Fluid resuscitation in the ICU: colloids vs. crystalloids

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University of Medicine (2), YGH
Where to **find the evidence**?
Animal experimental, human observational and RCT are needed to understand how the fluids to be infused work.

Prescribing intravenous fluids: the 5Rs

- Resuscitation (if needed)
- Routine maintenance
- Redistribution: Adjust maintenance
- Replacement: Add to maintenance
- Reassess
When to administer fluids?
Potential parameters to start fluid administration

- HR
- MAP
- SAP
- Lactate
- BE
- CVP
- LAP
- PAOP
- CI
- SV
- LVSWI
- SVO2
- Diuresis
- Medical judgement

Hypovolemia is frequent in all types of shock.
Fluid resuscitation practice patterns in intensive care units of the USA: a cross-sectional survey of critical care physicians

MAP
Diuresis
CVP
Cardiac Output
Fluid challenges in intensive care: the FENICE study

A global inception cohort study

Table 3 Indications and variables used to predict fluid responsiveness ($N = 2213$)

<table>
<thead>
<tr>
<th>Indication</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>1211 (58.7 [56.7–60.8])</td>
</tr>
<tr>
<td>Weaning vasopressor</td>
<td>146 (7.1 [6.0–8.2])</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>62 (3.0 [2.3–3.7])</td>
</tr>
<tr>
<td>Oliguria</td>
<td>372 (18.0 [16.4–19.6])</td>
</tr>
<tr>
<td>Skin mottling</td>
<td>36 (1.7 [1.2–2.2])</td>
</tr>
<tr>
<td>Lactate</td>
<td>128 (6.2 [5.2–7.2])</td>
</tr>
<tr>
<td>SvO$_2$/ScvO$_2$</td>
<td>10 (0.5 [0.2–0.8])</td>
</tr>
<tr>
<td>SVV/PPV</td>
<td>37 (1.8 [1.3–2.4])</td>
</tr>
<tr>
<td>CVP/PAOP</td>
<td>60 (2.9 [2.2–3.6])</td>
</tr>
</tbody>
</table>

Cecconi et al, Intensive Care Medicine 2015 (41): 1529-37
Hypotension is a late event in hypovolemic patients

In patients with suspected or confirmed hypovolemic, administration of fluids must be considered as an early strategy
How much to administer?
Hypovolemia and hypervolemia can both cause harm

Is edema just an esthetic issue?

Your tests reveal that you are retaining fluids!
A positive fluid balance is an independent prognostic factor in patients with sepsis

Angela Acheampong and Jean-Louis Vincent

Critical Care (2015) 19:251
Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study

Suvi T Vaara¹, Anna-Maija Korhonen¹, Kirsi-Maija Kaukonen¹, Sara Nisula¹, Outi Inkinen², Sanna Hoppu³, Jouko J Laurila⁴, Leena Mildh¹, Matti Reinikainen⁵, Vesa Lund⁶, Ilkka Parviainen⁷ and Ville Pettila¹,⁸, for The FINNAKI study group

**Fluid overload is related to worst outcomes**

![Graph showing cumulative survival and 90-day mortality](image)

Log-rank test P<0.001

Days from ICU admission

90-day mortality (%)

Fluid accumulation % (number of patients)

<0 (46) 0-5 (94) 5-10 (67) 10-15 (44) >15 (32)

Vaara et al. Critical Care 2012, 16:R197
Which one to use?
TYPES OF FLUIDS

• Different types of solutions can have
  – specific capacity of volume expansion,
  – duration of effect,
  – impact on vascular integrity,
  – acid-base balance,
  – inflammatory response,
  – changes in red blood cell rheology and haemostasis
Isotonic Crystalloids

- Most common type of fluids used to replace bodily fluids
- Three main compositions:

*For each 1 ml increase in vasculature fluid, you need to give 3-4 mls of isotonic fluid
CRISTRALLOIDS

• Normal saline (0.9% NaCl) is considered an isotonic solution, with osmolality closer to the plasma osmolality

• Sodium 154mEq/L and Chloride 154mEq/L

• 1.5-fold higher than the physiologic serum concentration of chloride ➔ (non-balanced solution)

• large volume infusions can promote hyperchloremic acidosis (dilution hyperchloremic acidosis), dilutional coagulopathy and renal dysfunction
<table>
<thead>
<tr>
<th>Type</th>
<th>Plasma</th>
<th>N/S</th>
<th>R/L</th>
<th>R/A</th>
<th>Plasma-lyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmo:</td>
<td>290</td>
<td>308</td>
<td>273</td>
<td>275</td>
<td>295</td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
<td>5.7</td>
<td>6.5</td>
<td>6.7</td>
<td>7.4</td>
</tr>
<tr>
<td>Na</td>
<td>140</td>
<td>154</td>
<td>130</td>
<td>131</td>
<td>140</td>
</tr>
<tr>
<td>Cl</td>
<td>103</td>
<td>154</td>
<td>109</td>
<td>109</td>
<td>98</td>
</tr>
<tr>
<td>K</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Ca</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Mg</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Buffer</td>
<td>HCO3</td>
<td>0</td>
<td>Lactate</td>
<td>Acetate</td>
<td>Acetate Gluconate</td>
</tr>
</tbody>
</table>
• Balanced solutions have been proposed as an alternative to normal saline
• Ringer Lactate, Ringer Acetate and Plasma-Lyte.
• A chloride-restrictive strategy in critically ill patients was associated with a significant decrease in the incidence of acute kidney injury and use of renal replacement therapy
COLLOIDS

• Higher oncotic pressure when compared to crystalloids
• Higher duration and capacity of intravascular expansion with lower volumes
• Colloids are not able to cross the semi impermeable vascular membrane due to their high molecular weight.
# Main colloidal solutions and their composition

<table>
<thead>
<tr>
<th></th>
<th>Albumin</th>
<th>Hydroxyethyl Starch</th>
<th>Dextran</th>
<th>Gelatins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4%,5%</td>
<td>20%,25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular weight</td>
<td>69</td>
<td>100-450</td>
<td>40-70</td>
<td>30-35</td>
</tr>
<tr>
<td>Osmolality (mOsm/L)</td>
<td>300</td>
<td>1500</td>
<td>280-324</td>
<td>300-350</td>
</tr>
<tr>
<td>Oncotic pressure (mmHg)</td>
<td>19-30</td>
<td>74-120</td>
<td>20-60</td>
<td>25-42</td>
</tr>
<tr>
<td>Plasmatic expansion (%)</td>
<td>70-100</td>
<td>200-300</td>
<td>100-200</td>
<td>80-140</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100-160</td>
<td>70-100</td>
</tr>
<tr>
<td>Duration of plasmatic expansion (h)</td>
<td>≤24</td>
<td>≤12</td>
<td>≤4-36</td>
<td>≤4-6</td>
</tr>
<tr>
<td>Plasma half-life (h)</td>
<td>16-24</td>
<td>2-12</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2-9</td>
<td></td>
</tr>
<tr>
<td>Possible adverse effects</td>
<td>High cost, risk of infection &amp; anaphyl reactions</td>
<td>Impairment coagulation, pruritus, acute kidney failure, and anaphylactic reactions</td>
<td>Changes in blood viscosity, coagulopathy, renal dysfunction, and anaphylactic reactions</td>
<td>Hypercalcemia and Anaphyl reactions</td>
</tr>
</tbody>
</table>
Hydroxyethyl starch (HES)

• One of the most frequently used colloidal plasma expanders worldwide, mainly due to their lower cost when compared to albumin

• avoided in the treatment of critically ill patients, specifically in those with sepsis

• 10% HES 200/0.5 or 6% HES 130/0.4

• solution concentration, mean mol. wt expressed in kilo Dalton (kDa), molar substitution (MS)
• In general, HES is used for restrictive fluid strategy due to a high plasma expansion capacity with lower volume administration

• Increase the risk of acute renal failure (Systematic review of RCT on the use of HES for fluid management in sepsis, BMC Emerg Med. 2008)
Albumin

• Based on its physiological effects, primarily binding and transportation of various substances (drugs and hormones) in the blood; antioxidant properties, nitric oxide modulation; and buffer capacity, not only to regulate osmotic pressure

• limitations for a broader use of albumin: high cost, potential risk of microorganisms transmission and allergic effects

• Those with traumatic brain injury, can have an increased risk of death when receiving albumin solutions.
Plasmatic Volume
Na: 143 mequiv/Lt  K: 4 mequiv/Lt
Alb: 5 gr/dl  Cl: 100 mequiv/Lt
3 Lt

Red blood cells
Na: 137 mequiv/Lt  K: 3 mequiv/Lt
Alb: 1 gr/dl  Cl: 105 mequiv/Lt
2 Lt

Endothelium

Cellular membrane

Na: 10 mequiv/Lt  K: 155 mequiv/Lt
Cl: 10 mequiv/Lt
23 Lt

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Volume (Lt)</th>
<th>Na (mequiv/Lt)</th>
<th>K (mequiv/Lt)</th>
<th>Cl (mequiv/Lt)</th>
<th>Alb (gr/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular</td>
<td>3</td>
<td>137</td>
<td>3</td>
<td>105</td>
<td>5</td>
</tr>
<tr>
<td>Interstitial</td>
<td>14</td>
<td>10</td>
<td>155</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>Intracellular</td>
<td>23</td>
<td>10</td>
<td>155</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

Body fluid compartment volumes and theoretical distribution of IV fluids in healthy people

Frost P. BMJ. 2015 Jan 6;350:g7620
Preferred plasma volume expanders for critically ill patients: results of an international survey

- France (n=162)
- Germany (n=62)
- United Kingdom (n=40)
- The Netherlands (n=35)
- Italy (n=35)
- European countries (n=517)
- Non-European countries (n=60)
International resuscitation fluid use – Safe TRIPS
Type of colloid used as a percentage of all colloid episodes by country

2007: Colloid choice varied among countries, artificial colloids prevailed

Resuscitation fluid use – evolution in 6 yrs in Australia - New Zealand

Cross-sectional point prevalence studies on the use of resuscitation fluids

- Pending publication of international trends (Fluid-TRIPS), changes in fluid preferences, including an increase of albumin use, were observed in Australia and New Zealand
  - In particular, a significant increase in the use of crystalloids and decrease in the use of colloids, specifically gelatin was observed

Proportion of all patients receiving selected types of crystalloid (a) and colloid (b) solutions between 2007 and 2013

Adapted from Hammond NE et al. 2015.¹

Even if fluids administration practices are highly variable and subjective, physiology is exactly the same everywhere.
Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

<table>
<thead>
<tr>
<th>Table 3. Incidence of Acute Kidney Injury Stratified by Risk, Injury, Failure, Loss, and End-Stage (RIFLE) Serum Creatinine Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. (%) [95% CI] of Patients</strong></td>
</tr>
<tr>
<td><strong>Control Period (n = 760)</strong></td>
</tr>
<tr>
<td><strong>Intervention Period (n = 773)</strong></td>
</tr>
<tr>
<td><strong>P Value</strong></td>
</tr>
<tr>
<td>RIFLE class</td>
</tr>
<tr>
<td>Risk</td>
</tr>
<tr>
<td>Injury</td>
</tr>
<tr>
<td>Failure</td>
</tr>
<tr>
<td>Injury and failure</td>
</tr>
</tbody>
</table>

*aThe control period was from February 18 through August 17, 2008, and the intervention period was from February 18 through August 17, 2009.*
Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit
The SPLIT Randomized Clinical Trial

Mortality 7%

Log-rank (through day 90) P = .85

Percentage Requiring Renal Replacement Therapy

Time, d

No. at risk
Buffered crystalloid 1152 341 134 62 36
Saline 1110 310 124 64 28

Young et al. JAMA. 2015 Oct 27;314(16):1701-10
Crystalloids vs. Colloids and crystalloids
Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: A prospective sequential comparison*

Ole Bayer, MD; Konrad Reinhart, MD; Yasser Sakr, MD, PhD; Bjoern Kabisch, PhD; Matthias Kohl, PhD; Niels C. Riedemann, MD; Michael Bauer, MD; Utz Settmacher, MD; Khosro Hekmat, MD; Christiane S. Hartog, MD

Table 3. Primary and secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Hydroxyethyl Starch Group (n = 118)</th>
<th></th>
<th>Adjusted p</th>
<th>Gelatin Group (n = 87)</th>
<th></th>
<th>Adjusted p</th>
<th>Crystalloid Group (n = 141)</th>
<th></th>
<th>Adjusted p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFLR risk, n (%)</td>
<td>15 (13)</td>
<td>.698</td>
<td>1.000</td>
<td>10 (11)</td>
<td>.831</td>
<td>1.000</td>
<td>15 (11)</td>
<td>.831</td>
<td>1.000</td>
</tr>
<tr>
<td>IFLR injury, n (%)</td>
<td>12 (10)</td>
<td>.842</td>
<td>1.000</td>
<td>14 (16)</td>
<td>.319</td>
<td>1.000</td>
<td>16 (11)</td>
<td>.319</td>
<td>1.000</td>
</tr>
<tr>
<td>IFLR failure, n (%)</td>
<td>56 (47)</td>
<td>&lt;.001</td>
<td>0.002</td>
<td>35 (40)</td>
<td>.018</td>
<td>.162</td>
<td>35 (25)</td>
<td>.018</td>
<td>.162</td>
</tr>
<tr>
<td>IFR, n (%)</td>
<td>83 (70)</td>
<td>&lt;.001</td>
<td>0.002</td>
<td>59 (68)</td>
<td>.003</td>
<td>.025</td>
<td>66 (47)</td>
<td>.003</td>
<td>.025</td>
</tr>
<tr>
<td>Renal replacement therapy, n (%)</td>
<td>40 (34)</td>
<td>.011</td>
<td>0.086</td>
<td>30 (34)</td>
<td>.019</td>
<td>.162</td>
<td>28 (20)</td>
<td>.019</td>
<td>.162</td>
</tr>
<tr>
<td>Sequential Organ Failure score maximum, median (IQR)</td>
<td>11 (9–14)</td>
<td>.355</td>
<td>1.000</td>
<td>13 (10–15)</td>
<td>.332</td>
<td>1.000</td>
<td>12 (9–14)</td>
<td>.332</td>
<td>1.000</td>
</tr>
<tr>
<td>Sequential Organ Failure score mean; median (IQR)</td>
<td>7 (6–10)</td>
<td>.032</td>
<td>.227</td>
<td>8 (6–10)</td>
<td>.122</td>
<td>.853</td>
<td>8 (6–11)</td>
<td>.122</td>
<td>.853</td>
</tr>
<tr>
<td>Intensive care unit mortality, n (%)</td>
<td>41 (35)</td>
<td>.506</td>
<td>1.000</td>
<td>23 (26)</td>
<td>.550</td>
<td>1.000</td>
<td>43 (30)</td>
<td>.550</td>
<td>1.000</td>
</tr>
<tr>
<td>Hospital mortality, n (%)</td>
<td>51 (43)</td>
<td>.311</td>
<td>1.000</td>
<td>27 (31)</td>
<td>.393</td>
<td>1.000</td>
<td>52 (37)</td>
<td>.393</td>
<td>1.000</td>
</tr>
<tr>
<td>Intensive care unit length of stay, days; median (IQR)</td>
<td>14 (6–28)</td>
<td>.070</td>
<td>.421</td>
<td>13 (6–26)</td>
<td>.167</td>
<td>1.000</td>
<td>10 (5–20)</td>
<td>.167</td>
<td>1.000</td>
</tr>
</tbody>
</table>

IQR, interquartile range.

*Five-fold increase in serum creatinine levels and/or urine output <0.5 mL/kg/hr for ≥24 hrs; ‡two-fold increase in serum creatinine levels and/or urine output <0.3 mL/kg/hr for ≥24 hrs; †three-fold increase in serum creatinine levels and/or renal replacement therapy, serum creatinine ≥354 μmol/L, with an acute increase of at least 44 μmol/L, and/or urine output <0.3 mL/kg/hr ≥24 hrs or anuria ≥12 hrs for ≥24 hrs; *defined by any RIFLE category; ‡within 28 days of admission to the intensive care unit. The p values were calculated with the Mann-Whitney test and Fisher’s exact test, as appropriate. For p value adjustment, the Bonferroni-Holm method was used.
Fluid resuscitation with only crystalloids was equally effective, resulted in a more positive fluid balance only on the first 2 days, and was associated with a lesser incidence of AKI (Critical Care Med 2011 Vol, No.6)
Other recent trials in fluid therapy

- **6S** (n = 800 [severe sepsis])
- **CHEST** (n = 7,000 [ICU-admitted])

RRT at 90-d: more need for HES (p = 0.04)

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CRISTAL trial

- **2,857 ICU-admitted patients**
  - 28 day mortality: 25.4% colloids vs. 27% crystalloids (p = 0.26)

Synthetic colloids are not a good option in septic patients considering their side effects on renal and coagulation systems.
Key milestones in the history of albumin

1941
First clinical use of human albumin solution in a patient with multiple trauma and circulatory shock

1943
One of the first published reports of human albumin use in 200 patients

1949
- Expert Working Party of the Committee on Safety of Medicines in UK concludes that there is insufficient evidence of harm to warrant withdrawal of albumin products
- Hospital and 3-month mortality rates are lower in the patients who received albumin (Study of 126 patients with cirrhosis and bacterial peritonitis)

1998
- Crone meta-analysis reports increased mortality rates in critically ill patients who received albumin

2001
Wilkes and Navickis’ meta-analysis including 55 trials reports no overall effect of albumin on mortality

2004
SAFE study shows no difference in mortality rates among groups, and suggests benefits of albumin in patients with severe sepsis and harm in those with traumatic brain injury

2005
- FDA states that the SAFE study had resolved the prior safety concerns raised in 1998
- Albumin use is associated with decreased mortality in critically ill patients (SOAP observational study)

2006
Organ function is improved in patients treated with albumin (Pilot study of 100 patients)

2008
- Hypoalbuminemia seen as a dose-dependent predictor of poor outcome and correction of serum albumin is associated with reduced complications (meta-analysis of 90 cohort studies and 9 prospective controlled trials)

2009
Hypoalbuminemia seen as a dose-dependent predictor of poor outcome and correction of serum albumin is associated with reduced complications

2010
ESICM taskforce Consensus suggests that albumin may be included in the resuscitation of severe sepsis patients (grade 2B)

2011
Report of survival benefit for septic patients who received albumin (meta-analysis including 17 studies)

2012
ALBIOS study shows no overall difference in 28-day or 90-day mortality rates but survival benefit at 90 days in patients with septic shock

2013
- Surviving Sepsis Campaign guidelines specifically suggest (grade 2C) use of albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids
- EARSS study shows no differences in mortality rates between groups

Adapted from Vincent, et al. 2014.
Key milestones in the history of albumin

1941
First clinical use of human albumin solution in a patient with multiple trauma and circulatory shock

1943
One of the first published reports of human albumin use in 200 patients

1949
- Cochrane meta-analysis reports increased mortality rates in critically ill patients who received albumin
  • FDA expresses serious concern over the safety of albumin administration in the critically ill population

1975
First randomized controlled trial of human albumin

1998
- Expert Working Party of the Committee on Safety of Medicines in UK concludes that there is insufficient evidence of harm to warrant withdrawal of albumin products
  • Hospital and 3-month mortality rates are lower in the patients who received albumin (Study of 126 patients with cirrhosis and bacterial peritonitis)

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2014
ALBIOS study shows no overall difference in 28-day or 90-day mortality rates but survival benefit at 90 days in patients with septic shock

Adapted from Vincent, et al. 2014.
Authors suggest that there is a survival advantage associated with albumin use in patients with severe sepsis.
### Fluid therapy

1. We recommend that a **fluid challenge technique** be applied where fluid administration is continued as long as hemodynamic factors continue to improve (BPS*).

2. We recommend **crystalloids as the fluid of choice** for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence).

3. We suggest using **either balanced crystalloids or saline** for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence).

4. We suggest using **albumin** in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).

5. We recommend **against using hydroxyethyl starches (HESs)** for intravascular volume replacement in patients with sepsis or septic shock (strong recommendation, high quality of evidence).

6. We suggest **using crystalloids over gelatins** when resuscitating patients with sepsis or septic shock (weak recommendation, low quality of evidence).

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*BPS: best practice statement

** Initial resuscitation recommendation: We recommend that, in the resuscitation from sepsis induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours (strong recommendation, low quality of evidence).

Thank you