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SPECIAL REPORT

Framework for Kidney Health Follow-Up Among Neonates With Critical Cardiac Disease: A Report From the Neonatal Kidney Health Consensus Workshop

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ABSTRACT: Acute kidney injury is common among neonates with critical cardiac disease. Risk factors and associations with kidney-related outcomes are heterogeneous and distinct from other neonates. As survival of children with critical cardiac disease increases to adulthood, the burden of chronic kidney disease is increasing. Thirty percent to 50% of adults with congenital heart disease have impaired kidney function, even in the absence of prior kidney injury episodes. This may be related to the current standardized acute kidney injury criteria, which may not fully capture clinically meaningful kidney injury and long-term kidney health risks. An improved understanding of which neonates with critical cardiac disease should undergo kidney health follow-up is imperative. During the National Institutes of Health–supported Neonatal Kidney Health Consensus Workshop to Address Kidney Health meeting conducted in February 2024, a panel of 51 neonatal nephrology experts focused on at-risk groups: (1) preterm infants, (2) critically ill infants with acute kidney injury, and (3) infants with critical cardiac disease. The critical cardiac disease subgroup, comprising multidisciplinary experts, used a modified Delphi process to achieve consensus on recommendations for kidney health follow-up. In this report, we review available data on kidney health follow-up in critical cardiac disease and summarize the 2 consensus-based recommendations. We introduce novel diagnostic and risk-stratification tools for acute kidney injury diagnosis in neonates with cardiac disease to guide follow-up recommendations. Finally, we identify important knowledge gaps, representing areas of focus for future research. These should be prioritized to understand and improve long-term kidney health in critical cardiac disease.

Key Words: cardiac ■ chronic kidney ■ health ■ kidney ■ neonate ■ renal

Acute kidney injury (AKI) is independently associated with increased morbidity and death in neonates with critical cardiac disease.[1–14] Herein, we refer to neonates with critical cardiac disease as any neonate with ≥1 of the following: (1) hospital admission before or after corrective/palliative surgery or catheter-based intervention for congenital heart defects, including heart transplant; (2) significant clinical complications related to their critical cardiac disease, such as low cardiac output syndrome, cardiovascular collapse from hemodynamically significant residual lesions, and sepsis; or (3) myocardial failure (acute) from a variety of pathogeneses, including but not limited to acute myocarditis, idiopathic cardiomyopathy, or genetic abnormalities.

These vulnerable neonates may experience single or multiple events that predispose them to AKI (≥1

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Nonstandard Abbreviations and Acronyms

ACEi	angiotensin-converting enzyme inhibition
AKI	acute kidney injury
CPB	cardiopulmonary bypass
ESCAPE	Effect of Strict Blood Pressure Control and Angiotensin-Converting Enzyme Inhibition (ACEi) on the Progression of Chronic Renal Failure in Pediatric Patients
KDIGO	Kidney Disease: Improving Global Outcomes
KHA	kidney health assessment
PARADIGM-HF	Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
TRIBE-AKI	Translational Research Investigating Biomarker Endpoints in AKI
uNGAL	urine neutrophil gelatinase–associated lipocalin

episodes) that increase the probability of long-term sequelae, including chronic kidney disease (CKD).[14–20] Unfortunately, challenges remain surrounding precision in AKI diagnosis in neonates with critical cardiac disease, and management of AKI remains largely supportive. In addition, the pathophysiological changes that occur because of palliated or repaired cardiac disease in neonates and children put them at risk for CKD, independent of prior AKI episodes.[21] In this review, we summarize the existing literature and outline the recommendations for follow-up in this population who are at substantially high risk for poor long-term kidney health, even in the absence of prior AKI episodes (Figure 1).

The first Neonatal Kidney Health Consensus Workshop meeting was conducted to address kidney health in neonates who are at risk for recurrent episodes of AKI, CKD, and overall poor kidney health.[22] We summarize the work performed and conclusions drawn by the critical cardiac disease workgroup, 1 of 3 a priori–defined subgroups.

METHODS

The National Institute of Health supported the "Consensus Workshop to Address Kidney Health in Neonatal Intensive Care Unit Graduates," which took place in Indianapolis, Indiana, February 27 to 28, 2024. This workshop followed the Acute Disease Quality Initiative modified Delphi process and is described in detail elsewhere.[23] This workshop aimed to provide expert-based statements and interpretation of current knowledge for use by clinicians according to professional judgment and identify evidence-based gaps to establish research priorities.[23] The workshop members included patient advocates, neonatologists, general pediatricians, adult nephrologists, and pediatric subspecialists in nephrology, critical care, cardiology, and cardiac critical care. In this consensus workshop, we addressed the primary question: "What are the unique considerations present in neonates with critical cardiac disease that warrant kidney health follow-up and dictate the cadence and essential elements of this follow-up?" This question served as the foundation for consensus statement development. These recommendations were presented iteratively to the panel to develop consensus and required at least two-thirds support for adoption. These consensus recommendations were based on existing evidence and expert opinion; thus, institutional approval was not required. All panel members consented to their inclusion in this article. Standards for Quality Improvement Reporting Excellence guidelines were followed whenever applicable.[24]

RESULTS

Kidney Health Consensus Statements (Recommendations)

1. We recommend that *high-risk* neonates with critical cardiac disease undergo a comprehensive kidney health assessment (KHA) performed at least every 6 months through age 2 years in addition to annual nephrology follow-up (Figure 2). We define high-risk neonates with critical cardiac disease as those with any of the following: stage 2/3 AKI, single-ventricle physiology, heart transplant, concomitant hypoxic–ischemic encephalopathy, preterm birth (<34 weeks' gestation), receipt of extracorporeal membrane oxygenation, or daily nephrotoxic medication exposure (meeting the Nephrotoxic Injury Negated by Just in Time Action criteria at discharge).[25]
2. We recommend that *at-risk* neonates (all with critical cardiac disease and no high-risk criteria) have a comprehensive KHA at age 2 years or sooner if there are significant exposures or events that modulate risk.

AKI Risk Factors and Diagnosis

Among neonates with critical cardiac disease, most AKI occurs during or immediately after cardiac surgery, although neonates with inadequate cardiac output or those exposed to nephrotoxins, including intravenous

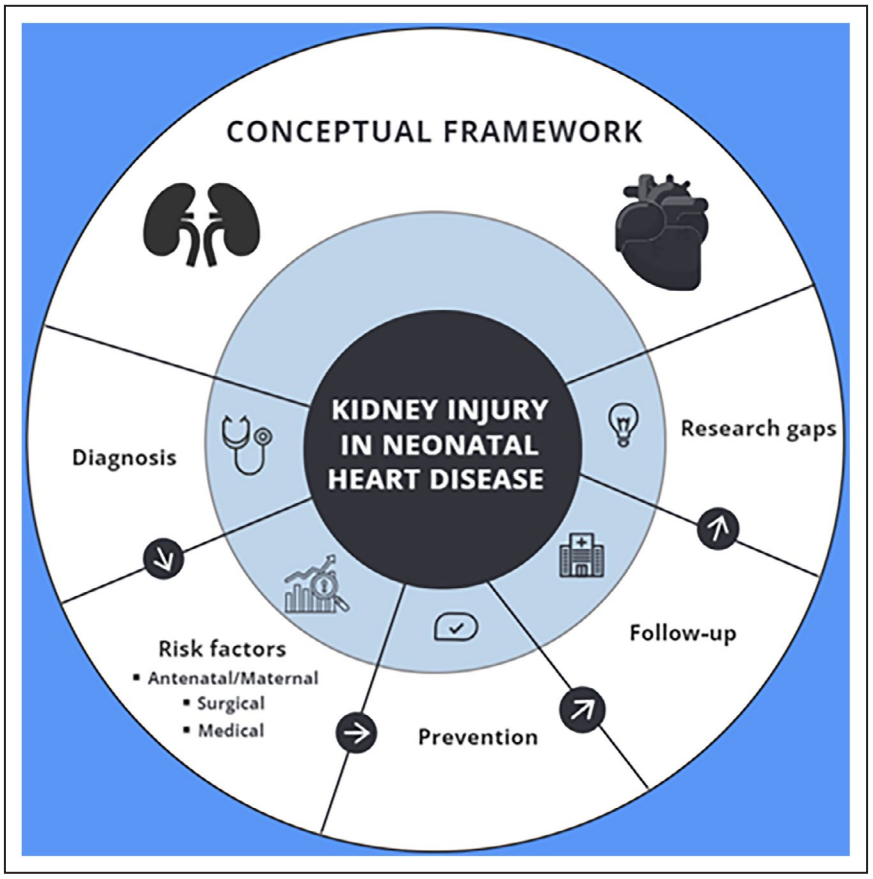

Figure 1. Conceptual framework for acute kidney injury and chronic kidney disease in neonates with critical heart disease.

contrast during catheter-based procedures, are also at increased risk outside the window of cardiac surgery.[1,4,12,19,25] The reported AKI incidence in this population varies due to cohort differences and inconsistent definitions. In a seminal paper evaluating AKI in the Neonatal and Pediatric Heart and Renal Outcomes Network study of over 2000 neonates undergoing surgery at <30 postnatal days, AKI occurred in 53% of neonates, with 22.6% developing moderate to severe (stage 2 or 3) AKI.[1] This study highlighted the substantial variation in AKI incidence ranging from 27% to 87% and AKI severity across 22 centers. These variations are attributable to intercenter practice differences such as intraoperative modified ultrafiltration and peritoneal catheters for passive drainage or dialysis that impact serum creatinine and urine output in the postoperative period. In addition, AKI diagnosis was considered across the entire spectrum of the postoperative period, beginning on arrival from the operating room, of which >50% had resolved by postoperative day 2. More recent data suggest these transient elevations in creatinine and decrements in urine output early after cardiac surgery are unrelated to kidney injury and are not associated with clinically relevant outcomes in children with critical cardiac disease.[26,27] Despite variations in incidence and definition, studies have consistently demonstrated the association of AKI with clinically important outcomes, including death, prolonged mechanical ventilation, infectious complications, and poor neurodevelopmental outcomes.[1,4,28,29] More recent studies have identified specific cardiac surgery–associated AKI subphenotypes to have stronger associations with short-term outcomes.[26,30] Using these subphenotype definitions decreases the heterogeneity in incidence across cardiac disease subtypes and strengthens association with outcomes. A summary of studies describing AKI incidence and outcomes in the short, medium, and long term in neonates, infants, and older children with critical cardiac disease is presented in the Table.

Various risk factors for the development of AKI in neonates with critical cardiac disease have been described and can be divided into 2 broad categories: (1) patient-related and (2) exposure-related. Patient-related risk factors include congenital anomalies of the kidney and urinary tract, prematurity, postnatal age, cardiac lesions affecting adequacy of kidney perfusion, and history of AKI.[31,32] Exposure-related risk factors include the burden of nephrotoxin administration, duration of

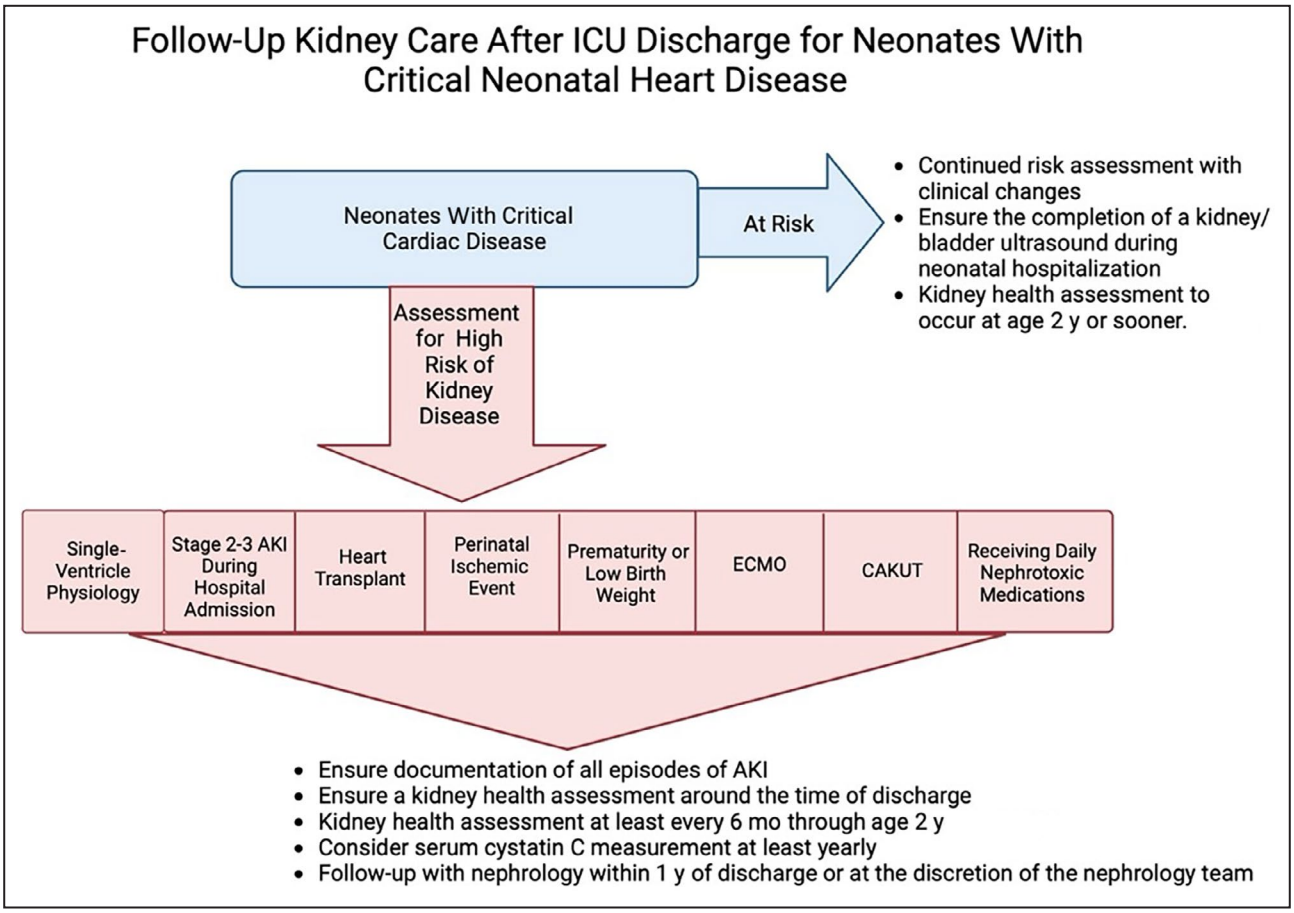

Figure 2. Kidney health follow-up recommendations for neonates with critical cardiac disease.
AKI indicates acute kidney injury; CAKUT, congenital anomalies of the kidneys and urinary tract; ECMO, extracorporeal membrane oxygenation; and ICU, intensive care unit.

cardiopulmonary bypass (CPB), use of extracorporeal membrane oxygenation, and poor cardiac output/hemodynamic instability.[32] Prolonged CPB, typically exceeding 180 minutes, is one of the most cited risk factors for AKI and may be due to combinations of pathogeneses, such as nonpulsatile flow, development of microemboli, ischemia/reperfusion injury, and global inflammation.[1,33] Furthermore, prolonged CPB likely serves as a surrogate of more significant cardiac disease or more complex surgical repair. AKI, however, still occurs, even when CPB is not used.[34] Nephrotoxin exposure is especially pertinent in this population, as many frequently used medications are unavoidable and may be administered in the setting of preexisting AKI. Whether the risks incurred from the simultaneous use of multiple nephrotoxic medications are additive or multiplicative remains unknown.[25,35] Furthermore, unlike in other neonatal populations with or without AKI episodes, many of the risk factors for AKI in neonates with critical cardiac disease persist after discharge. These include single-ventricle physiology and/or cyanosis, elevated central venous pressures, diminished cardiac output, recurrent need for surgery/catheter-based interventions (with or without CPB), and use of nephrotoxins, such as renin–angiotensin system blockade, radiologic contrast, and nephrotoxic medications including immunosuppression drugs, such as tacrolimus. Therefore, the risk of progression from AKI to CKD in this population is unique, and follow-up must be adjusted accordingly. Monitoring for progression to CKD is, in part, independent of prior AKI episodes.[36] This is the major rationale for recommending that at-risk neonates undergo a KHA at 2 years of age.

AKI is diagnosed using the modified Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine and urine output criteria in neonates.[37] Identifying AKI in sick neonates is challenging due to the known limitations of serum creatinine.[38,39] This may be further confounded in neonates with critical cardiac disease because of intravascular volume depletion and renal artery vasoconstriction induced by intraoperative ultrafiltration or inflammation during CPB that raises creatinine in the absence of kidney injury. In addition to the ubiquitous use of diuretic medications and the use of "prophylactic" peritoneal drainage catheters by some centers, AKI definitions rely on the decline

Table. Short, Mid and Long-Term Outcomes of Children With Critical Cardiac Disease

Short-term kidney outcomes						
Study	**Year of publication**	**No.**	**Inclusion**	**AKI definition**	**AKI, %**	**Associated outcomes**
Hasson et al (NEPHRON), Persistent acute kidney injury and fluid accumulation with outcomes after the Norwood procedure: report from Nephron.[26]	2024	347	Single ventricle s/p Norwood	Modified KDIGO	59	Persistent CS-AKI+>10% CFB 7.8× higher mortality rate
Sasaki et al (NEPHRON), Epidemiology of Neonatala acute kidney injury after cardiac surgery without cardiopulmonary bypass.[34]	2022	582	Nonbypass CS	Modified KDIGO	38	Aggregate daily CS-AKI prevalence peaked on POD 1 (17%) Prostaglandin use and single-ventricle surgery were associated with persistent/late CS-AKI. Higher baseline serum creatinine but not persistent/late CS-AKI longer ventilation and ICU LOS.
Alten et al (NEPHRON), Epidemiology of acute kidney injury after neonatal cardiac surgery: A report from the multucenter neonatal and pediatric heart and renal outcomes network.[1]	2021	22 040	Neonates major CS	Modified KDIGO	54	Stage 3 CS-AKI associated with death; CS-AKI varied across centers (27%–86%); CPB 1.5× higher odds of CS-AKI; open sternum+preoperative enteral feeds less CS-AKI
Ueno et al, Kidney Disease: Improving Global outcomes in neonates with acute kidney injury after cardiac surgery.[11]	2020	81	Neonates CS	Modified KDIGO	70	Patients with CS-AKIhad higher vasoactive-inotropic scores, longer operative times, and higher %FO than patients without CS-AKI. Increased CPB times and %FO were risk factors for the development of neonatal CS-AKI. Severe CS-AKI was associated with higher in-hospital mortality rate
Bennett et al, Preoperative levels of urinary uromodulin predict acute kidney injury after pediatric cardiopulmonary bypass surgery.[47]	2018	101	Pediatric CPB	Modified KDIGO	47	ROC analysis showed preoperative uUMOD strongly predicted postoperative AKI.
SooHoo et al, Acute kidney injury defined by fluid corrected creatinine in neonates after the Norwood Procedure.[9]	2018	95	Neonates Norwood procedure	KDIGO measured and fluid corrected creatinine	40–44	Correcting for FO increased the incidence of AKI and AKI severity; patients palliated with the mBTS had a 9.4 greater odds of fluid corrected AKI; a higher VIS on POD 0 was associated with fluid corrected AKI
Blinder et al, Acute kidney injury after pediatric cardiac surgery: A secondary analysis of the Safe Pediatric Euglycemia after Cardiac Surgery trial.[3]	2017	799	Age <3 y CS+CPB	AKIN	36	CS-AKI+patients were younger, underwent more complex surgery, and had longer CPB times. CS-AKI was associated with longer mechanical ventilation and ICU/hospital LOS and increased mortality.
Aydin et al, Acute kidney injury after surgery for congenital heart disease.[2]	2012	458	Age <18 y CS	RIFLE	51	Younger age, higher RACHS-1 category, and longer CPB time were associated with AKI. Incidence of AKI in <1 mo=61%, of which more than half required >72 h to recover. Use of CPB, lower preop serum creatinine, and higher preoperative BUN were associated with AKI; AKI was the only factor associated with longer ICU/hospital LOS
Short- and mid-/long-term kidney outcomes						
Van den Eynde et al, Risk factors for acute kidney injury after pediatric cardiac surgery: a meta-analysis.[32]	2022	19 680	Pediatric CS	AKIN, KDIGO, pRIFLE	34	Meta-analysis: AKI was associated with pulmonary hypertension, cyanotic heart disease, univentricular heart, RACHS-1 score ≥ 3, vasopressor use, CPB, reoperation, and sepsis

(*Continued*)

Table. Continued

Short-term kidney outcomes						
Study	**Year of publication**	**No.**	**Inclusion**	**AKI definition**	**AKI, %**	**Associated outcomes**
Van den Eynde et al, In hospital outcomes of acute kidney injury after pediatric cardiac surgery: A meta-analysis.[12]	2021	18334	Pediatric CS	AKIN, KDIGO, pRIFLE	32	Meta-analysis: CS-AKI was associated with higher rates of in-hospital death (OR, 7.22 [95% CI, 5.27–9.88]), need for RRT (OR, 18.8 [95% CI, 11.7–30.5]), cardiac arrhythmias (OR, 2.67 [95% CI, 1.86–4.80]), longer ventilation times, and PICU/hospital LOS
Sethi et al, Long-term renal outcomes in children with acute kidney injury post cardiac surgery.[17]	2021	2035	Pediatric CS+CPB 41-mo follow-up	KDIGO	10	AKI was associated with significantly higher urine NGAL, interleukin-18, KIM-1. No significant hypertension or proteinuria. Higher surgical complexity but not AKI was not associated with lower GFR at follow-up
Zappitelli et al (ASSESS-AKI), Acute kidney injury and risk of CKD and hypertension after pediatric cardiac surgery.[14]	2020	124	Age 1–18 y CS Interval follow-up 3–48 mo	KDIGO	46	Prospective follow-up: CKD 17%–20%; hypertension 22%–30%. AKI was not associated with CKD. AKI was associated with hypertension at 12 mo. Children aged <2 y at surgery had a significantly higher prevalence of hypertension during follow-up
Huynh et al, Follow-up after neonatal heart disease repair: watch out for chronic kidney disease and hypertension.[18]	2020	58	Neonatal CS 6-y follow-up	KDIGO	58	CKD 17%; hypertension 30% Postoperative cyanosis but not CS-AKI was associated with CKD
Hongsawong et al, Prevalence and associated factors of renal dysfunction and proteinuria in cyanotic congenital heart disease.[86]	2018	116	Age 1 mo to 15 y cyanotic CHD	NR	NR	Proteinuria 88%; albuminuria 41%; decreased GFR 32%
Hirano et al, Independent risk factors and 2-year outcomes of acute kidney injury after surgery for congenital heart disease.[85]	2017	418	Pediatric CS+2-y follow-up	pRIFLE	25	CS-AKI was associated with young age (<1 y), RACHS-1 score category ≥4, and long CPB time (≥90 min); 22% of patients with AKI died during the 2-y follow-up. The most significant contributor to risk of death was AKI
Madsen et al, Cardiac surgery in patients with congenital heart disease is associated with acute kidney injury and the risk of chronic kidney disease.[19]	2017	382	Age <15 y (77% <1 y) CS 5-y follow-up	KDIGO	33	5-y cumulative incidence of CKD in patients with CS-AKI 12% compared with 3% for patients without CS-AKI
Greenberg et al (TRIBE AKI), Kidney outcomes 5 Years after pediatric cardiac surgery: the TRIBE-AKI study.[62]	2016	131	Age 1 mo to 18 y CS+CPB 5-y follow-up	AKIN	44	CKD 18%; hypertension 17%; albuminuria 8%; GFR <90 13%
Long-term kidney outcomes						
Van den Eynde et al, Long-term consequences of acute kidney injury after pediatric cardiac surgery: A systematic review. [99]	2023	6701	Pediatric CS	AKIN, KDIGO, pRIFLE	21	Systematic review: 4 of 11 studies found a strong association between (absence of recovery from) CS-AKI and CKD; 3 of 5 studies found increased mortality rate in CS-AKI+; 1 of 4 studies found an association between AKI and hypertension at 1 y after surgery
Gillesen et al, Chronic kidney disease in patients with congenital heart disease: a nationwide, register-based cohort study.[21]	2022	71936	CHD age 0–47 y 13.5 y follow-up	NR	NR	CKD 6.4× higher in CHD compared with controls; highest in severe nonconotruncal defects

(*Continued*)

Table. Continued

Short-term kidney outcomes						
Study	Year of publication	No.	Inclusion	AKI definition	AKI, %	Associated outcomes
Cooper et al (FRAIL-AKI), Follow-up renal assessement of injury long-term after acute kidney injury.[84]	2016	372	Pediatric CS+CPB 7-y follow-up	pRIFLE	32	All patients had normal eGFR, proteinuria, and BP measurement at follow-up; Patients with AKI had higher urine concentrations of interleukin-18 and L-FABP than did patients without AKI

ADQI indicates Acute Disease Quality Initiative; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ARF, acute renal failure; BUN, blood urea nitrogen; CFB, cumulative fluid balance; CHD, congenital heart disease; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; CS, cardiac surgery; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; FO, fluid overload; GFR, glomerular filtration rate; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; KIM-1, kidney injury marker-1; L-FABP, liver-type fatty acid–binding protein; LOS, length of stay; mBTS, modified Blalock–Taussig shunt; NR, not reported; OR, odds ratio; PICU, pediatric intensive care unit; POD, postoperative day; RACHS, risk adjustment for congenital heart surgery; pRIFLE, Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease; RRT, renal replacement therapy; uUMOD, urinary uromodulin; and VIS, vasoactive inotrope score.

in urine output unreliable.[40,41] Furthermore, ascertainment of baseline serum creatinine in neonates can be challenging due to the persistence of maternal serum creatinine, slow postnatal maturation in kidney function or an early operation before the nadir occurs. For example, a neonate may undergo cardiac surgery on day of life 2, with a preoperative creatinine of 0.8 mg/dL and a postoperative day 2 creatinine of 1.08 mg/dL. While this neonate would not meet KDIGO stage 1 criteria, it stands to reason that this neonate demonstrates kidney injury and/or dysfunction. Fluid overload due to postoperative inflammation or heart failure may dilute serum creatinine, resulting in the underrecognition of AKI.[9,42] Thus, correcting creatinine for fluid balance has been shown to unmask AKI and strengthen the associations with poor kidney outcomes.[9,42] Finally, postoperative prophylactic peritoneal dialysis targeted at fluid balance management, when used, may lower creatinine through a small amount of clearance and mask creatinine-defined AKI.[41]

AKI Biomarkers and Subclinical Injury

Although not currently part of diagnostic criteria, the use of novel biomarkers, including urine neutrophil gelatinase–associated lipocalin (uNGAL), recently approved for use in critically ill children aged 3 months to 21 years by the US Food and Drug Administration, may aid in earlier identification and improved understanding of AKI severity in this population.[43] The 23rd Acute Disease Quality Initiative consensus group recommended incorporating urinary biomarkers into the existing KDIGO definition.[44] Biomarkers, including uNGAL, may allow the identification of AKI before a rise in serum creatinine and can potentially delineate specific subphenotypes of AKI. Subclinical injury, defined as damage without functional loss, is associated with worse kidney health and clinical outcomes.[45] We recently demonstrated that elevation of uNGAL in the presence of normal creatinine early after pediatric cardiac surgery was associated with day 2 to 4 AKI and increased hospital resource usage.[30] Higher concentrations of uNGAL have been shown to correlate with worse AKI and/or need for dialysis. A recent study of adults with hepatorenal syndrome demonstrated higher uNGAL to be associated with death and lower 90-day transplant-free survival.[46]

Urine uromodulin is another promising biomarker. In a recent study including children with congenital heart disease and normal estimated glomerular filtration rate (eGFR) for predicting AKI, researchers quantified urinary uromodulin levels immediately before CPB.[47] Despite a normal eGFR for both groups, 92% of patients in the lowest quartile for urine uromodulin concentrations developed AKI postoperatively, compared with only 8% in the highest quartile.[47] These studies suggest that while traditional markers of kidney function (eg, serum creatinine) may be normal in neonates and children with critical cardiac disease, biomarkers may prove more sensitive in the detection and early identification of AKI. However, it is unlikely that a single biomarker will be the "holy grail" for the identification of risk, subclinical injury, and ongoing tubular injury in follow-up. Therefore, adequate risk stratification and refinement of AKI diagnosis with multiple tools should be used to aid in prioritizing who would most benefit from long-term kidney follow-up.

In addition to assessing candidate biomarker values, quantifying kidney functional reserve is a promising, albeit not yet standardized, method to ascertain kidney health and fitness in high-risk patients.[48] Kidney functional reserve is the difference between the glomerular filtration rate measured at baseline and after protein stimulation.[49] A lack of kidney functional reserve has been demonstrated in certain medical conditions where a constant state of kidney hyperfiltration results in progressive damage.[50,51] Previous studies indicate that hyperfiltration may also contribute to the development of CKD in individuals with congenital heart disease,[20] making these patients an ideal population for

investigation of kidney functional reserve. In another study among adult patients undergoing elective cardiac surgery, preoperative kidney functional reserve was highly predictive of AKI.[52] Notably, an association of kidney function reserve with kidney outcomes in neonates with critical heart disease has yet to be published. In summary, the assessment of AKI-specific biomarkers and kidney functional reserve hold significant promise for adjudicating postoperative AKI risk. There is an opportunity to use these tools for clinical trial enrichment and aid in the prognostication of neonates with critical cardiac disease.

CKD and Need for Follow-Up

According to the 2024 Annual Data Report from the (National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases), more than 38 000 children in the United States with Medicaid insurance have broadly defined kidney disease. The most common comorbidities included hypertension (16%), obesity (11%), and anemia (11%).[53] Compared with the general population, in children with Medicaid in 2022, those with kidney disease were 15 times more likely to be hospitalized compared with those without kidney disease.[53] Cardiovascular disease is one of the most important and life-limiting complications of CKD in adults and children.[54,55] A seminal study of adults from 2 decades ago identified that the risk of death increased with a decline in eGFR.[54] Cardiovascular events, defined as hospitalization for coronary disease, heart failure, stroke, or peripheral artery disease, also increased with a decline in eGFR.[54] Cardiovascular disease is cited as one of the leading causes of death in children with advanced CKD and in young adults who developed CKD during their childhood. In the 2006 American Heart Association guidelines for reducing cardiovascular risk, CKD was stratified as the highest risk category for the development of cardiovascular disease.[56] A retrospective study using data from the US Renal Data Systems analyzed 1380 deaths among patients who started end-stage renal disease (ESRD) therapy as a child and died before age 30. Cardiac causes of death were categorized into 5 categories, including myocardial infarction, cardiac arrest, cardiomyopathy, arrhythmias, and others. The investigators found that cardiac-related deaths occurred in 23% of the population.[57]

Diabetes and hypertension are common causes of ESRD in adults and are strongly associated with other cardiovascular risk factors. In children, diabetes and symptomatic atherosclerosis are not often present at the time of CKD diagnosis. The causes of ESRD in children include congenital anomalies, inherited metabolic conditions, infections, and systemic diseases. The cause of cardiac death in children is most often reported secondary to cardiac arrest, followed by arrhythmia and cardiomyopathy, with myocardial infarction being rare. The mechanism by which CKD contributes to cardiovascular disease across the life span includes inflammation, abnormal blood pressure regulation, disordered bone and mineral metabolism, and vascular calcification.[58,59]

The number of patients with critical cardiac disease surviving to adulthood is increasing,[60,61] and thus, the prevalence of CKD is likely to increase. The current prevalence of CKD following neonatal AKI in those with critical heart disease is based on observational studies. It is now estimated that ≈30% to 50% of adult patients with acyanotic or cyanotic congenital heart disease have significantly impaired kidney function.[18,19,62] These data suggest that there is an urgency to monitor kidney health in this vulnerable population and identify ways to modulate the risk for progression to CKD. Young adults with congenital heart disease and an abnormal eGFR (<90 mL/min per 1.73 m^2) have worse survival compared with those with a normal eGFR (≥90 mL/min per 1.73 m^2).[63] In another study of patients with congenital heart disease who survived beyond age 65 years, the mortality risk associated with CKD was stronger than the association with heart failure, myocardial infarction, diabetes, and cancer.[64]

Unfortunately, follow-up after AKI is challenging, and rates are generally low. The TRIBE-AKI (Translational Research Investigating Biomarker Endpoints in AKI) study assessed kidney outcomes among children aged 1 month to 18 years at 5 years after cardiac surgery. Only 5 of the 131 patients assessed had been seen by a pediatric nephrologist.[62] At follow-up, 17% had hypertension, a rate that is 10 times higher than the general population, and 18% had CKD.[62] In addition, a recent review found that less than half of adult patients with the most severe form of AKI received specialized nephrology follow-up at discharge.[65] Some of the barriers to follow-up include failure to recognize or document AKI events in the medical record and inconclusive evidence of whether follow-up definitively improves outcomes, although a recent report from Taiwan demonstrated that those who underwent follow-up had a lower adjusted mortality rate and risk of major adverse cardiovascular events.[66] The FUSION (Nephrologist follow-up versus usual care after an acute kidney injury hospitalization: A randomized controlled trial) recently highlighted critical barriers to follow-up, where adult patients were randomized to receive usual care or early nephrology follow-up. Only a quarter of eligible patients consented to enrollment and randomization. Nonconsent reasons were captured and likely reflect real-life patient-centered challenges, including long travel times, hospital-related fatigue, the burden of multiple specialist visits, and lower prioritization of the AKI episode.[67] These challenges thus support our

recommendation for integrated KHA follow-up with the cardiologist and primary care physician for children with critical cardiac disease. In a 47-year population-based follow-up study of children with congenital heart disease from Finland, rates of follow-up were 99%; just over 40% of the 8600 eligible patients had a chronic condition necessitating medications.[68] Thus, opportunities for improving survival in neonates with critical cardiac disease exist, as has been demonstrated by the National Pediatric Cardiology Learning Network.[69] Intensive interstage monitoring and follow-up among patients with single-ventricle heart disease resulted in reduced admissions, decreased growth failure, and a lower mortality rate.[69] Integrating KHA into existing health care models like the National Pediatric Cardiology Learning Network has done with interstage monitoring has the potential to improve kidney-related outcomes.

Assessment of Kidney Health in Follow-Up

The 2012 KDIGO AKI guidelines recommend evaluating patients at least 3 months after AKI events for resolution or to identify new-onset or worsening of preexisting CKD[70] We recommend that a KHA include 3 key components: (1) appropriately obtained blood pressure, (2) assessment for microalbuminuria, and (3) kidney function tests including serum creatinine and cystatin C to allow calculation of eGFR. In addition, obtaining a kidney ultrasound before the index (neonatal) hospital discharge after birth is recommended to assess for congenital kidney anomalies and baseline kidney characteristics, including kidney size/volume.[71]

The American Academy of Pediatrics recommends early routine annual blood pressure (BP) measurements for infants with critical cardiac disease, those who are born prematurely or are of low birth weight, and/or are admitted to an intensive care unit, at each well-child visit before age 3 years given the increased risk of hypertension.[72] In addition, those with a history of AKI during the neonatal period may benefit from earlier and more frequent BP measurements.[72] BP measurements are often the mainstay of outpatient cardiology visits, aiding in the interpretation of progressive CKD, although hypertension may be related to underlying cardiac disease, so personalized management is necessary. In a small study, hypertension occurred with a prevalence of up to 17% of children 5 years after cardiac surgery[62] Hypertension (defined as BP ≥95th percentile for height, age, and sex) is a modifiable risk factor for the progression of CKD in children.[73] An appropriate technique for BP measurement is essential to diagnose hypertension accurately.[74]

While there are established criteria for measuring microalbuminuria, there is a lack of normative data for microalbuminuria in neonates, especially in cases of prematurity. As for kidney function assessment, there are a few important considerations. First, body surface area–adjusted eGFR values are only comparable to those of an adult after age 2 years. Second, measured glomerular filtration rate techniques, including inulin, iohexol, EDTA, or DTPA clearance, are often resource intensive, costly, and not universally available. Cystatin C is a functional kidney marker measured in the serum, increases independent of muscle mass, and can estimate kidney function in the setting of poor growth, thus making it useful in the follow-up of neonates and children with critical cardiac disease. Measurement of serum cystatin C is becoming more widely available in commercial and hospital-based laboratories and is increasingly used for monitoring eGFR in children with CKD.[75] Confirmatory testing in circumstances when eGFR based on serum creatinine alone is less accurate should be performed in alignment with KDIGO guidelines.[76] Considering these factors, it will be important to consider the use of published reference ranges for serum creatinine and cystatin C for children aged <1 year.[77–79] For children aged >1 year, there is a role for using pediatric glomerular filtration rate–estimating equations that use both cystatin C and creatinine, including the Chronic kidney Disease in Children U25 (https://ckid-gfrcalculator.shinyapps.io/eGFR/) and full age spectrum equations (https://kulak.kuleuven.be/egfr_calculator/).[80,81] The limitations of cystatin C should also be considered, where it can be altered in inflammatory states, thyroid dysfunction, or steroid use. Low muscle mass also affects cystatin C, particularly in adult patients with heart failure. Despite these limitations, the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial demonstrated the benefit of including cystatin C in estimating eGFR equations, where adult CKD patients with a lower eGFR using cystatin C–based equation had a significantly higher mortality rate. In addition, lower eGFR with creatinine–cystatin C compared with creatinine alone was associated with increased elevation of cardiac-specific biomarkers (NT-proBNP [N-terminal pro-B-type natriuretic peptide] and troponin) and worsening Kansas City Cardiomyopathy Questionnaire clinical summary score.[82] It has also been reported that greater discrepancies between creatinine and cystatin C estimating equations are associated with progression to ESRD and death in adults with mild to moderate CKD at study entry.[83] Comparative data in children, specifically those with critical cardiac disease, do not exist.

Biomarkers have been studied in children with a remote history of AKI. In a cross-sectional evaluation of children who had undergone cardiac surgery with CPB an average of 7 years prior and had normal eGFR, negative proteinuria, and normal blood pressure measurements, urinary kidney damage biomarkers were significantly higher in those who had experienced prior

AKI at long-term follow-up.[84] Thus, there may be utility in assessing AKI biomarkers for CKD, although more research is needed. Other studies have similarly assessed standard markers of CKD in follow-up of children who had undergone cardiac surgery.[19,85,86] The utility of neutrophil gelatinase–associated lipocalin, measured in the plasma, has also been evaluated as a prognostic marker in adult patients with heart failure. In a study of 562 adult patients with heart failure, higher plasma neutrophil gelatinase–associated lipocalin levels were associated with increased all-cause death, independent of CKD status, and outperformed both creatinine and cystatin C–based estimating equations in prognosticating outcomes.[87] Given the sparse data on the use of neutrophil gelatinase–associated lipocalin, measured in the urine and serum in follow-up in children with critical cardiac disease, we cannot recommend its routine use for prognostication in this population, and further studies are needed. Cardiac-specific biomarkers such as brain natriuretic peptide and NT-proBNP have been evaluated in children with CKD, both of which are abnormal compared with healthy controls.[88,89] Higher levels of both brain natriuretic peptide and NT-proBNP also correlated with an increased risk of cardiovascular events and subclinical myocardial damage, respectively.[88,89]

Evidence to Support Kidney Health Monitoring in Neonates at Risk for CKD

In children, multiple interventions have proven beneficial for delaying the progression of CKD. No data are isolated to children with critical cardiac disease. Herein, we describe seminal reports of therapies that delay CKD progression in children. Hypertension is known to accelerate and exacerbate the progression of CKD. The ESCAPE (Effect of Strict Blood Pressure Control and angiotensin converting enzyme inhibition [ACEi] on the Progression of Chronic Renal Failure in Pediatric Patients) trial demonstrated that intensified BP control delayed the progression of kidney function decline in children with CKD who received a fixed high-dose angiotensin-converting enzyme inhibitor.[90] In this study, there was a 35% reduction in the relative risk of losing 50% of kidney function or progression to ESRD within 5 years of ACEi therapy initiation.[90] The same group reported on the beneficial effects of ACEi for reducing proteinuria.[91] The investigators evaluated the initial proteinuria reduction from baseline to first measurement on ACEi (2.5±1.3 months) and then used Cox modeling to estimate the association between initial proteinuria reduction and the risk of reaching either a 50% decline in eGFR or ESRD. There was a 43% reduction in proteinuria with ACEi. There was also a significant reduction in reaching the end point relative to the degree of proteinuria reduction, independent of age, sex, CKD diagnosis, baseline eGFR, baseline proteinuria, initial BP, and BP reduction.[91]

Sodium–glucose cotransporter 2 inhibitors have been shown to offer kidney protection in adult patients with type 2 diabetes, especially when combined with ACEi or angiotensin receptor blockers.[92] A recent single-center retrospective study evaluated dapagliflozin's safety profile and effectiveness (sodium–glucose cotransporter inhibition) in children with CKD.[93] The investigators reported that over a 15-month period, there was stabilization of eGFR and a reduction in albuminuria and systolic BP in all patients.[93] Konduri and colleagues described their single-center experience of sodium–glucose cotransporter inhibition in children with single-ventricle heart disease and Fontan circulatory failure.[94] While they did not report on kidney function, the reduction in heart failure manifested as improved hemodynamics and cardiac index, which may translate into improved kidney function.[94] Further studies on the benefits of sodium–glucose cotransporter inhibition in children with critical cardiac disease are needed to evaluate the potential improvements in heart failure and whether kidney function is preserved. In summary, medications to delay the progression of CKD exist in children, and physicians should tailor the use of these medications to individual patients. Strict recommendations on the selection and prescription of the aforementioned medications are beyond the scope of this consensus document.

A Framework for Comprehensive Follow-Up in Critical Cardiac Disease (Suggestions)

We suggest that all at-risk and high-risk neonates with critical cardiac disease receive kidney-focused family education and counseling, with kidney-focused follow-up and ongoing risk assessment coordinated and synchronized with institutional-specific cardiac care.

Structured cardiac follow-up already exists for patients with critical cardiac disease. We recommend that all neonates with critical cardiac disease have a comprehensive KHA synchronized with institution-specific structured cardiac follow-up. Additionally, starting at index hospital discharge and continuing with every visit, we recommend that families receive education on the importance of kidney health, instruction to avoid nephrotoxic medications when possible, and advocating for outpatient BP checks at any health care encounter (*Recommendation Statement 1*). Patients with normal KHA (ie, normal BP measurements, normal serum creatinine, *and* normal kidney ultrasound) should have a repeat KHA every 2 years, which can be performed by the pediatric cardiologist. If concerns arise during the KHA, the patient should be referred to a pediatric nephrologist for follow-up.

There may be a subset of neonates with critical cardiac disease at even greater risk for AKI development, defined earlier in this review. In addition to the KHA and family education before discharge, we suggest that these patients have a repeat KHA every 6 months until at least age 2 years. Additionally, we recommend that these children have a consultation with a pediatric nephrologist by age 1 year of age or sooner, at the discretion of either the pediatric cardiologist or nephrologist (*Recommendation Statement 1*).

Expanding Our Knowledge on the Timely Diagnosis of Kidney Disease (Research Priorities)

Research Priority 1: Identification of Diagnostic Criteria That Integrate Biomarkers to Delineate Cardiac-Specific AKI Subphenotypes (Figure 3)

Timely AKI recognition and diagnosis are challenging in the critical cardiac disease population because of the heterogeneous nature of the studies on AKI, as well as the previously discussed limitations of serum creatinine and quantification of urine output. As such, it is imperative that diagnostic criteria capture adequate prognostic importance. Studies using predictive and prognostic enrichment strategies, leveraging novel biomarkers of AKI and CKD in the critical cardiac disease population, are an important step in optimizing the identification of neonates at risk for long-term consequences of AKI.[95] Subphenotypes, or classes within a heterogeneous population of individuals with a disease who share distinct characteristics, have been identified in adult patients with septic shock and AKI who respond differently to therapies.[96,97] The ability to identify subphenotypes of AKI within the neonatal cardiac population may improve risk prognostication and could inform just-in-time therapies and follow-up cadence in the future.

Research Priority 2: Identify Perioperative Best Practices That Decrease the Burden (Incidence, Severity, and Duration) of AKI and Associated Poor Outcomes (Figure 3)

While many risk factors are associated with the development of cardiac surgery–related AKI, several inherent patient factors are nonmodifiable. Modifiable intraoperative factors that are associated with subsequent AKI are understudied, especially in this vulnerable population. Anesthetic approach, use of modified ultrafiltration intensity and timing, CBP duration, BP goals, vasoactive support, fluid management strategies, and transfusion thresholds have all been identified as potential modifiable factors. We believe these should be studied in a multicenter prospective fashion, through qualitative or mixed-methods approaches, to

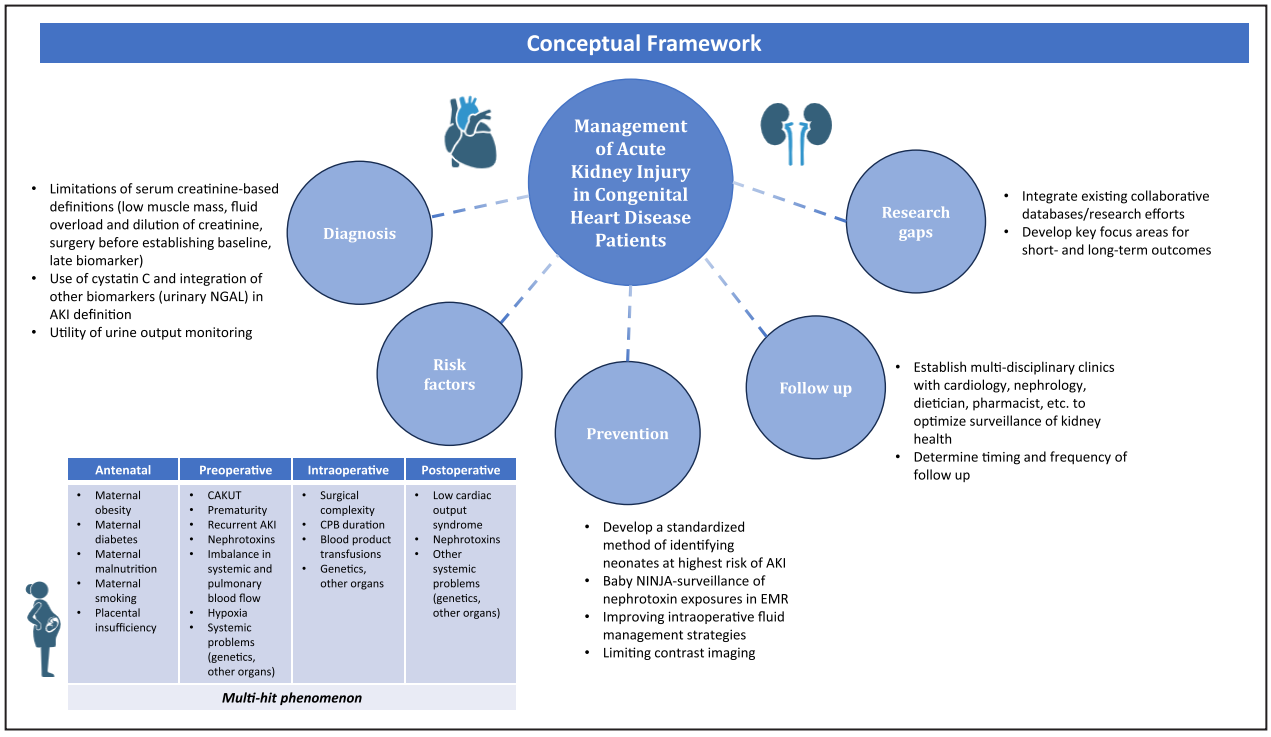

Figure 3. Conceptual framework for the comprehensive management of acute kidney injury in critical heart disease including diagnosis, risk factors, prevention, follow-up, and research gaps.
AKI indicates acute kidney injury; CAKUT, congenital anomalies of the kidneys and urinary tract; EMR, electronic medical record; and NGAL, neutrophil gelatinase-associated lipocalin.

identify and then adopt perioperative best practices to reduce cardiac surgery–associated AKI.[1,33]

Research Priority 3: Development of Prospective Multicenter Investigations Evaluating the Epidemiology of the Development of CKD in the Critical Cardiac Disease Population, Including the Development of Risk Stratification Tools for Progression to CKD (Figure 3)

Recently, the National Institutes of Health convened a National Heart, Lung, and Blood Institute workshop entitled "The Future of Pediatric Cardiovascular Research," which identified inefficient collaboration across data platforms and a lack of comprehensive clinical research strategies as gaps in advancing cardiovascular care in pediatrics.[98] Partnering with existing research collaboratives dedicated to the evaluation of the delivery and quality of care among patients with cardiac disease can provide the infrastructure for prospective investigations and meet these 2 major gaps in research. Specific opportunities exist to leverage the follow-up infrastructure to implement screening programs that will better define the epidemiology of the development of CKD in this population, allowing for the development of risk stratification tools.

Research Priority 4: The Start, Cadence, and Duration of Kidney-Focused Follow-Up in Neonates With Congenital Heart Disease Should Be Investigated (Figure 3)

Because survival into adulthood is now common and the risk of development of CKD is enduring among neonates with critical heart disease, the burden of follow-up must be delineated to optimize health throughout life. Leveraging natural variation in institutional care models, large administrative data sets, and emerging machine-learning technologies, we can evaluate existing structured follow-up and identify areas to fill gaps in care. With this and the engagement of family partners, we can delineate the optimal cadence and duration of kidney-focused follow-up of neonates with critical cardiac disease, as this is currently based on expert consensus rather than published data.

CONCLUSIONS

In conclusion, neonates with critical cardiac disease are at high risk for AKI and CKD. With improved survival to adulthood, neonates with critical cardiac disease are increasingly vulnerable to kidney-related complications. We outline consensus recommendations for a comprehensive KHA at discharge and follow-up for standard and high-risk neonates. We also identify important gaps in the literature that would be best investigated in a multicenter fashion.

APPENDIX

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Drs Starr, Selewski, Harer, Ambalavanan, Slagle, Askenazi, Gist, Menon, Defrietas, and Charlton reported serving on the board of the Neonatal Kidney Collaborative. Dr Starr reporting receiving funding from the National Institutes of Health (NIH) and the Gerber Foundation outside the submitted work. Dr Harer reporting receiving funding from the NIH outside the submitted work. Dr Steflik reported receiving grants from Baxter outside the submitted work. Dr Ambalavanan reported receiving grants from the NIH during the conduct of the study as well as serving on the data and safety monitoring board for Oak Hill Bio and serving as medical advisor to ResBiotic/AlveolusBio outside the submitted work. Dr Fuhrman reporting receiving funding from the NIH outside the submitted work. Dr Kwiatkowski reported receiving grants from NIH during the conduct of the study. Dr Menon reported receiving grants from the Gerber Foundation outside the submitted work. Dr Rumple reporting receiving funding from the Arkansas Biosciences Institute, the National Center for Advancing Translational Sciences of the NIH, and the Marion B. Lyon New Scientist Development Award through the Arkansas Children's Research Institute outside the submitted work. Dr Sanderson reporting receiving funding from the NIH/National Institute on Diabetes and Digestive and Kidney Diseases (NIDDK) outside the submitted work. Dr Schuh reported receiving research funding from Otsuka and the NIH/NIDDK outside the submitted work. Dr Segar reported support for a study from Medtronics and funding from the NIH outside the submitted work. Dr Slagle reported receiving personal fees from Mozarc Medical and Bioporto outside the submitted work. Dr Soranno reported receiving funding from the NIH outside the submitted work. Dr Charlton reported receiving grants from the NIH and the NIDDK, being an investor in Zorro-Flow, and consulting for Medtronics outside the submitted work. Dr Gist reported receiving consulting fees from Bioporto Diagnostics and Potrero Medical aswell as receiving grants from Gerber Foundation outside the submitted work. Dr Askenazi reported receiving personal fees from Nuwellis, Abbott, and Seastar; grants from Nuwellis, Bioporto, Leadiant, and Seastar; has a patent for Zorro-Flow; and being the founder and chief scientific officer of Zorro-Flow outside the submitted work. No other disclosures were reported.

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