Fluid in Paediatric Sepsis

It’s a drug – and we still don’t know the dose

John F Fraser
Background: Fluid resuscitation
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

**Table 4. Treatments Administered.***

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hours after the Start of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–6</td>
</tr>
<tr>
<td>Total fluids (ml)</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>3499±2438</td>
</tr>
<tr>
<td>EGDT</td>
<td>4981±2984</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Red-cell transfusion (%)</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>18.5</td>
</tr>
<tr>
<td>EGDT</td>
<td>64.1</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any vasopressor (%)†</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>30.3</td>
</tr>
<tr>
<td>EGDT</td>
<td>27.4</td>
</tr>
<tr>
<td>P value</td>
<td>0.62</td>
</tr>
<tr>
<td>Inotropic agent (dobutamine) (%)</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>0.8</td>
</tr>
<tr>
<td>EGDT</td>
<td>13.7</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical ventilation (%)</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>53.8</td>
</tr>
<tr>
<td>EGDT</td>
<td>53.0</td>
</tr>
<tr>
<td>P value</td>
<td>0.90</td>
</tr>
<tr>
<td>Pulmonary-artery catheterization (%)‡</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>3.4</td>
</tr>
<tr>
<td>EGDT</td>
<td>0.0</td>
</tr>
<tr>
<td>P value</td>
<td>0.12</td>
</tr>
</tbody>
</table>
Re-looking at EGDT

• Was it more effective really?
  – ARISE trial
  – PROCESS trial
  – PROMISE trial
Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

Critical Care
RESEARCH GROUP
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators

Cumulative In-Hospital Mortality to 60 Days

Cumulative Mortality to 1 Yr

Days

Mortality (%)

P=0.52 by log-rank test

Days

Mortality (%)

P=0.70 by log-rank test, 90 days
P=0.92 by log-rank test, 1 yr

Protocol-based EGDT
Protocol-based standard therapy
Usual care
Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*
Effect of an Early Resuscitation Protocol on In-hospital Mortality Among Adults With Sepsis and Hypotension: A Randomized Clinical Trial

Ben Andrews, MD; Matthew W. Semler, MD, MSc; Levy Muchemwa, MBChB; Paul Kelly, MD, FRCP; Shabir Lakhi, MBChB; Douglas C. Heimburger, MD, MS; Chileshe Mabula, MBChB; Mwango Bwalya, MBChB; Gordon R. Bernard, MD

N=212

Sepsis protocol: Median 4.0L/24h

Usual Care: Median 3.0L/24h

JAMA 2017;318:1233-40
What about Paediatric sepsis?
International Evidence for Paed Fluid resus guideline

Guidelines based on only 2 retrospective analyses from one centre; tertiary referral

Entry criteria: child survived to ICU admission: ventilated & inotrope dependant

Objective: Volume of fluid given in the first hour influence outcome (composite)

First study ICU: 5 year review: 34 children with septic shock

Conclusions: >40mls/kg initial fluid resuscitation (9 children) associated with better outcome (Carcillo et al, JAMA 1991)

Second study: 10 year review of Septic shock (91 children)

Conclusions: >60mls/kg over 15 mins: early reversal of shock improves outcome; each additional hour of uncorrected shock increasing risk of dying by 2-fold (Han Y et al, Pediatrics 2003)
Role of Early Fluid Resuscitation in Pediatric Septic Shock

Group 1 < 20ml/kg in 1st hour (n=14)
Group 2 20-40ml/kg in 1st hour (n=11)
Group 3 >40ml/kg in 1st hour (n=9) p<0.05

N=34
Early Reversal of Pediatric-Neonatal Septic Shock by Community Physicians Is Associated With Improved Outcome

Yong Y. Han, MD*§; Joseph A. Carcillo, MD*‡§; Michelle A. Dragotta, RN§; Debra M. Bills, RN§; R. Scott Watson, MD, MPH*‡§; Mark E. Westerman, RT§; and Richard A. Orr, MD*‡§

N=91

a) 96% survival in shock reversal from resuscitative efforts by community physicians; 63% survival in persistent shock patients (p<0.001)

b) 92% survival in resuscitation consistent with ACCM-PALS guideline (upto 60ml/kg/hr); 62% survival in non-ACCM-PALS guideline (p<0.001)
Mortality after Fluid Bolus in African Children with Severe Infection

Why was the FEAST trial necessary?

• In Africa ~ 50% of in-hospital paediatric deaths occur in first 24 hours

• Shock present in 15% of these in-hospital deaths

• Case fatality of those with shock ~ 15-30%

Could fluid bolus improve outcome?

• Emergency Triage and Treatment (ETAT) imminent role out

• Doctors in resource-poor hospitals concerned about potential harms of fluid bolus therapy

✓ The only way to test this was to conduct a controlled clinical trial
Treatment Guidelines:

Emergency Care: ‘strong’ recommendations: few based on evidence from clinical trials
FEAST mortality: 48 hours and 4 weeks

N=3141  99.5 % Follow Up
Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial.
FEAST: Shock reversal

Impaired perfusion at clinical review times over clinical review times

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Bolus</th>
<th>No Bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2097</td>
<td>1044</td>
</tr>
<tr>
<td>1</td>
<td>2070</td>
<td>1030</td>
</tr>
<tr>
<td>4</td>
<td>2011</td>
<td>1011</td>
</tr>
<tr>
<td>8</td>
<td>1972</td>
<td>996</td>
</tr>
<tr>
<td>24</td>
<td>1899</td>
<td>975</td>
</tr>
<tr>
<td>48</td>
<td>1876</td>
<td>968</td>
</tr>
</tbody>
</table>

% with any signs of impaired perfusion

SHOCK REVERSAL WITH FLUID
Detrimental effect of fluid resuscitation in the initial management of severely ill children in Africa

1. Bates Tropical Medicine, Liverpool School of Tropical Medicine and Hygiene, Pembroke Place, Liverpool, Merseyside
Remarkable consistency of adverse outcome of boluses

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Relative risk (95% CI)</th>
<th>Events, bolus</th>
<th>Events, no bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malaria:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1.59 (1.10, 2.31)</td>
<td>110/1202</td>
<td>34/591</td>
</tr>
<tr>
<td>Negative</td>
<td>1.43 (1.01, 2.04)</td>
<td>108/884</td>
<td>38/446</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.691)</td>
<td>1.51 (1.17, 1.95)</td>
<td>218/2086</td>
<td>72/1037</td>
</tr>
<tr>
<td><strong>Coma:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comatose</td>
<td>1.04 (0.73, 1.49)</td>
<td>78/317</td>
<td></td>
</tr>
<tr>
<td>Not comatose</td>
<td>1.69 (1.21, 2.36)</td>
<td>143/704</td>
<td></td>
</tr>
<tr>
<td>Subtotal (I-squared = 74.3%, p = 0.049)</td>
<td>1.40 (1.10, 1.79)</td>
<td>215/2039</td>
<td>73/1015</td>
</tr>
<tr>
<td><strong>Haemoglobin:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5 g/dL</td>
<td>1.71 (1.35, 2.15)</td>
<td>99/395</td>
<td>30/332</td>
</tr>
<tr>
<td>&gt;= 5 g/dL</td>
<td>1.06 (0.50, 2.24)</td>
<td>20/659</td>
<td>10/350</td>
</tr>
<tr>
<td>Subtotal (I-squared = 2.9%, p = 0.310)</td>
<td>1.54 (1.12, 2.13)</td>
<td>148/1399</td>
<td>44/680</td>
</tr>
<tr>
<td><strong>Base deficit:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;= 8 mmol/L</td>
<td>1.08 (1.18, 2.39)</td>
<td>128/740</td>
<td>34/330</td>
</tr>
<tr>
<td>&lt; 8 mmol/L</td>
<td>1.06 (0.50, 2.24)</td>
<td>20/659</td>
<td>10/350</td>
</tr>
<tr>
<td>Subtotal (I-squared = 14.8%, p = 0.279)</td>
<td>1.54 (1.12, 2.13)</td>
<td>148/1399</td>
<td>44/680</td>
</tr>
<tr>
<td><strong>Lactate:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5 mmol/L</td>
<td>1.38 (1.05, 1.81)</td>
<td>157/764</td>
<td>59/395</td>
</tr>
<tr>
<td>&lt;= 5 mmol/L</td>
<td>2.17 (1.14, 4.14)</td>
<td>49/1225</td>
<td>11/597</td>
</tr>
<tr>
<td>Subtotal (I-squared = 39.2%)</td>
<td>1.50 (1.17, 1.93)</td>
<td>206/1989</td>
<td>70/992</td>
</tr>
<tr>
<td><strong>Period:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before amendment</td>
<td>1.38 (1.05, 1.83)</td>
<td>172/1691</td>
<td>62/844</td>
</tr>
<tr>
<td>After amendment</td>
<td>1.72 (0.98, 3.05)</td>
<td>49/406</td>
<td>14/200</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.498)</td>
<td>1.45 (1.13, 1.86)</td>
<td>221/2097</td>
<td>76/1044</td>
</tr>
</tbody>
</table>

In every subgroup and at each study site fluid boluses were harmful.

Critical Care Research Group
Mortality after Fluid Bolus in African Children with Severe Infection

- Bolus
- No bolus

The NEW ENGLAND JOURNAL OF MEDICINE

Original Article

Research/evidence vs Guidelines

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock

POCKET BOOK OF Hospital care for children

GUIDELINES FOR THE MANAGEMENT OF COMMON CHILDHOOD ILLNESSES

Second edition

Critical Care RESEARCH GROUP
The Surviving Sepsis Campaign Bundle: 2018 Update

Mitchell M. Levy, MD, MCCM¹; Laura E. Evans, MD, MSc, FCCM²; Andrew Rhodes, MBBS, FRCA, FRCP, FFICM, MD (res)³

- Measure lactate level. Remeasure if initial lactate is >2 mmol/L.
- Obtain blood cultures prior to administration of antibiotics.
- Administer broad-spectrum antibiotics.
- **Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L.**
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg.
SEPSIS – The Old and The New

1) SIRS (systemic inflammatory response syndrome)
   – Fever, leukocytosis, hypotension*

2) Sepsis
   – At least 2 SIRS caused by known infection

3) Severe sepsis
   – Sepsis + acute organ dysfunction

4) Septic shock
   – Severe sepsis + persistent/refractory hypotension
New definitions (JAMA, 2016)

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

1) Sepsis
   - life-threatening organ dysfunction caused by a dysregulated host response to infection

2) Septic shock
   - Sepsis + profound circulatory, cellular and metabolic abnormalities associated with a greater risk of mortality
Mortality Excess with Boluses by Shock Definition

WHO/ETAT
Mortality
Bolus= 48%
Control=20%

Absolute Risk Difference
28% (3-53%) p=0.05

NEJM Oct 2011
Next step.............

Back to basics (pre-clinical/animal trial)
International research collaboration

Aim
Patient-centered (clinical outcomes)

FEAST
clinical trial (Africa)
MRC-UK

RESUS
pre-clinical trial (Australia)
NHMRC-Australia

RESEARCH GROUPS
1. CCRG (Australia)
2. KEMRI-WTRP (Kenya)
3. Mbale (Uganda)

FACILITATION/SUPPORT
1. NHMRC-funding
2. EMF-Foundation
3. TPCH-Foundation

Universities
1. UQ, Australia
2. Imperial College, UK

Multi-disciplinary / multi-speciality clinical teams
Pre-clinical model development


An Ovine Model of Hyperdynamic Endotoxemia and Vital Organ Metabolism.

Byrne L1,2,3, Obonyo NG1, Diab S3, Dunster K1,4, Passmore M1,5, Roon AC1,5, Hoe LS1,5, Hay K6, Van Haren F2,3, Tung JP1,7, Cullen L4,8, Shekar K1,9, Maitland K10, Fraser JF1,5,9.
Pre-clinical studies (RESUS trial)

- Designed to understand mechanism
- 2-hit model
  - Sepsis (1st hit)
  - Volume resuscitation (2nd hit)

**Diagram:**

1st hit:
- Sepsis (n=40)
- No sepsis (n=20)

2nd hit:
- No 2nd hit (n=8)
- 0.9% saline bolus (n=8)
- Balanced Electrolyte bolus (n=8)
- Fresh PRBCs (n=8)
- Stored PRBCs (n=8)
- 0.9% saline bolus (n=5)
- Balanced Electrolyte bolus (n=5)
- Fresh PRBCs (n=5)
- Stored PRBCs (n=5)

Aim 1: Sham
Aim 2: Fluid resuscitation
Aim 3: Blood transfusion
Aim 4: Confirm two-hit pathogenesis

Australian Government
National Health and Medical Research Council
Hypothesis: Two hit model

- First hit: Sepsis impairs cardiac function
- Second hit: Volume expansion treatment (fluids/transfusion) further worsen cardiovascular function
Results (saline resuscitation group vs control)
Unintended Consequences: Fluid Resuscitation Worsens Shock in an Ovine Model of Endotoxemia

Liam Byrne¹,²,³*, Nchafatso G. Obonyo¹, Sara D. Diab¹, Kimble R. Dunster¹,⁴, Margaret R. Passmore¹,⁵, Ai-Ching Boon¹,⁵, Louise See Hoe¹,⁵, Sanne Pedersen¹, Mohd Hashairi Fauzi⁶, Leticia Petti Pimenta¹, Frank Van Haren²,³,⁷, Christopher M. Anstey⁸, Louise Cullen⁵,⁹, John-Paul Tung¹,¹⁰, Kiran Shekar¹,¹¹, Kathryn Maitland¹², and John F. Fraser¹,⁵,¹¹

¹Critical Care Research Group and ¹¹Adult Intensive Care, The Prince Charles Hospital, Brisbane, Australia; ²Intensive Care, Canberra Hospital, Garran, Australia; ³Australia National University, Canberra, Australia; ⁴Queensland University of Technology, Brisbane City, Australia; ⁵University of Queensland, Brisbane, Australia; ⁶School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kelantan, Malaysia; ⁷University of Canberra, Bruce, Australia; ⁸Intensive Care, Sunshine Coast University Hospital, Birtinya, Australia; ⁹Royal Brisbane and Women’s Hospital, Herston, Australia; ¹⁰Australian Red Cross Blood Service, Brisbane, Australia; and ¹²Department of Paediatrics, Faculty of Medicine, Imperial College London, London, United Kingdom

At A Glance Commentary

Scientific Knowledge on the Subject: Fluid resuscitation is a common therapy used for the treatment of septic shock.

What This Study Adds to the Field: This study tests the effectiveness of the therapy in an animal model of sepsis and finds that it is actually harmful.
RESULTS: Cardiac Troponin at 12 hours

Troponin I (µg/L) - at 12 hours

Fraser et al. (RESUS trial)
At the mitochondrial level....
Microcirculation

Perfused vessel density, PVD (mm/m²)

Fraser et al. (RESUS trial)
Metabolism

Fraser et al. (RESUS trial)
Results: ELISA

**BAL**

- **IL-6**
- **IL-8**
- **IL-1β**

**Lung homogenate**

**IL-6**

**IL-8**

**IL-1β**

- *p<0.05
- **p<0.01
- ***p<0.001
What this means at inflammatory level

- 0.9% saline fluid bolus resuscitation resulted in lung-specific effects:
  - Increased cytokine gene expression
  - Increased inflammatory signalling
  - No change in MMP expression

- Longer duration studies needed to determine if there are MMP changes beyond 12 hours
Vasopressor dose (noradrenaline) – MAP

Norad Dose

- Sepsis Saline Resuscitation
- Sepsis No Fluid Resuscitation
- Control Saline Resuscitation

4 hrs

Less vasopressor needed, no saline group

Fraser et al. (RESUS trial)
Mortality after Fluid Bolus in African Children with Severe Infection
Ready for the next steps

• Safety and efficacy clinical studies;
  – Maintenance-only fluids and early vasopressor support (RESTRICT trial)

• Randomised controlled trial;
  – ARISE trial and REFRESH pilot study done
  – IV fluid sparing resuscitation and early vasopressors (ARISE-FLUIDS trial)

• Low volume/slower rate fluid + Early vasopressor
Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial

Peter B. Hjortrup, Nicolai Haase, Helle Bundgaard, Simon L. Thomsen, Robert Winding, Ville Pettilä, Anne Aaen, David Lodahl, Rasmus E. Berthelsen, Henrik Christensen, Martin B. Madsen, Per Winkel, Jørn Wetterslev, Anders Perner, The CLASSIC Trial Group, The Scandinavian Critical Care Trials Group

Restricted fluid resuscitation in suspected sepsis associated hypotension (REFRESH): a pilot randomised controlled trial

Stephen P.J. Macdonald, Gerben Keijzers, David McD Taylor, Frances Kinnear, Glenn Arendts, Daniel M. Fatovich, Rinaldo Bellomo, David McCutcheon, John F. Fraser, Juan-Carlos Ascencio-Lane, Sally Burrows, Edward Litton, Amanda Harley, Matthew Anstey, Ashesh Mukherjee, and for the REFRESH trial investigators

Restricted fluid bolus volume in early septic shock: results of the Fluids in Shock pilot trial

David Philip Inwald, Ruth Canter, Kerry Woolfall, Paul Mouncey, Zohra Zenasni, Caitlin O’Hara, Anjali Carter, Nicola Jones, Mark D Lyttle, Simon Nadel, Mark J Peters, David A Harrison, Kathryn M Rowan, on behalf of PERUKI (Paediatric Emergency Research in the UK and Ireland) and PICS SG (Paediatric Intensive Care Society Study Group)
Acknowledgements