Fluid Resuscitation in Sepsis

A Literature Review
"On the floor lay a girl of slender make and juvenile height, but with the face of a superannuated hag... The colour of her countenance was that of lead - a silver blue, ghastly tint; her eyes were sunk deep into sockets, as though they had been driven an inch behind their natural position; her mouth was squared; her features flattened; her eyelids black; her fingers shrunk, bent, and inky in their hue..."
NOTICE.

PREVENTIVES OF

CHOLERA!

Published by order of the Sanitary Committee, under the sanction of the Medical Counsel.

BE TEMPERATE IN EATING & DRINKING!
Avoid Raw Vegetables and Unripe Fruit!
Abstain from COLD WATER, when heated, and above all from Ardent Spirits, and if habit have rendered them indispensable, take much less than usual.

SLEEP AND CLOTHE WARM!
Do not sleep or sit in a draught of air,
Avoid getting Wet!
Attend immediately to all disorders of the Bowels.

TAKE NO MEDICINE WITHOUT ADVICE.

Medicine and Medical Advice can be had by the poor, at all hours of the day and night, by applying at the Station House in each Ward.

CALEG S. WOODHULL, Mayor.

JAMES KELLY, Chairman of Sanitary Committee.
The Pioneers
Dr Latta’s Saline Solution

Two to three drachms of muriate of soda (NaCl), two scruples of the bicarbonate of soda in six pints of water and injected it at temperature 112 Fah

( approximately 58mmol/l Na⁺, 49mmol/l Cl⁻, 9mmol/l HCO₃⁻)

Ten of the first fifteen patients died
180 years on.....
Current controversies in fluid therapy in septic patients

When to give fluid
How much fluid to give
Which fluid to use
Definitions

• **SIRS**: widespread inflammatory response that may or may not be associated with infection: 2 or more of
  – Temperature, tachycardia, tachypnoea and WCC

• **Sepsis**: SIRS in the presence of or as a result of suspected or proven infection

• **Septic shock**: Sepsis with cardiovascular dysfunction despite the administration of >40ml/kg isotonic fluid in one hour
Epidemiology

  – Estimated 750,000 cases of severe sepsis annually in US
  – Mortality of 28.6%
  – $22,100 per case

• Starship Hospital
  – 2010-2012
  – 90 cases of sepsis/septic shock
Pathophysiology
The Evidence

When to give fluid

How much fluid should we give
Early Paediatric Practices

• Early 1980’s
  – Slow cautious fluid bolus: 10-20ml/kg over 20-30 minutes
    • Era of limited paediatric ventilators/PICU
    • Awareness of SIADH in patients with sepsis and meningitis

• 1988
  – The AHA’s Textbook of PALS
  – Rapid 20ml/kg fluid boluses to a total of 60ml/kg or more in the first hour of resuscitation

- Children’s Hospital National Medical Centre
  - 1982-1989

- All patients with septic shock with a PAC at 6 hours
  - Group 1: up to 20ml/kg
  - Group 2: 20-40ml/kg and
  - Group 3: >40ml/kg in first hour

- End points: survival, ARDS, hypovolaemia at 6 hours

- 34 patients
  - Median age 13.5 months
  - Pre-existing chronic disease in 31%
  - 82% required ventilation
  - 100% required inotropic support

- Fluid resuscitation
  - Crystalloids (0.9% or lactated Ringer’s)
  - Colloids: 5% albumin or blood products (RBC, FFP, cryoprecipitate)
Fig 1.—The distribution of survivors and nonsurvivors within fluid resuscitation groups (see text for definition of groups). The asterisk indicates a significant difference in survival between group 3 and groups 1 and 2 individually and combined.

Colloid fluids in the form of normal saline or lactated Ringer’s solution. Colloid preparations consisted of 5% albumin or blood products including packed red blood cells, fresh frozen plasma, or cryoprecipitate. The average volume of fluid administered in the first hour was 33 mL/kg, of which 9 mL/kg was colloid
Survivors (n = 18)

42 ± 28†

97 ± 49

Nonsurvivors (n = 16)

23 ± 18

94 ± 37

*P < .05, comparing the mean volume administered at 1 hour in each group to the other groups.
†P < .05, comparing the mean volume administered at 6 hours in group 1 to group 2 or group 3.
‡P < .05, mean volume administered in first hour in survivors compared with nonsurvivors.
3 mm Hg, and 8 mm Hg, but did not have urine outputs of less than 1 mL/kg per hour and experienced no persistent episodes of hypotension after initial therapy. No patient who received more than 40 mL/kg of fluid in the first hour was hypovolemic at 6 hours (Fisher's Exact Test, \( P = .003 \)), and only one of nine patients in group 3 had a PCWP of less than 9 mm Hg; this patient survived.

The presence of ARDS was associated with an increased risk of death (Fisher's Exact Test, \( P = .029 \); Fig 2). The presence of preexisting chronic disease appeared to affect survival, but this association was not statistically significant (Fisher's Exact Test, \( P = .066 \)). There was no association between mortality and development of CPE. Indeed, four of five patients with CPE survived.
tions do not prove cause and effect. However, the study does suggest that following current pediatric advanced life support guidelines for fluid resuscitation may improve survival without any increase in morbidity in children with septic shock.

Until recently, the therapy for pediatric shock called for a fluid bolus of 10 to 20 mL/kg over 20 to 30 minutes with careful monitoring of the central venous pressure. We believe that relatively slow fluid resuscitation was founded in an era when pediatric ventilators and positive-end expiratory pressure measurements were not readily available to treat the child with ARDS or CPE. If central venous pressures and PCWPs were not measured, the presence of pulmonary arterial wedge pressure (PAWP)

- Criticisms
  - Treatment groups assigned non-randomly
  - Treatment based on clinical criteria
  - Criteria determined by different individuals

- But….findings suggested current PALS guidelines may improve survival in children with septic shock

- To evaluate the efficacy of EGDT before admission to ICU
  - Single center: Detroit Hospital
  - Emergency Department

- 263 patients: severe sepsis or septic shock
  - Randomly assigned
  - 6 hours of standard versus EGT
  - End points: MOF, mortality,
SIRS criteria and systolic blood pressure $\leqslant 90$ mm Hg or lactate $\geqslant 4$ mmol/liter

Assessment and consent

Standard therapy in emergency department ($n=133$)

Randomization ($n=263$)

Early goal-directed therapy ($n=130$)

Vital signs, laboratory data, cardiac monitoring, pulse oximetry, urinary catheterization, arterial and central venous catheterization

CVP $\geqslant 8-12$ mm Hg

MAP $\geqslant 65$ mm Hg

Urine output $\geqslant 0.5$ ml/kg/hr

Standard care

Hospital admission

Vital signs and laboratory data obtained every 12 hr for 72 hr

Did not complete 6 hr ($n=14$)

Follow-up

Did not complete 6 hr ($n=13$)

Continuous ScvO$_2$ monitoring and early goal-directed therapy for $\geqslant 6$ hr

CVP $\geqslant 8-12$ mm Hg

MAP $\geqslant 65$ mm Hg

Urine output $\geqslant 0.5$ ml/kg/hr

ScvO$_2$ $\geqslant 70$

SaO$_2$ $\geqslant 93$

Hematocrit $\geqslant 30$

Cardiac index

VO$_2$
Supplemental oxygen ± endotracheal intubation and mechanical ventilation

Central venous and arterial catheterization

Sedation, paralysis (if intubated), or both

CVP

- <8 mm Hg: Crystalloid
- 8–12 mm Hg
- >90 mm Hg: Colloid

MAP

- <65 mm Hg: Vasoactive agents
- >90 mm Hg: Inotropic agents

ScvO₂

- <70%: Transfusion of red cells until hematocrit ≥30%
- ≥70%: No

Goals achieved

- Yes: Hospital admission
- No: Repeat cycle
• **Results**

  – 263 patients
    
    • 8.7% excluded or did not consent
    
    • Similar baseline characteristics including adequacy and duration of antibiotic therapy

  – Standard patients in ED 6.3 hours v 8 hours (p<0.001)
    
    • No difference in HR or CVP
    
    • MAP’s significantly lower
### Table 3. Kaplan–Meier Estimates of Mortality and Causes of In-Hospital Death.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Therapy (N=133)</th>
<th>Early Goal-Directed Therapy (N=130)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>59 (46.5)</td>
<td>38 (30.5)</td>
<td>0.58 (0.38–0.87)</td>
<td>0.009</td>
</tr>
<tr>
<td>Patients with severe sepsis</td>
<td>19 (30.0)</td>
<td>9 (14.9)</td>
<td>0.46 (0.21–1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Patients with septic shock</td>
<td>40 (56.8)</td>
<td>29 (42.3)</td>
<td>0.60 (0.36–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Patients with sepsis syndrome</td>
<td>44 (45.4)</td>
<td>35 (35.1)</td>
<td>0.66 (0.42–1.04)</td>
<td>0.07</td>
</tr>
<tr>
<td>28-Day mortality†</td>
<td>61 (49.2)</td>
<td>40 (33.3)</td>
<td>0.58 (0.39–0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>60-Day mortality†</td>
<td>70 (56.9)</td>
<td>50 (44.3)</td>
<td>0.67 (0.46–0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Causes of in-hospital death‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden cardiovascular collapse</td>
<td>25/119 (21.0)</td>
<td>12/117 (10.3)</td>
<td>—</td>
<td>0.02</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>26/119 (21.8)</td>
<td>19/117 (16.2)</td>
<td>—</td>
<td>0.27</td>
</tr>
<tr>
<td>Treatment</td>
<td>Hours after the Start of Therapy</td>
<td></td>
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<tr>
<td>---------------------------------------</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>0–6</td>
<td>7–72</td>
<td>0–72</td>
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</tr>
<tr>
<td>Total fluids (ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>3499±2438</td>
<td>10,602±6,216</td>
<td>13,358±7,729</td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>4981±2984</td>
<td>8,625±5,162</td>
<td>13,443±6,390</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Red-cell transfusion (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>18.5</td>
<td>32.8</td>
<td>44.5</td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>64.1</td>
<td>11.1</td>
<td>68.4</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Any vasopressor (%)†</td>
<td></td>
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</tr>
<tr>
<td>Standard therapy</td>
<td>30.3</td>
<td>42.9</td>
<td>51.3</td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>27.4</td>
<td>29.1</td>
<td>36.8</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.62</td>
<td>0.03</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Inotropic agent (dobutamine) (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>0.8</td>
<td>8.4</td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>13.7</td>
<td>14.5</td>
<td>15.4</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>0.14</td>
<td>0.15</td>
<td></td>
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<tr>
<td>Mechanical ventilation (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>53.8</td>
<td>16.8</td>
<td>70.6</td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>53.0</td>
<td>2.6</td>
<td>55.6</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.90</td>
<td>&lt;0.001</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Pulmonary-artery catheterization (%)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>3.4</td>
<td>28.6</td>
<td>31.9</td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>0</td>
<td>18.0</td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.12</td>
<td>0.04</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

• Criticisms

  – Single center

  – Single physician

  – Treatment group mortality similar across centers
St. Mary’s Hospital, London

- Specialist Tertiary Referral Centre, 2002
  - High rates of meningococcal disease
  - Consultant led retrieval service
  - Telephone advice throughout the south of England
  - Centralization of meningococcal disease care

- Early aggressive fluid resuscitation
  - 4% Albumin

- 102 children with severe sepsis or fluid refractory septic shock
  - Randomly assigned to ACCM/PALS with or without ScvO2 goal-directed resuscitation for 72 hours

- Control group
  - ACCM/PALS therapies without continuous ScvO2
  - Fluid resuscitation (crystalloid or colloid), RBC or CVS drugs
  - Maintain normal perfusion pressure for age, UO >1ml/kg/hour, CRT of 2 seconds and normal pulses

- Intervention group
  - Endpoint of ScvO2 >70% using continuous monitoring
  - If <70% then more fluid, RBC (if Hb<10g/l) or inotropes were given

- Other supportive therapies: CMV, nutrition, antibiotics and RRT decided by medical team

• Intervention Group
  – 28 day mortality (11.8% v 39.2%)
  – More crystalloid (28 v 5mls/kg)
  – RBC transfusion (45.1% v 15.7%)
  – More inotropic support (29.4% v 7.8%)
  – Fewer new organ dysfunctions

• Support of the current ACCM/PALS guidelines
  – Goal-directed therapy using the endpoint of ScvO2 ≥70% provided a significant impact on the outcome of children
Guideline Update


Improved outcomes in paediatric septic shock

• Han et al. Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. Pediatrics 2003; 112:793-9

• Inwald et al. Emergency management of children with severe sepsis in the UK: the results of the Paediatric Intensive Care Society sepsis audit. Arch Disease in Childhood 2009;94:348-53
Mortality after Fluid Bolus in African Children with Severe Infection

Charles Engoru, M.B., Ch.B., M.Med., Peter Olupot-Olupot, M.B., Ch.B., Samuel O. Akech, M.B., Ch.B.,
Richard Nyeko, M.B., Ch.B., M.Med., George Mtove, M.D., Hugh Reyburn, M.B., B.S., Trudie Lang, Ph.D.,
Bernadette Brent, M.B., B.S., Jennifer A. Evans, M.B., B.S., James K. Tibenderana, M.B., Ch.B., Ph.D.,
and Diana M. Gibb, M.B., Ch.B., M.D., for the FEAST Trial Group*
Background

• Early aggressive fluid resuscitation in patients with shock

• sub-Saharan Africa
  – Malaria, sepsis and other infectious disease
  – High early mortality
  – Fluid resuscitation not practiced unless severe anaemia

• WHO recommends fluid resuscitation in advanced shock only
  – CRT > 3 seconds
  – Weak and fast pulse
  – Cold extremities
Aims

• FEAST trial designed to investigate the practice of:
  
  – Early resuscitation with a saline bolus as compared with no bolus (control)
  
  – With an albumin bolus as compared with a saline bolus
Study Design

• 2 stratum, multi-center, open, randomised controlled study
  – January 2009-2011
  – Age between 60 days and 12 years
  – 6 clinical centers: 1 Kenya; 1 Tanzania; 4 Uganda

• Stratum A
  – Children without severe hypotension

• Stratum B
  – Children with severe hypotension
    • $\text{SBP} < 50\text{mmHg if } < 12\text{ months}; < 60\text{mmHg if } 1\text{-}5\text{ years}; < 70\text{mmHg} > 5\text{ years}$
## Study Design

<table>
<thead>
<tr>
<th>Stratum A</th>
<th>Stratum B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomly assigned 1:1:1</td>
<td>Randomly assigned 1:1</td>
</tr>
<tr>
<td>Rapid volume expansion over 1 hour</td>
<td>Rapid volume expansion over 1 hour</td>
</tr>
<tr>
<td>20mls/kg (40ml/kg June 2010)</td>
<td>40ml/kg (60ml/kg June 2010)</td>
</tr>
<tr>
<td>1. 0.9% NaCl (saline-bolus group)</td>
<td>1. 0.9% or (saline-bolus)</td>
</tr>
<tr>
<td>2. 5% HAS (albumin-bolus group)</td>
<td>2. 5% HAS (albumin-bolus)</td>
</tr>
<tr>
<td>3. none (control group)</td>
<td></td>
</tr>
<tr>
<td>Additional 20ml/kg bolus at 1 hour if</td>
<td>Additional 20ml/kg bolus at 1 hour if</td>
</tr>
<tr>
<td>impaired perfusion (not in control group)</td>
<td>impaired perfusion</td>
</tr>
<tr>
<td>Severe hypotension: 40ml/kg of study fluid (saline in control group)</td>
<td>Severe hypotension: 40ml/kg of study fluid</td>
</tr>
</tbody>
</table>
## Study Population

<table>
<thead>
<tr>
<th>Inclusions</th>
<th>Exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 60 days to 12 years</td>
<td>Severe malnutrition</td>
</tr>
<tr>
<td>Severe febrile illness complicated by</td>
<td>Gastroenteritis</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>Non-infectious causes of shock</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>1. Trauma</td>
</tr>
<tr>
<td>Impaired perfusion</td>
<td>2. Surgery</td>
</tr>
<tr>
<td>1. CRT &gt; 3 seconds</td>
<td>3. Burns</td>
</tr>
<tr>
<td>2. Lower limb temperature gradient</td>
<td>Conditions for which volume expansion is contraindicated</td>
</tr>
<tr>
<td>3. Weak radial-pulse volume</td>
<td></td>
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<tr>
<td>4. Severe tachycardia</td>
<td></td>
</tr>
</tbody>
</table>
End Points

• Primary End Point
  – Mortality at 48 hours

• Secondary End Points
  – Mortality at 4 weeks
  – Neurologic sequelae at 4 & 24 weeks
  – Episodes of hypotensive shock within 48 hours after randomisation
  – Adverse events potentially related to fluid resuscitation
    • Pulmonary oedema
    • Increased ICP
    • Severe allergic reaction
Study Procedures

• Treated on general paediatric ward
  – Assisted ventilation bag-mask only
  – Provided with monitors for saturations and blood pressure
  – Training in triage & emergency paediatric life support

• Supportive management
  – IV maintenance fluids (2.5 – 4ml/kg/hour)
  – Antibiotics, anti-malarials, anti-pyretics, anticonvulsant drugs
  – Treated for hypoglycaemia (<2.5mmol/L)
  – RBC transfusion at 20ml/kg over 4 hours if Hb <5g/dl
Study Procedures

• Clinical case-report form completed at 1, 4, 8, 24 and 48 hours
  – Hypovolaemia, neurologic and cardiorespiratory status
  – Adverse events were reported

• Neurological assessment at 4 weeks
  – Reviewed by independent clinician
  – Reassessed at 24 weeks if neurological sequelae present
7838 Patients were assessed for eligibility

4668 Were excluded
2634 Did not meet inclusion criteria
1283 Met exclusion criteria
293 Declined to participate
458 Had other reasons

3170 Were enrolled

29 With severe hypotension were randomly assigned within stratum B

13 Were assigned to the albumin-bolus group
13 Received bolus

16 Were assigned to the saline-bolus group
16 Received bolus

1050 Were assigned to the albumin-bolus group
1045 Received bolus
1 Withdrawed before intervention
4 Died before intervention

1047 Were assigned to the saline-bolus group
1041 Received bolus
2 Withdrawed before intervention
4 Died before intervention

1044 Were assigned to the control (no bolus) group
1 Received bolus of saline

1 Did not fulfill eligibility criteria
7 Were lost to follow-up by 48 hr
2 Withdraw
5 Were taken from hospital (and 48-hr status unknown)
27 Were lost to follow-up by 28 days
6 Withdraw
5 Were taken from hospital
16 Could not be located

2 Did not fulfill eligibility criteria
8 Were lost to follow-up by 48 hr
3 Withdraw
5 Were taken from hospital (and 48-hr status unknown)
23 Were lost to follow-up by 28 days
4 Withdraw
5 Were taken from hospital
14 Could not be located

2 Were lost to follow-up by 48 hr
1 Withdraw
1 Was taken from hospital (and 48-hr status unknown)
20 Were lost to follow-up by 28 days
4 Withdraw
3 Were taken from hospital
13 Could not be located

1050 Were included in analysis
1047 Were included in analysis
1044 Were included in analysis
3141 Were randomly assigned within stratum A

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1045 Received bolus
1 Withdrew before intervention
4 Died before intervention

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1041 Received bolus
2 Withdrew before intervention
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- 13 Received bolus

- 16 Were assigned to the saline-bolus group
- 16 Received bolus
Table 1. Baseline Characteristics of the Children.\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Albumin Bolus (N = 1050)</th>
<th>Saline Bolus (N = 1047)</th>
<th>No Bolus (N = 1044)</th>
<th>Total (N = 3141)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic and anthropometric characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age — no</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median</td>
<td>23</td>
<td>23</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>14–37</td>
<td>13–37</td>
<td>14–40</td>
<td>13–38</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>474 (45)</td>
<td>480 (46)</td>
<td>498 (48)</td>
<td>1452 (46)</td>
</tr>
<tr>
<td>Mid-upper-arm circumference ≤11.5 cm — no./total no. (%)</td>
<td>21/982 (2)</td>
<td>24/974 (2)</td>
<td>25/1003 (2)</td>
<td>70/2959 (2)</td>
</tr>
<tr>
<td><strong>Findings at presentation</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Axillary temperature &gt;39°C — no. (%)</td>
<td>243 (23)</td>
<td>236 (23)</td>
<td>264 (25)</td>
<td>743 (24)</td>
</tr>
<tr>
<td>Hypothermia (temperature &lt;36°C) — no. (%)</td>
<td>59 (6)</td>
<td>64 (6)</td>
<td>66 (6)</td>
<td>189 (6)</td>
</tr>
<tr>
<td>Respiratory distress — no./total no. (%)</td>
<td>874/1048 (83)</td>
<td>854/1045 (82)</td>
<td>857/1037 (83)</td>
<td>2585/3130 (83)</td>
</tr>
<tr>
<td>Respiratory rate — breaths/min</td>
<td>58±15</td>
<td>58±15</td>
<td>57±15</td>
<td>58±15</td>
</tr>
<tr>
<td>Oxygen saturation &lt;90% — no. (%)(^†)</td>
<td>249/1015 (25)</td>
<td>253/1008 (25)</td>
<td>257/1015 (25)</td>
<td>759/3038 (25)</td>
</tr>
<tr>
<td>Bradycardia (&lt;80 beats/min) — no. (%)</td>
<td>13 (1)</td>
<td>7 (1)</td>
<td>10 (1)</td>
<td>30 (1)</td>
</tr>
<tr>
<td>Severe tachycardia — no. (%)</td>
<td>736 (70)</td>
<td>721 (69)</td>
<td>738 (71)</td>
<td>2195 (70)</td>
</tr>
<tr>
<td>Weak radial pulse — no. (%)</td>
<td>210 (20)</td>
<td>238 (23)</td>
<td>206 (20)</td>
<td>654 (21)</td>
</tr>
<tr>
<td>Capillary refill time — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 sec</td>
<td>712 (68)</td>
<td>720 (69)</td>
<td>673 (64)</td>
<td>2105 (67)</td>
</tr>
<tr>
<td>≥3 sec</td>
<td>263 (25)</td>
<td>299 (29)</td>
<td>257 (25)</td>
<td>819 (26)</td>
</tr>
<tr>
<td>Positive temperature gradient — no. (%)(^‡)</td>
<td>620 (59)</td>
<td>629 (60)</td>
<td>610 (58)</td>
<td>1859 (59)</td>
</tr>
<tr>
<td>Systolic blood pressure — mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>92</td>
<td>93</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>Moderate hypotension — no./total no. (%)(^§)</td>
<td>66/1030 (6)</td>
<td>69/1036 (7)</td>
<td>57/1034 (6)</td>
<td>192/3100 (6)</td>
</tr>
<tr>
<td>Dehydration — no. (%)</td>
<td>78 (7)</td>
<td>95 (9)</td>
<td>58 (6)</td>
<td>231 (7)</td>
</tr>
<tr>
<td>Severe pallor manifested in lips, gums, or inner eyelids — no. (%)</td>
<td>523 (50)</td>
<td>546 (52)</td>
<td>520 (50)</td>
<td>1589 (51)</td>
</tr>
<tr>
<td>Prostration — no./total no. (%)(</td>
<td>)</td>
<td>655/1048 (62)</td>
<td>667/1046 (64)</td>
<td>619/1044 (59)</td>
</tr>
<tr>
<td>Coma — no. (%)(|^|)</td>
<td>156 (15)</td>
<td>161 (15)</td>
<td>140 (13)</td>
<td>457 (15)</td>
</tr>
<tr>
<td>Convulsions during this illness — no./total no. (%)</td>
<td>414/1047 (40)</td>
<td>387/1045 (37)</td>
<td>371/1039 (36)</td>
<td>1172/3131 (37)</td>
</tr>
<tr>
<td>Hemoglobinuria (dark urine) — no. (%)</td>
<td>122 (12)</td>
<td>123 (12)</td>
<td>144 (14)</td>
<td>389 (12)</td>
</tr>
<tr>
<td>Jaundice visible to clinician — no. (%)</td>
<td>336 (32)</td>
<td>336 (32)</td>
<td>330 (32)</td>
<td>1002 (32)</td>
</tr>
<tr>
<td>Variable</td>
<td>Albumin Bolus (N=1050)</td>
<td>Saline Bolus (N=1047)</td>
<td>No Bolus (N=1044)</td>
<td>Total (N=3141)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------------------------</td>
<td>-----------------------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Laboratory assessments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive for malaria parasitemia</td>
<td>590/1044 (57)</td>
<td>612/1042 (59)</td>
<td>591/1037 (57)</td>
<td>1793/3123 (57)</td>
</tr>
<tr>
<td>Hémoglobine — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 g/dl</td>
<td>323/1024 (32)</td>
<td>332/1015 (33)</td>
<td>332/1015 (33)</td>
<td>987/3054 (32)</td>
</tr>
<tr>
<td>&gt;10 g/dl</td>
<td>231/1024 (23)</td>
<td>230/1015 (23)</td>
<td>244/1015 (24)</td>
<td>705/3054 (23)</td>
</tr>
<tr>
<td>Glucose — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.5 mmol/liter (45 mg/dl)</td>
<td>43/990 (4)</td>
<td>46/991 (5)</td>
<td>42/989 (4)</td>
<td>131/2970 (4)</td>
</tr>
<tr>
<td>&lt;3.0 mmol/liter (54 mg/dl)</td>
<td>67/990 (7)</td>
<td>61/991 (6)</td>
<td>59/989 (6)</td>
<td>187/2970 (6)</td>
</tr>
<tr>
<td>Lactate ≥5 mmol/liter — no./total no. (%)</td>
<td>357/1000 (36)</td>
<td>407/989 (41)</td>
<td>395/992 (40)</td>
<td>1159/2981 (39)</td>
</tr>
<tr>
<td>Base deficit ≥8 mmol/liter — no./total no. (%)</td>
<td>380/710 (54)</td>
<td>360/689 (52)</td>
<td>330/680 (49)</td>
<td>1070/2079 (51)</td>
</tr>
<tr>
<td>Severe acidemia (pH &lt;7.2) — no./total no. (%)</td>
<td>71/712 (10)</td>
<td>73/694 (11)</td>
<td>65/685 (9)</td>
<td>209/2091 (10)</td>
</tr>
<tr>
<td>Hyperkalemia (potassium &gt;6.5 mmol/liter) — no./total no. (%)</td>
<td>67/686 (10)</td>
<td>68/687 (10)</td>
<td>65/670 (10)</td>
<td>200/2043 (10)</td>
</tr>
<tr>
<td>Positive for HIV antibody — no./total no. (%)</td>
<td>37/817 (5)</td>
<td>28/827 (3)</td>
<td>41/839 (5)</td>
<td>106/2483 (4)</td>
</tr>
<tr>
<td>Positive blood culture — no. of positive cultures/total no. of cultures (%)</td>
<td>38/347 (11)</td>
<td>52/360 (14)</td>
<td>36/363 (10)</td>
<td>126/1070 (12)</td>
</tr>
<tr>
<td>Positive cerebrospinal fluid culture — no. of positive cultures/total no. of cultures (%)</td>
<td>2/94 (2)</td>
<td>4/102 (4)</td>
<td>4/96 (4)</td>
<td>10/292 (3)</td>
</tr>
</tbody>
</table>
Administered Fluids

• Adherence to protocol
  – 99.5% in albumin group
  – 99.4% in saline group
  – 99.9% in control group

• Median volume of all fluids (including blood):
  – Albumin Bolus Group: First hour: 20ml/kg; Second hour: 4.5ml/kg
  – Saline Bolus Group: First hour: 20ml/kg; Second hour: 5ml/kg
  – Control Group: First hour: 1.2ml/kg; Second hour: 2.9ml/kg
Fluid Administered

• Over course of 8 hours
  – Median cumulative volume of fluid
    • Albumin-bolus group: 40ml/kg (30-50)
    • Saline-bolus group: 40ml/kg (30.4-50)
    • Control: 10.1 ml/kg (10-25.9)

• RBC transfusion in 1408 children
  – 45% in albumin; 47% in saline; 43% in control
  – Initiated earlier in control group but proportions and volumes similar across all groups
<table>
<thead>
<tr>
<th>End Point</th>
<th>Albumin Bolus (N=1050)</th>
<th>Saline Bolus (N=1047)</th>
<th>No Bolus (N=1044)</th>
<th>Saline Bolus vs. No Bolus</th>
<th>Albumin Bolus vs. No Bolus</th>
<th>Albumin Bolus vs. Saline Bolus</th>
<th>Albumin and Saline Boluses vs. No Bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
<td></td>
<td>Relative Risk (95% CI)</td>
<td>P Value</td>
<td>Relative Risk (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td><strong>48 Hours</strong></td>
<td></td>
<td></td>
<td></td>
<td>Relative Risk (95% CI)</td>
<td>P Value</td>
<td>Relative Risk (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Death — no. (%)</td>
<td>111 (10.6)</td>
<td>110 (10.5)</td>
<td>76 (7.3)</td>
<td>1.44 (1.09–1.90)</td>
<td>0.01</td>
<td>1.45 (1.10–1.92)</td>
<td>0.008</td>
</tr>
<tr>
<td>Pulmonary edema — no. (%)</td>
<td>14 (1.3)</td>
<td>6 (0.6)</td>
<td>6 (0.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased intracranial pressure — no. (%)</td>
<td>16 (1.5)</td>
<td>18 (1.7)</td>
<td>11 (1.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hypotension — no. (%)*</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td>3 (0.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reaction — no. (%)</td>
<td>3 (0.3)</td>
<td>4 (0.4)</td>
<td>2 (0.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema, increased intracranial pressure, or both — no. (%)†</td>
<td>27 (2.6)</td>
<td>23 (2.2)</td>
<td>17 (1.6)</td>
<td>1.34 (0.72–2.51)</td>
<td>0.34</td>
<td>1.57 (0.87–2.88)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>4 Weeks</strong></td>
<td></td>
<td></td>
<td></td>
<td>Relative Risk (95% CI)</td>
<td>P Value</td>
<td>Relative Risk (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Death — no. (%)</td>
<td>128 (12.2)</td>
<td>126 (12.0)</td>
<td>91 (8.7)</td>
<td>1.38 (1.07–1.78)</td>
<td>0.01</td>
<td>1.40 (1.08–1.80)</td>
<td>0.01</td>
</tr>
<tr>
<td>Neurologic sequelae — no./total no. (%)‡</td>
<td>22/990 (2.2)</td>
<td>19/996 (1.9)</td>
<td>20/997 (2.0)</td>
<td>0.95 (0.51–1.77)</td>
<td>0.87</td>
<td>1.10 (0.61–2.01)</td>
<td>0.74</td>
</tr>
<tr>
<td>Neurologic sequelae or death — no./total no. (%)‡</td>
<td>150/990 (15.2)</td>
<td>145/996 (14.6)</td>
<td>111/997 (11.1)</td>
<td>1.31 (1.04–1.65)</td>
<td>0.02</td>
<td>1.36 (1.08–1.71)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*Includes patients who died during the first 4 weeks.
†Includes patients who had an intracranial pressure measurement greater than 20 mm Hg or an increase greater than 10 mm Hg from baseline.
‡Includes patients who had neurologic sequelae or died during the first 4 weeks.
A Mortality at 48 Hours

Cumulative Probability of Death

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Hr 1</th>
<th>Hr 2</th>
<th>Hr 3</th>
<th>Hr 4</th>
<th>Hr 5–8</th>
<th>Hr 9–24</th>
<th>Hr 24–48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin bolus</td>
<td>1050</td>
<td>1061</td>
<td>1047</td>
<td>1039</td>
<td>1024</td>
<td>1010</td>
<td>992</td>
</tr>
<tr>
<td>Saline bolus</td>
<td>1037</td>
<td>1033</td>
<td>1030</td>
<td>1021</td>
<td>1016</td>
<td>1010</td>
<td>980</td>
</tr>
<tr>
<td>No bolus</td>
<td>1044</td>
<td>1047</td>
<td>1044</td>
<td>1044</td>
<td>1044</td>
<td>1044</td>
<td>975</td>
</tr>
</tbody>
</table>

Died

| %       | 1.2 | 1.1 | 1.3 | 1.3 | 1.5 | 0.9 | 0.8 | 0.7 | 0.6 | 0.9 | 0.4 | 1.7 | 2.0 | 1.4 | 3.8 | 3.5 | 2.0 | 1.7 | 1.4 | 0.9 |

Legend:
- Albumin bolus
- Saline bolus
- No bolus
### Figure 3. Mortality at 48 hours in Prespecified Subgroups.

The sizes of the boxes are proportional to the Mantel–Haenszel weights. The $I^2$ statistic indicates the percentage of total variation that was due to heterogeneity.
Good Points

• Large numbers of children enrolled
• Multinational nature of sample
• Small numbers lost to follow up
• Blinding of treatment assignments
• High rate of adherence to assigned treatment
• Confirmed what we know about saline versus albumin
Limitations

- Setting
- Limited access to diagnostics
- Different pattern of disease e.g. cerebral malaria
- Exclusions: gastroenteritis, severe malnutrition or non-infectious causes of shock
- Few children recruited to stratum B
- Definitions of ‘shock’
Restricted Fluid Strategy

• Adult Literature
  – ARDS
  – Colorectal Surgery
  – Penetrating Trauma
What type of fluid?
# Types of IV Fluids

<table>
<thead>
<tr>
<th>Crystalloids</th>
<th>Colloids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isotonic</strong></td>
<td><strong>Natural</strong></td>
</tr>
<tr>
<td>0.9% Saline</td>
<td>4% Albumin (iso-oncotic)</td>
</tr>
<tr>
<td>Plasma-Lyte</td>
<td>20% Albumn (hyper-oncotic)</td>
</tr>
<tr>
<td>Hartman’s solution</td>
<td><strong>Synthetic Colloids</strong></td>
</tr>
<tr>
<td>Lactated Ringer’s Solution</td>
<td>Dextrans: 6% dextran 70; 10% dextran 40</td>
</tr>
<tr>
<td>Hypertonic</td>
<td>Gelatins: Gelofusin, Haemaccel, gelofundiol</td>
</tr>
<tr>
<td>3% Saline</td>
<td>HES preparations: Tetrastarch, Pentastarch, Voluven</td>
</tr>
</tbody>
</table>
## Crystalloid versus Colloid

<table>
<thead>
<tr>
<th>Crystalloids</th>
<th>Colloids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheap</td>
<td>Expensive</td>
</tr>
<tr>
<td>Readily available</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Hyperchloraemia</td>
<td>Coagulopathy</td>
</tr>
<tr>
<td></td>
<td>Exposure to blood products</td>
</tr>
<tr>
<td></td>
<td>Pruritis</td>
</tr>
</tbody>
</table>
Albumin

- Human albumin
  - Natural colloid, MW 69kDa
  - Accounts for 80% plasma oncotic pressure
  - Drug & hormone transport
  - Anti-oxidant and anti-inflammatory properties
  - Hypoalbuminaemic critically ill patients have a worse prognosis

- Albumin solutions
  - Safe, natural, well tolerated
  - Iso-oncotic (4% or 5%) or hyper-oncotic (20-25%)
Levin et al. Improved survival in children admitted to intensive care with meningococcal disease. 2nd Annual Spring Meeting of the RCPCH. University of York. 1998

**Shock?**
- Tachycardia, cold peripheries,
- increased capillary refill time (> 4 s)
- decreased urine output (< 1 ml/kg/h)
- tachypnoea/hypoxia
- confusion and decreasing conscious level
- hypotension (late sign)

Yes

**ABC and oxygen (10 l/min)**
and BM Stix
Insert 2 large iv cannulae (or intra-osseous)
Cefotaxime/Ceftriaxone
(80 mg/kg)

**Volume resuscitation**
(use 20 ml/kg of colloid as a bolus and repeat)
Observe closely for response/deterioration
DO NOT LUMBAR PUNCTURE

No

**Still shocked?**
after 40 ml/kg volume replacement

Yes

Continue volume resuscitation (boluses of 10–20 ml/kg of colloid)
Call anaesthetist and contact (P)ICU
Will need elective intubation and ventilation
Commence inotropes peripherally
Nasogastric tube
The Colloid versus Crystalloid Debate

• Cochrane Injuries Group Albumin Reviewers


  – 30 RCT including 1419 randomised patients
    • Burns, hypoalbuminaemia or hypovolaemia
    • 6% increased risk of death with albumin

- 331 children with MD admitted to PICU
  - 1992-1997
  - Case fatality rate 23% (1992/93) to 2% (1997)

- A significant improvement in outcome for children admitted with MD to a PICU as a result of improvements in the use of their algorithm:
  - 4% albumin boluses
  - Initial management at referring hospitals
  - Use of a mobile intensive care service
  - Centralization of care in a specialist unit
The SAFE Study

• 2001-2003
  – Multicenter, randomised, double-blind trial
  – Primary outcome: death from any cause/28 days

• Eligible patients
  – Anyone for whom fluid resuscitation required
  – Exclusions: cardiac surgery, liver transplant, burns
  – 4% albumin versus 0.9% saline
The SAFE Study

- 6997 patients
  - Similar baseline characteristics

- Fluids Administered
  - Albumin group: significantly less study fluid
  - Saline: Albumin of 1:1.4

- Haemodynamics
  - No differences in MAP
  - Albumin group: lower HR & higher CVP
### Total Fluids Administered

<table>
<thead>
<tr>
<th>Variable</th>
<th>Albumin Group</th>
<th>Saline Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study fluid (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>3410</td>
<td>3418</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 2</td>
<td>3659</td>
<td>3068</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 3</td>
<td>2210</td>
<td>2702</td>
<td>0.03</td>
</tr>
<tr>
<td>Day 4</td>
<td>1686</td>
<td>1664</td>
<td>0.57</td>
</tr>
<tr>
<td>Non-study fluid (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>3392</td>
<td>3405</td>
<td>0.30</td>
</tr>
<tr>
<td>Day 2</td>
<td>3651</td>
<td>3507</td>
<td>0.009</td>
</tr>
<tr>
<td>Day 3</td>
<td>2109</td>
<td>2191</td>
<td>0.15</td>
</tr>
<tr>
<td>Day 4</td>
<td>1680</td>
<td>1656</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Ratio</strong></td>
<td><strong>1:1.4</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Fluids Administered

- **Albumin**
  - Day 1: 2247 ml
  - Day 2: 3044 ml
  - Day 3: 2100 ml
  - Day 4: 1671 ml

- **Saline**
  - Day 1: 3096 ml
  - Day 2: 3572 ml
  - Day 3: 2182 ml
  - Day 4: 1649 ml

### Other Measurements

- **Mean arterial pressure (mm Hg)**
  - Day 1: 81.4 ± 4.4
  - Day 2: 84.4 ± 5.1
  - Day 3: 87.2 ± 13.3
  - Day 4: 88.8 ± 13.9

- **Heart rate (beats/min)**
  - Day 1: 88 ± 20.2
  - Day 2: 88 ± 19.3
  - Day 3: 88 ± 19.1
  - Day 4: 89 ± 18.9

- **Central venous pressure (mm Hg)**
  - Day 1: 11.2 ± 4.8
  - Day 2: 11.6 ± 4.9
  - Day 3: 11.4 ± 4.8
  - Day 4: 11.1 ± 4.8

- **Serum albumin (g/liter)**
  - Day 1: 28.7 ± 7.0
  - Day 2: 30.3 ± 6.4
  - Day 3: 30.8 ± 6.4
  - Day 4: 30.0 ± 6.2
The SAFE Study

• 28 day mortality
  – 726 deaths (20.9%; albumin) v 729 deaths (21.1% saline)

• Single organ and multiple-organ failure similar
  – No differences in ICU days, hospital days, days of mechanical ventilation, days of RRT
• Sub–group analysis in severe sepsis
  – Improved outcomes with albumin
    • Saline group 35.3% died
    • Albumin group 30.7% died
  – RR of death 0.87 amongst those in the albumin group
    • RR of death 1.05 without severe sepsis
Paediatric Albumin Trials


• Maitland et al. Mortality after fluid bolus in African children. NEJM Jun 30;364(26):2483-95
Current Trials

• The PRECISE Trial
  – Evolution of an Early Septic Shock Fluid Resuscitation Trial
  – Canadian Critical Care Trials Group.
  – 5% albumin versus 0.9% NaCl on 90 day mortality

• ALBIOS Trial
  – The Volume Replacement with Albumin in Severe Sepsis
  – 1350 Italian ICU patients
  – 28- and 90-day mortality; organ dysfunction (secondary end-point)
  – Albumin plus crystalloid versus crystalloid only


- Recommends the use of either crystalloid or colloid for the early resuscitation of patients with sepsis
Gelatins

- Synthetic colloid
  - Hydrosylates of connective tissue of animal origin
  - MW limited to 30-35 kDA
    - Tendency to gel at higher molecular weights
    - Much lower than albumin
    - Limited oncotic effects; intravascular persistence 2-3 hours
Gelatins

- Upadhyay et al. Randomized evaluation of fluid resuscitation with crystalloid (saline) and colloid (polymer from degraded gelatin in saline) in pediatric septic shock. Indian Pediatr 2005; 42(3):223-31
  - 60 children with septic shock
  - 20ml/kg boluses of saline or gelatin
  - Equally effective as a resuscitation fluid
Gelatin

- Acute Kidney Injury
  - Schabinski et al. Effects of a predominantly HES based and a predominantly non HES based fluid therapy on renal function in surgical ICU patients. Intensive Care Medicine 2009; 35:1539-1547
  - 6% HES 130/0.4 versus gelatin
  - Gelatin exposure independent RF for ARF (OR 1.99)

- Anaphylactoid reactions reported
Hydroxyethyl Starch

• Commonest colloid used in European ICU’s
  – HES 58%; gelatin 35%; albumin 5%
  – Synthesised by partial hydrolysis of maize or potato starch, amylopectin

• 4 Elements
  – Concentration: 6% or 10%
  – Molecular weight: 70-670kDa
  – Degree of substitution: 0.4 (tetrastarch), 0.7 (hetastarch)
  – C2/C6 ratio

• 3 Generations
HES & Bleeding

- Cardiac surgery RCT’s
  - HES 120/0.7, 130/0.4, 200/0.5, 450/0.7 impaired TEG assessed clotting compared with albumin
  - Blood loss increased with HES 130/0.4 and 450/0.7 (greater blood transfusion) compared with albumin

- General paediatric surgery patients
  - HES 130/0.4 caused deterioration in TEG parameters in a RCT compared with albumin
Acute Kidney Injury

  – 129 French patients with severe sepsis
  – 6% HES 200/0.6 increased risk of RF by 2.57 compared with gelatin

  – 10% HES, 200kDa versus Ringer’s lactate
  – Higher incidence of renal failure and RRT
Acute Kidney Injury

Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. Intensive Care Medicine 2012; 38(3):368

- Recommend against using HES>200kDa and/or degree of substitution of 0.4 in patients with severe sepsis or risk of AKI

- Suggest not using 6% HES 130/0.4 in these populations
Anaphylactoid Reaction

  – RCT of 383 children
  – Severe allergic reactions more frequent after
  – Dextran 70>HES 200/0.5>Ringer’s lactate

• Case reports described in patients exposed to gelatins, HES and albumin
Pruritis

  – Systematic review of 18 clinical studies; 3239 patients
  – All HES solutions of all molecular weights, substitutions and C2/C6 ratios
  – Incidence
    • 13-34% in ICU
    • 22% in cardiac surgery
    • 3-54% in stroke
Current Trials

• The CHEST Trial
  – Crystalloid Versus Hydroxyethyl Starch Trial
  – 7000 ANZ ICU patients
  – HES 130/0.4 versus saline
  – 90 day mortality; need for RRT (secondary end-point)

• The Scandinavian Starch for Severe Sepsis/Septic Shock Trial
  – 800 ICU patients
  – HES 130/0.4 or Ringer’s acetate
  – Mortality or dialysis dependence at 90 days after infusion
Time to put it all together
Summary

• When should fluid be given:
  – Fluid should be given in a time-sensitive manner

• How much fluid to give
  – Directed toward the goal of improved stroke volume as evidenced by return of HR to normal, CRT <2 second, peripheral pulses and BP as well as correction of Hb and ScvO2≥70%

• Crystalloid or albumin?
  – Probably doesn’t matter
  – No place for HES, gelatins or dextrans in paediatric septic shock