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Fluid Resuscitation in Sepsis

A Systematic Review and Network Meta-analysis

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Background: Fluid resuscitation is the cornerstone of sepsis treatment. However, whether balanced or unbalanced crystalloids or natural or synthetic colloids confer a survival advantage is unclear.

Purpose: To examine the effect of different resuscitative fluids on mortality in patients with sepsis.

Data Sources: MEDLINE, EMBASE, *ACP Journal Club*, CINAHL, HealthSTAR, the Allied and Complementary Medicine Database, and the Cochrane Central Register of Controlled Trials through March 2014.

Study Selection: Randomized trials that evaluated different resuscitative fluids in adult patients with sepsis or septic shock and death. No language restrictions were applied.

Data Extraction: Two reviewers extracted data on study characteristics, methods, and outcomes. Risk of bias for individual studies and quality of evidence were assessed.

Data Synthesis: 14 studies (18 916 patients) were included with 15 direct comparisons. Network meta-analysis at the 4-node level showed higher mortality with starches than with crystalloids (high confidence) and lower mortality with albumin than with crystalloids (moderate confidence) or starches (moderate confidence). Network meta-analysis at the 6-node level showed lower mortality with albumin than with saline (moderate confidence) and low-molecular-weight starch (low confidence) and with balanced crystalloids than with saline (low confidence) and low- and high-molecular-weight starches (moderate confidence).

Limitations: These trials were heterogeneous in case mix, fluids evaluated, duration of fluid exposure, and risk of bias. Imprecise estimates for several comparisons in this network meta-analysis contribute to low confidence in most estimates of effect.

Conclusion: Among patients with sepsis, resuscitation with balanced crystalloids or albumin compared with other fluids seems to be associated with reduced mortality.

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Resuscitation with crystalloids compared with colloids for critically ill patients has been evaluated in large randomized, controlled trials (1–6) and meta-analyses (7–13). One meta-analysis (10) including 74 trials reported no difference in mortality between critically ill patients resuscitated with crystalloids and albumin (relative risk [RR], 1.01 [95% CI, 0.93 to 1.10]), hydroxyethyl starch (HES) (RR, 1.10 [CI, 0.91 to 1.32]), gelatin (RR, 0.91 [CI, 0.49 to 1.72]), or dextran (RR, 1.24 [CI, 0.94 to 1.65]). Another meta-analysis (8) reported that resuscitation with an albumin-containing solution in patients with sepsis may decrease mortality compared with solutions containing no albumin (RR, 0.82 [CI, 0.67 to 1.00]).

Recent evidence suggests that starches, compared with other fluids and regardless of molecular weight, may be associated with acute kidney injury in the general population of critically ill patients and in those with sepsis (5, 11, 13–15). A recent large pragmatic trial comparing colloids (mostly starches) with crystalloids (mostly 0.9% sodium chloride) suggested a 90-day mortality benefit with colloids (RR, 0.92 [CI, 0.86 to 0.99]) (16).

Crystalloids can be characterized on the basis of tonicity and electrolyte content. The presence of an organic anion (for example, lactate, acetate, or gluconate) and correspondingly lower chloride content that more closely resembles the composition of plasma suggest that a crystalloid is "balanced" (for example, Ringer lactate and acetate solutions) (17). The most commonly used crystalloid, normal saline (0.9% sodium chloride), is far from "normal," with a pH much less than 7.0 and a supraphysiologic chloride content of 154 mmol/L (18, 19). Compared with a balanced crystalloid solution, normal saline predisposes patients to hyperchloremic metabolic acidosis, decreased renal blood flow to the glomerulus, and impaired smooth-muscle contractility (20).

Investigators have not done randomized, controlled trials (RCTs) comparing balanced and unbalanced crystalloids. However, 1 large before–after study of critically ill patients showed that balanced versus unbalanced fluid solution was associated with a lower incidence of acute kidney injury (8.4% vs. 14%; $P < 0.01$) and renal replacement therapy (6.3% vs. 10%; $P = 0.05$) but no differences in hospital mortality (18).

Colloids include natural compounds, such as albumin, and synthetic compounds of HES, gelatin, or dextran. Expansion of plasma volume increases in proportion to the

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osmotic or oncotic potential, and colloids theoretically require less volume than crystalloids to achieve equivalent hemodynamic effect (19). Limitations of colloids include development of acute kidney injury and coagulation disorders with starches (14) and albumin creates risk for exposure to blood products (19). Another important consideration is the biochemical properties of the crystalloid solution in which the colloid is dissolved. For example, the chloride concentrations in HES may vary between 154 mmol/L (Voluven, Fresenius Kabi) and 118 mmol/L (Tetraspan, B. Braun Medical) (21).

Whether any of these fluid properties translate into a survival advantage remains unclear, particularly regarding the optimal fluid for resuscitation in patients with sepsis. Fluid resuscitation, in addition to antibiotics and source control, is a cornerstone of initial management of sepsis (22). However, fluid management in patients with sepsis varies widely in practice (16, 23, 24).

Meta-analyses of fluid resuscitation have been limited by not focusing on patients with sepsis (7, 9, 10), not considering electrolyte composition (5, 8, 10, 11), considering only 2 or 3 categories of fluid (25), not including direct and indirect comparisons in the same model, and omission of recent large RCTs (3–5, 16). Therefore, we did a network meta-analysis (NMA) considering direct and indirect comparisons of all types of fluid resuscitation tested in RCTs in patients with severe sepsis and septic shock, focusing on the effect of these interventions on mortality.

METHODS

Data Sources and Searches

This review was done using a predefined protocol. Initially, we searched MEDLINE (1948 to December 2012), EMBASE (1980 to December 2012), *ACP Journal Club* (1991 to December 2012), the Cochrane Central Register of Controlled Trials, HealthSTAR, the Allied and Complementary Medicine Database, and CINAHL. We updated the MEDLINE and EMBASE searches in August 2013 and March 2014. We screened previously published meta-analyses for relevant citations. **Supplement 1** (available at www.annals.org) presents the search terms used.

Six reviewers working in 3 pairs screened the titles and abstracts to determine potential eligibility, and entries identified by any reviewer proceeded to the full-text eligibility review. Pretested eligibility forms were used for full-text review, which was also done in duplicate. A third adjudicator helped to resolve disagreements through consensus.

Study Selection

We selected parallel-group RCTs, including factorial designs, but excluded quasi-randomized and crossover trials. We excluded all studies published by Dr. Joachim Boldt because of suspected lack of integrity (26, 27). We did not apply restrictions on language or publication date.

We included studies that involved adult (aged ≥16 years) critically ill patients with severe sepsis or septic shock as defined by the investigators and who required fluid resuscitation (defined as the administration of a bolus of intravenous fluid exceeding the amount required for maintenance or replacement fluids). We included studies with mixed critically ill populations whenever separate data for patients with sepsis were available. We excluded studies in which most patients had the systemic inflammatory response syndrome secondary to other causes (such as burn, pancreatitis, and trauma) without a clear sepsis subgroup and those focusing on patients after elective surgery.

Interventions studied included any fluid or fluid strategy used for resuscitation compared with another fluid or fluid strategy. We excluded studies in which the primary goal was to assess short-term hemodynamic response.

Our outcome was 90-day mortality or, if not available, 30-day, intensive care unit, or hospital mortality, whichever was longest.

Data Extraction

Pairs from the same 6 reviewers abstracted data in duplicate. Another clinician reviewed disagreements, and consensus was reached by discussion. We contacted authors of primary publications for missing or unclear information.

Risk of Bias

Independently and in duplicate, reviewers assessed risk of bias using a modified version of the Cochrane Collaboration assessment tool (28, 29). We judged each included study as having low, probably low, probably high, or high risk of bias for randomization-sequence generation, randomization concealment, blinding, incomplete data, selective reporting, and free of other bias (including intention-to-treat analysis). The overall rating of risk of bias for each study was the lowest rating for any of the criteria (**Appendix Table**, available at www.annals.org).

Data Synthesis and Analysis

Our analysis classified fluids as crystalloids (divided into balanced and unbalanced solutions) and colloids (divided into albumin, gelatin, and low- and high-molecular-weight HES [threshold molecular weight, 150 000 kDa]). We considered fluid balanced if it contained an anion of a weak acid (buffer) and its chloride content was correspondingly less than in 0.9% sodium chloride (21). The relevant analyses were a 4-node NMA (crystalloids vs. albumin vs. HES vs. gelatin), a 6-node NMA (crystalloids vs. albumin vs. HES vs. gelatin, with crystalloids divided into balanced or unbalanced and HES divided into low or high molecular weight), and a conventional direct frequentist fixed-effects meta-analytic comparison of crystalloids versus colloids.

To calculate direct estimates of treatment effect for each pair of treatments in the 4- and 6-node networks, we

did a frequentist fixed-effects meta-analysis. We reported the results as odds ratios (ORs) and corresponding 95% CIs. We evaluated heterogeneity by estimating the variance between studies (chi-square test and I^2 statistic) (30, 31).

Using a Bayesian framework, we did 4- and 6-node fixed-effects NMAs for each treatment. We reported the results as ORs and corresponding 95% credibility intervals (CrIs), which are the Bayesian analogue of 95% CIs (32). The ORs reported are relative effects of compared fluids. The models are based on 80 000 iterations with a burn-in of 40 000 and a thin of 10. We used a random seed and vague priors. We assessed nonconvergence on the basis of Brooks–Gelman–Rubin plots (33).

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess confidence in estimates of effect (quality of evidence) associated with specific comparisons, including estimates from direct, indirect, and final NMAs (**Supplement 2**, available at www.annals.org) (34). Our confidence assessment addressed risk of bias, incoherence, imprecision, inconsistency, indirectness, and publication bias.

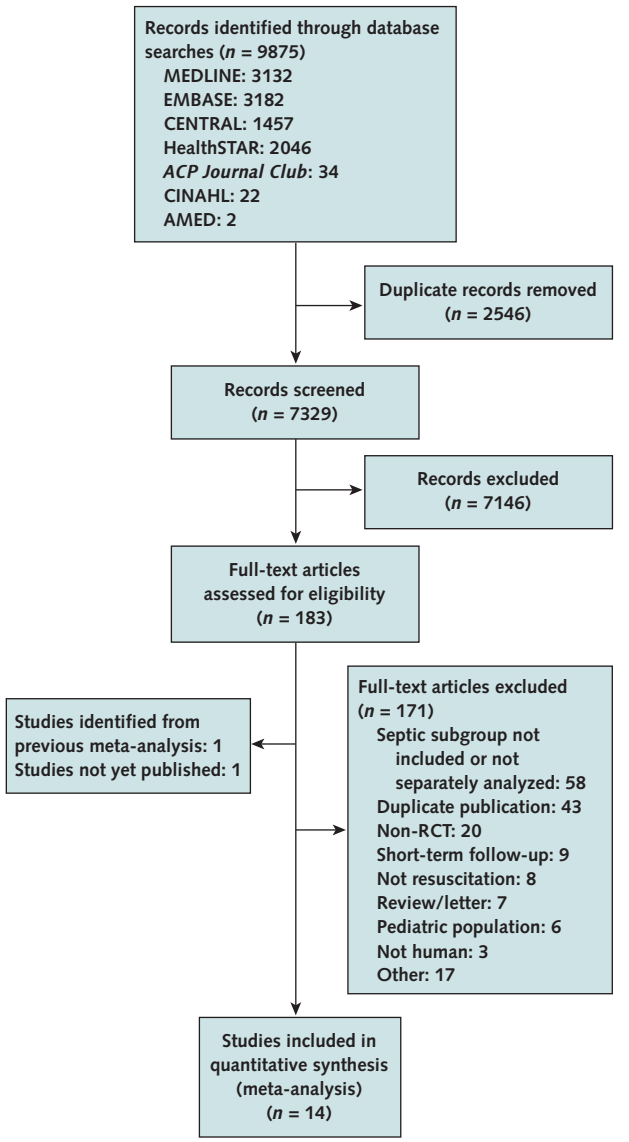
The starting point for confidence in direct and indirect estimates was "high." However, indirect estimates were potentially rated down for intransitivity (that is, differences in patients, co-interventions, or settings that could lead to effect modification and thus a misleading comparison of fluid management strategies). We inferred confidence in indirect estimates by examining the connecting loops associated with the particular comparison.

The confidence rating chosen was the lowest of the direct estimates contributing to the indirect comparison. For example, consider a comparison of A versus B that is informed by comparisons of A versus C and B versus C. If A versus C was rated as high confidence and B versus C as moderate confidence, the overall indirect confidence rating was initially based on the comparison of B versus C and was then potentially rated down to low for indirectness. Precision was judged on the basis of the CrI around the point estimate from the indirect comparison.

The overall NMA confidence rating was the higher confidence in the direct and indirect comparisons with the possibility of rating up further for gains in precision with pooling of direct and indirect comparisons. Confidence was lowered 1 level for incoherence if the CrIs between the direct and indirect estimates did not significantly overlap. The approach we used was consistent with preliminary GRADE guidance and GRADE methods for direct comparisons (35, 36).

We did the Bayesian analysis for the NMA using WinBUGS 1.4.3 (Medical Research Council Biostatistics Unit; www.mrc-bsu.cam.ac.uk/software/bugs/), and all frequentist analysis was done using Review Manager 5.2.3 (Nordic Cochrane Centre; http://ims.cochrane.org/revman/download).

Figure. **Summary of evidence search and selection.**



AMED = Allied and Complementary Medicine Database; CENTRAL = Cochrane Central Register of Controlled Trials; RCT = randomized, controlled trial.

Role of the Funding Source

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RESULTS

Of 9875 titles identified during the primary search (7329 after duplicates were removed), 7146 were judged as ineligible, leaving 185 studies for full-text review (**Figure**).

Table 1. **Study Characteristics**

Study, Year (Reference)	Centers, *n*	Country	Randomly Assigned Patients, *n*	Sepsis*	Mean APACHE II Score
Haupt and Rackow, 1982 (38)	1	United States	17	NR	NR
Rackow et al, 1989 (42)	1	United States	20	Yes	NR
Schortgen et al, 2001 (43)	3	France	129	Yes	NR
Finfer et al, 2004 (2)	16	Australia and New Zealand	6997	Yes	18.9
Brunkhorst et al, 2008 (1)	18	Germany	537	Yes	20.0
Li et al, 2008 (39)	1	China	60	Yes	18.0
McIntyre et al, 2008 (41)	4	New Zealand and Canada	40	Yes	20.6
Dubin et al, 2010 (37)	2	Argentina	25	Yes	NR**
Siegemund, 2011 (44)	1	Switzerland	241	NR	Not included
Guidet et al, 2012 (6)	24	France and Germany	196	Yes	NR**
Lv et al, 2012 (40)	1	China	42	NR	NR
Myburgh et al, 2012 (3)	32	Australia and New Zealand	7000	NR	17.0
Perner et al, 2012 (4)	26	Scandinavia	804	Yes	NR§§
Annane et al, 2013 (16)	57	Worldwide	2857	Yes	NR‖‖

AL = albumin; APACHE = Acute Physiology and Chronic Health Evaluation; COL = colloid; CRY = crystalloid; GL = gelatin; HES = hydroxyethyl starch; H-HES = high-molecular-weight hydroxyethyl starch; HS = hypertonic saline; ICU = intensive care unit; L-HES = low-molecular-weight hydroxyethyl starch; NR = not reported; NS = normal saline; RA = Ringer acetate; RL = Ringer lactate.
* According to international sepsis definition or similar. Definition from reference 45.
† Except where noted.
‡ Mean.
§ Hospital stay.
‖ ICU stay.
¶ Intervention was unblinded.
** Mean Sequential Organ Failure Assessment score, 8.5.
†† Median.
‡‡ Study fluid administered during the first 4 d of the study.
§§ Mean Sequential Organ Failure Assessment score, 7.0.
‖‖ Mean Sequential Organ Failure Assessment score, 8.0.

This total included 2 unpublished studies, 1 found through screening titles included in a previous meta-analysis (5) and another (since published) found through author correspondence (16). Of these 185 RCTs, 171 were ineligible, leaving 14 eligible RCTs (1–6, 16, 37–43).

Table 1 summarizes the characteristics of 14 trials involving 18 916 adults available for analysis (44). In 4 included trials (2, 3, 16, 38), septic patients were a subgroup of all patients enrolled; only 1 of these 4 studies (16) stratified randomization on the basis of the diagnosis of sepsis. Through contact with primary authors or authors of previous reviews, we obtained relevant data for 10 of the 14 studies. No additional data were needed for the other 4 studies.

Most included studies used a definition of sepsis consistent with international consensus (45). Five studies reported mean Acute Physiology and Chronic Health Evaluation II scores between 17.0 and 20.6, whereas another 4 studies reported median Sequential Organ Failure Assessment scores between 7.0 and 8.5. The fluid intervention period lasted between 24 hours and 90 days. The observation period for outcome assessment varied between 30 days and 1 year.

Appendix Figures 1 and **2** (available at www.annals.org) present network nodes showing direct and indirect comparisons and the number of studies available for comparisons. **Table 2** indicates the contribution of individual studies and the subclassification of each fluid at each level of analysis.

4-Node Analysis

Table 3 presents the results of the 4-node analysis. The results suggest higher mortality with starches than with crystalloids (OR, 1.13 [95% CrI, 0.99 to 1.30]; high

Table 1—Continued

Intervention and Cumulative Dose	Blood Products Transfused, *n/N (%)*†	Intervention Period (Mortality Observation Period)	Overall Risk of Bias	Deaths, *n/N*	Industry Sponsor
NS: 6371 mL‡ AL: 3134 mL‡ H-HES: 4466 mL‡	NR	24 h§	Probably low	NS: 3/4 AL: 5/7 H-HES: 3/6	Cutter
AL: 975 mL H-HES: 900 mL	NR	<24 h§	Probably low	AL: 5/10 H-HES: 5/10	Dupont Critical Care; Cutter
GL: 43 mL/kg H-HES: 31 mL/kg	NR	GL: Until ICU discharge‖ H-HES: 4 d‖	Low	GL: 29/64 H-HES: 28/65	NR
NS: >3000 mL AL: >2000 mL	NR	28 d (31 d)	Low	NS: 217/615 AL: 185/603	CSL Behring
RL: 1.32 × HES dose HES: 70.4 mL/kg	RL: 189/275 (68.7) HES: 199/262 (76)	21 d (90 d)	Low¶	RL: 93/274 HES: 107/261	B. Braun Medical; Novo Nordisk; HemoCue
HES/HS: NR HES: NR HS: NR NS: NR	NR	<24 h (31 d)	Probably low¶	HES/HS: 5/15 HES: 9/15 HS: 10/15 NS: 10/15	NR
NS: 2100 mL H-HES: 1900 mL	NS: 5/19 (26) H-HES: 10/21 (48)	<24 h§	Low	NS: 7/19 H-HES: 9/21	Bristol-Myers Squibb; Edward Life Sciences
NS: 6254 mL L-HES: 2610 mL	NS: 18% L-HES: 22%	24 h (31 d)	Probably low¶	NS: 7/13 L-HES: 3/12	NR
NS: NR L-HES: 3775 mL††	NR	5 d (1 y)	Low	NS: 50/124 L-HES: 44/117	Fresenius
NS: 2788 mL L-HES: 2615 mL	NS: 20/96 (21) L-HES: 29/100 (29)	4 d (90 d)	Low	NS: 32/95 L-HES: 40/99	Fresenius Kabi
RL: 3460 mL L-HES: 2770 mL	NR	Not clear‖	Probably low¶	RL: 12/20 L-HES: 7/22	NR
NS: 2456 mL‡‡ L-HES: 2104 mL‡‡	NR	90 d (90 d)	Low	NS: 224/945 L-HES: 248/976	Fresenius Kabi
RA: 3000 mL† L-HES: 3000 mL†	RA: 204/380 (54) L-HES: 243/376 (65)	90 d (90 d)	Low	RA: 173/400 L-HES: 202/398	B. Braun Medical
CRY: 3000 mL in 7 d COL: 2000 mL in 7 d	CRY: 358/1443 (24.8) COL: 377/1414 (26.7)	Until ICU discharge (90 d)	Low	CRY: 286/779 COL: 252/774	None

confidence) and lower mortality with albumin than with crystalloids (OR, 0.83 [CrI, 0.65 to 1.04]; moderate confidence) and starches (OR, 0.73 [CrI, 0.56 to 0.95]; moderate confidence) (**Table 3**).

6-Node Analysis

Table 4 presents the results of the 6-node analysis. Evidence suggests that albumin is superior to saline (OR, 0.82 [CrI, 0.65 to 1.04]; moderate confidence) and low-molecular-weight starch (OR, 0.79 [CrI, 0.59 to 1.06]; low confidence). It also suggests that balanced crystalloids are superior to saline (OR, 0.78 [CrI, 0.58 to 1.05]; low confidence), high-molecular-weight starch (OR, 0.82 [CrI, 0.60 to 1.13]; moderate confidence), and low-molecular-weight starch (OR, 0.75 [CrI, 0.58 to 0.97]; moderate confidence).

Post Hoc Sensitivity Analysis

Supplement 3 (available at www.annals.org) shows the results of 2 sensitivity analyses that were done at the request of peer reviewers. The first analysis incorporates the recently published ALBIOS (Albumin Italian Outcome Sepsis) trial (46). Given that the aim of fluid administration in this trial was not clearly resuscitative, we had initially excluded it from our review. Inclusion of the ALBIOS trial in this post hoc analysis did not affect our results. The second analysis was done to investigate the effect of excluding the older studies by Haupt and Rackow (38) and Rackow and colleagues (42), both with low event rates and few patients. This requested post hoc analysis also did not affect our results.

Crystalloids Versus Colloids

A crude analysis showed no difference in mortality between colloids and crystalloids for fluid resuscitation in adult patients (OR, 0.99 [CI, 0.89 to 1.10]; $P = 0.85$; chi-square = 23.20; $I^2 = 53\%$; moderate confidence [because of inconsistency]) (**Appendix Figure 3**, available at www.annals.org).

DISCUSSION

The results of this NMA highlight potentially important differences in mortality between crystalloid solutions. Our findings suggest an advantage of balanced crystalloids versus saline (low confidence) and low- or high-molecular-weight starch (moderate confidence), with similar mortality results for balanced crystalloids and albumin (very low confidence) (**Table 4**). These differences were not detectable using a standard meta-analytic approach directly comparing "any crystalloids versus any colloids," the results of which are consistent with previous meta-analyses (7, 10) and a recent large RCT (16).

Table 2. **Contribution of Individual Studies to Each Level of Analysis**

Fluid Name, by Study, Year (Reference)	Trade Name	Crystalloid vs. Colloid	4-Node Analysis	6-Node Analysis
Haupt and Rackow, 1982 (38)				
Normal saline	Saline	Crystalloid	Crystalloid	Saline
5% albumin	Albumin	Colloid	Albumin	Albumin
6% HES	Hespan (B. Braun Medical)	Colloid	HES	H-HES
Rackow et al, 1989 (42)				
5% albumin	Albumin	Colloid	Albumin	Albumin
10% HES	Pentastarch	Colloid	HES	H-HES
Schortgen et al, 2001 (43)				
3% gelatin	Plasmagel (Laboratoire Roger Bellon)	Colloid	Gelatin	Gelatin
6% HES	HAES-steril (Fresenius Kabi)	Colloid	HES	H-HES
Finfer et al, 2004 (2)				
Normal saline	Saline	Crystalloid	Crystalloid	Saline
4% albumin	Albumex (CSL Behring)	Colloid	Albumin	Albumin
Brunkhorst et al, 2008 (1)				
RL	RL	Crystalloid	Crystalloid	Balanced crystalloid
10% HES	Pentastarch	Colloid	HES	H-HES
Li et al, 2008 (39)				
HES in hypertonic saline	NR	Colloid	HES	H-HES
HES	NR	Colloid	HES	H-HES
Hypertonic saline	NR	Crystalloid	Crystalloid	Saline
Normal saline	NR	Crystalloid	Crystalloid	Saline
McIntyre et al, 2008 (41)				
Normal saline	Saline	Crystalloid	Crystalloid	Saline
10% HES	Pentastarch	Colloid	HES	H-HES
Dubin et al, 2010 (37)				
Normal saline	Saline	Crystalloid	Crystalloid	Saline
6% HES	Voluven (Fresenius Kabi)	Colloid	HES	L-HES
Siegemund, 2011 (44)				
Normal saline	Saline	Crystalloid	Crystalloid	Saline
6% HES	Voluven (Fresenius Kabi)	Colloid	HES	L-HES
Guidet et al, 2012 (6)				
Normal saline	Saline	Crystalloid	Crystalloid	Saline
6% HES	Voluven (Fresenius Kabi)	Colloid	HES	L-HES
Lv et al, 2012 (40)				
RL	RL	Crystalloid	Crystalloid	Balanced crystalloid
6% HES	Voluven (Fresenius Kabi)	Colloid	HES	L-HES
Myburgh et al, 2012 (3)				
Normal saline	Saline	Crystalloid	Crystalloid	Saline
6% HES	Voluven (Fresenius Kabi)	Colloid	HES	L-HES
Perner et al, 2012 (4)				
RA	RA	Crystalloid	Crystalloid	Balanced crystalloid
6% HES	Tetraspan (B. Braun Medical)	Colloid	HES	L-HES
Annane et al, 2013 (16)				
Any crystalloid	NA	Crystalloid	Not included in analysis	Not included in analysis
Any colloid	NA	Colloid	Not included in analysis	Not included in analysis

HES = hydroxyethyl starch; H-HES = high-molecular-weight hydroxyethyl starch; L-HES = low-molecular-weight hydroxyethyl starch; NA = not applicable; NR = not reported; RA = Ringer acetate; RL = Ringer lactate.

Biological rationale is consistent with the findings of lower mortality with balanced crystalloid solutions than with saline, because balanced fluids mimic the homeostatic composition of body fluids to a greater extent than unbalanced fluids (17, 18). Which component of balanced solutions—the pH, electrolyte composition, or presence of a buffer—contributes to this potential benefit is unclear. These results raise concerns about whether using mostly unbalanced crystalloids in the acute resuscitation of patients with sepsis is optimal. Our findings may partially explain the higher 90-day mortality rates observed in the crystalloid group compared with the colloid group of a

Table 3. **NMA Results of 4-Node Analysis, Including Confidence Assessments**

Comparison	Trials With Direct Comparisons, *n*	Direct Estimate (95% CI); Quality of Evidence	Indirect Estimate (95% CrI); Quality of Evidence	NMA Estimate (95% CrI)*; Quality of Evidence
Starch vs. crystalloid	10	1.14 (0.99–1.30); high	0.81 (0.13–5.14); very low†‡	1.13 (0.99–1.30); high
Albumin vs. crystalloid	2	0.81 (0.64–1.03); moderate§	1.13 (0.18–7.32); very low†‡	0.83 (0.65–1.04); moderate
Gelatin vs. crystalloid	0	–	1.24 (0.61–2.55); very low†§	1.24 (0.61–2.55); very low
Albumin vs. starch	2	1.40 (0.35–5.56); low‡	0.71 (0.54–0.94); moderate†	0.73 (0.56–0.95); moderate
Gelatin vs. starch	1	1.09 (0.55–2.19); low‡	–	1.10 (0.54–2.22); low
Gelatin vs. albumin	0	–	1.51 (0.71–3.20); very low†‡	1.51 (0.71–3.20); very low

CrI = credibility interval; NMA = network meta-analysis.
* Higher of direct or indirect confidence.
† Rated down for indirectness.
‡ Rated down 2 levels for imprecision.
§ Rated down for imprecision.

recent trial in which 86% of the patients randomly assigned to crystalloids received normal saline (16).

We found that the effects of different colloids may also vary, with albumin seeming to be equivalent or superior to all alternatives. Starches, regardless of molecular weight, seem inferior to alternative resuscitation fluids (that is, albumin and balanced crystalloids). Data on gelatin are markedly less robust. Gelatin is associated with increased mortality relative to some other resuscitation fluids; however, only 1 small trial contributes directly to this analysis. The heterogeneity of effects observed across different types of colloids renders crude comparisons of colloids versus crystalloids uninformative (**Appendix Figure 3**).

The strengths of this review include a precise clinical question restricted to patients with sepsis rather than all critically ill patients. It focuses on resuscitation rather than maintenance fluid and distinguishes between balanced and unbalanced crystalloids and between starches of different molecular weight. We did a comprehensive search and risk-of-bias assessment, with both processes involving duplicate review and third-party adjudication. Using rigorous NMA methods (32), we incorporated direct and indirect evidence. The GRADE approach, seldom applied to NMA, allowed reporting of confidence in estimates of effect during interpretation of each unique fluid comparison.

The limitations of our review include the small number of studies relative to the number of comparisons considered, resulting in low confidence in estimates for many key analyses. Although all included studies focused on fluid for resuscitation, protocols were somewhat heterogeneous, with the amount administered and durations of the intervention varying.

Some observed results may be related to the interplay of different fluid properties, particularly the differential presence of chloride in each colloid. For example, the albumin used in the largest albumin study (2) was dissolved in a crystalloid solution containing greater than 6 mmol of caprylate and 128 mmol of chloride per liter and suggested a trend toward benefit compared with saline (chloride content, 154 mmol/L of chloride) in the sepsis subgroup (47).

Table 4. **NMA Results of 6-Node Analysis, Including Confidence Assessments**

Comparison	Trials With Direct Comparisons, *n*	Direct Estimate (95% CI); Quality of Evidence	Indirect Estimate (95% CrI); Quality of Evidence	NMA Estimate (95% CrI)*; Quality of Evidence
L-HES vs. saline	4	1.07 (0.89–1.29); moderate†	0.59 (0.25–1.35); very low†‡§	1.04 (0.87–1.25); moderate
H-HES vs. saline	3	0.64 (0.30–1.37); moderate†	1.13 (0.71–1.80); very low†‡	0.95 (0.64–1.41); moderate
Albumin vs. saline	2	0.81 (0.64–1.03); moderate†	0.96 (0.14–6.31); very low‡‖	0.82 (0.65–1.04); moderate
Balanced crystalloid vs. saline	0	–	0.78 (0.58–1.05); low†‡	0.78 (0.58–1.05); low
Gelatin vs. saline	0	–	1.04 (0.46–2.32); very low†‡	1.04 (0.46–2.32); very low
H-HES vs. L-HES	0	–	0.91 (0.63–1.33); low†‡	0.91 (0.63–1.33); low
Albumin vs. L-HES	0	–	0.79 (0.59–1.06); low†‡	0.79 (0.59–1.06); low
Balanced crystalloid vs. L-HES	2	0.80 (0.61–1.04); moderate§	0.44 (0.19–0.97); moderate‡	0.75 (0.58–0.97); moderate
Gelatin vs. L-HES	0	–	1.00 (0.44–2.21); very low†‡	1.00 (0.44–2.21); very low
Albumin vs. H-HES	2	1.40 (0.35–5.56); low‖	0.83 (0.52–1.33); low†‡	0.87 (0.55–1.36); low
Balanced crystalloid vs. H-HES	1	0.74 (0.52–1.05); moderate†	1.35 (0.63–2.92); very low‡‖	0.82 (0.60–1.13); moderate
Gelatin vs. H-HES	1	1.09 (0.55–2.19); low‖	–	1.10 (0.54–2.21); low
Balanced crystalloid vs. albumin	0	–	0.95 (0.65–1.38); very low†‡	0.95 (0.65–1.38); very low
Gelatin vs. albumin	0	–	1.26 (0.55–2.90); very low‡‖	1.26 (0.55–2.90); very low
Gelatin vs. balanced crystalloid	0	–	1.34 (0.61–2.89); very low‡‖	1.34 (0.61–2.89); very low

CrI = credibility interval; H-HES = high-molecular-weight hydroxyethyl starch; L-HES = low-molecular-weight hydroxyethyl starch; NMA = network meta-analysis.
* Higher of direct or indirect confidence.
† Rated down for imprecision.
‡ Rated down for indirectness.
§ Rated down for inconsistency (I^2 = 80%; P = 0.03 for heterogeneity).
‖ Rated down 2 levels for imprecision.

Given our results suggesting lower mortality associated with balanced solutions, the apparent trend favoring albumin may be at least partly related to the solution in which it was dissolved. In a similar manner, 1 study on starches (1) found statistically significant benefit of balanced crystalloid that contained 45 mmol of lactate and 106 mmol of chloride per liter compared with starch dissolved in saline (chloride content, 154 mmol/L). The mortality difference may be partly due to the balanced versus unbalanced nature of the solutions.

This analysis provides a current, comprehensive summary of the effect of resuscitation fluids on mortality in patients with sepsis. The presence of buffering substances and chloride content is often overlooked when resuscitative fluids are being chosen in the clinical setting and is rarely transparently reported in clinical trials, which should no longer be the case. Our analyses suggest that balanced solutions may be preferable to unbalanced solutions if crystalloids are used and that, in sepsis, albumin may be a reasonable alternative to other resuscitation fluids. However, relative to balanced crystalloids, albumin confers a small risk associated with transfusion of blood products and costs markedly more.

This NMA suggests that clinicians should be aware of the possible effect of the mineral content and the presence or absence of buffering anions in resuscitation fluids. Future trials on resuscitation for septic shock should evaluate the pH and chloride content of the fluids being compared and are needed to confirm or refute these findings.

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Note: Dr. Cook coauthored a fluid trial cited in this review, and Dr. Annane was principal investigator of a fluid trial cited in this review.

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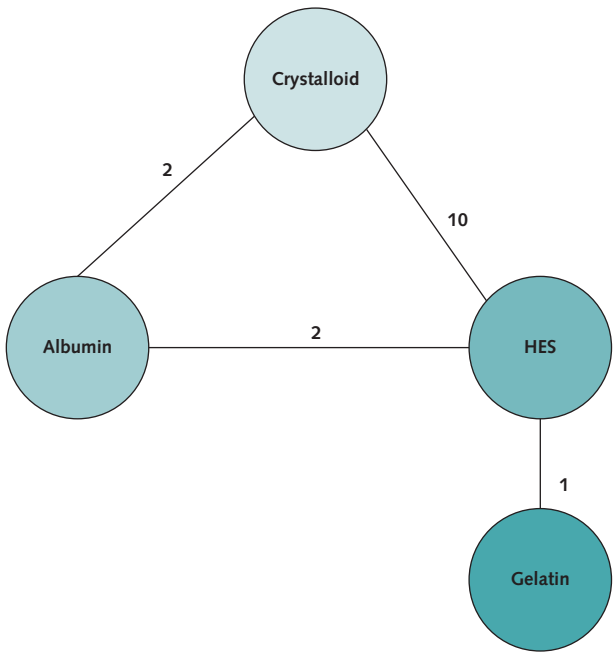
Appendix Table. **Risk of Bias, by Study**

Study, Year (Reference)	Randomization-Sequence Generation	Randomization Concealment	Blinding	Incomplete Data	Selective Reporting	Other*	Overall for Mortality
Myburgh et al, 2012 (3)	Low	Low	Low	Low	Low	Low	Low
Guidet et al, 2012 (6)	Low	Low	Low	Low	Low	Low	Low
Perner et al, 2012 (4)	Low	Low	Low	Low	Low	Low	Low
Haupt and Rackow, 1982 (38)	Probably low	Probably low	Low	Low	Low	Low	Probably low
Rackow et al, 1989 (42)	Probably low	Probably low	Probably low	Low	Low	Low	Probably low
Brunkhorst et al, 2008 (1)	Low	Low	Low	Low	Low	Low	Low
Dubin et al, 2010 (37)	Low	Probably low	Low	Low	Low	Low	Probably low
Li et al, 2008 (39)	Probably low	Probably low	Probably low	Probably low	Probably low	Probably low	Probably low
Lv et al, 2012 (40)	Probably low	Probably low	Probably low	Probably low	Probably low	Probably low	Probably low
McIntyre et al, 2008 (41)	Low	Low	Low	Low	Low	Low	Low
Finfer et al, 2004 (2)	Low	Low	Low	Low	Low	Low	Low
Annane et al, 2013 (16)	Low	Probably low	Low	Low	Low	Low	Probably low
Siegemund, 2011 (44)	Low	Low	Low	Low	Low	Low	Low
Schortgen et al, 2001 (43)	Low	Low	Low	Low	Low	Low	Low

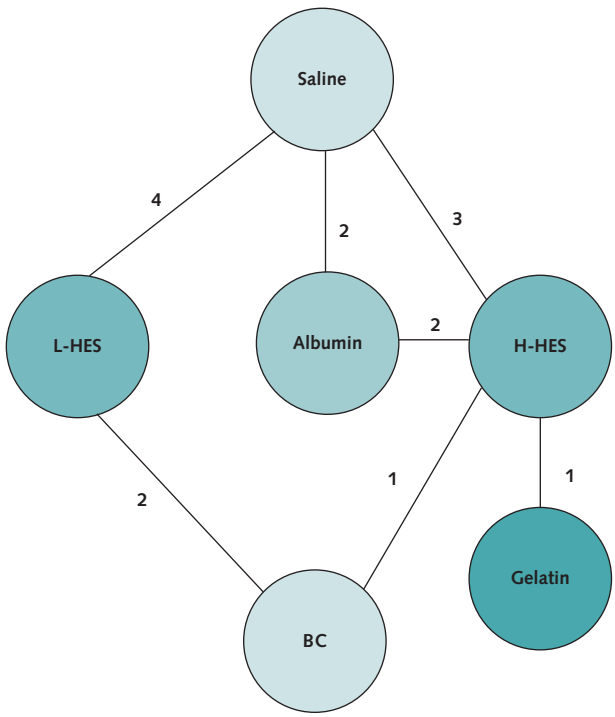
* Including intention-to-treat analysis.

Appendix Figure 1. **Network map for 4-node analysis.**



HES = hydroxyethyl starch.

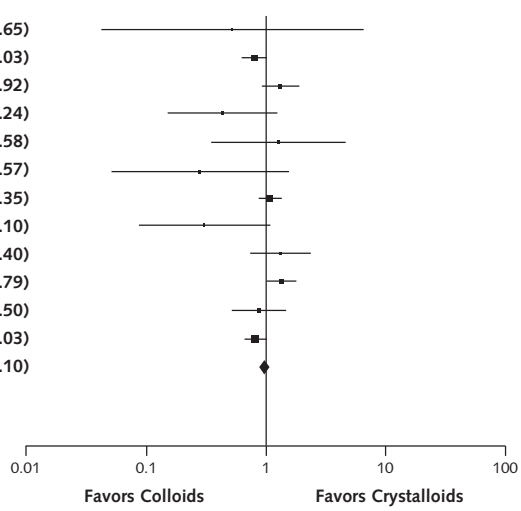
Appendix Figure 2. **Network map for 6-node analysis.**



BC = balanced crystalloid; H-HES = high-molecular-weight hydroxyethyl starch; L-HES = low-molecular-weight hydroxyethyl starch.

Appendix Figure 3. **Forest plot for mortality in direct comparisons of all crystalloids vs. all colloids.**

Study, Year (Reference)	Events/Total, *n/N*		Weight, %	Odds Ratio: M–H, Fixed (95% CI)
	Colloids	Crystalloids		
Haupt and Rackow, 1982 (38)	8/13	3/4	0.2	0.53 (0.04–6.65)
Finfer et al, 2004 (2)	185/603	217/615	20.4	0.81 (0.64–1.03)
Brunkhorst et al, 2008 (1)	107/261	93/274	7.3	1.35 (0.95–1.92)
Li et al, 2008 (39)	14/30	20/30	1.5	0.44 (0.15–1.24)
McIntyre et al, 2008 (41)	9/21	7/19	0.6	1.29 (0.36–4.58)
Dubin et al, 2010 (37)	3/12	7/13	0.7	0.29 (0.05–1.57)
Myburgh et al, 2012 (3)	248/976	224/945	23.3	1.10 (0.89–1.35)
Lv et al, 2012 (40)	7/22	12/20	1.2	0.31 (0.09–1.10)
Guidet et al, 2012 (6)	40/99	32/95	2.7	1.33 (0.74–2.40)
Perner et al, 2012 (4)	202/398	173/400	11.6	1.35 (1.02–1.79)
Siegemund, 2011 (44)	44/117	50/124	4.2	0.89 (0.53–1.50)
Annane et al, 2013 (16)	252/774	286/779	26.4	0.83 (0.67–1.03)
Total	3326	3318	100.00	0.99 (0.89–1.10)
Total events	1119	1124		
Heterogeneity: chi-square = 23.20; I^2 = 53%				
Test for overall effect: Z = 0.18 (P = 0.85)				



M–H = Mantel–Haenszel.