The use of cardiopulmonary bypass (CPB) during cardiac surgery is associated with the development of systemic inflammatory response syndrome (SIRS) and ischaemia–reperfusion injury. These events stimulate the production and release of cytokines, complement activation products, endotoxin, and adhesion molecules. The effects of these proteins, particularly the pro-inflammatory cytokines, include a widespread increase in microvascular permeability leading to interstitial oedema and an increase in total body oxygen consumption, and direct injury to major organs. In the clinical setting, SIRS commonly manifests as a low cardiac output syndrome (LCOS), which is seen in up to 25% of infants and children after CPB. LCOS can result in major adverse events (cardiac arrest, emergency chest reopening, requirement for extracorporeal membrane oxygenation [ECMO] and death), prolonged mechanical ventilation, longer intensive care unit (ICU) and hospital stay, and organ injury.

Several therapies that modulate CPB-induced SIRS are currently being used or studied in clinical trials; these include glucocorticoid therapy, modified ultrafiltration, use of heparin-bonded circuits and, very recently, nitric oxide infused through the oxygenator in the CPB circuit. Collectively, these strategies and other developments may have been responsible for improvements in post-operative outcomes. However, as all these treatments are applied in the pre-operative or intraoperative period, their roles in attenuating continued SIRS and release of inflammatory mediators, and in providing sustained protection in the post-operative period of intensive care, are expected to be minimal.

Peritoneal dialysis (PD), a type of renal replacement therapy, is often used in infants and children after cardiac surgery. It offers bidirectional exchange of fluid and solute between the dialysis fluid and blood across the peritoneal membrane. PD has also been used for the management of LCOS, as a way of reducing tissue oedema and improving organ function by removing CPB-induced inflammatory mediators. While the normal peritoneal membrane is relatively impermeable to...
protein, in SIRS following CPB there is a marked increase in capillary permeability. Studies of paediatric patients have shown that after cardiac surgery the peritoneal fluid has high concentrations of inflammatory mediators and that removal of peritoneal fluid might lower serum concentrations of these mediators.\textsuperscript{11-13} Observational studies have shown an association between early commencement of PD after cardiac surgery and decreased mortality.\textsuperscript{14,15}

Taken together, evidence from mainly observational studies suggests that early PD (initiated soon after admission to ICU following cardiac surgery) may be associated with lower mortality, a more negative fluid balance, shorter duration of mechanical ventilation, and shorter ICU length of stay. To our knowledge, these observations have not previously been tested in a randomised controlled trial. PD is a low cost intervention that could have important positive implications for the outcomes of childhood heart disease globally. We therefore plan to randomly assign infants ≤180 days of age who are admitted to intensive care after cardiac surgery to early prophylactic PD (initiated at time of ICU admission) or conventional management. The objective of this study — the Early Peritoneal Dialysis in Infants after Cardiac Surgery (EPICS) trial — is to test the hypothesis that PD initiated soon after admission to ICU following cardiac surgery would result in a lower rate of major adverse events such as cardiac arrest, emergency chest reopening, requirement for ECMO and death. The study will also test whether early PD results in a shorter duration of mechanical ventilation, and ICU and hospital length of stay.

\textbf{Methods}

\textbf{Trial design and participants}

The EPICS trial is a 312-patient, open, randomised (1:1 ratio), two-group, single-centre clinical study of infants ≤180 days of age who are recovering from surgery for congenital heart disease that involved cardiopulmonary bypass. It will be conducted in the Cardiac Intensive Care Unit of the Royal Children’s Hospital Melbourne in Victoria, Australia.

\textbf{Screening, identification and recruitment}

Potential study participants will be identified by the research team from the pre-operative cardiac surgery list and from patients already in intensive care who are due to have cardiac surgery. In this setting, the study will be described to each potential participant’s parent or legal guardian, who will also be provided with written information on the study. A member of the study research team will then have an informed consent discussion with the parent or legal guardian. Written informed consent will be obtained from the parent or legal guardian before any study-related procedures are performed. A record will also be maintained of all patients screened for the study and reasons for non-participation. When all the inclusion and exclusion criteria (Table 1) have been addressed and the eligibility of a participant confirmed, the participant will be assigned to a study arm.

\textbf{Study arms and study intervention}

Infants in the treatment arm will start to receive PD as soon as possible after admission to ICU following cardiac surgery (no later than 60 minutes after ICU admission). PD will be commenced using 1.5% dextrose dialysate solution at a dose of 10 mL/kg body weight using 1-hour cycles. Each cycle will be divided into a 10-minute cycle-in duration, a 30-minute dwell duration and a 20-minute cycle-out duration. The treatment will be provided for a total of 24 hours (24 cycles). If an infant is extubated within 24 hours after cardiac surgery, the treatment will be stopped before extubation. The treatment will be administered by the bedside nurse looking after the infant.

Infants in the control arm will not routinely receive PD during the first 24 hours after ICU admission. The PD catheter will be left clamped during this period. However, PD may be started in the first 24 hours in the control group if the patient has:
- a serum potassium level of ≥6.5 mmol/L;
- severe metabolic acidosis (pH < 7.25 with arterial partial pressure of carbon dioxide of <40 mmHg); or
- a urine output of <0.5 mL/kg/h for 6 hours or more despite furosemide infusion.

\begin{table}
\centering
\begin{tabular}{|l|}
\hline
\textbf{Table 1. Study inclusion and exclusion criteria} \tabularnewline
\hline
\textbf{Inclusion criteria} & \tabularnewline
\hline
- Aged ≤180 days old & \\
- Underwent cardiac surgery (in RACHS-1 categories 3–6) with cardiopulmonary bypass & \\
- Has peritoneal dialysis catheter in place at time of admission to intensive care unit & \\
- Expected to be ventilated for at least 24 hours & \\
\hline
\textbf{Exclusion criteria} & \tabularnewline
\hline
- On ECMO when leaving operating theatre & \\
- Already participated in the same trial during a previous cardiac surgery & \\
- Withdrawal of treatment is being considered & \\
- Consent not provided by parent or legal guardian & \\
\hline
\end{tabular}
\caption{ECMO = extracorporeal membrane oxygenation. RACHS-1 = Risk-Adjusted Classification for Congenital Heart Surgery version 1.}
\end{table}
Randomisation and blinding

Eligible infants will be randomly assigned at the time of ICU admission to early PD (treatment group) or no early PD (control group). A randomisation sequence will be computer generated, facilitated by an independent statistician, using REDCap (Research Electronic Data Capture) — a secure, web-based application designed to support data capture for research studies. Randomisation will be in blocks and stratified by RACHS-1 category (category 3 or 4, or category 5 or 6). The randomisation sequence will be determined before the study starts and concealed. Equal numbers of patients will be allocated to each study group. Given the nature of the study, bedside clinicians, nurses and families will be aware of the study group assignment.

Study outcomes

The primary outcome will be a composite of one or more of: death from any cause, cardiac arrest, emergency chest reopening, and requirement for ECMO within 90 days after randomisation. The secondary outcomes will be:

- duration of mechanical ventilation;
- ICU length of stay;
- hospital length of stay;
- cumulative per cent fluid balance by end of Day 2 (with day of admission defined as Day 1);
- events (death from any cause, cardiac arrest, emergency chest reopening and requirement for ECMO) within 90 days;
- vasoactive-inotropic score (VIS) at 24 hours after randomisation, maximum VIS in the first 24 hours, and number of days receiving vasoactive medications within 90 days (with medications used in the calculation of VIS data being adrenaline, dobutamine, dopamine, milrinone, noradrenaline and vasopressin);
- incidence of post-operative hospital-acquired infection (blood stream, pulmonary, urinary tract, wound and other) within 90 days;
- volume of packed red blood cell transfusion (indexed to body weight) within 90 days;
- rate of readmission to ICU within 90 days;
- renal injury requiring renal replacement therapy within 90 days;
- incidence of brain injury (new seizures or neuroimaging findings) within 90 days;
- acute health care costs at 12 months after randomisation (overall hospital costs based on ICU and hospital length of stay) calculated using previously defined methods;
- and
- long term health-related quality of life of study participants, measured 3 years after study intervention via telephone interview of parents and guardians using the Pediatric Quality of Life (PedsQL) tool.

Biomarkers

We also plan to measure and analyse levels of inflammatory biomarkers (interleukin 6, interleukin 8, interleukin 10, tumour necrosis factor alpha), cardiac biomarkers (troponin, brain natriuretic peptide), renal biomarkers (interleukin 18, neutrophil gelatinase-associated lipocalin) and renal tubular stress biomarkers (tissue inhibitor of metalloproteinase 2, insulin-like growth factor binding protein 7) in blood samples of study participants at three time points — at baseline (ICU admission, before study intervention), at 6 hours of ICU admission and at 24 hours of ICU admission. Blood samples will be processed, placed in microfuge tubes, and stored at −80°C for later batch analysis. Among organs, the kidneys are particularly vulnerable to the effects of CPB; it is estimated that up to 50% of children develop acute kidney injury after cardiac surgery. Oxidative stress, inflammation and ischaemia are prominent mechanisms leading to acute kidney injury after CPB and we plan to analyse biomarkers of all these mechanisms. Creatinine is the most widely used biomarker of renal function in clinical practice. Pre-operative creatinine and serial daily creatinine measurements from routine blood measurements will be collected and analysed to see if there are differences in acute kidney injury between study groups, and examine possible relationships between creatinine and other renal biomarkers.

Data collection and management

The study investigators will ensure accuracy, completeness and timeliness of data reporting. The main source document for each participant will be their electronic medical record, and the study research team will maintain data collection in the study database. REDCap will be used for data collection and management.

Data relating to key screening and eligibility variables will be collected. A draft study consort flow chart is shown in Figure 1. For infants ≤ 180 days old who are undergoing surgery with CPB (in RACHS-1 categories 3–6), consent for participation will be sought before surgery and random assignment will be done at the end of surgery, when study eligibility is confirmed (eg, when it is confirmed that they had a procedure including CPB, are not on ECMO when leaving the operating theatre, and have a PD catheter). Patients for whom consent is obtained but who are not randomly assigned (due to being on ECMO when leaving the operating theatre or other exclusion criteria) will not be included in the study analysis. Data relating to baseline variables (demographics and cardiac diagnosis), operative variables (nature and type of surgery, RACHS-1 category, CPB and
cross-clamp duration, use of intraoperative steroids, use of modified ultrafiltration, use of deep hypothermic circulatory arrest, and open chest when leaving the operating theatre), post-operative variables (VIS, volume of fluid given, fluid balance on midnight of Day 2, pre-operative and post-operative serial creatinine levels, and post-operative steroid use) along with previously mentioned primary and secondary endpoints will be collected in REDCap.

**Adverse events**

All adverse events will be recorded in the intervention arm and their relationship with the study intervention will be assessed by the study investigators. Most adverse events related to peritoneal catheters are mechanical and include leakage around the exit site, catheter blockage (sometimes necessitating catheter replacement), accidental dislodgment, inadequate drainage, hydrothorax and haemoperitoneum. Peritonitis and intestinal perforation are rare complications that have been reported. Haemodynamic instability (hypotension requiring treatment) due to fluid shifts is an expected adverse event and may occur with PD use. Adverse events can be either expected or unexpected, and the causality of adverse events will be graded as not related, possibly related, probably related and definitely related to the study intervention. It is well known that infants recovering from cardiac surgery may experience aberrations in their clinical condition and laboratory parameters; events that are part of the natural history of the post-operative low cardiac output state or related to the critical nature of the infant’s illness will not be reported as adverse events. Events that are either primarily or secondarily collected as study outcomes will not be separately reported as adverse events.

**Ethics approval**

The Human Research Ethics Committee at Royal Children’s Hospital Melbourne reviewed the study protocol, parent information, consent form and other study documents, and provided approval for the trial (HREC/17/RCHM/246) before it started. Any changes to the study protocol or parent information will be documented and added as an amendment to the study documents. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001614381).

**Data and safety monitoring committee**

An independent data and safety monitoring committee (DSMC) will oversee the safety and progress of the trial. The DSMC will consist of senior clinicians, researchers and a statistician. The DSMC will review the study’s progress and
provide advice to the principal investigator. The DSMC will advise if the trial should be stopped owing to:
• futility, if it is evident that no clear outcome can be obtained from the current study;
• efficacy, based on a P value of < 0.001 after at least 50% or 75% of composite primary outcome events, using the Haybittle–Peto rule; or
• safety (serious side effects from PD), determined using the Pocock stopping rule with a P value of < 0.0221 (if three interim analyses are planned) or P value of < 0.01 (if 5–10 interim analyses are planned) after at least 50% or 75% of the planned sample size (or at any time the DSMC determines).

The DSMC will also review major proposed modifications to the trial (such as termination, or an increase in sample size) and provide advice to the principal investigator. The DSMC will meet face to face or by conference call before the start of the study, after the first 50 patients are randomly assigned, and at about 6–9-month intervals after that (or as determined by the DSMC).

Sample size
Data collected in the Cardiac Intensive Care Unit of the Royal Children’s Hospital Melbourne during the period 2012–2015 were used to calculate the primary endpoint rate in children who had a PD catheter after cardiac surgery. Out of 239 infants started on PD during this period, early PD was associated with the composite primary outcome in 5% and late PD in 20%. Based on an expected composite primary outcome rate of 20% in the control group and 5% in the treatment group, we calculated that we would need a total of 39 primary endpoints using an alpha of < 0.01 and power of 90%. This would require a total of 312 participants — 156 infants per study arm.

Statistical analysis plan
The analysis will be done on an intention-to-treat basis. For analysis of the primary outcome, Cox regression adjusted for age at the time of randomisation, body weight, CPB duration and RACHS-1 category, and with censoring at the time of loss to follow-up, will be used to calculate hazard ratios with 95% confidence intervals (CIs). Alternatively a test (or Fisher’s exact test) may be used for the primary outcome if loss to follow-up is minimal. Risk ratios and risk differences between groups will also be calculated (with 95% CIs). Measures of the spread of the data will include 95% CI, standard deviation, and interquartile range as appropriate. For secondary outcomes, appropriate tests for proportions (test or Fisher’s exact test) will be used for categorical variables, and the unpaired t test (if normality assumptions are met) or the rank-sum test will be used for continuous variables. For duration of mechanical ventilation, ICU length of stay and hospital length of stay, Poisson regression (with robust standard errors) or negative binomial regression (with robust standard errors) as appropriate will be used to obtain incidence rate ratios (with 95% CIs). For data on creatinine and other biomarkers, repeated measures linear mixed models will be used to report differences in estimates between study groups. The difference in health-related quality of life between groups will be analysed using ordinary linear regression, adjusting for baseline differences, and reported as mean difference (95% CI).

The pre-specified groups for subgroup analyses are: RACHS-1 category (category 3 or 4 versus category 5 or 6) and CPB duration (≤ 150 minutes versus > 150 minutes). An appropriate interaction term will be used to test whether the subgroups are associated with different treatment outcomes. All statistical tests will be two sided. For the primary outcome variable, a lower P value will be used to allow for appropriate alpha spending, determined by the number of planned interim analyses. Statistical analysis will be performed using Stata software (StataCorp).

Potential study implications
PD is used in the majority of paediatric cardiac intensive care units. Around 1.35 million children are born each year with congenital heart disease; 90% of them live in low income and middle income countries, which are increasingly performing complex cardiac operations in paediatric patients but lack access to adequate care. PD is a low-cost intervention and, if the study hypothesis can be confirmed, it could have important positive implications for childhood heart disease globally.

Summary
The EPICS trial is an open, randomised, two-group, single-centre clinical study that will determine whether early PD initiated soon after admission to intensive care following cardiac surgery results in a lower rate of a composite outcome (one or more of death from any cause, cardiac arrest, emergency chest reopening and requirement for ECMO) within 90 days after randomisation. The trial will also study the effect of the intervention on other important outcomes such as duration of mechanical ventilation, length of ICU stay, length of hospital stay, acute health care costs and long term health-related quality of life.

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Competing interests
All authors declare that they do not have any potential conflict of interest in relation to this article.

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References