
DATE: 25 May 2010

CONTEXT AND POLICY ISSUES:

The administration of fluids is accepted as common practice for resuscitation of critically ill patients in different clinical circumstances, such as septic shock, hemorrhagic shock, trauma and major surgery. The rational of this therapy is to replace fluid loss to maintain homeostasis and to prevent the failure of organ function. Current guidelines on fluid therapy recommend infusion of either natural or synthetic colloids or crystalloids. Crystalloid solutions include normal saline and balanced fluids such as Ringer’s lactate. Human albumin preparations are natural colloids while dextran, gelatin, and starch products are synthetic colloids, also called synthetic plasma volume expanders. Fluid therapy and volume expansion in critically ill patients using crystalloids requires more fluid and results in more edema than therapy with colloids.

Albumin is derived from human plasma and plays a key role in maintaining colloid osmotic pressure. In addition, it plays other roles related to its capacity to bind molecules and ions, such as buffering through binding hydrogen ions, transporting hormones and drugs, and neutralizing toxins. Different manufacturing methods can affect the properties of albumin that may have different effects on endothelial function and antioxidiant activity. Although the mechanism of action of therapeutic albumin in support of colloidal osmotic pressure is well understood, albumin’s position continues to be questioned and challenged by cheaper synthetic colloids, particularly “third generation” hydroxyethyl starch preparations.

Available synthetic plasma volume expanders include dextrans, modified gelatin and hydroxyethyl starches (HES). These colloids are diluted in isotonic (0.9% saline), hypotonic, hypertonic (7.2 – 7.5% saline), or balanced isotonic electrolytes solutions.

- Dextran are neutral, high molecular weight glucopolysaccharides based on glucose monomers. Dextrans have low production costs and can be stored on a long-term basis (up to 10 years) at room temperature. However, dextrans had multiple adverse events including anaphylactoid reactions and risk of kidney failure.
Modified gelatin products are produced from bovine collagen and prepared as dispersive solutions by multiple chemical modifications. Gelatins are inexpensive and can be stored for two to three years at room temperature. Gelatins have minimal effects on coagulation and renal function. However, gelatin infusion is associated with increased diuresis and the rate of anaphylactic reactions of gelatin is highest among synthetic colloids.

Hydroxyethyl starch (HES) products are produced from amylopectin, a highly branched polymer of glucose, obtained from waxy-maize or potato starch. Due to its multibranched structure, HES has a globular configuration similar to albumin. It has a much less viscosity than dextran or gelatin. Mean molecular weight of different HES preparations ranges between 70 to 670 kDa. The average number of hydroxyethyl residues per glucose molecule is specified by the molar substitution, varying from 0.4 (tetrastarch), 0.5 (pentastarch), 0.6 (hexastarch), to 0.7 (hetastarch). The latest third generation HES consists of modern tetrastarch having average molecular weight 130 kDa and molar substitution 0.4 or 0.42 (HES 130/0.4 and HES 130/0.42). HES had been effectively used as a plasma substitute. The modern tetrastarches appear to have a safe pharmacokinetic profile. However, older preparations of HES (hetastarch, hexastarch and pentastarch) may have negative effects on haemostasis and kidney function. The anaphylactic potential of HES is lowest among synthetic colloids.

The report reviews the recent evidence on the clinical effectiveness, cost-effectiveness, and guidelines for the use of albumin versus synthetic plasma volume expanders in patients with hemodynamically unstable.

RESEARCH QUESTIONS:

1. What is the comparative clinical effectiveness of albumin versus synthetic plasma volume expanders for use in patients who are hemodynamically unstable?

2. What are the guidelines regarding the use of albumin and synthetic plasma volume expanders in patients who are hemodynamically unstable?

3. What is the cost-effectiveness of albumin and synthetic plasma volume expanders for use in patients who are hemodynamically unstable?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 4, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between Jan 1, 2005 and April 26, 2010. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, observational studies, economic studies, and guidelines.
HTIS reports are organized so that the higher quality evidence is presented first. Therefore, systematic reviews and meta-analyses are presented first. These are followed by randomized controlled trials (RCTs), economic evaluations, and evidence-based guidelines. Controlled clinical trials and observational studies were not included due to the high number of RCTs.

SUMMARY OF FINDINGS:

Three systematic reviews and meta-analyses,8-10 fourteen RCTs,11-24 one economic study,25 and one guideline2 were identified.

Systematic reviews and meta-analyses

Three systematic reviews and meta-analyses8-10 were identified.

Dart et al., 20108 conducted a systematic review and meta-analysis to examine the effects of HES on kidney function compared to other fluid resuscitation therapies in different patient populations. The comparator fluids included modified gelatin, human albumin, Ringer’s lactate, and normal saline. Thirty-four RCTs from 1982 to 2008 with a total population of 2607 participants met the inclusion criteria. The authors found that a large number of studies did not clearly state their methods for allocation concealment, and only few studies were blinded. Two main primary outcomes were renal replacement therapy and kidney failure. Subgroup analyses for these outcomes were conducted on the basis of sepsis and non-sepsis patients, and no comparisons were made between HES and each of the comparator fluids. Appendix 1 summarizes the effect sizes of the two main primary outcomes.

Twelve studies with a total of 1236 patients reported renal replacement therapy outcome. The overall relative risk (95% CI) for renal replacement therapy for the comparison between HES and other fluid type was 1.38 (0.89 to 2.16). Subgroup analyses showed that sepsis patients receiving HES had a 59% increased risk of requiring dialysis (relative risk: 1.59, 95% CI: 1.20 to 2.10; n=702). Quality of the evidence was graded from moderate to high.

Nine studies with a total of 1199 patients reported author-defined kidney failure outcome. The overall relative risk (95% CI) of kidney failure for the comparison between HES and other fluid type was 1.50 (1.20 to 1.87). Subgroup analyses showed that sepsis patients receiving HES had a 55% increased risk of developing kidney failure (relative risk: 1.55, 95% CI: 1.22 to 1.96; n=832). Quality of the evidence was graded from moderate to high.

For secondary outcome measures such as acute kidney injury, creatinine clearance, and serum creatinine levels, there was no evidence of the differential effects between groups. Heterogeneity between studies was substantial for these outcomes. The authors concluded that sepsis patients, but not surgical/trauma patients, receiving HES therapy had potential risk of developing kidney failure or needed for dialysis compared to albumin.

Bunn et al., 20089 conducted a systematic review and meta-analysis to compare the effects of different colloid solutions in patients who required volume replacement. Mortality was the primary outcome of the review. Secondary outcomes included the amount of blood transfused and adverse events. Seventy RCTs from 1980 to 2006 with a total population of 4375 participants (critically ill and surgical patients) met the inclusion criteria. Of the 70 identified trials, 46 had information on death. Pathophysiological outcomes were not analyzed since, according to the authors, they might prone to measurement error or bias reporting.
Appendix 2 summarizes the relative risks of death of the comparison between human albumin or plasma protein fraction and synthetic plasma substitutes (etherified starches, modified gelatins, and dextrans). Comparisons between synthetic plasma volume expanders on mortality were also given. Based on the pooled relative risks and the corresponding 95% confidence intervals, there was no evidence that any of the colloids are more effective than another. For the amount of blood transfused, no quantitative synthesis was given since the data was reported in various ways. Nineteen trials reported that there was no incidence of adverse events.

The authors concluded that there is no evidence that one colloid solution was more effective or safe than another. Limitations among included studies were variation in the length of follow-up (ranging from hours to months), small numbers of participants, and the presence of older trials whose treatment protocols might be obsolete.

Jacob et al., 2008\textsuperscript{10} conducted a systematic review of RCTs to compare the clinical effects of albumin to other fluid therapies on clinical endpoints such as morbidity, major organ function, length of stay, and cost of care in acutely ill patients, to which qualitative summarization was given since those endpoints were often not well-defined and not reported in a consistent and standardized manner. However, quantitative meta-analysis was performed on the mortality outcome. Twenty-five RCTs with a total of participants of 1485 patients were included in the review. The intervention was albumin and the control regimen consisted of HES (9 trials), crystalloid (4 trials), no albumin (6 trials), lower-dose of albumin (1 trial), and two separate control regimens (5 trials). The qualitative summarization was given according to patient populations, which were classified into eight categories: surgical, trauma, liver disease, sepsis, high-risk neonates, brain injury, intradialytic hypotension, and nephritic syndrome. The authors stated that, of the included trials, four were blinded, and four had adequate allocation concealment. Other limitations reported by the authors included diverse clinical indications, relatively small number of trials focusing in any single indication, small number of participants in some trials, and no more than two trials assessed clinically relevant outcomes at the same type.

- **Surgery:** Of five trials, three were of cardiac surgery (n=113) and two were of non-cardiac surgery (n=48). The intervention was 20% or 25% albumin and the control regimen was 3%, 6%, or 10% HES 200/0.5, 3.5% gelatin, no albumin, Ringer’s lactate, or saline. In cardiac surgery, albumin was more effective than control regimens in maintaining colloid oncotic pressure (albumin versus HES, gelatin), in preserving renal function (albumin versus HES), and resulted in a greater increase in cardiac output (albumin versus saline). In non-cardiac surgery, albumin was more effective than control regimens in maintaining colloid oncotic pressure (albumin versus no albumin or HES), and in preventing impairment of coagulation (albumin versus HES).

- **Trauma:** Five trials (n=266) were included in trauma patients. The intervention was 20% albumin and the control regimen was 10% HES 200/0.5. In three reports (n=86), albumin showed no apparent clinical advantage over HES. In the other two reports (n=180), HES increased cardiac index and oxygenation relative to albumin.

- **Sepsis:** Seven trials in sepsis patients were included (n=328). The intervention was 20% albumin and the control regimen was 10% HES 200/0.5 or 6% HES 130/0.4. HES administration resulted in higher cardiac index (better cardiac function) and oxygenation than albumin in three trials (n=200). HES maintained higher gastric intramucosal pH...
than albumin in two trials (n=58), and improved Acute Physiologic and Chronic Health Evaluation II score in one trial (n=20).

- **Liver disease**: Three trials (n=272) were included. The intervention was 20% or 25% albumin and the control regimen was no albumin or 6% HES 200/0.5. Compared to diuretics alone, albumin plus diuretics increased treatment response rate, shortened hospital stay, and reduced cost of care (1 trial, n=126). In patients developing spontaneous bacterial peritonitis, albumin reduced the incidence of renal impairment compared with no albumin (1 trial, n=126), and improved circulatory function compared with HES 200/0.5 (1 trial, n=20).

- **High-risk neonates**: 20% albumin was compared with no albumin in three trials (n=81). Albumin was found to reduce the frequency of illness, lessened whole body edema, improved respiratory function, and lower hospital stay. The comparator of synthetic plasma volume expanders to albumin was not found in this population.

- **Brain injury**: One trial (n=300) compared normovolemic hemodilution with 20% albumin versus crystalloids, and found that albumin reduced mortality and disability at 3 months in the subgroup with normal hematocrit compared with crystalloids. One trial (n=18) compared high-oncotic pressure therapy using 25% albumin versus normal-oncotic pressure therapy, and found that all patients receiving high-oncotic pressure recovered with minimal or no neurological deficit, while 30% of those receiving normal-oncotic pressure therapy remained in vegetative state or died. The comparators of interest (synthetic plasma volume expanders) were not found in this population.

- **Intradialytic hypotension**: In two trials (n=19), 20% albumin and 10% HES 200/0.5 were reported as equally effective and better than saline in controlling blood volume and systolic blood pressure.

- **Nephrotic syndrome**: In three trials (n=40), 20% albumin potentiated the diuretic effect of furosemide compared with no albumin. The comparators of interest (synthetic plasma volume expanders) were not found in this population.

- **Mortality**: Twenty-four trials (n=1287) were included. Overall, there was no significant difference in survival between albumin and the control group (including HES, crystalloids or other therapies) (relative risk 0.95; 95% CI 0.78 to 1.17).

The authors concluded that in some indications, small-volume resuscitation with albumin had several benefits such as decreases in morbidity, renal impairment and edema. Albumin had no effect on overall survival rate compared to HES or other therapies. However, firm conclusions about clinical benefit in defined indications are difficult to draw due to the aforementioned limitations.

**Randomized controlled trials**

Fourteen RCTs comparing the effects of HES or gelatin to albumin were identified. The results of the trials were summarized according to the therapeutic goal in critically ill patients. The study characteristics and outcomes are reported in Appendix 3.

- **Adult Surgery**: Of the eight RCTs\(^{11-18}\) (n=527), five\(^{11,12,14-16}\) were in cardiac surgery patients (n=346), and three\(^{13,17,18}\) were in non-cardiac surgery patients (n=181).
In patients undergoing coronary artery bypass grafting,\(^{11}\) high-volume priming of the cardiopulmonary bypass circuit with 6% HES 130/0.42 (n=25) in a balanced electrolyte solution resulted in reduced inflammation, less endothelial damage, and fewer alterations in renal function compared to 5% albumin (n=25).

In patients undergoing off-pump coronary artery bypass grafting,\(^{12}\) administration of 6% HES 450/0.7 (n=78) during surgery increased the likelihood of receiving transfusion and the volume of chest tube drainage postoperatively compared to 5% albumin (n=78). No mortality occurred before discharge.

In patients undergoing elective primary cardiac surgery,\(^{14}\) a short-time infusion of 6% HES 130/0.4 (n=15) or 6% HES 200/0.5 (n=15) after surgery impaired coagulation formation whereas 4% albumin did not. HES 130/0.4 and HES 200/0.5 had similar effects on coagulation.

In hypoalbunemic patients over 80 years of age undergoing cardiac surgery using cardiopulmonary bypass,\(^{15}\) preoperative administration of 6% HES 130/0.4 (n=25) had similar effects compared to 5% albumin (n=25) in inflammatory response and renal function. HES had lower endothelial activation than albumin until the end of the study.

In patients undergoing cardiac surgery,\(^{16}\) infusion of 6% HES 200/0.5 (n=15) or 6% HES 130/0.4 (n=15) in the early postoperative phase resulted in better hemodynamic parameters than 4% albumin (n=15).

In patients undergoing liver transplantation,\(^{13}\) perioperative administration of 6% HES 130/0.4 (n=20) resulted in comparable outcomes (perioperative data, cumulative fluid balance, diuretics use, renal function, laboratory data, and mortality) as 5% albumin (n=20).

In patients undergoing major orthopedic, gastrointestinal, or gynecological surgery with expected large fluid and transfusion requirements,\(^{17}\) infusion of 6% HES 200/0.5 (n=20) led to a reduction of albumin values and a significant reduction in binding parameters compared to 4% albumin.

In patients undergoing primary total hip replacement,\(^{18}\) infusion of 4% HES 120/0.7 (n=53) and 4% albumin (n=48) had comparable effects on blood loss intra- and postoperatively. There was no difference in clotting parameters between groups.

- **Pediatric surgery:** Of the three RCTs, one was with cardiac surgery\(^{19}\) (n=119) and two were with non-cardiac surgery\(^{20,21}\) (n=124).
  - In pediatric patients (46 months old or younger) undergoing cardiac surgery with cardiopulmonary bypass,\(^{19}\) priming and intraoperative infusion of 6% HES 130/0.4 (n=60) resulted in equivalent blood loss and postoperative outcomes compared to 4% albumin. Compared to albumin, fewer number of children in HES group required blood transfusion, and the intraoperative fluid balance was lower in HES group.
  - In pediatric patients (under 2 years of age) undergoing non-cardiac surgery,\(^{20}\) both 6% HES 130/0.4 (n=41) and 5% albumin (n=41) were equally effective for hemodynamic stabilization with no impact on coagulation parameters, hospital stay, and mortality.
  - In pediatric patients (10 to 14 months) undergoing surgery (cranial facial, tumor resection, abdominal),\(^{21}\) infusion of 5% albumin (n=14) or 4% modified gelatin (n=14)
resulted in comparable coagulation parameters. However, infusion of 6% HES 130/0.4 (n=14) impaired coagulation time, clot formation, clot firmness, and fibrinogen/fibrin polymerization compared to albumin and gelatin.

- **Sepsis**: Two trials\(^{22,23}\) (n=90) compared two different types of HES with albumin.
  - In patients who were artificially ventilated and developed severe sepsis,\(^{22}\) patients administered 6% HES 130/0.4 (n=26) had significantly higher extravascular lung water index (pulmonary edema) than patients given 20% albumin (n=30).
  - In patients with sepsis,\(^{23}\) infusion of 6% HES 200/0.5 (n=10) or 10% HES 200/0.5 (n=11) had comparable or better in hemodynamic parameters compared to 4% albumin (n=13).

- **Malaria**: A phase III trial\(^{24}\) compared the resuscitation effects of 4.5% albumin (n=44) versus 4% modified gelatin (n=44) in children with severe malaria. Albumin had higher survival benefit than modified gelatin (2.3% versus 16%, p=0.06), despite comparable effects on the resolution of acidosis and shock.

Overall, the results of the RCTs were highly variable due to the differences in products used, comparisons, and patient indications.

**Economic evaluations**

One economic study\(^{25}\) was identified. Moreau et al., 2006\(^{25}\) assessed the clinical and economic impact of albumin (20%) compared with modified gelatin (3.5% polygeline) in patients with cirrhosis and ascites. Patients between the age of 18 years and 74 years were randomized to receive albumin (n=30) or polygeline (n=38). This was a double-blinded, multi-centered RCT conducted in hospital settings. The length of follow-up was 6 months. The primary end points were a composite of renal impairment and marked hyponatremia after fluid loading, and survival. The effectiveness analysis showed that albumin was more effective in preventing liver-related complications than polygeline in patients with cirrhosis and ascites.

A cost minimization analysis was performed from the perspective of the hospital. The effectiveness evidence was derived from the study’s clinical data conducted in France. The price year was 2002. No sensitivity analyses were performed. The cost results showed that the total median cost adjusted to 30-day period was 1,915 euros in the albumin group and 4,612 euros in the polygeline group. The authors concluded that human albumin was more effective than polygeline in preventing complications in patients with cirrhosis and ascites, thus resulting in decreased hospital costs in France.

**Guidelines and recommendations**

One guideline on the use of HES in fluid management was identified.\(^{2}\) In October 2006, the British Association for Parenteral and Enteral Nutrition (BAPEN), the Association of Clinical Chemistry, the Association of Surgeons of Great Britain and Ireland, the Society of Academic and Research Surgery, the Renal Association, and the Intensive Care Society nominated core members of a steering committee to establish consensus for good perioperative fluid prescribing. Delegates of the named societies worked through a structured agenda of presentations, large and small group discussion, and graffiti exercises. Draft recommendations were produced and circulated to wider groups for comment. In March 2008, a final meeting was set up to consider the comments and incorporate them into the final version. Levels of evidence
were assigned using the definitions from the Oxford Center for Evidence-based Medicine Levels of Evidence.26

Of the 28 recommendations, two were related to the use of HES and none specifically mentioned about the use of albumin:

Recommendation 24: Based on current evidence, higher molecular weight hydroxyethyl starch (hetastarch and pentastarch MW ≥ 200 kDa) should be avoided in patients with severe sepsis due to an increased risk of acute kidney injury – Evidence level 1b (p9)2

Recommendation 25: Higher molecular weight hydroxyethyl starch (hetastarch and pentastarch MW ≥ 200 kDa) should be avoided in brain-death kidney donors due to reports of osmotic-nephrosis-like lesions) – Evidence level 2b (p9)2

**Limitations**

No comparisons were made between albumin and each of the synthetic colloids in two out of three systematic reviews and meta-analyses. The first systematic review grouped trials of different HES products and compared with a pool of other fluids including modified gelatin, human albumin, Ringer’s lactate, and normal saline. The other systematic review compared the clinical effects of albumin to other fluid therapies including synthetic colloids and crystalloids. Many trials were open-label and had relatively small number of participants (less than 50 in each arm). Comparisons between HES and albumin were conducted with diverse clinical indications. Trials using plasma volume expanders for the same indication often reported different clinical outcomes that make it difficult to draw a concrete conclusion and limits the generalizability of the findings. No cost-effectiveness data of albumin versus HES or dextran was found. Guidelines with recommendations on the use of albumin or synthetic plasma volume expanders in fluid therapy were limited.

**CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:**

In many indications, the evidence was mixed for the clinical efficacy of albumin and synthetic plasma volume expanders, particularly HES, with respect to hemodynamics and other biochemical end points. It is therefore difficult to draw firm conclusions about their clinical benefits. In term of mortality, the effect of albumin was not different compared to synthetic plasma volume expanders. The use of high molecular weight high molar substitution HES in septic patients was associated with increased risk of developing kidney failure or need for dialysis compared to albumin. The British Guidelines recommend that those HES should be avoided in patients with severe sepsis. Results of recent randomized controlled studies suggest that new generations of HES (130/0.4 or 130/0.42) might be better than or as effective as albumin, and could be used as alternative for hypovolaemic treatment in patients undergoing surgery. Cost-minimization analysis revealed that albumin appears is superior to polygeline in preventing complications in patients with cirrhosis and ascites. Cost-effectiveness data of albumin versus HES or dextran were not found. Although numerous studies were found on synthetic plasma volume expanders, particularly HES and albumin, the varied results may be a consideration for decision-making.
REFERENCES:


Appendix 1: Comparisons between hydroxyethyl starch and other fluid therapies on kidney function from the Dart et al. systematic review (2010)\(^8\)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number of studies (number of patients)</th>
<th>Effect sizes (RR [95% CI]; random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HES vs. other fluids (gelatin, 7 studies; albumin, 3 studies; Ringer’s lactate, 1 study; normal saline, 1 study)</td>
<td>Renal replacement therapy</td>
<td>12 (1236)</td>
<td>1.38 [0.89, 2.16]</td>
</tr>
<tr>
<td>1. Non-sepsis (surgical/trauma)</td>
<td>8 (487)</td>
<td>0.44 [0.14, 1.38]</td>
<td></td>
</tr>
<tr>
<td>2. Sepsis</td>
<td>3 (702)</td>
<td>1.59 [1.20, 2.10]</td>
<td></td>
</tr>
<tr>
<td>3. Deceased organ donor</td>
<td>1 (47)</td>
<td>6.67 [0.92, 48.45]</td>
<td></td>
</tr>
<tr>
<td>HES vs. other fluids (gelatin, 5 studies; albumin, 7 studies; normal saline, 1 study)</td>
<td>Kidney failure (author defined)</td>
<td>9 (1199)</td>
<td>1.50 [1.20, 1.87]</td>
</tr>
<tr>
<td>1. Non-sepsis (surgical/trauma)</td>
<td>5 (367)</td>
<td>1.13 [0.57, 2.25]</td>
<td></td>
</tr>
<tr>
<td>2. Sepsis</td>
<td>4 (832)</td>
<td>1.55 [1.22, 1.96]</td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; HES: hydroxyethyl starch; RR: relative risk; vs: versus

Appendix 2: Comparisons between blood products (human albumin, plasma protein fraction) and synthetic plasma volume expanders (etherified starches, modified gelatin, dextrans) from the Bunn et al. systematic review (2008)\(^9\)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number of studies (number of patients)</th>
<th>Effect sizes (RR [95% CI]; fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA or PPF vs. HES</td>
<td>Death</td>
<td>25 (1234)</td>
<td>1.14 [0.91, 1.43]</td>
</tr>
<tr>
<td>HA or PPF vs. Gelatin</td>
<td>Death</td>
<td>7 (636)</td>
<td>0.97 [0.68, 1.39]</td>
</tr>
<tr>
<td>HA or PPF vs. Dextran</td>
<td>Death</td>
<td>4 (360)</td>
<td>3.75 [0.42, 33.09]</td>
</tr>
<tr>
<td>Gelatin vs. HES</td>
<td>Death</td>
<td>18 (1337)</td>
<td>1.00 [0.80, 1.25]</td>
</tr>
<tr>
<td>Gelatin vs. Dextran</td>
<td>Death</td>
<td>2 (42)</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

CI: confidence interval; HA: human albumin; HES: hydroxyethyl starch; PPF: plasma protein fraction; RR: relative risk; vs: versus
### Appendix 3: Characteristics and outcomes of included randomized controlled trials

<table>
<thead>
<tr>
<th>Study / Objective</th>
<th>Intervention; control; duration</th>
<th>Participants / Setting</th>
<th>Outcomes</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Boldt et al., 2009<sup>11</sup>  
RCT, prospective, parallel, two arms  
Source of funding: hospital grant  
To evaluate the influence of high-volume priming with a modern balanced hydroxyethyl starch (HES) preparation on coagulation, inflammation, and organ function compared with albumin-based cardiopulmonary bypass priming regimen | **Intervention**: 6% HES 130/0.42 in a balanced electrolyte solution  
**Control**: 5% human albumin (HA)  
**Duration**: 2 days | **Participants**: Patients (about 70 years) undergoing elective coronary artery bypass grafting  
**N**: 50; 25 patients in each arm  
**Setting**: Intensive care units (ICU) | **Coagulation**:  
Thromboelastometry data (clotting time and clot formation time) were higher in the HA group compared to HES group (p=0.004)  
Platelet function in the HA group dropped significantly at end of surgery and 5 h postoperative compared to that in the HES group (p<0.05) | High volume priming of the cardiopulmonary bypass circuit with a modern balanced HES solution resulted in reduced inflammation, less endothelial damage, and fewer alterations in renal tubular integrity compared with an albumin-based priming |
| Dolecek et al., 2009<sup>22</sup>  
RCT, prospective, parallel, two arms  
Source of funding: Public funding  
To investigate whether | **Intervention**: 6% HES 130/0.4 (Voluven) every 6 h  
**Control**: 20% HA every 12 h  
**Duration**: 72 h | **Participants**: Adult patients (≥18 years) who were artificially ventilated and developed severe sepsis  
**N**: 56; 26 in HES and 30 in HA | **EVLW**: HA was associated with significant decrease (p<0.05) in EVLW index throughout the 72 h compared with HES  
**Oxygenation functions**: improved in both groups | Albumin reduces in a higher amount and earlier the extravascular lung water (pulmonary edema) than HES |
<table>
<thead>
<tr>
<th>Study / Objective</th>
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<tbody>
<tr>
<td>colloid osmotic pressure (COP) (20% COP – COP=80 mmHg) decrease in extravascular lung water (EVLW) in ventilated patients with new (&lt;24 h) severe sepsis and increased EVLW (&gt;7 ml/kg) is better than colloids with lower COP (6% 130/0.4 HES, COP=36 mmHg). Secondary outcomes were cardiorespiratory functions and mortality.</td>
<td>Setting: ICU</td>
<td>Mortality: no difference between groups</td>
<td>6% HES 130/0.4 may represent an alternative to 4% albumin for intraoperative fluid volume replacement in children undergoing cardiac surgery</td>
<td></td>
</tr>
<tr>
<td>Hanart et al., 2009</td>
<td>Intervention: 6% HES 130/0.4 (50 ml/kg) Control 4% HA (50 ml/kg)</td>
<td>Participants: Pediatric patients (≤6 months) undergoing cardiac surgery with cardiopulmonary bypass N = 119; 60 in HES and 59 in HA Setting: ICU</td>
<td>Blood loss: no difference between groups Blood transfusion: higher number of children in the HA group required allogenic blood transfusion (78% vs. 57%, p=0.0188) Intraoperative fluid balance: lower in HES group (12 vs. 23 ml/kg, p=0.005) Postoperative outcomes (laboratory, hemodynamic, and blood-gas derived parameters): no difference between groups</td>
<td>6% HES 130/0.4 may represent an alternative to 4% albumin for intraoperative fluid volume replacement in children undergoing cardiac surgery</td>
</tr>
<tr>
<td>Hecht-Dolnik et al., 2009</td>
<td>Intervention: 6% HES 450/0.7 (1 liter) given</td>
<td>Participants: Adult patients (mean age 64 years)</td>
<td>Transfusion requirement on post-op day 1:</td>
<td>In patients undergoing off-pump coronary artery</td>
</tr>
</tbody>
</table>

**Study / Objective**

- Hanart et al., 2009
  - RCT, prospective, parallel, two arms
  - Source of funding: not reported
  - To compare 4% HA with 6% HES 130/0.4 in terms of perioperative blood loss and intraoperative fluid requirements in children undergoing cardiac surgery

- Hecht-Dolnik et al., 2009
  - Intervention: 6% HES 450/0.7 (1 liter) given
  - Participants: Adult patients (mean age 64 years)
  - Transfusion requirement on post-op day 1:
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<tr>
<td>RCT, prospective, parallel, blinded, two arms</td>
<td>intraoperatively Control: 5% HA (1 liter) given intraoperatively Duration: 24 h post-op</td>
<td>undergoing off-pump coronary artery bypass grafting N = 156; 78 in each group Setting: ICU</td>
<td>• Red blood cell: 1.14 units (HES) vs. 0.40 units (HA), p=0.017 • Fresh-frozen plasma: 0.57 units (HES) vs. 0.15 units (HA), p=0.009 • Platelets: 0.35 units (HES) vs. 0.10 units (HA), p=0.013 Likelihood of receiving transfusion on post-op day 1: 46.2% in HES vs. 25.6% in HA, p=0.012 Volume of chest tube drainage 12 h post-op: 732.0 ml in HES vs. 563.6 ml in HA, p&lt;0.001 Mortality: no subject died before hospital discharge</td>
<td>bypass, the intraoperative administration of hetastarch (HES 450/0.7) increases the postoperative transfusion requirement and the volume of blood drained postoperatively</td>
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<td>Mukhtar et al., 2009</td>
<td>Intervention: 6% HES 130/0.4 (50 ml/kg) Control: 5% HA (50 ml/kg) Duration: 4 days after surgery</td>
<td>Participants: Adult patients (&gt;18 years) undergoing liver transplantation N = 40; 20 in each group Setting: ICU</td>
<td>Perioperative data: no difference between groups Cumulative fluid balance: higher in the HES group than HA group (p=0.029) Diuretics use: greater in the HES group compared to Ha group (p&lt;0.05) Renal function: (creatinine and CrCl): similar in both groups</td>
<td>The use of HES 130/0.4 as an alternative to human albumin resulted in equivalent renal outcome after liver transplantation</td>
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| Schramko et al., 2009<sup>14</sup> | Intervention: 6% HES 130/0.4 or 6% HES 200/0.5  
Control: 4% HA  
Duration: 2 h infusion; 1 day follow-up after surgery | Participants: Adult patients (>18 years) undergoing elective primary cardiac surgery  
N = 45; 15 in each group  
Setting: ICU | Other laboratory data: no difference between groups  
Mortality: one in each group | A short-time infusion of rapidly degradable HES solutions after cardiac surgery produces impairment in fibrin formation and clot strength in thromboelastometry tracings. HA does not impair whole blood coagulation.  
6% HES 130/0.4 and 6% HES 200/0.5 have similar effects on coagulation |
| Boldt et al., 2008<sup>15</sup> | Intervention: 6% HES 130/0.4  
Control: 5% HA  
Duration: 60 days follow-up | Participants: Adult patients (>80 years) undergoing cardiac surgery using cardiopulmonary bypass  
N = 50; 25 in each group  
Setting: ICU and hospital | Inflammatory response: similar in both groups  
Endothelial activation: significantly lower in HES than in HA group until the end of the study (p<0.05)  
Renal function: None of the patients developed renal failure requiring renal replacement therapy | The use of albumin in hypoalbuminemic patients aged >80 years undergoing cardiac surgery was without benefit with respect to inflammatory response, endothelial activation, and renal function compared to HES 130/0.4 |
| Friedman et al., 2008<sup>23</sup> | Intervention: 6% HES 200/0.5; 10% HES 200/0.5 | Participants: Adult patients (>18 years) with sepsis | Hemodynamic parameters:  
- Cardiac index, stroke | HES is as effective as albumin for volume |
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<td>To compare the hemodynamic effects of two different concentrations of HES 200/0.5 solutions with 4% HA solution for fluid resuscitation</td>
<td>Control: 4% HA Duration: 40 minutes infusion; monitoring up to 160 minutes</td>
<td>N = 34; 10% HES (n=11), 6% HES (n=10), 4% HA (n=13) Setting: ICU</td>
<td>Volume index, and left ventricular stroke work index increased more in the 10% HES group than the 6% HES or albumin groups (p&lt;0.05) • Oxygen delivery increased only in 10% HES group • All three groups had decrease in hemoglobin concentrations, with greatest in 10% HES</td>
<td>Resuscitation in septic patients</td>
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<td>Niemi et al., 2008&lt;sup&gt;16&lt;/sup&gt; RCT, prospective, open-label, three arms Source of funding: public To compare the hemodynamics and acid-base equilibrium after infusion of two rapidly degradable HES solutions or HA in cardiac surgical patients</td>
<td>Intervention: 6% HES 200/0.5; 6% HES 130/0.4 Control: 4% HA Duration: 18 hours</td>
<td>Participants: Adult patients (33-77 years) undergoing cardiac surgery N = 45; 15 in each group Setting: ICU</td>
<td>Hemodynamics: Mean cardiac index was higher in HES groups than HA group after infusion (p=0.002), but no differences were detected at 2 and 18 hours. Oxygen delivery increased in both HES groups but not in HA groups. Acid-base equilibrium: pH was not different between study groups, but base excess and bicarbonate decreased less in both HES groups than in HA group</td>
<td>The effect of HA on cardiac performance is inferior to that of HES 130/0.4 or HES 200/0.5 in early postoperative phase after cardiac surgery.</td>
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<td>Reine et al., 2008&lt;sup&gt;17&lt;/sup&gt; RCT, prospective, parallel, two arms</td>
<td>Intervention: 6% HES 200/0.5 (Haes-Steril®) Control: 4% HA</td>
<td>Participants: Adult patients (&gt;18 years) undergoing major orthopedic, gastrointestinal, or</td>
<td>Serum albumin: during operation, serum albumin decreased (26.8 to 15.3 g/l) in HES group</td>
<td>Infusion of albumin during surgery resulted in maintained albumin values and almost maintained</td>
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Albumin versus Synthetic Plasma Volume Expanders
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<tr>
<td>Source of funding: not reported To study the drug-binding capacity in serum from surgical patients receiving pharmaceutical-grade albumin or synthetic colloids</td>
<td>Duration: median 4h (range 1-11h) infusion during surgery, 1 day follow-up after surgery</td>
<td>gynecological surgery with expected large fluid and transfusion requirements N = 40; 20 in each group Setting: ICU</td>
<td>(p&lt;0.001), while it remained unchanged (29.2 g/l) in the albumin group Unbound drugs: percent free concentrations of drugs (Naproxen, Warfarin, Digitoxin) was higher in HES group compared to albumin group</td>
<td>binding parameters for the study drugs. The use of starch solutions led to a reduction of albumin values and a significant reduction in binding parameters</td>
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<td>Standl et al., 2008&lt;sup&gt;20&lt;/sup&gt; RCT, prospective, parallel, two arms Source of funding: industry To compare the effects of 6% HES 130/0.4 with 5% HA with regard to hemodynamics in children &lt;2 years scheduled for elective non-cardiac surgery</td>
<td>Intervention: 6% HES 130/0.4 (Voluven&lt;sup&gt;R&lt;/sup&gt;) Control: 5% HA Duration: 1 day after operation</td>
<td>Participants: Pediatric patients (&lt;2 years) undergoing non-cardiac surgery N = 82; 41 in each group Setting: ICU</td>
<td>Hemodynamic parameters: no different between groups Coagulation parameters: no different between groups Other laboratory values: no different between groups ICU stay: median 3.5 days in HES and 6 days in HA Hospital stay: median 12 days in both groups Mortality: 1 in HA vs. 0 in HES</td>
<td>Both HES 130/04 and HA were effective for hemodynamic stabilization in non-cardiac surgery of young infants with no adverse impact on coagulation or other safety parameters</td>
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<td>Haas et al., 2007&lt;sup&gt;21&lt;/sup&gt; RCT, prospective, parallel, three arms Source of funding: not reported To investigate the effects of artificial colloids on clot</td>
<td>Intervention: 6% HES 130/0.4; 4% modified gelatin Control: 5% HA Duration: hours after surgery</td>
<td>Participants: Pediatric patients (10-14 months) undergoing surgery (cranial facial, tumor resection, abdominal) Total: 42; 14 in each group Setting: ICU</td>
<td>Coagulation: changes in standard coagulation tests and thromboelastometry values were similar with albumin and gelatin. In contrast, HES infusion significantly impaired coagulation time, clot formation, clot firmness</td>
<td>From a haemostatic point of view, it might be preferable to use gelatin solution as an alternative to albumin; HES showed the greatest effects on the overall coagulation process</td>
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<td>formation process in children undergoing surgery and needing colloid replacement</td>
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<td>and fibrinogen/fibrin polymerization compared with albumin and gelatin</td>
<td>In children with severe malaria, albumin had higher survival benefit than modified gelatin, despite comparable effects on the resolution of acidosis and shock</td>
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| Akech et al., 2006<sup>24</sup> | Intervention: 4% modified gelatin  
Control: 4.5% HA  
Duration: one month after discharge | Participants: Pediatric patients (>3 months) presenting with severe malaria, metabolic acidosis, and clinical features of shock  
N = 88; 44 in each group  
Setting: Hospital | Resolution of shock and acidosis: no differences between groups  
Mortality: 16% in gelatin versus 2.3% in albumin (p = 0.06) | In children with severe malaria, albumin had higher survival benefit than modified gelatin, despite comparable effects on the resolution of acidosis and shock |
| Niemi et al, 2005<sup>18</sup> | Intervention: 4% HES 120/0.7  
Control: 4% HA  
Duration: 3 days | Participants: Adult patients (>18 years) undergoing primary total hip arthroplasty  
N = 101; HA (n=48), HES (n=53)  
Setting: hospital | Blood loss and transfusion: no difference between groups  
Clotting parameters: no difference between groups | HES 120/0.7 and HA had comparable effects on blood loss intra- and postoperatively in primary total hip replacement patients |

GFR: glomerular filtration rate; GST: glutathione S-transferase; h: hour; HA: human albumin; HES: hydroxyethyl starch; ICAM-1: intracellular adhesion molecule-1; ICU: intensive care unit; IL: interleukin; N: number of patients; NGAL: neutrophil gelatinase-associated lipocalin