Review

Author for correspondence:
Elizabeth J. Thompson, MD, Department of Pediatrics, Duke University School of Medicine, PO Box 17969, Durham, NC 27715, USA.
Tel: 919-684-8111; Fax: 919-681-7892.
E-mail: elizabeth.j.thompson@duke.edu

CROSSMARK

A systematic review of the evidence supporting post-operative diuretic use following cardiopulmonary bypass in children with Congenital Heart Disease

Henry P. Foote[1], Christoph P. Hornik[1,2] , Kevin D. Hill[1,2], Alexandre T. Rotta[1], Reid Chamberlain[1] and Elizabeth J. Thompson[1]

[1]Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA and [2]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA

Abstract

Background: Paediatric cardiac surgery on cardiopulmonary bypass induces substantial physiologic changes that contribute to post-operative morbidity and mortality. Fluid overload and oedema are prevalent complications, routinely treated with diuretics. The optimal diuretic choice, timing of initiation, dose, and interval remain largely unknown. *Methods:* To guide clinical practice and future studies, we used PubMed and EMBASE to systematically review the existing literature of clinical trials involving diuretics following cardiac surgery from 2000 to 2020 in children aged 0–18 years. Studies were assessed by two reviewers to ensure that they met eligibility criteria. *Results:* We identified nine studies of 430 children across four medication classes. Five studies were retrospective, and four were prospective, two of which included randomisation. All were single centre. There were five primary endpoints – urine output, acute kidney injury, fluid balance, change in serum bicarbonate level, and required dose of diuretic. Included studies showed early post-operative diuretic resistance, suggesting higher initial doses. Two studies of ethacrynic acid showed increased urine output and lower diuretic requirement compared to furosemide. Children receiving peritoneal dialysis were less likely to develop fluid overload than those receiving furosemide. Chlorothiazide, acetazolamide, and tolvaptan demonstrated potential benefit as adjuncts to traditional diuretic regimens. *Conclusions:* Early diuretic resistance is seen in children following cardiopulmonary bypass. Ethacrynic acid appears superior to furosemide. Adjunct diuretic therapies may provide additional benefit. Study populations were heterogeneous and endpoints varied. Standardised, validated endpoints and pragmatic trial designs may allow investigators to determine the optimal diuretic, timing of initiation, dose, and interval to improve post-operative outcomes.

CHD represents almost one-third of all major congenital birth defects, occurring in about 1% of all live births and leads to roughly 40,000 paediatric cardiac operations in the United States per year.[1,2] Although post-operative survival has improved over the past 30 years, surgical repair or palliation with cardiopulmonary bypass still carries significant morbidity, with a risk of major complication up to 38% for the highest risk children.[2,3]

Cardiopulmonary bypass leads to a systemic inflammatory response driven by numerous factors including interactions with the bypass circuit, tissue ischaemia and reperfusion, haemolysis, altered flow characteristics, and complement and cytokine activation.[4] The resulting increased endothelial permeability and interstitial oedema, combined with neurohormonal changes, activate the renin-aldosterone system, increase anti-diuretic hormone release, and contribute to fluid overload after cardiac surgery with cardiopulmonary bypass.[5-7] Fluid overload is estimated to occur in up to 40% of children following cardiopulmonary bypass and is seen more commonly in children who are younger, have cyanotic heart lesions, and undergo more complex surgeries.[8-14] Fluid overload is associated with increased morbidity and mortality, including higher risk of acute kidney injury and need for renal replacement therapy, prolonged duration of mechanical ventilation and inotropic support, prolonged ICU and hospital stay, and decreased overall survival.[8-14] Understanding the drivers of fluid overload is critical to developing potential therapies and improving post-operative outcomes.

To improve fluid balance, several classes of diuretics are used in the post-operative setting despite no current labelling for this indication by the US Food and Drug Administration.[15] Label guidance for appropriate diuretic dosing and adjunct therapies may allow for improved efficacy with lower risk of adverse events.[7] However, studies to determine optimal dosing strategies in children with CHD are difficult to perform due to both limited numbers and disease heterogeneity, as well as challenges obtaining informed consent in a vulnerable population when there may be parental reluctance to enroll in placebo-controlled trials.[15,16] Additionally, a lack of

consistent, validated endpoints may make interpreting study results difficult and can prevent comparisons across studies. This systematic review aims to summarise the existing literature of diuretic use following cardiac surgery with cardiopulmonary bypass in children with CHD to guide clinical practice and inform areas where further research is needed.

Methods

Search strategy

PubMed and EMBASE were searched to identify studies investigating the use of diuretics in children after cardiac surgery with cardiopulmonary bypass, similarly to research previously described.[17] Studies from 2000 to 2020 were included to reflect medication use in the context of current clinical practice. Children were defined as birth to age 18 years. The search terms "postoperative care," "heart surgery," "cardiopulmonary bypass," "pediatric," and "diuretic" were used to generate an initial group of studies. We excluded animal studies, studies in a language other than English, and studies focused on pre- or intraoperative medication use. Case reports, letters, editorials, and comments were excluded. The search strategies are shown in the Appendix. A total of 124 studies were identified.

Study selection

Identified studies were imported into EndNote (Clarivate Analytics, Philadelphia, PA, USA). Two reviewers independently screened and reviewed study abstracts and titles. Studies were eligible for inclusion if the primary focus was diuretic administration in the post-operative period for children following cardiac surgery with cardiopulmonary bypass. The full article was then reviewed to ensure appropriateness prior to data extraction. A total of nine studies were included in the final analysis.

Data extraction and synthesis

A standardised data collection form was used to extract the relevant data from each eligible study. The following data were collected: study characteristics (including study design and years of study), study population characteristics (including age and cardiac defects), intervention (including medication administered and the presence and type of control used), study endpoints, and results. For each medication, the dose, timing of administration, primary outcome, and secondary outcomes were compiled and analysed.

Results

Overall, nine studies in 430 children met our inclusion criteria, all of which were single centre.[18-26] Study characteristics are summarised in Table 1. Three studies were prospective trials, one was a post hoc analysis of a prospective trial, and five were retrospective cohort studies. Of the prospective studies, two were randomised controlled trials comparing two therapies without a placebo arm, and one was an open-label, one-arm trial without a control group. Seven studies used a surrogate marker of efficacy as the primary outcome, most commonly urine output or fluid balance. One study used development of acute kidney injury as a primary endpoint, and none evaluated mortality as a primary outcome, although two studies explored this as a secondary outcome. None of the included studies evaluated pharmacokinetic data in their design or analysis. Medications studied were loop diuretics

(furosemide [8/9], ethacrynic acid [2/9]), thiazides (chlorothiazide [1/9]), vasopressin antagonists (tolvaptan [2/9]), and carbonic anhydrase inhibitors (acetazolamide [1/9]).[18-26] The median age in all studies was ≤12 months.

Loop diuretics

Loop diuretics act at the ascending loop of Henle and reversibly bind to the Na-K-2Cl cotransporter to reduce NaCl reabsorption.[27] Loop diuretics are extensively protein bound and require active transport to reach the tubular lumen to block active sodium transport, with sodium excretion proportional to urinary drug excretion rather than serum concentration.[28] Loop diuretics include furosemide, torsemide, and bumetanide, differing by duration of action and potency.[29] Ethacrynic acid is a non-sulfonamide loop diuretic that is less commonly used due to concern for increased ototoxicity and cost.[30,31]

The loop diuretics furosemide and ethacrynic acid are labelled for use as diuretics in paediatric populations: Intravenous and oral furosemide are labelled by the Food and Drug Administration for the treatment of oedema in paediatric patients of all ages with congestive heart failure, hepatic cirrhosis, and renal disease,[32] and oral ethacrynic acid is Food and Drug Administration-labelled for the short-term management of oedema in hospitalised paediatric patients with CHD or nephrotic syndrome.[33] Notably, both intravenous and oral ethacrynic acid are contraindicated for use in infants by Food and Drug Administration labelling.

Furosemide is the most commonly used loop diuretic in children and was included in all studies as either active drug, comparator, or standard of care. No studies on torsemide or bumetanide met inclusion criteria. In an uncontrolled, prospective trial of 12 infants (postnatal age range 0–33 weeks) with fluid overload, continuous furosemide infusion, started at a mean of 30 (range 21–48) hours postoperatively, up to a mean rate of 0.175 (± 0.045) mg/kg/h, resulted in significantly increased urine output.[25] In a single-centre randomised controlled trial of 74 children (mean age 4 months [± 180 days]), continuous ethacrynic acid infusion was superior to continuous furosemide infusion, each starting at 0.2 mg/kg/h of furosemide equivalent dose, titratable up to 0.8 mg/kg/h to achieve net even or negative fluid balance on post-operative day 0. Compared to furosemide, ethacrynic acid resulted in improved urine output and net fluid balance on post-operative day 0 (mean urine output 6.9 ml/kg/h vs. 4.6 ml/kg/h, p = 0.002; mean fluid balance −43 ml/kg/h versus −17 ml/kg/h, p = 0.01).[24] Although no difference was seen on subsequent post-operative days, the ethacrynic acid group trended towards shorter duration of mechanical ventilation and had significantly shorter ICU stays (mean 14 days vs. 16 days, p = 0.046). A significantly lower dose of ethacrynic acid was required compared to furosemide (mean 0.22 mg/kg/h vs. 0.33 mg/kg/h, p < 0.0001).

A post hoc analysis of this cohort demonstrated high initial loop diuretic doses (median dose 0.34 mg/kg/h on post-operative day 0) with a significant decrease over the following 48 hours (p = 0.04).[20] Urine output remained stable over the study period, suggesting an initial loop diuretic resistance in these infants that improved over 72 hours postoperatively. Lower blood pH after the first post-operative day and longer cross-clamp time both independently predicted the need for increased loop diuretic dose.

None of these studies found deleterious effects on renal function, with continuous infusions being associated with improving serum creatinine over time in one study.[25] Metabolic alkalosis and hypokalaemia were common, with more severe alkalosis seen

Table 1. Characteristics of included diuretic studies and study populations

Reference	Medication Studied	Study design (Study years)	N	Study Population	Route, dose, and time to drug initiation	Primary outcome	Findings
van der Vorst et al., 2001[25]	Continuous furosemide infusion for 72 h	Single-centre prospective observational	12	Infants with volume overload requiring inotropic support Median age 13 weeks (range 0 – 33 weeks)	IV Mean dose of 0.093 (± 0.016) mg/kg/h on day 1, 0.175 (± 0.045) mg/kg/h on day 2, and 0.15 (± 0.052) mg/kg/h on day 3 Started at a mean 30 h postoperatively	Serum Cr, UOP, and furosemide excretion	9/12 infants required an increase in furosemide rate. Although no change in serum furosemide level was seen, the median furosemide excretion increased significantly over 72 h, which paralleled a significant increase in Na excretion and UOP and decrease in serum Cr. Consider starting at higher furosemide infusion doses immediately postoperatively.
Ricci et al., 2015[24]	Continuous furosemide or EA for 72 h	Single-centre, prospective randomised double-blinded trial (2012–2013)	74	Infants with signs of fluid overload Mean age 4 months (± 180 days)	IV Furosemide mean dose of 0.33 mg/kg/h, EA mean dose of 0.22 mg/kg/h Furosemide started at a mean 11 h postoperatively, EA started at a mean 12 h postoperatively	Mean UOP at end of POD0	14/36 of EA infants and 9/36 of furosemide infants switched to bolus dosing by POD2 due to polyuria and excessively negative fluid balance. EA group with significantly higher UOP (p = 0.002) and net negative fluid balance (p = 0.01) over first POD, with no difference over the subsequent 48 h EA group with significantly shorter ICU LOS (16 days v 14 days, p = 0.046) Cardiac index was higher in EA group as measured from arterial waveform (p = 0.008).
Haiberger et al., 2016[20]	Continuous furosemide or EA for 72 h	Post hoc analysis of single-centre prospective randomized double-blinded (2012–2013)	67	Infants with signs of fluid overload. Median age 48 days (IQR 13–139 days)	IV Median diuretic dose of 0.34 (IQR 0.25–0.4) mg/kg/h at the end of POD0, 0.25 (IQR 0.17–0.4) mg/kg/h at the end of POD1, and 0.2 (0.12–0.4) mg/kg/h at the end of POD2 Furosemide started at a mean 11 h postoperatively and EA started at a mean 12 h postoperatively	Required dose of diuretic	Diuretic dose significantly decreased over time (p = 0.004). UOP was stable over time, suggesting a time-dependent increase in UOP response to dose. In multivariate analysis, increased cross-clamp time, lower blood pH at end of first POD, and use of furosemide rather than EA were all independently associated with increased diuretic dose.
Borasino et al., 2018[18]	Single furosemide dose	Single-centre retrospective cohort (2012–2015)	90	Infants Mean age 12 days (range 6–56 days)	IV Average dose of 1.1 (± 0.3) mg/kg Median time to first dose of 7.7 (IQR 4.4–9.5) h	Development of postop AKI	41/90 infants developed AKI. Infants who developed AKI had significantly lower UOP response to furosemide dose (p = 0.03). Furosemide response was associated with a significant reduction in need for prolonged PD or mechanical ventilation and frequency of fluid overload.
Kwiatkowski et al., 2017[23]	Intermittent furosemide versus PD	Single-centre prospective randomised unblinded (2011–2015)	73	Infants with postoperative oliguria Median age 8 days (IQR 6–15 days)	IV Dose of 1 mg/kg every 6 h for two doses, then interval at the discretion of the treating clinician Infants in the furosemide group	Incidence of negative fluid balance on POD1	No difference was seen in rate of achieving negative fluid balance. Infants in the furosemide group were more at risk for developing further fluid overload (OR 3.0, 95% CI 1.3–6.9) and more

(Continued)

Table 1. (*Continued*)

Reference	Medication Studied	Study design (Study years)	N	Study Population	Route, dose, and time to drug initiation	Primary outcome	Findings
					received a median of 3–4 doses/day over the first 5 POD		likely to have prolonged ventilation time (OR 3.1, 95% CI 1.2–8.2).
Carpenter et al., 2020[26]	Chlorothiazide in addition to standard therapy of high-dose furosemide for 48 h	Single-centre retrospective cohort (2009–2011)	73	Infants less than 6 months Median age 91 days (IQR 3–162 days)	IV 1–2 mg/kg every 6–12 h, Mean dose 3.83 (± 1.93) mg/kg/day Therapy started median 3 days post-op (IQR 2–5 days) All patients were on high-dose furosemide (mean dose 5.28 ± 1.68 mg/kg/day)	Change in UOP and fluid balance after 24 h of therapy	Addition of chlorothiazide was associated with a significant increase in UOP (mean 5.6 vs. 3.8 ml/kg/h, p < 0.001) and improvement in fluid balance (mean net negative 25 ml/kg/day versus net positive 16 ml/kg/day, p < 0.001). Mean VIS decreased significantly after chlorothiazide addition (p < 0.001). Cr remained stable, but significant serum electrolyte changes were seen: Na mean decrease by 1.1 mEq/L (p < 0.01), K mean decrease by 0.12 mEq/L (p = 0.02), Cl mean decrease by 4.9 mEq/L (p < 0.001), and bicarb mean increase by 2.9 mEq/L (p < 0.001).
Lopez et al., 2016[19]	Acetazolamide in addition to standard diuretic therapy (furosemide, spironolactone, ± thiazide)	Single-centre retrospective cohort (2010–2014)	40	Children with post-operative metabolic alkalosis Median age 6 months (IQR 3–45 months)	Enteral Median dose 8.7 mg/kg/day divided every 12 h (IQR 5–10, maximum 20 mg/kg/day) Acetazolamide started mean 8.1 days postoperatively, with a median duration of 4 (IQR 3–6) days	Change in serum bicarbonate level	Significant decrease in serum bicarbonate (mean decrease 4.5 mmol/L, p < 0.001) as well as pCO2 (mean decrease 3.9 mmHg, p = 0.007) over 48 h of therapy, with net decrease in pH (mean decrease 0.03, p = 0.008) Significant increase in UOP (mean increase 0.6 ml/kg/h, p = 0.02) and decrease in overall diuretic requirement (p = 0.012)
Kerling et al., 2019[22]	Tolvaptan in addition to standard of care diuretic therapy (various combinations of furosemide, thiazide, spironolactone, and EA)	Single-centre retrospective cohort (2011–2017)	25	Children with refractory capillary leak syndrome* Median age 36 days (range 9–549 days)	Enteral Median dose was 0.5 mg/kg daily (range 0.13–1.05 mg/kg Medication started at a median 13 (range 2–44) days postoperatively for a median duration of 8 (range 1–47) days	Positive response to tolvaptan: defined as increase in UOP by 10% within first 24 h of therapy	17 of 25 patients had positive response to therapy. Responders had significantly shorter overall ICU stay (p = 0.016) and were more likely to be extubated during treatment course (p = 0.042). Responders had significant weight reduction over first 7 days of therapy with no change seen in non-responders. No difference between responders or non-responders in age, CPB time, or complexity of surgery Increased mean BP on day 2 after starting tolvaptan and increased UOP 24 h after starting tolvaptan, both predictive of positive response

Table 1. (Continued)

Katayama et al., 2017[21]	furosemide and spironolactone +/- tolvaptan	Single-centre retrospective cohort (2013–2016)	43	Children with simple left-right shunts Median age 12 months (range 2–192 months)	Enteral 0.45 mg/kg tolvaptan single dose after extubation (mean 3.7 h postoperatively) in tolvaptan cohort. All patients received oral furosemide (0.67–1 mg/kg) and oral spironolactone (0.67–1mg/kg) every 8 h	Cumulative UOP and in-out balance on POD1	Tolvaptan cohort had significantly higher UOP (difference not quantified, p = 0.043) but no overall difference in cumulative in-out balance. Tolvaptan cohort had decreased need for additional IV furosemide but also a smaller decrease in CVP at POD1.

AKI = acute kidney injury; CI = confidence interval; CPB = cardiopulmonary bypass; Cr = Creatinine; CVP = central venous pressure; EA = ethacrynic acid; IQR = interquartile range; IV = intravenous; LOS = length of stay; Na = sodium; PD = peritoneal dialysis; POD = post-operative day; OR = odds ratio; SD = standard deviation; UOP = urine output; VIS = vasoactive infusion score
*Capillary leak syndrome defined by clinical symptoms (volume overload, intravascular hypovolaemia) and subcutaneous-thoracic ratio > 97th percentile

in children receiving ethacrynic acid than those receiving furosemide.

No studies that met our inclusion criteria compared continuous dosing to bolus dosing regimens. Bolus dosing of intravenous furosemide was compared to peritoneal dialysis in a single-centre randomised trial of 73 infants (median age 9 days for furosemide group, 8 days for peritoneal dialysis group).[23] All randomised infants had a peritoneal dialysis catheter placed in the operating room and upon development of oliguria during the first post-operative day were randomised to bolus dosing of 1 mg/kg furosemide every 6 hours or peritoneal dialysis. No difference was seen in the primary outcome – incidence of negative fluid balance on the first post-operative day. However, the furosemide group was at higher risk for developing at least 10% fluid overload (OR 3.0, 95% CI 1.3–6.9) and for needing prolonged mechanical ventilation (OR 3.1, 95% CI 1.2–9.2).

A retrospective study of 90 infants (mean age 12 days, range 6–56 days) found that urine output response following a bolus dose of furosemide predicted development of acute kidney injury as well as need for prolonged mechanical ventilation and prolonged peritoneal dialysis.[18] However, no specific cutoff point or urine output threshold that could be used to prospectively predict acute kidney injury risk in future children was defined.

Thiazides

Thiazide diuretics inhibit the Na-Cl cotransporter in the distal convoluted tubule, blocking sodium and chloride reabsorption.[34] Their use as a diuretic is primarily in combination with loop diuretic therapy to augment diuresis and blunt loop diuretic resistance, with well-documented efficacy in adult patients with congestive heart failure.[7,35,36] Thiazides, including chlorthalidone and hydrochlorothiazide, are used in children with CHD, but their usage remains off-label.[37] Two retrospective studies have looked at thiazide usage in the paediatric cardiac ICU, suggesting that the thiazide-like metolazone, but not chlorthalidone, was associated with increased urine output.[38,39] Neither study specifically investigated the post-operative population. One study of chlorothiazide met our inclusion criteria.

In a single-centre retrospective study of 73 children (median age 91 days, interquartile range 9–162 days), the addition of chlorothiazide (mean dose 3.83 mg/kg/day, started at a median 3 days postoperatively) to furosemide was associated with a significant increase in urine output and improvement in fluid balance after 24 hours of therapy (mean urine output 3.6 ml/kg/h vs. 5.6 ml/kg/h, p < 0.001; mean fluid balance +16 ml/kg/day versus −25 ml/kg/day, p < 0.001).[26] Of note, the dose of furosemide also increased significantly after chlorothiazide initiation (mean dose 0.20 vs. 0.24 mg/kg/h, p < 0.001), but the improvements in urine output and fluid balance persisted after adjusting for furosemide dose. Although serum creatinine remained stable with chlorothiazide therapy, its initiation was associated with significant electrolyte changes, notably, decreased serum sodium (mean 136.6 vs. 135.5 mEq/L, p < 0.01), potassium (mean 3.36 vs. 3.24 mEq/L, p = 0.02), and chloride (mean 101.0 vs. 96.1 mEq/L, p < 0.001) and increased metabolic alkalosis (mean serum bicarbonate 29 vs. 32 mEq/L, p < 0.001).

Vasopressin receptor antagonists

Tolvaptan is a selective vasopressin 2 receptor antagonist that leads to increased renal free water excretion without increased electrolyte wasting and is only available in an oral formulation.[40] In adult

patients with acute heart failure, tolvaptan improved weight loss and oedema but had no mortality benefit.[41] Recently, tolvaptan has been shown to be safe in a paediatric heart failure population, leading to improved urine output in children with acute heart failure exacerbations, but its use in paediatric populations remains off-label.[42] The inflammatory and neurohormonal response after cardiopulmonary bypass leads to interstitial oedema and free water retention, suggesting a potential role of tolvaptan for enhanced free water excretion in the acute post-operative setting.[6] Two studies of tolvaptan met our inclusion criteria.

A retrospective study of 43 children (median age 12 months, range 2–192 months) compared cohorts before and after instituting a policy of a single dose of 0.45 mg/kg tolvaptan in addition to standard oral diuretic therapy following extubation after surgical repair of simple left to right shunts.[21] The addition of tolvaptan was associated with increased urine output (p = 0.043) but similar net fluid balance to the control group on the first postoperative day. In a separate study, the addition of daily doses of tolvaptan (starting dose 0.25 mg/kg/day) in post-operative infants with capillary leak syndrome (median age 35 days for responders, 37.5 days for nonresponders, range 9–549 days) was associated with at least a 10% increase in urine output in 17 of the 25 children, although no control group was used.[22] Therapy was started a median of 13 days postoperatively. Responders were able to be extubated significantly earlier (10/17 of responders vs. 1/7 of nonresponders were extubated during treatment course; p = 0.042) with shorter overall length of stay (median days after tolvaptan administration 15 vs. 41; p = 0.016). Both studies looked at the effect of therapy on renal function and serum sodium concentration. Treatment was overall well tolerated, with only one child developing significant hypernatremia and no evidence of worsening glomerular filtration rate.

Carbonic anhydrase inhibitors

Post-operative metabolic alkalosis is common, especially in infants less than 1 year old, and is often driven by high-dose loop diuretic use.[43] Alkalosis is associated with decreased respiratory drive and increased mortality in critically ill patients.[44,45] Hypochloremic metabolic alkalosis is associated with loop diuretic resistance, leading to higher required doses.[46] Acetazolamide is a carbonic anhydrase inhibitor that causes increased urinary sodium and bicarbonate excretion and improvement of metabolic alkalosis. It has been used safely in the paediatric population despite being used off-label.[47-49]

One study of acetazolamide met our inclusion criteria. In a single-centre retrospective study of 40 children (mean age 6 months) who developed post-operative metabolic alkalosis (mean 8.1 days postoperatively), the addition of acetazolamide was associated with a significant improvement in serum bicarbonate (p < 0.001) and pH (p=.006).[19] After 48 hours of therapy, these children also had a significant increase in urine output (p = 0.02) and a decrease in total diuretic requirement (p = 0.012). All children were concomitantly treated with both furosemide and spironolactone, with over half on high doses of continuous furosemide infusion (58% on >0.3 mg/kg/h) at therapy initiation. Treatment was associated with an improvement of hypercapnia in ventilated children, but the study was not designed to assess mechanical ventilation duration as an outcome.

Discussion

Our review identified nine trials in 430 children across four medication classes. The majority of these studies were retrospective. Of those that were prospective, only two trials of 147 children had a control arm. None of the studies were multicentre trials, and both the intervention – single dose, repeated bolus dosing, or continuous infusion – and outcome were variable between studies, limiting comparisons across trials and the broader application of their findings.

Diuretic resistance is seen early in the post-operative period, suggesting that higher initial doses of diuretic may decrease fluid overload, although timing of diuretic initiation remains unknown.[25] Current evidence suggests that ethacrynic acid may be superior to furosemide but may result in increased electrolyte abnormalities.[20,24] The use of adjunct diuretic therapies may improve urine output and fluid balance, but may also adversely affect electrolytes.[19,21,22,26]

One major limitation in comparing conclusions across studies and translating these conclusions into clinical practice is the lack of validated, standardised endpoints for diuretic medications. The included studies primarily used urine output or fluid balance as their primary endpoint. Previous studies have demonstrated a correlation between fluid overload and morbidity and mortality, but it has not been clearly demonstrated that therapy directed toward improving fluid overload improves those outcomes.[8-12] Endpoints of morbidity – prolonged intubation time, prolonged hospital stay – or mortality may be more clinically relevant but require a large sample size and face significant confounding factors in these complex children. All identified studies included 90 or fewer children, limiting the power to detect significant differences in mortality, and preventing correlation between improvements in the surrogate markers of urine output or fluid balance and the more clinically important markers of morbidity and mortality.

For assessment of dose response to a single drug, urine output may be a feasible and immediate outcome to monitor. However, to assess efficacy for treating fluid overload in critically ill children post-cardiopulmonary bypass, overall fluid balance may be a more physiologically relevant marker. Previous studies from the late 1990s compared intermittent dosing to continuous infusions of furosemide, with some data suggesting that larger intermittent urine output required additional compensatory fluid administration to stabilise haemodynamics, limiting the total net volume decrease.[50-52] Further, differences in fluid overload have been associated with clinically important outcomes such as length of intubation, length of hospital stay, and overall mortality.[8,10-12] Active de-escalation and improvement of fluid balance have also been associated with reduced mortality in critically ill adult patients.[53] Accordingly, using fluid balance as a surrogate marker of diuretic efficacy may allow for smaller sample sizes, real time data collection and analysis, and better comparison of medications across trials if this association holds in paediatric populations.

Most (6/9) of our included studies looked at diuretic use in the first 72 hours after surgery, during which children require inotropic support and undergo significant volume shifts and profound physiologic alterations. These effects may alter both drug disposition and exposure–response relationships. Haiberger et al demonstrated a time-dependent increase in urine output response to loop diuretic dose during this early period, suggesting early diuretic resistance, but dose response at other times remains unknown.[20] Underlying cardiac diagnosis, such as one- or two-ventricle physiology, and developmental related changes also affect drug disposition, but most (8/9) studies also did not evaluate outcomes in this context.[54,55] These factors should be considered in future studies to inform optimal regimens (diuretic type, dose, duration, and timing of initiation) and appropriate adjunct therapies specific to underlying physiology.

Although there are over 40,000 paediatric cardiac surgeries annually, only nine studies with 430 total children met our inclusion criteria over a 20-year period.[2] The paucity of trials is reflective, at least in part, of the complexity of conducting traditional trials in this vulnerable and high-risk population with complex clinical care needs. Pragmatic trial designs, master protocols, and the use of real-world data may provide feasible alternatives to traditional clinical trials by simplifying protocols, supporting enrollment, allowing for collaboration across sites, and minimising the need for trial-specific data collection and analysis.[15,56,57] Additionally, combining dosing and demographic data from the electronic health record with advanced pharmacokinetic/pharmacodynamic modelling may allow for dose optimisation in specific populations while avoiding the challenges of performing clinical trials.

Our objective was to evaluate the existing evidence for diuretic use in children with CHD following surgery with cardiopulmonary bypass. We found that ethacrynic acid may be superior to furosemide, and adjunct therapies may be beneficial in treating fluid overload. Higher initial diuretic doses should be considered. Significant study heterogeneity, limited enrollment, and lack of validated, consistent endpoints make trial results difficult to translate into clinical practice. Novel trial designs may allow for improved evidence-based drug selection and delivery, resulting in improved outcomes in children with CHD undergoing surgery with cardiopulmonary bypass.

References

1. Liu Y, Chen S, Zuhlke L, et al. Global birth prevalence of congenital heart defects 1970–2017: updated systematic review and meta-analysis of 260 studies. Int J Epidemiol 2019; 48: 455–463.
2. Jacobs JP, Mayer JE, Jr., Pasquali SK, et al. The Society of Thoracic Surgeons Congenital Heart Surgery Database: 2019 update on outcomes and quality. Ann Thorac Surg 2019; 107: 691–704.
3. Jacobs ML, O'Brien SM, Jacobs JP, et al. An empirically based tool for analyzing morbidity associated with operations for congenital heart disease. J Thorac Cardiovasc Surg 2013; 145: 1046–1057 e1.
4. Kozik DJ, Tweddell JS Characterizing the inflammatory response to cardiopulmonary bypass in children. Ann Thorac Surg 2006; 81: S2347–S2354.
5. Nadim MK, Forni LG, Bihorac A, et al. Cardiac and vascular surgery-associated acute kidney injury: the 20th International Consensus Conference of the ADQI (Acute Disease Quality Initiative) Group. J Am Heart Assoc 2018; 7: e008834.
6. Seghaye M-C, Grabitz RG, Duchateau J, et al. Inflammatory reaction and capillary leak syndrome related to cardiopulmonary bypass in neonates undergoing cardiac operations. J Thorac Cardiovasc Surg 1996; 112: 687–697.
7. McCammond AN, Axelrod DM, Bailly DK, Ramsey EZ, Costello JM Pediatric Cardiac Intensive Care Society 2014 Consensus Statement: pharmacotherapies in cardiac critical care fluid management. Pediatr Crit Care Med 2016; 17: S35–S48.
8. Shi S, Zhao Z, Liu X, et al. Perioperative risk factors for prolonged mechanical ventilation following cardiac surgery in neonates and young infants. Chest 2008; 134: 768–774.
9. Hazle MA, Gajarski RJ, Yu S, Donohue J, Blatt NB Fluid overload in infants following congenital heart surgery. Pediatr Crit Care Med 2013; 14: 44–49.
10. Hassinger AB, Wald EL, Goodman DM Early postoperative fluid overload precedes acute kidney injury and is associated with higher morbidity in pediatric cardiac surgery patients. Pediatr Crit Care Med 2014; 15: 131–138.
11. Seguin J, Albright B, Vertullo L, et al. Extent, risk factors, and outcome of fluid overload after pediatric heart surgery. Crit Care Med 2014; 42: 2591–2599.
12. Lex DJ, Toth R, Czobor NR, et al. Fluid overload is associated with higher mortality and morbidity in pediatric patients undergoing cardiac surgery. Pediatr Crit Care Med 2016; 17: 307–314.
13. Arikan AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. Pediatr Crit Care Med 2012; 13: 253–258.
14. Vaara ST, Korhonen AM, Kaukonen KM, et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. Crit Care 2012; 16: R197.
15. Torok RD, Li JS, Kannankeril PJ, et al. Recommendations to enhance pediatric cardiovascular drug development: report of a multi-stakeholder think tank. J Am Heart Assoc 2018; 7: e007283.
16. Zimmerman K, Gonzalez D, Swamy GK, Cohen-Wolkowiez M Pharmacologic studies in vulnerable populations: using the pediatric experience. Semin Perinatol 2015; 39: 532–536.
17. King CE, Thompson EJ, Foote HP, et al. An evidence-based review of the use of vasoactive and inotropic medications in post-operative paediatric patients after cardiac surgery with cardiopulmonary bypass from 2000 to 2020. Cardiol Young 2020: 30: 1757–1771.
18. Borasino S, Wall KM, Crawford JH, et al. Furosemide response predicts acute kidney injury after cardiac surgery in infants and neonates. Pediatr Crit Care Med 2018; 19: 310–317.
19. Lopez C, Alcaraz AJ, Toledo B, Cortejoso L, Gil-Ruiz MA Acetazolamide therapy for metabolic alkalosis in pediatric intensive care patients. Pediatr Crit Care Med 2016; 17: e551–e558.
20. Haiberger R, Favia I, Romagnoli S, Cogo P, Ricci Z Clinical factors associated with dose of loop diuretics after pediatric cardiac surgery: post hoc analysis. Pediatr Cardiol 2016; 37: 913–918.
21. Katayama Y, Ozawa T, Shiono N, Masuhara H, Fujii T, Watanabe Y Safety and effectiveness of tolvaptan for fluid management after pediatric cardiovascular surgery. Gen Thorac Cardiovasc Surg 2017; 65: 622–626.
22. Kerling A, Toka O, Rüffer A, et al. First experience with Tolvaptan for the treatment of neonates and infants with capillary leak syndrome after cardiac surgery. BMC Pediatr 2019; 19: 57.
23. Kwiatkowski DM, Goldstein SL, Cooper DS, Nelson DP, Morales D, Krawczeski CD Peritoneal dialysis vs furosemide for prevention of fluid overload in infants after cardiac surgery. JAMA Pediatr 2017; 171: 357–364.
24. Ricci Z, Haiberger R, Pezzella C, Garisto C, Favia I, Cogo P Furosemide versus ethacrynic acid in pediatric patients undergoing cardiac surgery: a randomized controlled trial. Crit Care 2015; 19: 2.

25. van der Vorst MM, Ruys-Dudok van Heel I, Kist-van Holthe JE, et al. Continuous intravenous furosemide in haemodynamically unstable children after cardiac surgery. Intensive Care Med 2001; 27: 711–715.

26. Carpenter RJ, Kouyoumjian S, Moromisato DY, Lieu P, Amirnovin R Lower-dose, intravenous chlorothiazide is an effective adjunct diuretic to furosemide following pediatric cardiac surgery. J Pediatr Pharmacol Ther 2020; 25: 31–38.

27. Wittner M, Di Stefano A, Wangemann P, Greger R How do loop diuretics act? Drugs 1991; 41: 1–13.

28. Brater DC Pharmacodynamic considerations in the use of diuretics. Ann Rev Pharmacol Toxicol 1983; 23: 45–62.

29. Brater DC Clinical pharmacology of loop diuretics. Drugs 1991; 41: 14–22.

30. Ikeda K, Oshima T, Hidaka H, Takasaka T Molecular and clinical implications of loop diuretic ototoxicity. Hear Res 1997; 107: 1–8.

31. Ker GL, Gangadharan S Management of fluid overload in the pediatric ICU. Pediatric Critical Care 2019: 193–209.

32. Furosemide Injection, USP [package insert]. Shirley, NY: American Regent; 2011.

33. Ethacrynic Acid Tablets USP [package insert]. Parsippany, NJ: Edenbridge Pharmaceuticals; 2014.

34. Ellison DH, Velazquez H, Wright FS Thiazide-sensitive sodium chloride cotransport in early distal tubule. Am J Physiol 1987; 253: F546–F54.

35. Ellison DH The physiologic basis of diuretic synergism: its role in treating diuretic resistance. Ann Intern Med 1991; 114: 886–894.

36. Jentzer JC, DeWald TA, Hernandez AF Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol 2010; 56: 1527–1534.

37. Pasquali SK, Hall M, Slonim AD, et al. Off-label use of cardiovascular medications in children hospitalized with congenital and acquired heart disease. Circ Cardiovasc Qual Outcomes 2008; 1: 74–83.

38. Moffett BS, Tsang R, Kennedy C, Bronicki RA, Akcan-Arikan A, Checchia PA Efficacy of sequential nephron blockade with intravenous chlorothiazide to promote diuresis in cardiac intensive care infants. Cardiol Young 2017; 27: 1104–1109.

39. Wise RT, Moffett BS, Akcan-Arikan A, Galati M, Afonso N, Checchia PA Enhancement of diuresis with metolazone in infant paediatric cardiac intensive care patients. Cardiol Young 2018; 28: 27–31.

40. Amin HZ, Danny SS Tolvaptan: A novel diuretic in heart failure management. J Teh Univ Heart Ctr 2015; 11: 1–5.

41. Konstam MA, Gheorghiade M, Burnett JC, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure. JAMA 2007; 297: 1319–1331.

42. Higashi K, Murakami T, Ishikawa Y, et al. Efficacy and safety of tolvaptan for pediatric patients with congestive heart failure. Multicenter survey in

the working group of the Japanese Society of PEdiatric Circulation and Hemodynamics (J-SPECH). Int J Cardiol 2016; 205: 37–42.

43. Wong HR, Chundu KR Metaboic alkalosis in children undergoing cardiac surgery. Crit Care Med 1993; 21: 884–887.

44. Wilson RF, Gibson D, Percinel AK, et al. Severe alkalosis in critically ill surgical patients. Arch Surg 1972; 105: 197–203.

45. Anderson LE, Henrich WL Akalemia-associated morbidity and mortality in medical and surgical patients. South Med J 1987; 80: 729–733.

46. Hanberg JS, Rao V, Ter Maaten JM, et al. Hypochloremia and diuretic resistance in heart failure: mechanistic insights. Circ Heart Fail 2016; 9: 10.1161/CIRCHEARTFAILURE.116.003180 e003180.

47. Moviat M, Pickkers P, van der Voort PH, van der Hoeven JG Acetazolamide-mediated decrease in strong ion difference accounts for the correction of metabolic alkalosis in critically ill patients. Crit Care 2006; 10: R14.

48. Moffett BS, Moffett TI, Dickerson HA Acetazolamide therapy for hypochlorimic metabolic alkalosis in pediatric patients with heart disease. Am J Therapeut 2007; 14: 331–335.

49. Andrews MG, Johnson PN, Lammers EM, Harrison DL, Miller JL Acetazolamide in critically ill neonates and children with metabolic alkalosis. Ann Pharmacother 2013; 47: 1130–1135.

50. Singh NC, Kissoon N, Al Mofada S, Bennett M, Bohn DJ Comparison of continuous versus intermittent furosemide administration in postoperative pediatric cardiac patients. Crit Care Med 1992; 20: 17–21.

51. Klinge JM, Scharf J, Hofbeck M, Gerling S, Bonakdar S, Singer H Intermittent administration of furosemide versuse continuous infusion in the postoperaive managment of children following open heart surgery. Intensive Care Med 1997; 23: 693–697.

52. Luciani GB, Nichani S, Chang AC, Wells WJ, Newth CJ, Starnes VA Continuous versus intermittent furosemide infusion in critically ill infants after open heart operations. Ann Thorac Surg 1997; 64: 1133–1139.

53. Silversides JA, Fitzgerald E, Manickavasagam US, et al. Deresuscitation of patients with iatrogenic fluid overload is associated with reduced mortality in critical illness. Crit Care Med 2018; 46: 1600–1607.

54. van Saet A, de Wildt SN, Knibbe CA, Bogers AD, Stolker RJ, Tibboel D The effect of adult and pediatric cardiopulmonary bypass on pharmacokinetic and pharmacodynamic parameters. Curr Clin Pharmacol 2013; 8: 297–318.

55. Bailey JM, Miller BE, Lu W, Tosone SR, Kanter K, Tam VK The pharmacokinetics of milrinone in pediatric patients after cardiac surgery. Anesthesiology 1999; 90: 1012–1018.

56. Hill KD, Baldwin HS, Bichel DP, et al. Rationale and design of the STeroids to REduce Systemic inflammation after infant heart Surgery (STRESS) trial. Am Heart J 2020; 220: 192–202.

57. Woodcock J, LaVange LM Master protocols to study multiple therapies, multiple diseases, or both. N Engl J Med 2017; 377: 62–70.