Relative Survival Benefit and Morbidity with Fluids in Severe Sepsis - A Network Meta-Analysis of Alternative Therapies

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Abstract: *Background*: Fluid resuscitation is widely practiced in intensive care units for the treatment of sepsis. A comparison of the evidence base of different fluids may inform therapeutic choice.

Methods: The risks of mortality and morbidity (the need for renal replacement therapies (RRT)) were assessed in patients with severe sepsis. A network meta-analysis compared trials for crystalloids, albumin and hydroxyethyl starch (HES). A literature search of human randomized clinical trials was conducted in databases, the bibliographies of other recent relevant systematic reviews and data reported at recent conferences. Mortality outcomes and RRT data with the longest follow up period were compared. A Bayesian network meta-analysis assessed the risk of mortality and a pair-wise meta-analysis assessed RRT using crystalloids as the reference treatment.

Results: 13 studies were identified. A fixed-effects meta-analysis of mortality data in the trials demonstrated an odds-ratio (OR) of 0.90 between crystalloids and albumin, 1.25 between crystalloids and HES and 1.40 between albumin and HES. The probability that albumin is associated with the highest survival was 96.4% followed by crystalloid at 3.6%, with a negligible probability for HES. Sub-group analyses demonstrated the robustness of this result to variations in fluid composition, study source and origin of septic shock. A random-effects pairwise comparison for the risk of RRT provided an OR of 1.52 favoring crystalloid over HES.

Conclusion: Fluid therapy with albumin was associated with the highest survival benefit. The higher morbidity with HES may affect mortality and requires consideration by prescribers.

Keywords: Albumin, crystalloid, hydroxyethyl starch, meta-analysis, resuscitation, sepsis, septic shock, severe sepsis.

INTRODUCTION

Sepsis is a systemic, deleterious inflammatory host response to infection. It can evolve to severe sepsis (acute organ dysfunction secondary to documented or suspected infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation) [1]. Severe sepsis and septic shock are major healthcare problems increasing in incidence [2-6]. Mortality is about 33.3% in the patients with severe sepsis who are hospitalized [7] while treated with the current standard of care in the US. Hypovolemia is a feature of sepsis which is treated with fluids. Among several fluid treatments available for treating sepsis, the first line of treatment is generally crystalloids in a range of formulations [1, 8], followed by colloid if large amounts of crystalloid are administered.

A wide range of colloids are used [9]. They include human albumin solutions which have been used in acute care for decades [10]. Albumin's repertoire of molecular functions includes correction of hypoalbuminaemia [11] and antioxidant properties which are sustained in septic patients [12]. Synthetic colloids include hydroxyethyl starches (HES) which have been used in a range of clinical applications in lieu of albumin [8]. Recent large randomized clinical trials (RCTs) provide insight in determining the efficacy of the fluids and have compared albumin with crystalloid [11, 13, 14] and HES with crystalloid [15-17] but no large head to head randomized controlled trials comparing the two colloids have been reported. Estimates of relative efficacy for all treatments are required to inform clinical decisions, treatment guidelines and economic studies such as cost effectiveness analyses.

A number of meta-analyses have also indicated different mortality and morbidity outcomes with the different drugs [18-23]. None of these standard meta-analytic techniques, which evaluate the relative efficacy of one treatment compared with a single comparator, have compared different colloids or compared crystalloid with albumin. Network meta-analytic techniques have recently been developed that estimate the relative efficacy of any number of different treatments by taking account of the entire network of RCT evidence [24-26]. Given the paucity of head-to -head trials comparing HES and albumin or comparing crystalloid with both colloids [27, 28], the network method of meta-analysis may inform comparisons between fluid treatments. The present study proposes a network meta-analysis [29] utilizing direct and indirect treatment comparison of randomized trials with common comparators to assess the primary outcome of risk of mortality and a secondary

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outcome in the form of a need for renal replacement therapy. Using this approach allowed the inclusion of trials comparing the two colloids, albumin and HES, and concurrent comparison of each colloid with crystalloid.

METHODS

Systematic Review

A literature search of human clinical trials was conducted in PubMed, ClinicalTrials.gov and within the bibliographies of other recent relevant systematic reviews [23, 30]. In addition, data for mortality for treatment and control arms from the Early Albumin Resuscitation for Sepsis and Septic Shock (EARSS) trial [14] and the Albumin Italian Outcomes Study (ALBIOS) trial [31] for albumin in septic shock were extracted from the results reported as referenced. The search terms used were sepsis, septicemia, systemic inflammatory response syndrome, septic shock, fluid therapy, resuscitation, plasma substitute, albumin, serum albumin, starch, hydroxyethyl starch, hetastarch, pentastarch, tetrastarch and mortality. "Crystalloids" was not included in the initial search strategy as all colloid trials have included crystalloid as a control fluid; including "crystalloids" in a subsequent search did not yield any differences or additional studies.

Inclusion Criteria

Only randomized controlled trials based on an *intent-to-treat* criterion and providing mortality outcomes were included. Trials with all formulations of crystalloids, HES and albumin (see Discussion) comparing two or all three treatments were included. All age groups were included. In trials with multiple endpoints, mortality outcomes after the longest follow up period were used. Only trials which reported specific data for patients with severe sepsis or septic shock were included. Trials which reported such data as a result of a pre-defined sub-group were also included. Only English language publications from 2000 to date were included. In total, 391 studies were extracted of which 13 were chosen to be included in the analysis as shown in Fig. (**1**). The studies used are listed in Table **1**.

Data Extraction and Validity Assessment

The studies were first screened by their titles and abstracts by a reviewer (MB). In the second screening, two reviewers (AF, MB) were involved. In this screening, full texts were reviewed and articles were excluded on the basis of no relevant comparators, not a randomized clinical trial, not an intent-to-treat analysis, no outcomes for only sepsis patients or no mortality results (Fig. **1**). The chosen studies were validated, shown in Table **2**, for the method of randomization and allocation concealment, blinding, presentation of an intention to treat analysis and loss to follow-up of >5% of patients for the primary outcome [32]. Any discrepancy was resolved by consulting with a third reviewer (SB).

Statistical Methods

The indirect comparison was conducted using the Bayesian method for a binomial likelihood, fixed effects network meta-analysis [29]. The analysis was conducted using OpenBUGS version 3.2.1. This package uses Bayesian Markov chain Monte Carlo Gibbs sampling methods [33]. The program code used is available in NHS Evidence Synthesis documents [29]. As conducted in previous research, [25, 34, 35] non-informative prior distributions were used for all the treatment effects; see program code for more details (Program 1 (d): http://www.nicedsu.org.uk/TSD2%20General%20meta%20analysis%20corrected%20Mar2013.pdf).

Studies were included using crystalloids as a reference treatment compared to any composition of colloid fluid

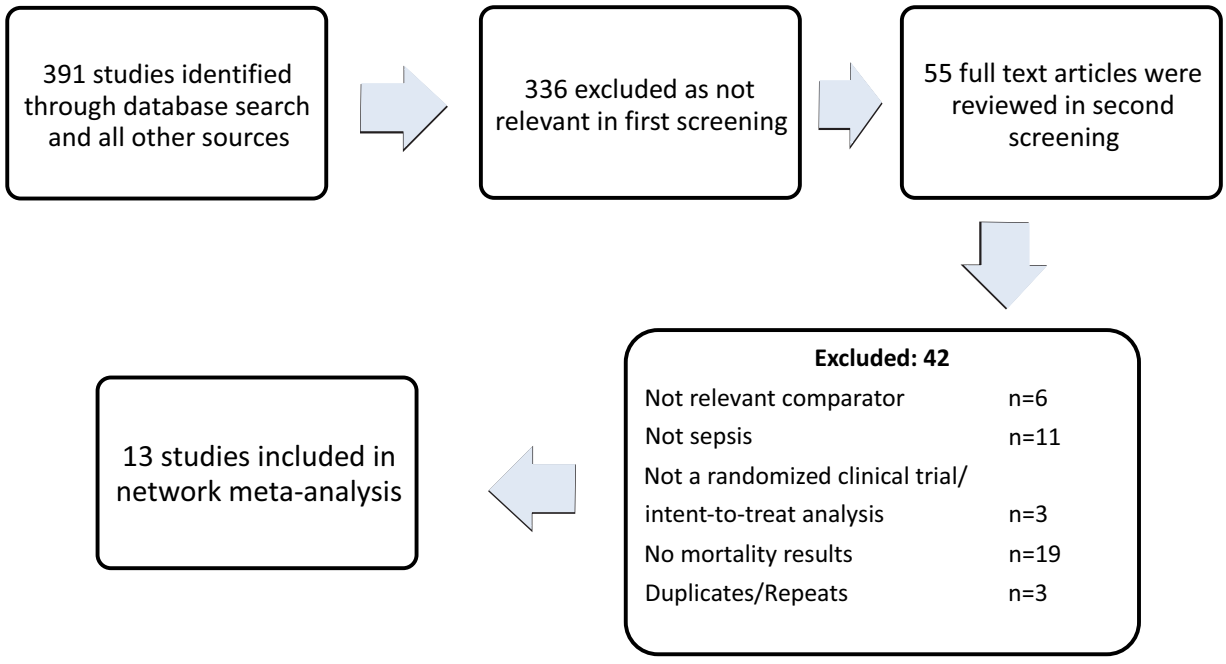


Fig. (1). Study Flow diagram.

(albumin or HES) treatment in septic patients and head-to-head trials of colloid fluids; no trials originating from the group of Joachim Boldt, which have been retracted from the peer-reviewed literature because of scientific misconduct, [36] were included.

The choice for fixed or random effect model was made by assessing model fit using Deviance Information Criteria (DIC) and heterogeneity between the trials [37]. The consistency of the model was assessed as described by National Institute for Health and Clinical Excellence (NICE) [26].

The Bayesian analysis ranked the treatments and provided probability of attaining that rank based on the proportion of Markov chain iterations in which treatment had the highest probability of lowering risk of mortality. The OR and corresponding 95% credible intervals were obtained with 50,000 iterations and convergence was seen at around 15,000 iterations. The 95% credible interval is used to assess statistical difference between comparators and can be interpreted as a 95% probability that true mean change falls within that range. In Bayesian statistical analysis, p-values are not provided [38].

Secondary Outcome

The secondary outcome was the need for renal replacement therapy for the 90-day follow up period only. The trials sourced through the search for mortality data were reviewed for data relating to RRT. In addition, a specific search was conducted for RRT within the PubMed database. The Bayesian, two treatments, pair-wise meta-analysis was used as this outcome was only reported in HES *vs* crystalloid RCTs. The analysis was conducted in OpenBUGS version 3.2.1; see code for details (Program 1 (a) in [37]. Other adverse events associated with colloids including hypotension, bleeding and pruritus [39] were considered for inclusion in the analysis but were not fully reported or were associated with low incidence (<1%) in the trials chosen. Hence, analysis was limited to the widely reported issue of renal dysfunction as assessed through the need for renal replacement therapy.

Sub-group Analysis

Sub-group analyses with different formulations of HES and albumin were performed, in order to assess recent conclusions that the drugs behaved as classes with no therapeutic differences between different compounds [40]. Most of the included RCTs had a population above 60 years of age. The small trial of Dolecek *et al*., [11, 41] had a population between 40-50 years of age. The studies of Maitland et. al. had a much younger population with infants in two trials [42, 43] and youth in the FEAST trial [13]. Further analysis was performed with patients in different age groups, as most of the included RCTs had populations of elderly (> 60 years) patients, and also without the inclusion of the malaria trials of Maitland *et al.,* [13, 42, 43]. All the trials assessed severe sepsis or septic shock except the trials of Maitland *et al.*, which were done on patients with malaria and where the pathophysiology mimics that of sepsis [44]. As two of the largest trials selected - ALBIOS and EARSS - have only been reported as conference proceedings [14, 31], a subgroup analysis excluding these two studies was performed. Further analysis explored outcomes for in-hospital, 28-day *vs* 90-day mortality to see the effect of follow-up period on the mortality outcomes.

RESULTS

Studies Identified

In the literature search, 391 studies were identified. 336 of these were excluded in the first screening. Fig. (**1**) shows that 13 studies were finally included in the analysis. As shown in Fig. (**2**), there was only one qualifying head-to-head trial that compared albumin and HES and only one other small trial that included all three fluid treatments. Out of the remaining 11 crystalloid controlled trials, 6 were with HES and rest with albumin. The larger trials included CHEST, ALBIOS, VISEP, SAFE, EARSS, FEAST and 6S [11, 13, 14, 16, 17, 31, 45] and all were quite recent studies. The mortality data were provided for only the sepsis sub-group but RRT data was presented for all the ICU patients in the CHEST trial. The trial characteristics are summarized in Table **1**.

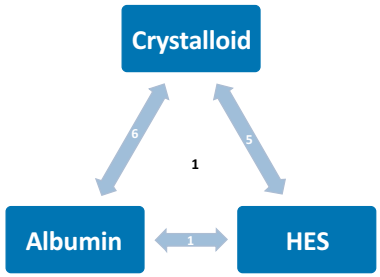


Fig. (2). Network diagram of type of fluid used in treatment of sepsis. Each intervention is a node in the network. The links between the nodes are trials of the study arms. The numbers represent number of studies found for each connection. The number in the center represents the number of trials studying all arms together.

Choice of Model - Random Effect vs Fixed Effect

The DIC was 182.5 for the random effects model and 180.7 for the fixed effect. The posterior mean of the residual deviance for random effects model was more than the fixed effect at 17.2 *vs* 15.1. The standard deviation with random effect was also quite small at 0.09 thus exhibiting very low heterogeneity between trials. These statistical outcomes indicate that the fixed effect model produced the best fit for the data [26].

Consistency of the Model

The assessment showed similar effect sizes and DICs for the consistency (DIC=180.9) and inconsistency (DIC = 182.9) models in case of the fixed effect analysis. As shown in Fig. (**3**), most of the posterior mean deviances of the individual data points lie around one on the line of equality suggesting consistency.

Table 1. Basic Characteristics of the Included Randomized Clinical Trials

Study	Population	Mean Age (Years)	Treatment Arms	Type of Crystalloid (If Any)	Albumin/ HES Composition	Follow-Up Duration	Crystalloid		Albumin		HES	
							Deaths/ RRT	Total	Deaths	Total	Deaths/ RRT	Total
ALBIOS 2012 [31]	Sepsis or septic shock	66.3- A, 66.3-S	Crystalloid, Albumin	crystalloids	20% A	hospital discharge	342	907	326	908		
Charpentier *et al.,* (EARSS) 2011 [14]	Septic shock	66 for both	Crystalloid, Albumin	0.9% saline	20% A	28 days	103	393	96	399		
Finfer S (SAFE study) 2006 [11]	Severe sepsis	58.6-A, 58.5-S	Crystalloid, Albumin	0.9% saline	4% A	28 days	217	615	185	603		
Maitland 2005 [42]	Children w severe malaria and sepsis as a sub-group	1.6 (for all txs)	Crystalloid, Albumin	0.9% saline	4.5% A	hospital discharge	3	20	4	23		
Maitland 2005 [43]	Children w severe malaria and moderate or severe metabolic acidosis (sepsis as a sub-group)	2.8 (for all txs)	Crystalloid, Albumin	0.9% saline	4.5% A	hospital discharge	11	61	2	56		
Maitland K, (FEAST Trial Group) 2011 [13]	Patients with severe febrile illness and impaired perfusion (sepsis as a sub-group)	23-A, 23-S	Crystalloid, Albumin	0.9% saline	5% A	30 days	126	1047	128	1050		
Myburgh (CHEST) 2012 [17]	Adult patients with sepsis (subgroup)	63.1-H, 62.9-S	Crystalloid, HES	0.9% saline	6% H (130/0.4)	90 days	224/196*	958			248/235*	979
Brunkhorst (VISEP) 2008 [45]	Patients with severe sepsis	64.9-S, 64.4-H	Crystalloid, HES	ringer's lactate	10% H (200/0.5)	28 days	66	275			70	262
						90 days	93/51	275			107/81	262
Guidet (CRYSTMAS) 2012 [15]	Severe sepsis	65.8-H, 65.9-S	Crystalloid, HES	NaCl fluid	6% H (130/0.4)	28 days	24	96			31	100
						90 days	32/19	96			40/24	100
Mcintyre (FINESS) 2008 [46]	Patients with septic shock	63.6-S, 63.1-H	Crystalloid, HES	normal saline		ICU	6	19			6	21
						28 days	6/1	19			9/3	21
Perner (6S) 2012 [16]	Patients with severe sepsis	66-H, 67-S	Crystalloid, HES	ringer's acetate	6% H (130/0.4)	28 days	144	400			154	398
						90 days	172/65	400			201/87	398
Dolecek 2009 [41]	Adult patients with severe sepsis	47-A, 43-H	Albumin, HES		6% H (130/0.4), 20% A	28 days			4	30	6	26
Veneman 2004 [27]	Severely ill patients with sepsis and post-surgical patients with systemic inflammatory response syndrome	67-S, 72-A, 68-H	Crystalloid, Albumin, HES	0.9% saline	20% A, 10% H	30 days	5	16	8	15	18	30

*In CHEST 2012 study, RRT is analyzed for all patients in the ICU. Sepsis is a sub-group of those patients. Total ICU patients under crystalloids: 3375, HES:3352.
S - Crystalloid, A- albumin, H - Hydroxyethyl starch (HES), RRT - Renal Replacement Therapy, ICU- Intensive care unit.

Table 2. Quality Assessment of the Trial

	Allocation Concealment	Intention-to-Treat	Blinding	No Loss of Follow Up*	Randomization
ALBIOS 2012 [31]	No	Yes	No	Yes	Yes
Myburgh (CHEST) 2012 [17]	Yes	Yes	Yes	Yes	Yes
Brunkhorst (VISEP) 2008 [45]	No	Yes	No	Yes	Yes
Charpentier (EARSS) 2011 [14]	No	Yes	No	Yes	Yes
Dolecek 2009 [41]	No	Yes	No	Yes	Yes
Finfer (SAFE) 2010 [11]	Yes	Yes	Yes	Yes	Yes
Guidet (CRYSTMAS) 2012 [15]	Yes	Yes	Yes	Yes	Yes
Maitland 2005 [42]	Yes	Yes	No	Yes	Yes
Maitland 2005 [43]	Yes	Yes	No	Yes	Yes
Maitland (FEAST) 2011 [13]	Yes	Yes	No	Yes	Yes
McIntyre (FINESS) 2008 [46]	Yes	Yes	Yes	Yes	Yes
Perner (6S) 2012 [16]	Yes	Yes	Yes	Yes	Yes
Veneman 2004 [27]	Yes	Yes	No	Yes	Yes

*Loss to follow-up of >5% of patients.

Baseline Results

The pairwise ORs and their respective 95% credible intervals are presented in Fig. (**4**). The fixed effect network meta-analysis in the forest plot (Fig. **4**) resulted in ORs of 0.90, 1.25 and 1.40 favoring albumin versus crystalloid, crystalloid versus HES and albumin versus HES, respectively. The random effects model showed similar results (0.89 for albumin *vs* crystalloid, 1.28 for HES *vs* crystalloid and 1.45 for HES *vs* albumin). The Frequentist pairwise fixed effect meta-analysis showed an OR of 0.90 favoring albumin versus crystalloid and 1.24 favoring crystalloid over HES. The baseline 95% credible intervals showed no significant statistical differences between the treatments.

Ranking of the Treatment

The Bayesian framework ranked the treatments and also assigned a probability to each rank that a treatment can achieve in terms of lowering the risk of mortality. Fig. (**5**) displays the share of these distributions under each rank. The higher the share in the distribution under a rank, the more likely the treatment will hold that rank. Albumin ranks first 96% of the times versus the other two treatments. The second place is shared in a majority by crystalloid and HES populates mostly the third place. Thus, according to the shares occupied by the treatments, albumin is the most effective treatment followed by crystalloid, and HES is the least effective. The odds-ratio (1.52) for RRT favored

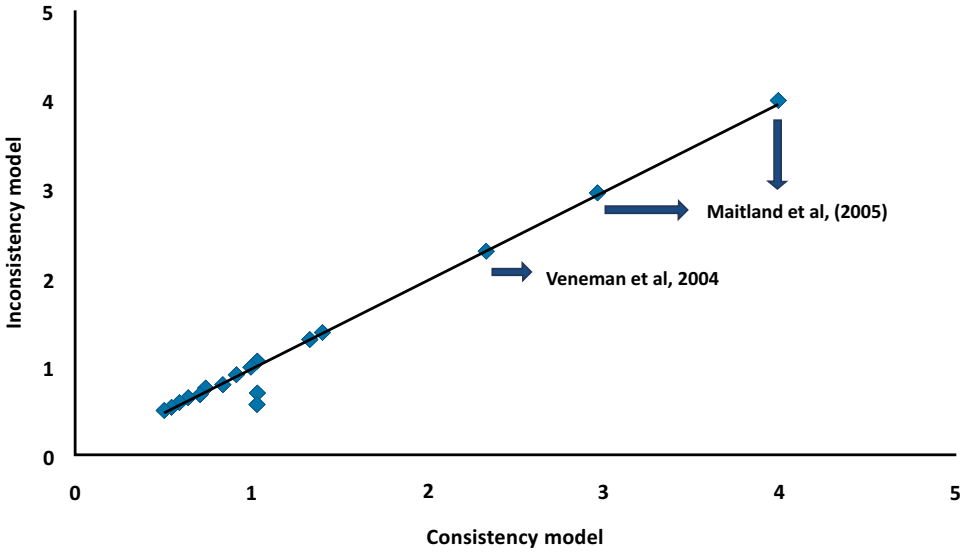


Fig. (3). Plot of individual mortality data points' posterior mean deviance contributions for the consistency model (horizontal axis) and the inconsistency model (vertical axis) along with the line of equality. Each data point is expected to have a posterior mean deviance contribution of about 1.0, with higher contributions suggesting a poorly fitting model [26]. Since Maitland *et al.*, [43] and Veneman *et al.*, [27] had data points much higher than 1.0, a sub-group analysis was conducted without the studies of Maitland *et al.*, [13, 42, 43] and another analysis without Veneman *et al.,* [27].

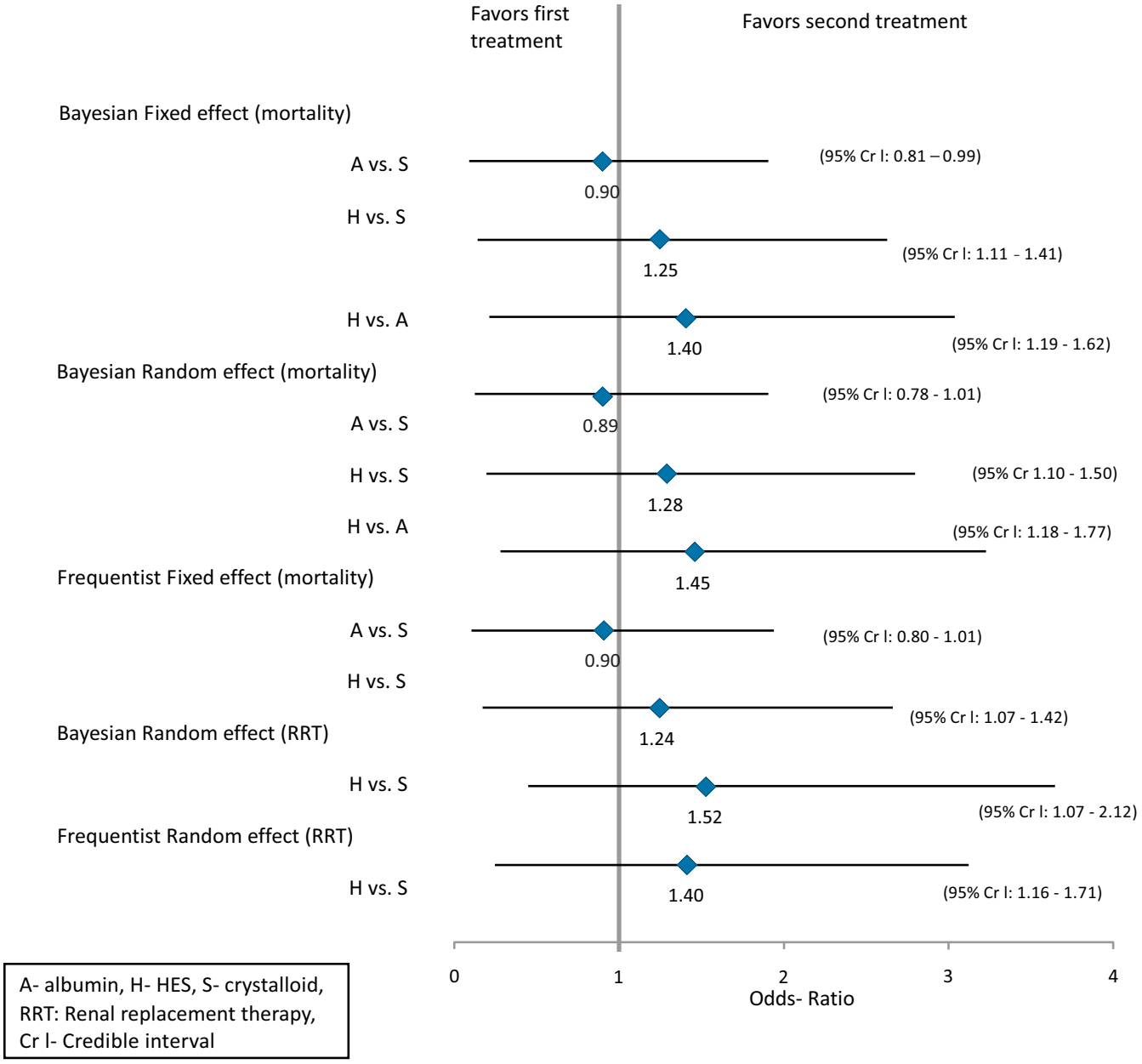


Fig. (4). Forest plot of results of Bayesian network meta-analysis of mortality and renal replacement therapy outcomes in severe sepsis and septic shock. 95% Cr I which does not include the null value, 0.00, indicates <5% probability that there is no difference between the two comparators [38].

crystalloids in comparison to the HES in the random effects Bayesian analysis.

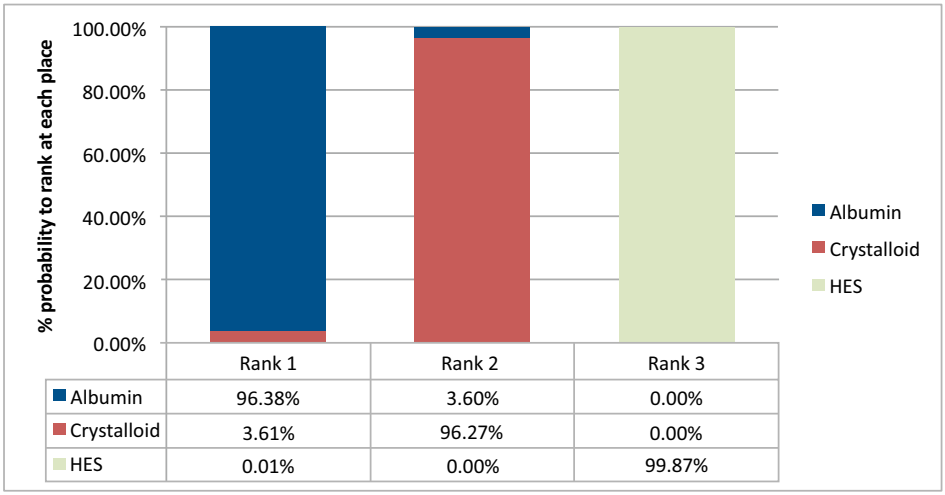
Sub-Group Results

Table **3** summarizes the results of sub-group analyses when excluding the trials of Maitland *et al.,* [13, 42, 43], when follow up was for 28days compared to the base case (longest follow-up period), when elderly patients were studied and when different formulations of the colloid solutions were studied. The relative rankings in the survival benefit were not affected in any of the sub-groups (Table **3**). In addition, the exclusion of the hitherto not fully published EARSS and ALBIOS trials also did not affect the key outcome.

DISCUSSION

The present study found a 96.4% probability that, of the fluid treatments assessed, albumin provides the highest survival benefit in patients with sepsis through lowering the risk of mortality. In this analysis, the longest follow-up mortality data in trials were included. The trials with longer observation periods found more cases of adverse effects such as renal toxicity in patients treated with HES [16, 17, 45]. This finding is augmented by the sub-group analysis in this study, which showed that there is higher risk of mortality in the long term for patients treated with HES.

The recent meta-analyses compared HES either with other colloids or crystalloids in critically ill patients. Gattas *et al.,* [18] concluded that with HES there is a 6%



	Rank 1	Rank 2	Rank 3
Albumin	96.38%	3.60%	0.00%
Crystalloid	3.61%	96.27%	0.00%
HES	0.01%	0.00%	99.87%

Fig. (5). Barplots for the ranking probabilities of competing fluid treatments. Horizontal axis is the possible rank of each treatment (from best to worse). The size of each bar corresponds to the probability of each treatment to be at specific rank.

increase in relative risk of death and a significant 25% increase in relative risk of being treated with RRT. Zarychanski *et al.,* [20] also showed in their analysis that removing the studies by Boldt, there was a clear survival benefit with other control fluids in critically ill patients. Patel *et al.,* [47] conducted a meta-analysis on trials with severe septic patients treated with 6% HES (130/0.4 or 130/0.42). The control fluid showed a higher survival benefit in the 90-day follow up period. Haase *et al.,* [19] found higher rate of RRT and blood transfusion in patients treated with HES 130/0.38-0.45 but no significant difference in risk of death. Delaney *et al.,* [23] compared albumin with any control fluid and found albumin to be superior in reducing the risk of mortality.

The methodology of these routine meta-analyses does not allow the assessment of comparative effectiveness and safety of specific treatments in the absence of direct head to head trials. The present study applied network meta-analysis using a Bayesian approach to compare and rank the different fluid therapies available for severe sepsis so as to inform clinical decision making. This approach has been used to compare therapies in similar circumstances, in areas including pain management, diabetic neuropathy [48] and antifibrinolytic therapy in cardiac surgery [49], and has been shown to be not increase the bias relative to routine meta-analysis [50].

The inclusion of data from two recently reported large trials - ALBIOS and EARSS - which assessed the effect of albumin versus crystalloid in severe sepsis from the reported conference proceedings required caution as such data can lead to inconsistencies [51], and sensitivity analysis without this data was performed and confirmed the robustness of the analysis. Similarly, further sub-group analysis was performed in order to assess the effect of including the trials of Maitland *et al.,* on children with malaria [13, 42, 43] which has a pathophysiology with many features in common with sepsis [44]. The sub-group analysis confirmed that the outcomes of the base case were not affected by the incision of these trials. Maitland *et al.,* also demonstrated a survival benefit in children receiving albumin compared to gelofusine [52] but the present study was restricted to HES as this is the predominant synthetic colloid globally [9].

An underlying presumption in comparing outcomes in different clinical trials through techniques like meta-analysis is that different therapeutic preparations within each arm are biopharmaceutically equivalent. Hence, the different compositions of HES and albumin are assumed to have the same therapeutic effect when compared in meta-analyses such as that in the present study. Crystalloids also form a very broad category with differently formulated solutions. Any differences in formulation, manufacturing method etcetera between different fluids within the same broad class (crystalloids, albumin and HES) are assumed to not affect their therapeutic properties. Equivalent efficacy and safety profiles have been shown for albumin produced by different methods [53]. The most recent HES products have been claimed to be associated with fewer adverse events than earlier products [54] but the outcomes of meta-analysis [30, 55] and recent trials [16,17] have disputed this, and have led the US Food and Drug Administration (FDA) to conclude that in relation to these effects, all HES products behave as a class [40]. This has led the European Medicines Agency to conclude that the negative risk-benefit balance associated with these products justifies the removal of their marketing authorization [56]. Similarly, crystalloid solutions formulated to approximate physiological conditions have been claimed to be therapeutically superior to normal saline [57]. This has not been supported in a systematic review of mortality and morbidity in patients [58]. To test this assumption further, we performed the analysis with different formulations of albumin and HES and obtained similar results. Hence, we propose that the results of previous analyses, [30, 55] and the current study are not affected by any differences in the preparations *within* each treatment arm.

Similarly, we acknowledge that variability in the patient populations recruited in the individual trials may influence the results of this analysis, although the populations studied, consisting of severe sepsis and septic shock patients, were very similar in terms of age (all populations in the different fluid arms were in the age group 61 to 68) with the exception of the pediatric populations studied in the malaria trials of Maitland *et al.,* We have assessed the effect of variability resulting from patient population, follow up time, product

Table 3. Sub-Group Analyses

Sub-Group	Odds- Ratio (95%Cr I)		
	A *vs* S	**H *vs* S**	**H *vs* A**
Excluding trials (mortality)			
All trials except Maitland *et al*. trials	0.88 (0.77-1.01)	1.25 (1.08-1.44)	1.42 (1.16-1.72)
All trials except Veneman *et al.,* trial	0.88 (0.66-1.05)	1.28 (1.03-1.60)	
All trials except ALBIOS and EARSS trials	0.88 (0.76-1.01)	1.25 (1.11-1.41)	1.44 (1.19-1.71)
Follow-up time			
Trials with 28-day* or in-hospital mortality	0.90 (0.80-1.01)	1.21(0.98-1.49)	1.36 (1.06-1.71)
Trials with 28-day* or in-hospital mortality except Maitland *et al.,*	0.89 (0.77-1.01)	1.21(0.98-1.48)	1.38 (1.07-1.74)
Trials with 28-day* mortality	0.85 (0.72-0.99)	1.21 (1.01-1.43)	1.44 (1.13-1.80)
Trials with in-hospital mortality	1.12 (0.23-1.94)		
Trials with 90 days of mortality		1.29 (0.90-1.81)	
Formulation			
Trials with 130/0.4 HES on mortality		1.37 (0.90-1.93)	
Trials with 130/0.4 HES on RRT		1.80 (0.73-2.35)	
Trials with 20% albumin on mortality	0.93 (0.81-1.06)	2.17 (0.97-4.00)	2.33 (1.05-4.30)
Trials with 4-6% albumin on mortality	1.05 (0.21-1.99)		
Population (mortality)			
Trials with 60+ age population	0.93 (0.79-1.09)	1.25 (1.08-1.44)	1.36 (1.08-1.68)

A-albumin, S-crystalloid, H-hydroxyethyl starch, Cr I- Credible interval, RRT- Renal replacement therapy.
*Includes both 28-day and 30-day mortality data.

composition and patient age through sub-group analyses which demonstrated no effect on the final result of this study (Table **3**), but it is possible that variability in these and other factors may influence the results, as with all meta-analyses.

Our sub-group analysis of trials with 28-day mortality showed a lower risk with HES than our analysis of trials with 90-day mortality outcomes. This suggests that more adverse outcomes from HES ensue after a prolonged period after use, as was shown in both the VISEP [45] and 6S [16] large clinical trials of different generation HES products. A high fraction of HES is taken up and deposited in tissues [59], where its long-term toxic effects on the kidney, liver, and bone marrow [60, 61] may explain the relative time frame of the mortality outcomes. There is a lower risk of mortality with HES and crystalloid in older patients in as assessed through the sub-group analysis in the present study but the relative ranking in survival benefit is not affected. This could be speculatively attributed to a higher incidence of other comorbidities in elderly patients, thus diminishing the difference between the efficacies of the fluid treatments.

All the trials with RRT outcomes had a 90-day follow up period. The indication was severe sepsis or septic shock for all included trials except the CHEST study [17] which assessed all the patients in the ICU setting. Sepsis was a sub-group in the CHEST trial, and the findings of the sub-group have not been published but have been reported (Myburgh J, Presentation at the International Symposium on Intensive Care and Emergency Medicine, Brussels March 2013). The need for RRT in all trials comparing albumin with other fluids did not show any increased risk with albumin, possibly due to albumin's lack of renal toxicity [62, 63] compared to HES [64].

Direct data on mortality in fluid resuscitation with sepsis, comparing albumin, HES and crystalloids, are minimal and thus the present study may inform therapeutic choice. Moreover, network meta-analysis and indirect comparison is receiving increased acceptance in health care decision making (Pharmaceutical Benefits Advisory Committee in Australia, Canadian Agency for Drugs and Technologies in Health [CADTH], National Institute for Health and Clinical Excellence [NICE] in the UK) [29, 65, 66]. Even when direct evidence is available and conclusive, combining direct and indirect results may yield more refined and precise estimates of the interventions and broaden inference to the population sampled. Network meta-analysis links and maximizes existing information within the network of treatment comparisons [24, 25, 67]. We propose that such an approach should assist policy makers, manufacturers, physicians and patients, when making a choice between fluid-resuscitation treatments.

CONFLICT OF INTEREST

Bansal M, Farrugia A and Balboni S provide services to the plasma protein therapeutics industry, which includes the manufacturers of therapies described in this work.

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All the authors were involved in study design. Bansal M contributed to literature review, meta-analysis and

manuscript preparation. Farrugia A contributed to literature review and manuscript preparation, Balboni S was involved in literature and manuscript review and Martin G reviewed the manuscript.

PATIENT CONSENT

Declared none.

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