

ATTENTION: The analysis and conclusions of this article are being revised by the authors. This is due to the journal *Anesthesia and Analgesia's* retraction of a paper by Dr. Joachim Boldt, an author in seven of the studies analyzed in this review. As such, the editors of *Open Medicine* recommend interpreting this review with extreme caution until Zarychanski et al. publish a new analysis and interpretation in *Open Medicine*. For more information, see *Anesthesia and Analgesia's* [press release](#).

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

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ABSTRACT

Background: Hydroxyethyl starch (HES) is a type of colloid fluid that is commonly used for volume resuscitation of patients admitted to the intensive care unit. Data regarding the renal consequences of HES are conflicting.

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

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

Study selection: We included only randomized controlled trials of acute volume resuscitation of critically ill patients comparing HES fluid with an alternative resuscitation fluid.

Data synthesis: Two reviewers independently assessed trial eligibility, extracted data and evaluated trial quality. Random-effects models were used for all summary measures of effect.

Results: Twenty-two trials (n = 1865 patients) were included. Patients who received HES were more likely to have received renal replacement therapy (odds ratio [OR] 1.90, 95% confidence interval [CI] 1.22–2.96, I² 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 that included 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 in association 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 of critically ill patients, and in particular those with severe sepsis and septic shock, appeared to be associated with increased use of renal replacement therapy. Further randomized controlled trials evaluating clinically important end points are required to examine the efficacy and safety of HES fluids for critically ill patients.

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Competing interests: Lauralyn McIntyre has received unrestricted grant support from Bristol Myers Squibb and Abbott Laboratories. The remaining authors have no conflicts of interest to declare.

Funding: 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), Canadian Blood Services and the Ottawa Health Research Institute (Ottawa, Canada). Deborah Cook holds a Canada Research Chair of Research Transfer in Intensive Care from the Canadian Institutes of Health Research. These agencies were not involved in the design or conduct of the review.

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INTRAVENOUS FLUID RESUSCITATION IS ESSENTIAL for preventing organ failure and death¹ in critically ill patients. Intravenous fluids are broadly categorized as crystalloids (solutions that can pass through a semipermeable membrane) or colloids (suspensions in which fine particles of one substance are spread evenly throughout another).

Crystalloid solutions are inexpensive and readily available, and they do not cause allergic reactions or infection. Colloid resuscitation requires less volume and less time and may sustain intravascular volume for longer durations than crystalloid resuscitation.² Despite considerable research over several decades, debate persists regarding which of these types of solution offers the greatest relative advantage.³

Hydroxyethyl starch (HES) is one example of a colloid solution that is widely used for fluid resuscitation. However, acute kidney injury has been intermittently reported with the use of HES in various patient populations.⁴⁻⁷ Although the pathophysiologic mechanism is unclear, it is possible that microscopic changes referred to as “osmotic nephrosis-like lesions” (histologic lesions that are thought to be related to changes in osmotic pressure)^{4,8} may cause the kidney damage. Acute kidney injury is an important adverse outcome in critically ill patients because it is an independent risk factor for mortality, increasing the risk of long-term morbidity, impaired quality of life and possible dependence on dialysis.⁹⁻¹² Some critically ill patients, such as those with severe sepsis or septic shock, are at increased risk of 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 the effects of resuscitation fluids known to adversely affect kidney function. The evidence about adverse renal outcomes associated with administration of HES from observational studies¹³⁻¹⁶ and randomized controlled trials^{7,17-19} is conflicting.

Previously published systematic reviews of colloids for resuscitation have focused on patients with sepsis or have not reported renal outcomes.^{2,20-22} The objective of the current study was to perform a quantitative systematic review of randomized controlled trials comparing HES with some other intravenous fluid for acute fluid resuscitation of critically ill patients. Our primary outcome of interest was rate of acute kidney injury. Our secondary outcomes were mortality, duration of mechanical ventilation, duration of stay in the intensive care unit (ICU), allergic reactions, bleeding and transfusion of packed red cell units.

Methods

Study sources and searches. Before commencing this systematic review, we planned all aspects of the study protocol, including the clinical question, search strategy, outcomes and analysis.

We first developed a strategy to search Ovid MEDLINE (1950 to 2007 August week 2). This search strategy was adapted to search EMBASE (1980 to 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, who incorporated highly sensitive terms to identify clinical studies.²³ The search was updated in December 2008. The complete MEDLINE search strategy is presented in Appendix 1. We also searched the SCOPUS abstract and citation database to pick up studies from relevant journals missed by the preceding search methods. To identify in-progress or planned studies, we searched 3 trial registries: the UK National Research Register, the Australian New Zealand Clinical Trials Registry and the ClinicalTrials.gov database. We used the chemical abstracts database of the Scientific and Technical Information Network and Google Scholar to identify relevant grey literature. We contacted the manufacturers of HES products (Bristol-Myers Squibb, Fresenius Kabi, B. Braun, BioTime and Abbott Laboratories) to identify published, unpublished and in-progress studies of HES for resuscitation. We searched the abstracts and conference proceedings of the European Society of Intensive Care Medicine, the International Symposium on Intensive Care Medicine, the Society of Critical Care Medicine, the American College of Chest Physicians, the American Thoracic Society, the American Society of Anesthesiologists, the Canadian Anesthesiologists' Society, the International Anaesthesia Research Society and the American Association for the Surgery of Trauma from 2002 to 2007. We also searched the reference lists of all included studies and relevant reviews for suitable trials not identified by the electronic searches. No language restrictions were applied.

We included randomized controlled trials enrolling patients 18 years of age or older who were admitted to an ICU or emergency department and who had an indication for acute fluid resuscitation (hypovolemia, hypotension, inadequate indicators of preloading or filling pressures) and that compared HES with crystalloids, albumin, gelatins or dextran. The comparator fluids chosen are used for acute volume resuscitation in ICUs and emergency departments throughout the world. We excluded

crossover trials, trials in which blood was the comparator fluid and trials examining HES fluids in elective surgery or for acute normovolemic hemodilution. Although several different types of HES solutions are available for use, a uniform mechanism of injury was presumed to occur with all of these products. Thus, all HES solutions were considered in this review, but they were 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)²⁴ and the measurement of urinary biomarkers indicative of kidney injury. Secondary clinical outcome measures were mortality, duration of mechanical ventilation, duration of ICU stay, allergic reactions, bleeding and transfusion of 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 by individuals who were fluent in the language of publication and who had specific training in medical sciences. Two reviewers (RZ and LM) then 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.²⁵ Non-English articles were adjudicated by a single reviewer (RZ) after translation. Discrepancies were resolved by discussion and consensus with a third reviewer (DAF).

Data extraction and quality assessment. Two reviewers (RZ, AFT) independently abstracted data from the English-language trials using a standardized data abstraction form, which had been piloted to ensure completeness and feasibility. For each non-English trial, 1 reviewer fluent in the language of publication abstracted the data. 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,²⁶ which generates 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 ranged from

0 to 5; we considered a score of 3 or greater to represent high methodologic quality. We assessed allocation concealment using the method developed by Schulz and colleagues²⁷ and scored it as “adequate,” “unclear” or “inadequate.” We used a double data-entry system to minimize transcription errors.

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 (ORs) with 95% confidence intervals (CIs). An OR of more than 1 suggests a higher odds of the outcome among patients receiving HES than among 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 that is due to heterogeneity (minimum and maximum values 0% and 100%). We investigated sources of heterogeneity by conducting subgroup analyses based on clinical and methodologic characteristics, which were defined a priori: patient population, type of HES, type of fluid comparator, high- versus low-quality trials, presence or absence of allocation concealment and single-centre versus multicentre trials. We used funnel plots to visually examine the potential for publication bias.

Role of the funding source. There was no external funding source for this work.

Results

Of the 2381 reports identified, 2220 were excluded after initial screening (Fig. 1). We retrieved full-text articles for 161 studies published in 8 languages. Of these 161 articles, 23 met the inclusion criteria. Substantial agreement between the 2 reviewers at level 1 and level 2 screening is reflected in kappa values of 0.64 and 0.68, respectively.²⁸ All discrepancies were resolved by discussion and consensus. During data extraction, we found that 2 publications were separate analyses of the same trial population;^{29,30} we included only the article that was most informative for the purposes of this review.³⁰ From trial registries, we identified 3 randomized trials in progress, but we did not include these in our analyses.

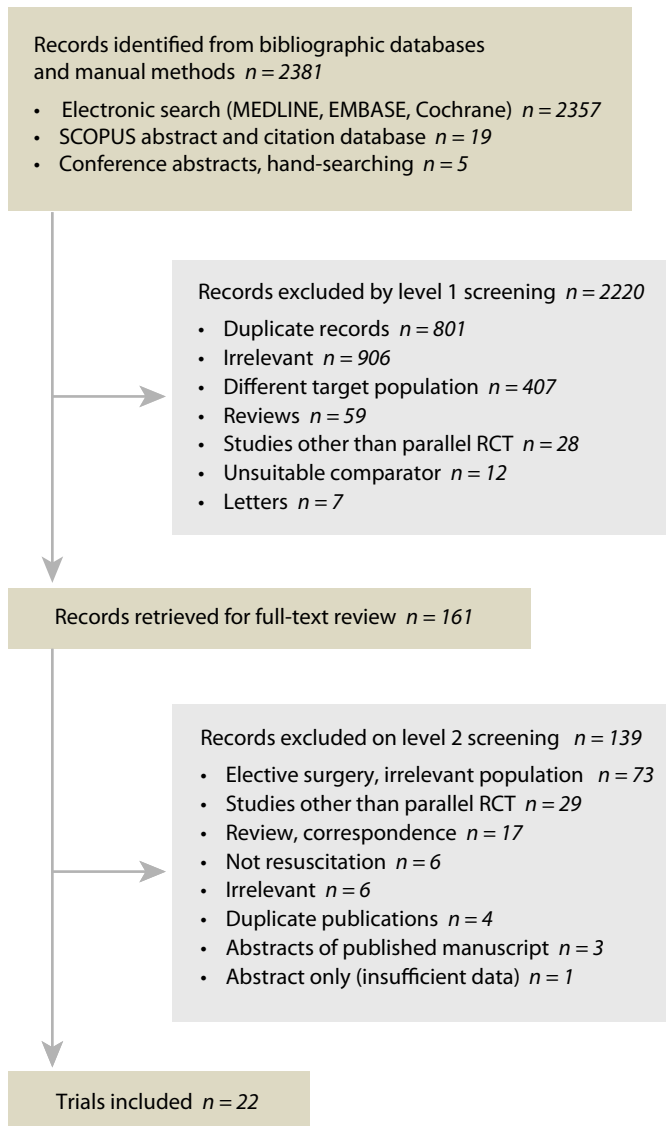


Figure 1: Study flow diagram

The 22 trials accounted for a total of 1865 patients, with a median of 48 patients enrolled per trial (range 12–537). Twenty-one trials were published in peer-reviewed journals, and 1 was published in abstract form.³¹ Twenty trials were reported in English-language journals,^{7,8,18,19,30–45} 1 was in French⁴⁶ and 1 was in German.⁴⁷ Five trials were conducted in North America,^{19,30,40,42,44} 16 in Europe^{7,8,18,31–39,41,43,46,47} and 1 in South America.⁴⁵ Four trials received grant funding from manufacturers of HES,^{18,19,42,44} 2 received government support,^{7,41} and 16 trials reported no funding source.^{8,30–40,43,45–47}

Eight trials enrolled patients with sepsis, severe sepsis or septic shock but no trauma,^{7,18,19,38,40,41,43,44} 6 enrolled patients with trauma,^{31,32,37,42,45,46} 5 enrolled patients with trauma or sepsis,^{33–36,39} and 1 enrolled patients with

“hypovolemic shock”;³⁰ 1 study did not report the type of critically ill patients who formed the study population.⁴⁷ One trial involved organ donors with brain death, who were randomly assigned to receive either HES or gelatin;⁸ in that study, the final unit of analysis was number of transplanted kidneys.

The trials compared HES with 20% albumin,^{33–39,43} 5% albumin,^{30,40,44} gelatin,^{7,8,31,32,41,46,47} dextran,³¹ or a crystalloid solution (Table 1).^{18,19,30,42,45} Two trials included pentoxifylline as a third-arm comparator, but these arms were not included in this systematic review because pentoxifylline is not used for resuscitation.^{37,38} Six different HES fluids, varying by molecular weight and molar substitution, were represented.

All of the trials enrolled patients requiring urgent fluid resuscitation; however, the eligibility criteria varied widely and were not explicitly stated in 2 of the full publications^{32,47} or the single abstract.³¹ Many trials used either low systolic blood pressure or low mean arterial blood pressure as justification for fluid administration.^{7,18,19,30,40,42,44–46} Three trials incorporated increased arterial lactate and cardiac index less than 2.2 L/min as criteria for fluid loading.^{30,40,44} In 8 trials, central venous pressure or pulmonary capillary wedge pressure less than 10–15 mm Hg served as the single trigger for volume loading.^{33–39,43} One trial incorporated clinical signs of hypoperfusion.⁴⁶ Two trials used echocardiographic indicators as surrogates for hypovolemia.^{8,41}

The amount and type of fluid received before randomization was reported in 4 trials.^{18,19,36,43} The duration of the study protocol varied from less than 2 hours to 21 days. Twelve protocols involved administration of HES within the first 24 hours after presentation.^{8,19,30–32,40–42,44–47} The total amount of study fluid administered differed considerably among the trials; in particular, the mean volume of HES given varied from 364 mL (standard deviation [SD] 64)⁴⁵ to 5350 mL (SD 650).³⁸

Relevant cointerventions were reported for several studies. All patients in the trials conducted by Boldt and colleagues^{33–39} received continuous infusions of dopamine at 3 µg/kg per minute. In 1 trial, gelatin was administered to the HES group after they had received 2000 mL of the study colloid.⁴⁶ In another trial, the protocol specified that the components of early goal-directed therapy would include transfusion of red blood cells and infusion of inodilators, in addition to the study fluid.¹⁹ In all studies, vasopressors and inotropes were used when necessary, generally after initial volume resuscitation.

Four trials listed renal sequelae as primary or secondary outcomes.^{7,8,18,19} Four trials reported the requirement

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

Trial (year)	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 ¹⁸ 2008	537 262 / 275	Severe sepsis and septic shock	APACHE II 20.1 / 20.3	CVP < 8 mm Hg or if MAP < 70 mm Hg or SvO ₂ < 70%	HES (200/0.5) To maintain end points based on MAP, CVP and SvO ₂ ; max dose 20 mL/kg per day, then Ringer's lactate	Ringer's lactate To maintain end points based on MAP, CVP and SvO ₂ ; no max dose	HES (median): 70.4 mL/kg (IQR 33.4–144.2)	21 d
McIntyre ¹⁹ 2008	40 21 / 19	Septic shock	APACHE II 21.1 / 20.3	MAP < 65 mm Hg, SBP < 90 mm Hg or SBP > 40 mm Hg below baseline	HES (260/0.45) 500-mL boluses with end points based on MAP, CVP and SvO ₂ ; max dose 28 mL/kg or 3 L in a 12-h period, then open-label normal saline	Normal saline 500-mL boluses with end points based on MAP, CVP and SvO ₂ ; max dose 28 mL/kg or 3 L in a 12-h period, then open-label normal saline	HES: 2100 mL (SD 600) Saline: 1900 mL (SD 600)	12 h
Palumbo ⁴³ 2006	20 10 / 10	Severe sepsis	APACHE II (combined) 18.9	PCWP < 15 mm Hg	HES (130/0.4) To maintain PCWP 15–18 mm Hg	20% albumin To maintain PCWP 15–18 mm Hg	NR	5 d
Molnar ⁴¹ 2004	30 15 / 15	Septic shock	SAPS II 34 / 34	Intrathoracic blood volume < 750 mL/kg	HES (200/0.6) 250-mL boluses every 15 min until intrathoracic blood volume > 900 mL/m ² ; max 1000 mL	Gelatin 250-mL boluses every 15 min until intrathoracic blood volume > 900 mL/m ² ; max 1000 mL	HES: 750 mL (SD 274) Gelatin: 714 mL (SD 254)	1 h
Schortgen ⁷ 2001	129 65 / 64	Severe sepsis and 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 amended during the trial to include max therapy duration of 4 d or to cumulative limit of 80 mL/kg	Gelatin At the discretion of the physician; no dose limitation	HES (median): 31 mL/kg (IQR 19–51) Gelatin (median): 43 mL/kg (IQR 19–60)	4 d
Carli ⁴⁶ 2000	164 85 / 79	Patients with traumatic injuries being transported to hospital	Revised trauma score 5.5 / 5.7	SBP < 100 mm Hg with signs of peripheral hypoperfusion	HES (200/0.5) To keep SBP > 100 mm Hg; max volume 2000 mL	Gelatin To keep SBP > 100 mm Hg; max volume 2000 mL	HES: 820 mL (SD 63) Gelatin: 840 mL (SD 56)	Time to hospital transport: (55–60 min)
Allison ³² 1999	59 30 / 29	Blunt trauma	Injury severity score 20.0 / 18.1	NR	HES (260/0.45) As necessary as the only resuscitation colloid for the first 24 h	Gelatin As necessary as the only resuscitation colloid for the first 24 h	HES: 2744 mL (SD 1068) Gelatin: 3132 mL (SD 914) (first 24 h)	24 h
Boldt ³⁹ 1998	300 150 / 150	Trauma or sepsis secondary to major surgery	APACHE II 20.5 / 20.7	PCWP < 12 mm Hg	HES (200/0.5) To maintain PCWP between 12 and 15 mm Hg	20% albumin To maintain PCWP between 12 and 15 mm Hg	HES: 4970 mL (SD 835) Albumin: 2160 mL (SD 325)	5 d

Table 1 continued

Trial (year)	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
Younes ⁹⁸ ⁴⁵	23 12 / 11	Traumatic injuries in the emergency department	Revised trauma score 9.2 / 8.6	SBP < 90 mm Hg	HES (260/0.45) 250-mL boluses until SBP > 100 mm Hg	Normal saline 250-mL boluses until SBP > 100 mm Hg Saline: 1420 mL (SD 298)	HES: 364 mL (SD 64) Saline: 1420 mL (SD 298)	Until SBP > 100 mm Hg
Jovanovic ³¹ 1997 (abstract)	60 HES: 20 Dextran: 20 Gelatin: 20	Patients with multiple trauma and hemorrhagic shock	NR	Hemorrhagic shock, not otherwise specified	HES (450/0.7) Single bolus of 10–15 mg/kg	Dextran: Single bolus of 7–10 mg/kg Gelatin: Single bolus of 10–15 mL/kg	NR	Less than 2 h
Cittanova ⁸ 1996	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 LV cavity at end systole	HES (200/0.6) 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 procurement
Boldt ³⁴ 1996	56 28 / 28	Trauma or sepsis secondary to major surgery	APACHE II 19.5 / 20.2	CVP or PCWP < 12 mm Hg	HES (200/0.5) To maintain CVP or PCWP at 12–16 mm Hg	20% albumin To maintain CVP or PCWP 12–18 mm Hg	HES: 4065 mL (SD 890) Albumin: 1820 mL (SD 390)	5 d
Boldt ³⁶ 1996	60 30 / 30	Trauma or sepsis secondary to major surgery	APACHE II 19.4 / 19.3	PCWP < 12 mm Hg	HES (200/0.5) To maintain PCWP 12–18 mm Hg	20% albumin To maintain PCWP 12–18 mm Hg	HES: 4720 mL (SD 1155) Albumin: 2030 mL (SD 300)	5 d
Boldt ³⁷ 1996	30 15 / 15	Trauma	APACHE II 20.3 / 20.0	CVP or PCWP < 12 mm Hg	HES (200/0.5) To maintain CVP or PCWP 12–18 mm Hg	20% albumin To maintain CVP or PCWP 12–18 mm Hg	HES: 4880 mL (SD 510) Albumin: 1390 mL (SD 330)	5 d
Boldt ³⁵ 1996	56 28 / 28	Trauma or sepsis secondary to major surgery	APACHE II 18.5 / 18.5	PCWP < 10 mm Hg	HES (200/0.5) To maintain CVP or PCWP 10–15 mm Hg	20% albumin To maintain CVP or PCWP 10–15 mm Hg	HES: 4125 mL (SD 750) Albumin: 2025 mL (SD 375)	5 d
Boldt ³⁸ 1996	28 14 / 14	Sepsis	APACHE II 24.3 / 22.9	CVP or PCWP < 10 mm Hg	HES (200/0.5) To maintain CVP or PCWP 10–15 mm Hg	20% albumin To maintain CVP or PCWP 10–15 mm Hg	HES: 5350 mL (SD 650) Albumin: 2525 mL (SD 350)	5 d
Boldt ³³ 1995	60 30 / 30	Trauma or sepsis secondary to major surgery	APACHE II 20.2 / 20.2	CVP or PCWP < 12 mm Hg	HES (200/0.5) To maintain CVP or PCWP 12–16 mm Hg	20% albumin To maintain CVP or PCWP 12–16 mm Hg	HES: 4170 mL (SD 745) Albumin: 1835 mL (SD 300)	5 d

Table 1 continued

Trial (year)	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
Nagy ¹² 1993	41 21 / 20	Patients with traumatic injuries presenting to a trauma unit	Injury severity score 18.4 / 18.4	SBP < 90 mm Hg	HES (260/0.45) Repeated boluses until SBP > 100 mm Hg and urine output > 30 mL/h; max 4 L, then Ringer's lactate	Ringer's lactate Repeated boluses until SBP > 100 mm Hg and urine output > 30 mL/h	HES: 1750 mL Ringer's lactate: 3629 mL	Until SBP > 100 mm Hg and urine output > 30 mL/h
Rackow ⁴⁴ 1989	20 10 / 10	Severe sepsis	NR	SBP < 90 mm Hg, lactate > 2 mmol/L, CI < 2.2 L/min or PCWP < 12 mm Hg	HES (260/0.45) 250-mL boluses every 15 min until PCWP > 15 mm Hg; max 2000 mL	5% albumin 250-mL boluses every 15 min until PCWP > 15 mm Hg; max 2000 mL	HES: 900 mL (SD 205) Albumin: 975 mL (SD 169)	Until PCWP > 15 mm Hg
Falk ⁴⁰ 1998	12 6 / 6	Septic shock	NR	SBP < 90 mm Hg, CI < 2.2 L/min or lactate > 2 mmol/L	HES (450/0.7) 250-mL boluses every 15 min until PCWP > 15 mm Hg; fluid then continued at 100 mL/h for 24 h	5% albumin 250-mL boluses every 15 min until PCWP > 15 mm Hg; fluid then continued at 100 mL/h for 24 h	HES: 4934 mL (SD 1354) Albumin: 3067 mL (SD 256)	24 h
Hopt ⁶⁷ 1987	87 42 / 45	Critically ill patients requiring resuscitation	NR	NR	HES (70/0.58) 1000-mL bolus, thereafter 500-mL Ringer's lactate, 500 mL 5% dextrose in water and 500 mL levulose 5% every 12 h	Gelatin 1000-mL bolus, thereafter 500 mL Ringer's lactate, 500 mL 5% dextrose in water and 500 mL levulose 5% every 12 h	HES: 1000 mL Gelatin: 1000 mL	24 h
Haupt ³⁰ 1982	26 HES: 9 Albumin: 9 Saline: 8	Hypovolemic shock, not traumatic	NR	SBP < 90 or lactate > 18 mg/dL, and PCWP < 15 mm Hg and CI < 2.2 L/min	HES (450/0.7) 250-mL bolus every 15 min until PCWP 10–15 mm Hg; PCWP maintained for 24 h with additional study fluid	1: Normal saline 2: 5% albumin 250-mL bolus every 15 min until PCWP 10–15 mm Hg; PCWP maintained for 24 h with additional study fluid	HES: 4466 mL (SD 477) Albumin: 3134 mL (SD 370) Saline: 6371 mL (SD 1088)	24 h

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, LVED = left ventricular end diastolic, LV = left ventricular.

for renal replacement therapy,^{7,8,18,19} and 5 trials reported a definition for acute renal failure based on creatinine concentration.^{7,8,18,32,39} Patients with evidence of renal impairment or renal failure, defined by serum creatinine or the need for hemodialysis, were excluded from 9 trials.^{7,18,19,32–36,43} Baseline renal function (serum creatinine) was reported in 5 trials.^{7,8,18,19,39} Comorbidities and risk factors for renal injury were detailed in 2 trials.^{7,18}

Most of the trials included in this review were small, involved a single centre and had low methodologic quality (Table 2). We could not assess most aspects of the

methodologic quality of the study that was available in abstract form only.³¹ Four trials were of high methodologic quality (Jadad score of at least 3).^{7,8,18,19} Adequate allocation concealment was reported in 5 trials.^{7,18,19,45,46} Nine of the 21 evaluable trials reported blinding,^{8,19,33–39} but only 1 described the blinding method.¹⁹ Losses to follow-up were reported in 5 trials.^{7,8,18,19,32} Analysis according to the intention-to-treat principle was reported in 4 trials.^{7,8,18,19} The method of analysis was unclear in 16 trials because information about losses to follow-up was not reported.^{30,33–47}

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

Study	RCT type	Sponsor	Jadad score*					
			Total	Randomization	Blinding	Attrition information	Allocation concealment	ITT analysis
Brunkhorst ¹⁸	Multicentre	Unrestricted industry grant plus public funds	3	2	0	1	Adequate	Yes
McIntyre ¹⁹	Multicentre	Bristol Myers Squibb (unrestricted grant)	5	2	2	1	Adequate	Yes
Palumbo ⁴³	Single centre	NR	1	1	0	0	Unclear	Unclear
Molnar ⁴¹	Single centre	Ministry of Education, Hungary	1	1	0	0	Unclear	Unclear
Schortgen ⁷	Multicentre	Assistance Publique-Hôpitaux de Paris	3	2	0	1	Adequate	Yes
Carli ⁴⁶	Multicentre	NR	1	1	0	0	Adequate	Unclear
Allison ³²	Single centre	NR	1	0	0	1	Inadequate	No
Boldt ³⁹	Single centre	NR	2	1	1	0	Unclear	Unclear
Younes ⁴⁵	Single centre	NR	1	1	0	0	Adequate	Unclear
Jovanovic ³¹ (abstract)	NE	NR	NE	1	NE	NE	NE	NE
Cittanova ⁸	Single centre	NR	3	1	1	1	Unclear	Yes
Boldt ³⁴	Single centre	NR	2	1	1	0	Unclear	Unclear
Boldt ³⁶	Single centre	NR	2	1	1	0	Unclear	Unclear
Boldt ³⁷	Single centre	NR	2	1	1	0	Unclear	Unclear
Boldt ³⁵	Single centre	NR	2	1	1	0	Unclear	Unclear
Boldt ³⁸	Single centre	NR	2	1	1	0	Unclear	Unclear
Boldt ³³	Single centre	NR	2	1	1	0	Unclear	Unclear
Nagy ⁴²	Single centre	American Critical Care	1	1	0	0	Unclear	Unclear
Rackow ⁴⁴	Single centre	Dupont	1	1	0	0	Unclear	Unclear
Falk ⁴⁰	Single centre	NR	1	1	0	0	Unclear	Unclear
Hopf ⁴⁷	Single centre	NR	1	1	0	0	Unclear	Unclear
Haupt ³⁰	Single centre	NR	1	1	0	0	Unclear	Unclear

*The Jadad scale allows assignment of a 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 range from 0 to 5, with a score of 5 indicating high methodologic quality.

RCT = randomized controlled trial, ITT = intention to treat, NR = not reported, NE = not evaluable.

Primary outcome: acute kidney injury. The pooled OR for renal replacement therapy associated with HES fluid for the 4 trials that reported this outcome was 1.90 (95% CI 1.22–2.96, I^2 9.5%, $n = 749$)^{7,8,18,19} (Fig. 2). 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.¹⁸ Three of these 4 trials included patients with severe sepsis or septic shock,^{7,18,19} for which the pooled OR of renal replacement therapy was 1.82 (95% CI 1.27–2.61, I^2 0%, $n = 702$). HES use was also associated with greater odds of renal replacement therapy in the single trial of kidney transplant recipients (OR 9.5, 95% CI 1.09–82.72, $n = 47$).⁸ Further sensitivity analyses were limited by the low number of trials that reported renal outcomes. In 1 study reporting renal replacement therapy as an outcome, the baseline measures of renal function differed between the HES and control groups (see below).⁷

Indices reflecting changes in serum creatinine were reported in 5 trials but were not suitable for pooling because of variable definitions of acute kidney injury and variable timing of laboratory measurements.^{7,8,18,32,39} In the trial involving kidney transplant donors and recipients, serum creatinine values were higher in the first 10 days after transplantation among patients who received

kidneys from donors resuscitated with HES than among patients who received kidneys from donors resuscitated with gelatin ($p < 0.01$).⁸ In another trial of resuscitation in septic shock, the median peak serum creatinine was higher among those who received HES 200/0.60 (molecular weight/molar substitution) than among those who received gelatin (2.5 [interquartile range 1.5–3.8] mg/dL v. 1.9 [1.2–3.1] mg/dL, $p = 0.04$).⁷ However, in that trial, the baseline serum creatinine concentrations were significantly higher among patients randomly assigned 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 the ICU at day 5.^{32,39} None of the trials evaluated acute kidney injury according to the RIFLE categories or characterized changes in urinary biomarkers.

For the 2 trials that enrolled patients with severe sepsis and septic shock, the pooled OR for 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%, $n = 666$) among patients receiving HES.^{7,18} In 1 trial, which reported acute kidney injury as creatinine above 221 $\mu\text{mol/L}$ or urine output less than 20 mL/h, there were no differences between the 2 groups.³⁹

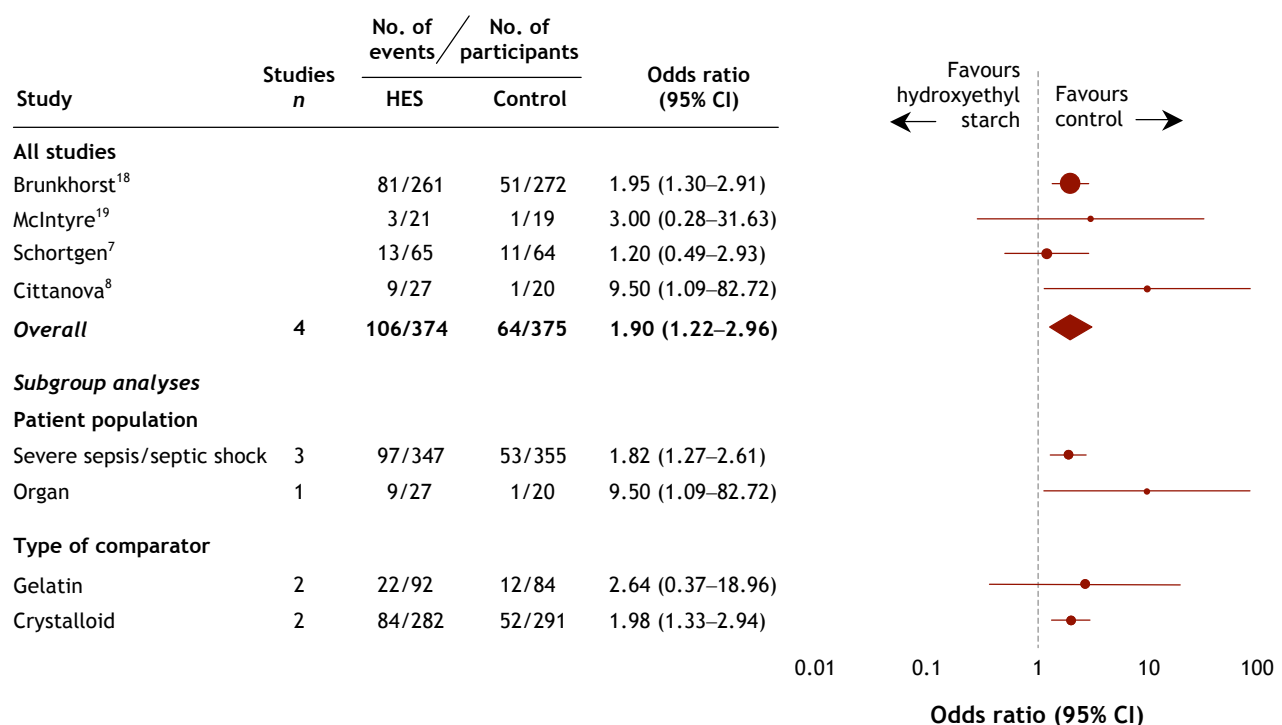


Figure 2: Renal replacement therapy associated with hydroxyethyl starch (HES)

Secondary outcomes: mortality, duration of mechanical ventilation and ICU stay. Mortality was reported for 17 of the 22 trials (Fig. 3). The pooled OR for death associated with HES was 1.07 (95% CI 0.85–1.34, I^2 0%, $n = 1657$). For 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 0.92–1.64, I^2 0%, $n = 782$);^{7,18,19,38,41,44} in trials of patients with trauma, the OR for death was 1.52 (95% CI 0.48–4.75, I^2 25%, $n = 294$); and in trials that included patients with either sepsis or trauma, the OR for death was 0.82 (95% CI 0.55–1.21, I^2 0%, $n = 532$) (Fig. 4). No significant differences in ORs for death were evident with different durations of the study protocols or with use of early goal-directed therapy (data not shown). Similarly, no significant differences in the OR for death occurred with the various fluid comparator groups or when specific molecular weights of HES were analyzed (Fig. 4).

In the 3 trials of higher methodologic quality (Jadad score 3–5) that provided mortality data, the pooled OR for death was 1.27 (95% CI 0.93–1.72, I^2 0%, $n = 704$).^{7,18,19}

In the 5 trials with adequate allocation concealment, the summary OR for death associated with the use of HES was 1.28 (95% CI 0.96–1.72, I^2 0%, $n = 891$) (Fig. 4).^{7,18,19,45,46} 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%, $n = 868$).^{7,18,19,46}

The duration of mechanical ventilation^{39,42} and ventilator-free days¹⁸ was similar for the 3 trials reporting these outcomes. The mean⁴¹ or median^{7,18,19} duration of the ICU stay was comparable between the HES and control groups in 4 of the trials of septic shock. In 1 trial of 59 patients with acute traumatic injuries, mean (SD) ICU length of stay was shorter (8.8 [3.3] days v. 11.1 [3.4] days, $p = 0.01$) among patients who received HES.³²

Safety outcomes. Three of the 22 included trials reported information about allergic reactions or anaphylaxis secondary to administration of HES.^{8,44,46} No allergic reactions were reported in these 3 studies, which accounted for 11% ($n = 211$) of all patients enrolled. One study ($n = 23$) explicitly reported no complications

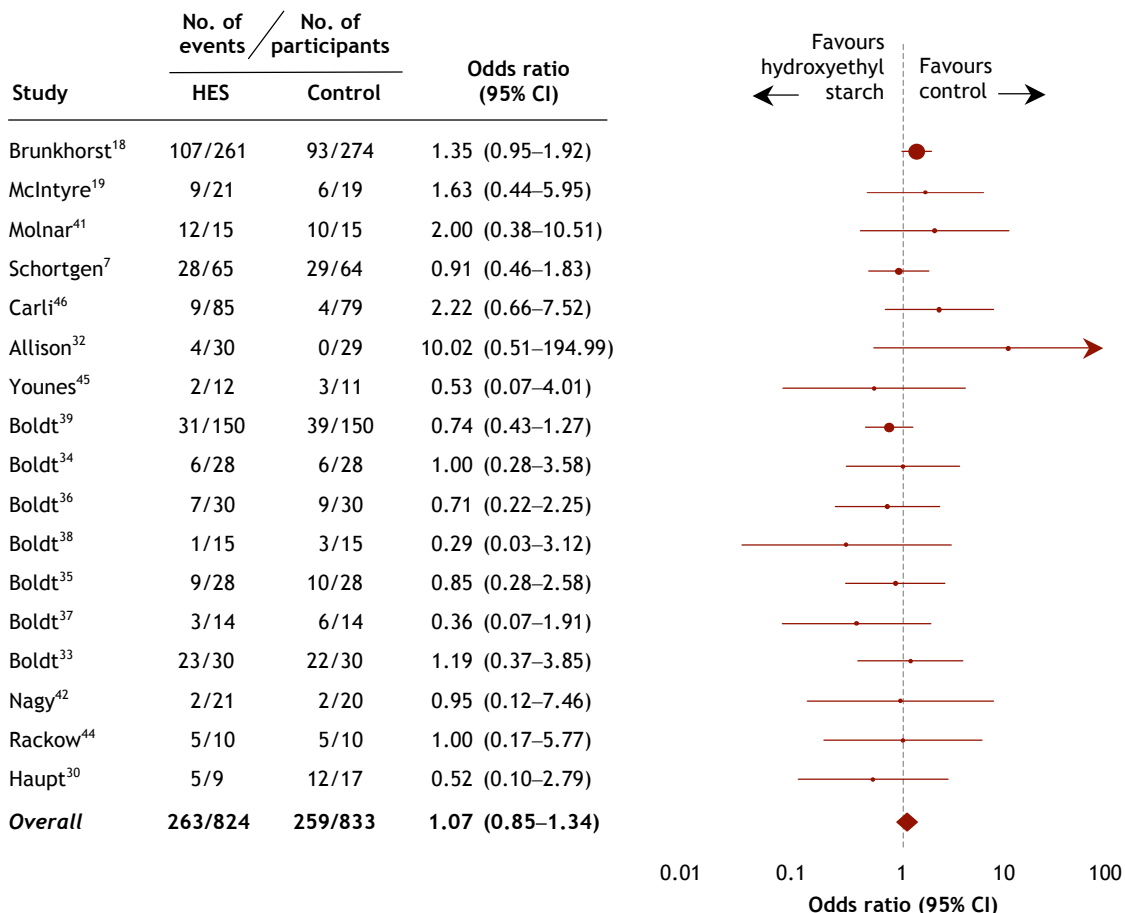


Figure 3: Overall mortality of all included studies

related to the infusion of HES,⁴⁵ and 1 study reported no differences in a composite measure of serious adverse events, which included allergic reactions and bleeding.¹⁸

Insufficient and heterogeneous reporting of coagulopathy, bleeding and red cell transfusions precluded pooled analyses and summary statements for these adverse events.

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 because only 4 trials reported such outcomes. No pattern consistent with publication bias was evident on the funnel plots generated for the outcome of mortality (Fig. 5).

Discussion

In this systematic review, we found that the use of HES for acute volume resuscitation of critically ill patients was associated with 90% greater odds of renal replacement therapy for the 4 trials reporting this outcome (OR 1.90, 95% CI 1.22–2.96). For the 3 trials that enrolled

patients with severe sepsis or septic shock, the odds of receiving renal replacement therapy was 82% greater (OR 1.82, 95% CI 1.27–2.61). No difference in overall mortality was found; however, among studies enrolling patients with severe sepsis and septic shock, and in trials that involved more than one centre, that had high methodologic quality or that reported adequate allocation concealment, there was a trend toward greater odds of death in association with HES. Serious adverse events, including bleeding or coagulopathy, were poorly characterized and inadequately reported.

HES solutions are effective volume expanders but are deposited widely in the tissues, including the skin, liver, muscle, spleen, endothelial cells and kidneys.^{48,49} Just as persistent and significant pruritus is now recognized as a deleterious consequence of starch administration,⁴⁹ so too are the potential consequences for the kidney.^{48,50} Case reports, observational studies and randomized controlled trials involving various patient populations exposed to different HES fluids have inconsistently reported the occurrence of adverse kidney outcomes.^{4,13,14,16,17,48} Although each HES compound has unique pharmacokinetic properties that depend on the

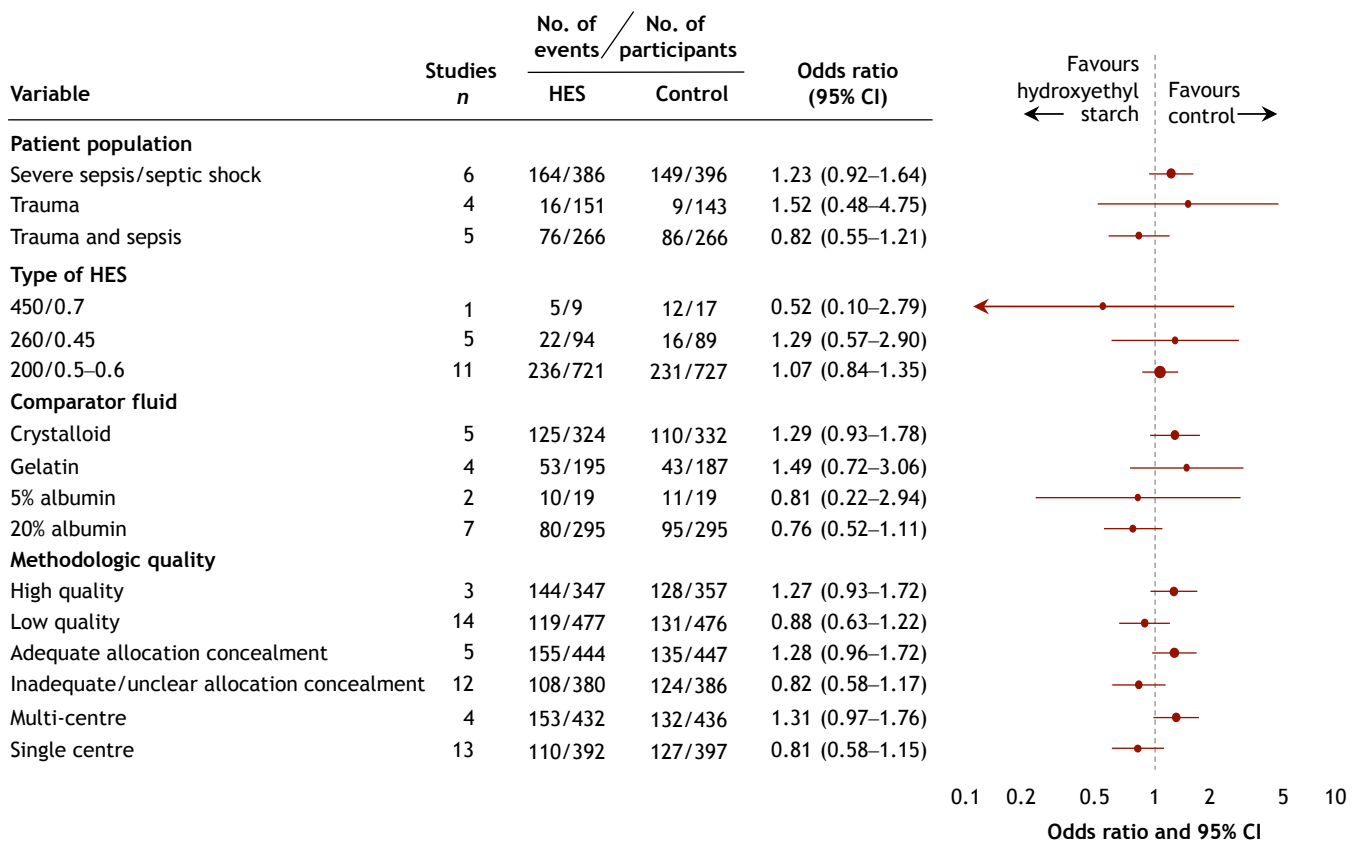


Figure 4: Mortality according to patient population, type of HES, type of comparator fluid and methodologic quality

mean molecular weight, the degree of substitution and the C2:C6 ratio,⁵¹ it is unclear whether these differences affect clinically important outcomes.

This systematic review had several limitations. Although patients assigned to receive HES were more likely to receive renal replacement therapy across all trials that reported this outcome, the pooled analyses were substantially influenced by 1 large trial of patients with severe sepsis and septic shock.¹⁸ Notably, this trial was not blinded, there were violations of the fluid protocols in both study arms (for 26% of the patients in the HES arm and 27% of those in the crystalloid arm), and the dose limit for HES (20 mL/kg per day) was exceeded in 38% of patients on at least day 1 of the study protocol.

In addition, the heterogeneous clinical and methodologic characteristics of the trials included in this review presented challenges for making inferences. Differences in the primary and secondary outcome rates might have been influenced by the patient population and duration of follow-up in each study. Similarly, event rates might have differed according to the type of HES and the comparator fluids, as well as the dosing, duration of exposure and reasons for administering fluid. Few trials reported important baseline characteristics, such as illness severity, or potential risk factors or exposures for acute kidney injury, which would be essential for ensuring that study groups were similar at randomization. Few trials reported relevant cointerventions or details of key renal outcomes such as the duration of renal replacement therapy, renal recovery, the progression to chronic kidney disease or dependence on dialysis. Nevertheless, the development of acute kidney injury in critically ill patients, independent of receiving renal replacement therapy, has been associated with higher mortality.¹² Whether or not patients with severe sepsis or septic shock should receive colloids, especially HES, for initial (e.g., “early goal-directed”) volume resuscitation requires further investigation.

An HES fluid with lower molecular weight and less substitution is currently available and is being marketed as having an excellent safety profile;⁵² however, there is

as yet no published evidence from large, definitive randomized controlled trials in critically ill patients to confirm the efficacy or safety of this solution. Moreover, all manufacturers of starch solutions list kidney dysfunction and/or oliguria as contraindications.

The clinical use of colloidal starch solutions, including HES, has increased despite their higher cost relative to crystalloid solutions (M. Baker, Concordia Hospital, Winnipeg, Manitoba; M. Haun, Canadian Blood Services, Ottawa, Ontario; personal communications by email, 2008) and a lack of evidence of their clinical superiority.^{2,20,21,48} HES products now appear in several resuscitation guidelines, including the those of the US Hospital Consortium.⁵³ However, our systematic review has documented that HES administered to critically ill patients appears to be associated with greater use of renal replacement therapy. This finding was consistent across the 3 studies of patients with severe sepsis and septic shock that reported this adverse outcome. It is unclear whether this adverse effect applies to all HES fluids and all critically ill patients. Methodologically rigorous, adequately powered randomized controlled trials 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 such studies become available, we do not recommend the routine use of starches for acute volume resuscitation in critically ill patients, particularly patients with severe sepsis or septic shock.

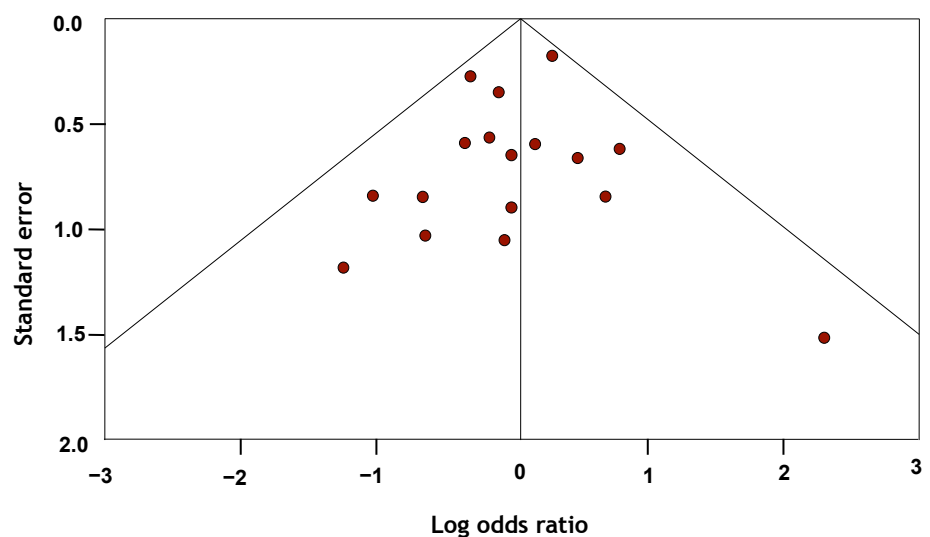


Figure 5: Assessment of publication bias for overall mortality

Contributors: All listed authors made substantial contributions to the conception and design of this study and to the acquisition, analysis and interpretation of data. Ryan Zarychanski drafted the original article, which was substantially revised for important intellectual content by all authors. Each author approved the final version of the article before submission for publication.

Acknowledgments: 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 would also like to thank several anonymous reviewers for their suggestions on earlier drafts of this manuscript.

Citation: Ryan Zarychanski, Alexis F Turgeon, Dean A Fergusson, Deborah J Cook, Paul Hébert, Sean M Bagshaw, Danny Monsour, Loralyn McIntyre. Renal outcomes and mortality following hydroxyethyl starch resuscitation of critically ill patients: systematic review and meta-analysis of randomized trials. *Open Med* 2009;3(4):e196-209.

Published: 27 October 2009

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Appendix 1: MEDLINE search strategy

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