Overview

Introduction to cardiac surgery

Hypoalbuminaemia: predictor of poor outcome in cardiac surgery

**Albumin** volume effect in cardiac surgery
- **Albumin** for pump priming in cardiac surgery
  - Platelets, fluid balance and clinical outcomes
  - Erythrocyte crenation
- **Albumin** for volume expansion in cardiac surgery
  - Mortality
  - Bleeding
  - Haemostasis

**Albumin**: effects on renal function

HES: effects on bleeding

Summary and conclusion
Introduction to cardiac surgery
Cardiac surgery

Different types of cardiac surgery

- Coronary artery bypass grafting (CABG)
- Heart valve repair/replacement
- Implantation of medical devices to support heart function
- Heart transplantations

Two general methods

- On-pump (cardiopulmonary bypass; CPB)
- Off-pump

Fluids are frequently required during cardiac surgery and are indicated for:

- Perioperative volume expansion (CPB and off-pump surgery)
- Pump priming for CPB

Risks of cardiac surgery potentially modifiable by fluid management

**Excessive bleeding**
- Frequent, serious and unpredictable
- May necessitate reoperation

**Fluid overload**
- Increased morbidity, mortality, duration of ICU/hospital stay, ICU readmission and major post-operative complications

**Renal failure**
- One of the major complications of cardiac surgery
- Incidence rate up to 30%, with 4% requiring renal replacement therapy

**Systemic inflammatory response syndrome**
- Increased vascular permeability
- Poor microcirculation

---

Hypoalbuminaemia: predictor of poor outcome in cardiac surgery
Risks of pre-operative hypoalbuminaemia

- Retrospective study of 5168 consecutive cardiac surgery patients
- 15% of patients severely hypoalbuminaemic (serum albumin <2.5 g/dL)

### Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds ratio (95% CI)*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.0 (1.3, 3.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>2.0 (1.3, 3.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Re-exploration for bleeding</td>
<td>1.4 (1.0, 2.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>ICU stay &gt; 3 days</td>
<td>1.7 (1.4, 2.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*<2.5 vs >3.5 g/dL serum albumin as adjusted for other risk factors

Pre-operative hypoalbuminaemia is an independent risk factor for multiple poor outcomes in cardiac surgery.

Albumin administration may be valuable prior to cardiac surgery.

CI, confidence interval
Effect of pre-operative hypoalbuminaemia on long-term survival after CABG surgery

- Kaplan-Meier analysis was performed to estimate long term survival of 588 propensity-matched patients
  - 294 (albumin levels <3.5 g/dL)
  - 294 (albumin levels ≥3.5 g/dL)

Preoperative hypoalbuminemia (<3.5 g/dL) independently predicted poorer long-term survival after CABG surgery

Preoperative albumin administration may improve long-term survival after CABG surgery

8-year mean survival rate, ± SE (%)

- <3.5 (n=21)
- ≥3.5 (n=40)

HR 2.2 (95% CI 1.4, 3.6)
p=0.001

CABG, coronary artery bypass graft; HR, hazard ratio CI, confidence interval; SE, standard error
Risks of post-operative hypoalbuminaemia after off-pump cardiac surgery

- Retrospective study of 690 patients undergoing off-pump cardiac surgery

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds ratio (95% CI)*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure</td>
<td>7.98 (1.59, 40.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Need for IABP†</td>
<td>13.7 (1.53, 125)</td>
<td>0.02</td>
</tr>
<tr>
<td>Reoperation for bleeding</td>
<td>4.33 (1.02, 18.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Use of inotropes in ICU</td>
<td>1.79 (1.12, 2.86)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*<2.3 vs ≥2.3 g/dL serum albumin as adjusted for other risk factors
†Intra-aortic balloon pump

Post-operative hypoalbuminaemia† is an independent predictor for multiple poor outcomes after off-pump cardiac surgery

Albumin administration post-surgery may improve outcomes

Albumin levels <2.3 g/dL

Risks of post-operative hypoalbuminaemia after CPB surgery

- Retrospective study of 454 patients undergoing cardiac surgery with CPB

*Albumin levels ≤1.8 g/dL, ‡From logistic regression analysis model

CPB, cardiopulmonary bypass; ICU, Intensive care unit; CI, confidence interval


Post-operative hypoalbuminaemia* is predictive of higher 28-day mortality (OR 0.86; 95% CI 0.84–0.89; p<0.001)‡ after cardiac surgery with CPB

Albumin administration post-surgery may improve patient survival
Albumin volume effect in cardiac surgery
Albumin is more effective than saline for plasma volume expansion in cardiac surgery patients

- Randomised study comparing the effect of saline or 5% albumin on haemodynamic endpoints in 40 cardiac surgery patients
- Albumin and saline had comparable effects on oxygen delivery and changes in interstitial and extracellular fluid volume

5% albumin is approximately five times more efficient as a plasma volume expander compared with normal saline in postoperative cardiac surgical patients

PV, plasma volume
Ernest et al. Distribution of normal saline and 5% albumin infusions in cardiac surgical patients. Crit Care Med 2001; 29: 2291–302
Hyperoncotic albumin is more effective than Ringer’s lactate in plasma volume expansion

- Prospective study in patients undergoing normovolaemic haemodilution (N=10)

1097 (± 285) mL whole blood withdrawn

Simultaneously replaced by 3-fold Ringer’s lactate (3430 (± 806) mL)

- 245 (± 64) mL of 20% human albumin restored blood volume to baseline values
- Human albumin volume effect: 184 ± 64%

- Significant hypovolaemia: ↓ in blood volume (-459 [± 185] mL, p<0.05)
- Significant ↑ in interstitial water content (2157 [± 606] mL)
- Ringer’s lactate volume effect: 17 (± 10)%

Hyperoncotic albumin (with a volume effect of more than 100%) is a good option to recruit interstitially stored fluid toward the circulatory compartment

Jacob et al. The intravascular volume effect of Ringer’s lactate is below 20%; a prospective study in humans. Crit Care 2012; 16: R86
Albumin for pump priming in cardiac surgery: effect on platelets, fluid balance and clinical outcomes
### Russell et al. meta-analysis: Effects of pump priming fluid choice in cardiac surgery

| Background | • Albumin is commonly added as constituent of pump priming fluid during cardiac surgery  
  − Coats the fluid pathway surface, diminishing contact between blood and non-biological surface  
  − Maintains COP to avoid oedema |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim</td>
<td>• To determine the effects of pump priming fluid choice (albumin or crystalloid) on platelets, fluid balance, and clinical outcomes</td>
</tr>
<tr>
<td>Study design</td>
<td>• Meta-analysis of 21 RCTs involving 1346 patients undergoing cardiopulmonary bypass (CPB)</td>
</tr>
</tbody>
</table>
| Endpoints | • Platelet counts  
• Colloid oncotic pressure  
• On-bypass fluid balance  
• Post-operative weight gain  
• Colloid usage |

COP, colloid osmotic pressure; RCT, randomised controlled trial

Russell et al. meta-analysis: Albumin is favoured for pump priming compared with crystalloid prime

Compared to crystalloid prime, albumin prime:

- **Reduced on-bypass drop on platelet counts** (mean reduction $23.8 \times 10^9$/L)
- **Reduced on-bypass positive fluid balance** (mean reduction 584 mL)
- **Associated with a smaller reduction in COP**
  - On-bypass (mean reduction 3.6 mmHg)
  - After surgery (mean reduction 2.0 mmHg)
- **Reduced post-operative weight gain** (mean reduction 1 kg)
- **Reduced post-operative colloid usage** (mean reduction 612 mL)

COP, colloid osmotic pressure; CPB, cardiopulmonary bypass

As albumin prime has a more favourable effect on peri- and post-operative outcomes in cardiac surgery with CPB compared with crystalloid prime

Albumin is a preferable option for pump priming

Albumin for pump priming in cardiac surgery: effect on erythrocyte crenation
Albumin prevents erythrocyte crenation in patients undergoing extracorporeal circulation

- Free fatty acid-induced erythrocyte crenation† has been reported in patients undergoing extracorporeal circulation during CPB surgery
- Crenated erythrocytes are thought to impair microcirculatory flow and tissue oxygenation
- Controlled study of 38 patients undergoing CPB with 0, 25 g or 50 g albumin in prime solution (prime albumin concentration 0, 1.6% and 2.9% respectively)

- Erythrocyte crenation almost completely prevented by administration of 50 g albumin
- Protective effect of albumin due to binding of free fatty acids

*Shrinkage and acquisition of a notched appearance
CPB, cardiopulmonary bypass
Albumin for volume expansion in cardiac surgery: effect on mortality
**Albumin administration associated with reduced mortality rate after CABG**

- Database study of 19,578 cardiac surgery patients

**Variables**

<table>
<thead>
<tr>
<th>Albumin use (vs synthetic colloids†)</th>
<th>Odds ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower risk of death</td>
<td>0.80 (0.67, 0.96)</td>
</tr>
<tr>
<td>Higher risk of death</td>
<td>1.32 (1.20, 1.45)</td>
</tr>
<tr>
<td></td>
<td>1.66 (1.38, 1.98)</td>
</tr>
<tr>
<td></td>
<td>2.11 (1.67, 2.65)</td>
</tr>
</tbody>
</table>

- Age (10-year increments)
- Female gender
- Simultaneous valve procedure

**Odds ratio (95% CI)**

- **After multivariable analysis**
- **Hetastarch or dextran**

**Patients who received albumin had a lower incidence of mortality than those who received synthetic colloids (2.47% vs 3.03%, p=0.02)**

**In multivariable analysis, the mortality rate was 25% lower in the patient group receiving albumin compared to those receiving synthetic colloids**

- Approximately five to six lives were saved for every 1,000 patients who underwent CABG surgery when albumin rather than synthetic colloids were used

---

CABG, coronary artery bypass graft; CI, confidence interval

Albumin for volume expansion in cardiac surgery: effect on bleeding
Navickis et al. meta-analysis: Effect of albumin vs HES on bleeding outcomes after cardiopulmonary bypass surgery

| Aim | To compare effect of albumin vs HES (including lower MW HES) administration on post-operative bleeding |
| Study design | Meta-analysis of 18 randomised controlled trials  
Comparison between HES solutions also included |
| Patient population | Patients undergoing cardiopulmonary bypass (CPB)  
N=970 patients |
| Primary endpoint | Cumulative blood loss during 24 hours following CPB |
| Secondary endpoints | During 24 hours following CPB  
Re-operation for bleeding  
Post-operative blood product transfusion |

MW, molecular weight; HES, hydroxyethyl starch
Navickis et al. meta-analysis: Albumin significantly decreased post-operative blood loss vs HES

<table>
<thead>
<tr>
<th>Resuscitation fluids compared</th>
<th>Number of RCTs</th>
<th>Pooled standardised mean difference (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HES 450/0.7 vs albumin</td>
<td>9</td>
<td>36.2</td>
<td>17.1–55.4</td>
</tr>
<tr>
<td>HES 200/0.5 vs albumin</td>
<td>6</td>
<td>28.5</td>
<td>4.2–52.8</td>
</tr>
<tr>
<td>HES 450/0.7 and HES 200/0.5 combined vs albumin</td>
<td>15</td>
<td>33.3</td>
<td>18.2–48.3</td>
</tr>
<tr>
<td>HES 130/0.4 vs HES 200/0.5</td>
<td>4</td>
<td>15.7</td>
<td>-8.6–40.1</td>
</tr>
</tbody>
</table>

- Albumin decreased post-operative blood loss by 33.3% of a pooled SD, compared with HES (p<0.001)
- No significant differences in post-operative blood loss (vs albumin) observed between HES 450/0.7 and HES 200/0.5 (p=0.62)
- Importantly, no significant difference observed between HES 200/0.5 and HES 130/0.4 (p=0.21)

HES, hydroxyethyl starch; CI, confidence interval; RCT, randomised controlled trial; SD, standard deviation

Navickis et al. meta-analysis: Albumin significantly decreased risk of re-operation vs HES

No significant differences in re-operation for bleeding observed between HES 450/0.7 and HES 200/0.5, both vs albumin (p=0.87)

Importantly, the risk of reoperation for bleeding was similar for HES 130/0.4 and HES 200/0.5 (p=0.62)

*HES 450/0.7 and HES 200/0.5 combined
HES, hydroxyethyl starch; RR, relative risk; CI, confidence interval
Navickis et al. meta-analysis: HES significantly increased transfusion of blood products vs albumin

*No significant differences between HES 450/0.7 and HES 200/0.5* in terms of increased transfusion of blood products (vs albumin) observed (RBC, p=0.36; FFP, p=0.47; platelets, p=0.74)

Importantly, *no significant differences between HES 130/0.4 and HES 200/0.5* in transfusion of RBC (p=0.24), FFP (p=0.70) and platelets (p=0.046)

CI, confidence interval; FFP, fresh frozen plasma; HES, hydroxyethyl starch; RBC, red blood cell; SD, standard deviation

Navickis *et al.* meta-analysis: Albumin is associated with better bleeding outcomes after CPB vs HES

- Compared with HES 450/0.7 or HES 200/0.5, albumin significantly reduced:
  - Post-operative blood loss
  - Risk of reoperation for bleeding
  - Transfusion of blood products
- No significant differences in these parameters observed between HES 450/0.7 and HES 200/0.5
- No significant differences observed between HES 200/0.5 and HES 130/0.4, which suggests that *albumin would also be associated with better outcomes than HES 130/0.4*
  - This is inferred from indirect comparisons and should be confirmed in future prospective clinical trials

- No evidence to show that lower molecular weight and substitution mitigates the risks of HES for CPB
- As albumin is associated with better outcomes after CPB compared with HES, it may be preferable for volume expansion in patients undergoing cardiac surgery

CPB, cardiopulmonary bypass; HES, hydroxyethyl starch
Albumin reduces blood loss and post-operative transfusion requirements after CABG

- Randomised controlled trial comparing albumin and HES 450/0.7 for fluid replacement in off-pump CABG patients with target enrollment of 330 patients
  - Study halted after enrolment of 156 patients due to excessive bleeding in patients receiving HES 450/0.7

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Mean (SD)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Albumin</td>
<td>HES 450/0.7</td>
</tr>
<tr>
<td>Blood loss in first 12 h (mL)</td>
<td>563.9 (197.9)</td>
<td>728.7 (323.5)</td>
</tr>
<tr>
<td>Red blood cells (units)</td>
<td>0.40 (0.89)</td>
<td>1.13 (2.52)</td>
</tr>
<tr>
<td>Fresh frozen plasma (units)</td>
<td>0.15 (0.56)</td>
<td>0.56 (1.24)</td>
</tr>
<tr>
<td>Platelets (superpacks; 12-packs)</td>
<td>0.13 (0.38)</td>
<td>0.35 (0.77)</td>
</tr>
</tbody>
</table>

Compared with HES, albumin reduced blood loss, amount of blood products transfused and the need for any blood product (RR 1.80, p=0.012)

* Results of multivariate analyses examining the association of HES 450/0.7 use with outcomes on post-operative day 1, while controlling for age and BMI

Albumin for volume expansion in cardiac surgery: effect on haemostasis
Unlike HES, albumin administration after CPB does not impair haemostasis

- Randomised trial comparing effect of albumin, HES 200/0.5 or HES 130/0.4 on blood coagulation (assessed by thromboelastometry) in 45 cardiac surgery patients
- Administration of HES 130/0.4 and HES 200/0.5 significantly prolonged clot formation time and reduced maximum clot firmness compared with albumin

- Albumin administration did not impair coagulation after CPB\(^1\)
- HES 130/0.4 and HES 200/0.5 had similar adverse effects on coagulation\(^1\)
  - Finding contradicts earlier reports that HES 130/0.4 had no negative effects on haemostasis in cardiac surgical patients\(^2\)

HES, hydroxyethyl starch; CPB, cardiopulmonary bypass
Albumin does not impair haemostasis after CPB compared with HES and gelatin

- Randomised study comparing effect of albumin, HES 200/0.5 or gelatin on coagulation in 45 cardiac surgery patients
- Administration of gelatin and HES increased clot formation time and decreased maximum clot firmness compared with albumin

Administration of gelatin or HES 200/0.5 (but not albumin) impaired coagulation after CPB, which may predispose patients to increased blood loss

CPB, cardiopulmonary bypass; HES, hydroxyethyl starch
### Effect of administration of different fluids on haemostasis after CPB surgery: Summary of two studies

<table>
<thead>
<tr>
<th>Fluids</th>
<th>Coagulation time</th>
<th>Clot formation time</th>
<th>Clot strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Gelatin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>No change</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>HES 200/0.5&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>HES 130/0.4&lt;sup&gt;1&lt;/sup&gt;</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

Albumin is preferable for volume expansion in patients undergoing cardiac surgery as, unlike gelatin or HES, it does not impair haemostasis after CPB.

---

Albumin: effects on renal function
Wiedermann et al. meta-analysis: Effects of hyperoncotic albumin on AKI

| Aim | • Compare the effects of hyperoncotic albumin or HES on AKI |
| Study design | • Meta-analysis of RCTs |
| Studies included | • Evaluated AKI following infusion of hyperoncotic colloid vs control (crystalloid, 4–5% hypo-oncotic albumin or no fluid):
  • 20–25% albumin (7 studies)
  • 10% HES (4 studies) |
| Patient population | • N=1220
  • Surgery (3 studies), ascites (4 studies) or spontaneous bacterial peritonitis (2 studies)
  • Severe sepsis or septic shock (1 study)
  • Early septic shock (1 study) |
| Primary endpoint | • Does hyperoncotic albumin or HES increase AKI risk vs control? |
| Secondary endpoint | • Mortality |

AKI, acute kidney injury; HES, hydroxyethyl starch; RCT, randomised controlled trial
Wiedermann et al. meta-analysis: Hyperoncotic albumin significantly decreases risk of AKI vs control

OR 0.24
(95% CI 0.12, 0.48)

*p<0.0001

*Crystalloid, 4–5% hypo-oncotic albumin or no fluid; AKI, acute kidney injury; CI, confidence interval; OR, odds ratio

Further evidence that albumin may have beneficial effects on renal function

Albumin can be thought of as having a ‘renoprotective effect’: it preserves renal function even in patients with pre-existing kidney abnormalities\(^1\)

Albumin is the only colloid in which renal safety is supported by a large, multi-centre, double-blind RCT in critically ill patients\(^2\)

A recent study comparing chloride-liberal with chloride-restrictive intravenous fluid administration in critically ill patients demonstrated that a chloride-restrictive strategy with 20% albumin* was associated with a significant decrease in the incidence of acute kidney injury and failure (p<0.001), and the use of RRT (p=0.005)\(^3,4\)

* Increase in average dose of albumin from 34 g to 74 g per person, resulting in elevated serum albumin levels

RCT, randomised controlled trial; RRT, renal replacement therapy

HES: effect on bleeding

HES, hydroxyethyl starch
Systematic review on comparative safety of colloids: Bleeding after HES infusion

HES, hydroxyethyl starch; MW, molecular weight; MS, molar substitution
Further evidence that HES has detrimental effects on bleeding

Systematic review of studies that measured the effects of HES 130/0.4 on blood clotting using viscoelastic devices revealed that clots tended to be smaller and less stable following the use of HES 130/0.4 compared with other resuscitation fluids.¹

50:50 dilution of plasma samples with HES 130/0.4 has been shown to cause significant over-estimation of fibrinogen levels, as determined by a number of in vitro assays.²

• This has implications for the management of bleeding in patients treated with HES and could lead to a delay in patients receiving treatment

Review of the effects of HES on coagulation in patients undergoing cardiac surgery (in nine RCTs) concluded that HES 130/0.4 resulted in a similar extent of blood loss to HES 200/0.5.³

HES safety concerns and recommendations: FDA

Recommendations and conclusions from a dedicated workshop convened by the US FDA to assess the risks and benefits of HES solutions

- HES solutions should not be used in critically ill adult patients, including patients with sepsis*
- Coagulation status of patients (who have received HES) undergoing open heart surgery in association with CPB should be monitored†
- Renal function should be monitored for at least 90 days in all patients following HES administration
- Increased mortality and renal injury in critically-ill patients, and excess bleeding in patients undergoing CPB surgery, are considered to be HES class effects

Major agenda items:
- renal safety concerns
- adverse effects on bleeding

*A Boxed Warning to include the risk of mortality and severe renal injury in these patient populations is warranted
†Excess bleeding had been reported in this population; a warning about excessive bleeding is needed in the Warnings and Precautions Section of the package insert

HES safety concerns and recommendations: EMA

Recommendations of the EMA PRAC on the use of HES-containing solutions

- Endorsed by the CMDh, representing EU member states
- The European Commission has endorsed the CMDh position, and adopted a final legally binding decision valid throughout the EU

HES solutions must no longer be used to treat patients with sepsis or burn injuries, or critically ill patients because of an increased risk of kidney injury and mortality.

HES solutions should not be used for more than 24 hours and patients’ kidney function should be monitored after HES administration.

HES solutions should only be used for the treatment of hypovolaemia due to acute blood loss, when treatment with crystalloids alone are not considered sufficient.

CMDh, Coordination Group for Mutual Recognition and Decentralised Procedures (Human); EMA, European Medicines Agency; PRAC, Pharmacovigilance Risk Assessment Committee

HES safety concerns and recommendations: EMA

Assessment by the PRAC on the benefits and risks of HES products

Selected instructions and precautions to be included in the SmPC of HES products

Use of HES should be **restricted** to
- the lowest possible dose with a maximum daily dose of 30 mL/kg
- the initial phase of volume resuscitation with a maximum time interval of 24 hours

Use of HES is **not recommended**
- in patients undergoing cardiac surgery in association with CPB (due to risk of excessive bleeding)
- for use in children

Other available options should be considered for patients undergoing surgery or trauma (due to lack of robust long-term safety data on HES use)

Renal function of patients to be monitored for 90 days following HES administration

CPB, cardiopulmonary bypass; EMA, European Medicines Agency; HES, hydroxyethyl starch; PRAC, Pharmacovigilance Risk Assessment Committee; SmPC, Summary of Product Characteristics

### Comparison of albumin vs HES

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HES&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Albumin&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Hypovolaemia due to acute blood loss (only when crystalloids are considered insufficient for volume replacement)</td>
<td>Hypovolaemia (EU) (&gt;10 additional indications are licensed in US and ROW)</td>
</tr>
</tbody>
</table>
| **Contraindications** | • Critically ill  
• Sepsis  
• Burns  
• Renal impairment  
• Severe coagulopathy | • Prior allergic reaction to albumin                                               |
| **Not recommended** | • Cardiac surgery  
• Children  
• Surgery and trauma |                                                                                   |
| **Administration** | • Lowest possible dose  
• Maximum use up to 24 h  
• Maximum daily dose 30 mL/kg | • Dose according to patient’s individual requirement  
• No maximum time restriction  
• No maximum dose restriction |
| **Long-term monitoring** | Renal function to be monitored for at least 90 days after administration | Not necessary                                                                       |

HES, hydroxyethyl starch; ROW, rest of world

2. Alburex® 5  Summary of Product Characteristics. Available at: [http://www.medicines.org.uk/emc/medicine/27449/SPC/Alburex%2c+50g+I%2c2c+solution+for+infusion](http://www.medicines.org.uk/emc/medicine/27449/SPC/Alburex%2c+50g+I%2c2c+solution+for+infusion) [accessed December 2013].
Summary and conclusion

Volume expansion in cardiac surgery
- Albumin is significantly more efficient than saline as a plasma volume expander in cardiac surgery patients
- Albumin is associated with better bleeding outcomes after CPB compared with HES
- Albumin does not impair haemostasis after CPB compared with HES or gelatin
- Albumin has been shown to have beneficial effects on renal function and inflammation
- HES has been shown to have detrimental effects on bleeding

**Albumin is preferable to synthetic colloids for volume expansion**

Pump priming in cardiac surgery
- Albumin is associated with better clinical outcomes compared with crystalloids
- As a colloid, albumin has the advantage of maintaining COP and reducing oedema
- Albumin avoids the complication of fluid overload associated with crystalloids

**Albumin is preferable to crystalloids for pump priming**

**Albumin is the fluid of choice for cardiac surgery**
References (A-H)

- Ernest *et al*. Distribution of normal saline and 5% albumin infusions in cardiac surgical patients. *Crit Care Med* 2001; 29: 2291–302
- Fenger-Eriksen *et al*. Fibrinogen estimates are influenced by methods of measurement and hemodilution with colloid plasma expanders. *Transfusion* 2010; 50: 2571–6
- Haase *et al*. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. *BMJ* 2013; 346: f839
References (H-R)

• Hartog et al. Influence of hydroxyethyl starch (HES) 130/0.4 on hemostasis as measured by viscoelastic device analysis: a systematic review. *Intensive Care Med* 2011; 37: 1725–37


• Hydroxyethyl-starch solutions (HES) should no longer be used in patients with sepsis or burn injuries or in critically ill patients – CMDh endorses PRAC recommendations. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/10/news_detail_001930.jsp&mid=WC0b01ac058004d5c1 [accessed December 2013]

• Jacob et al. The intravascular volume effect of Ringer’s lactate is below 20%: a prospective study in humans. *Crit Care* 2012; 16: R86


• Patel et al. Randomised trials of 6 % tetrastarch (hydroxyethyl starch 130/0.4 or 0.42) for severe sepsis reporting mortality: systematic review and meta-analysis. *Intensive Care Med*. 2013; 39: 811–22


References (S-Y)

- SAFE study investigators. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive Care Med* 2011; 37: 86–96
- Toraman *et al.* Highly positive intraoperative fluid balance during cardiac surgery is associated with adverse outcome. *Perfusion* 2004; 19: 85–91
- What is heart surgery? Available at: http://www.nhlbi.nih.gov/health/health-topics/topics/hs/ [accessed December 2013]
**Prescribing information: Human Albumin 20% Behring**

**Name:** Human Albumin 20% Behring, low salt. Solution for infusion. **Qualitative and quantitative composition:** Active ingredients: Solution containing 200 g/L of total protein of which at least 96% is human albumin. 50 mL contain at least 9.6 g of human albumin. The solution is hyperoncotic. Other ingredients: Sodium ions, Caprylate, N-acetyl-D,L-tryptophan, Chloride ions, HCl or NaOH (in small amounts for pH adjustment), Water for injections. **Therapeutic indications:** Increase in oncotic pressure in case of oncotic deficiency; diluted as a 4 – 5% solution for iso-oncotic volume replacement with long-term effect; therapy of albumin deficiency. **Contraindications:** Hypersensitivity to albumin preparations or to any of the excipients of the product. **Special warnings and precautions for use:** Suspicion of allergic or anaphylactic type reactions (reaction like an allergic shock) requires immediate discontinuation of the injection. In case of shock, standard medical treatment for shock should be implemented. Albumin should be used with caution in conditions where hypervolaemia (oversized blood volume) and its consequences or haemodilution (dilution of the blood) could represent a special risk for the patient. Examples of such conditions are: Decompensated cardiac insufficiency (severe heart muscle deficiency), hypertension (increased blood pressure), oesophageal varices (disease of the gullet vessels), pulmonary oedema, haemorrhagic diathesis (increased tendency to bleeding), severe anaemia (severe red blood cell deficiency), renal and post-renal anuria (kidney failure). The colloid-osmotic effect of human albumin 200 or 250 g/L is approximately four times that of blood plasma. Therefore, when highly concentrated albumin is administered, care must be taken to assure adequate hydration (fluid supply) of the patient. Patients should be monitored carefully to guard against circulatory overload or hyperhydration (increased volume of total body water). 200 – 250 g/L human albumin solutions are relatively low in electrolytes compared to the 40 – 50 g/L human albumin solutions. When albumin is given, the electrolyte status of the patient should be monitored and appropriate steps taken to restore or maintain the electrolyte balance. Albumin solutions must not be diluted with water for injections as this may cause haemolysis (destruction of red cells) in recipients. If comparatively large volumes are to be replaced, controls of coagulation and haematocrit are necessary. Care must be taken to ensure adequate substitution of other blood constituents (coagulation factors, electrolytes, platelets and erythrocytes). Hypervolaemia may occur if the dosage and rate of infusion are not adjusted to the patients circulatory situation. At the first clinical signs of cardiovascular overload (headache, dyspnoea [difficulty in breathing], jugular vein congestion), or increased blood pressure, raised venous pressure or pulmonary oedema, the infusion is to be stopped immediately. Human Albumin 20% Behring, low salt contains 125 mmol sodium per 1000 mL. To be taken into consideration by patients on a controlled diet. **Pregnancy and lactation:** The safety of Human Albumin 20% Behring, low salt, for use in human pregnancy has not been established in controlled clinical trials. However, clinical experience with albumin suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected, particularly since human albumin is a normal constituent of human blood. No animal reproduction studies have been conducted with Human Albumin 20% Behring, low salt. Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or foetus, the course of gestation and peri- and postnatal development. **Virus safety:** When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections. There are no reports of virus infections with albumin manufactured to European Pharmacopoeia specifications by established processes. It is strongly recommended that every time you receive a dose of Human Albumin 20% Behring, low salt, the name and batch number of the product are recorded in order to maintain a record of the batches used. **Interactions with other medicinal products and other forms of interactions:** No specific interactions of human albumin with other medicinal products are known. Incompatibilities: Human Albumin 20% Behring, low salt, must not be mixed with other medicinal products (except the recommended diluents), whole blood and packed red cells. **Undesirable effects:** The following adverse reactions are based on post marketing experience and were observed very rarely (<1 / 10,000 including reported single cases): General disorders and administration site conditions: Chills, fever, nausea, vomiting, headache, malaise and flush. Immune system disorders: Hypersensitivity reactions or allergic-anaphylactic reactions such as rash, itching, urticaria, dyspnoea, tachycardia, bradycardia, hypotension. These reactions might in single cases be reaching as far as life-threatening shock. Mild reactions normally disappear rapidly after the infusion rate has been slowed down or the infusion stopped. In case of severe reactions (e.g. anaphylactic shock) the infusion has to be stopped immediately and appropriate treatment instituted. **Prescription status:** Prescription-only drug. **Name and address of the Manufacturer and Marketing Authorisation Holder:** CSL Behring GmbH, Emil-von-Behring-Str. 76, D-35041 Marburg. **Date of revision of the text:** March 2008.
Prescribing information: Albumin (Human) USP, 20%, Albuminar®-20

Active substance: Albumin (Human) 20%, Albuminar®-20 is a sterile aqueous solution of albumin obtained from adult human venous plasma. Each 100 mL contains 20 g serum albumin Excipients: Sodiumacetyltryptophanate, sodium caprylate. Prescription-only medicine. Pharmaceutical form: Solution for infusion. Therapeutic indications: Emergency treatment of shock and other conditions requiring urgent restoration of blood volume. Treatment of burns to prevent marked haemoconcentration and maintain electrolyte balance. Hypoproteinaemia, with or without oedema. Posology and method of administration: Albuminar®-20 may be given intravenously undiluted or diluted with normal saline or 5% dextrose. 250 mL / litre is approximately isotonic and iso-osmotic with citrated plasma. In patients with normal blood volume, the infusion rate of undiluted solution should be slow enough (1 mL / min) to prevent too rapid expansion of plasma volume. In shock, the dose and duration of therapy are based on the patient’s responsiveness. The initial dose may be followed by additional albumin within 15 – 30 minutes if necessary. In the treatment of burns, suggested therapy during the first 24 hours includes administration of large volumes of crystalloid solution. Thereafter more albumin and less crystalloid solution are required to prevent haemoconcentration and maintain electrolyte balance. In Hypoproteinaemia, 250 to 350 mL may be required to reduce oedema and normalise serum protein levels. Since blood volume in such patients is usually normal, doses over 100 mL should not be given faster than 100 mL in 30 to 45 minutes. If slower administration is desired, mix 200 mL with 300 mL of 10% dextrose solution and administer by continuous drip at 100 mL / hour. Contraindications: Albuminar®-20 may be contraindicated in patients with severe anaemia, cardiac failure or a history of allergy to human albumin. Special warnings and precautions for use: Infusion of protein containing solutions excessively or inappropriately diluted with hypotonic solutions may cause severe haemolysis and acute renal failure. Do not use if solution is turbid. Since this product contains no preservative, do not begin administration more than 4 hours after opening. If dehydration is present, administer additional fluids concomitantly or subsequently. Administration of large quantities of albumin should be supplemented with or replaced by packed red blood cells to combat the subsequent relative anaemia. The quick blood pressure response which may follow rapid administration of concentrated albumin necessitates careful observation. Albuminar®-20 should be administered with caution to patients with low cardiac reserve or no albumin deficiency because of the risk of circulatory compromise. In hypertension, a slower administration rate is desired. If anaphylactic or severe anaphylactoid reactions occur, discontinue infusion immediately. Infusion rates and the patient’s clinical state should be monitored closely during infusion. Safety and effectiveness in paediatric patients have not been established. Viral safety: The risk of transmission of pathogenic agents by products manufactured from human blood is reduced by screening plasma donors, testing for virus infections, and inactivating and/or removing certain viruses during manufacture. Despite this, the risk of transmission of infectious agents, including those not yet known or identified, cannot be totally eliminated. Based on effective donor screening and product manufacturing processes, the risk of transmission of viral diseases or Creutzfeldt-Jakob disease is extremely remote. Pregnancy and lactation: It is not known whether Albuminar causes foetal harm when administered to pregnant women or affects reproduction capacity. Albuminar®-20 should be given during pregnancy only if clearly needed. Undesirable effects: The incidence of untoward reactions to Albuminar®-20 is low. There are reports of sometimes severe anaphylaxis and of hypersensitivity reactions (including urticaria, skin rash, pruritus, oedema, erythema, hypotension and bronchospasm). Nausea, vomiting, increased salivation, chills and febrile reactions have also been reported. Pack sizes: 50 mL vials containing 10 g albumin, 100 mL vials containing 20 g albumin. Marketing authorisation holder: CSL Behring LLC, Kankakee, IL 60901 USA. Date of revision of the text: August 2010.
Prescribing information: Alburex® 20

Name: Alburex® 20, 200 g/L, solution for infusion. Qualitative and quantitative composition: Alburex® 20 is a solution containing 200 g/L of total human plasma protein of which at least 96% is human albumin. Alburex® 20 is hyperoncotic to normal plasma. Pharmaceutical form: Solution for infusion. Therapeutic indications: Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated and use of a colloid is appropriate. The choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient, based on official recommendations. Contraindications: Hypersensitivity to albumin preparations or to any of the excipients. Special warnings and precautions for use: Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the infusion. In case of shock, standard medical treatment for shock should be implemented. Albumin should be used with caution in conditions where hypervolaemia and its consequences or haemodilution could represent a special risk for the patient. Examples of such conditions are: decompensated cardiac insufficiency, hypertension, oesophageal varices, pulmonary oedema, haemorrhagic diathesis, severe anaemia, renal and post-renal anuria. The colloid-osmotic effect of human albumin 200 g/L is approximately four times that of blood plasma. Therefore, when concentrated albumin is administered, care must be taken to assure adequate hydration of the patient. Patients should be monitored carefully to guard against circulatory overload and hyperhydration. Albumin solutions must not be diluted with water for injections as this may cause haemolysis in recipients. Hypervolaemia may occur if the dosage and infusion rate are not adjusted to the patient’s circulatory situation. At the first clinical signs of cardiovascular overload (headache, dyspnoea, jugular vein congestion), or increased blood pressure, raised venous pressure and pulmonary oedema, the infusion is to be stopped immediately and the patient’s haemodynamic parameters carefully monitored. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation / removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. There are no reports of proven virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes. It is strongly recommended that every time that Alburex® 20 is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product. Pregnancy and lactation: The safety of Alburex® 20 for use in human pregnancy has not been established in controlled clinical trials. However, clinical experience with albumin suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected. Undesirable effects: Mild reactions such as flush, urticaria, fever and nausea occur rarely. These reactions normally disappear rapidly when the infusion rate is slowed down or the infusion is stopped. Very rarely, severe reactions such as shock may occur. In these cases, the infusion should be stopped immediately and an appropriate treatment should be initiated. Manufacturer: CSL Behring AG, Wankdorfstrasse 10, 3000 Bern 22. Date of revision of the text: November 2009.