Fluid Therapy in Septic Patients: Crystalloids OR Colloids; Which, what product, when and how

Part II: Synthesising the latest literature

Tim Hardcastle
Trauma Surgeon
Durban – South Africa
No conflict of interest other than that I am a colloid believer........!
Overview

- Statement of the problem
- Recent trials of colloids versus crystalloids
- The role of the glycocalix
- Where are we now?
  - Surviving sepsis.....really?
  - Rational fluid therapy
- Concluding statements
The problem

• Sepsis is a common problem in critically ill patients
  – May be the presenting problem in Surgical patients
• Fluids are an important drug in the therapy of sepsis and colloids have been given a bad rep!
  – Adverse effects must be balanced against benefits
  – Comparator must be carefully assessed
• Microvascular changes affect outcome
The recent trials

– Sepsis is a syndrome not a diagnosis
– Trial design is a challenge
– Limited numbers of surgical patients
– Abstracts don’t reflect the fine print
– Ignore some important variables
  • ACS
  • Surgical anastomotic leaks
• RCT conducted in France and Germany
  – 196 patients
  – HES 130/0.4 versus N/S
• Pre-admission fluids were not included other than total volume
• Examined volume, LOS, renal and bleeding
• 90 day mortality
• EXCLUDED pre-existing renal dysfunction
What did CHRYSTMAS show?

• **Less HES** needed to achieve HDS

• **No difference**
  – LOS
  – SOFA score
  – AKI incidence of need for RRT (AKIN/RIFLE)
  – Renal biomarkers
  – Bleeding complications

• **Conclusion: HES is safe in sepsis!**
What were the problems?

• Underpowered to show renal effects longterm
• Small numbers of “surgical” patients (<30%)
• Small adverse event rates in both groups
“6S” Hydroxyethyl Starch 130/0.42 versus Ringer’s Acetate in Severe Sepsis

Scandinavian Starch for Severe Sepsis/Septic Shock

• 798 patients (<30% surgical)
• Included if severe sepsis within past 24 hours
  IN ICU – fluid prior to ICU not included
• Trial fluid stopped if reaction or bleeding or need for RRT

DOI: 10.1056/NEJMoa1204242
Copyright © 2012 Massachusetts Medical Society.
Results

• 398 in Starch group / 400 in RA group
• No difference in AKI at baseline
• Higher mortality at 90D in starch group
  – Kaplan-Meier splits after 28 days
• More blood product and RRT use in starch group, but no difference in bleeding complications

<table>
<thead>
<tr>
<th>Blood products†††</th>
<th>Day –1**</th>
<th>Day 1¶</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Total‡‡‡</th>
</tr>
</thead>
</table>
| 90/392            | 838      | 480–1435 | 88/399 | 600 | 490–1195 | 0.69
| 109/397           | 590      | 300–1100 | 89/400 | 600 | 490–980  | 0.13 |
| 115/378           | 600      | 350–1100 | 78/379 | 526 | 300–1030 | 0.001|
| 81/327            | 500      | 300–980  | 68/326 | 598 | 300–750  | 0.28 |
| 243/376           | 1340     | 566–2700 | 204/380 | 1055 | 600–2755 | 0.003|
Blaming this on 3-4 days of colloid – really?
<table>
<thead>
<tr>
<th>Outcome</th>
<th>HES 130/0.42 (N=398)</th>
<th>Ringer’s Acetate (N=400)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead or dependent on dialysis at day 90 — no. (%)</td>
<td>202 (51)</td>
<td>173 (43)</td>
<td>1.17 (1.01–1.36)</td>
<td>0.03</td>
</tr>
<tr>
<td>Dead at day 90 — no. (%)</td>
<td>201 (51)</td>
<td>172 (43)</td>
<td>1.17 (1.01–1.36)</td>
<td>0.03</td>
</tr>
<tr>
<td>Dependent on dialysis at day 90 — no. (%)</td>
<td>1 (0.25)</td>
<td>1 (0.25)</td>
<td>—</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Secondary outcome measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead at day 28 — no. (%)</td>
<td>154 (39)</td>
<td>144 (36)</td>
<td>1.08 (0.90–1.28)</td>
<td>0.43</td>
</tr>
<tr>
<td>Severe bleeding — no. (%)†</td>
<td>38 (10)</td>
<td>25 (6)</td>
<td>1.52 (0.94–2.48)</td>
<td>0.09</td>
</tr>
<tr>
<td>Severe allergic reaction — no. (%)†</td>
<td>1 (0.25)</td>
<td>0</td>
<td>—</td>
<td>0.32</td>
</tr>
<tr>
<td>SOFA score at day 5 — median (interquartile range)</td>
<td>6 (2–11)</td>
<td>6 (0–10)</td>
<td>—</td>
<td>0.64</td>
</tr>
<tr>
<td>Use of renal-replacement therapy — no. (%)‡</td>
<td>87 (22)</td>
<td>65 (16)</td>
<td>1.35 (1.01–1.80)</td>
<td>0.04</td>
</tr>
<tr>
<td>Use of renal-replacement therapy or renal SOFA score ≥3 — no. (%)§</td>
<td>129 (32)</td>
<td>108 (27)</td>
<td>1.20 (0.97–1.48)</td>
<td>0.10</td>
</tr>
<tr>
<td>Doubling of plasma creatinine level — no. (%)†</td>
<td>148 (41)</td>
<td>127 (35)</td>
<td>1.18 (0.98–1.43)</td>
<td>0.08</td>
</tr>
<tr>
<td>Acidosis — no. (%)††</td>
<td>307 (77)</td>
<td>312 (78)</td>
<td>0.99 (0.92–1.06)</td>
<td>0.72</td>
</tr>
<tr>
<td>Alive without renal-replacement therapy — mean % of days‖</td>
<td>91</td>
<td>93</td>
<td>—</td>
<td>0.048</td>
</tr>
<tr>
<td>Use of mechanical ventilation — no. (%)†</td>
<td>325 (82)</td>
<td>321 (80)</td>
<td>1.02 (0.95–1.09)</td>
<td>0.61</td>
</tr>
<tr>
<td>Alive without mechanical ventilation — mean % of days‖</td>
<td>62</td>
<td>65</td>
<td>—</td>
<td>0.28</td>
</tr>
<tr>
<td>Alive and out of hospital — mean % of days‖</td>
<td>29</td>
<td>34</td>
<td>—</td>
<td>0.048</td>
</tr>
</tbody>
</table>
In conclusion, patients with severe sepsis who received fluid resuscitation with HES 130/0.42, as compared with those who received Ringer’s acetate, had a higher risk of death at 90 days, were more likely to receive renal-replacement therapy, and had fewer days alive without renal-replacement therapy and fewer days alive out of the hospital.

But are the differences CLINICALLY significant?
CHEST

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

- Australian ICU study
- 7000 patients – death @ 90 days and AKI/RRT
  – Often delayed randomisation

The treating clinicians determined the initial and subsequent volumes and the rate of administration of resuscitation fluid, depending on clinical signs and the subsequent response to fluid administration.

All other aspects of patient care, including maintenance fluids and nutrition, cardiovascular monitoring, pharmacologic support, and respiratory and renal support, were conducted at the discretion of the treating clinicians.

This article was published on October 17, 2012, at NEJM.org.

DOI: 10.1056/NEJMoal209759
Copyright © 2012 Massachusetts Medical Society.
Results

• Well matched cohorts
• NO mortality difference

In addition, patients were recruited after admission to the ICU, when the requirements for fluid resuscitation are often less than those for patients in the emergency department or the operating room.

• Trend to better renal outcome yet higher use of RRT – unexplained
  – Also no difference in RRT duration
• Longer ICU stays – on average 0.5 day!
### Secondary outcomes — no./total no. (%)

#### Renal outcomes

<table>
<thead>
<tr>
<th></th>
<th>1788/3309 (54.0)</th>
<th>1912/3335 (57.3)</th>
<th>0.94 (0.90 to 0.98)</th>
<th>0.007</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIFLE-R</td>
<td>1130/3265 (34.6)</td>
<td>1253/3300 (38.0)</td>
<td>0.91 (0.85 to 0.97)</td>
<td>0.005</td>
</tr>
<tr>
<td>RIFLE-I</td>
<td>336/3243 (10.4)</td>
<td>301/3263 (9.2)</td>
<td>1.12 (0.97 to 1.30)</td>
<td>0.12</td>
</tr>
<tr>
<td>RIFLE-F</td>
<td>235/3352 (7.0)</td>
<td>196/3375 (5.8)</td>
<td>1.21 (1.00 to 1.45)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

#### New organ failure†

<table>
<thead>
<tr>
<th></th>
<th>540/2062 (26.2)</th>
<th>524/2094 (25.0)</th>
<th>1.05 (0.94 to 1.16)</th>
<th>0.39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>663/1815 (36.5)</td>
<td>722/1808 (39.9)</td>
<td>0.91 (0.84 to 0.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>142/2987 (4.8)</td>
<td>119/3010 (4.0)</td>
<td>1.20 (0.95 to 1.53)</td>
<td>0.13</td>
</tr>
<tr>
<td>Coagulation</td>
<td>55/2830 (1.9)</td>
<td>36/2887 (1.2)</td>
<td>1.56 (1.03 to 2.36)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

#### Service utilization — no.

<table>
<thead>
<tr>
<th></th>
<th>7.3±0.2</th>
<th>6.9±0.2</th>
<th>0.4 (0.0 to 0.9)</th>
<th>0.07</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days in ICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days in hospital</td>
<td>19.3±0.3</td>
<td>19.1±0.3</td>
<td>0.2 (0.8 to 1.1)</td>
<td>0.72</td>
</tr>
<tr>
<td>Days receiving mechanical ventilation</td>
<td>6.0±0.2</td>
<td>5.7±0.2</td>
<td>0.4 (0.1 to 0.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Days receiving renal-replacement therapy</td>
<td>5.6±0.4</td>
<td>5.5±0.4</td>
<td>0.1 (0.1 to 1.2)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

#### Treatment-related adverse events‡

<table>
<thead>
<tr>
<th></th>
<th>180/3416 (5.3)</th>
<th>95/3358 (2.8)</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>137/3416 (4.0)</td>
<td>73/3358 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>34/3416 (1.0)</td>
<td>16/3358 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9/3416 (0.3)</td>
<td>6/3358 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events — no./total no. (%)§</td>
<td>2/3416 (0.1)</td>
<td>2/3358 (0.1)</td>
<td>0.98</td>
</tr>
</tbody>
</table>
I’m not alone in being skeptical

Hemodynamical parameters are reported only for the first 24 hours. Although the trial theoretically went on for 90 days, the length of hospital and ICU stay is not reported and the use of study and non-study fluids is only stated for the first 3 days. It has to be concluded that we do not know enough about what actually happened to these patients. Obviously, in this trial the majority of the “crystalloid” group received colloids during initial stabilization, i.e., with a good indication and 1/3 even during the trial. After stabilization, they were randomized into a rational (crystalloids) or an irrational (colloid) maintenance protocol, receiving HES in high amounts and over a prolonged period of time. Considering the lack of a proper indication in the majority and an absolute contraindication in a large part of the patients, negative effects are not surprising. It is simply not possible to conclude pure crystalloidal treatment to be superior to the use of colloids from a study where practically every patient also in the crystalloid group received some kind of colloid.

Notably, 30% of the patients were septic and in this subgroup no differences in mortality, renal failure or renal replacement therapy were observed [11,12]. Importantly, not one of them evaluated the initial 6-hour phase shown to be crucial for patient outcome [10]. However, in all trials colloids were given to the majority of patients in this crucial phase, also in the crystalloid groups. In the starch groups, the wrong fluid

Chappell and Jacob Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine 2013, 21:61
http://www.sjtrem.com/content/21/1/61
CRISTAL

• RCT, stratified case mix, Open label with blinded assessment = really pragmatic
• 2857 ICU patients – rapid randomisation
  – No prior fluid therapy
  – Documented hypotension / acute hypovolaemia
• End-point: 28 day mortality
• 57 ICU’s in 5 countries including an LMIC

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock
The CRISTAL Randomized Trial

Results

- Well matched groups including subgroups

<table>
<thead>
<tr>
<th>Death</th>
<th>No. of patients</th>
<th>Mean (SD)</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 28 d</td>
<td>359 (25.4)</td>
<td>390 (27.0)</td>
<td>0.95 (0.88 to 1.04)</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>
</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>
</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>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of days alive and without the following treatment or condition</th>
<th>Mean (SD)</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilation within the first 7 d</td>
<td>2.1 (2.4)</td>
<td>0.30 (0.09 to 0.48)</td>
</tr>
<tr>
<td>Mechanical ventilation within the first 28 d</td>
<td>14.6 (11.4)</td>
<td>1.10 (0.14 to 2.06)</td>
</tr>
</tbody>
</table>

No difference in blood product use, less deaths at 90 days (p=0.03) in Colloid group
Interestingly less RRT use in the Colloid group
### Treatment versus outcome

<table>
<thead>
<tr>
<th>Reason for ICU Admission</th>
<th>Colloids Group (n=1414)</th>
<th>Crystalloids Group (n=1443)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of Deaths</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Other causes of hypovolemic shock</td>
<td>555</td>
<td>131</td>
<td>572</td>
</tr>
<tr>
<td>Sepsis</td>
<td>774</td>
<td>215</td>
<td>779</td>
</tr>
<tr>
<td>Trauma</td>
<td>85</td>
<td>13</td>
<td>92</td>
</tr>
<tr>
<td>All patients</td>
<td>1414</td>
<td>359</td>
<td>1443</td>
</tr>
</tbody>
</table>

The graph on the right shows a comparison of HR (95% CI) between the Colloids and Crystalloids groups for different reasons of ICU admission, favoring both Colloids and Crystalloids.
Surviving Sepsis in context

- Aggressive fluid therapy,
  - Crystalloids, albumin aiming for a 30ml/kg volume
  - MAP 65mmHg / CVP of 8-12mmHg.
  - Source control **within 12 hours** if surgical cause
  - Recommended against HES
    - Based on VICEP (which used older starches), CHEST (which did not randomise the RTT group) and CHRYSTMAS (which was underpowered to examine renal outcomes)
    - Point out that CRISTAL was “not considered”!
    - Support Albumin despite SAFE finding “no benefit”.
    - Advocate Hb 7-9g/dl (TRIC study, excluded shocked patients)
  - Ignore multiple studies that show less leaks with Colloid
What is this Glycocalix thing?

- Recently discovered endothelial glycoprotein layer
- Role in endothelial permeability
  - Starling is no longer alone
- Plasma and HES shown to repair damaged glycocalix – after trauma, shock or sepsis
  - “reperfusion injury”
- Saline reduces microcirculatory flow
Natural Capillary Haemodynamics

\[ J_v = K_f ([P_c - P_i] - \sigma [\pi_c - \pi_i]) \]
Figure 4. Cell surface syndecan-1 expression in pulmonary alveolar cells. After hemorrhagic shock and resuscitation, lungs were immunostained with antisyndecan-1 monoclonal antibodies (magnification original 200). The negative control is a technical control for staining without using primary antibody. Immunostaining revealed that cell surface syndecan-1 is expressed abundantly in sham animals (A) in comparison with negative controls (B), but expression is markedly decreased after hemorrhagic shock (C), and by lactated Ringer’s (LR) solution (D), but further enhanced by plasma (E) resuscitation. Means notated with letters indicated statistical differences between groups. Sham versus shock, P 0.001; sham versus LR, P 0.002; shock versus plasma, P 0.001; LR versus plasma, P 0.014.

Kozar RA et al. Anesthesia and Analgesia 2011;112:1289-95
Fig. 6. Electron microscopic views of hearts stained to reveal the glycocalyx (representative of two hearts each). (A) Control experiment, infusion of 5% albumin (HA); (B) control experiment, infusion of 6% hydroxyethyl starch (HES); (C) after ischemia (intervention 1) and infusion of HA; (D) after ischemia (intervention 1) and infusion of HES; (E) after heparinase application without ischemia (intervention Hep); (F) after heparinase application during ischemia (intervention 1-Hep).
Where to now?

- Fluids are drugs
- Avoid excess crystalloid – affects the Glycocalix
- Use natural colloids and be circumspect with the synthetics
- Don’t use colloids if HD-stable
- HES may not be as bad as made out in real-life
  – Probably better (safer) than Gelatins
Aside: “What about trauma?

• Best is to give the patient that what they have lost
  – Sushruta Samhita circa 700BC

  Bleeding blood
  Give whole blood
  Best empiric alternative: 1:1:1 till lab guided
Limit Crystalloid early

- Salt water does not carry oxygen
- Salt water damages the endothelium
- Salt water dilutes clotting factors
If you aim at nothing, you’re sure to hit it! Yogi Berra

IT IS NOT AN ABSOLUTE

Optimal ratio under investigation PROMPPT

1:1
Coagulopathy still kills

What about TXA?

• Crash2 – 274 hospitals/40 countries
  – Cheap, safe and will save lives....!
  – REALLY?
    • 75% of patients were from LMIC’s
    • Huge relative risk reduction
    • ABSOLUTE REDUCTION only 0.8%
    • 802 of 1192 “high-risk patients” died

• The treatment of bleeding is to stop the bleeding! Give to everyone?????

Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial.
CRASH-2 Trial collaboration. Lancet 2010;376:23-32
MATTERS Study (US Military)

Lethal problems in Australasian trauma centres. Thrombotic complications were reported very rarely in the CRASH-2 study (PE, 0.7% of all patients; DVT, 0.4%), probably because they were not actively sought in many of the participating hospitals. In contrast, the MATTERs study showed that rates of PE and DVT among patients who received TxA were, respectively, 9 and 12 times the rates among those who did not. Furthermore, more elderly patients are treated within Australasian trauma systems than were included in the CRASH-2 and MATTERs studies, and the interactions of TxA with age-related comorbidities and pharmacotherapy are not well understood.

Quoting Gruen again!

opened trauma systems, hypotheses about TxA should be re-investigated. North American trauma experts recently argued that a prospective randomised study performed in a controlled environment with laboratory monitoring of coagulation and standardised transfusion protocols is essential before TxA becomes standard care in trauma.3


WATCH THIS SPACE: PATCH IS SOON TO FOLLOW
ROTEM P-O-C based coagulation testing
Examples of ROTEM traces using the EXTEM test: a. normal test result. b. reduced maximum clot firmness (MCF). c. delayed initiation of coagulation (prolonged coagulation time [CT]). d. prolonged CT and reduced MCF. e. hyperfibrinolysis
Algorithm for treating bleeding in patients with trauma-induced coagulopathy

**Temperature**
- BGA
- Electrolytes
- Blood cell count

**Optimize preconditions**
- Temperature >34°C
- pH >7.2
- Calcium >1 mmol/L
- Haematocrit >24%

**Severe trauma (ISS >16) and/or severe shock**
- TXA 15–20 mg/kg BW

**Run ROTEM (EXTEM, INTEM, FIBTEM, APTEM)**

1. Focus on: hyperfibrinolysis
   - EXTEM CT > APTEM CT

2. Focus on: fibrin deficit
   - Later on, repeat step 2 if necessary

3. Focus on: thrombin generation deficit

4. Focus on: platelet deficit

**Severe clot deficiency**

**Parameter**
- Hyperfibrinolysis
- Activation
- Propagation
- Platelets
- Platelet function

**Intervention**
- Tranexamic acid
- PCC
- Fibrinogen
- Desmopressin, platelets
- Platelets

JIT, ‘just-in-time’; LAN, local area network; WLAN, wireless local area network; PCC, prothrombin complex concentrate.

ROTEM may also identify:

- Potential heparin exposure (e.g., cell-saver blood)
- Clot instability not related to hyperfibrinolysis

- HEPTEM CT < INTEM CT
- Treat heparin effect
  - Protamine 1000–2000 U

- EXTEM ML >15%
- and APTEM ML >15%
- Consider
  - Factor XIII 1250 U
Thank you