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Acute Kidney Injury and Fluid Overload in Pediatric Cardiac Surgery

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Abstract

Purpose of Review: Acute kidney injury (AKI) and fluid overload affect a large number of children undergoing cardiac surgery, and confers an increased risk for adverse complications and outcomes including death. Survivors of AKI suffer long-term sequelae. The purpose of this narrative review is to discuss the short and long-term impact of cardiac surgery associated AKI and fluid overload, currently available tools for diagnosis and risk stratification, existing management strategies, and future management considerations.

Recent Findings: Improved risk stratification, diagnostic prediction tools and clinically available early markers of tubular injury have the ability to improve AKI-associated outcomes. One of the major challenges in diagnosing AKI is the diagnostic imprecision in serum creatinine, which is impacted by a variety of factors unrelated to renal disease. In addition, many of the pharmacologic interventions for either AKI prevention or treatment have failed to show any benefit, while peritoneal dialysis catheters, either for passive drainage or prophylactic dialysis may be able to mitigate the detrimental effects of fluid overload.

Summary: Until novel risk stratification and diagnostics tools are integrated into routine practice, supportive care will continue to be the mainstay of therapy for those affected by AKI and

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Conflicts of Interest

There are no conflicts of interest.

Human and Animal Rights and Informed Consent

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fluid overload after pediatric cardiac surgery. A viable series of preventative measures can be taken to mitigate the risk and severity of AKI and fluid overload following cardiac surgery, and improve care.

Keywords

acute kidney injury; congenital heart disease; cardiac surgery; fluid overload

Introduction

Acute kidney injury (AKI) is common among critically-ill adult and pediatric patients. A recent large multi-national study among critically ill children admitted to the pediatric intensive care unit reported an overall AKI incidence of 27%. Severe AKI incidence, defined as Kidney Disease Improving Global Outcome (KDIGO) stage 2 or 3 occurred in 11.6% of patients (1, 2). Severe AKI in this study conferred increased odds of 28-day mortality (2●). Similarly, in a multi-national study of neonates admitted to a level 2 or 3 neonatal intensive care unit, AKI incidence was 30%, varied by gestational age, and conferred a greater risk for longer length of stay and mortality (3●). AKI after congenital heart surgery is common, with an incidence ranging from 20-60% (4-8). This wide variation in incidence is related to subject selection and the definition of AKI utilized. In fact, a recent multicenter report from the Neonatal and Pediatric Heart and Renal Outcomes Network reported significant center variability in AKI incidence among neonates undergoing cardiac surgery using the modified KDIGO definition (9●). AKI also confers a significantly greater odds of death in patients after cardiac surgery (10, 11).

Cardiac surgery associated AKI (CS-AKI) is unique from other causes of AKI. A known period of ischemia-reperfusion injury and hypothermia with concomitant host maladaptive inflammatory responses and oxidative stress occur during and after cardiopulmonary bypass. Endothelial dysfunction, capillary leak and vasomotor instability ensue. These factors contribute to ongoing kidney tubular injury (12, 13). Unfavorable intra or post-operative hemodynamics, low cardiac output syndrome, fluid overload and the concurrent use of nephrotoxic medications have the potential to worsen the already present tubular injury. A relative reduction in effective circulating volume in the presence of low cardiac output stimulates the kidneys to reabsorb salt and water ultimately leading to oliguria. Administration of resuscitation fluids leads to progressive fluid overload that independently and synergistically (with AKI) leads to worse outcomes (6●●, 14●-18). Together, CS-AKI is a syndrome carrying significant risks for patients and these risks are bidirectionally deleterious.

The purpose of this narrative review is to discuss the short and long-term impact of cardiac surgery associated AKI and fluid overload, currently available tools for diagnosis and risk stratification, existing management strategies, and future management considerations. We also provide a framework for consideration in these high-risk patients (Figure 1).

Short and long-term complications and outcomes of AKI: A systemic disease

AKI confers an increased risk for both short and long-term adverse outcomes including death, longer duration of mechanical ventilation and hospitalization, irrespective of the underlying cause (4-8, 10). Infants, children and adults who develop acute kidney injury (AKI) after cardiopulmonary bypass (CPB) have at least a 5 times greater odds of dying compared to similar patients without AKI (5, 19, 20). These adverse effects are so significant that each episode of AKI imposes a substantial increase in health care costs (21-23).

The most well-known complications of AKI, including hyperkalemia, uremic platelet dysfunction and fluid overload can be managed with renal replacement therapy. However, it is now widely recognized that AKI is a systemic disease that predisposes patients to a variety of other complications for which renal replacement therapy is not helpful (24●). These systemic complications including sepsis, increased infection risk, respiratory failure and heart failure, are responsible for the high rate of death in patients with established AKI (25-30). This paradigm suggests that reducing the morbidity and mortality of AKI will require prevention and management of these complications.

In pediatric cardiac surgery, there are several established factors that increase the risk for CS-AKI. These include younger age at surgery, higher surgical complexity, presence of cyanotic lesions, longer cardiopulmonary bypass duration (typically greater than 180 minutes), use of hypothermic circulatory arrest, fluid overload, and higher vasoactive requirements in the immediate post-operative period (7, 17, 31-33). In adults, identification of risk factors for the prediction of Major Adverse Kidney Events within 30 days (MAKE30), a composite outcome of persistent renal dysfunction, new renal replacement therapy and in-hospital mortality may allow for improved risk stratification, target therapy and facilitate the conduct of clinical trials. The risk of Major Adverse Cardiovascular Events (MACE) are highlighted by the hazard of death in adults who developed AKI after myocardial infarction being 3 to 7 times greater than in those without AKI (34).

While the immediate effects of CS-AKI can be detrimental, the long-term effects are also cause for concern. Repeated episodes of CS-AKI from a variety of causes, including unfavorable hemodynamics and high nephrotoxin burden may lead to acute and chronic kidney disease (CKD) (35-37). In the Follow-up Renal Assessment of Injury Long-Term After AKI (FRAIL-AKI) study, there was no difference in measures of CKD (glomerular filtration rate, proteinuria, and blood pressure) between those with and without AKI, but AKI positive patients had persistent elevation of urinary AKI biomarkers seven years after the initial CS-AKI event (35). The multicenter TRIBE-AKI study reported CKD and hypertension 5 years after pediatric cardiac surgery, but this was not associated with perioperative AKI (36). The data do demonstrate, however, even those who have complete recovery of AKI are still at risk for long-term morbidity such as infectious complications, MACE, and mortality (29, 38-40). Studies also show that patients with one prior episode of AKI after pediatric cardiac surgery may be at risk for subsequent AKI episodes (41, 42). Multiple AKI episodes may also increase the risk for earlier onset CKD.

AKI and Fluid Overload, Synergistic and Problematic?

AKI and fluid overload (FO) demonstrate the physiology of bidirectional risk(43●●). The kidney is sensitive to expansion of the interstitial space and increased venous pressure, resulting in increased renal subcapsular pressure and lowered renal blood flow and glomerular filtration rate. Concurrently, decreased glomerular filtration rate and tubular dysfunction during AKI predisposes patients to volume retention and fluid accumulation. FO alone, or in conjunction with AKI is detrimental to patient outcomes (6, 44). It is associated with longer duration of ventilatory support, hospital stay, and higher risk of infection. Increased FO at initiation of renal replacement therapy in the intensive care unit has been associated with increased risk of death in both adults (45) and children (46, 47). In a recent secondary analysis of the prospective observational AKI in Children Expected by Renal Angina and Urinary Biomarkers (AKI-CHERUB) study, intensive care unit length of stay was significantly longer in the phenotypic classification of FO and AKI positivity after adjusting for severity of illness (14). In this same study, FO in the absence of AKI increased the odds of death (48). Finally, correcting creatinine for fluid balance may refine diagnosis and unmask AKI associated with associated significant complications. Thus, earlier initiation of interventions for fluid removal has the potential to decrease morbidity and mortality.

The traditional approach to post-operative FO often encompasses the administration of an intravenous diuretic either as intermittent bolus dosing or a continuous infusion. Loop diuretics such as furosemide and bumetanide are the most common first line agents with thiazide diuretics used for their synergistic effect with loop diuretics. Although the traditional dogma of diuretic use remains pervasive in the post-operative period, new experiences with peritoneal dialysis may mitigate FO in the initial post-operative period and are discussed further in the management section.

Diagnostics: Limitations of current modalities render opportunities for improvement

Existing diagnostic modalities render an imprecise definition of AKI. For example, serum creatinine during the first few days of life reflects maternal levels (48), thus there is inherent difficulty in defining a baseline for determination of the magnitude of rise in post-operative creatinine and possible misclassification of tubular injury. The co-existence of FO may mask AKI diagnosis because serum creatinine is diluted as demonstrated in 2 prior neonatal studies. Correction of creatinine for the degree of fluid overload leads to more sensitive detection of AKI and has strengthened the association of CS-AKI with poor outcomes (15, 16). The multifactorial etiology of CS-AKI has made prevention and/or treatment challenging. To date, there is no single or consistently effective therapy for AKI, and supportive care continues to be the mainstay of management. Some of the lack of efficacy of the published studies may be due to limitations in appropriately stratifying and enrolling those most at risk for developing AKI, as well as limitations in the diagnostic methodology, specifically as they relate to the limitations of creatinine.

Alternative strategies that identify AKI, or the risk for AKI before a rise in serum creatinine have the potential to improve outcomes through improved risk stratification and optimization of medical management. The renal angina index (RAI) is a context driven bedside tool that combines AKI risk factors and early signs of kidney injury for use in critically ill children (49). The RAI provides clinicians with tools to expedite AKI recognition on the day of admission for those at greatest risk for suffering day 3 AKI after intensive care unit (ICU) admission (49). Incorporation of urine NGAL into the RAI model significantly enhanced the predictive performance for day 3 AKI (50). Unfortunately, RAI utilization is not appropriate for assessment of AKI risk following pediatric cardiac surgery. Recent derivation and validation of a vasoactive-ventilation-renal score was found to be predictive of duration of mechanical ventilation and ICU length of stay encompasses creatinine measures (51, 52). Derivation of a cardiac renal angina index that encompasses pre-, peri and post-operative risk factors as well as early signs of kidney injury may facilitate improved AKI diagnostic precision, especially when combined with clinically available urinary biomarkers.

Markers of actual renal function may afford a more precise description of tubular injury. The action of furosemide requires the functional elements of proximal tubular migration, intraluminal transport, and handling at the basolateral membrane of the loop of Henle; a standardized assessment of the response to furosemide may offer clues to renal dysfunction. The furosemide stress test is a standardized assessment of urine output in response to a dose of furosemide. When tested in critically ill adults, urine flow rate at 2 and 6 hours after an index dose of furosemide was able to discriminate AKI progression and need for renal replacement therapy, and was superior to serum or AKI urinary biomarkers (53). Furosemide use is ubiquitous after pediatric cardiac surgery, and several pediatric cardiac surgery studies have demonstrated that lower urine output following furosemide administration was independently associated with subsequent CS-AKI and longer length of stay (54●-56). Ongoing prospective pediatric trials will likely better elucidate the dose response related to furosemide and aide in ongoing diagnosis of CS-AKI and management in the post-operative period.

Despite the widespread literature on the use of AKI biomarkers, only 2 are currently available for clinical use: neutrophil gelatinase associated lipocalin (NGAL) and the product of tissue inhibitor matrix metalloproteinase-2 and insulin like growth factor binding protein-7, (TIMP-2*IGFBP-7). There are many studies assessing the timing and predictive performance of both NGAL and TIMP-2*IGFBP-7 after pediatric cardiac surgery (57, 58), but incorporation into clinical practice is limited because of the availability of testing platforms within clinical laboratories. Varnell *et al* recently reported on the clinical utility of urine NGAL utilization in clinical practice in which several cases are presented in non-cardiac surgical patients, and found it to be helpful in risk stratifying patients for need for dialysis or separating from dialysis (59).

Existing Management Strategies of AKI and Fluid Overload: Some more effective than others

Numerous clinical trials have been conducted in order to assess the efficacy of a variety of pharmacologic interventions for the prevention and/or treatment of AKI. A summary of these trials is included in Table 1.

Fenoldapam, a selective dopamine-1 receptor agonist was administered to neonates (60) and infants (61) undergoing cardiac surgery. High dose fenoldapam utilization during biventricular repair (61) was associated with decreased diuretic and vasodilator utilization and the reduction in urinary levels of NGAL and cystatin C. Low dose fenoldapam in neonates did not augment urine output or reduce AKI incidence (60).

Aminophylline is a methylxanthine nonselective adenosine receptor antagonist that has been shown to increase glomerular blood flow. Intravenous theophylline administration carries a class 2B indication for neonates with severe perinatal asphyxia that are at high risk for AKI (1). Two recent clinical trials randomized patients to receive aminophylline for AKI prevention (62) or for the treatment of oliguria (63). Overall, there was no perceived benefit of aminophylline use after pediatric cardiac surgery.

The benefits of methylprednisolone/corticosteroids have also been explored for the prevention of AKI, with no perceived benefit (64-67). These data are supported by a recent large (n=7286) randomized controlled trial of adult patients undergoing cardiac surgery with cardiopulmonary bypass in which no benefit was demonstrated when steroids were administered for the prevention of CS-AKI in patients with moderate to high-risk of perioperative death (68). The role of acetaminophen and dexmedetomidine have also been evaluated in pediatric cardiac surgery patients (69-72). There appears to be a reduction in both AKI incidence and severity with both treatment strategies. However, for dexmedetomidine use, there was either no assessment on the impact of outcomes (71), or there was no effect on outcomes at all (72).

Despite these existing randomized controlled trials and retrospective studies assessing the benefits of a variety of pharmacologic therapies for AKI prevention and treatment, a recent meta-analysis found no firm evidence of the protective roles of the studied medications for pediatric patients undergoing cardiac surgery (73). With this, we continue to be left with supportive care strategies in these high-risk patients undergoing cardiac surgery.

Some patients experience complications after cardiac surgery that necessitate additional imaging such as contrast computed tomography or diagnostic/interventional cardiac catheterization. Both modalities utilize contrast, which can be associated with contrast induced nephropathy. Pediatric patients with existing AKI or marginal hemodynamics may be at risk for AKI progression with contrast exposure. The PRESERVE (Prevention of Serious Adverse Events Following Angiography) trial was a prospective randomized controlled trial that tested the effects of isotonic sodium bicarbonate versus intravenous isotonic saline and oral N-acetylcysteine versus oral placebo on the prevention of a composite outcome of need for urgent renal replacement therapy, 90-day acute kidney

disease and 90-day mortality (74). The study was terminated early due to lack of benefit in an interim analysis among patients at high risk for composite outcome (74). Thus, current strategies for these patients have shifted toward hydration and avoidance of concurrent nephrotoxic medications.

Early identification and mitigation of FO is crucial in the management of the post-operative patient. Strict monitoring of intake and output, daily weights, and careful mitigation of excess volume administration when able is a crucial aspect of the early post-operative management plan. Several studies have shown potential benefit related to the early use of prophylactic peritoneal dialysis in high-risk patients undergoing cardiac surgery (Table 2). Use of a peritoneal catheter for passive drainage or dialysis has been associated with a decreased duration of mechanical ventilation, improved urine output, lower vasoactive medication needs and earlier time to negative fluid balance (75-80). Kwiatkowski *et al* performed a single center randomized controlled of furosemide versus prophylactic peritoneal dialysis in high-risk patients less than 6 months of age who were undergoing cardiac surgery (80●●). Patients were randomized based on 4 hours of oliguria (<1ml/kg/hour) during the first 24 post-operative hours. In this study, patients randomized to furosemide were 3 times more likely to develop >10% fluid overload, 3 times more likely to require prolonged mechanical ventilation and 1.6 times more likely to have a prolonged ICU length of stay. This was accompanied by a greater need for electrolyte replacement. There was no difference in mechanical ventilation duration and mortality between groups (80). A separate study by Ryerson and colleagues evaluated the time to negative fluid balance and outcomes in a cohort of neonates undergoing the Norwood operation (81). Patients who received a peritoneal catheter for either passive drainage or prophylactic dialysis did not achieve a faster time to negative fluid balance or difference in outcomes. In fact, nearly 50% of the patients with a peritoneal catheter experienced adverse events including cardiac arrest (81). These studies highlight the heterogeneity in outcomes and provides pause for a one-size-fits-all approach to fluid removal through utilization of passive peritoneal drainage or prophylactic peritoneal dialysis in pediatric cardiac surgery.

Invariably a select group of patients will need renal replacement therapy despite judicious attempts at fluid management using either diuretics, passive peritoneal drainage or prophylactic peritoneal dialysis. Continuous renal replacement therapy (CRRT), of which continuous veno-venous hemodiafiltration (CVVHDF) is the most commonly utilized modality, allows for minute to minute adjustment in fluid removal rates which may be preferable for the hemodynamically unstable patient in the cardiac ICU. In addition, mitigation of azotemia and electrolyte dyscrasia is often easier with CRRT when compared with PD as rapid adjustments may be made to the dialysate and filtration rates. Although CRRT requires central venous access, it does not require an abdominal surgery.

Aquapheresis is a new modality which is gaining increasing traction for removal of fluid/ultrafiltration in the smallest of patients in which either two, single-lumen catheters or a slightly larger double-lumen catheter can be used to achieve adequate fluid removal (82). Benefits of this therapy include lower priming volumes with tolerance of lower flow rates. Although large trials studying the efficacy of this technology are ongoing, aquapheresis may

provide a unique opportunity for mitigation of FO in the appropriately selected patient (82, 83).

Next Generation Management Strategies: Opportunities to improve outcomes

Extraction of data from the electronic health record (EHR) and real-time incorporation into clinical decision support tools may allow us to successfully prevent AKI entirely, or prevent its progression to a more severe stage. Tools which alert the clinician to AKI diagnosis may also enhance apparent awareness of factors known to increase AKI severity through implementation of specific care bundles. A recent retrospective study reported that community-acquired AKI diagnosis was missed in 93% of patients who presented to a large quaternary care pediatric emergency department (84). Development of AKI alert tools accompanied by care bundles have shown to be beneficial in adult studies across a wide variety of disease states (85, 86). With respect to AKI, the implementation of a small set of reliably executed practices to minimize nephrotoxic injury, prevent volume overload, promote prompt treatment of underlying conditions and minimize nephrotoxin exposure can be incorporated into a care bundle to promote best practice (86). Recent studies have shown that proper implementation of care bundles in adult populations can lead to lower in hospital mortality and lower incidence of AKI progression (87). Wang *et al* recently reported on an EHR-based predictive model that would identify patients in whom serum creatinine testing should be performed (88). They derived separate models for ICU and non-ICU patients that were not reliant on existing creatinine measures, but rather incorporated variables that were associated with development of AKI. The c-statistic for both models was in the 0.7 range suggesting good model performance (88). Incorporating such a model across different EHR's may be challenging and costly and is not yet ready for clinical use.

Finally, a quality improvement program targeting reduced nephrotoxin exposure implemented across a non-ICU cohort of children has demonstrated the ability to reduce both exposure rate and AKI incidence (37, 89, 90). EHR based nephrotoxin medication alert tools are already in place in some pediatric hospitals. There has been both an initial and sustained reduction in AKI incidence utilizing these tools in the non-intensive care unit setting (89, 90). Incorporation and assessment into the cardiac intensive care unit may provide additional tools to mitigate AKI incidence and severity. Because nephrotoxin medication exposure is potentially modifiable, there is the potential to reduce post-operative AKI incidence if addressed in at-risk patients. A recent retrospective study evaluated the epidemiology of nephrotoxin exposure and nephrotoxin-associated AKI among children undergoing cardiac surgery (91). In this study, at least one nephrotoxin was used in 85% of patients, with 20% receiving ≥ 3. While AKI occurred more commonly in those exposed to ≥ 3 nephrotoxins, there was no independent association with nephrotoxin use on AKI suggesting the multifactorial etiology of AKI in this population (91). Future incorporation of nephrotoxin medication alert systems that leverage the EHR have the potential to reduce AKI incidence and severity in the highest risk patients.

Conclusion

In conclusion, AKI is common after pediatric cardiac surgery and significantly impacts short and long-term outcomes. Current pharmacologic therapies have failed to show any benefit in AKI prevention and treatment. Improved AKI diagnostics and risk stratification in conjunction with next generation management strategies have the potential to improve both AKI incidence and outcomes.

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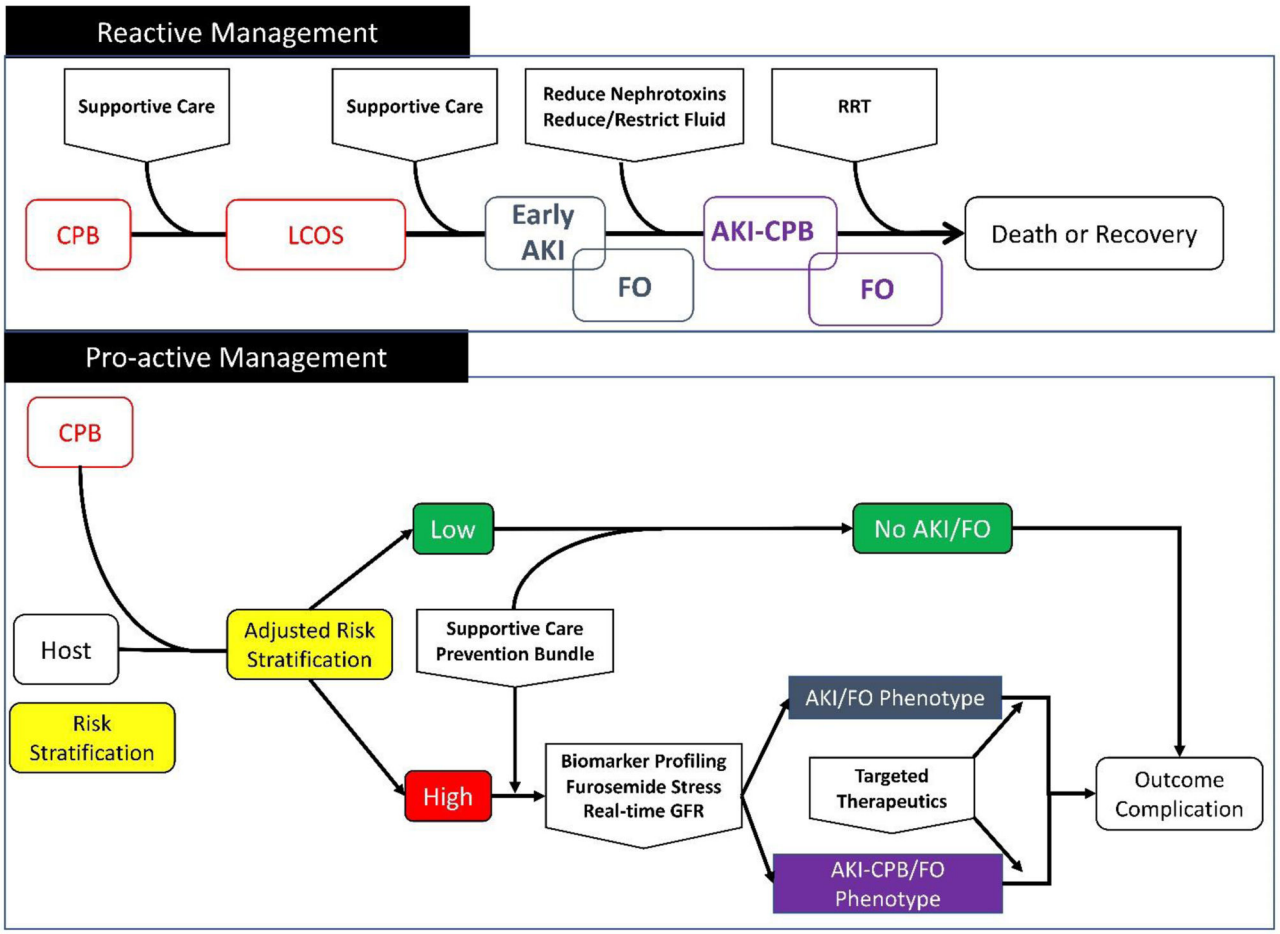

Figure 1. Framework for risk stratification, improved diagnostic prediction tools and laboratory measures and treatment strategies for AKI and its complications.

In this construct, the presence of fluid overload independently and synergistically (with AKI) leads to worse outcomes.

AKI = acute kidney injury, RRT = renal replacement therapy, LCOS = low cardiac output syndrome, CPB = cardiopulmonary bypass. Adapted with permission from RK Basu.

Table 1:

Pharmacologic Interventions for Acute Kidney Injury

Study	Journal	Year	Study Type	Sample Size	Findings
Fenoldopam					
Ricci et al (60)	Interact Caridovascular and Thoracic Surgery	2008	RCT	40	· Low dose fenoldopam was well tolerated in a selection of neonates following CPB. There was no change in AKI, volume overload, or urine output
Ricci et al (61)	Crit. Care	2011	RCT	80	· High dose fenoldopam during CPB decreased urinary NGAL, Cystatin C, and reduced used of vasodilators and diuretics during CPB in biventricular repair
Aminophylline					
Onder et al (63)	Peds. Crit Care	2016	Retro. Cohort	200	· Intraoperative aminophylline was more effective than furosemide in reversal of oliguria in the early post operative period. Less renal replacement was used in the aminophylline group
Axelrod et al (62)	Peds. Crit Care	2016	RCT	144	· Placebo controlled trial showing no difference in rates of acute kidney injury using aminophylline following CPB
Acetyl Cysteine					
Weisbord et al (74)	NEJM	2018	RCT	4993	· In high risk adult patients undergoing angiography the use of acetyl cysteine and bicarbonate did not change rates of death, renal replacement, or kidney injury
Steroids					
Jahnukainen et al (64)	Anaesthesiologica Scandinavica	2017	RCT	40	· Patients randomized to steroids following CPB had decreased inflammatory markers but no change to AKI rates when compared with placebo
Pesonen et al (65)	Peds Critical Care Med	2016	RCT	36	· Methylprednisolone prior to cardiopulmonary bypass leads to profound decreases in NGAL
Dalili et al (66)	Res Cardiovasc Med	2015	RCT	100	· Single dose methylprednisolone following tetralogy of fallot repair does not significantly change outcomes
Bronicki et al (67)	Ann Thoracic Surgery	2000	RCT	28	· Dexamethasone administration prior to CPB leads to decreased troponin I levels
Keski-Nisula et al (92)	Ann Thoracic Surgery	2013	RCT	40	· Methylprednisolone prior to cardiopulmonary bypass leads to decreased inflammatory response but no improvement in clinical outcome
Dexmedetomidine					
Kwiatkowski et al (72)	Pediatric Critical Care Medicine	2016	Retro. Cohort	204	· Pediatric patients receiving dexmedetomidine following cardiac surgery had lower rates of AKI but no change in outcomes

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Jo et al (71)	2017	RCT	29	· Intraoperative dexmedetomidine during pediatric cardiac surgery may decrease rates AKI and suppress post-bypass eGFR decline

Table 2:

Peritoneal Dialysis in Pediatric Cardiac Surgery

Study	Journal	Year	Study Type	Sample Size	Findings
Sorof et al (93)	Peds. Nephrology	1999	Case-Control	20	· Improved urine output and decreased vasoactive need with PD
Alkan et al (77)	Am Soc. For Artificial Internal Organs Journal	2006	Case-Control	756	· Improved fluid balance, decreased vasoactive need with prophylactic PD
Saini et al (79)	European Journal of Cardio-Thoracic Surgery	2011	Retro. Cohort	36	· Passive PD drainage promotes negative fluid balance following AVSD repair
Bojan et al (75)	Kidney International	2012	Retro. Cohort	146	· Early PD showed decreased 30- and 90-day mortality
Ozker et al (94)	Renal Failure	2012	Retro. Cohort	82	· In patients undergoing arterial switch, patients who received PD drains had longer hospital stay and delayed sternal closure
Madenci et al (95)	Journal of Thoraacic and CV Surgery	2013	Retro. Cohort	28259	· In a large retrospective cohort patients receiving PD had higher mortality. These patients were younger, had higher rates of CPB, and higher rates of renal failure
Kwiatkowski et al (96)	Journal of Thoracic and CV Surgery	2013	Retro. Cohort	84	· Early PD placement showed more negative fluid balance, fewer electrolyte corrections, and earlier extubation
Sasser et al (97)	Congenital Heart Disease	2014	Pro. Cohort	52	· Early PD showed more negative fluid balance, lower inotrope scores, and decreased inflammatory cytokines
Ryerson et al (81)	Congenital Heart Disease	2014	RCT	22	· Prophylactic PD did not lead to more negative fluid balance in a population following Norwood procedure
Kwiatkowski et al (80●●)	JAMA Peds	2017	RCT	73	· Prophylactic PD compared to diuretics led to more negative fluid balance, shorter duration of mechanical ventilation, and fewer electrolyte abnormalities

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