THE SALINE VS ALBUMIN FLUID EVALUATION - EXTRAPOLATION TO PAEDIATRIC INTENSIVE CARE (SAFE-EPIC) STUDY: STATISTICAL ANALYSIS PLAN

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Introduction

Parenteral resuscitation fluid administration is one of the commonest interventions in any critically ill infant or child in the intensive care unit. Nevertheless, the volume and type of fluid used and the exact timing and indications for this intervention remain poorly described. Unlike adult intensive care where several studies have attempted to identify benefit associated with crystalloid or colloid resuscitation fluids, there is at present no firm evidence upon which to base practice in critically ill infants and children.

The SAFE-EPIC study is an international collaboration led by the Australian and New Zealand Intensive Care Society - Paediatric Study Group (ANZICS-PSG) and The George Institute for Global Health in collaboration with international research partners.

MAIN AIMS, OUTCOMES AND PLANNED STATISTICAL ANALYSIS

The 4 main aims of SAFE-EPIC are described here, together with the planned analysis of data and estimated power of SAFE-EPIC to determine each outcome of interest.

STUDY AIM 1: Document current practice and specifically the proportion of paediatric patients (0 – 16 years old) that receive a fluid resuscitation bolus in intensive care on the study day.

This will be determined for the cohort as a whole and also for each region or grouping with sufficient numbers of patients to allow an accurate estimate to be made. The number of patients required to adequately power this estimate is based on data from a pilot study with similar methodology conducted in Australia and New Zealand paediatric intensive care units, which showed that 14% of patients received any fluid resuscitation bolus (including blood products) on the study day[1]. Allowing a 5% precision error and aiming for confidence interval of 95%, it is estimated that at least 185 patients need to be included for each region or grouping in the analysis. If however the actual proportion of patients receiving a fluid resuscitation bolus in the study cohort is similar to that reported in adult intensive care (37%)[2], the number of patients required for each region or grouping is 359.

Descriptive statistics will be used to describe all patients in the study cohort (i.e. the denominator) and to report the following:

- Unit characteristics (Paediatric/Adult/Mixed and Cardiac/Medical/Surgical)
- Demographics (age, gender, weight)
- ICU admission type and source
- Diagnosis and Diagnostic categories (utilising ANZICS Paediatric Registry classification and pre-determined criteria for trauma/cyanotic heart disease/sepsis/ARDS or ALI)
- Paediatric Index of Mortality (PIM 2) risk of death, organ dysfunction (PeLOD) risk of death, renal failure (creatinine) and oedema scores
- Prevalence of red blood cell transfusion on the study day
- ICU and Hospital length of stay and outcomes on Day 28 (or hospital discharge if earlier)

In addition, the following will be described in patients receiving any fluid bolus on the study day (i.e. the numerator):

- The type of resuscitation fluid given (crystalloid vs colloid)
- Main indication for fluid resuscitation
- Other indications for fluid resuscitation
- Prescriber characteristics (position, age group, level and speciality, experience)

- Physiological and biochemical status of the patient prior to fluid administration
- Fluid bolus characteristics (volume [per kg], rate of infusion)
- Method of administration of fluid resuscitation
- Fluid totals for the study day

STUDY AIM 2: Describe regional and national variations in choice of resuscitation fluids.

Descriptive statistics will be used to outline the type of fluid used in each country and each region in the study cohort. Predetermined regions or groupings are based on established regional intensive care networks, or published levels of national wealth and healthcare expenditure, ascertained by reported per capita Gross Domestic Product (GDP) and per capita Health Spend (HS) respectively[3]. Estimates of numbers of patients likely to be included in each region or grouping are made from data submitted by sites willing to participate in SAFE-EPIC as part of the formal Expression of Interest (EOI). Variation within and between regions will be described. The statistical challenges of analysis of this type of inception cohort study are compounded by the possibility of multiple fluid resuscitation boluses in the same patient on the study day. Hence the study design has specified the inclusion of *only the first fluid resuscitation bolus* on the study day. Using this method, it is hoped that sufficient numbers of patients may be recruited in each region to achieve the secondary aim of demonstrating any regional variation in type of fluid used (colloid vs crystalloid).

STUDY AIM 3: Determine identifiable unit and patient characteristics that influence choice of resuscitation fluids.

In order to determine significant unit and patient factors (as well as regional factors) associated with fluid choice, a logistic regression analysis will be conducted, with fluid choice as a dichotomous outcome (colloid vs crystalloid).

A preliminary analysis will be conducted to assess the strength of association between each individual factor of interest (including regional, demographic and clinical factors) and fluid choice. The variables to be considered are listed below. Covariates with an associated p value of < 0.2 will be identified, and a logistic regression analysis will then be conducted using these predictor variables, with colloid vs crystalloid choice as a dichotomous outcome. Results from this analysis will be considered significant if $p<0.05$.

Two predictive models will be developed:

Model 1 – What factors predict administration of a fluid resuscitation bolus in ICU? (Relates to Aim 1):

Predictor variables to be considered for inclusion in model 1 are:

- Season
    - summer
    - winter
- Region (recognised network or geographical proximity / per capita GDP grouping / per capita health spend grouping) – see Table 1 to 3 in Appendix 1 for subgroups
- Unit characteristics (Paediatric/Adult/Mixed and Cardiac/Medical/Surgical)
    - Paediatric vs Adult and Paediatric ("Mixed") intensive care unit
    - Paediatric cardiac case-mix only
    - Paediatric medical and/or (non-cardiac) surgical case-mix only
    - Paediatric cardiac and medical +/- (non-cardiac)surgical case mix (i.e. "all")

- Demographic variables (gender, age)
    - Gender:
        - Male
        - Female
    - Age
        - Neonate (0-28 days)
        - Infant (>28 days – 1 year)
        - Child (>1 year - 12 years)
        - Adolescent (>12 – 17 years)
- ICU admission type/source
    - Emergency department
    - Hospital floor (Ward)
    - Transfer from another ICU
    - Transfer from another hospital (except from another ICU)
    - Admitted from operating theatre
- Emergency or elective admission
- Cardiopulmonary bypass immediately prior to admission ICU (Yes/No)
- Diagnostic category
    - Trauma as admission diagnosis (yes/no)
    - Sepsis on study day (yes/no)

    - ARDS or ALI on study day (yes/no)
- Admission PIM score (% predicted risk of death)
    - 0-1%
    - >1-5%
    - >5-15%
    - >15-30%
    - >30%
- Predicted risk of death (%) from study day PELOD score (= 1/ (1 +_exp[7.64-0.30*dayPELOD score])
    - 0-<1%
    - 1-<5%
    - 5-<15%
    - 15-<30%
    - ≥30%
- Oedema score (0 – 3)
    - None (=0)
    - Mild (=1)
    - Moderate (=2)
    - Severe (=3)
- Any Red Blood Cell transfusion on study day
    - Yes
    - No

Model 2 - What factors predict the type of fluid resuscitation bolus given to children that receive a fluid resuscitation bolus in ICU? (Relates to Aim 2 and 3):

Predictor variables to be considered for inclusion in model 2 include ALL FACTORS considered in model 1 PLUS the following:

- Intensive care treatments on the study day (mechanical ventilation, non-invasive respiratory support, CPR, ECMO, renal replacement therapy, intracranial pressure monitor, vasopressors or inotropes, red cell transfusion). All as individual Yes/No fields.
- Clinical and laboratory results (Heart rate, CVP, systolic ABP, urine output, base excess or deficit, arterial blood lactate, arterial pH, creatinine, albumin, haemoglobin, platelet, INR, activated partial thromboplastin time, fibrinogen)

- Heart rate (bpm)
  - <12years
    - 50 – 195
    - <50 or >195
  - ≥12 years
    - 40 – 150
    - <40 - >150
- CVP (mmHg)
  - All ages
    - <5
    - 5 – 10
    - >10
- Systolic Blood Pressure (mmHg)
  - <28 days
    - <35
    - 35 – 65
    - >65
  - 28 days - <1 year
    - <35
    - 35 – 75
    - >75
  - 1 - <12 years
    - <45
    - 45 – 85
    - >85
  - ≥12 years
    - <55
    - 55 – 95
    - >95
- Urine output (ml/kg/hr)
  - All ages
    - 0 - <0.5
    - 0.5 - <1.0
    - ≥ 1.0

- Base excess or deficit (mEq/L)
  - All ages
    - 0-<7
    - ≥7
- Lactate (mmol/L)
  - All ages
    - <2
    - ≥2
- Arterial pH
  - All ages
    - <7.30
    - ≥7.30
- Creatinine (µmol/L)
  - <7 days
    - >140
    - 0 – 140
  - 7 days – 1 year
    - >55
    - 0 – 55
  - >1 – 12 years
    - >100
    - 0 – 100
  - >12 years
    - >140
    - 0 – 140
- Albumin (g/L)
  - All ages
    - <25
    - 25 – 40
    - >40
- Haemoglobin (g/dL)
  - All ages
    - <7
    - 7 – 10

        - >10
    - Platelet
        - All ages
            - <35
            - ≥35
    - INR
        - All ages
            - >2
            - ≤2
    - APTT (s)
        - All ages
            - >60
            - ≤60
    - Fibrinogen (g/L)
        - All ages
            - <1
            - ≥1
- Main indication for fluid resuscitation
    - Hypotension
    - Increasing inotrope or vasopressor requirements
    - Low CVP
    - Tachycardia
    - Low urine output
    - Low measured cardiac output
    - Low SvO2 or ScvO2
    - Ongoing bleeding
    - Other ongoing fluid loss
    - Prolonged capillary refill time as evidence of poor peripheral perfusion
    - Other evidence of poor perfusion
    - Increasing or persisting acidosis or blood lactate
    - Any other
- Main and Other indications for fluid resuscitation
    - Hypotension
    - Increasing inotrope or vasopressor requirements

- Low CVP
- Tachycardia
- Low urine output
- Low measured cardiac output
- Low SvO2 or ScvO2
- Ongoing bleeding
- Other ongoing fluid loss
- Prolonged capillary refill time as evidence of poor peripheral perfusion
- Other evidence of poor perfusion
- Increasing or persisting acidosis or blood lactate
- Any other

- Prescriber characteristics
  - Prescriber type: Position, age group, level and speciality, experience)
    - ICU doctor
    - Non-ICU Surgical doctor
    - Non-ICU Medical or Paediatric doctor
    - ICU Nurse
    - Any Other
  - Prescriber age
    - ≤ 30 years
    - 31-40 years
    - 41-50 years
    - 51-60 years
    - > 60 years
  - Experience as medical specialist
    - 0 years
    - 1-5 years
    - 6-10 years
    - 11-15 years
    - 16-20 years
    - 21-25 years
    - 26-30 years
    - > 30 years

- Non-medical health professional

DATABASE DESIGN, DATA CLEANING AND MISSING DATA

The case report form collected data on all patients in ICU on the study day, including PICU and hospital outcomes on day 28 following the study day. Additional information on the first fluid resuscitation episode (excluding blood or platelets) was collected only if respondents answered yes to a 2-part question that confirmed the amount and purpose of fluid administration.

Other fields have been designed to be either/or fields, or in other words for the electronic database to reveal only relevant questions and to conceal others depending on how a trigger question has been answered. In this way it should not be possible for participants to describe more than one fluid resuscitation bolus for the first instance of fluid resuscitation. This function also forces respondents to only describe a crystalloid or a colloid fluid resuscitation bolus.

Following completion of both study dates, a systematic data cleaning process will be undertaken. The first step will be to check study records for duplicate entries and to close the study database to any new patient records. The data-cleaning process will then check to see if submitted data for the site is within specified data ranges. Age of participant on the study day will be used to remove any study subjects 17 years or older from the final analysis. For other fields relating directly to missing data or inconsistent data relating to a fluid resuscitation bolus, a direct email query will be sent to the study site prior to a final decision on whether to exclude these data. Data outside of the specified ranges will not be used in the analysis unless an email is received back from the study site confirming the data is correct.

Missing Data

Missing data will be minimised by the automatic generation of an error notice by the electronic database during data entry. There will be no imputation for missing data unless specified in an existing publication as part of normal process for missing data pertaining to a mortality[3] or organ failure scoring system[4]. The exact numbers of patients involved in the analysis for each data point will be given as part of the final analysis.

Participating Centre and Units of Measurement Checks

The units specified for a given data field in a participating centre's submitted patient records will be cross-checked against plausible ranges for the reported parameter in that unit of measurement. In cases where data is noted to be within a plausible data range consistent with only one of the units of measurement offered in the CRF, then the units will be confirmed with the site or reallocated by the study CI. Where data falls between two plausible data ranges, the unit entered into the CRF will be retained.

Where no unit is entered on the CRF, then in cases where data is noted to be within the plausible data range of only one of the units of measurement offered in the CRF, then the unit will be appropriately allocated by the study CI. Where data falls between two plausible data ranges, then an email query sent to all participating centres requesting confirmation of units used in submitted data will be used to allocate the appropriate unit. If no response to data querying is received from the participating centre, or where the unit confirmed by the participating centre still results in data outside of plausible ranges, then the data point will be omitted from analysis and noted as missing.

Appendix 1: Description of the study cohort by region or economic grouping

Table 1: Geographical regions or intensive care networks

Region or Network	Countries (Networks) included	Estimated number of study participants
ANZ	Australia, New Zealand (ANZICS)	242
Asia	China, India, Japan, Malaysia, Sri Lanka, Singapore, Vietnam	158
Canada	Canada (CCCTG)	164
Europe*	Belgium, Czech Republic, France, Germany, Italy, Luxembourg, Netherlands, Portugal, Romania, Slovenia, Spain, Switzerland, Turkey (ESPNIC)	734
South America	Argentina, Brazil	140
United Kingdom	United Kingdom (PICS_UK)	418
United States of America	United States of America (PALISI)	724
Africa and Saudi Arabia	Saudi Arabia, South Africa, Tunisia	188

*excludes United Kingdom, includes Turkey

Table 2: Per capita Gross Domestic Product

Per Capita GDP (US$)	Countries included	Estimated number of study participants
<30,000	Argentina, Brazil, China, Czech Republic, India, Malaysia, Portugal, Romania, Saudi Arabia, South Africa, Slovenia, Spain, Sri Lanka, Tunisia, Turkey, Vietnam	370
≥30,000 - <40,000	France, Italy, New Zealand, United Kingdom	414
≥40,000 - <50,000	Belgium, Germany, Japan, Netherlands, United States of America	662
≥50,000	Australia, Canada, Luxembourg, Singapore, Switzerland	330

*from World Bank (2012) (http://data.worldbank.org/indicator/NY.GDP.PCAP.D)

Table 3: Per capita health spend

Per Capita Health Spend (US$)	Countries included	Estimated number of study participants
<1,000	Argentina, China, India, Malaysia, Romania, Saudi Arabia, South Africa, Sri Lanka, Tunisia, Turkey, Vietnam	257
≥1,000 - <3,500	Brazil, Czech Republic, Italy, Portugal, Singapore, Slovenia, Spain	205
≥3,500 - <4,500	Japan, New Zealand, United Kingdom	354
≥4,500 - <6,000	Australia, Belgium, Canada, France, Germany, Netherlands	366
≥6,000	Luxembourg, Switzerland, United States of America	569

*from World Bank (2012) (http://data.worldbank.org/indicator/SH.XPD.PCAP/countries)[5]

Appendix 2: Table skeletons for planned analysis

Table 4: Proportion of study participants receiving fluid resuscitation according to country and geographical region

Country / Region	No. participating ICUs (n/% of total)	No. children surveyed (n/% of total)	No. children given resuscitation fluid (n/% of total)
Country 1			
Country 2			
etc			
Region A			
Country 7			
Country 8			
etc			
Region B			
Country xx			
Region C			
etc			
TOTAL			

Table 5: Characteristics of children who received a fluid resuscitation bolus (n= x x)

(Note: this is a descriptive table to show demographic data and other patient characteristics including outcome)

Age
Sex
Admission source
• Emergency department
• Hospital floor/ward
• Transfer from another ICU
• Transfer from another hospital (except an ICU)
• Operating theatre (following elective surgery)
• Operating theatre (following emergency surgery)
Completed days in intensive care
PIM risk of death on admission to intensive care
dPELOD risk of death on study day
28-day mortality (died in hospital or ICU ≤28 days after study date)
Completed days in ICU prior to death or ICU discharge

Table 6: Association between fluid resuscitation and key hospital, prescriber and patient variables

		Crude logistic regression		Adjusted logistic regression*	
	Prevalence (95% CI)	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Intensive Care Unit Characteristics					
Season					
Geographical region					
National per capita GDP grouping					
Per capita health spend grouping					
Unit type					
Patient Characteristics					
Gender					
Age					
Admission source					
Admission type (elective/emergency)					
CPB immediately prior to admission					

Diagnostic category					
Admission PIM ROD					
dPELOD ROD					
Oedema score					
Any blood transfusion on the study day					

* Adjust OR and its p-value for a variable are reported only if the variable is included into multiple logistic model (crude p-value>0.2) and has a p-value<0.05 in the adjusted model

Table 7: Characteristics of fluid resuscitation bolus

Volume of resuscitation fluid bolus given
• Crystalloid
• Colloid
Rate of administration
• Crystalloid
• Colloid
Mode of administration (device /method used) - all
• Fluid infusion pump
• Syringe driver
• Manual push using syringe
• Manual push using intravenous rapid infuser set
• Other

Table 8: Association between type of fluid used for resuscitation and key hospital, prescriber and patient variables

		Crude logistic regression		Adjusted logistic regression*	
	Prevalence (95% CI)	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Intensive Care Unit Characteristics					
Season					
Geographical region					
National per capita GDP grouping					
Per capita health spend grouping					
Unit type					
Patient Characteristics					
Gender					
Age					
Admission source					
Admission type (elective/emergency)					
CPB immediately prior to admission					
Diagnostic category					
Admission PIM ROD					
dPELOD ROD					
Oedema score					
Intensive care therapies					
Clinical and laboratory data					
HR					
CVP					
Systolic BP					
Urine output					
Base excess or deficit					
Lactate					
Arterial pH					
Creatinine					
Albumin					
Hb					
Platelets					
INR					
APTT					
Fibrinogen					
Main indication for fluid resuscitation					
Prescriber Characteristics					

Prescriber specialty					
Prescriber age					
Prescriber experience					

*Adjust OR and its p-value for a variable are reported only if the variable is included into multiple logistic model (crude p-value>0.2) and has a p-value<0.05 in the adjusted model

See Aim 3 and Appendix 1 for additional information for this table / analysis

Appendix 3: Figure description and type

Figure 1: Vertical bar graph to show proportion of children receiving fluid resuscitation according to completed days in PICU

(x-axis: 0, 1, 2, 3, 4 , 5, 6+ completed days of ICU)

(y-axis: 2 columns per day of ICU. First column % total cohort on that day NOT receiving fluid, 2nd column % total cohort on that day receiving fluid resuscitation)

Figure 2: Vertical bar graph to show number of fluid resuscitation episodes given as crystalloid and colloid according to country and geographical region

(x-axis: too many countries to include all, hence plan to include up to 5 countries max per region, selecting the countries with greatest number of fluid resuscitation episodes, plus "others in region" and summary bars for each region and total)

(y-axis: crystalloid and colloid bars. Colloid bar to show division into 3 subcategories: albumin, FFP or, artificial colloid [any])

Figure 3: Vertical bar graph to show number of fluid resuscitation episodes given as crystalloid and colloid according to diagnostic category

(x-axis categories to include: trauma-no head injury [include burns], head injury, emergency or elective admission from operating theatre [no cardiopulmonary bypass], emergency or elective admission from operating theatre following cardiopulmonary bypass, sepsis, ARDS [include ALI])

(y-axis: crystalloid and colloid bars. Colloid bar to show division into 3 subcategories: albumin, FFP or, artificial colloid [any])

NB: It is possible that some patients may be in more than 1 category

Figure 4: Vertical bar graph (histogram) of main indication for fluid resuscitation

Note: Only one indication per patient "main indication", question 2.3 on CRF.

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