HYDROXYETHYL STARCHES (HES) IN CRITICALLY ILL OR SEPTIC PATIENTS-UPDATE

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VHA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary decision. Documents will be placed in the Archive section when the information is deemed to be no longer current.

INTRODUCTION

In September 2011, the VHA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives reviewed the monograph for the newest hydroxyethyl starch (6% 130/0.4) Voluven®) to become available for prophylaxis and management of hypovolemia.[1] This particular hydroxyethyl starch (HES) is frequently referred to as a third-generation or newer generation starch developed with the goal of reducing known adverse events that may occur with the older HES solutions including severe, delayed-onset pruritis, impaired coagulation and renal dysfunction. Starches with a higher molecular weight, higher degree of molar substitution and higher C2/C6 ratio have a greater persistence within the intravascular space but are also believed to be associated with a greater risk for tissue accumulation and adverse events. Hydroxyethyl starch 6% 130/0.4 has a lower molecular weight, a lower degree of molar substitution but a higher C2/C6 ratio.

At the time the hydroxyethyl starch 6% 130/0.4 (Voluven®) monograph was written, evidence was limited comparing the newer generation HES to older generation HES solutions or to crystalloids in critically ill or septic patients. Due to the lack of evidence, it could not be concluded that newer generation HES solutions offered substantive advantages or had substantive disadvantages over other products used for fluid resuscitation in critically ill or septic patients. Because of the lack of data in general, as well as inconsistent data of their effect on renal function, the FDA required the manufacturer to complete a trial in septic patients, with or without renal disease. Two trials were already underway 1) "6S-Scandinavian Starch for Severe Sepsis/Septic Shock Trial" comparing HES 130/0.4 to crystalloids in 800 patients with severe sepsis with a primary outcome measure of a composite of mortality and end-stage kidney failure; and 2) "Crystalloid versus Hydroxyethyl Starch Trial (CHEST)" comparing HES 130/0.4 to crystalloids (saline) in 7,000 critically ill patients in the intensive care unit. The primary outcome measure was death from all causes at 90 days.

Since the Voluven® monograph was completed (September 2011), 6S and CHEST have been published. In addition, several meta-analyses, systematic reviews and consensus statements in critically ill or septic patients have been recently published or updated after removal of retracted (questionable/fraudulent) studies in which Dr. Joachim Boldt was an investigator *(refer to page 3 of this document for explanation of reason for study retraction).*

The purpose of this update is to examine the existing evidence for the use of HES solutions in critically ill or septic patients and determine if continued use of these colloidal solutions in these patients is justified.

SUMMARY OF THE EVIDENCE/CONCLUSIONS *(Details from 6S and CHEST, systematic reviews, meta-analyses, consensus statement and guidelines are included in Tables 1,2 and 3 in Appendix A)*

<u>6S and CHEST</u>

With regard to mortality, there was one study (6S) in approximately 800 patients with severe sepsis in which a statistically higher risk for mortality was observed with 6% HES 130/0.4 in Ringer's acetate (Tetraspan®) vs. Ringer's acetate. However, there was no difference in mortality reported in the CHEST trial comparing 6% HES 130/0.4 in saline (Voluven®) to saline in 7,000 critically ill patients. In both trials, there was a higher risk for acute kidney injury or use of renal replacement therapy in the HES vs. the crystalloid group. Both authors concluded that HES does not offer benefit over crystalloids in these patient populations and may be associated with a greater risk for harm.

Systematic Reviews/Meta-Analysis

There have been five systematic reviews/meta-analyses that have been recently published. Although they differ in their criteria for trial inclusion (critically ill vs. septic diagnosis), the number of included trials and outcomes examined, all concluded that HES solutions do not offer benefit over crystalloids or other non-HES solutions for fluid resuscitation in critically ill or septic patients and may cause harm (Inconsistent finding of increased mortality, consistent finding of increased need for renal replacement therapy and serious adverse events). Concluding statements from all authors are consistent in that since HES solutions do not offer benefit over crystalloids or other non-HES colloids, are more costly than crystalloids, and may increase harm, their use cannot be justified or their use is not warranted in critically ill or septic patients.

Consensus Statements/Guidelines

Consensus statements or guidelines for fluid resuscitation in these patient populations support the recent data and generally recommend avoidance of HES solutions. However, the ESICM consensus statements "suggest" avoidance of newer starches but these consensus statements were made available prior to the publication of 6S and CHEST.

RECOMMENDATIONS

Recent evidence supports no additional benefit of the HES solutions (including both the newer generation starches such as 6% HES 130/0.4 in saline [Voluven®]) over other resuscitation fluids and a potential for harm in critically ill or septic patients. As a result, these solutions should be avoided in the fluid resuscitation of critically ill or septic patients and crystalloids should be utilized instead. In those patients requiring large amount of crystalloid solutions (>30ml/kg/d), use of albumin can also be considered.

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Explanation for the retraction of multiple studies in which Dr. Joachim Boldt was an investigator:
**(*In October 2010, a study comparing cardiopulmonary bypass pump priming using a high dose of balanced HES (not available in the US) versus albumin was retracted by editors of Anesthesia and Analgesia*[2-3] *The retraction was prompted by an investigation by the Rheinland State Medical Board revealing that there was no IRB approval, informed consent, randomization process or follow-up questionnaire as described in the study.*[4] *The investigation was initiated because several readers who questioned the plausibility of the results contacted the editor with their concerns.*[5-6] *Since that time, at least 88 studies in which Dr. Joachim Boldt was included as an author have been retracted by a number of journals because IRB approval could not be verified.*[7] *Dr. Boldt contributed many of the studies supporting improved safety of modern HES solutions (HES 130/0.4) leading clinicians to question the validity of the literature on the safety and efficacy of 6% HES 130/0.4 solution.*[8]*).*

APPENDIX A.
EVIDENCE TABLES

A medline search was performed using the terms hydroxyethyl starch, HES, Voluven®, colloids, critically ill and sepsis.

The results from individual clinical trials will not be detailed in Table 1 since the vast majority have been included in the meta-analyses or systematic reviews presented in Table 3. However, detailed results from 6S and CHEST are included in Table 1 since both trials were published within the past year; were designed specifically to address the efficacy and safety of newer HES solutions in critically ill or septic patients; and included clear and relevant primary outcomes (death or use of renal replacement therapy). See Table 1 for trial details.

Table 1. Individual Clinical Trials in Critically Ill or Septic Patients (6S and CHEST)

Clinical Trial	Population/Intervention	Outcome Measures	Results	Comments
Perner[9] R, MC, DB N=804 6S Clinical Trial (Denmark, Norway, Finland and Iceland) Funded by grants: Danish Research Council, Rigshospitalet Research Council and the Scandinavian Society of Anesthesiology and Intensive Care Med. B. Braun provided the solutions	Population: Patients with severe sepsis in ICU **Surgery:** Emergency: 29% Elective: 9-12% No difference btwn groups **Source of ICU admit:** ED 24-27% General ward: 44-49% OR or RR: 14-15% Other ICU: 4-5% Other hospital: 8-10% No difference btwn groups **Source of sepsis:** Lungs: 53-57% Abdomen: 33% Urinary tract: 12-14% Soft tissue: 10-12% Other: 8-11% No difference btwn groups **Other:** Median SOFA 7 Shock: 84% AKI: 35-36% Mechan. Vent: 60-61% No difference btwn groups Intervention: 6% HES 130/0.4 in Ringer's acetate (Tetraspan®)* or Ringer's acetate for a maximum of 90 days. Maximum daily dose was 33 ml/kg of IBW If higher doses were needed, Ringer's acetate was used for both groups. Randomization was stratified by: 1) presence or absence of shock, 2) presence or absence of active hematologic cancer and 3) admission to university or non-university hospital	Primary: Composite of death or dependence upon dialysis 90 days after randomization (use of RRT within 86-94 days). The composite outcomes were also analyzed separately. +Two predefined subgroups for analysis: Presence of shock or AKI at baseline. Secondary: Death at 28 days, death at last follow-up, severe bleeding (requiring ≥3 units PRBC within 24 hrs), severe allergic rxn, SOFA score at day 5, development of acute kidney injury (renal SOFA of 3 or > when score was 2 or < when randomized), doubling of Scr, acidosis (arterial pH <7.35), % days alive without RRT, days alive without mechanical ventilation, and days alive out of hospital 90 days after randomization.	798 patients completed the trial and were analyzed. N=398 HES N=400 RA Note: 4 patients excluded, 2 no consent obtained, two met exclusion criteria and never received fluid. +Both groups received a median of 3000 mL of fluid (p=0.20), 44 ml of IBW for HES and 47 ml of IBW for RA (p=0.18). +39 HES and 38 RA received open-label colloids +28 HES and 41 RA received > protocol-specific max daily study fluid; only 2 pts received >50 mL of HES. 50 ml/kg/d is the maximum recommended daily dose. Primary: Composite: N=202 (51%) HES N=173 (43%) RA RR=1.17, 1.01-1.36, p=0.03) Death: N=201 (51%) HES vs. n=172 (43%) RA, RR 1.17, 1.01-1.36, p=0.03 Dialysis dependent: N=1 (0.25%) HES, N=1 (0.25%) RA, p=1 NS +The predefined subgroups of presence of shock or AKI at randomization showed no heterogeneity. Secondary: +Use of RRT: N=87 (22%) HES vs. N=65 (16%) RA, RR=1.35, 1.01-1.80, p=0.04 +Number of pts alive and without RRT or alive and out of the hospital was also	The difference in the primary composite endpoint was driven by an increased risk of death in the HES group since only 1 patient in each group was dialysis dependent. Absolute risk of death was increased by 8% in the HES group for a NNH of 13. Author comments: +The increased risk of death in 6S is similar to the number of deaths observed in the VISEP trial[10] (n=537), which utilized a different HES solution (200/0.05) in patients with severe sepsis. +In VISEP, a planned interim analysis was done after enrolling 600 pts. There was a trend towards a higher 90-day mortality and a statistically significant increase in renal failure in the HES vs. RL groups so the study was suspended. Final publication includes results for 537 patients. +In 6S and VISEP, survival curves separate around day 20, late deaths by HES? +Both trials observed a higher use of RRT and PRBCs vs. crystalloids Author conclusions: Use of HES vs. RA in patients with severe sepsis was associated with an

			different favoring RA (p=0.048 for both measures) + More HES pts received blood products than RA (RR=1.2, 1.07-1.36, p=0.002) including PRBCs +Death at 28 days, severe bleeding, severe allergic rxn, SOFA at day 5, doubling of Scr and other secondary measures were not difference between groups but numbers favored RA in nearly all measures.	increased risk of death at 90 days and a greater likelihood of receiving RRT.
Myburgh[11] R, MC, DB N=7,000 CHEST (Australia and New Zealand) Funded by: National Health and Medical Research Council of Australia, Ministry of Health, New South Wales Government and Fresenius Kabi	Population: Adult patients who were admitted to the ICU and upon the judgment of the treating clinician required fluid resuscitation (bolus of fluid over and above that needed for maintenance or replacement. Intervention: 6% HES 130/0.4 in 0.9% saline (Voluven®) or 0.9% saline in the ICU until discharge, death or 90 days after randomization. HES was administered up to a maximum of 50 ml/kg/d followed by open-label saline for the remainder of the day if max dose met. Fluid therapy was stopped if RRT was utilized.	Primary: All cause mortality 90 days after randomization +6 predefined subgroups were analyzed including presence or absence of AKI, sepsis, trauma with or without brain injury, APACHE II score <25 vs. ≥25 and receipt or non-receipt of HES prior to randomization. Secondary: Incidence of AKI within 90 days follow-up (using RIFLE criteria, those with >4 weeks of or complete loss of kidney function or end-stage kidney disease), use of RRT, new organ failure (CV, respiratory, coagulation and liver systems-defined by a SOFA score of 3 or>), during of mechanical ventilation and RRT and cause-specific mortality. Tertiary: Duration of ICU stay, hospital admission and rate of death in the ICU or hospital.	7,000 pts enrolled and randomized: HES 130/0.4 in saline N=3,500 Saline N=3,500 Primary: HES: 597 (18%) vs. Saline: 566 (17%), (RR 1.06, 0.96-1.18, p=0.26) For the 6 predefined subgroups, there was no heterogeneity of treatment on 90-day mortality. Secondary: +RRT was used in 235 (7%) of HES vs. 196 (5.8%) of saline recipients, (RR 1.21, 1-1.45, p=0.04) ARR 1.2%, NNH 83 +RIFLE-R (risk for renal dysfunction): HES 1788 (54%) vs. 1912 (57.3%) saline, (RR 0.94, 0.09-0.98, p=0.007) +RIFLE-I (risk for renal injury): HES 1130 (34.6%) vs. saline 1253 (38%), (RR 0.91, 0.85-0.97, p=0.005), +RIFLE-F (risk for renal failure): HES 336 (10.6%) vs. saline 301 (9.2%), (RR 1.12, 0.97-1.30, p=0.12) +New CV organ failure was higher in saline vs. HES (p=0.03) and new liver organ failure was higher in HES vs. saline (p=0.03) + No other differences in secondary endpoints except higher rate of ADEs in the HES vs. saline group 180 (5.3%) vs. 95 (2.8%), respectively (p<0.001), primarily pruritis and rash.	Author comments: A limitation of the study was in the lower than expected death rate that could have been due to exclusion of patients with intracranial hemorrhage, those who were unlikely to survive, and those patients who had elective surgery. Furthermore patients were recruited after they were already in the ICU and the need arose for fluid replacement. It is likely that fluid resuscitation may be less for these patients versus those coming from the ED or the OR. The authors felt that the patients in CHEST were at a lower risk for death than those enrolled in 6S and VISEP. Despite this, the authors considered the point estimate for increased relative death and AKI in this trial to be consistent with other studies. RIFLE is a composite measure that considers both Scr and urine output. HES had opposing effects on the two variables. Urine output increased in patients with less severe AKI, which could be due to increased intravascular volume and a diuretic-type effect. While the Scr levels were consistently higher in the HES vs. saline group supporting more severe AKI. Author Conclusion: No difference in overall 90-

			POST-HOC: +Scr increased and urine output decreased significantly in the HES vs. saline group in the first 7 days. +When Scr and urine-output components of each RIFLE category were analyzed separately, RR for meeting the criteria for risk for renal dysfunction, or renal injury were higher in the HES vs. saline groups.	day mortality was observed between HES and saline but fluid resuscitation with HES resulted in a statistically higher use of RRT (ARR 1.2%, NNH 83) Fluid resuscitation with HES 130/0.4 does not provide any clinical benefit to ICU patients versus use of saline.

ADE=adverse events, APACHE II score=Acute Physiology and Chronic Health Evaluation II score (Scores range from 0-71 with higher scores indicating increased risk of death), ARR=absolute risk reduction, DB=double-blind, ED=emergency department, IBW=ideal body weight, ICU=intensive care unit, MC=multicenter, NNH=number needed to harm, OR=operating room, PRBC=packed red blood cells, R=randomized, RA=Ringer's acetate, RIFLE criteria for acute kidney dysfunction=Risk, Injury, Failure, Loss and End-stage kidney disease, RR=relative risk, RL=Ringer's Lactate, RRT=renal replacement therapy, Scr=serum creatinine, SOFA=sepsis related organ failure assessment (subscores ranging from 0-4 for each of the following: lungs, circulation, liver, kidney and coagulation. Higher scores indicate more severe organ failure), VISEP=Volume Substitution and Insulin Therapy in Severe Sepsis.
*Not available in the US

Table 2. Systematic Reviews and/or Meta-Analyses of Fluid Resuscitation with Hydroxyethyl Starch in Critically Ill or Septic Patients

Systematic Review/ Meta-Analysis	Findings	Comments/Conclusions
Perel[12] Cochrane Review RCTs of colloids vs. crystalloids in critically ill pts requiring volume replacement and reporting mortality. Trials in pregnant women or neonates were excluded. 74 trials eligible, 66 included mortality data. Outcome: Mortality	**Colloids vs. crystalloids:** **1. Albumin or PPF:** 24 trials presented mortality data (n=9920 pts). Pooled RR 1.01, 95% CI 0.93-1.10. When poor-quality trials were excluded, the results did not change. **2. HES:** 21 trials presented mortality data (n=1385 pts). Pooled RR 1.10, 95% CI 0.91-1.32 **3. Modified Gelatin:** 11 trials (n=506 pts). Pooled RR=0.91, 95% CI 0.49-1.72 **4. Dextran:** 9 trials (n=834 pts). Pooled RR 1.24, 95% CI 0.94-1.65. *No change in results for albumin, HES or gelatin vs. crystalloids when trials by Boldt, et al were removed.	1. Data from CHEST and 6S weren't included in the review. 2. Authors of the systematic review focused on trials reporting mortality. Did not analyze other outcomes, including AKI or RRT. 3. Included all trials of HES including older and newer generation starches. 4. a) Authors concluded that no evidence exists to support that fluid resuscitation with colloids reduces death compared to resuscitation with crystalloids in critically ill patients having experienced trauma, burns or surgery. b) Since colloids aren't associated with an improvement in survival and since they are more costly than crystalloids, it is difficult to justify their continued use in these critically ill patients. 5. Review of these trials found no evidence that colloids reduced the risk of dying vs. use of crystalloids.
Zarychanski[13] RCTs of HES vs. other fluids in critically ill pts receiving acute volume resuscitation. Risk of bias was assessed using the risk bias tool and strength of evidence was assessed using GRADE methodology. 38 trials were included. Outcomes: Mortality, AKI and use of RRT	**Mortality Data:** 10,880 pts in the trials reporting mortality data. 1. HES: RR for death 1.07, 95% CI 1-1.14, statistical heterogeneity 0%, AR 1.20%, 95% CI -0.26%-2.66%. Results included trials by Boldt, et al. 2. HES: Excluding trials by Boldt, et al. (n=590 pts) RR for death 1.09, 95% CI 1.02-1.17, statistical heterogeneity 0%, AR 1.51%, 95% CI 0.02%-3%. 3. Statistical heterogeneity between trials conducted by Boldt vs. other investigators was high (59.4%) **Renal Failure:** 8725 pts in the trials reporting data on renal failure. 1. HES: RR 1.27, 95% CI 1.09-1.47, statistical heterogeneity 26%, AR 5.45%, 95% CI 0.44-10.47%. **RRT:** 9258 pts in the trials reporting data on RRT. 1. HES: RR 1.32, 95% CI 1.15-1.5, statistical heterogeneity 0%, AR 3.12%, 95% CI 0.47-5.78%.	1. Majority of trials had unclear or high risk of bias. 2. Data from CHEST and 6S were included. 3. Systematic review and meta-analysis included trials comparing HES to other colloids (albumin, gelatin) or crystalloids. 4. Included trials of HES, including older and newer generation starches. 5. Use of HES in patients requiring acute fluid resuscitation was not associated with a reduction in mortality. In fact, after excluding retracted studies by Boldt, etal., HES was associated with a statistically increased risk of mortality and AKI. 6. Authors conclude that use of HES for acute fluid resuscitation is not warranted due to serious safety concerns.

Gattas[14] RCTs of 6% HES (130/0.4 or 130/0.42) in acutely ill pts vs. other resuscitation fluids. 35 trials enrolling 10,391 pts were included.	**Mortality Data:** 1. Death occurred in 19.8% of HES vs. 18.5% control fluids. HES RR for death: 1.08, 95% CI 1-1.17, statistical heterogeneity 0% **RRT:** 1. Treatment with RRT was used in 8.9% HES vs. 7.2% of control fluids. RR for RRT with HES: 1.25, 95% CI 1.08-1.44, statistical heterogeneity 0%.	1. The three largest trials published in 2012 had the lowest risk of bias and enrolled 77% of participants. (CHEST, 6S and an unpublished trial by Siegemund M. (BaSES trial) 2. Systematic review of modern HES solutions to crystalloids or non-HES colloids (e.g., gelatin, albumin) 3. Data from CHEST and 6S were included. 4. Authors concluded that critically ill patients given fluid resuscitation with HES 6% 130/0.4 or 0.42 are at a higher risk for treatment with RRT vs. other resuscitation fluids (crystalloids, gelatin, albumin). Although the authors do acknowledge limitations to their study, including not contacting authors for unpublished data. However, the findings are consistent with other published reviews.
Patel[15] RCTs of HES 130/0.4 or 0.42 vs. other non-HES resuscitation fluids in patients with severe sepsis Six trials were identified (n=3,033) Outcome: 90-day mortality, others	**90-day Mortality:** RR HES for death vs. crystalloid: 1.13, 95% CI 1.02-1.25, p=0.02. NNH 28.8 (95% CI 14.6-942.5). Publication bias and statistical heterogeneity were not found. **Overall Mortality (secondary outcome):** RR for HES was the same as above but NNH 29.2 (95% CI 14.9-896.7). **RRT (tertiary outcome):** 21.4% HES vs. 13.9% control fluids received RRT: RR for RRT with HES 1.41, 95% CI 1.08-1.84, p=0.01). AKI severity was not found to be different using a creatinine based score. Author comments that one cannot rule out harm or benefit based on this. **28-day Mortality (tertiary outcome):** RR HES vs. other fluids: 1.10, 95% CI 0.93-1.30, p=0.28). (Statistical power was lacking, CHEST did not report 28-day mortality for pre-define sepsis group) **Allogeneic transfusion (tertiary outcome):** 29% HES vs. 21% control fluids (crystalloid). RR in those receiving HES vs. control: 1.21, 95% CI 1.08-1.36, p=0.001). NNH 9.9 **Pruritis:** RR HES 1.81, 95% CI 1.37-2.38, p<0.00001, NNH 56.1.	1. Three trials published in 2012 had low risk of bias. 2. Limited included trials to those with pre-defined group or subgroup of sepsis, reporting of mortality at 90 days and/or 28 days and/or another follow up time point and reporting at least one death. 3. The authors concluded based upon their findings that tetrastarches (HES 130/0.4 or 0.42) should be avoided as part of initial fluid resuscitation in septic patients since alternatives to HES do exist and since HES was associated with harm in their analysis.
Haase[16] RCTs of HES 130/0.38-0.45 vs. crystalloids or albumin in patients with sepsis. Nine trials were identified (3456 pts) Outcomes: Mortality, kidney injury, bleeding and serious ADEs in pts with sepsis.	**Mortality:** HES RR 1.04, 95% CI 0.89-1.22 (8 trials, 3414 pts), Trial sequential analysis was used to widen confidence intervals in case the data are too limited to draw conclusions. Despite this statistical technique, differences were not observed. In the 3 trials with a low risk of bias, RR of mortality with HES: 1.11, 95% CI 1-1.23, p=0.05. A post-hoc subgroup analysis showed that there was a significant increase in mortality for those trials with follow up >28 days (RR 1.11, 95% CI 1.01-1.22, p=0.04, Statistical heterogeneity 0%) Alternatively, a NS decreased in mortality in trials with a follow-up of 28 days or less (RR 0.63, 95% CI 0.35-1.15, p=0.13) **RRT (anytime during observation period):** RR for HES: 1.36, 95% CI 1.08-1.72, p=0.009, statistical heterogeneity 0%. Trial sequential analysis did not change statistically increased risk for RRT with HES. **AKI:** Defined as a two-fold increase in Scr during observation (since this was consistently reported in 4 trials with data on renal changes) RR with HES: 1.18, 95% CI 0.99-1.4, p=0.07) **Bleeding, risk of transfusion and blood loss:** Risk for transfusion with RBCs: RR with HES 1.29, 95% CI 1.13-1.48, p<0.001). Trial sequential analysis did not change finding.	1. Not all included trials reported data on specific outcomes of interest, so specific outcome was generally not from the full 9 trials. So data in the analysis was limited. 2. About 1/3 of the trials was determined to have unclear or high rate of bias. 3. Compared modern HES to crystalloid or albumin in patients with sepsis. 4. Authors commented that even with the use of trial sequential analysis, there was a higher risk for treatment with RRT and need for transfusions in patients received HES vs. crystalloids or albumin. 5. HES wasn't associated with an overall higher risk for all-cause mortality; however, it didn't have a mortality benefit either. 6. From their analysis, the authors conclude that HES 130/0.38-0.45 increases the risk for RRT, transfusion with RBCs and serious ADEs vs. use of crystalloids or albumin in patients with sepsis. "It seems unlikely that HES 130/0.38-0.45 provides overall clinical benefit in sepsis." 7. Authors note in their discussion that HES is frequently used in the surgical setting and may continue despite the safety concerns. They recommend that if use continues in the surgical population, trials are needed to ensure safety of HES in these patients.

	Number of patients having blood loss or bleeding episode did not differ between HES and other fluids. **Serious ADEs:** RR for HES: 1.30, 95% CI 1.02-1.67, p=0.03, statistical heterogeneity 0%. Trial sequential analysis changed 95% CI to 0.93-1.83.	

ADE=adverse events, AKI=acute kidney injury, AR=absolute risk, GRADE=Grades of Recommendation, Assessment, Development and Evaluation, HES=hydroxyethyl starch, NNH=number needed to harm, PPF=plasma protein fraction, RBCs=red blood cells, RCTs=randomized controlled trials, RR=risk ratio, RRT=renal replacement therapy, Scr=serum creatinine

Table 3. Professional Society Guidelines or Consensus Statements for Fluid Resuscitation in Critically Ill or Septic Patients

Consensus Statement/ Guidance	Recommendations
The European Society for Intensive Care Medicine (ESICM): Consensus Statement of the ESICM Task Force on Colloid Volume Therapy in Critically Ill Patients[17]	1. Recommend not using HES with molecular weight ≥ 200 kDa and/or degree of substitution >0.4 in patients with severe sepsis (grade 1B) and not to use in other intensive care patients with risk of acute kidney injury (grade 1C). 2. Suggest not to use HES 6% 130/0.4 or gelatin in these patients. 3. Recommend not to use colloids in patients with head injury and not to provide HES or gelatin to organ donors. 4. Suggest not using hyperoncotic solutions for fluid resuscitation. 5. Recommend that before any new colloid is used in clinical practice, patient-important safety parameters must first be established. *Data from 6S and CHEST not considered. (Submitted for publication January 2012, published February 2012)
Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012[18-19]	1. Recommend crystalloids be used as initial fluid choice in resuscitation of severe sepsis and septic shock (grade 1B) 2. Recommend against the use of HES for fluid resuscitation of severe sepsis and septic shock (grade 1B) 3. Recommend the use of albumin in fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C) *Data from 6S and CHEST were considered. SAFE study showed no difference between 4% albumin and saline in fluid resuscitation outcomes of nearly 7,000 patients in the intensive care unit.[20]