Fluid resuscitation in critically ill patients

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I keep six honest serving-men:  
(They taught me all I knew)  
Their names are What and Where and When  
And How and Why and Who
Why?

Thomas Aitchinson Latta
c1790-1833
Mean arterial pressure
Cardiac output
Right atrial pressure
Mean systemic pressure
Perfusion pressure
Unstressed volume
Stressed volume
Venous return
Arteriolar tone

Guyton 1955
Ernest Starling
1866-1927

Thomas Graham
1805-1869

Crystalloids
“substances such as salt, sugar and urea that could be crystallised with ease”

Colloids (from Κθλλη, glue)
“non-crystallisable, form gummy masses when evaporated to dryness, diffuse with extreme slowness and would not pass through animal membranes”
A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Albumin Group</th>
<th>Saline Group</th>
<th>Relative Risk (95% CI)</th>
<th>Absolute Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status at 28 days — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>726/3473 (20.9)</td>
<td>729/3460 (21.1)</td>
<td>0.99 (0.91 to 1.09)</td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>Alive in ICU</td>
<td>111/3473 (3.2)</td>
<td>87/3460 (2.5)</td>
<td>1.27 (0.96 to 1.68)</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Alive in hospital†</td>
<td>793/3473 (22.8)</td>
<td>848/3460 (24.5)</td>
<td>0.93 (0.86 to 1.01)</td>
<td></td>
<td>0.10</td>
</tr>
</tbody>
</table>
Saline or Albumin for Fluid Resuscitation in Patients with Traumatic Brain Injury

The SAFE Study Investigators

SAFE Study Investigators: NEJM 2007

Mortality at 28 days

Mortality at 2 years
Albumin Resuscitation for Traumatic Brain Injury: Is Intracranial Hypertension the Cause of Increased Mortality?

ICP monitoring ceased during first week (day 1-7)

- **ICP (mmHg)**
- **Study day**
- **Dead** (solid line) vs **Alive** (dashed line)

**Albumin**
- Mean ICP
- \( p = 0.0006 \)

**Saline**

Cooper: J Neurotrauma 2013
Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units

Choice of Colloid: Severe sepsis

SAFE TRIPS Investigators: Crit Care 2010
Tissue accumulation and HES

“Hydrops lysosomalis generalisatus”

Renal
Dickenmann: AJKD 2005

Hepatic
Schmidt-Hieber: Eur J Haem 2006

Skin
Sirtl: BJA 1999
Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

70mL/kg (33 to 114.2)

Hydroxyethyl Starch 130/0.42 versus Ringer’s Acetate in Severe Sepsis

44Lm/kg (24 to 75)

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

17mL/kg (9 to 31)
Tissue accumulation and gelatin

GELATIN NEPHROSIS
Renal Tissue Changes in Man Resulting from the Intravenous Administration of Gelatin
OLAF K. SKINNSNES, M.D., Ph.D., New York, New York
## Colloids vs crystalloids

<table>
<thead>
<tr>
<th>Colloid</th>
<th>Trials</th>
<th>n</th>
<th>RR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>56</td>
<td>9920</td>
<td>1.01</td>
<td>0.93 to 1.10</td>
</tr>
<tr>
<td>HES</td>
<td>25</td>
<td>9147</td>
<td>1.10</td>
<td>1.02 to 1.19</td>
</tr>
<tr>
<td>Gelatin</td>
<td>11</td>
<td>506</td>
<td>0.91</td>
<td>0.49 to 1.72</td>
</tr>
<tr>
<td>Dextran</td>
<td>9</td>
<td>834</td>
<td>1.24</td>
<td>0.94 to 1.65</td>
</tr>
</tbody>
</table>

### Authors’ conclusions

There is no evidence from randomised controlled trials that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery. Furthermore, the use of hydroxyethyl starch might increase mortality. As colloids are not associated with an improvement in survival and are considerably more expensive than crystalloids, it is hard to see how their continued use in clinical practice can be justified.
What about crystalloids?

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Na⁺</th>
<th>Cl⁻</th>
<th>K⁺</th>
<th>Mg²⁺</th>
<th>Ca²⁺</th>
<th>HCO₃⁻</th>
<th>Glucose</th>
<th>Acetate</th>
<th>Gluconate</th>
<th>Osmolality (mOsm/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal plasma</td>
<td>142</td>
<td>103</td>
<td>4.5</td>
<td>1.25</td>
<td>2.5</td>
<td>24</td>
<td>0.08</td>
<td></td>
<td></td>
<td>291</td>
</tr>
<tr>
<td>0.9 % saline</td>
<td>154</td>
<td>154</td>
<td>5</td>
<td>1.5</td>
<td>2.5</td>
<td>24</td>
<td>0.08</td>
<td></td>
<td></td>
<td>308</td>
</tr>
<tr>
<td>5% glucose</td>
<td>140</td>
<td>98</td>
<td>5</td>
<td>1.5</td>
<td>2.5</td>
<td>24</td>
<td>27</td>
<td>23</td>
<td></td>
<td>294</td>
</tr>
<tr>
<td>0.18% saline in 4% dextrose</td>
<td>131</td>
<td>111</td>
<td>5</td>
<td>2</td>
<td>29 (as lactate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>278</td>
</tr>
<tr>
<td>Plasma-Lyte 148</td>
<td>130</td>
<td>109</td>
<td>4</td>
<td>1.5</td>
<td>28 (as lactate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>273</td>
</tr>
</tbody>
</table>
Why does saline cause an acidosis?

A “balanced” crystalloid will reduce extracellular SID at a rate that precisely counteracts a dilutional alkalosis induced by weak acids.
Why does saline cause an acidosis?

Need to give lots of saline
Need to give it fast
Chloride-liberal vs. chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis

Single centre, sequential pilot observational trial
6m saline, gelatin, 4% albumin / 6m RL, PL-148, 20% albumin
n=760

KDIGO AKI 2 and 3
HR 1.32

Use of RRT in ICU
HR 1.44
When?

<table>
<thead>
<tr>
<th>Phase Focus</th>
<th>0-24h</th>
<th>24-72h</th>
<th>72-96h</th>
<th>&gt;96h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salvage</strong></td>
<td>Obtain a minimal acceptable blood pressure</td>
<td>Provide adequate oxygen availability</td>
<td>Provide organ support</td>
<td>Wean from vasoactive agents</td>
</tr>
<tr>
<td></td>
<td>Perform lifesaving measures</td>
<td>Optimize cardiac output, SvO₂, lactate</td>
<td>Minimize complications</td>
<td>Achieve a negative fluid balance</td>
</tr>
</tbody>
</table>

The difficulty lies, not in new ideas, but in escaping old ones, which ramify, for those brought up with them, as most of us have been, into every corner of our minds.
The physiological fallacy

Fluid bolus therapy is self-evidently beneficial

Based on a common phenotype and surrogate variables

An inference, that cannot be measured, is made that the patient has inadequate organ blood flow.

The second inference, that also cannot be measured, is that a fluid bolus will restore the complexity of altered haemodynamics in a predictable and safe fashion for the duration of the illness.
FBT and haemodynamics

A. Change in heart rate with time
B. Changes in cardiac index with time
C. Change in mean arterial pressure with time
D. Change in central venous pressure with time
FBT and renal function

Saotome: Int Care Med 2010

Wan: Anesth Anal 2007
Mortality after Fluid Bolus in African Children with Severe Infection

Multicentred open-label RCT

2009-2011

Albumin vs saline bolus vs no bolus in febrile hypotensive children

n=3141/3600

Primary outcome: Mortality at 48h

Mortality at 4 hours

Mortality at 4 weeks

The endothelial glycocalyx model
**Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy**

### Crystalloid to colloid volume ratios

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAFE</td>
<td>(4% albumin)</td>
<td>1.4:1</td>
</tr>
<tr>
<td>VISEP</td>
<td>(HES 200/0.5)</td>
<td>1.4:1</td>
</tr>
<tr>
<td>CHEST</td>
<td>(HES 130/0.4)</td>
<td>1.4:1</td>
</tr>
<tr>
<td>6-S</td>
<td>(HES 130/0.42)</td>
<td>1.0:1</td>
</tr>
<tr>
<td>CHRYSMAS</td>
<td>(HES 130/0.4)</td>
<td>1.2:1</td>
</tr>
<tr>
<td>FIRST</td>
<td>(HES 130/0.4)</td>
<td>1.4:1</td>
</tr>
</tbody>
</table>

**Editor’s key points**

- The classic Starling principle does not hold for fluid resuscitation in clinical settings.
- The endothelial glycocalyx layer appears to have a major role in fluid exchange.
- A revision of Starling incorporating the glycocalyx model appears to explain better the responses seen clinically.
Fluid volumes and outcomes

VASST study: fluid balance / CVP at 12h and 4d
n=778
Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

Multicentred open-label RCT

Protocolised liberal v conservative fluid strategy x 7d: ALI

n=1001

Primary outcome: Mortality at 60d

FACCT follow-up: 122 of 213/406 survivors
Neuropsychological assessment at 12 months

OR 4.03 (1.53–10.59), p= 0.004
Fluids are unvalidated, lethal drugs

**Drug:** A term of varied usage. In medicine, it refers to any substance with the potential to prevent or cure disease or enhance physical or mental welfare. (www.WHO.int)
How and why?

Fluids should be administered with the same caution that is used with any intravenous drug.

Consider the type, dose, indications, contraindications, potential for toxicity and cost.

Resuscitation fluids should only be used in patients with symptomatic hypovolaemia.
How?

Fluid resuscitation is a component of a complex physiological process

Identify the fluid that is most likely to be lost and replace the fluid lost in equivalent volumes

Consider serum osmolality and the acid-base status when selecting a resuscitation fluid

Consider cumulative fluid balance and actual body weight when selecting the dose of resuscitation fluid

Consider the early use of catecholamines as concomitant treatment of shock
When, how and why?

Fluid requirements change over time in critically ill patients.

The cumulative dose of resuscitation and maintenance fluids is associated with pathological oedema that is associated with adverse outcomes.

The use of a fluid challenge in the post-resuscitation period (>24 hours) is questionable.
Who and what?

Specific considerations apply to different categories of patients.

Bleeding patients require control of haemorrhage and transfusion

Isotonic, buffered salt solutions are pragmatic initial resuscitation fluids for the majority of acutely ill patients.

Consider saline in patients with hypovolaemia and alkalosis

Consider albumin during early resuscitation of patients with sepsis
Specific considerations apply to different categories of patients.

Saline or isotonic crystalloids are indicated in traumatic brain injury.

Albumin is contraindicated in traumatic brain injury.

Hydroxyethyl starch should not be used in any patient population.

The safety of other semi-synthetic colloids has not been established.
“The dose makes the poison”