardiac function resulting in AKI [24]. Other subtypes of cardiorenal syndromes include chronic CRS type 2 which occurs secondary to chronic abnormalities in cardiac function leading to chronic kidney disease and occurs in ~63% of patients with congestive heart failure (CHF), acute renocardiac syndrome type 3 secondary to abrupt worsening of renal function, chronic renocardiac syndrome type 4 secondary to chronic kidney disease which presents an exponential relationship between renal dysfunction severity and the risk for all-cause mortality and CRS type 5 which is secondary to systemic abnormalities leading to simultaneous dysfunction of both organs [21–24].

1.3. Pathophysiology of AKI in Neonates With Heart Disease

Renal embryogenesis is completed by the 35th week of gestation, resulting in 0.6 to 1.2 million nephrons in each kidney. However, several factors make newborn infants, especially those born preterm, more susceptible to renal failure than older infants or children. These include: developmental immaturity that limits the function of the immature kidney, hemodynamic changes that occur at birth and in the early neonatal period that affect the kidney and an increased risk of hypovolemia because of large insensible water losses. Several changes in renal function occur in the perinatal period. Renal blood flow (RBF) increases substantially soon after birth because renal vascular resistance decreases and systemic blood pressure increases. As a proportion of cardiac output, RBF increases from 2% to 4% in the fetus to approximately 10% by one week after birth (the normal adult value is approximately 20%). Interference with this transition, as may occur with congenital heart disease or decreased myocardial function, may lead to diminished renal function [25–26].

Autoregulation of RBF, in which small changes in systemic pressure produce parallel changes in renal vascular resistance so that RBF is maintained, is set at a lower range of blood pressure than in adults. This reduces a newborn's ability to compensate for significant hemodynamic changes and may lead to compromised renal function. Impaired autoregulation can predispose to acute kidney injury (AKI) when the blood pressure is reduced [25–26]. Urine concentrating ability is limited in the newborn compared with the older infant. The maximum urine concentration that can be achieved increases from 400 mosmol/kg in the first few days after birth to 1200 mosmol/kg at 1 year of age. The reasons for poor urine concentrating ability in infants include low corticomedullary solute gradient, decreased formation of cyclic AMP in response to antidiuretic hormone (ADH), short loop of Henle, and interference by prostaglandins [27–28].