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Acute Kidney Injury in Pediatric Heart Failure

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Abstract: Acute kidney injury (AKI) is very common in pediatric medical and surgical cardiac patients. Not only is it an independent risk factor for increased morbidity and mortality in the short run, but repeated episodes of AKI lead to chronic kidney disease (CKD) especially in the most vulnerable hosts with multiple risk factors, such as heart transplant recipients. The cardiorenal syndrome, a term coined to emphasize the bidirectional nature of simultaneous or sequential cardiac-renal dysfunction both in acute and chronic settings, has been recently described in adults but scarcely reported in children. Despite the common occurrence and clinical and financial impact, AKI in pediatric heart failure outside of cardiac surgery populations remains poorly studied and there are no large-scale pediatric specific preventive or therapeutic studies to date. This article will review pediatric aspects of the cardiorenal syndrome in terms of pathophysiology, clinical impact and treatment options.

Keywords: Acute kidney injury, cardiorenal syndrome, chronic kidney disease, congenital heart surgery, pediatric heart failure.

INTRODUCTION

Acute kidney injury (AKI) defined as an "abrupt and sustained change in renal function" - is very common in pediatric cardiac patients and is an independent risk factor for increased morbidity and mortality [1-4]. Children with heart failure as well as those with congenital heart disease are at risk for AKI. For many years, in both the acute and chronic setting, clinicians have recognized the frequent presence of concomitant renal and cardiac dysfunction. Despite the common occurrence of this clinical phenomenon, AKI in pediatric heart failure has been poorly studied largely due to a lack of standardized definitions and stratifications.

DEFINING AKI – THE CHALLENGES

Assessing the prevalence of AKI has previously been difficult, as until just 10 years ago there was no consensus definition, and reported studies had variable descriptions for AKI. The three consensus definitions that have recently unfolded, RIFLE, AKIN and most recently KDIGO, have changed the topography of AKI research, and have increased the awareness AKI in the medical community. A common thread in all three definitions is a two-pronged approach, where relative changes in serum creatinine (or creatinine clearance) compared to baseline values as well as differing durations of oliguria are considered separately and discretely to be indicators of AKI, without having to coexist for diagnosis. The Acute Dialysis Quality Initiative proposed a consensus definition for adult AKI in 2004 called the RIFLE criteria, which stratifies AKI as mild (Risk), moderate (Injury), and severe (Failure) [5]. A pediatric version, pRIFLE, has been extensively validated in separate pediatric populations [6, 7]. AKIN criteria were proposed by the Acute Kidney Injury Network as a modified version of the RIFLE criteria, and rather than evaluating kidney function over 7 days examines a 48-hour window using absolute changes in serum creatinine as well as a seemingly small increase in serum creatinine of 0.3 mg/dl as indicators for AKI [8]. KDIGO criteria, proposed by the Kidney Disease Improving Global Outcomes foundation, a non-profit organization aimed at improving the care of patients with kidney disease globally, can be viewed as a combination of the previous two definitions. Of note, the KDIGO definition includes pediatric-specific elements adapted from the pRIFLE criteria. AKIN criteria have also been modified for use in pediatrics and the KDIGO criteria have recently been validated in heterogeneous pediatric populations [1, 2, 4, 9] (Table **1**).

Studies in both adults and children have shown that detection of AKI differs depending on the definition used [10-12]. Most published reports have evaluated the serum creatinine based definitions of AKI, as urine output remains a difficult to ascertain parameter in the clinical setting. In actuality, oliguria is a sensitive and quite specific marker for severe AKI in adults and children and has prognostic implications. In a study of 102 children with AKI, oliguric patients had the highest mortality (53.9%, $p = 0.01$) and were ~ 23 times more likely than their non-oliguric counterparts to be initiated on renal replacement therapy (RRT) [13]. Opinion regarding the use of oliguria-based definitions for an AKI diagnosis in patients with cardiac diseases

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Table 1. Criteria for Diagnosis and Classification of Acute Kidney Injury KDIGO, pAKIN, and pRIFLE.

KDIGO		
AKI Staging	**Serum Creatinine**	**Urine Output**
Stage 1	1.5 - 1.9 times baseline or ≥0.3 mg/dl increase	<0.5 ml/kg/h for 6 - <12 hours
Stage 2	2.0 to 2.9 times baseline	<0.5 ml/kg/h for ≥ 12 hours
Stage 3	* 3.0 times baseline or increase to ≥4.0mg/dl * Initiation of RRT * <18 years - eGFR to <35 ml/min/1.73 m	* <0.3 ml/kg/h for ≥24 hours * Anuria for ≥12 hours
Pediatric-modified AKIN (pAKIN)		
AKI Staging	**Serum Creatinine**	**Urine Output**
Stage 1	* ≥125-200% (1.25 to 2-fold) from baseline * Increase of ≥0.3 mg/dl	<0.5 ml/kg/h for ≥6 hours
Stage 2	Increase of ≥200-300% (2- to 3-fold) from baseline	<0.5 ml/kg/h for ≥12 hours
Stage 3	* Increase of ≥300% from baseline or * ≥4.0mg/dl with an acute increase of ≥0.5 mg/dl * Requires Renal Replacement Therapy	* <0.5 ml/kg/h for ≥24 hours * Anuria for 12 hours
Pediatric-modified RIFLE (pRIFLE)		
AKI Staging	**Serum Creatinine**	**Urine Output**
Risk	eCCl decrease by 25%	0.5 ml/kg/h for 8 hours
Injury	eCCl decrease by 50%	0.5 ml/kg/h for 16 hours
Failure	* eCCl decrease by 75% * eCCl <35 ml/min/1.73 m^2	Anuric for 12 hours
Loss	Persistent failure >4 weeks	
End stage	Persistent failure >3 months	

Adapted from RIFLE, risk, injury, failure, loss, end-state, Acute Dialysis Quality Initiative (ADQI) Group (5); AKIN, Acute Kidney Injury Network (*AKIN*); pRIFLE, pediatric risk, injury, failure, loss and end-stage renal disease (6) KDIGO, Kidney Disease: Improving Global Outcomes (KDIGO Work Group 2012); SCr, serum creatinine; GFR, glomerular filtration rate; eCCl, estimated creatinine clearance. For AKIN and RIFLE, only one * criterion needs to be fullfilled. pRIFLE class is based on worst of either GFR or output criteria.

is mixed; most authors have claimed that due to the frequent use of diuretics as part of the standard of care in patients with heart failure and following cardiac surgery, oliguria is not a reliable AKI measure in these patient populations [14].

Even when only the serum creatinine definition is used, studies have shown differences in the detection of AKI, underscoring the need to adopt a single unified definition [2]. Lex *et al*. compared three different AKI definitions in pediatric cardiac surgery and found pRIFLE to be the most sensitive and AKIN the most specific for the most severe patients while KDIGO performed in between [11]. In all staging systems, the most severe AKI is associated with the worst outcomes and mortality. Both pRIFLE and KDIGO captured more patients than AKIN and pRIFLE captured 5% of patients that no other classification scheme captured.

Another challenge in establishing the diagnosis of AKI occurs in patients who lack a baseline creatinine, making the application of current definitions difficult. In a recent review of our institution's admissions for acute decompensated heart failure, 50% of patients did not have a baseline serum creatinine. Of these patients, 10% would have a missed diagnosis of AKI if admission serum creatinine were used as baseline, as these patients already had AKI (author's data, submitted). Similarly, in another recent single center retrospective study of over 2000 critically ill children, 30% did not have a baseline serum creatinine and were assigned an imputed value based on age and sex [1].

Since the glomerular filtration rate (GFR) in patients younger than two years of age is a function of age, the diagnosis of AKI with standardized definitions using universal threshold values is problematic in infants, especially in those younger than 12 months of age who have the fastest rate of change in GFR. Using age expected normal cut-offs levels is possible, though not very practical at the bedside, making the diagnosis of AKI more complicated and not easily achievable. Special considerations occur in neonates during the first 1-2 weeks of life. The serum creatinine is a reflection of maternal creatinine, and premature infants have physiological lower GFRs and therefore cannot be included in any of the predefined groups. The diagnosis of neonatal AKI is

challenging with in the confines of the present standardized definitions. Zappitelli *et al.* have proposed using the preoperative serum creatinine measurement closest to surgery as the baseline level however it is confounded by maternal creatinine [9]. Cystatin C, a proteinase inhibitor present in all nucleated cells and completely metabolized by intact proximal tubular epithelial cells after filtration, has been proposed as an alternative GFR marker as it is thought to be less influenced by age, sex and muscle mass, but it has not yet been validated in neonates [15-17].

The epidemiology of pediatric AKI in current practice has changed, shifting from primary renal disorders to that seen in the context of systemic disease often with multiple organ dysfunction [18, 19]. AKI in critically ill patients has been shown to have a strong association with mortality, regardless of underlying disease etiology, increasing in parallel with the severity of AKI [6, 19]. However, data has largely been limited to single center studies. The forthcoming (AWARE-Assessment of Worldwide AKI in pediatrics, Renal angina, and Epidemiology) study will be the largest and most accurate reflection to date of the incident rate and associated causes leading to pediatric ICU-related AKI including cardiac ICU patients (NCT01987921).

THE CARDIORENAL SYNDROME

The cardio-renal syndrome (CRS) is a recently coined term defining the co-existence of cardiac and renal dysfunction. The term stresses the bidirectional nature of heart and kidney interactions [20]. It was created in order to standardize the definition and to provide a framework to facilitate clinical studies, leading to an enhanced understanding of the syndrome (Fig. **1**). The typical attribution of poor kidney function due to poor perfusion oversimplifies the pathophysiology of the CRS. The relationship is dynamic and multifactorial, involving volume status, neurohormonal interactions, inflammation, and the use of pharmaceutical agents [21] (Fig. **1**).

Poor cardiac output and a decrease in arterial flow are sensed by the kidneys as effective hypovolemia starting a neurohormonal cascade that ends in increased sodium and thus water reabsorption (Fig. **2**). When the kidneys perceive hypovolemia, sodium reabsorption is increased. Mechanoreceptors in the left ventricle, aortic arch, carotid sinus, and the kidney's juxtaglomerular apparatus are stimulated, resulting in increased central nervous system sympathetic outflow, renin-angiotensin system activation, non-osmotic arginine vasopressin release, and thirst stimulation. These upregulatory mechanisms lead to dysregulated sodium and water retention in a systemic attempt to increase cardiac output and renal perfusion [22, 23].

With the increase in sodium and water reabsorption, systemic venous congestion is exacerbated, which may impede forward flow through the renal vasculature leading to decreased glomerular filtration and increased protein excretion [24]. Decreased glomerular filtration leads to relative oliguria, exacerbating fluid overload, and leading to worsening heart failure. Seemingly trivial changes in serum creatinine, even as little as 0.3 mg/dL, have been shown to predict morbidity and mortality in adult patients with heart failure [25-30]. The congestive state, not just inadequate perfusion contributes to the symptomatology in most patients with heart failure and has a significant role in CRS progression [31]. Patients with cardiac dysfunction and minimal congestion fair better than those with congestion alone [32, 33].

The ramifications of impaired renal perfusion and venous congestion resulting in AKI are profound. Even slight changes in serum creatinine impact patient morbidity and mortality, and have been associated with an increased risk of hospitalization and death [34, 35]. Incident rates in adults of worsening renal function (a serum creatinine increase of only 0.3 mg/dl) during hospitalization vary from 27% to 33%, and has been associated with an increased length of stay of 2–4 days [29]. The risk for rehospitalization and mortality within 6 months increases from 18% in patients with heart failure to 28% in patients with heart failure who have also developed

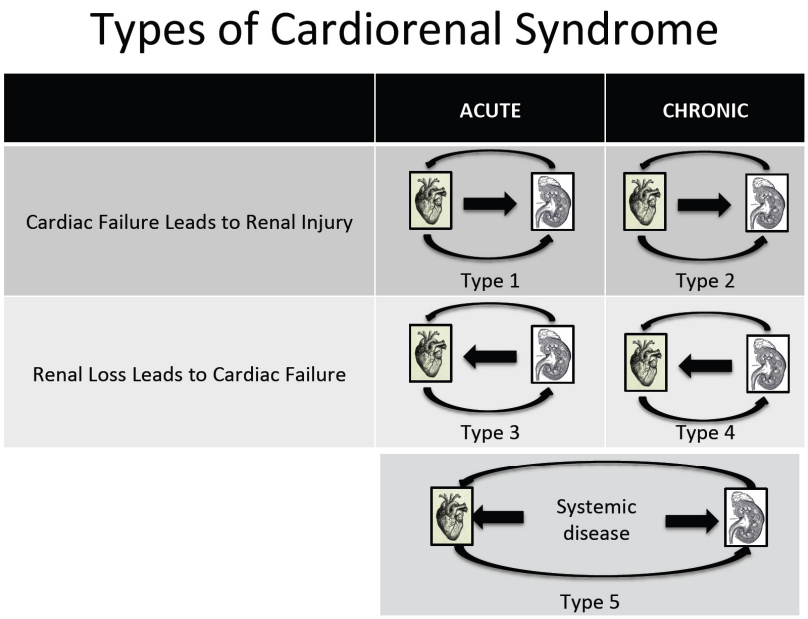

Fig. (1). Schematic representation of cardiorenal syndrome types.

worsening renal function during hospitalization [35]. Additionally, worsening renal function has been associated with a 47% increased risk of hospitalization or death over 4 years [36].

CARDIORENAL SYNDROME – SUBTYPES

In 2008, Ronco proposed 5 subtypes of CRS (Figs. 1 and **3**) [37]. CRS type 1 (acute CRS) is an acute worsening of cardiac function with secondary AKI. CRS type 2 (chronic CRS) is chronic congestive heart failure that leads to chronic kidney disease. CRS type 3 (acute renocardiac syndrome) is primary AKI leading to an acute heart disorder (such as acute glomerulonephritis causing fluid overload, and heart failure and AKI with resultant hyperkalemia causing an arrhythmia). CRS type 4 (chronic renocardiac syndrome) is chronic kidney disease that leads to worsening heart function, including increased cardiovascular events and left ventricular hypertrophy. CRS type 5 (secondary CRS) is com-

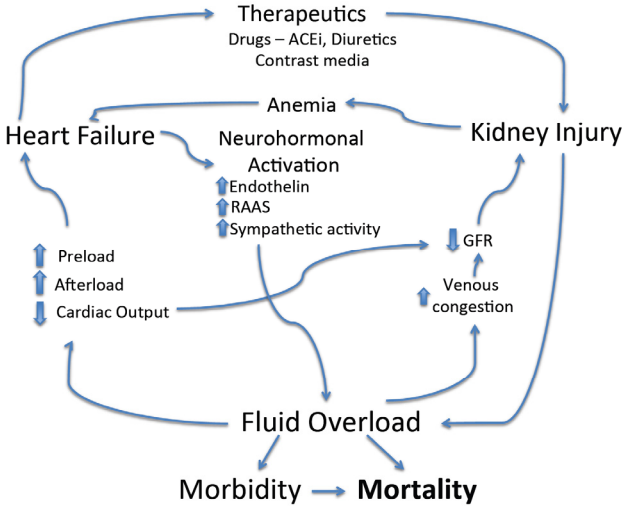

Fig. (2). Proposed mechanisms and interactions responsible in organ cross-talk in cardiorenal syndrome.

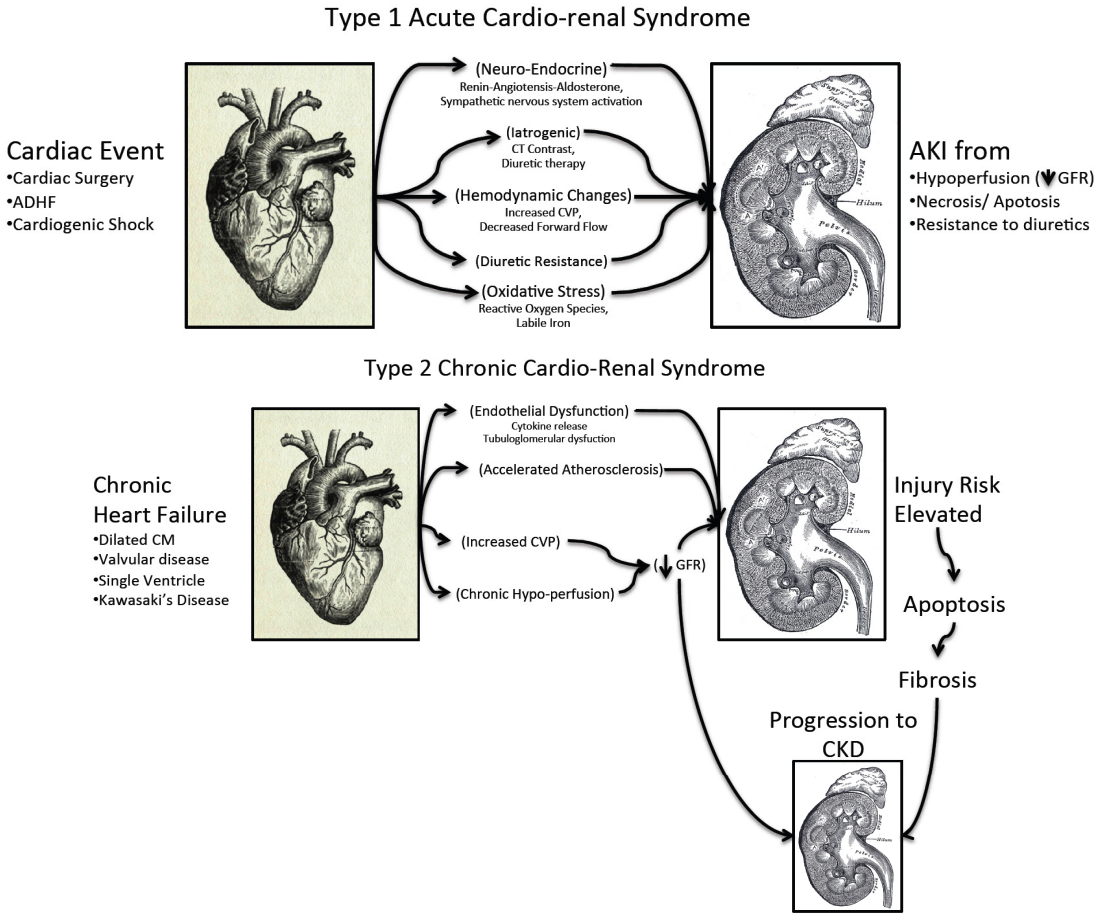

Fig. (3). Pathogenesis of cardiorenal syndrome type 1 and 2.

bined heart and kidney disease resulting from systemic diseases such as systemic lupus erythematous and oncologic disease. These classification schemes are not meant to be exclusive and patients can move between the different types fluidly, further accentuating the co-dependent close relationship between the heart and the kidney. In this review we will focus on CRS types 1 and 2.

PEDIATRIC CARDIORENAL SYNDROME

While well defined in the adult population, available pediatric data on the cardiorenal syndrome is scarce. Subtle worsening of renal function has been shown to be associated with adverse outcomes including the need for mechanical circulatory support and mortality in pediatric patients with heart failure [38]. In a retrospective epidemiologic study of pediatric ICU patients, of 254 cases of AKI, 17% occurred in patients with comorbid cardiac conditions, of whom approximately 1 in 4 were newborns with congenital heart disease who had associated renal ischemia/reperfusion injury [18]. In a cohort of over 1000 critically ill children, 20% of patients with primary cardiac dysfunction were also diagnosed with AKI during the hospitalization. Conversely, nearly half of the patients with AKI subsequently developed cardiac dysfunction or cardiac arrest as a complication of kidney disease [19].

In the context of systemic disease and multiple organ dysfunction associated AKI, pediatric cardiac surgical patients have been extensively studied, with testing and validation of various AKI definitions. In fact, there are more than 75 descriptive studies of AKI and associated risk factors in pediatric patients undergoing surgery for congenital heart disease. Cardiopulmonary bypass, with or without associated aortic cross-clamping and deep hypothermic circulatory arrest, is an attractive backdrop by which to study AKI. In contrast, there are only a handful published reports regarding AKI in children with cardiomyopathies. Common cardiovascular comorbidities that plague adult patients such as coronary artery disease from atherosclerosis, peripheral artery disease, diabetes, and smoking do not exist in the typical pediatric patient. As such, pediatric patients could be considered the ideal candidates to explore CRS epidemiology and clinical outcomes.

CARDIORENAL SYNDROME TYPE 1

Acute Decompensated Heart Failure

The first study to evaluate heart failure and kidney dysfunction in children included 73 patients with acute decompensated heart failure who were observed for worsening renal function, defined as an increase in serum creatinine of $\geq$ 0.3 mg/dL at any time during the hospitalization [38]. Approximately 4 in 5 patients had a rise in serum creatinine (median 0.2 mg/dL) and nearly half had worsening renal function, which was independently predictive of death or the need for mechanical circulatory support during the hospitalization, and was also associated with a longer hospital stay.

Cardiac Surgery-associated AKI

Multiple aspects of cardiopulmonary bypass may contribute to the development of AKI [39]. Following surgery patients may experience low cardiac output syndrome and often are exposed to nephrotoxic medications both of which may contribute to the development of or a worsening of AKI [39, 40] (Table **2**). Congenital heart surgery in infants has been shown to have an incidence of AKI of 10-25% or higher [41-43]. The presence of AKI following cardiac surgery in pediatric and adult patients has been associated with a greater demand for renal replacement therapy, longer hospital stays, higher mortality rates, and lower long-term survival [44-47]. Longer CPB time, younger age at operation, an abnormal preoperative serum creatinine, a need for increased postoperative support such as inotropic support and nitric oxide, cyanosis, and complexity of surgery are reported to be associated with an increased propensity to develop AKI [14, 48]. In a single-center retrospective study, severe AKI based on the pRIFLE-F criteria increased the odds of mortality almost 70-fold [48]. Eight percent of patients who did not have AKI during the first three postopera-

Table 2. Overview of common diuretics used in treatment of congestive heart failure. PCT proximal convoluted tubule, DCT distal convoluted tubule, TAL thick ascending loop of Henle, ENaC epithelial sodium channel.

Drug class	example	Mechanism of action
Carbonic anhydrase	acetazolamide	Inhibition of PCT NaHCO3 absorption
loop	Furosemide Bumetanide Toresamide	Inhibition of Na/K/2Cl contransporter in TAL
Thiazide-type	Hydrochlorothiazide metolazone	Inhibition of Na/Cl cotransporter in DCT
K-sparing	Amiloride triamterene	Inhibition of aldosterone-responsive ENaC in distal nephron+collecting tubule
Aldosterone antagonist	Spironolactone Eplerenone	Inhibition of aldosterone receptors in distal nephron+collecting tubule, reducing Na channel and N/K/ATpase
Vasopressin antagonist	Conivaptan tolvaptan	Inhibition of V2 receptors in distal nephron, collecting tubule, reducing number of aquaporin channels

tive days developed AKI subsequently, demonstrating the importance of close surveillance. AKI is associated with higher resource utilization and non-renal morbidity. After propensity matching, low cardiac output syndrome, renal replacement therapy (RRT), and the incidence of infection were higher in patients with AKI, and these patients experienced longer durations of mechanical ventilation and lengths of stay in the ICU. Of note, sepsis and sternal wound infections were more frequent in patients with AKI, demonstrating an infrequently reported but critical non-renal morbidity observed in AKI, which is an increased risk of infection [14].

Mechanical Support and AKI

A special consideration in pediatric heart failure complicated by AKI is the role of mechanical circulatory support. Advances in technology enable more patients with complicated conditions to be successfully supported with mechanical circulatory devices as a bridge to transplantation or to home care. The nonpulsatile flow of venoarterial extracorporeal membrane oxygenation (VA-ECMO) might adversely affect renal perfusion leading to increased AKI while paracorporeal pulsatile pumps are thought to provide optimal renal perfusion and therefore perhaps less AKI. However, in a single center retrospective review of renal function that compared ECMO to the ventricular assist device (VAD), the initial improvement in renal function observed in patients supported with a VAD was not sustained; though patients supported with ECMO were substantially younger than those patients supported with a VAD and as such would have been expected to have a lower GFR making absolute comparisons difficult [49]. Most importantly, most patients suffer varying degrees and duration of low cardiac output that necessitates transition to mechanical support and likely develop AKI as a result of a low cardiac output state. Philip *et al.* reported pre-ECMO renal function to be associated with functional outcome at hospital discharge [50].

Heart Transplantation and Renal Function

In the patient receiving orthotopic heart transplantation (OHT), there are a myriad of risk factors for developing AKI, including pre-transplant low cardiac output; over diuresis and inability to optimize decongestion in volume overloaded patients prior to OHT; ischemia/reperfusion during transplantation - particularly if the OHT is for failed single ventricle palliation as the duration of CPB may be longer; isolated right heart failure; primary graft failure or delayed function; and the use of calcineurin inhibitors (CNI) amongst other nephrotoxic medications. The CPB induced capillary leak and vasoactive agents commonly used following surgery combined with CNIs could lead to changes in renovascular resistance and therefore alter renal perfusion [51]. The incidence of AKI in OHT patients varies according to the definitions used. The incidence of AKI prior to OHT is reported to be 2.5 - 42% depending on the definitions used [52]. More frequent AKI prior to OHT leads to more frequent AKI after OHT [53]. Overall, 5% of pediatric OHT recipients require RRT, however, 60% of patients who need RRT before OHT need RRT after OHT. AKI in the first week after OHT is associated with increased length of stay, need for mechanical circulatory support, and early mortality.

CARDIORENAL SYNDROME TYPE 2

Data on pediatric patients with chronic HF and chronic renal dysfunction is scarce. Most of our knowledge in this area comes from mid- to long-term follow-up of heart transplant patients. A majority of heart transplant patients experience at least mild CKD [53]. Similar to AKI, the incidence of CKD in heart transplant patients vary according to the definitions used [54]. Three percent of pediatric heart transplant patients develop end stage renal disease by 10 years; the prevalence of CKD is 4% at 5 years, 10% at 10 years. The International Society of Heart and Lung Transplant (ISHLT) fifteenth pediatric registry in 2012 reports 10% of heart transplant patients need chronic dialysis or renal transplant by 15 years after transplantation. It is necessary to point out that the ISHLT registry defines CKD as a creatinine of >2.5 mg/dl, an extremely conservative cutoff especially in younger patients.

Blinder *et al.* reported that postoperative AKIN stage 2 AKI was associated with worse left ventricular systolic function 30 days after surgery, underlining the bidirectional nature or cardiac-renal injury even in the mid-term [3]. Cyanotic nephropathy, most frequently described in patients with Eisenmenger syndrome is a well-known entity though never systematically studied [55]. However, 50% of adults with congenital heart disease have CKD, and this number increases to over 70% in patients with Eisenmenger physiology, and is associated with increased mortality [56].

MODIFIABLE RISK FACTORS

As most of the perioperative risk factors associated with the development of AKI are non-modifiable, such as age and the nature of the underlying heart disease, most approaches have focused on optimizing perfusion and the avoidance of nephrotoxic medications. Even the pharmacological treatments used to optimize cardiac output such as vasoactive amines could pose potential risks by altering renal perfusion. Near-infrared spectroscopy (NIRS) is a relatively new technology that allows for the assessment of regional tissue oxygenation. The intraoperative use of NIRS monitoring to assess renal oxygenation has been reported to predict the development of postoperative AKI [57, 58]. Basu *et al.* have reported a combination of biomarkers (urinary NGAL and plasma cystatin C) that could predict persistent AKI as early as two hours into CPB [59]. These two approaches could make studies of intraoperative renal protective strategies possible. In a novel approach, Ricci *et al.* tested the use of high dose fenoldopam as a strategy to prevent CPB-induced AKI during surgery for congenital heart disease, and relied on changes in urinary and serum NGAL and cystatin C in addition to pRIFLE scoring to establish the diagnosis [60]. Urine NGAL and cystatin C levels were increased in both groups, but significantly less so in the intervention group. There were fever patients with AKI by pRIFLE in the intervention group but this did not reach statistical significance, as the study was underpowered to detect differences in AKI. However, in adults undergoing cardiac surgery, the use of fenoldopam during the onset of AKI on postoperative day one did not decrease the need for RRT or mortality yet caused more hypotension. The study was stopped early for futility. Noting the potentially beneficial effects of fenoldo-

pam in children during CPB, it might be suggested that any intervention should happen earlier, prior to the development of AKI [60]. Among other pharmacological treatments, angiotensin-converting enzyme inhibitors may increase the risk of AKI in heart failure exacerbations, while β-blockade may be protective [3].

DIAGNOSIS OF AKI

The evaluation of serum creatinine remains the mainstay of diagnosis of AKI. Serum creatinine is a by-product of muscle metabolism and is impacted by gender, muscle mass, hydration status, and critical illness [61]. It is freely filtered and secreted by the intact nephron and therefore creatinine clearance overestimates the actual glomerular filtration rate. Moreover, serum creatinine is a late marker of declining GFR, peaking 2-3 days after the insult, and is further impacted by fluid overload, which becomes important in patients with congestive heart failure potentially masking true AKI [62].

In addition, most children with chronic heart failure are malnourished with diminished muscle mass, thereby leading to less creatinine generation and a lower overall baseline serum creatinine. Particularly in pediatric patients where a smaller rise in serum creatinine suggests a greater degree of kidney dysfunction than in adults, it may be argued that there is even a greater need to be able to accurately detect AKI earlier. Urinary and plasma biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule (KIM)-1, liver-fatty acid binding protein (L-FABP), N-Acetyl-β-D-Glucosaminidase (NAG), and IL-18 have been demonstrated in studies of infants undergoing congenital heart repair to indicate kidney injury within hours of injury, compared to the lag in serum creatinine that may take 2 to 3 days [23, 41, 44, 63]. Though relatively well studied in children undergoing cardiac surgery, none of these biomarkers are ready for clinical use, nor have they been well studied in patients with CRS type 2.

The high incidence of peritoneal dialysis in high complexity surgeries in some centers and protocolized PD in others makes the diagnosis of AKI based on changes in creatinine more difficult because creatinine is cleared by peritoneal dialysis. A nondialyzable biomarker should ideally be followed in those cases. Both micro- and macroalbuminuria, defined as 30-300 mg and > 300 mg albumin per gram creatinine, respectively, have been shown to be a risk factor for cardiovascular disease and mortality even without associated diabetic or hypertensive disease [64]. Increasing albuminuria has been shown to predict increasing heart failure hospitalizations and death from cardiovascular causes in at least three large studies of adult patients initially enrolled with stable heart failure [65-67]. The pathophysiology relating heart failure and albuminuria is poorly understood, and it is unknown if measures aimed to reduce albuminuria will impact the progression of heart failure.

Natriuretic peptides, particularly B-type natriuretic peptide, have been well studied in CKD associated renal dysfunction (CRS type 4) but reports on its usefulness in CRS type I and II are conflicting [68]. Recently, urinary tissue inhibitor of metalloproteinase 2 and insulin like growth factor binding protein (TIMP-2x, IGFBP7), both markers of G1 cell cycle arrest, were found to be increased in children undergoing CPB predicting the development of AKI as early as 4 hours after CBP [69].

TREATMENT OPTIONS - DECONGESTIVE STRATEGIES

Diuretics

Diuretic therapy, specifically loop diuretics are the mainstay of decongestive treatment in the fluid overloaded patient (Table **3**). Almost all patients receive diuretic therapy for the treatment of acute decompensated heart failure [70]. Paradoxically, diuretic use has been associated with worsening kidney function, progression of heart failure, and increased mortality [22, 71-75]. Although worsening kidney function during the treatment of acute decompensated heart failure is associated with poor outcomes [29, 76-78], decongestion and a decrease in total body water may unmask preexisting AKI. This is a difficult relationship to elucidate when the goal of treatment is fluid removal and the marker of AKI is serum creatinine, which is inversely proportional to total body water.

Table 3. Cardiopulmonary bypass associated factors leading to AKI.

Cardiopulmonary bypass run associated AKI risk factors
Ischemia/reperfusion
Inflammation
Shear stress
Endothelial activation
Embolic phenomena
Drug induced renal injury (Aprotinin, historical interest)
Hemolysis
Non-pulsatile flow

Diuretics might have unintended consequences such as further activation of neurohumoral systems, leading to vasoconstriction as well as sodium and water retention. In patients with chronic heart failure and decreased kidney function, a single intravenous dose of furosemide is linked to early elevations in systemic vascular resistance with a concomitant increase in neurohormonal levels [71]. However, the use of a vasodilator in addition to a diuretic results in a decrease in neurohormonal activation and systemic vascular resistance [79, 80]. The use of a continuous infusion of loop diuretics or a combination of different classes of diuretics, a strategy to overcome diuretic resistance that involves sequential nephron blockade, is commonly used to treat refractory congestion although it has not been well studied in children [81, 82]. Aquaretics represent a new class of diuretics that act on V2 receptors and promote free water excretion are currently being studied for use in children with euvolemic or hypervolemic hyponatremia.

Mechanical Fluid Removal

Extracorporeal ultrafiltration using hemodialysis membranes or peritoneal dialysis has been used in diuretic-

refractory patients with heart failure [83-89]. Several recent studies of patients with acute decompensated heart failure have compared the efficacy of ultrafiltration and diuretics [88, 90, 91]. The RAPID-CHF (Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure) study was the first randomized controlled trial to compare ultrafiltration and diuretic therapies in patients with acute decompensated heart failure. They found greater fluid removal and weight loss as well as improved symptoms, without a change in kidney function at 24 hours in those patients receiving ultrafiltration [91]. The UNLOAD (Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure) study is a large randomized controlled study comparing ultrafiltration to intravenous diuretics. They found a decrease in rehospitalization days and overall rehospitalization rate in the ultrafiltration arm [88].

With mechanical fluid removal there is an amelioration of maladaptive neurohumoral activation accompanied by improvements in renal perfusion pressure and a dramatic increase in diuresis [92]. Agostoni and colleagues compared neurohormone levels after similar amounts of volume removal with ultrafiltration and diuretics in 16 patients with chronic heart failure. In both groups, there was an immediate increase in neurohormone levels, but patients treated with ultrafiltration had a sustained decrease to less than baseline values after 48 hours whereas levels remained elevated at higher than baseline values for up to 3 months in the diuretic treated patients [93]. A post hoc analysis of the UNLOAD trial investigated renal effects of treatment, where fluid removal was similar between diuretic and ultrafiltration arms and found no significant differences in renal blood flow and GFR, though there were more patients in the ultrafiltration group with elevated serum creatinine levels [94]. In the CARRESS trial (Cardiorenal Rescue Study in Acute Decompensated Heart Failure), the largest randomized non-blinded trial to date in patients with decompensated heart failure and cardiorenal syndrome, ultrafiltration failed to improve kidney function and relieve congestion compared with protocolized stepwise pharmacologic care with diuretics [95]. Data in children is lacking. The development of newer miniaturized extracorporeal circuits to deliver clearance and fluid removal to younger children might facilitate the use of mechanical fluid removal trials in pediatrics [96-99].

Renal Replacement Therapy

In addition to the well-accepted indications of clearance, fluid removal and the buffering of acidosis with RRT in severe AKI, some pediatric cardiovascular surgery centers use peritoneal dialysis in a protocolized fashion for higher complexity cases. In small single center studies, the use of early peritoneal dialysis in the postoperative period has been associated with negative fluid balance, shorter length of ventilation and ICU stay [100, 101]. We now know that the use of peritoneal dialysis does not delay renal recovery after cardiac surgery [102]. Prospective randomized protocolized studies of targeted RRT use in CRS type 1 are needed to guide strategies for optimal fluid management.

Follow-up

Upwards of 25% of patients are discharged from the PICU with abnormal serum creatinine values [103]. Up to 60% of patients who recover from an episode of AKI during a PICU stay have evidence of renal dysfunction with decreased GFR, hyperfiltration, or hypertension at follow up several years later [104]. Among patients who received CRRT at a quaternary pediatric center, only 50% of patients had follow up appointment with a nephrologist following discharge (authors' data, unpublished). In another single center longitudinal follow up study, only 30% of patients who were treated with peritoneal dialysis after cardiac surgery were available for follow-up at 3.5-10 years as the others had died [105]. Similarly, Watkins *et al.* showed that the mortality risk associated with severe AKI persists beyond the immediate perioperative period, for as long as one year after surgery [106]. Early and regular monitoring by nephrologists of patients with any type of cardiorenal syndrome is crucial for optimizing outcomes.

CONCLUSION

The cardiorenal syndrome is common, costly, and adversely impacts both short and long-term outcomes. Clinicians should use standardized definitions with stratification in order to identify and follow at risk patients. Studies aimed at the identification of and intervention for modifiable risk factors are urgently needed. Biomarkers to identity AKI at earlier time points, though well studied, have not found a place in clinical application, though seem most ideally suited for the care of patients following cardiac surgery where the timing of injury is known. Mechanical fluid removal in pediatrics has an unknown safety and efficacy profile, however newly developed miniaturized machines with intelligent software may lead to changes in practice patterns that allow for safer and perhaps more effective treatment of pediatric patients. As the child with heart disease is at risk for developing CKD due to the simultaneous occurrence of multiple risk factors, a multidisciplinary approach with intensivists, cardiologists and nephrologists, both in the short and the long run will optimize outcomes.

LIST OF ABBREVIATIONS

ADHF	=	Acute Decompensated Heart Failure
AKI	=	Acute Kidney Injury
CKD	=	Chronic Kidney Disease
CPB	=	Cardiopulmonary Bypass
ECMO	=	Extracorporeal Membrane Oxygenation
ESRD	=	End Stage Renal Disease
GFR	=	Glomerular Filtration Rate
LCOS	=	Low Cardiac Output Syndrome
OHT	=	Orthotopic Heart Transplantation
PD	=	Peritoneal Dialysis
RRT	=	Renal Replacement Therapy
VAD	=	Ventricular Assist Device

WRF = Worsening Renal Function

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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