Hydroxyethyl starch (HES) for volume replacement:

Overview and safety concerns from two recent large scale RCTs

January 2013
Overview

Background to HES

HES: safety concerns
• Role of molecular weight and molar substitution
• Third-generation HES: recent results from two large RCTs – 6S and CHEST

Albumin: safety and efficacy

Summary and conclusions
Background to HES
# Introduction to plasma volume expanders

Colloids
- Large molecules
- Artificial:
  - HES
  - gelatins
  - dextrans
- Natural:
  - albumin

Crystalloids
- Small electrolytes in water
- Saline
- Ringer’s lactate,
  Ringer’s acetate

Colloids are more efficient volume expanders than crystalloids
→ faster stabilisation of haemodynamic parameters
→ greater linear increase in cardiac output, filling and stroke work
→ 20% albumin is able to recruit excess interstitial fluid

HES composition

- Synthesised from partial hydrolysis of starch from potato or waxy maize\(^1\)

- Hydroxyl (-OH) groups of glucose units substituted with hydroxyethyl groups at carbon positions C2, C3 and C6\(^1\)
  - reduces *in vivo* degradation by amylase

- Solutions polydisperse\(^3\)
  - range of molecular weights
  - extent/pattern of substitution

HES nomenclature

• Type of HES solution denoted by series of numbers, for example:

6% HES 130/0.4

- Concentration of HES
- Mean molecular weight
- Molar substitution
HES classification and indication

- **Concentration**
  - Iso-oncotic: 6% HES 130/0.4 replaces 100% of lost volume.

- **Mean MW**
  - Influences rate of degradation and PK parameters. However, reducing MW has no beneficial effect on tissue uptake.

- **MS**
  - Average no. of hydroxyethyl groups per glucose unit
  - Influences water solubility and degradation by amylase. However, reducing MS has no beneficial effect on tissue uptake.

- **C2:C6 ratio**
  - Ratio of hydroxyethylation at position C2 to hydroxyethylation at position C6
  - Determines the susceptibility to breakdown by amylase as C2-hydroxyethylation is most resistant to amylase.

- **Solvent**
  - For example saline

- **Indication**
  - Treatment of hypovolaemia when plasma volume expansion is needed

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MS, molar substitution; MW, molecular weight; PK, pharmacokinetic

History of HES (1)

Development of HES solutions

First generation
- High MW and MS (e.g., HES 450/0.7)
- ‘Hetastarch’

Second generation
- Lower MW and MS (e.g., HES 200/0.5, HES 200/0.62)
- ‘Pentastarch’/‘hexastarch’

Third generation
- Lower MW and MS (e.g., HES 130/0.4)
- ‘Tetrastarch’

Complications

Bleeding complications, pruritus

Bleeding complications, pruritus, AKI, mortality

Bleeding complications, pruritus, RRT, liver failure, mortality

AKI, acute kidney injury; MS, molar substitution; MW, molecular weight; RRT, renal replacement therapy

History of HES (2)

- Currently available HES solutions approved on ‘old authorisations’ rather than Phase III efficacy and safety studies\(^1\)

- Newer HES solutions approval based on non-inferiority results shown by small bridging studies, as stated by the German Regulatory Agency BfArM approval process for HES preparations:\(^1\)

…”all recent HES authorisations are indeed based on references to old authorisations, with the old data having been linked to the more recent products by smaller pharmacokinetics, pharmacodynamics and bioequivalence bridging studies as well as by smaller efficacy and safety studies…”

\(^1\) BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
1. Reinhart et al. *Intens Care Med* 2012; 38: 368–383 (Electronic Supplementary Materials A)
HES: safety concerns

Role of molecular weight and molar substitution
First-generation HES associated with adverse effects

Reported since the late 1960s:
- Coagulation defects\(^1,2\)
  - decreased FVIII and VWF
  - bleeding complications
- Anaphylactoid reactions\(^3\)
- Pruritus\(^4\)
- Liver complications\(^5\)
  - ascites
- Renal impairment\(^6\)

Initial strategies to minimise complications:
1. Lower dose to 20 mL/kg per day
2. Develop lower MW/MS solutions

FVIII, factor VIII; MS, molar substitution; MW, molecular weight; VWF, von Willebrand factor
VISEP study: methods and comments

**Design**
Multicentre, randomised, two-by-two factorial, open trial

**Aim**
Safety and efficacy:
- Intensive (n=247) vs conventional (n=290) insulin therapy
- 10% HES 200/0.5 (n=262) vs Ringer’s lactate (n=275)

Max HES dose (20 mL/kg/day) exceeded in 100 out of 262 patients in HES group
- Subgroup analysis looked at the safety implications of this dose escalation

NB: Study was halted prematurely for safety reasons
VISEP, Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis
VISEP results: higher HES 200/0.5 dose increases 90-day mortality compared with lower HES 200/0.5 dose*

Figure reproduced with permission from Brunkhorst et al. N Engl J Med 2008; 358: 125–139

NB: Study was halted prematurely for safety reasons. *Based on post hoc multivariate analysis
VISEP, Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis
VISEP results: cumulative HES 200/0.5 increases RRT requirements and 90-day mortality compared with Ringer’s lactate

Renal replacement therapy

Death at 90 days


NB: Study was halted prematurely for safety reasons
RRT, renal replacement therapy; VISEP, Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis
VISEP: concerns and conclusions

• Hypotheses made to rationalise findings of VISEP, such as the fact that 10% HES is hyperoncotic\(^1\) and that excessive crystalloid/colloid volume was used,\(^1,5\) as well as concerns regarding the patient population\(^1,2,4\) and data discrepancies\(^3\)

• Despite these hypotheses, results from this large scale, multicentre, randomised, open trial contributed to growing body of evidence against second generation HES:\(^6–9\)
  – Post-operative bleeding complications,\(^1\) anaphylactoid reactions and pruritus,\(^2\) increased ARF incidence,\(^3\) increased AKI and mortality with hyperoncotic HES 200/0.5\(^4\)

ARF, acute renal failure; AKI, acute kidney injury; VISEP, Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis
Development of third-generation HES

1st and 2nd generation HES cause adverse effects

Even lower MW and MS HES developed to improve safety and pharmacological parameters

→ 3rd generation tetrastarches (HES 130/0.4 and 130/0.42)

Aims of development:

1. Promote HES degradation and accelerate plasma clearance
2. Minimise plasma and tissue retention (HES in plasma and tissues may increase risk of clinical complications)

Note: dose increased with 3rd generation HES to 50 mL/kg

However, hypothesis that lower MW and MS improve safety by decreasing postoperative bleeding and tissue uptake is not supported by recent studies:


MS, molecular substitution; MW, molecular weight
Study of comparative safety of colloids

Systematic review on comparative safety of colloids (update of clinical studies conducted since 2002): 69 studies in critically ill patients

Findings

• Albumin safety profile more favourable than HES
• Increased prominence of HES nephrotoxicity as a safety issue since 2002
• Safety differences between various HES solutions not supported by available evidence

→ lowering HES MW and MS does not appear to improve safety

MS, molecular substitution; MW, molecular weight
HES in CPB: worse bleeding outcomes than albumin (meta-analysis of 18 RCT)\(^1\)

Adverse effects of HES on bleeding outcomes not mitigated by lower MW and MS

- Other studies have shown that HES 130/0.4 leads to formation of a smaller and weaker clot\(^2\)

CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; MS, molar substitution; MW, molecular weight; RBC, red blood cells; RCT, randomised controlled trial

HES administration interferes with coagulation parameters measurement

Fibrinogen measurements commonly required in critically ill patients receiving fluid replacement\(^1\)
- Indicative of risk of thromboembolic event
- Involved in controlling perioperative bleeding

In addition to increasing bleeding,\(^2\) 30% and 50% plasma dilution with HES 130/0.4 leads to significant overestimation of fibrinogen levels \textit{in vitro}\(^1\)

HES: tissue uptake

Tissue uptake is one of HES clearance mechanisms and has been linked to increased risk of clinical complications.\textsuperscript{1–4}


Proximal renal tubular cells\textsuperscript{5}  
Hepatocytes\textsuperscript{6}  
Vascular endothelial cells\textsuperscript{7}
Lower MW and MS actually increased tissue uptake of HES

MW, molecular weight; MS, molecular substitution

*24-hour cumulative urinary excretion; **plasma persistence 24 hours after HES infusion; †tissue uptake at 24 hours

HES: safety concerns

Third-generation HES: recent safety results from two large RCTs – 6S and CHEST
Safety of third-generation HES: evaluation in two large high-quality RCTs


6S, Scandinavian Starch for Severe Sepsis/Septic Shock; CHEST, Crystalloid versus Hydroxyethyl Starch Trial; ICU, intensive care unit; RCT, randomised controlled trial
# 6S: methods

<table>
<thead>
<tr>
<th><strong>Aim</strong></th>
<th>Evaluate safety of HES 130/0.42 in Ringer’s acetate* vs Ringer’s acetate alone in severe sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>Multicentre, parallel group, blinded, randomised</td>
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</tbody>
</table>
| **Comparison** | 6% HES 130/0.42 (n=398)  
Ringer’s acetate (n=400)  
Maximum daily dose: 33 mL/kg ideal body-weight/day† |
| **Patients** | ≥18 years  
Severe sepsis within previous 24 hours  
Required fluid resuscitation in the ICU |
| **Primary endpoint** | Death or end-stage kidney failure (dependence on dialysis), 90 days post-randomisation |
| **Secondary endpoints††** | Development of AKI in the ICU within 90 days post-randomisation (RRT or ↑ in renal SOFA score from ≤2 at randomisation to ≥3)  
Doubling of plasma creatinine level in the ICU post-randomisation |

*Title of paper states 130/0.4, but the HES studied was 130/0.42; †Lower than maximum daily dose of HES recommended by the manufacturer (50 mL/kg); ††A number of other endpoints were pre-specified

AKI, acute kidney injury; ICU, intensive care unit; RRT, renal replacement therapy; SOFA, sepsis-related organ failure assessment

6S: increased mortality after HES infusion versus control

Low dose HES 130/0.42 (max. daily dose 33 mL/kg) increased odds of mortality by 17% vs Ringer’s acetate in patients with severe sepsis*

*Multivariate analysis adjusting for mortality or AKI risk factors at baseline did not alter the result.
CI, confidence interval; RR, relative risk
6S: HES 130/0.42 increases risk of RRT versus control

RR 1.35
(95% CI 1.01, 1.80)

p=0.04

35%
(RR)

HES 130/0.42 increased risk of RRT by 35% vs Ringer's acetate*

*Multivariate analysis adjusting for mortality or AKI risk factors at baseline did not alter the result

CI, confidence interval; RR, relative risk; RRT, renal replacement therapy

6S: more patients receiving HES 130/0.42 required blood product transfusion than controls*

RR 1.20
(95% CI 1.07, 1.36)

p=0.002

20%
(RR)

HES 130/0.42 increased likelihood of blood product transfusions by 20% vs Ringer’s acetate*

*Includes packed red blood cells, fresh-frozen plasma and platelets
CI, confidence interval; RR, relative risk
6S: summary and conclusions

- Comparison of HES 130/0.42 and Ringer’s acetate in patients with severe sepsis
- Patients required fluid resuscitation in the ICU
- HES 130/0.42 significantly increased risk of mortality and RRT, and incidence of blood product transfusions, vs Ringer’s acetate
- Study adds to the growing body of evidence showing the adverse renal effects of HES

ICU, intensive care unit; RRT, renal replacement therapy
# CHEST: methods

<table>
<thead>
<tr>
<th>Aim</th>
<th>• Evaluate safety of HES 130/0.4 vs saline in ICU patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>• Multicentre, parallel group, double-blinded, randomised</td>
</tr>
<tr>
<td>Comparison</td>
<td>• 6% HES 130/0.4* in 0.9% saline (n=3384)</td>
</tr>
<tr>
<td></td>
<td>• 0.9% saline (n=3358)</td>
</tr>
<tr>
<td></td>
<td>• Maximum daily dose: 50 mL/kg of body-weight/day</td>
</tr>
<tr>
<td>Patients</td>
<td>• ≥18 years</td>
</tr>
<tr>
<td></td>
<td>• Required fluid resuscitation in the ICU</td>
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<tr>
<td>Primary endpoint</td>
<td>• All cause mortality 90 days post-randomisation</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td>• Development of AKI</td>
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<tr>
<td></td>
<td>• Use of RRT</td>
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<tr>
<td></td>
<td>• New organ failure for cardiovascular, respiratory, coagulation and liver system not present at baseline (SOFA score ≥3)</td>
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</tbody>
</table>

*Mean degree of HES substitution was 0.44
AKI, acute kidney injury; ICU, intensive care unit; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment
CHEST: significant proportion of patients representative of general surgery population

7000 patients enrolled

2829 (40%) elective/emergency surgery patients

CHEST: trend towards increased 90-day mortality with HES 130/0.4 versus saline

Rate of death was lower than expected due to patient exclusions (17% 90-day mortality in control group)

- However, a non-statistically significant increase in mortality at day 90 was observed with HES 130/0.4 compared with saline

CI, confidence interval; RR, relative risk
Subgroup mortality in CHEST: critical analysis of results

- No significant difference in mortality in all predefined subgroups of patients in CHEST; no difference in SAEs between patients receiving HES 130/0.4 or saline\(^1\)
  - e.g., \(p=0.78\) for patients with sepsis – \(p=0.31\) for patients with TBI – \(p=0.98\) for SAEs

  **However**

- Endpoint analysed in patients with sepsis of any severity, rather than severe sepsis as in other trials (SAFE, 6S, VISEP)\(^2\)–\(^4\)
  - comparatively lower risk of death in CHEST sepsis subgroup as indicated by control group
    - 90-day mortality of 24% (vs 43% in 6S severe sepsis patients)

- Low numbers of patients with TBI enrolled (58 total patients) and low number of SAEs (4 in total) make comparisons meaningless
Subgroup mortality in CHEST: results in context

Recent meta-analysis on effect of HES 130/0.4 on mortality,\(^1\) recently updated with 6S and CHEST results, shows that HES 130/0.4-0.42 significantly increases mortality (RR=1.10; 95% CI 1.02, 1.19; \(p=0.018\))^2

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6S, Scandinavian Starch for Severe Sepsis/Septic Shock; CHEST, Crystalloid versus Hydroxyethyl Starch Trial.
CHEST: HES 130/0.4 increases incidence of RRT by 21% compared with saline

RR 1.21 (95% CI 1.00, 1.45)  
p=0.04

HES 130/0.4 significantly increased risk of RRT vs saline

HES 130/0.4 also significantly increased plasma creatinine levels (p=0.004) and significantly decreased urine output (p=0.003) vs saline*

*Post hoc analysis, during the first 7 days  
CI, confidence interval; RR, relative risk; RRT, renal replacement therapy  
CHEST: implications of increased RRT incidence in patients receiving HES 130/0.4 rather than saline

RRT incidence was 7.0% in the HES 130/0.4 group versus 5.0% in the saline group\(^1\)

→ NNH=83 for treatment with HES 130/0.4 to cause one case of kidney failure requiring RRT

With HES 130/0.4 having been used to treat close to 30 million patients worldwide,\(^2\) this treatment may have led to approximately 360,000 RRTs

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NNH, number-needed-to-harm; RRT, renal replacement therapy
Renal outcomes in CHEST: critique of clinical endpoints

- RIFLE scoring system also used to assess kidney failure in CHEST:
  - Composite endpoint of creatinine levels + urine output
    - Risk and injury scores significantly higher in the saline group versus the HES 130/0.4 group. No significant differences in failure score observed

  However

- Separate analysis of creatinine and urine output endpoints:
  - When creatinine levels were analysed separately, all 3 scores for risk, injury and failure were significantly higher in the HES 130/0.4 group compared with the saline group, indicative of more serious kidney injury

- Patient-important outcome (versus surrogate markers):
  - Administration of HES 130/0.4 resulted in a 21% increase in the incidence of RRT compared with saline

CHEST, Crystalloid versus Hydroxyethyl Starch Trial; RIFLE, Risk Injury Failure Loss and End stage; RRT, renal replacement therapy
CHEST: HES 130/0.4 increases incidence of liver failure by 56% compared with saline

HES 130/0.4 significantly increased risk of liver failure vs saline

Liver-related adverse events observed with HES solutions have been linked to lysosomal storage in Kupffer cells and hepatocytes

CI, confidence interval; RR, relative risk

CHEST: HES 130/0.4 increases incidence of adverse events, in particular pruritus, versus saline

HES 130/0.4 significantly increased risk of treatment-related adverse events vs saline (p<0.001), in particular pruritus

CHEST: HES 130/0.4 increases use of blood products versus saline

During the first 4 days of the study, patients randomised to HES 130/0.4 received significantly less study fluid and non-study fluid than the saline group and significantly more blood products than the saline group. Note: mean daily average of HES 130/0.4 administered was lower than maximum daily dose allowed (50 mL/kg)

6S & CHEST: adverse events observed despite cumulative HES dose < max. daily dose*

*Maximum daily dose allowed as per manufacturer’s recommendations was 50 mL/kg
CHEST: summary and conclusions (1)

- Comparison of HES 130/0.4 and 0.9% saline for fluid resuscitation in 7000 ICU patients
- Results applicable to general surgery population as significant proportion of elective/emergency surgery patients included (40%)
- Administered HES dose lower than allowed maximum dose of 50 mL/kg/day (daily average 526±425 mL)
- Differences in mortality observed at day 90 were not significant
  - however, observed rate of death was lower than predicted
  - point estimate for increased relative risk of death consistent with 6S study results

6S, Scandinavian Starch for Severe Sepsis/Septic Shock; ICU, intensive care unit
CHEST: summary and conclusions (2)

- HES 130/0.4 infusion increased incidence of RRT by 21% compared with saline

- HES 130/0.4 administration also significantly increased incidence of blood product transfusion, risk of liver failure and treatment-related AEs, such as pruritus
  - results consistent with findings from 6S study, despite different patient population

- As with 6S study, CHEST results add to growing body of evidence showing adverse effects associated with administration of HES

6S, Scandinavian Starch for Severe Sepsis/Septic Shock; AEs, adverse events; RRT, renal replacement therapy
6S and CHEST: quality of the evidence*

• High level of evidence\(^1\)
  – multicentre, blinded, randomised controlled trials
  – level 1 (USDHHS)

• Sound methodology
  – large patient populations\(^2,3\)
  – low risk of bias\(^2,3\)
  – pragmatic design\(^4\)
    • applicable to routine clinical practice
    • help policy makers and practitioners make the best use of limited resources

*See ‘Assessing the quality of data: a brief guide’ slide deck for further guidance on assessing the quality of data
USDHHS, US Department of Health and Human Services
Evidence for safety of HES?

Studies cited as evidence for safety of HES are generally inappropriately designed to assess this endpoint\(^1\)

There have also been reports of incomplete disclosure of trial data\(^2,3\)

Safety endpoints reported in the CRYSTMAS trial publication\(^2\)
- ARF incidence
- RIFLE and AKIN data
- Mortality rate
- Coagulation complications
- Pruritus incidence

Safety endpoints not reported in the CRYSTMAS trial publication (ONLY reported in Voluven\(^\circledR\) package insert\(^4\))
- No. of patients undergoing RRT
- Duration of RRT
- Kaplan-Meier time to RRT

In their reply to criticisms, the study authors state that the FDA requested post hoc analyses on 7 May 2012, however the date on the Voluven\(^\circledR\) insert is 2 May 2012\(^3\)

AKIN, Acute Kidney Injury Network; ARF, acute renal failure; CRYSTMAS, Effects of Voluven on Hemodynamics and Tolerability of Enteral Nutrition in Patients With Severe Sepsis; FDA, Food and Drug Administration; RRT, renal replacement therapy; RIFLE, Risk Injury Failure Loss and End stage criteria for kidney disease

HES safety concerns: FDA workshop

FDA convened a dedicated workshop to assess the risks and benefits of HES solutions (6–7 September 2012, Bethesda, USA)

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

Majority consensus: HES solutions are harmful as a class

FDA, Food and Drug Administration
Following 6S and CHEST results, the EMA has initiated a review of HES solutions use in critically ill patients.

‘The European Medicines Agency will evaluate the benefit–risk balance of HES-containing solutions for infusion and issue an opinion on whether their marketing authorisations should be maintained, varied, suspended or withdrawn across the EU.’
Albumin: safety and efficacy
### SAFE: methods

<table>
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<th>Evaluate safety of albumin vs saline in ICU patients</th>
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<tbody>
<tr>
<td>Study design</td>
<td>Multicentre, parallel group, double-blinded, randomised</td>
</tr>
</tbody>
</table>
| Comparison | 4% albumin (n=3497)  
0.9% saline (n=3500) |
| Patients | ≥18 years  
Required fluid resuscitation in the ICU |
| Primary endpoint | All cause mortality 28 days post-randomisation |
| Secondary endpoints | Survival time  
Incidence of new organ failure for cardiovascular, respiratory, renal, haematologic and liver system not present at baseline (SOFA score ≥3)  
Duration of mechanical ventilation, RRT, ICU and hospital stays |

ICU, intensive care unit; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment

No significant differences in mortality at day 28 observed with 4% albumin compared with saline
SAFE: safety of albumin vs saline

Similar RRT requirements for patients receiving 4% albumin or saline (duration of RRT 0.48±2.28 days and 0.39±2.0 days, respectively; p=0.41)

Number of patients developing single or multiple new organ failure* similar in the two groups (p=0.85†)

Survival time and length of ICU or hospital stay comparable between albumin and saline groups

ICU, intensive care unit; RRT, renal replacement therapy
*Data were available for 2649 patients in the albumin group and 2673 patients in the saline group. New organ failure was defined as a Sequential Organ-Failure Assessment score of 0, 1, or 2 in any individual organ system at baseline, followed by an increase in the score to 3 or 4 in the same system.
†The p value pertains to the comparison between the albumin and saline groups in the numbers of patients who had no new organ failure or new failure of one, two, three, four, or five organs
SAFE: sepsis subgroup

Prospectively defined subgroup of ICU patients from the SAFE study with severe sepsis at the time of randomisation

Severe sepsis at baseline defined as follows:
- Presence of a defined focus of infection
- ≥2 SIRS criteria
- Infection-related organ dysfunction (SOFA score)

Multivariate analysis to assess mortality at day 28 by treatment group, after adjustment for baseline characteristics
SAFE: albumin reduces the risk of mortality compared with saline in patients with severe sepsis

**Total severe sepsis patient group (N=1218)**

- **OR 0.87** (95% CI 0.74, 1.02)
  - p=0.09
- **OR 0.71** (95% CI 0.52, 0.97)
  - p=0.03

**Multivariate analysis group (N=919)**

- **OR 0.87** (95% CI 0.74, 1.02)
  - p=0.09
- **OR 0.71** (95% CI 0.52, 0.97)
  - p=0.03

CI, confidence interval; OR, odds ratio

*Multivariate analysis after adjustment for baseline characteristics, in patients with complete baseline data

Further evidence for the safety of albumin use in patients with sepsis: meta-analysis by Delaney et al (2011)

Estimate pooled OR for mortality for patients resuscitated with albumin, compared with other fluids: 0.82 (95% CI 0.67, 1.0; p=0.047)

These results remained similar when the SAFE study was omitted from the analysis (estimate pooled OR 0.84; 95% CI 0.59, 1.18; p=0.31)

When studies by Boldt et al were excluded, the odds ratio estimate became 0.76 (95% CI 0.62, 0.95; p=0.015)

Resuscitation with albumin in patients with sepsis is associated with a lower risk of mortality compared with other resuscitation fluids

CI, confidence interval; OR, odds ratio
Outlook: albumin in sepsis trials

**EARSS**\(^1\) (NCT00327704)
- Multicentre RCT
- 20% albumin vs saline in septic shock
- 800 patients in France
- Primary outcomes: 28-day mortality

**ALBIOS**\(^3\) (NCT00707122)
- Multicentre RCT
- 20% albumin vs crystalloid in sepsis or septic shock
- 1800 patients in Italy
- Primary outcomes: mortality at 28 and 90 days

Publication expected 2013–2014
Preliminary results: trend towards reduced mortality with albumin vs saline; no evidence of renal dysfunction with albumin\(^2\)

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RCT, randomised controlled trial
Liver disease: albumin

- Intravenous fluids required in several liver disease indications
- Albumin has demonstrated beneficial effects as an adjunctive treatment in a number of these:
  - prevention of PPCD\(^1\)
  - prevention of the development of renal impairment following SBP\(^2\)
  - treatment of type 1 HRS\(^3\)

Use of albumin in the management of liver disease is advocated in European and American guidelines\(^4,5\)

HRS, hepatorenal syndrome; PPCD, post-paracentesis circulatory dysfunction; SBP, spontaneous bacterial peritonitis
Liver disease: HES

Evidence against HES, despite limited data; no beneficial effects – may even worsen outcomes:

- Higher incidence of PPCD observed in patients receiving HES 200/0.5 following LVP compared with albumin¹
- No evidence of beneficial effect of HES 200/0.5 on haemodynamic parameters in patients with SBP vs albumin²
- Worsening liver disease in patients who received repeated infusions of HES (MW=200 kDa)³
  - associated with tissue uptake of HES³
  - meta-analysis revealed increased tissue uptake of HES 130/0.4 compared with HES 200/0.5⁴

LVP, large volume paracentesis; MW, molecular weight; PPCD, post-paracentesis circulatory dysfunction; SBP, spontaneous bacterial peritonitis
Summary and conclusions
Summary

HES 130/0.4 was developed to mitigate the adverse events seen with earlier, higher MW, HES solutions. However...

Lowering MW and MS actually increased the uptake of HES into tissues

Adverse effects of HES on bleeding and renal function not mitigated by lower MW and MS

Both findings confirmed in two recent multicentre, randomised, double-blind, controlled studies

FDA safety workshop concluded that HES solutions are harmful as a class

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FDA, Food and Drug Administration; MS, molecular substitution; MW, molecular weight
Class effects of HES solutions

HES-related adverse events appear to be a class effect and remain evident with the third generation HES:

- Kidney failure
- Liver failure
- Bleeding
- Anaphylactoid reactions
- Pruritus

Absence of clinical benefit of new generation HES in two large RCTs\(^1,2\)

This suggests that the future scope of HES usage is likely to be restricted

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RCT, randomised controlled trial
Comparison with albumin:

Albumin:

- Has a better safety profile than HES\(^1\)
- Reduces mortality in patients with sepsis\(^2\)
- Has demonstrated renal safety\(^3\)
- Is beneficial in a number of liver disease indications\(^4–6\)
- Is recommended for use in severe sepsis/septic shock patients requiring large amounts of crystalloids\(^7\)