JAMA Pediatrics | Original Investigation

# Peritoneal Dialysis vs Furosemide for Prevention of Fluid Overload in Infants After Cardiac Surgery
## A Randomized Clinical Trial

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**IMPORTANCE** Fluid overload after congenital heart surgery is frequent and a major cause of morbidity and mortality among infants. Many programs have adopted the use of peritoneal dialysis (PD) for fluid management; however, its benefits compared with those of traditional diuretic administration are unknown.

**OBJECTIVE** To determine whether infants randomized to PD vs furosemide for the treatment of oliguria have a higher incidence of negative fluid balance on postoperative day 1, as well as avoidance of 10% fluid overload; shorter duration of mechanical ventilation, intensive care unit stay, and inotrope use; and fewer electrolyte abnormalities.

**DESIGN, SETTING, AND PARTICIPANTS** This single-center, unblinded, randomized clinical trial compared methods of fluid removal after cardiac surgery from October 1, 2011, through March 13, 2015, in a large tertiary pediatric hospital in Ohio. The parents or guardians of all eligible infants (aged <6 months) undergoing cardiac surgery with catheter placement for PD were approached for inclusion. No patients were withdrawn for adverse effects. Recruitment was powered for the primary outcome, and analysis was based on intention to treat. Patients randomized to PD were hypothesized to have superior outcomes.

**INTERVENTIONS** Infants received intravenous furosemide (1 mg/kg every 6 hours) or a standardized PD regimen.

**MAIN OUTCOMES AND MEASURES** The primary end point was incidence of negative fluid balance on postoperative day 1. Secondary end points included incidence of fluid overload, duration of mechanical ventilation and intensive care unit stay, electrolyte abnormalities and repletion doses, duration of inotropic administration, and mortality.

**RESULTS** Seventy-three patients (47 boys [64%] and 26 girls [35%]; median age, 8 [interquartile range (IQR), 6-14] days) received treatment and completed the trial. No difference was found between the PD and furosemide groups in the incidence of negative fluid balance on the first postoperative day. The furosemide group was 3 times more likely to have 10% fluid overload (odds ratio [OR], 3.0; 95% CI, 1.3-6.9), was more likely to have prolonged ventilator use (OR, 3.1; 95% CI, 1.2-8.2), and had a longer duration of inotrope use (median, 5.5 [IQR, 4-8] vs 4.0 [IQR, 3-6] days) and higher electrolyte abnormality scores (median, 6 [IQR, 4-7] vs 3 [IQR, 2-5]) compared with the PD group. No statistically significant differences in mortality (3 patients [9.4%] in the furosemide group vs 1 patient [3.1%] in the PD group) or length of cardiac intensive care unit (median, 7 [IQR, 6-12] vs 9 [IQR, 5-15] days) or hospital (15 [IQR, 10-28] vs 14 [IQR, 9-22] days) stay were observed. No serious complications were observed. Dialysis was discontinued early in 9 of 41 patients in the PD group for pleural-peritoneal communication.

**CONCLUSIONS AND RELEVANCE** Use of PD is safe and allows for superior fluid management with improved clinical outcomes compared with diuretic administration. Use of PD should be strongly considered among infants at high risk for postoperative acute kidney injury and fluid overload.

**TRIAL REGISTRATION** clinicaltrials.gov Identifer: NCT01709227

*JAMA Pediatr*. 2017;171(4):357-364. doi:10.1001/jamapediatrics.2016.4538
Published online February 20, 2017.

Supplemental content

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Infants are at high risk for fluid overload after cardiac surgery secondary to impaired hemodynamics, acute kidney injury (AKI), and capillary leak. Fluid overload is commonly self-limited and often marginalized as an expected stage in recovery. However, studies have shown that overload is associated with worse outcomes in critically ill patients.[1-3] Among infants after cardiac surgery, fluid overload independently predicts mortality and morbidity.[4-6]

The paradigm of early renal replacement therapy has gained attention as studies have demonstrated associations with lower mortality and improved outcomes after cardiac surgery.[7-11] Among infants, peritoneal dialysis (PD) is the most common modality of dialysis, proven to be a safe method of fluid removal.[7,9,12-14] A previously published retrospective study[13] demonstrated that PD is associated with improved outcomes, including duration of mechanical ventilation. However, to our knowledge, PD has not been compared prospectively with diuretic administration, the traditional postoperative therapy in the context of oliguria.

In this randomized clinical trial, we aimed to determine whether the modality of fluid removal (PD vs a standardized furosemide regimen) is associated with fluid balance and clinical outcomes. We hypothesized that, compared with infants receiving furosemide, infants randomized to PD would be more likely to have a negative fluid balance on postoperative day (POD) 1, would be less likely to develop 10% fluid overload, would have less time to negative fluid balance, and would have superior clinical outcomes, including duration of mechanical ventilation, length of stay, vasoactive infusion use, electrolyte level abnormalities, oxygenation indices, and mortality.

### Key Points

**Question** In infants who undergo cardiac surgery, is peritoneal dialysis associated with improved fluid balance compared with furosemide treatment?

**Findings** In this randomized clinical trial that included 73 infants, patients receiving peritoneal dialysis had a lower incidence of fluid overload and no significant adverse outcomes compared with patients receiving furosemide.

**Meaning** Use of peritoneal dialysis after cardiac surgery is safe and associated with a lower incidence of fluid overload than is furosemide treatment among infants at high risk for postoperative acute kidney injury.

## Methods

This single-center, randomized clinical trial among infants with oliguria after cardiac surgery with cardiopulmonary bypass (CPB) compared patients undergoing PD vs furosemide administration. Parents or guardians of all infants (aged <6 months) undergoing cardiac surgery with CPB at Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, with planned PD catheter (PDC) placement as part of routine practice were approached for enrollment. Patients with preexisting kidney disease (estimated glomerular filtration rate, <60 mL/min/1.73m$^2$) were excluded. Patients were removed from the study before randomization if they did not undergo CPB or if a PDC was not placed as planned or after randomization if the patient died or required a second operation or extracorporeal membrane oxygenation within the first postoperative 24 hours, although their data were collected for the safety analysis. Patient screening was performed by review of the cardiac intensive care unit (CICU) census and operating room schedule. The study protocol is available in Supplement 1. The study protocol was approved by the institutional review board of the Cincinnati Children's Hospital with independent Data Safety Monitoring Board supervision. Written informed consent was obtained preoperatively from the parents or the guardians of patients.

### PD Management

Per institutional protocol, a PDC was placed in patients deemed to be at high risk for AKI (eTable 1 in Supplement 2). Nephrology services were consulted preoperatively. The PD system was maintained as a closed circuit, replaced every 72 hours with minimal circuit manipulation by dialysis nurses.

After CPB, a 2-cm transverse midline incision was placed 2 cm below the sternotomy by the cardiac surgeon. The 37-cm catheter (Pediatric Tenckhoff; Quinton Instrument Company) was placed by perforating the peritoneum above the diaphragm via the sternotomy. A right-angle clamp was placed into the peritoneum and passed through the abdominal wall into the skin incision. The catheter was pulled into the peritoneum, positioned in the right lower quadrant, and sutured to the abdominal wall. The peritoneum was closed. The PDC was tested for leaks, connected to a closed system, and clamped until randomization or study completion.

### Study Procedures

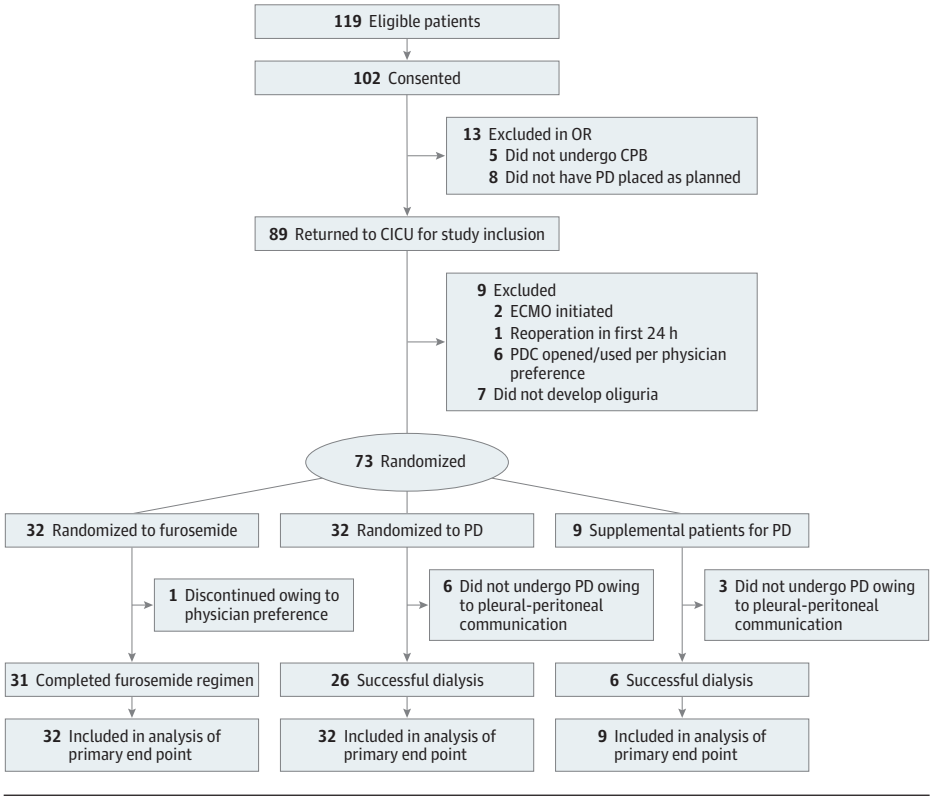
The surgical procedure, CPB, and perfusion were performed with the surgeon blinded to study inclusion. Thus, a decision to not place a PDC could occur regardless of enrollment.

Postoperative oliguria was defined as any 4 total hours of urine output of less than 1 mL/kg per hour during the first postoperative 24 hours. Infants who developed oliguria were randomized to PD or furosemide (**Figure**). Patients without oliguria received standard care without study intervention.

Patients randomized to PD had an initial regimen of PD solution, 1.5%, 10 mL/kg (Dianeal; Baxter Healthcare) with 2 to 3 mEq/L of potassium chloride and 200 U/L of unfractionated heparin. Standard initial peritoneal dialysis regimen was to fill the peritoneal cavity with the PD solution for 5 minutes, allow the solution to dwell for 45 minutes, then drain it passively for 10 minutes. This cycle was repeated for the duration of PD using a closed system setup (Gesco; Utah Medical Products). This regimen is our standard initial infant treatment. The percentage of glucose, dwell volumes, or cycle duration was adjusted with nephrology consultation.

Patients randomized to furosemide treatment were prescribed 1 mg/kg intravenously every 6 hours for 2 doses, then per physician direction. Chlorothiazide sodium was added on POD 2 at physician discretion. A urine output of less than

Figure. CONSORT Flow Diagram




CONSORT flow diagram depicts study enrollment, completion, and withdrawals. CICU indicates cardiac intensive care unit; CPB, cardiopulmonary bypass; ECMO, extracorporeal circulation membrane oxygenation; OR, operating room; PD, peritoneal dialysis; and PDC, PD catheter.

1 mL/kg per hour during the 16 hours after the first furosemide dose was considered to be a poor response, and these patients were allowed to initiate PD or undergo catheter drainage. If patients developed late fluid overload unresponsive to diuretic therapy, PD use was outside the study protocol.

All patients received inotrope and vasoactive medications as dictated by clinical status. Fluid administration was two-thirds maintenance (Holliday-Segar method) on POD 1, three-fourths maintenance on POD 2, and 100% maintenance thereafter as standard therapy. Patients received electrolyte supplementation and fluid boluses as needed.

Randomization was block stratified 1:1 by the risk adjustment for congenital heart surgery (RACHS-1) severity score using 2 strata (score 2-5 and score 6; range, 0-6, with higher scores indicating higher risk for inpatient mortality).[15] The randomization scheme was created using a permuted block method with a random number generator with blocks of 2, 4, and 6 patients. The cardiology division statistician confidentially prepared envelopes and maintained the assignment log. After randomization, the statistician was blinded to the study. Medical records were interrogated by clinical research coordinators from the Heart Institute Research Core, Cincinnati Children's Hospital Medical Center, and transferred to a REDCap database using double-data entry with appropriate data cleaning.

## Study Variables

Baseline intraoperative variables included surgical procedure and RACHS-1 score, CPB and aortic cross-clamp times, and use of deep hypothermic circulatory arrest, regional-cerebral perfusion, or modified ultrafiltration. The primary outcome data consisted of the percentage of patients with a negative fluid balance on POD 1, calculated as the net difference between all inputs and outputs. Secondary outcomes included the rate of 10% fluid overload (fluid balance divided by preoperative weight, expressed as a percentage), number of 8-hour shifts until negative fluid balance was achieved, duration of mechanical ventilation to the first extubation and vasoactive infusions (in days), electrolyte repletion doses, morning electrolyte abnormality score (range, 0-4, with higher scores indicating more abnormalities)[13] from PODs 1 to 5, modified oxygenation index[13] and level of brain-type natriuretic peptide at postoperative 24 and 48 hours, CICU and hospital lengths of stay, days to chest closure if applicable, and in-hospital mortality (eTable 2 in Supplement 2). Prolonged mechanical ventilation was defined post hoc as longer than 3 days and prolonged CICU stay was defined as longer than 7 days.

Incidence of AKI was not calculated because PD modulates postoperative creatinine and urine output. Furthermore, PD use defines AKI by established guidelines.

## Study Withdrawals

Randomized patients who did not complete their assigned treatment were replaced with the next eligible patient with an identical RACHS-1 score after completion of standard enrollment. Analysis was performed using all patients in an intention-to-treat format and with those completing protocol treat-

Table 1. Baseline Characteristics

| Characteristic | Study Group | |
|---|---|---|
| | Furosemide (n = 32) | Peritoneal Dialysis (n = 41) |
| Male, No. (%) | 21 (66) | 26 (63) |
| Race/ethnicity, No. (%) | | |
| White | 28 (88) | 36 (88) |
| Black | 2 (6) | 2 (5) |
| Asian | 1 (3) | 0 |
| Hispanic | 1 (3) | 1 (2) |
| Other | 0 | 2 (5) |
| Age, median (IQR), d | 9 (7-14) | 8 (6-15) |
| Weight, median (IQR), kg | 3.4 (3.0-3.8) | 3.4 (3.0-3.8) |
| Length, median (IQR), cm | 50 (47-53) | 50 (47-52) |
| Baseline creatinine level, median (IQR), mg/dL | 0.4 (0.4-0.5) | 0.4 (0.3-0.5) |
| RACHS-1 score, median (IQR)[a] | 4.0 (3.0-4.5) | 4.0 (3.0-4.0) |
| Intraoperative duration, median (IQR), min | | |
| Bypass | 216 (154-284) | 216 (158-256) |
| Cross-clamping | 110 (54-140) | 112 (43-139) |
| Regional-cerebral perfusion, No. (%) | 16 (50) | 17 (41) |
| DHCA, No. (%) | 10 (31) | 12 (29) |

Abbreviations: DHCA, deep hypothermic circulatory arrest; IQR, interquartile range; RACHS, risk adjustment for congenital heart surgery.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

[a] Scores range from 1 to 6, with higher scores indicating higher risk for inpatient mortality.

ment. For clarity, we report intention to treat with per protocol treatment in eTables 3 and 4 in Supplement 2.

### Statistical Analysis

Demographic and clinical characteristics were summarized using measures of central tendency, variability, and frequency. Appropriate statistical tests were applied to describe treatment groups and compare the characteristics. Outcomes were analyzed using the $\chi^2$ test, Fisher exact test, 2-sample *t* test, or Wilcoxon rank sum test as appropriate. Difference in medians of continuous variables was determined using the Hodge-Lehmann estimator[16] with 95% CIs calculated by the exact distribution of the Mann-Whitney test statistic. All tests were 2-sided, with $P < .05$ considered to be statistically significant. Data were analyzed using SPSS software (version 23.0; IBM SPSS Statistics).

Power calculations were performed on the primary outcome, initially using conservative estimates, but recalculated using a prospectively planned adaptive study design with the outcomes of the first 20 enrolled patients. Among these patients (10 in each group), 9 (90%) in the PD group and 6 (60%) in the furosemide group had negative fluid balance. Using a 2-group $\chi^2$ test with a 2-sided significance level of .05, 32 patients per group were required for 80% power to detect difference (90% vs 60%; odds ratio [OR], 6.0; 95% CI, 0.5-67.7) (nQuery Advisor, version 7.0; Statistical Solutions).

## Results

Enrollment lasted from October 1, 2011, through March 13, 2015. Of 119 eligible patients, 102 consented for inclusion (Figure). Twenty-nine patients were removed per protocol or did not meet randomization criteria. Of the original 32 patients randomized to PD, 6 did not undergo PD owing to a pleural-peritoneal communication. This occurrence resulted in 9 replacement patients (3 replacements also had communications), leading to 41 patients randomized to PD and 32 randomized to furosemide (73 randomized patients; 47 boys [64%] and 26 girls [35%]; median age, 8 [interquartile range (IQR), 6-14] days).

We found no differences in baseline or demographic data, including median weight, age, and baseline creatinine level (**Table 1**). Cohorts had similar RACHS-1 scores, duration of CPB and aortic cross-clamping, use of regional-cerebral perfusion, deep hypothermic circulatory arrest, and modified ultrafiltration. Represented surgical procedures are listed in **Table 2**. Mean (SD) volume of fluid administered included 98 (26) vs 104 (23) mL/kg per day on POD 1, 108 (30) vs 116 (31) mL/kg per day on POD 2, 111 (30) vs 116 (26) mL/kg per day on POD 3, 115 (30) vs 121 (32) mL/kg per day on POD 4, and 125 (29) vs 123 (31) mL/kg per day on POD 5. No difference in nutritional volume administered was found.

Patients randomized to furosemide treatment received a median (IQR) daily dose of 3 (3-4), 4 (3-4), 3 (3-4), 3 (3-4), and 3 (3-4) mg/kg on PODs 1 to 5, respectively. Nine patients (28%) received a peak daily dose of more than 4 mg/kg per day. Similarly, 15 patients (47%) were given chlorothiazide on POD 2 and 16 (50%) on POD 3. Eight patients in the furosemide group had inadequate diuretic response after 24 hours and had their PDC opened to drain (4 patients) or used for dialysis (4 patients), which was initiated in 1 patient before the second furosemide dose (Figure).

We found no statistically significant difference in the percentage of patients who attained a negative fluid balance on POD 1 (29 of 41 [71%] vs 21 of 32 [66%]; $P = .80$) (**Table 3**). However, patients randomized to furosemide were 3 times more likely to develop 10% fluid overload (OR, 3.0; 95% CI, 1.3-6.9). In addition, although not statistically significant, the PD cohort achieved a net negative fluid balance 1 shift sooner and had superior median fluid balances on POD 1 (55 [IQR, −25 to 194] vs 118 [IQR, 51 to 197] mL), POD 2 (−251 [IQR, −379 to −125] vs −201 [IQR, −343 to −100] mL), and POD 3 (−89 [IQR, −210 to −14] vs −66 [IQR, −193 to 54] mL).

Patients randomized to furosemide treatment were more likely to require prolonged mechanical ventilation (OR, 3.1; 95% CI, 1.2-8.2), although without a statistically significant difference in the median duration of mechanical ventilation (3 [IQR, 2-4] vs 4 [IQR, 20-6] days). Patients in the PD group were less likely to have prolonged CICU stays (OR, 1.6; 95% CI, 1.0-2.7) but had a nonsignificant difference in actual duration of CICU stay (median, 7 [IQR, 6-12] vs 9 [IQR, 5-15] days). Dichotomous outcomes were defined post hoc. Patients treated with PD had fewer electrolyte repletion doses (median, 1 [IQR, 0-2] vs 2 [IQR, 1-5]) and lower electrolyte abnormality scores (median, 3 [IQR, 2-5] vs 6 [IQR, 4-7]). The PD cohort had a 1.5-day

shorter duration of vasoactive infusion use (median, 4.0 [IQR, 3-6] vs 5.5 [IQR, 4-8] days). Eighteen patients had delayed sternal closure with a median of 2.5 (IQR, 2-3) days per cohort. In-hospital mortality included 4 patients (5.5%) among all randomized patients, with no statistically significant difference (3 patients [9.4%] in the furosemide group vs 1 [2.4%] in the PD group).

Among all 92 patients with PDC placement, regardless of study intervention, 2 PD-related adverse outcomes occurred. Neither included peritonitis or bowel injury. One nonrandomized patient had self-resolving bloody drainage from their PDC (in addition to typical postsurgical bleeding) and received a blood transfusion. This catheter was later used for effective PD outside the study protocol. One patient had a patent processus vaginalis and developed a hydrocele that resolved after PD was completed, requiring no intervention.

Pleural-peritoneal communications were present in 9 of 41 patients in the PD group. This condition was diagnosed by drainage of dialysis fluid via chest tubes. This procedural complication is the correlate of pericatheter leak in patients with a direct transcutaneous PDC placement and was more frequent in patients weighing less than 3 kg (4 of 8 [50%] vs 5 of 33 [15%]; OR, 5.6; 95% CI, 1.0-30.1). These patients did not use PD as assigned; however, the complications were not considered to be adverse events because no harm occurred.

Table 2. Surgical Procedures by Group

| Diagnosis by RACHS-1 Score[a] | Study Group, No. of Patients | |
|---|---|---|
| | Furosemide (n = 32) | Peritoneal Dialysis (n = 41) |
| 6 | | |
| Norwood procedure with Blalock-Taussig shunt | 8 | 6 |
| Norwood procedure with Sano shunt | 0 | 1 |
| Norwood procedure with Glenn shunt (hybrid stage II) | 0 | 1 |
| 4 | | |
| Truncus arteriosus repair | 3 | 3 |
| Arterial switch operation with VSD repair | 2 | 1 |
| Arterial switch operation with repair of subpulmonary stenosis | 1 | 0 |
| Neonatal total anomalous pulmonary vein repair | 0 | 3 |
| Repair of single ventricle by VSD enlargement | 0 | 1 |
| Neonatal aortic root replacement | 0 | 1 |
| Aortopulmonary window and interrupted aortic arch repair | 0 | 1 |
| Hypoplastic aortic arch repair with pulmonary artery band | 1 | 4 |
| Hypoplastic aortic arch repair | 7 | 7 |
| 3 | | |
| Blalock-Taussig shunt/pulmonary arterioplasty | 1 | 2 |
| Arterial switch operation | 6 | 9 |
| Atrioventricular canal repair | 1 | 1 |
| 2 | | |
| Tetralogy of Fallot repair | 1 | 0 |
| Not listed | | |
| Tetralogy of Fallot with absent pulmonary valve repair | 1 | 0 |

Abbreviations: RACHS, risk adjustment for congenital heart surgery; VSD, ventricular septal defect.

[a] Scores range from 1 to 6, with higher scores indicating higher risk for inpatient mortality.

## Discussion

Prevention of fluid overload in critically ill children is one of few modifiable risk factors in postoperative management. As evidence of the perils of fluid overload mounts, the conversation must shift toward treatment and prevention. This study reveals that early PD is a superior method of fluid management with a very low risk for adverse events and is associated with less-prolonged mechanical ventilation, fewer inotropic requirements, and fewer electrolyte abnormalities.

We did not find a statistically significant difference in the percentage of patients attaining negative fluid balance on POD 1. This result may be attributable to fluid removal limitations related to hemodynamic instability and ongoing capillary leak as well as timing of PD initiation, often within POD 1, which limits the net effects in this time frame. However, patients randomized to PD were less likely to develop fluid overload and had improved fluid management, including time to negative fluid balance and daily fluid balance.

Our data build on previous studies. Postoperative fluid overload has been associated with prolonged mechanical ventilation, more inotropic requirements, longer hospital stay, and increased mortality.[2,4,6,17] Positive fluid balance is associated with impaired gas exchange and reduced lung compliance.[18] Drainage of free abdominal fluid increases oxygenation.[19] Cardiac output and stroke volume are diminished in fluid overload and improve with ultrafiltration.[20]

Patients randomized to PD were less likely to require prolonged duration of mechanical ventilation. Avoidance of mechanical ventilation may decrease the incidence of ventilator-associated pneumonia, use of sedative and paralytic agents, and overall use of resources.[21-23] Ventilator-associated pneumonia is the most common nosocomial infection in the intensive care unit, associated with a doubling of mortality.[24] Furthermore, infants with congenital heart disease often have improved hemodynamics with spontaneous ventilation. Of note, prolonged ventilation was a post hoc definition, and this association must be interpreted cautiously and confirmed in future studies.

Peritoneal dialysis facilitated more fluid removal while also achieving improved electrolyte levels. Electrolyte balance is important for optimal cardiac function and prevention of serious arrhythmias. Imbalance is a risk factor for death among critically ill infants.[25] Hypokalemia may increase the risk for ventricular arrhythmias and sudden cardiac death and cause diastolic dysfunction.[26] Diuretic-induced metabolic alkalosis decreases respiratory drive and delays ventilator weaning.[27]

In a previous matched-cohort study of infants with intraoperative PDC placement,[13] patients undergoing PD had improved fluid balance, earlier extubation, improved inotrope

Table 3. Fluid Balance and Clinical Outcomes

| Outcome | Study Group[a] | | OR or DOM (95% CI) |
|---|---|---|---|
| | Peritoneal Dialysis (n = 41) | Furosemide (n = 32) | |
| Negative FB on POD 1, No. (%) | 29 (71) | 21 (66) | OR: 0.8 (0.3 to 2.1) |
| Secondary outcomes | | | |
| 10% fluid overload, No. (%) | 6 (15) | 14 (44) | OR: 3.0 (1.3 to 6.9) |
| Time to negative FB, h | 16 (8 to 32) | 24 (16 to 36) | DOM: 0 (0 to 8) |
| FB by POD | | | |
| 1 | 55 (−25 to 194) | 118 (51 to 197) | DOM: 5 (−62 to 59) |
| 2 | −251 (−379 to −125) | −201 (−343 to −100) | DOM: 42 (−26 to 118) |
| 3 | −89 (−210 to 14) | −66 (−193 to 54) | DOM: 33.5 (−53 to 116) |
| Mechanical ventilation, d | 3 (2 to 4) | 4 (2 to 6) | DOM: 1 (0 to 2) |
| Delayed extubation, No. (%)[b] | 12 (29) | 18 (56) | OR: 3.1 (1.2 to 8.2) |
| Duration of CICU stay, d | 7 (6 to 12) | 9 (5 to 15) | DOM: 1 (−1 to 4) |
| Prolonged CICU stay, No. (%)[c] | 15 (37) | 19 (59) | OR: 1.6 (1.0 to 2.7) |
| Length of hospital stay, d | 14 (9 to 22) | 15 (10 to 28) | DOM: 0.5 (−3 to 5) |
| Electrolyte finding | | | |
| Abnormality score[d] | 4 (3 to 5) | 6 (4 to 7) | DOM: 2 (1 to 3) |
| No. of repletion doses[e] | 1 (0 to 3) | 2 (1 to 5) | DOM: 1 (0 to 2) |
| BNP level by POD, pg/mL | | | |
| 1 | 1168 (555 to 2439) | 1334 (901 to 2764) | DOM: 300.5 (−251 to 886) |
| 2 | 663 (486 to 1593) | 1110 (611 to 2221) | DOM: 266.5 (−116 to 753) |
| Oxygenation index by POD[f] | | | |
| 1 | 4.0 (.03 to 5.4) | 4.0 (3.2 to 5.2) | DOM: 0 (−0.8 to 0.8) |
| 2 | 2.8 (2.2 to 4.6) | 3.8 (2.4 to 5.4) | DOM: 0.5 (−0.4 to 1.5) |
| Duration of inotropic support, d | 4.0 (3 to 6) | 5.5 (4 to 8) | DOM: 2 (0 to 3) |
| Day of delayed sternal closure | 2.5 (2 to 3) | 2.5 (2 to 3) | NA |
| Mortality, No. (%) | 1 (2) | 3 (9) | OR: 4.1 (0.4 to 41.8) |

Abbreviations: BNP, brain-type natriuretic peptide; CICU, cardiac intensive care unit; DOM, difference of medians; FB, fluid balance; IQR, interquartile range; NA, not applicable; OR, odds ratio; POD, postoperative day.

SI conversion factor: To convert BNP to nanograms per liter, multiply by 1.0.

[a] Data are presented as median (IQR), unless otherwise indicated.

[b] Indicates more than 3 days.

[c] Indicates more than 7 days.

[d] Total from PODs 1 to 5. Scores range from 0 to 4, with higher scores indicating more abnormalities.

[e] Total from PODs 1 to 5.

[f] Calculated as mean airway pressure times fraction of inspired oxygen.

scores, and fewer electrolyte level imbalances. Another cohort study[12] showed association of prophylactic PD with negative fluid balance and decreased inotrope requirements compared with passive drainage. Similarly, a propensity score-guided study[7] demonstrated that earlier PD was associated with decreased mortality among those requiring dialysis. Furosemide is used aggressively for oliguria in many CICU settings, despite studies refuting this practice among patients with AKI.[28,29]

Peritoneal dialysis faces skepticism fueled by underpowered studies. A randomized study of PD after Norwood palliations reported that PD was not associated with negative fluid balance, but more adverse effects.[30] The authors reported that 4 of 10 patients randomized to PD had cardiac arrest; however, 3 had cardiac arrest before PD initiation. The PD group had worse preoperative cardiac function and lactate levels and almost half never underwent dialysis. Some critique PD for increased costs; however, PD expenditures are offset by decreased resource use resulting in unchanged costs.[13]

We did not find a mortality difference. Surgical advancements have made death rare, and thus interventions that may affect mortality require very large samples to reveal treatment effect. Similarly, we could not comment on time to delayed sternal closure with only 18 applicable patients. We are unable to assess renal protection, because dialysis clears creatinine and long-term follow-up is not yet available.

The mechanistic effects of PD are multifactorial. Peritoneal dialysis allows for direct drainage of extravascular fluid and a decrease in edema. This effect may improve venous and lymphatic drainage and increase renal perfusion pressure.[31] Peritoneal dialysis may also modulate the cytokine milieu implicit in post-CPB capillary leak syndrome. Many investigators[12,32] postulate that PD may remove maladaptive cytokines, specifically interleukins 6 and 8, thus limiting protein and large molecule extravasation and thereby preventing capillary leak. Cytokine clearance may also prevent nephron damage, improving renal clearance.[32]

We reported adverse outcomes in all 92 randomized and nonrandomized patients undergoing PDC placement. The 2 events were minor and did not affect outcomes. Of importance, no patient had peritonitis, bowel injury, or discontinuation of PD for hemodynamic instability, cited in older studies.[9,13] Our safety profile is similar to that of most recent studies and largely attributed to the intraoperative catheter placement, use of a closed circuit replaced every 72 hours, low dwell volumes, and circuit care by trained dialysis nurses.[9,33,34] Multiple catheter placement techniques have been described with varying complication rates.[35] Our institution uses cuffed catheters placed by indirect transperitoneal methods with the cuff remaining outside the skin. Half of patients undergoing PD and weighing less than 3 kg were unable to receive dialysis owing to pleural-peritoneal communication, which likely

involved incomplete maintenance of a watertight seal after a defect was created in the extremely thin peritoneum prone to leakage. Even if dialysis does not work initially, adhesion formation may allow functional catheter use several days later.

Our findings only slightly varied when including patients who had nonfunctioning catheters in the analysis. We believe that our results are most valid and generalizable using intention-to-treat analysis. In practice, the PDC may malfunction, a problem that needs to be considered in a risk-benefit analysis.

### Limitations and Strengths

This study is, to our knowledge, the first randomized clinical trial to evaluate PD in infants and is notable for a relatively large size and regimented treatment arms. However, our study has limitations. Although the single-center design may limit generalizability, it allows control of confounding variables and was used with equipoise such that nearly all patients received the assigned treatment, avoiding withdrawal after randomization for personal preference. The starting furosemide dose (1 mg/kg every 6 hours) may be less than some would choose in particular scenarios but was chosen to avoid early postoperative hemodynamic instability. The protocol allowed dose increases after the first 2 doses. Patients randomized to the furosemide arm with inadequate diuresis were also allowed to receive dialysis at clinical discretion. Although this procedure may introduce bias, we believed this was ethically necessary, because all patients underwent PDC placement per our standard practice. Similarly, recruitment was limited to patients with normal baseline renal function because we believe that keeping a PD catheter clamped on a patient with baseline renal dysfunction and a high risk for AKI is ethically improper. Removal of these biases would only strengthen our findings. Last, our study design was potentially biased by not blinding physicians. However, all patients had PDCs, which somewhat limited this effect. Delaying randomized therapy until oliguria also potentially limited treatment effects.

This study was not powered to determine a difference in clinical outcomes. Although not statistically significant, differences in ventilation and CICU days between groups carry clinical importance and potentially statistical significance in larger cohorts. In subcategory analysis, differences were not statistically significant, presumably owing to sample size.

Additional studies on the utility of PD can be strengthened by a multicentered design and use of novel biomarkers or genetic polymorphisms predictive of AKI[36] in a biomarker-directed study. These adaptations would allow better confounder control and earlier initiation of treatment. Biomarker-guided recruitment would maximize treatment effect and study power because only high-risk patients would receive the intervention.

## Conclusions

We reveal that PD is safe and allows superior fluid management with improved clinical outcomes compared with diuretic administration among infants with oliguria after cardiac surgery. Peritoneal dialysis use should be strongly considered among those at high risk for AKI and subsequent fluid overload. Our findings highlight the need for a larger, multicentered study to understand the benefits of PD.


### ARTICLE INFORMATION

**Accepted for Publication:** November 20, 2016.

**Published Online:** February 20, 2017. doi:10.1001/jamapediatrics.2016.4538

**Author Contributions:** Dr Kwiatkowski had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Kwiatkowski, Goldstein, Nelson, Morales, Krawczeski.
*Acquisition, analysis, or interpretation of data:* Kwiatkowski, Goldstein, Cooper, Nelson, Krawczeski.
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*Study supervision:* Kwiatkowski, Goldstein, Nelson, Morales, Krawczeski.

**Conflict of Interest Disclosures:** Dr Goldstein reports consulting, speaker's bureau, and grant support from Baxter International/Gambro Renal Products and consulting for Akebia Therapeutics, AM-Pharma BV, Bellco Health Corporation, La Jolla Pharmaceutical Company, and Otsuka Pharmaceutical Company. No other disclosures were reported.

**Funding/Support:** This study was supported by grant 13POST16240002 from the American Heart Association–Great Rivers Affiliate and internal funding from Cincinnati Children's Hospital Medical Center.

**Role of the Funder/Sponsor:** The funders had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.


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