Renal outcomes and mortality following hydroxyethyl starch resuscitation in critically ill patients: A meta-analysis of randomized trials

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Running head: HES and renal outcomes

Keywords: Hydroxyethyl starch, renal failure, sepsis, critical care, meta-analysis

Word Count: 3559

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Trials Included (n= 22)

Conflict of Interest/Competing interest statement:

Lauralyn McIntyre has received unrestricted grant support from Bristol Myers Squibb and

Abbott Laboratories. The remaining authors have no such conflicts of interest to declare.

Abstract

Background: Hydroxyethyl starch (HES) fluids are commonly used for fluid resuscitation in patients admitted to the intensive care unit but there is insufficient evidence from randomized controlled trials about their safety and efficacy.

Purpose: To evaluate the impact of HES solutions on adverse renal outcomes and mortality in critically ill patients requiring acute volume resuscitation.

Data Sources: We searched electronic databases from 1950 to 2008 (MEDLINE, EMBASE, the Cochrane Central Registry of Controlled Trials, and the SCOPUS database). Conference proceedings and grey literature sources were searched from 2002-2007.

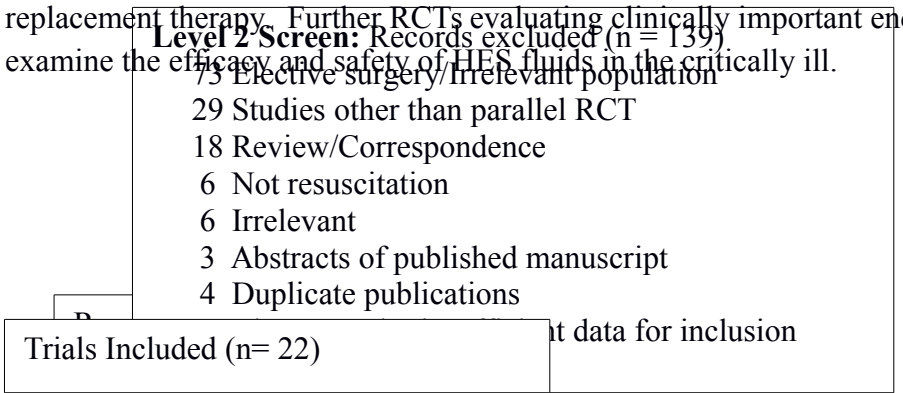
Study Selection: Randomized controlled trials (RCTs) of acute volume resuscitation with HES fluid compared to an alternative resuscitation fluid in the critically ill.

Data extraction: Two reviewers independently assessed trial eligibility, extracted data, and evaluated trial quality.

Data Synthesis: Twenty-two trials (n=1865) were included. Patients receiving HES were more likely to receive renal replacement therapy [odds ratio [OR] 1.90 (95% confidence interval [CI] 1.22-2.96, I^2 9.5%); n=749]. There was no difference in overall mortality [OR 1.07 (95%CI 0.85-1.34); n=1657]. However, in trials including patients with severe sepsis and septic shock, in high quality and multicentre trials, and in trials with adequate allocation concealment, there was a trend toward increased risk of death associated with HES.

Limitations: Data regarding adverse events, including renal outcomes, were not reported in the majority of published randomized trials. Considerable clinical and methodologic heterogeneity existed among trials.

Conclusions: The use of HES for acute volume resuscitation in critically ill patients, and in particular severe sepsis and septic shock, appears to be associated with increased use of renal replacement therapy. Further RCTs evaluating clinically important endpoints are required to examine the efficacy and safety of HES fluids in the critically ill.

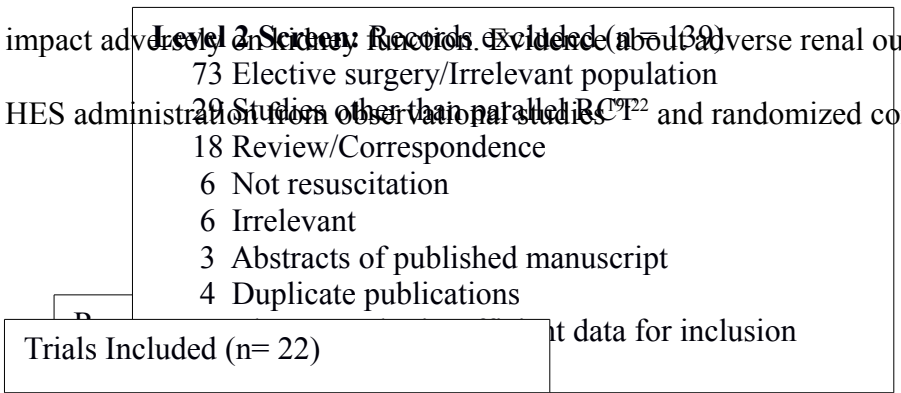


Introduction

In the management of critically ill patients, fluid resuscitation is paramount to prevent organ failure and death[1]. Many resuscitation fluids exist and are broadly categorized as crystalloids (solutions that can pass through a semi-permeable membrane) or colloids (suspensions whereby fine particles of one substance are spread evenly throughout another). Despite considerable research over several decades, debate remains regarding the relative advantage of either type of solution[2].

The use of colloidal starch solutions, have increased in practice despite the higher cost of these products compared to crystalloid solutions[3,4] and a lack of evidence demonstrating their clinical superiority[5-7]. Hydroxyethyl starches (HES) now appear in several resuscitation guidelines, including the US Hospital Consortium Guidelines[6,8]. Adverse events associated with short term HES exposure include coagulopathy and allergic reactions such as anaphylaxis[5,9]; continuous use is associated with severe and long-lasting pruritus[10]. Acute kidney injury has also been intermittently reported with the use of HES in various patient populations [11-14].

Acute kidney injury is an important adverse outcome in critically ill patients because it is an independent risk factor for mortality, and confers increased risk of long term morbidity, impaired quality of life and possible dialysis dependence[15-18]. Some critically ill patients such as those with severe sepsis or septic shock are at increased risk for developing acute kidney injury because of underlying chronic kidney disease and other comorbidities, older age, and/or the septic process itself. This population may be especially vulnerable to resuscitation fluids that impact adversely on kidney function. Evidence about adverse renal outcomes associated with HES administration from observational studies [19-22] and randomized controlled trials[14,23-26] are



conflicting. Moreover, clinical trials of starch solutions are published in various journals with diverse visibility, making it difficult for clinicians and investigators to be aware of the totality of the evidence. Given the significance of renal failure in critically ill patients we undertook this systematic review and meta-analysis to evaluate the effect of HES on adverse renal outcomes and mortality in patients admitted to an intensive care unit.

Methods

Study Sources and Searches

Before commencing this systematic review, we (RZ, LM, AFT, and DF) planned and finalized all aspects of the study protocol, including the clinical question, search strategy, outcomes, and analysis.

We developed a strategy to search OVID MEDLINE (1950-2007 August week 2). This search strategy was adapted to search EMBASE (1980-2007 week 33) and the Cochrane Central Register of Controlled Trials (to third quarter 2007). The search strategy was refined by an information specialist at The Ottawa Hospital, incorporating highly sensitive terms to identify clinical studies[27], and was updated in December 2008. The complete MEDLINE search strategy is presented in Appendix I. We also searched the SCOPUS abstract and citation database so that studies from relevant journals were not missed by the preceding search methods. To identify ongoing or planned studies, we searched 3 trial registries including the UK National Research Register, the Australian Clinical Trials Registry and the ClinicalTrials.gov database. We used the Scientific and Technical Information Network chemical abstracts database and Google Scholar to assist in the identification of relevant grey literature. We contacted the manufacturers of HES (Bristol Myers Squibb, Fresenius Kabi, Bruan, BioTime, and Abbott Laboratories) to identify

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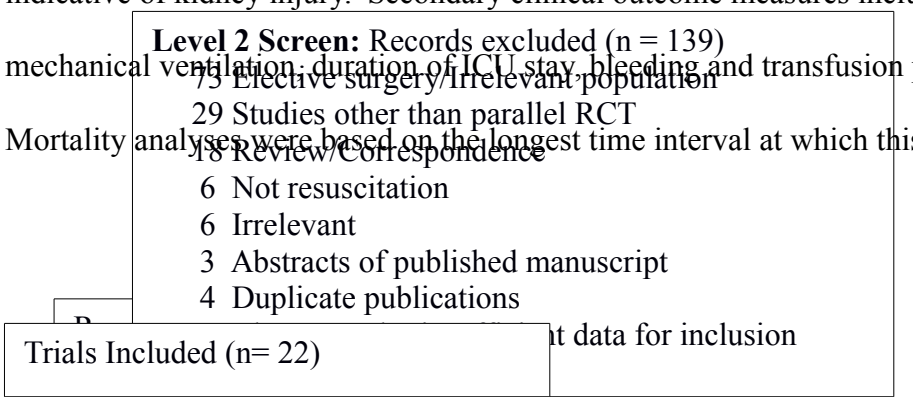
published, unpublished, and ongoing studies of HES for resuscitation. We searched the abstracts and conference proceeding from the European Society of Intensive Care Medicine, International Symposium on Intensive Care Medicine, Society of Critical Care Medicine, American College of Chest Physicians, American Thoracic Society, American Society of Anaesthesiology, Canadian Anesthesiologists' Society, and International Anaesthesia Society, and the American Association for the Surgeons of Trauma from 2002-2007. We also searched the bibliographies of all included studies and relevant reviews for suitable trials not identified in the electronic search strategy. No language restrictions were applied.

We included randomized controlled trials enrolling patients 18 years of age or older who had an indication for acute fluid resuscitation (hypovolemia, hypotension, inadequate indicators of pre-load or filling pressures) and that compared HES with crystalloids, albumin, gelatins, or dextran. We excluded cross over trials, trials including blood as the comparator fluid, and trials examining HES fluids in elective surgery or for acute normovolemic hemodilution. Though HES solutions have varied over time, a uniform mechanism of injury is presumed to occur between products. Thus, all HES solutions were considered in this review, but analyzed separately according to available data.

Our primary outcome was acute kidney injury, defined by the use of renal replacement therapy. Supplementary renal outcomes included the severity of kidney injury as defined by the RIFLE criteria (Risk of renal dysfunction; Injury to the kidney; Failure of kidney function, Loss of kidney function and End-stage kidney disease)[28] and the measurement of urinary biomarkers indicative of kidney injury. Secondary clinical outcome measures included mortality, duration of mechanical ventilation, duration of ICU stay, bleeding and transfusion packed red cell units. Mortality analyses were based on the longest time interval at which this outcome was assessed.



The title, abstract and keywords of each record in English were independently screened for relevance by 2 reviewers (RZ and DM). Records excluded by both reviewers were eliminated at this stage. Full-text articles were obtained for all remaining records. Non-English records were translated as required. Two reviewers (RZ and LM) independently adjudicated each full-text article applying the inclusion and exclusion criteria to select relevant trials. We calculated inter-rater agreement using Cohen's kappa statistic[29]. Non-English articles were adjudicated by a single reviewer (RZ) after translation. Discrepancies were resolved by discussion and consensus with a third reviewer (DF).

Data Extraction and Quality Assessment

Two reviewers abstracted data from the English language trials independently using a standardized data abstraction form (RZ, AT) which had been piloted to ensure completeness and feasibility. Data from non-English language trials were abstracted by one reviewer fluent in the language of publication. If essential data were ambiguous or missing, we contacted the first author or corresponding author by email.

Two reviewers assessed the methodologic quality of each trial using the Jadad scale[30] which provides a score based on the description of randomization (0 to 2 points), double blinding (0 to 2 points), and participant withdrawals (1 point). Possible scores varied from 0 to 5; we considered a score of 3 or greater to be of 'high' methodological quality. We assessed allocation concealment using the method developed by Schultz and colleagues and scored it as 'adequate,' 'unclear,' or 'inadequate'[31]. We used a double-data entry system to minimize transcription errors.

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Data Synthesis and Analysis

Group sample means were compared using Welsh's unpaired t-test for unequal variances. Summary effect measures were calculated using Review Manager (Version 4.2 for Windows, The Cochrane Collaboration, Oxford, England). We performed analyses according to the intention-to-treat principle using eligible randomized patients. We employed a random-effects model using inverse variance weights for all summary measures of effect, expressing these as odds ratios with 95% confidence intervals. An odds ratio of more than 1 suggests a higher odds of the outcome among patients receiving HES compared to patients in the control group.

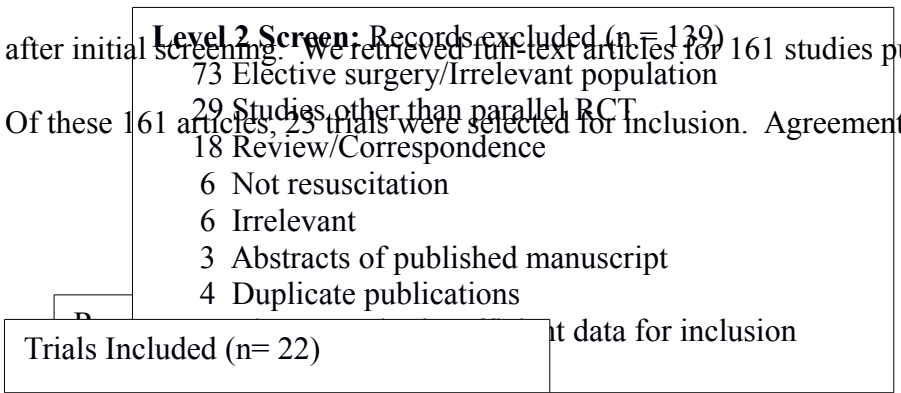
We assessed for evidence of statistical heterogeneity using the I^2 statistic. This statistic is interpreted as the proportion of total variation across trials due to heterogeneity (min-max, 0%-100%). We investigated sources of heterogeneity by conducting subgroup analyses based on clinical and methodologic characteristics defined *a priori*; these included the patient population, type of HES, type of fluid comparator, high versus low quality trials, presence or absence of allocation concealment, and single versus multi-centre trials. We visually examined the potential for publication bias using funnel plots.

Role of the funding source:

There was no external funding source for this work.

Results

In Figure 1, we present a description of all citations and trials identified and reasons for their exclusion at each level of screening. Of the 2381 reports identified, 2220 were excluded after initial screening. We retrieved full-text articles for 161 studies published in 8 languages. Of these 161 articles, 23 trials were selected for inclusion. Agreement between the 2 reviewers



at level 2 screening is reflected in kappa = 0.68. Discrepancies were resolved by discussion and consensus. During data extraction, we found that 2 publications were separate analyses of the same trial population[32,33]; thus, we included the article that was most informative for the purposes of this review[33]. From trial registries, we identified 3 ongoing randomized trials which were not included in our analyses.

A total of 1865 patients were randomized in 22 trials, with a median of 48 patients enrolled per trial (range 12 to 537). Twenty trials were published in peer-reviewed journals, 1 trial is currently in press[26], and 1 has only been published in abstract form[34]. Twenty trials were reported in English language journals[14,24-26,33-48], 1 was in French[49] and 1 in German[50]. Five trials were conducted in North America[26,33,43,45,47], 16 in Europe[14,24,25,34-42,44,46,49,50], and 1 in South America[48]. Four trials received grant funding from manufacturers of HES[22,24,45,47], and 16 trials reported no funding source[25,33-43,46,48-50].

Eight trials exclusively enrolled patients with sepsis, severe sepsis or septic shock[14,24,26,41,43,44,46,47], 6 with trauma[34,35,40,45,48,49], 5 with trauma and sepsis[36-39,42], 1 with 'hypovolemic shock'[33], and 1 in which the type of critically ill patients were not reported[50]. One trial randomized brain dead organ donors to either HES or gelatin[25]; the final unit of analysis was number of transplanted kidneys in the recipients.

Trials compared HES to 20% albumin[36-42,46], 5% albumin[33,43,47], gelatin[14,25,34,35,44,49,50], dextran[34], or a crystalloid solution[24,26,33,45,48]. Two trials included pentoxifylline as a comparator; however, these arms were not incorporated into this systematic review[40,41]. Six different HES fluids, varying by molecular weight and molar substitution, were represented (Table 1).

All trials enrolled patients requiring urgent fluid resuscitation; however, justification for volume loading varied widely and was not explicitly stated in 2 full publications[35,50] and 1

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abstract[34]. Many trials used either systolic blood pressure or mean arterial blood pressure as justification for fluid administration[14,24,26,33,43,45,47-49]. Three trials enrolling patients with severe sepsis/septic shock also incorporated increased arterial lactate and cardiac index of <2.2 L/min as criteria for fluid loading[33,43,47]. In 8 trials, a central venous pressure or pulmonary capillary wedge pressure of <10-12 mmHg served as the single trigger for volume loading[36-42,46]. One trial incorporated clinical signs of hypoperfusion[49]. Two trials used echocardiographic indicators as surrogates for hypovolemia[25,44].

The amount and type of fluid received prior to randomization was reported in 4 trials[24,26,39,46]. The duration of study protocols varied from less than 1 hour to a maximum of 21 days. Twelve protocols administered HES within the first 24 hours of clinical presentation[25,26,33-35,43-45,47-50]. Total study fluid administered differed considerably among trials: the mean volume of HES given varying from 364 ml (SD 64)[48] to 5,350 ml (SD 650)[41].

Regarding relevant co-interventions, all patients in trials conducted by Boldt et al. received continuous dopamine infusions at 3 mcg/kg/min[36-42]. Gelatin was administered to the HES group after receiving 2000 ml of the study colloid in 1 trial[49]. In 1 trial, the components of early goal directed therapy protocolized the use of red blood cell transfusions and inodilators in addition to fluid[26]. Vasopressors and inotropes were used when necessary in all studies, generally after initial volume resuscitation.

Four trials listed renal sequelae as primary or secondary outcomes[14,24-26]. Four trials reported the requirement for renal replacement therapy[14,24-26] and 5 trials reported variable definitions for acute renal failure with creatinine concentrations[14,24,25,35,42]. Patients with evidence of renal impairment at enrollment, defined by serum creatinine or the need for hemodialysis, were excluded from nine trials[14,24,26,35-39,46]. Baseline renal function (serum creatinine)

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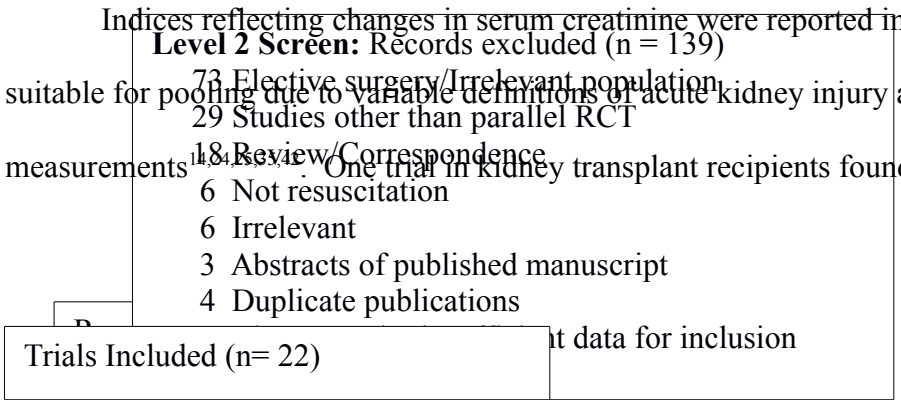
was reported in 5 trials[14,24-26,42]. Comorbidities and risk factors for renal injury were detailed in 2 trials[14,24].

Most included trials were small, single centered, and of low methodologic quality (Table 2). Assessing the methodologic quality of 1 published abstract was not possible without an available manuscript[34]. Four trials were of high methodologic quality[14,24-26]. Adequate allocation concealment was reported in 5 trials[14,24,26,48,49]. Nine of 21 evaluable trials reported blinding[25,26,36-42], but only 1 described the blinding methods[26]. Losses to follow-up were reported in 5 trials[14,24-26,35]. Analysis according to the intention to treat principle was reported in 4 trials[14,24-26] and the method was unclear in 16 trials due to the absence of information regarding losses to follow-up[33,36-50].

Primary Outcome: Acute Kidney Injury

The pooled odds ratio (OR) for renal replacement therapy associated with HES fluid in the 4 trials that reported this outcome was 1.90 (95% CI 1.22-2.96, I^2 9.5%, n=749)[14,24-26]. The summary statistic was heavily influenced by the findings of a single large randomized controlled trial that accounted for 70% of the pooled statistical weight[24]. Three of these 4 trials included patients with severe sepsis or septic shock for which the pooled OR of renal replacement therapy was 1.82 (95% CI 1.27-2.61, I^2 0%, n=702)[14,24,26]. HES use was also associated with an increased odds of renal replacement therapy in the 1 trial of kidney transplant recipients (OR 9.5 and 95% CI 1.09-82.72, n=47). Further sensitivity analysis was limited by the low number of trials that reported renal outcomes.

Indices reflecting changes in serum creatinine were reported in 5 trials but were not suitable for pooling due to variable definitions of acute kidney injury and timing of laboratory measurements[14,24,25,34,42]. One trial in kidney transplant recipients found higher serum creatinine



values in patients who received kidneys from donors resuscitated with HES as compared with donors who were resuscitated with gelatin in the first 10 days after transplantation ($p<0.01$)[25]. In another trial of resuscitation in septic shock, the median peak serum creatinine was higher in those receiving HES:200/0.62 compared to those receiving gelatin [2.5 (IQR 1.5-3.8) mg/dl vs. 1.9 (1.2-3.1) mg/dl, $p=0.04$][14]. However, in this trial, baseline serum creatine concentrations were significantly higher in patients randomized to receive HES. Two trials that included patients with trauma and sepsis or trauma alone reported similar mean serum creatinine values in the HES and control groups; these analyses were based on patients remaining in ICU at day 5[35,42]. No trial evaluated acute kidney injury according to RIFLE categories or characterized changes in urinary biomarkers.

In the 2 trials enrolling patients with severe sepsis and septic shock, the pooled OR of acute kidney injury, defined as a doubling of serum creatinine or the requirement for renal replacement therapy, was 1.91 (95% CI 1.36-2.68; I^2 0%, n=662) in patients receiving HES[14,24]. In 1 trial that reported acute kidney injury as a creatinine >221 μmol/L or urine output <20 ml/hr, there were no differences between the 2 groups[42].

Secondary Outcomes: mortality, duration of mechanical ventilation and ICU stay

Mortality was reported in 17 of 22 trials (Figure 3). The pooled odds ratio for death associated with HES was 1.07 (95%CI 0.85-1.34), I^2 0%, n=1657. In the 6 trials that enrolled patients with severe sepsis or septic shock, the pooled OR for death associated with HES was 1.23 (95% CI 0.92-1.65, $I^2=0\%$)[14,24,26,32,41,44]; in trauma, the OR for death was 1.52 (95% CI 0.48-4.75); and in trials that included sepsis and trauma patients, the OR for death was 0.82 (95% CI 0.55-1.21) (Figure 4). No significant differences in the odds ratios for death were evident with

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different durations of the study protocols or with use of early goal directed therapy (data not shown). No significant differences in the odds ratio for death existed with the different fluid comparator groups or when specific molecular weights of HES were analyzed (Figure 4).

In the 3 trials of higher methodologic quality (Jadad score 3-5) the pooled OR for death was 1.27 (95% CI 0.93-1.72, I^2=0%)[14,24,26]. In the 4 multicentre trials, HES administration was associated with an OR for death of 1.31 (95% CI 0.97-1.76, I^2=0%)[14,24,26,49]. In the 5 trials with adequate allocation concealment, the summary OR for death associated with the of HES was 1.28 (95% CI 0.96-1.72, I^2=0%)[14,24,26,48,49](Figure 4).

The duration of mechanical ventilation[42,45] and ventilator free-days[24] were similar in the 3 trials reporting these outcomes. The mean[44] or median[14,24,26] duration of ICU stay was comparable between the HES and control groups in the 4 trials of septic shock. In 1 trial of 59 patients suffering acute traumatic injuries, mean (±SD) ICU length of stay was shorter (8.8 days (3.3) vs. 11.1 days (3.4), p=0.01) in patients receiving HES[35].

Safety Outcomes:

Three of 22 included trials reported information concerning allergic reactions or anaphylaxis secondary to HES administration[25,47,49]. No allergic reactions were reported in these 3 studies which included 11% (n=211) of the total patients enrolled. One study (n=20) explicitly reported no complications related to the infusion of HES[48], and 1 study reported no differences in a composite measure of serious adverse events which included allergic reactions and bleeding[24].

Insufficient and heterogeneous reporting of coagulopathy, bleeding and red cell transfusions precluded a pooled analyses and summary statements.

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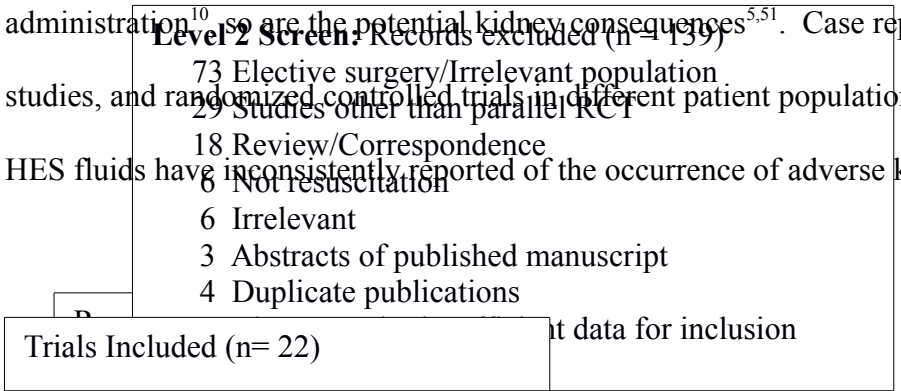
Publication bias

We minimized the potential for publication bias by conducting an extensive search of the literature including grey literature sources, consulting content experts and avoiding language restrictions. Funnel plot analysis was not possible for renal outcomes since only 4 trials reported these outcomes. No pattern consistent with publication bias was evident on the funnel plots generated for the outcome of mortality (Figure 5).

Discussion:

In this systematic review, we found that the use of HES for acute volume resuscitation in critically ill patients was associated with a 2 fold increase in the odds of renal replacement therapy in the 4 trials reporting this outcome. In the 3 trials that enrolled patients with severe sepsis and septic shock, the odds of receiving renal replacement therapy was increased by 82%. No difference in overall mortality was found; however, among studies enrolling patients with severe sepsis and septic shock, and in trials that were multicentred, of high methodological quality, or that reported adequate allocation concealment, there was a trend toward increased odds of death associated with HES. Serious adverse events, including bleeding or coagulopathy, were poorly characterized and inadequately reported.

Hydroxyethyl starch solutions are effective volume expanders but deposit widely into tissues, including the skin, liver, muscle, spleen, endothelial cells, and kidneys[5,10]. Just as persistent and significant pruritus is now recognized as a deleterious consequence of starch administration[10], so are the potential kidney consequences[5,51]. Case reports, observational studies, and randomized controlled trials in different patient populations exposed to different HES fluids have inconsistently reported of the occurrence of adverse kidney outcomes[5,11,19,20,22,23]



Though the pathophysiologic mechanism of acute renal injury is unclear, microscopic changes referred to as 'osmotic-nephrosis-like lesions' have been observed[11,25]. Although different HES compounds have unique pharmacokinetic properties which vary according to the mean molecular weight, the degree of substitution, and the C2:C6 ratio[52], it is unclear whether these differences affect clinically important outcomes.

There are several limitations to this systematic review. Though patients allocated to HES were more likely to receive renal replacement therapy across all trials that reported this outcome, pooled analyses were substantially influenced by 1 large trial of patients with severe sepsis and septic shock[24]. Notably, this trial was unblinded, there were fluid protocol violations in both study arms (26% HES and 27% crystalloid arm), and the dose limit for HES (20 ml/kg/day) was exceeded in 38% of patients on at least day 1 of the study protocol.

The heterogeneous clinical and methodologic characteristics of included trials in this review presents challenges when making inferences about these data. Variable primary and secondary outcome rates could have been influenced by the patient population and the duration of follow-up. Similarly, event rates may have varied based on the type of HES and comparator fluids, as well as the dosing, duration of exposure, and the reasons for fluid administration. Few trials reported important baseline characteristics, such as illness severity, or potential risk factors/exposures for acute kidney injury, which would be essential for ensuring study groups were similar at randomization. Few trials transparently reported relevant co-interventions or details of key renal outcomes such as the duration of renal replacement therapy, renal recovery, the progression to chronic kidney disease, or dialysis dependence. Nevertheless, the development of acute kidney injury in critically ill patients, independent of receiving renal replacement therapy, has been associated with increased mortality[18]. Whether or not patients with

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severe sepsis or septic shock should receive colloids, and especially HES for initial, ('early gold directed') volume resuscitation requires further careful.

A lower molecular weight, and less substituted HES fluid is currently available and marketed as having an excellent safety profile[53]. Although a safer HES fluid is likely to be valued highly by clinicians, at present there is no published clinical evidence from large definitive randomized controlled trials in the critically ill that demonstrates the safety of this product, or superior safety compared to previously marketed products. Moreover, all manufacturers of starch solutions list kidney dysfunction and/or oliguria as contraindications.

In conclusion, our systematic review documented that HES administered to critically ill patients appears to be associated with increased use of renal replacement therapy. This finding was consistent among the 3 studies of severe sepsis and septic shock that reported this adverse outcome. It is unclear whether these adverse effects apply to all HES fluids and all critically ill patients. Methodologically rigorous, adequately powered RCTs with the newer, lower molecular weight and less substituted starch solutions are necessary to define the clinical benefits and potential risks associated with their use in critically ill patients. Until the results of future studies become available, prudence regarding the use of HES solutions in critically ill patients, particularly in patients with severe sepsis or septic shock should be considered.

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Acknowledgement

The authors thank Mrs. Risa Shorr (information specialist) for her assistance with the final search strategy and Jodi Peters for her assistance in formatting this manuscript. We also acknowledge the translation assistance for adjudicating non-English and non-French trials: Mr. Hongbin Xu (Japanese), Mr. Pavel Milman (Russian), Mr. Jess Riis Jensen (Danish), Dr. Mauro Verrelli (Italian), Dr. Andrew Czarnecki (Polish), and Dr. Sandra Froeschl (German). We would also like to thank several anonymous reviewers for their suggestions on earlier drafts of this manuscript.

Funding Sources:

No specific funds were obtained for this systematic review. Lauralyn McIntyre holds a Canadian Institutes of Health Research/Canadian Blood Services New Investigator award. Ryan Zarychanski is the recipient of a research fellowship supported by Cancercare Manitoba (Winnipeg, Canada) and Canadian Blood Services & the Ottawa Health Research Institute (Ottawa, Canada). Deborah Cook holds a Canada Research Chair of the Canadian Institutes of Health Research. These agencies were not involved in the design or conduct of the review.

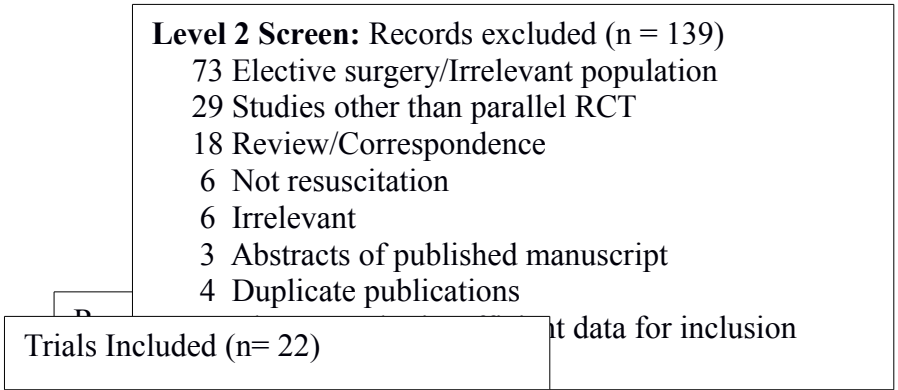


Figure 1: Study Flow Diagram

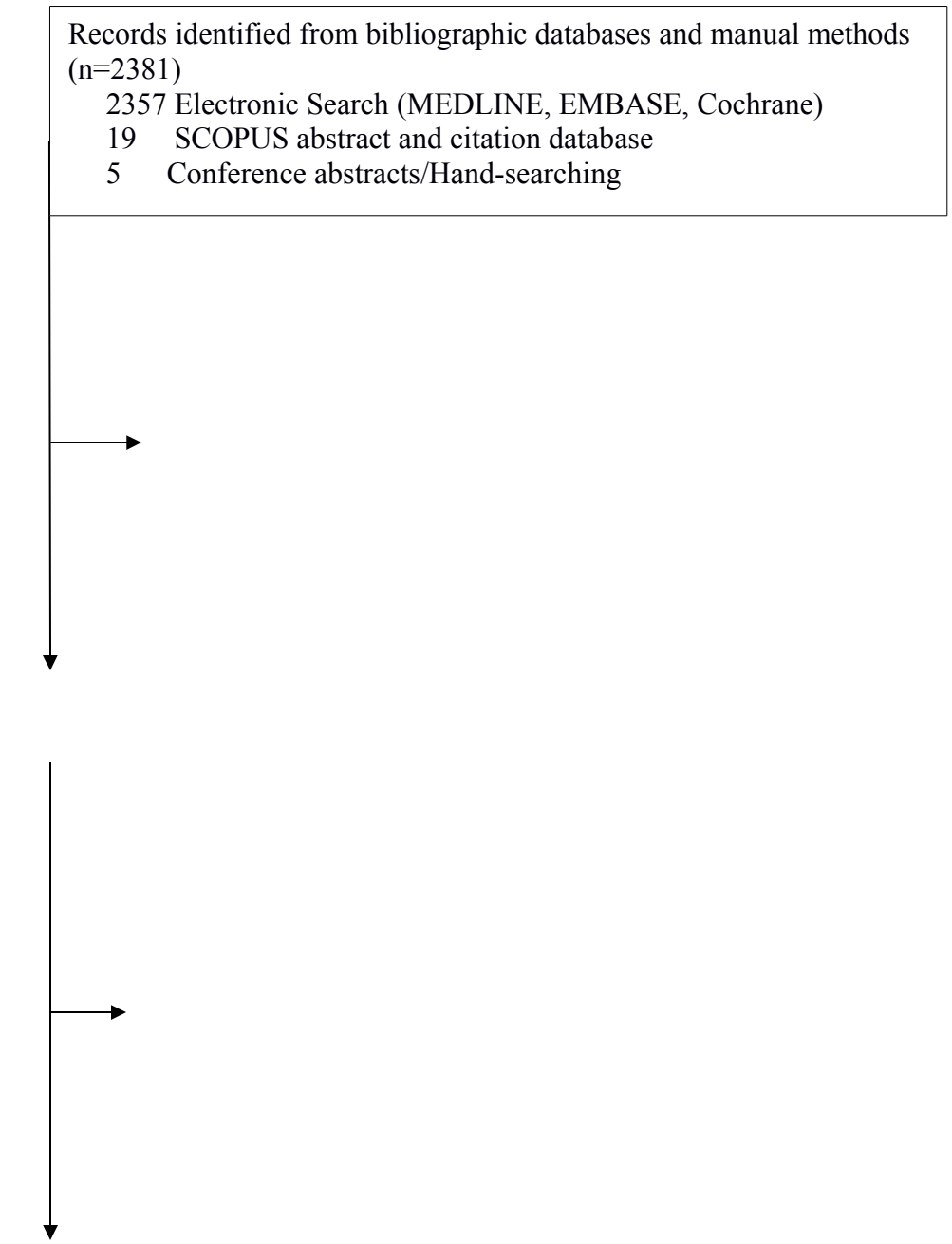


Table 1: Characteristics of the 22 studies included in the systematic review

Trial/Year (reference)	**No. of patients:** Total HES/control	**Population**	**Severity of illness score** HES/control	**Rationale for Fluid Administration**	**Intervention Protocol** (molecular weight/molar substitution)	**Control Protocol**	**Total Study Fluid given**	**Duration of Study Protocol**
Brunkhorst/08[24]	537 262 / 275	Severe Sepsis & Septic Shock	APACHE II 20.1 / 20.3	CVP <8 mmHg or if MAP<70 mmHg or SvO2 <70%	HES: (200/0.5) To maintain endpoints based on MAP, CVP, and ScvO2; Max dose 20 ml/Kg/day, then Ringers Lactate	Ringers Lactate To maintain endpoints based on MAP, CVP, and ScvO2; No Max dose	HES: (median) 70.4 ml/kg (IQR 33.4-144.2)	21 days
McIntyre/08[26]	41 21 / 20	Septic shock	APACHE II 21.1 / 20.3	MAP<65 mmHg, SBP<90 mmHg, or a SBP of >40 mmHg below baseline	HES (260/0.45) 500 ml boluses with endpoints based on MAP, CVP and ScvO2; Max dose 28 ml/kg or 3 L in a 12 hour period, then open label Normal Saline	Normal Saline 500 ml boluses with endpoints based on MAP, CVP and ScvO2; Max dose 28 ml/kg or 3 L in a 12 hour period, then open label Normal Saline	HES: 2100 ml (SD 600) Saline: 1900 ml (SD 600)	12 hours
Palumbo/06[46]	20 10 / 10	Severe Sepsis	APACHE II (combined) 18.9	PCWP <15 mmHg	HES: 130/0.4 To maintain PCWP 15-18 mmHg	20% albumin To maintain PCWP 15-18 mmHg	NR	5 days
Molnar/04[44]	30 15 / 15	Septic shock	SAPS II 34 / 34	Intra-thoracic blood volume <750 ml/kg	HES: (200/0.6) 250 ml boluses every 15 minutes until intrathoracic blood volume >900 ml/m^2; Max 1000 ml	Gelatin 250 ml boluses every 15 minutes until intrathoracic blood volume >900 ml/m^2; Max 1000 ml	HES: 750 ml (SD 274) Gelatin: 714 ml (SD 254)	1 hour
Schortgen/01[14]	129 65 / 64	Severe sepsis & Septic shock	SAPS II 53.0 / 50.0	Hypotension or signs and symptoms of acute organ dysfunction or hypoperfusion	HES: (200/0.6) 500 ml boluses: Max dose, 33 ml/kg on day 1; then 20 ml/kg. Protocol emended during the trial to include max duration therapy of 4 days or to a cumulative limit of 80 ml/kg	Gelatin At the discretion of the physician; no dose limitation	(Median) HES: 31 ml/kg (IQR 19-51) Gelatin: 43 ml/kg (IQR 19-60)	4 days

APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, simplified acute physiology score; MAP, mean arterial pressure; SBP, systolic blood pressure; HES, hydroxyethyl starch; Max, maximum; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure, CI, cardiac index; SvO2, systemic venous oxygen saturation; IQR, interquartile range; SD, standard deviation; NR, not reported.

Carli/00[49]	164 85 / 79	Patient's with traumatic injuries being transported to the hospital	Revised Trauma Score 5.5 / 5.7	systolic BP <100 mmHg with signs of peripheral hypo-perfusion	HES: (200/0.5) To keep systolic BP >100 mmHg; max volume 2000 ml	Gelatin To keep systolic BP >100 mmHg; max volume 2000 ml	HES: 820 ml (SD 63) Gelatin: 840 ml (SD 56)	Time to hospital transport: (55-60 minutes)
Allison/99[35]	59 30 / 29	Blunt trauma	Injury Severity Score 20.0 / 18.1	Not reported	HES: (260/0.45) As necessary as the only resuscitation colloid for the first 24 hours	Gelatin As necessary as the only resuscitation colloid for the first 24 hours	(1st 24 hours) HES: 2744 ml (SD 1068 ml) Gelatin: 3132 ml (SD 914)	24 hours
Boldt/98[42]	300 150 / 150	Trauma or sepsis secondary to major surgery	APACHE II 20.5 / 20.7	PCWP <12 mmHg	HES: (200/0.5) To maintain a PCWP between 12 and 15 mmHg	20% Albumin To maintain a PCWP between 12 and 15 mmHg	HES: 4970 ml (SD 835) Albumin: 2160 ml (SD 325)	5 days
Younes/98[48]	23 12 / 11	Traumatic injuries in the emergency department	Revised Trauma Score 9.2 / 8.6	SBP < 90 mmHg	HES: (260/0.45) 250 ml boluses until SBP >100 mmHg	Normal Saline 250 ml boluses until SBP >100 mmHg	HES: 364 ml (SD 64) Saline: 1420 ml (SD 298)	Until SBP >100 mmHg
Jovanovic/97[34] (abstract)	60 HES: 20 Dextran: 20 Gelatin: 20	Poly-traumatized patients with hemorrhagic shock	NR	Hemorrhagic shock, not otherwise specified	HES: (450/0.7) A single bolus of 10-15 mg/kg	Dextran: A single bolus of 7-10 mg/kg Gelatin: A single bolus of 10-15 ml/kg	NR	Less than 2 hours
Cittanova/96[25]	27 15 / 12 Patients (Final unit of analysis was kidneys; n=47 kidneys)	Brain dead kidney donors	NR	LVED area <5.5 cm^2/m^2 or obliteration of the LV cavity at end systole	HES: (200/0.62) For hypovolemia up to a maximum of 33 ml/kg; then gelatin as necessary	Gelatin As necessary with no maximum	HES: 2100 ml (SD 660) Gelatin: 2875 ml (SD 1384)	Until organ procure-ment

Boldt/96[37]	56 28 / 28	Trauma or sepsis secondary to major surgery	APACHE II 19.5 / 20.2	CVP or PCWP < 12 mmHg	HES: (200/0.5) To maintain CVP or PCWP 12-16 mmHg	20% Albumin To maintain CVP or PCWP 12-16 mmHg	HES: 4065 ml (SD 890) Albumin: 1820 ml (SD 390)	5 days
Boldt/96[39]	60 30 / 30	Trauma or sepsis secondary to major surgery	APACHE II 19.4 / 19.3	PCWP <12 mmHg	HES: (200/0.5) To maintain PCWP 12-18 mmHg	20% Albumin To maintain PCWP 12-18 mmHg	HES: 4720 ml (SD 1155) Albumin: 2030 ml (SD 300)	5 days
Boldt/96[40]	30 15 / 15	Trauma	APACHE II 20.3 / 20.0	CVP or PCWP <12 mmHg	HES: (200/0.5) To maintain CVP or PCWP 12-18 mmHg	20% Albumin To maintain CVP or PCWP 12-18 mmHg	HES: 4880ml (SD 510) Albumin: 1390 ml (SD 330)	5 days
Boldt/96[38]	56 28 / 28	Trauma or sepsis secondary to major surgery	APACHE II 18.5 / 18.5	PCWP <10 mmHg	HES: (200/0.5) To maintain CVP or PCWP 10-15 mmHg	20% Albumin To maintain CVP or PCWP 10-15 mmHg	HES: 4125 ml (SD 750) Albumin: 2025 ml (SD 375)	5 days
Boldt/96[41]	28 14 / 14	Sepsis	APACHE II 24.3 / 22.9	CVP or PCWP < 10 mmHg	HES: (200/0.5) To maintain CVP or PCWP 10-15 mmHg	20% Albumin To maintain CVP or PCWP 10-15 mmHg	HES: 5350 ml (SD 650) Albumin: 2525 ml (SD 350)	5 days
Boldt/95[36]	60 30 / 30	Trauma or sepsis secondary to major surgery	APACHE II 20.2 / 20.2	CVP or PCWP <12 mmHg	HES: (200/0.5) To maintain CVP or PCWP 12-16 mmHg	20% Albumin To maintain CVP or PCWP 12-16 mmHg	HES: 4170 ml (SD 745) Albumin: 1835 ml (SD 300)	5 days
Nagy/93[45]	41 21 / 20	Traumatic injuries presenting to a trauma unit	Injury severity score 18.4 / 18.4	SBP <90 mmHg	HES: (260/0.45) Repeated boluses until SBP >100 and urine output >30 cc/hr. Max 4 L, then Ringers Lactate	Ringers Lactate Repeated boluses until SBP >100 and urine output >30 cc/hr.	HES: 1750 ml Ringers Lactate: 3629 ml	Until SBP >100 mmHg and urine output >30 mmHg

Rackow/89[47]	20 10 / 10	Severe sepsis	NR	SBP <90 mmHg, lactate >2mmol/L CI <2.2, or PCWP <12 mmHg	HES: (260/0.45) 250 ml boluses every 15 minutes until PCWP >15: Max 2000 ml	5% Albumin 250 ml boluses every 15 minutes until PCWP >15: Max 2000 ml	HES: 900 ml (SD 205) Albumin: 975 ml (SD 169)	Until PCWP >15 mmHg
Falk/88[43]	12 6 / 6	Septic shock	NR	SBP <90 mmHg, CI <2.2 L/min or lactate > 2 mmol/L	HES: (450/0.7) 250 ml boluses every 15 minutes until PCWP >15; fluid then continued at 100 ml/hour for 24 hours	5% Albumin 250 ml boluses every 15 minutes until PCWP >15; fluid then continued at 100 ml/hour for 24 hours	HES: 4934 ml (SD 1354) Albumin: 3067 ml (SD 256)	24 hours
Hopf/87[50]	87 42 / 45	Critically ill patients requiring resuscitation	NR	NR	HES: (70/0.58) 1000 ml bolus, thereafter 500 ml Ringers Lactate, 500 ml D5W, and 500 ml Laevulose 5% every 12 hours	Gelatin 1000 ml bolus, thereafter 500 ml RL, 500 ml D5w, and 500 ml Laevulose 5% every 12 hours	HES: 1000 ml Gelatin: 1000 ml	24 hours
Haupt/82[33]	26 HES: 9 Albumin: 9 Saline: 8	Hypovolemic shock, not traumatic	NR	SBP <90 or lactate >18 mg/dl, and PCWP <15 and CI <2.2 L/min	HES: (450/0.7) 250 ml bolus every 15 minute until PCWP 10-15 mmHg. PCWP maintained for 25 hours with additional study fluid	1.) Normal Saline 2.) 5% Albumin 250 ml bolus every 15 minute until PCWP 10-15 mmHg. PCWP maintained for 25 hours with additional study fluid	HES: 4466 ml (SD 477) Albumin: 3134 ml (SD 370) Saline: 6371 ml (SD 1088)	24 hours

APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, simplified acute physiology score; MAP, mean arterial pressure; SBP, systolic blood pressure; HES, hydroxyethyl starch; Max, maximum; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure, CI, cardiac index; SvO2, systemic venous oxygen saturation; IQR, interquartile range; SD, standard deviation; NR, not reported.

Table 2: Methodologic quality and potential risks of bias in the included randomized controlled trials

			Jadad Score*					
Study/Year	**RCT type**	**Sponsor**	**Total**	**Random-ization**	**Blinding**	**Attrition Information**	**Allocation Concealment**	**Intention-to-treat analysis**
Brunkhorst/08[24]	Multicentre	Unrestricted Industry grant plus public funds	3	2	0	1	Adequate	Yes
McIntyre/08[26]	Multicentre	Bristol Myers Squibb (unrestricted grant)	5	2	2	1	Adequate	Yes
Palumbo/06[46]	Single centre	NR	1	1	0	0	Unclear	?
Molnar/04[44]	Single centre	Ministry of Education, Hungary	1	1	0	0	Unclear	?
Schortgen/01[14]	Multicentre	Assistance Publique-Hôpitaux de Paris	3	2	0	1	Adequate	Yes
Carli/00[49]	Multicentre	NR	1	1	0	0	Adequate	?
Allison/99[35]	Single centre	NR	1	0	0	1	Inadequate	No
Boldt/98[42]	Single centre	NR	2	1	1	0	Unclear	?
Younes/98[48]	Single centre	NR	1	1	0	0	Adequate	?
Jovanovic/97[34] (abstract)	?	?	?	1	?	?	?	?
Cittanova/96[25]	Single centre	NR	3	1	1	1	Unclear	Yes
Boldt/96[37]	Single centre	NR	2	1	1	0	Unclear	?
Boldt/96[39]	Single centre	NR	2	1	1	0	Unclear	?
Boldt/96[40]	Single centre	NR	2	1	1	0	Unclear	?
Boldt/96[38]	Single centre	NR	2	1	1	0	Unclear	?
Boldt/96[41]	Single centre	NR	2	1	1	0	Unclear	?
Boldt/95[36]	Single centre	NR	2	1	1	0	Unclear	?
Nagy/93[45]	Single centre	American Critical Care	1	1	0	0	Unclear	?
Rackow/89[47]	Single centre	Dupont	1	1	0	0	Unclear	?
Falk/98[43]	Single centre	NR	1	1	0	0	Unclear	?
Hopf/87[50]	Single centre	NR	1	1	0	0	Unclear	?
Haupt/82[33]	Single centre	NR	1	1	0	0	Unclear	?

*The Jadad scale assigns methodologic quality score based on the reported methods and description of randomization (0-2 points), blinding (0-2 points) and the reporting of participant withdrawals (0-1 point). Possible scores vary from 0 to 5, with a score of 5 indicating high methodologic quality.
NR, not reported

Figure 2: Renal replacement therapy associated with hydroxyethyl starch

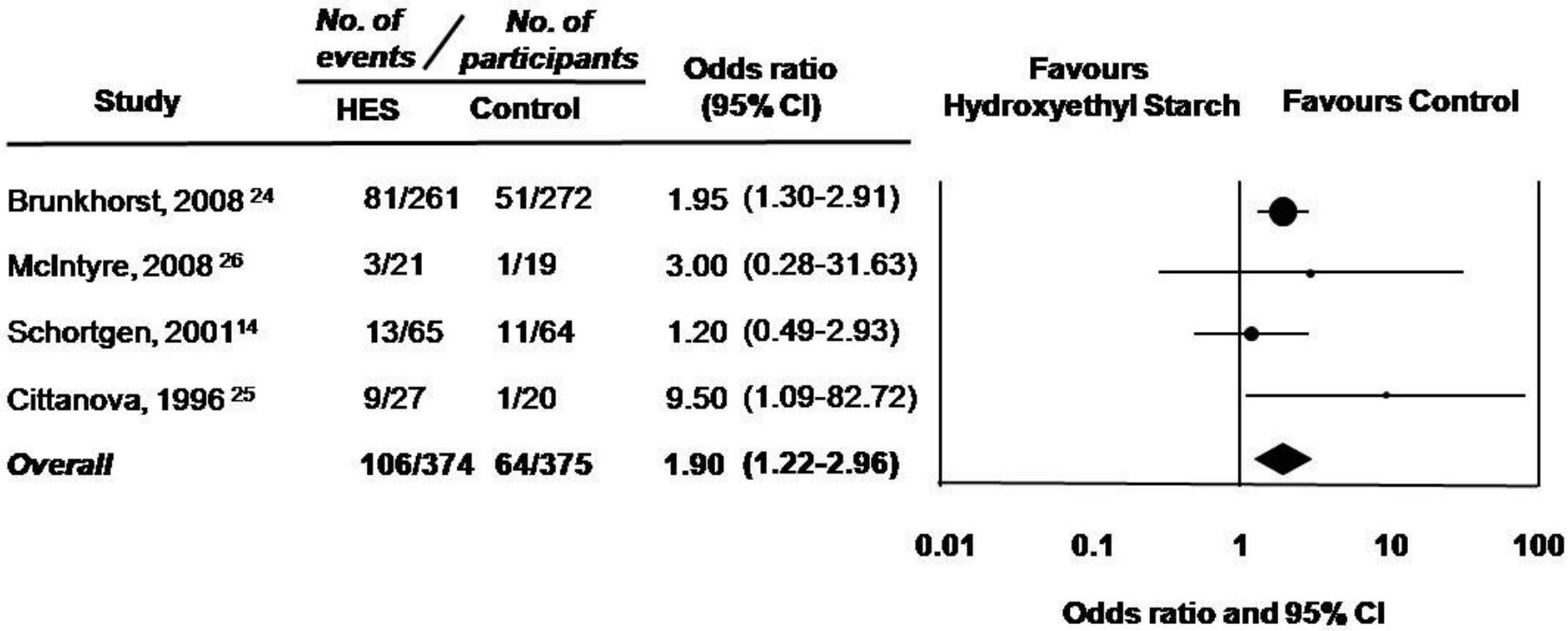


Figure 3: Overall mortality of all included studies

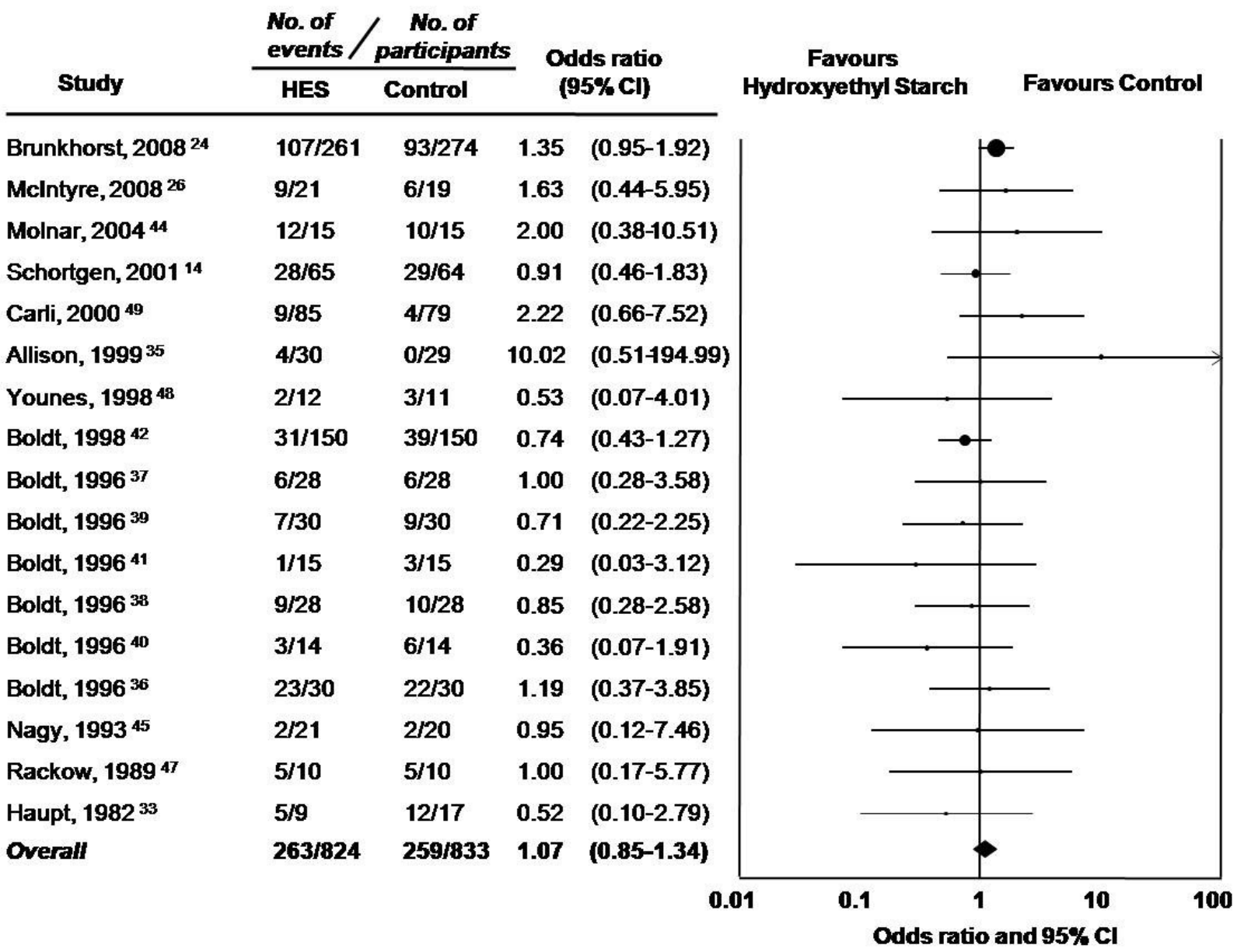


Figure 4: Mortality according to duration of treatment protocol, enrolled population, resuscitation strategy, type of HES, type of comparator fluid, and methodologic quality

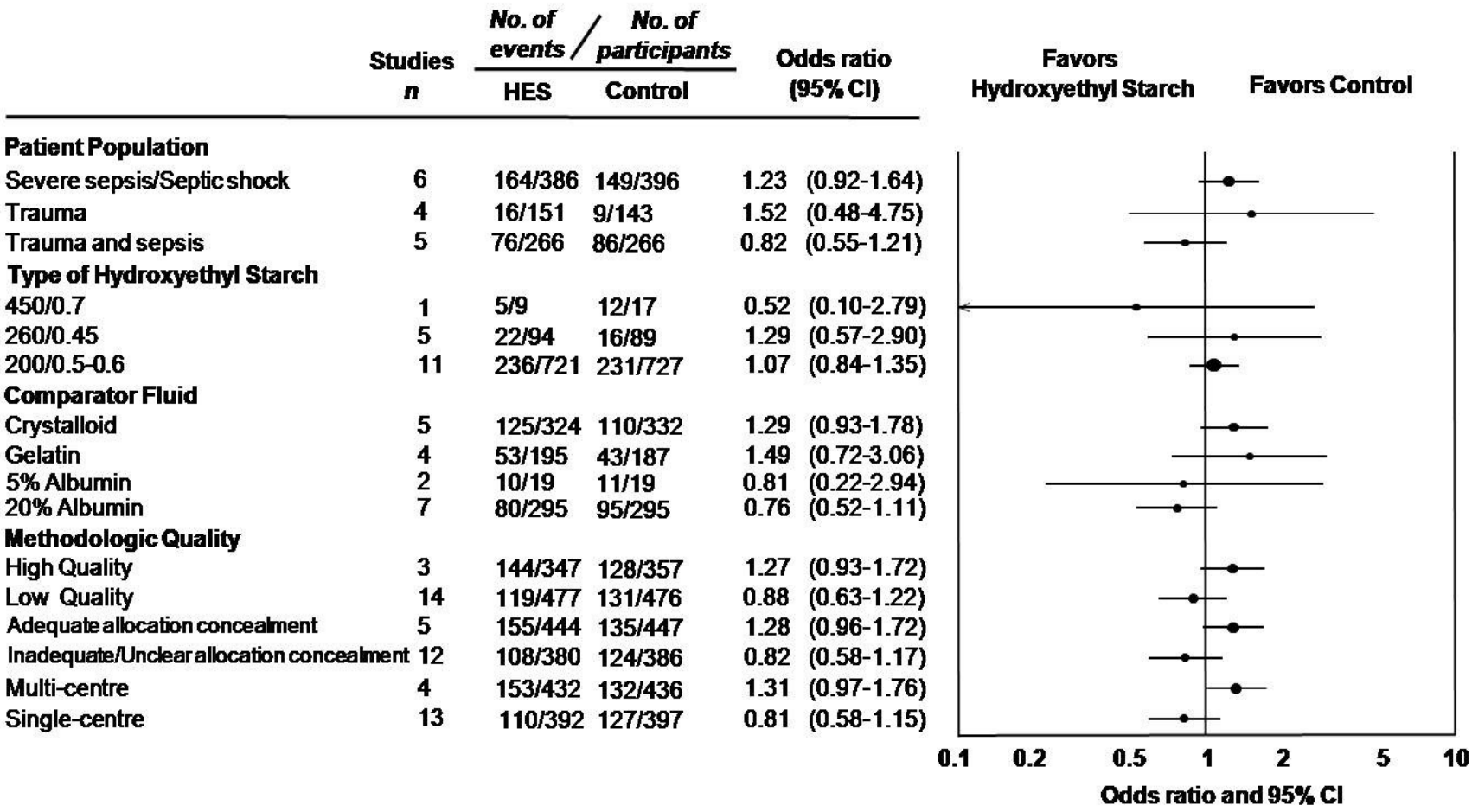
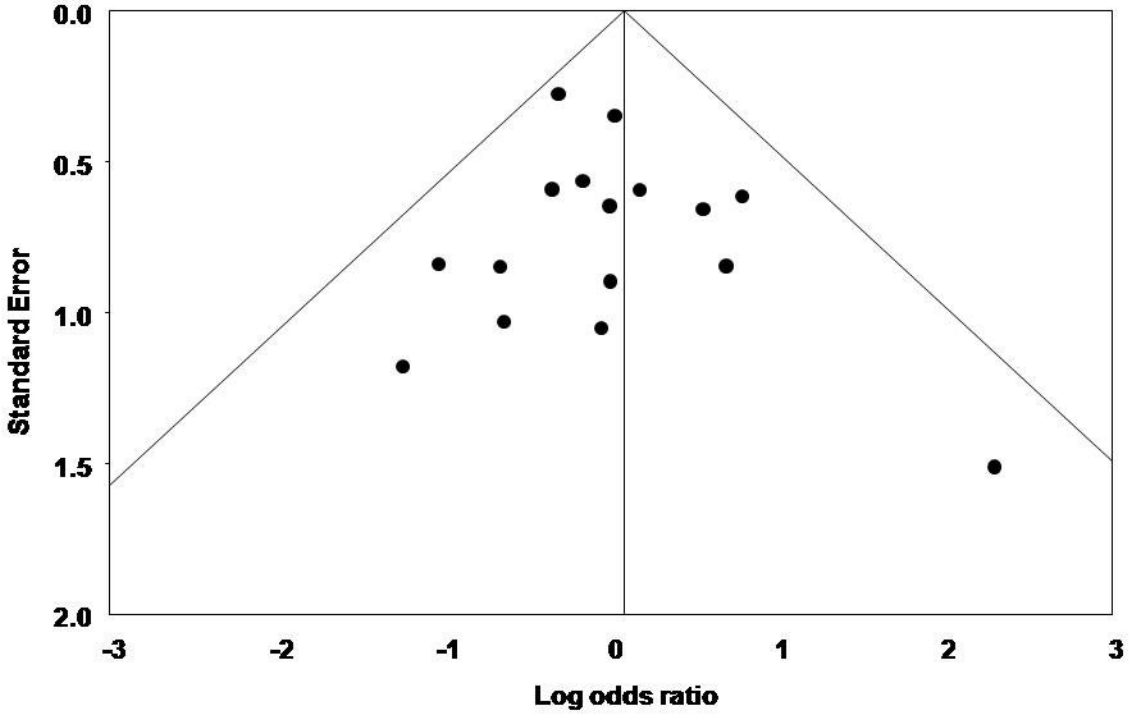


Figure 5: Assessment of publication bias for overall mortality


0.0
0.5
1.0
1.5
2.0
Standard Error
-3
-2
-1
0
1
2
3
Log odds ratio

Appendix 1: Medline Search Strategy

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Database: Ovid MEDLINE(R) <1950 to August Week 2 2007>
Search Strategy:

--------------------------------------------------------------------------------
1     hetastarch/ (1694)
2     hetastarch$.tw. (324)
3     (hydroxyethyl starch$ or hydroxyethylstarch$).tw. (1747)
4     pentastarch$.tw. (100)
5     (haes-steril or Hextend or Elohes or Expafusin or Voluven or
      hemohes or hespan or pentafraction or pentaspan
      or plasmasteril).tw. (214)
6     hes.tw. (2087)
7     or/1-6 (3725)
8     randomized controlled trial.pt. (240431)
9     controlled clinical trial.pt. (75750)
10     randomized controlled trials.sh. (50403)
11     random allocation.sh. (58745)
12     double blind method.sh. (92784)
13     single-blind method.sh. (11237)
14     clinical trial.pt. (439656)
15     exp clinical trials/ (195189)
16     (clin$ adj25 trial$).ti,ab. (134236)
17     ((singl$ or doubl$ or trebl$ or tripl$) adj25
        (blind$ or mask$)).tw. (92205)
18     placebo$.sh. (27848)
19     placebo$.ti,ab. (104329)
20     random$.ti,ab. (382044)
21     research design.sh. (48798)
22     comparative study.pt. (1358262)
23     exp evaluation studies/ (610724)
24     follow up studies.sh. (344218)
25     prospective studies.sh. (226595)
26     (control$ or prospectiv$ or volunteer$).ti,ab. (1825986)
27     or/8-26 (3854705)
28     animals/ not humans/ (3168650)
29     27 not 28 (3008945)
30     7 and 29 (1177)


Updated December Week 2 2008
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