Fluids in anesthesia and ICU – are synthetic colloids still dead?

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Hydroxyethyl-starch solutions (HES) no longer to be used in patients with sepsis or burn injuries or in critically ill patients

HES will be available in restricted patient populations
Since December 2013:

HES **should no** longer be used in **critical ill patients/burns**.

HES **could be used** in patients with **hypovolemia** due to acute blood loss.

HES **should not** be used for more than **24 hours**.

**Kidney function has to be monitored for at least 90 days.**
1. Vasopressor instead of volume replacement
2. Crystalloid/Saline
3. Plasma
4. Albumin
5. Gelatin

Plan B
1. Vasopressor instead of volume replacement
2. Crystalloid/Saline
3. Plasma
4. Albumin
5. Gelatin
Cardiac Output and **Preload**

![Graph showing the relationship between cardiac output and pressure right atrium.](image-url)
Cardiac Output and Afterload
Mottling score predicts survival in septic shock.
Ait-Outfella et al. Intensive Care Med 2011
# Blood pressure and microcirculation

<table>
<thead>
<tr>
<th></th>
<th>Before CPB</th>
<th>CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before phenylephrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenylephrine</td>
</tr>
<tr>
<td><strong>Systemic variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfusion pressure (mm Hg)</td>
<td>72.5 (10.8)</td>
<td>47.0 (8.8)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>68.1 (7.0)†‡</td>
</tr>
</tbody>
</table>

**before Phenylephrine** | **during Phenylephrine** | **after Phenylephrine**

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Independent HR for mortality

Early vasopressor
- 12 h
- 24 h

Aggressive volume therapy
- 12 h
- 24 h

Independent HR for mortality (95% CI)

Early volume resuscitation: 40% reduction of mortality

Sperry J: J Trauma 2008;64:9
1. Vasopressor instead of volume replacement
2. Crystalloid/Saline
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5. Gelatin

Plan A
Plan B
## Fluid Compartments and Resuscitation

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Glucose 5%</th>
<th>Crystalloid</th>
<th>Colloid</th>
</tr>
</thead>
<tbody>
<tr>
<td>intravascular</td>
<td><img src="up" alt="up" /></td>
<td><img src="up" alt="up" /></td>
<td><img src="up" alt="up" /></td>
</tr>
<tr>
<td>interstitial</td>
<td><img src="up" alt="up" /></td>
<td><img src="up" alt="up" /></td>
<td></td>
</tr>
<tr>
<td>intracellular</td>
<td><img src="up" alt="up" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The intravascular volume effect of Ringer’s lactate is below 20%: a prospective study in humans. Jacob M et al. Crit Care 2012

Exact Measurement of volume effect of 6% HES 130/0.4 during acute normovolemic hemodilution. Jacob M et al. Anaesthesist 2012.
Fishman A.

Shock lung a distinctive nonentity. Circulation 1973

“Thus, on the battlefield, overzealous administration of liquids, particularly of crystalloidal solutions, predisposes to pulmonary congestion and edema“

“wet lung“ ...“shock lung“ ...“Da Nang Lung“
“Hamster skinfold window preparation”, a microcirculation model that allows for chronic and direct observation of microvessels by intravital microscopy.
<table>
<thead>
<tr>
<th></th>
<th>A63 (Saline)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>40%</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Hct</td>
<td>48</td>
<td>34</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Hb</td>
<td>14,3</td>
<td>8,5</td>
<td>6,9</td>
<td>5</td>
</tr>
<tr>
<td>pH</td>
<td>7,4</td>
<td>7,3</td>
<td>7,3</td>
<td>7,3</td>
</tr>
<tr>
<td>BE</td>
<td>9,3</td>
<td>-0,2</td>
<td>-3,9</td>
<td>-10,8</td>
</tr>
<tr>
<td></td>
<td>A58 (Gelofusin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Base</td>
<td>40%</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Hct</td>
<td>52</td>
<td>38</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Hb</td>
<td>15,8</td>
<td>11,8</td>
<td>6,8</td>
<td>4,3</td>
</tr>
<tr>
<td>pH</td>
<td>7,3</td>
<td>7,3</td>
<td>7,3</td>
<td>7,5</td>
</tr>
<tr>
<td>BE</td>
<td>8,3</td>
<td>8,9</td>
<td>6,5</td>
<td>2,1</td>
</tr>
</tbody>
</table>
Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock
The CRISTAL Trial Randomized Controlled Trial

Djillali Annane, MD, PhD; Shidasp Siami, MD; Samir Jaber, MD, PhD; Claude Martin, MD, PhD; Souheil Elatrous, MD; Adrien Descors Declère, MD;

<table>
<thead>
<tr>
<th></th>
<th>No. (%) of Patients</th>
<th></th>
<th>RR (95% CI)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Colloids (n = 1414)</td>
<td>Crystalloids (n = 1443)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 28 d</td>
<td>359 (25.4)</td>
<td>390 (27.0)</td>
<td>0.96 (0.88 to 1.04)</td>
<td>.26</td>
</tr>
<tr>
<td>Within 90 d</td>
<td>434 (30.7)</td>
<td>493 (34.2)</td>
<td>0.92 (0.86 to 0.99)</td>
<td>.03</td>
</tr>
<tr>
<td>In ICU</td>
<td>355 (25.1)</td>
<td>405 (28.1)</td>
<td>0.92 (0.85 to 1.00)</td>
<td>.06</td>
</tr>
<tr>
<td>In hospital</td>
<td>426 (30.1)</td>
<td>471 (32.6)</td>
<td>0.94 (0.87 to 1.02)</td>
<td>.07</td>
</tr>
</tbody>
</table>
1. Vasopressor instead of volume replacement
2. Crystalloid/Saline
3. Plasma
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5. Gelatin
We suggest that fresh frozen plasma not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (grade 2D). In addition, transfusion of fresh frozen plasma usually fails to correct the prothrombin time in nonbleeding patients with mild abnormalities. No studies suggest that correction of more severe coagulation abnormalities benefits patients who are not bleeding.
Prospective multicentre observational study including 1.923 ICU admissions

Reasons for plasma transfusion:
48% bleeding, 15% pre-procedural prophylaxis, 36% prophylaxis without any procedure

Indication for FFP transfusion: PT prolongation
Transfusion of FFP Gabe was associated with:

- **VAP** with (RR 5.42) and without shock (RR 1.97)
- **septic shock with positive blood culture** (RR 3.35)
- **non specified septic shock** (RR 3.22)
- **RR for transfusion of FFP and all infections**: 2.99
Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy*

Saqib I. Dara, MD; Rimki Rana, MD; Bekele Afessa, MD; S. Breanndan Moore, MD; Ognjen Gajic, MD

Table 2. Outcome of patients who did and did not receive fresh frozen plasma (FFP) transfusion

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FFP (n = 44)</th>
<th>No FFP (n = 71)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New bleeding episodes, n (%)</td>
<td>3 (6.8)</td>
<td>2 (2.8)</td>
<td>.369</td>
</tr>
<tr>
<td>New onset acute lung injury, n (%)</td>
<td>8 (18.2)</td>
<td>3 (4.2)</td>
<td>.021</td>
</tr>
<tr>
<td>Hospital mortality, n (%)</td>
<td>11 (25.6)</td>
<td>20 (28.2)</td>
<td>.763</td>
</tr>
<tr>
<td>Median (IQR) ICU length of stay, days*</td>
<td>2.4 (1.7–6.8)</td>
<td>2 (0.9–3)</td>
<td>.184</td>
</tr>
</tbody>
</table>

Conclusion:
- no difference in new bleeding episodes
- new onset acute lung injury was more frequent in the transfused group (18% vs. 4%, p = .021).
- risk-benefit ratio of FFP transfusion in critically ill medical patients with coagulopathy may not be favorable.
Impact of plasma transfusion in trauma patients who do not require massive transfusion.
K Inaba et al. J Am Coll Surg 2010
1. Vasopressor instead of volume replacement
2. Crystalloid/Saline
3. Plasma
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Albumin
1. **Costs:** Most *expensive* colloid.

2. **Virus-safety:** (eg. nvCJD) Albumin is pasteurized for 10 Std. at +60 C. (The Paul-Ehrlich Institute recommends 3-fold virus inactivation steps for plasma products). *No experience according slow virus infection/priones:*

3. **Carrier solution:** 5% Albumin is dissolved in 154 mmol NaCl which may cause acidosis.

4. **Distribution:** Administration of Albumin inhibits the synthesis. *Less than 40% of the infused albumin stays in the intravascular compartemente.* Long lasting increase of plasma albumin is only possible via nutrition.


5. **Critical Care Medicine:** A prospective cohort analysis showed an *increase in moratlity* in patients receiving albumin (n=3.147).

6. **Kidney**: 20% Albumin increased the number of **acute kidney failure** in a prospective cohort analysis in critical ill patients (n=1,013) and decreased GFR.


7. **Albumin** binds furosemide in the renal tubule and inactivates it.


8. **Volume-effect**: In case of sepsis/capillary leak, shift of Albumin into the interstitium is increased by factor-13. The **half life time of albumin in the interstitium is about 19 days**.


9. **Albumin causes a significant decrease of the antibacterial potency** of PHMB-based antiseptics.

Is albumin administration in the acutely ill associated with increased mortality? Results of the SOAP study

Jean-Louis Vincent¹, Yasser Sakr¹, Konrad Reinhart², Charles L Sprung³, Herwig Gerlach⁴, V Marco Ranieri⁵ for the 'Sepsis Occurrence in Acutely Ill Patients' investigators

Kaplan-Meier survival curves in patients who received albumin (lower curve) and their propensity matched pairs without albumin administration.
Serum albumin level was monitored and kept to a level of 30 g/L

N = 1.810 patients

300 mL of 20% albumin solution (total amount, 60 g).

Higher blood pressure and lower net fluid balance.

No improvement in survival (28 and 90 days)!

Conclusion

In ICU patients, the use of 4 % albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.
Saline or Albumin for Fluid Resuscitation in Patients with Traumatic Brain Injury

The SAFE Study Investigators*

**probability of survival at 28 days**

P=0.007

**probability of survival at 24 months**
Conclusion
Development of Gelatine Plasma Substitutes

The use of Gelatin in the treatment of shock goes back to World War I (Hogan, 1915).

The second era of the Gelatine plasma substitutes opened during the 50s, when modified gelatines were developed:

- **Oxypoligelatin** (1951), e.g. Gelifundol (not available anymore)
- **Urea-cross linked gelatin** (1958), e.g. Haemaccel
- **Succinylated gelatine** (1962), e.g. Gelofusine/Gelaspan

Decades of medical experience with gelatin demonstrate its safety and efficacy as plasma volume substitutes.
## Succinylated gelatin vs. urea-cross linked gelatin

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Gelofusine</th>
<th>Gelofusin Iso/Gelaspan</th>
<th>Haemaccel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of gelatin</strong></td>
<td>Succinylated</td>
<td>Succinylated</td>
<td>Urea-linked</td>
</tr>
<tr>
<td><strong>Gelatin concentration</strong></td>
<td>4%</td>
<td>4%</td>
<td>3.5%</td>
</tr>
<tr>
<td><strong>Osmolarity [mOsm/l]</strong></td>
<td>274</td>
<td>284</td>
<td>293</td>
</tr>
<tr>
<td><strong>Mean Mw</strong></td>
<td>30 Kd</td>
<td>30 Kd</td>
<td>35 Kd</td>
</tr>
<tr>
<td><strong>Volume Effect</strong></td>
<td>100%, 3-4 h</td>
<td>100%, 3-4 h</td>
<td>~70%, 1-2 h</td>
</tr>
<tr>
<td><strong>Na⁺ [mmol/l]</strong></td>
<td>154</td>
<td>151</td>
<td>145</td>
</tr>
<tr>
<td><strong>Cl⁻ [mmol/l]</strong></td>
<td>120</td>
<td>103</td>
<td>145</td>
</tr>
<tr>
<td><strong>K⁺ [mmol/l]</strong></td>
<td>0</td>
<td>4</td>
<td>5.1</td>
</tr>
<tr>
<td><strong>Ca²⁺ [mmol/l]</strong></td>
<td>0</td>
<td>1</td>
<td>6.25</td>
</tr>
<tr>
<td><strong>Mg²⁺ [mmol/l]</strong></td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Acetate [mmol/l]</strong></td>
<td>0</td>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>
Succinylated gelatin vs. Urea-cross linked gelatin

**Succinylated gelatin**
- e.g. in Gelofusine/Gelaspan
- stretched molecule
- negatively charged (added succinate)

**Urea- cross linked gelatin**
- e. g. in Haemaccel®
- more globular molecule
- little negative charge
Influences on passage through membrane pores

- Stretched molecule, strong negative charge
- Globular molecule, little negative charge

Succinylated gelatin

- Elimination through kidneys is slower
- Duration of volume effect prolonged

Urea-cross linked gelatin

Effect of volume loading with 1 liter of 0.9% saline, 4% gelatine and 6% hydroxyethyl starch on blood volume and endocrine responses.
Lobo DN et al. Crit Care 2010
Anaphylactic Reactions

I THINK I'M ALLERGIC TO MORNING.
Results in terms of frequency of anaphylactic reaction by:

*identified trigger*

786 cases (63%) IgE-mediated

0.852% (352 patients; 3 reactions; 1/117)

0.325% (8,907 patients; 29 reactions; 1/307)

0.146% (6,151 infusions; 9 reactions; 1/683)

0.066% (6,028 infusions; 4 reactions; 1/1507)

0.075% (120,531 units; 91 reactions; 1/1324)

Laxenair et al 1994

Ring & Messmer 1977

Lundsgaard & Tschirren 1981
Kidney function
Metabolism/Elimination

**Gelatin/Gelofusin** is eliminated via the kidneys. Small molecules are eliminated due to filtration, while molecules with larger size are downsized by proteolytic breakdown. **Even in case of kidney failure, degradation is not affected.** Accumulation and organ/tissue storage can not occur.
69 brain dead patients randomized to receive 6% HES 200/0.6 or gelatin

**HES group:** received 33 ml/kg HES and afterwards gelatin

**Gelatin group:** only modified gelatin
Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients

M L Cittanova, I Leblanc, Ch Legendre, C Mouquet, B Riou, P Coriat
Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients

M L Cittanova, I Leblanc, Ch Legendre, C Mouquet, B Riou, P Coriat

Figure 3: Kidney biopsy specimen
Normal proximal tubule (white arrow) with osmotic-nephrosis-like lesions in most tubules (black arrow) in patient of hydroxyethylstarch-gelatin group (3400, trichrome Masson). Courtesy of L H Noël (Hôpital Necker, Paris).

...group’s mean serum creatinine. The renal biopsies in nine kidney recipients showed osmotic-nephrosis-like lesions only in the hydroxyethylstarch-gelatin group. Mostly proximal but also distal tubules were affected. These lesions were found in kidney-transplant biopsy specimens as long as 2 years after transplantation (data from ChL),...
129 patients with sepsis/septic shock in three centres were randomized to receive:

6% HES 200/0.6-0.66 or 3% gelatin.

Primary endpoint: ARF (=2-fold increase in serum creatinine or need for RRT).
Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study

Lancet 2001; 357: 911–16

Frédérique Schortgen, Jean-Claude Lacherade, Fabrice Bruneel, Isabelle Cattaneo, François Hemery, François Lemaire, Laurent Brochard
Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study

Lancet 2001; 357: 911–16

Frédérique Schortgen, Jean-Claude Lacherade, Fabrice Bruneel, Isabelle Cattaneo, François Hemery, François Lemaire, Laurent Brochard
Meta-analysis: 30 randomised controlled trials involving 2.709 patients

When compared to starches, gelatin solutions were associated with a lower risk of acute renal failure (odds ratio 0.43, 95% confidence interval 0.20 to 0.92; P=0.03).

No differences compared to crystalloids.

These findings suggest that using gelatin solutions is associated with a lower risk of acute renal failure compared to older starches.

Amount of gelatin (ml/kg/24h) in ICU patients (n=1,259) with and without need for RRT. (Patients treated in 2010 - 2013 at the Department for General and Surgical Critical Care Medicine, Innsbruck)
Intrinsic (damage to structures within the kidney)

Prerenal (marked decrease in renal blood flow)

Postrenal (obstruction of urine outflow from the kidney)
Coagulation
Volume resuscitation and coagulation ...

**Crystalloids**
- dilution

**Gelatin**
- dilution
- fibrin polymerization disturbance +

**HES**
- dilution
- acquired vWillebrand Syndrome, decrease of FVIII
- decrease of GpIIbIIIa receptor
- platelet coating – reducing the availability of the fibrinogen receptor
- fibrin polymerization disturbances +++
Innsbruck Concept ....

+ balance
1.500 ml antibiotics
1.440 ml nutrition
1.200 ml i.v. drugs
In total: 4.140
Innsbruck Concept ....

+ balance
1.500 ml antibiotics
1.440 ml nutrition
1.200 ml i.v. drugs
In total: 4.140

- balance
960 ml urine (0.5ml/kg/h)
500 chest drains
500 ml perspiration
In total: 1.960

Per day + 2.180 ml
Per week + 15.260
Innsbruck Concept ....

+ balance
1.500 ml antibiotics
1.440 ml nutrition
1.200 ml i.v. drugs
In total: 4140

4.140 ml/d
170 ml/h

Urine output: 170 ml/h
The “Equiline – concept”

Balanced crystalloid solution

Infusion pump connected to a weight

Weight system to measure the urinary output

Hemofiltration CVVH
Resuscitation practice in critically ill patients

ICU admission

ICU discharge
Administartion of colloids *AFTER* initial hemodynamic stabilisation:
Infusion of colloids without any indication ... *Fluid overload* ...!
ICU mortality of gelatin treated ICU patients (n=1.259) in Innsbruck (Patients treated in 2010 - 2013 at the Department for General and Surgical Critical Care Medicine, Innsbruck)
1. Avoid HYPOvolemia
We recommend aggressive and timely stabilisation of cardiac preload throughout the surgical procedure, as this appears beneficial to the patient
ESA 1B

2. Avoid HYPERvolemia
We recommend avoiding hypervolemia with crystalloids or colloids to a level exceeding the interstitial space in steady state, and beyond an optimal cardiac preload
ESA 1B

3. Crystalloid – Colloid
Compared with crystalloids, hemodynamic stabilisation with isooncotic colloids such as human albumin and hydroxyethyl starch caused less tissue oedema.
ESA 2C
Gelatin ...

... same volume effect compared to HES

... no accumulation

... no kidney injury

... less effects on hemostasis

... but ... rare data!!!