Fluid Therapy in Sepsis and Acute Care: Absorbing the Evidence

ALBERT FARRUGIA
Body Fluid Compartments

Total body fluid

2/3 Intracellular fluid (ICF)

Extracellular fluid

1/3 Extracellular fluid (ECF)

80% Interstitial fluid

20% Plasma

(b) Exchange of water among body fluid compartments

CAPILLARY FILTRATION

HYDROSTATIC FORCES

OSMOTIC FORCES

ONCOTIC PRESSURE

ALBUMIN

BALANCE

STARLING’S HYPOTHESIS

\[ Q_f = k (P_c + \pi_i) - (P_i + \pi_p) \]
Current concepts of fluid exchange

Classic Starling principle: \( F = (P_c - P_i) \cdot (\pi_p - \pi_l) \)

Revised Starling principle: \( F = (P_c - P_g) \cdot (\pi_p - \pi_g) \)
Microvascular Endothelium

400 – 7000 m²

Active participation in
Leukocyte adhesion and activation
Platelet adherence
Coagulation
Compliment activation
Shock

“Inadequate Tissue Perfusion”

Categories:
- Hemorrhagic
- Cardiogenic
  - Intrinsic
  - Extrinsic
- Neurogenic
- Septic
Ischaemia in one organ system triggers a **systemic response** that persists even after adequate resuscitation.

Pathophysiology of the **multiple organ system failure** that commonly follows severe haemorrhagic shock.
Severe Sepsis

- Major cause of morbidity and mortality worldwide.
  - Leading cause of death in non-coronary ICU.
  - 11th leading cause of death overall.
- More than 750,000 cases/Y of severe sepsis in US.
- In the US, > 500 patients die of severe sepsis daily.
- Consumes significant healthcare resources:
  - Survivors of sepsis:
    - ICU stay prolonged an additional 8 days.
    - Additional costs incurred were $40,890/patient.
- Estimated annual healthcare costs due to severe sepsis in U.S. exceed $16 billion.
Systemic Inflammatory Response Syndrome (SIRS): The systemic inflammatory response to a variety of severe clinical insults (For example, infection).

Sepsis: The systemic inflammatory response to infection.
- Known or suspected infection, plus
- >2 SIRS Criteria.

Severe Sepsis:
- Sepsis plus >1 organ dysfunction.
- MODS.
- Septic Shock.
  - Sepsis induced with hypotension despite adequate resuscitation
  - Perfusion abnormalities which may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.
Fluid Resuscitation of Shock

Crystalloid Solutions

- “Normal” saline
- “Balanced” solutions
  - Ringers Lactate solution
  - Plasmalyte

Colloid Solutions

- Hydroxyethyl Starch(es)
- Blood products (albumin, RBC, plasma)
An ideal resuscitative fluid would maintain intravascular volume without expanding the interstitial space.

Crystalloid solutions are universally used for initial volume resuscitation in sepsis and septic shock......

Colloid solutions achieve hemodynamic goals more quickly than crystalloids with significantly less volume.

As sepsis proceeds,......significant tissue accumulation of resuscitation fluid occurs, and this may result in adverse effects..
Perioperative buffered versus non-buffered fluid administration for surgery in adults (Review)

Burdett E, Dashianthan A, Bennett-Guerrero E, Cro S, Gan TJ, Grocott MPW, James MFM, Mythen MG, O'Malley CMN, Roche AM, Rowan K

The administration of buffered fluids to adult patients during surgery is equally safe and effective as the administration of non-buffered saline-based fluids. The use of buffered fluids is associated with less metabolic derangement, in particular hyperchloraemia and metabolic acidosis. Larger studies are needed to assess robust outcomes such as mortality.
But....... Association of a chloride-restrictive (vs chloride-liberal) intravenous fluid strategy with AKI in critically ill patients

Fluids used:
- 2008 Cl- = 120 – 150 mmol/l
- 2009 Cl- = 19 – 109 mmol/l
The role of albumin as a resuscitation fluid for patients with sepsis: A systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95% CI)</th>
<th>Events, Albumin</th>
<th>Events, Control</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rackow (31)</td>
<td>2.08 (0.26, 15.77)</td>
<td>5/7</td>
<td>6/11</td>
<td>0.70</td>
</tr>
<tr>
<td>Merlidi (30)</td>
<td>0.45 (0.04, 5.81)</td>
<td>10/12</td>
<td>11/12</td>
<td>0.97</td>
</tr>
<tr>
<td>Rackow (32)</td>
<td>1.00 (0.17, 5.77)</td>
<td>5/10</td>
<td>5/10</td>
<td>1.32</td>
</tr>
<tr>
<td>SAFE (4)</td>
<td>0.81 (0.64, 1.03)</td>
<td>185/603</td>
<td>217/615</td>
<td>78.61</td>
</tr>
<tr>
<td>Vaneman (34)</td>
<td>1.31 (0.26, 6.72)</td>
<td>5/8</td>
<td>14/25</td>
<td>1.34</td>
</tr>
<tr>
<td>Maltland (28)</td>
<td>1.19 (0.22, 5.11)</td>
<td>4/23</td>
<td>3/20</td>
<td>1.40</td>
</tr>
<tr>
<td>Maltland (29)</td>
<td>0.17 (0.04, 0.80)</td>
<td>2/56</td>
<td>11/61</td>
<td>5.36</td>
</tr>
<tr>
<td>Atecher (19)</td>
<td>0.12 (0.01, 1.05)</td>
<td>1/44</td>
<td>7/44</td>
<td>3.61</td>
</tr>
<tr>
<td>Friedman (27)</td>
<td>0.85 (0.23, 3.21)</td>
<td>5/15</td>
<td>10/27</td>
<td>2.51</td>
</tr>
<tr>
<td>van der Heijden (33)</td>
<td>0.79 (0.11, 5.49)</td>
<td>2/6</td>
<td>7/18</td>
<td>1.23</td>
</tr>
<tr>
<td>Doboeck (26)</td>
<td>0.51 (0.13, 2.07)</td>
<td>4/36</td>
<td>6/26</td>
<td>2.94</td>
</tr>
<tr>
<td>Overall</td>
<td>0.76 (0.62, 0.95)</td>
<td>228/814</td>
<td>297/869</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Microcirculatory perfusion in sepsis
Potentially impairing factors

- Redistibution of organ blood flow
- DIC
- Cardiopulmonary pathology
- Disturbance of red and white cell rheology
- Congestion and hemorrhage
- Intravascular pooling
- Edema formation
- Increased microvascular permeability
- Decreased red cell deformability
- Opening of AV shunts
- Viscosity alterations
- Vasoplegia
- Altered microvascular blood flow and vascular resistance
Fluid Therapy in Septic Patients

Albumin is retained intravascularly...

...and expands plasma volume

SAFE investigators Int Care Med 2011, 37 (1), 86-96

Ernest et al Critical Care Medicine: Volume 27(1)January 1999 pp 46-50
Multicentre open-label RCT
- Severe sepsis
- 20% albumin + crystalloid: >30g/L vs. crystalloid
  - N=1800

Primary outcome: day 90 mortality

Completed recruitment

No difference in day 90 mortality (~42%)

Post hoc subgroup: septic shock

Albumin: significant reduction in day 90 mortality
Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units

Simon Finfer¹*, Bette Liu¹², Colman Taylor¹, Rinaldo Bellomo³, Laurent Billot¹, Deborah Cook⁴, Bin Du⁵, Colin McArthur⁶, John Myburgh¹ for the SAFE TRIPS Investigators¹
HES and mortality – A class effect

Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

SepNet (VISEP) 2008


Hydroxyethyl Starch 130/0.4 versus Ringer’s Acetate in Severe Sepsis

6S 2012
Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

<table>
<thead>
<tr>
<th>Variable</th>
<th>HES</th>
<th>Saline</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome of death at day 90 — no./total no. (%)</td>
<td>597/3315 (18.0)</td>
<td>566/3336 (17.0)</td>
<td>1.06 (0.96 to 1.18)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

| Secondary outcomes — no./total no. (%)        |                |                |                        |         |
| Renal outcomes                                |                |                |                        |         |
| RIFLE-R                                       | 0.94 (0.90 to 0.98) | 0.90 (0.85 to 0.97) | 0.94 (0.90 to 0.98) | 0.005   |
| RIFLE-I                                       | 0.91 (0.85 to 0.97) | 0.91 (0.85 to 0.97) | 0.91 (0.85 to 0.97) | 0.12    |
| RIFLE-F                                       | 1.12 (0.97 to 1.30) | 1.12 (0.97 to 1.30) | 1.12 (0.97 to 1.30) | 0.04    |
| Use of renal-replacement therapy              | 1.21 (1.00 to 1.45) | 1.21 (1.00 to 1.45) | 1.21 (1.00 to 1.45) | 0.03    |

| New organ failure†                             |                |                |                        |         |
| Respiratory                                   | 1.05 (0.94 to 1.16) | 1.05 (0.94 to 1.16) | 1.05 (0.94 to 1.16) | 0.39    |
| Cardiovascular                                | 0.91 (0.84 to 0.99) | 0.91 (0.84 to 0.99) | 0.91 (0.84 to 0.99) | 0.03    |
| Coagulation                                   | 1.20 (0.95 to 1.53) | 1.20 (0.95 to 1.53) | 1.20 (0.95 to 1.53) | 0.13    |
| Hepatic                                       | 1.56 (1.03 to 2.36) | 1.56 (1.03 to 2.36) | 1.56 (1.03 to 2.36) | 0.03    |

![Creatinine Concentration Graph](image)

*P* = 0.004
<table>
<thead>
<tr>
<th>Systematic review</th>
<th><strong>HES preparation</strong></th>
<th>Comparator</th>
<th>Patient population</th>
<th>Mortality RR (95% CI)</th>
<th>RRT RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gattas</td>
<td>6% HES (130/0.4-042)</td>
<td>Isotonic saline Hypertonic saline Lactated Ringer's Acetated Ringer’s Albumin 4%, 5%, 20% Gelatin 4% Polygeline 3.4% Dextran 70 HES (200/0.5) HES (670/0.75)</td>
<td>Acutely ill patients in intensive care, perioperative and operative setting</td>
<td>1.08 (1.00 to 1.17)</td>
<td>1.25 (1.08-1.44)</td>
</tr>
<tr>
<td>Haase</td>
<td>6% HES (130/0.4-0.42)</td>
<td>Isotonic saline Lactated Ringer’s Acetated Ringer’s Albumin 20%</td>
<td>Sepsis/septic shock</td>
<td>1.04 (0.89 to 1.22)</td>
<td>1.36 (1.08 to 1.72)</td>
</tr>
<tr>
<td>Zarychanski</td>
<td>6-10% HES (130/0.4-0.42) 6-10% HES (200/0.43-0.66)</td>
<td>Isotonic saline Hypertonic saline Lactated Ringer’s Acetated Ringer’s Albumin 4%, 5%, 20% Gelatin 3%, 4% Plasma</td>
<td>Critically ill patients in emergency or intensive care setting</td>
<td>1.06 (1.00 to 1.13)</td>
<td>1.32 (1.15 to 1.50)</td>
</tr>
<tr>
<td>Patel</td>
<td>6% HES (130/0.4-0.42)</td>
<td>Isotonic saline Acetated Ringer’s Albumin 20%</td>
<td>Severe sepsis</td>
<td>1.13 (1.02 to 1.25)</td>
<td>1.42 (1.09 to 1.85)</td>
</tr>
</tbody>
</table>
“...the harms of hydroxyethyl starch most likely outweigh the benefits and suggest that these products should not be used for acute volume resuscitation of critically ill patients.”
Network MA for studies in sepsis

Search strategy

391 studies identified through database search and all other sources

336 excluded as not relevant in first screening

55 full text articles were reviewed in second screening

Excluded: 42
Not relevant comparator n=6
Not sepsis n=11
Not a randomized clinical trial n=3
No mortality results n=19
Duplicates/Repeats n=3

13 studies included in network meta-analysis

Crystalloid

6

Albumin

1

HES

5

1
Network MA for studies in sepsis
Ranking of competing fluid treatments

<table>
<thead>
<tr>
<th>Fluid Type</th>
<th>Rank 1</th>
<th>Rank 2</th>
<th>Rank 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>96.38%</td>
<td>3.60%</td>
<td>0.00%</td>
</tr>
<tr>
<td>Crystalloid</td>
<td>3.61%</td>
<td>96.27%</td>
<td>0.00%</td>
</tr>
<tr>
<td>HES</td>
<td>0.01%</td>
<td>0.00%</td>
<td>99.87%</td>
</tr>
</tbody>
</table>
• Do not use HES solutions in critically ill adult patients including those with sepsis, and those admitted to the ICU.
• Avoid use in patients with pre-existing renal dysfunction.
• Discontinue use of HES at the first sign of renal injury.
• Need for renal replacement therapy has been reported up to 90 days after HES administration.
• Continue to monitor renal function for at least 90 days in all patients.
• Avoid use in patients undergoing open heart surgery in association with cardiopulmonary bypass due to excess bleeding.
• Discontinue use of HES at the first sign of coagulopathy.
PRAC recommends suspending marketing authorisations for infusion solutions containing hydroxyethyl-starch

Recommendation to suspend marketing authorisations for hydroxyethyl-starch solutions to be re-examined
Trauma and sepsis result in lowered tissue perfusion and can manifest shock requiring volume replenishment.

A variety of fluids for the treatment of critically ill patients have been proposed.

Colloids may be required after initial crystalloid infusion.

Physiological indications that balanced crystalloids are preferable have not been confirmed in clinical trials in patients.

Albumin has been shown to improve outcomes in septic patients, but is detrimental in traumatic brain injury [TBI].

HES has been shown to increase mortality and cause renal damage.

In decision-making, a focus on total, long term costs needs to replace short term considerations of individual interventions.