The role of albumin as a resuscitation fluid for patients with sepsis: A systematic review and meta-analysis*

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Objective: **To assess whether resuscitation with albumin-containing solutions, compared with other fluids, is associated with lower mortality in patients with sepsis.**

Data Sources: **MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases, the metaRegister of Controlled Trials, and the Medical Editors Trial Amnesty Register.**

Study Selection: **Prospective randomized clinical trials of fluid resuscitation with albumin-containing solutions compared with other fluid resuscitation regimens, which included a population or subgroup of participants with sepsis, were included.**

Data Extraction: **Assessment of the validity of included studies and data extraction were conducted independently by two authors.**

Data Synthesis: **For the primary analysis, the effect of albumin-containing solutions on all-cause mortality was assessed by using a fixed-effect meta-analysis.**

Results: **Seventeen studies that randomized 1977 participants were included in the meta-analysis. There were eight studies that included only patients with sepsis and nine where patients with sepsis were a subgroup of the study population. There was no evidence of heterogeneity, $I^2 = 0\%$. The use of albumin for resuscitation of patients with sepsis was associated with a reduction in mortality with the pooled estimate of the odds ratio of 0.82 (95% confidence limits 0.67–1.0, $p = .047$).**

Conclusions: **In this meta-analysis, the use of albumin-containing solutions for the resuscitation of patients with sepsis was associated with lower mortality compared with other fluid resuscitation regimens. Until the results of ongoing randomized controlled trials are known, clinicians should consider the use of albumin-containing solutions for the resuscitation of patients with sepsis. (Crit Care Med 2011; 39:386–391)**

KEY WORDS: sepsis; resuscitation; albumin-containing solutions; meta-analysis

The basic principles of management for patients with sepsis continue to be resuscitation, antibiotic therapy, and source control (1). The cornerstone of the resuscitation is fluid therapy. Although there is some evidence to guide clinicians in their choice of resuscitation goals in this patient group (2), albeit somewhat controversial (3), there is little high quality evidence to guide the choice of fluid (1).

The Surviving Sepsis Campaign guidelines recommend the use of either crystalloid or colloid for the early resuscitation of patients with sepsis (1), a recommendation that is based largely upon the results of the saline vs. albumin fluid evaluation study, which compared the effects of fluid resuscitation with 4% human albumin or 0.9% saline (4). While the overall results of the saline vs. albumin fluid evaluation study showed no difference in mortality in a heterogeneous population of patients who required resuscitation in the intensive care unit (ICU), a prespecified subgroup analysis of patients with severe sepsis suggested the use of albumin might be beneficial. However, there are well-known problems with drawing conclusions based upon the results of subgroup analyses (5, 6). Previous meta-analyses that have examined the effectiveness of albumin solutions for resuscitation have concentrated on critically ill patients and subgroups of patients with burns and hypoalbuminemia (7–9). No previous systematic review has focused on the use of albumin as a resuscitation fluid for patients with sepsis.

Therefore we performed a systematic review and meta-analysis to attempt to address the following question: For patients with sepsis, is fluid resuscitation with albumin-containing solutions, compared with other fluids, associated with lower mortality?

MATERIALS AND METHODS

Eligibility Criteria. We searched for randomized controlled trials (RCTs) that compared fluid resuscitation with albumin-containing fluids to other fluid resuscitation regimens. Eligible studies had to include human participants, with a definable population with sepsis. We included studies in which the population with sepsis was a subgroup within a larger group of patients. Studies needed to report mortality in the sepsis cohort to be eligible for inclusion in the review.

Search Strategy. The primary electronic search was conducted in MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials databases. We used medical subject heading and keyword searches for sepsis or septicemia or the systemic inflammatory response syndrome, combined with medical subject heading and keyword searches for fluid therapy or resuscitation or plasma substitute or albumins or serum albumin along with appropriate filters for RCTs (10, 11). There was no language restriction placed on the search. Each database was searched from inception until April

***See also p. 418.**

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10, 2010. We also searched bibliographies of relevant review articles and the included RCTs, searched the metaRegister of Controlled Trials (12), including the Medical Editors Trials Amnesty and contacted experts in the field to identify any unpublished trials.

Study Selection. One author (AD) screened the results of the search, and full text manuscripts of all potentially eligible articles were obtained. Two authors (AD and JM) independently applied the inclusion criteria to all potentially eligible articles. Any disagreement was resolved by discussion or by consultation with a third reviewer (APD).

Validity Appraisal and Data Extraction. All included articles were appraised, independently by two authors (AD and JM) to ascertain their internal validity, with disagreements resolved by discussion or by consulting a third reviewer (APD). Each trial was assessed for the method of randomization and allocation concealment, blinding, presentation of an intention to treat analysis (13), and loss to follow-up of >5% of patients for the primary outcome. For studies that presented a subgroup of patients with sepsis, we assessed the manuscript for evidence of an *a priori* definition of the subgroup and the number of subgroups reported in the RCT (14).

The primary outcome for this analysis was all-cause mortality. When mortality was presented at more than one time point, we preferentially used the mortality at the time point with longest complete follow-up. When mortality data were not available in the primary manuscript, the authors of the study were contacted and asked to provide these data. We extracted data from the studies, including the volumes of fluid used, comparator fluid regimens, and the endpoints used to guide the administration of fluid therapy. Two reviewers (AD and JM) independently extracted data onto data forms designed specifically for the study; data were checked for accuracy by a third reviewer (APD).

Data Analysis. A fixed-effect meta-analysis was used to pool the results. Heterogeneity among the included trials was assessed by using a chi-square test and the I^2 statistic, with an I^2 statistic of >50% indicating at least moderate heterogeneity (15). The potential for bias was assessed by inspection of a funnel plot, and Egger's statistic (16). The results were pooled using a pooled odds ratio (OR) (17). We assessed the effect of the concentration of albumin used (20% to 25% compared with 4% to 5%) and the population included in the study (adult or pediatric) by assessing for an interaction term in separate single covariate metaregressions. To assess the robustness of the results, we performed an analysis excluding the results of the saline vs. albumin fluid evaluation study and also used a random effects model to pool the data. We performed separate analyses comparing albumin with each of the comparator fluids groups. Following a recent announcement by *Anesthesia and Analgesia* (18), we conducted a sensitivity analysis in which we excluded the trials by Boldt et al (19–24).

We also took into account the fact that the studies included in this analysis were often subgroups of larger studies. It is well known that subgroup analyses often lack statistical power and may report spuriously positive results (6). The correct statistical approach to the interpretation of subgroup analyses is to look for effect modification by assessing the interaction term between the treatment allocation (in this case albumin or control) and the baseline characteristic of interest (in this case the presence or absence of sepsis at the time of randomization) (25). We extracted the p value from this test when it was reported in the primary manuscript, or we performed a logistic regression with an appropriate interaction term when the data were not available. Due to the small numbers of events in some studies, it was not possible to perform this analysis in all cases. The p values for the interaction term were then pooled using a meta-analysis of p values. The result of this analysis provides an indication of whether the effect of albumin in patients with sepsis is likely to be different from the effect in the overall populations included in the RCTs. All analyses were preformed by using STATA 10.1 (College Station, TX).

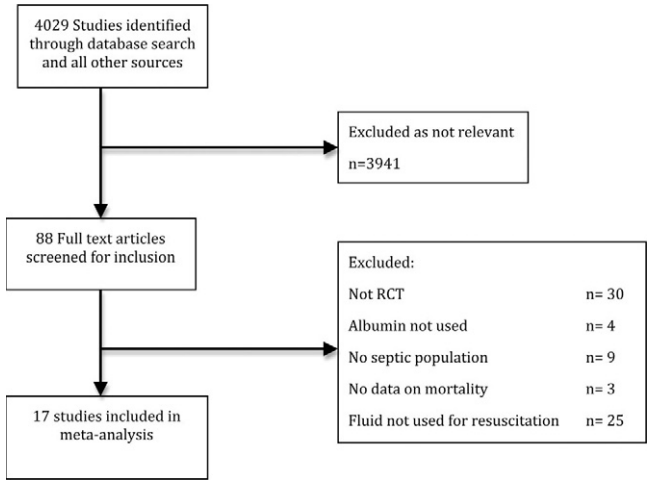

Figure 1. Flow diagram showing results of search and reasons for exclusion of studies. *RCT*, randomized controlled trial.

RESULTS

The initial search returned 4029 records. After examination of the titles and abstracts, there were 88 potentially eligible studies assessed for inclusion. After application of the inclusion criteria, 17 studies (4, 20–35) that randomized 1977 participants to receive albumin or control fluid resuscitation regimens were included in the meta-analysis. The flow of studies, including the reasons for exclusion of studies, is shown in Figure 1.

Study Characteristics and Validity Assessment. The characteristics of the included studies are shown in Table 1. The results of the validity assessments are shown in Table 2.

Quantitative Data Synthesis. Mortality data were available in all 17 included studies. There was no evidence of bias on inspection of the funnel plot, shown as Appendix 1, and this was confirmed with Egger's statistic ($p = .86$). There was no evidence of significant statistical heterogeneity, the $\chi^2 = 0.73$ and the $I^2 = 0\%$. The estimate of the pooled OR for mortality of patients with sepsis resuscitated with albumin-containing fluid regimens compared with control fluid regimens was 0.82 (95% confidence limits 0.67–1.0, $p = .047$) (Fig. 2).

When the saline vs. albumin fluid evaluation study is omitted, the results of the pooled analysis remain similar, with an estimate of the OR for mortality of 0.84 (95% confidence limits 0.59–1.18, $p = .31$). Utilizing a random effects model to pool the results of all studies produces an estimate of the OR for mortality of 0.84 (95% confidence limits 0.69–1.02, $p = .08$). The results of the sensitivity analysis excluding the trials by Boldt et al (19–24), which do not alter the conclusions of our analysis, are given in an online data supplement (see Supplemental Digital Content 1, http://links.lww.com/CCM/A220).

Table 1. Characteristics of the included studies

Authors	Year	Study Population	Total Study Participants	Albumin Concentration (%)	Mean Albumin Volume (mL)	Control Fluid(s)	Mean Control Fluid Volume	Resuscitation End Point	Duration of Follow-up
Rackow et al (32)	1983	Adult patients with septic or hypovolaemic shock	26	5	2833	0.9% saline 6% HES	8356 mL (saline) 4569 mL (HES)	PCWP ≥15	Hospital discharge
Metildi et al (31)	1984	Adult patients with acute respiratory distress syndrome	46	5	9400	Ringers lactate	12,500 mL	To maintain normal pH, base deficit, and S_vO_2	Hospital discharge
Rackow et al (33)	1989	Adult patients with severe sepsis	20	5	975	10% Pentastarch	900 mL	PCWP ≥15	Hospital discharge
Boldt et al (20)	1995	Adult patients with trauma and sepsis	60	20	1750	10% Hetastarch	3340 mL	PCWP 12–16	ICU discharge
Boldt et al (19)	1996	Adult patients with trauma and sepsis	60	20	2110	10% Hetastarch	4550	PCWP 12–18	ICU discharge
Boldt et al (21)	1996	Adult patients with trauma and sepsis	56	20	1950	10% Hetastarch	3950	PCWP 10–15	ICU discharge
Boldt et al (22)	1996	Adult patients with trauma and sepsis	56	20	1790	10% Hetastarch	3260	CVP or PCWP 12–16	ICU discharge
Boldt et al (23)	1996	Adult patients with severe sepsis	42	20	2525	10% Hetastarch	5350	CVP or PCWP 10–15	ICU discharge
Boldt et al (24)	1998	Adult patients with trauma and sepsis	150	20	2240	10% Hetastarch	5030	PCWP 12–15	ICU discharge
The SAFE study investigators (4)	2004	Patients in ICU requiring fluid resuscitation	6997	4	Not reported	0.9% saline	Not reported	Discretion of the treating clinician	28 days
Veneman et al (35)	2004	Severely ill patients with sepsis and post surgical patients with systemic inflammatory response syndrome	63	20	1200	0.9% saline 10% HES	3000 (saline) 1500–3000 (HES)	CVP 5–10, Mean arterial pressure >70	30 days
Maitland et al (29)	2005	Children with severe malaria, metabolic acidosis, anaemia and respiratory distress	61	4.5	20 mL/kg	0.9% saline	20 mL/kg	20 mL/kg	Hospital discharge
Maitland et al (30)	2005	Children with severe malaria and moderate or severe metabolic acidosis	150	4.5	45 mL/kg moderate acidosis 63 mL/kg severe acidosis	0.9% saline	48 mL/kg moderate acidosis 69 mL/kg severe acidosis	To avoid hypotension, oliguria, worsening or refractory acidosis	Hospital discharge
Akech et al (26)	2006	Children with malaria, severe metabolic acidosis and shock	88	4.5	46 mL/kg moderate acidosis, 50 mL/kg severe acidosis	Gelofusine	44 mL/kg moderate acidosis, 52 mL/kg severe acidosis	20–60 mL/kg Titrated to clinical resolution of shock	Hospital discharge
Friedman et al (28)	2008	Adult patients with sepsis and suspected hypovolemia	42	4	400	6% HES 10% HES	400 mL	To maintain haemodynamic stability	Hospital discharge
van der Heijden et al (34)	2009	Adult patients with sepsis and nonseptic patients hypovolemic and at risk for acute lung injury/acute respiratory distress syndrome	48	5	1467	0.9% saline gelofusine 6% HES	1800 mL saline, 1358 gelofusin, 1317 HES	Fluid challenge protocol	ICU discharge
Dolecek et al (27)	2009	Adult patients with severe sepsis	56	20	600	6% HES	3000	Intrathoracic blood volume index >850 mL/m^2 and cardiac index >3.5l/min/m^2	28 days

HES, hydroxy ethyl starch; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; ICU, intensive care unit.

There were eight studies including 383 participants that used more concentrated (≥20%) albumin solutions, and nine studies including 1594 participants that used more dilute solutions (4%, 4.5%, or 5%). The pooled estimate of the OR for death in studies that used concentrated albumin solutions was 1.08 (95% confidence limits 0.7–1.68, $p = .73$), and the pooled estimate of the OR in studies that used more dilute albumin solutions was 0.76 (95% confidence limits 0.61–0.95, $p = .02$). The p value for the interaction for albumin concentration was 0.09. There were three studies including 248 participants in studies in pediatric populations. The estimate of the pooled OR for the effect

Table 2. Results of the validity appraisal of the included studies

Authors	Allocation Concealment	Intention to Treat Analysis	Blinding	Loss to Follow-Up	Predefined Sepsis Subgroup	Number of Subgroup Pairs
Rackow et al (32)	No	Yes	No	No	No	1
Metildi et al (31)	No	Yes	No	No	No	7
Rackow et al (33)	No	Yes	No	No	N/A	0
Boldt et al (20)	No	Yes	No	No	Yes	1
Boldt et al (19)	No	Yes	No	No	Yes	1
Boldt et al (21)	No	Yes	No	No	Yes	1
Boldt et al (22)	No	Yes	No	No	Yes	1
Boldt et al (23)	No	Yes	No	No	N/A	0
Boldt et al (24)	No	Yes	No	No	Yes	1
The SAFE study investigators (4)	Yes	Yes	Yes	No	Yes	3
Veneman et al (35)	Yes	Yes	No	No	N/A	0
Maitland et al (29)	Yes	Yes	No	No	N/A	0
Maitland et al (30)	Yes	Yes	No	No	N/A	0
Akech et al (26)	No	Yes	No	No	N/A	0
Friedman et al (28)	Yes	Yes	No	No	N/A	0
van der Heijden et al (34)	Yes	Yes	No	No	Yes	1
Dolecek et al (27)	No	Yes	No	No	N/A	0

N/A, not applicable.

of albumin used to resuscitate children with sepsis was 0.29 (95% confidence limits 0.12–0.72, $p = .008$). In the adult populations, there were 15 studies including 1729 participants. The estimate of the OR in the adult populations was 0.87 (95% confidence limits 0.71–1.07, $p = .18$. The p value for the interaction test for population was 0.01. Table 3 summarizes the pooled estimate of the effect of albumin on mortality compared with each of the comparator fluid in patients with sepsis.

To address the question of whether there is evidence that the effect of albumin is different in patients with and without sepsis, a meta-analysis of p values was performed. Nine studies reported a subgroup of participants with sepsis. Meta-analysis of p values for these nine studies gives an overall $p = .67$, indicating no significant evidence that the effect of albumin on mortality is different in patients with sepsis compared with the overall results of the included studies.

DISCUSSION

We performed a systematic review and meta-analysis to investigate the relationship between the use of albumin-containing fluids as a resuscitation fluid and mortality in septic patients. We found 17 trials including 1977 septic patients who

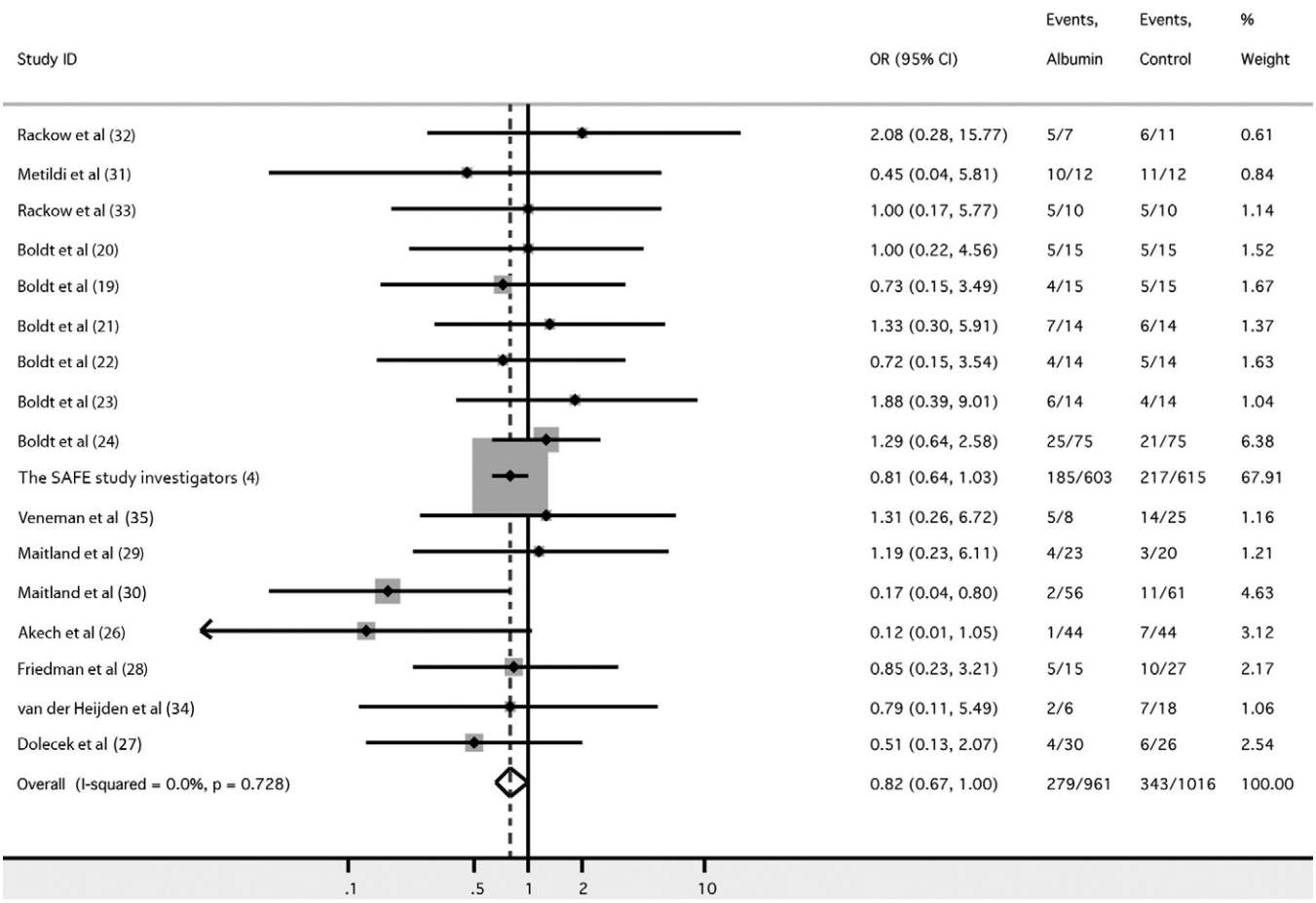

Figure 2. Forrest plot showing the pooled estimate of the effect of resuscitation with albumin-containing solutions on mortality for patients with sepsis. *OR*, odds ratio; *CI*, confidence limit.

Table 3. Pooled estimates of the effect of resuscitation fluid regimens compared with albumin in patients with sepsis

Fluid	Number of Studies	Total Participants	I^2	Estimate of Odds Ratio	95% Confidence Limits	p
Crystalloid	7	1441	0%	0.78	0.62–0.99	.04
Starch	12	463	0%	1.04	0.7–1.54	.84
Gelofusine	2	100	40.1%	0.27	0.06–1.14	.08

were randomized to resuscitation that included albumin solutions. The trials often only included patients with sepsis as a subgroup of the total populations studied, and the methodological quality of the studies was variable. We found evidence that suggests that albumin reduces mortality when used as a resuscitation fluid for patients with sepsis. The overall estimate of treatment was consistent when the largest study was removed from the analysis.

There are a number of possible mechanisms by which albumin could have a beneficial effect in patients with sepsis. As much of the beneficial effect of albumin was in comparison with resuscitation with crystalloid, it is possible that the effect was due to the additional intravascular volume expansion that albumin provides compared with crystalloids, even though the resuscitation targets were similar. Additional to volume expansion effects, albumin has an important physiologic role as a transporter of biologically active molecules, as a drug binder, in the maintenance of colloid osmotic pressure, and in maintaining the permeability of the capillary membrane, in the inhibition of platelet aggregation, and as a free-radical scavenging antioxidant (36, 37). Restoration of physiologic levels of serum albumin may allow these functions to continue and provide benefits to patients with sepsis; the antioxidant function in particular may be crucial in the pathophysiology of sepsis (37). However, although there are theoretical advantages to maintaining serum albumin within the normal range, high quality evidence that supplementing albumin in critically ill patients is beneficial is currently lacking (38).

There are a number of limitations to our analysis. As with all meta-analyses, the results of the overall pooled analysis are only as reliable as the results of the included studies. In this analysis, the methodological quality of the included studies was often not optimal. Although the p value for the primary analysis was statistically significant, when a random effects model was used to pool the data, the p value fell short of the traditional level of statistical significance, casting some doubt on the robustness of the analysis. The other major limitation to drawing strong conclusions from these data are that the included studies often included only a subgroup of patients with sepsis. Given that the p value for the interaction test returned a statistically nonsignificant result, it may be that the effect of albumin in patients with sepsis is not different to the overall effect of albumin in patients who require resuscitation, that is, it may not have an effect on mortality. The data to evaluate other outcomes and potential adverse effects of albumin or to assess the impact of timing of administration were not available in the studies included in the meta-analysis, nor were the data available to evaluate the economic implications of using albumin as a resuscitation fluid for all patients with sepsis.

The results of this analysis are different from those of previous meta-analyses of albumin in the critically ill (8, 9). This analysis has focused on a more specific population, rather than the heterogeneous populations included in previous studies. It may also be that the results of this analysis are a chance finding; they certainly need to be confirmed in further adequately powered, well-conducted RCTs. It is well known that the results of meta-analyses may be refuted by subsequent adequately powered RCTs (39).

Further research will be needed before definitive recommendations can be made regarding the optimal choice of fluid for resuscitation of patients with sepsis. There are currently at least three ongoing randomized trials of albumin in patients with sepsis. The Efficacy of Albumin Administration for Volume Replacement in Patients with Severe Sepsis or Septic Shock–the ALBumin Italian Outcome Sepsis study (NCT00707122) plans to enroll 1350 patients and to finish May 2010. The Multicenter, Early Albumin Resuscitation During Septic Shock study (NCT00327704) completed enrolment of 800 patients in March 2010. The Five Percent Albumin vs. Normal Saline as Fluid Resuscitation Strategies for the Management of Early Suspected Septic Shock (NCT00819416) study completed enrollment of 47 patients in February 2010. The results of these studies should provide further guidance as to the optimal fluid for the resuscitation of patients with sepsis.

The results of this meta-analysis suggest that resuscitation with albumin may result in lower mortality compared with resuscitation with other fluids. Until additional data are available, clinicians may consider albumin as a first line resuscitation fluid for patients with sepsis.

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REFERENCES

1. Dellinger RP, Levy MM, Carlet JM, et al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med* 2008; 34:17–60
2. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
3. Peake S, Webb S, Delaney A: Early goal-directed therapy of septic shock: We honestly remain skeptical. *Crit Care Med* 2007; 35: 994–995; author reply 995
4. The SAFE study investigators: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350:2247–2256
5. Sun X, Briel M, Walter SD, et al: Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010; 340:c117
6. Assmann SF, Pocock SJ, Enos LE, et al: Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* 2000; 355: 1064–1069
7. Bunn F, Trivedi D, Ashraf S: Colloid solutions for fluid resuscitation. *Cochrane Database Syst Rev* 2008; CD001319
8. Perel P, Roberts I: Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2007; CD000567
9. Wilkes MM, Navickis RJ: Patient survival after human albumin administration. A meta-

analysis of randomized, controlled trials. *Ann Intern Med* 2001; 135:149–164
10. Haynes RB, McKibbon KA, Wilczynski NL, et al: Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: Analytical survey. *BMJ* 2005; 330:1179
11. Wong SS, Wilczynski NL, Haynes RB: Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *J Med Libr Assoc* 2006; 94:41–47
12. Boldt J, Knothe C, Zickmann B, et al: Influence of different intravascular volume therapies on platelet function in patients undergoing cardiopulmonary bypass. *Anesth Analg* 1993; 76:1185–1190
13. Jüni P, Altman DG, Egger M: Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001; 323: 42–46
14. Oxman AD, Guyatt GH: A consumer's guide to subgroup analyses. *Ann Intern Med* 1992; 116:78–84
15. Higgins JP, Thompson SG, Deeks JJ, et al: Measuring inconsistency in meta-analyses. *BMJ* 2003; 327:557–560
16. Egger M, Davey Smith G, Schneider M, et al: Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629–634
17. Deeks JJ: Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Stat Med* 2002; 21:1575–1600
18. Shafer SL: Notice of retraction. *Anesth Analg* 2010; 111:1567
19. Boldt J, Heesen M, Müller M, et al: The effects of albumin versus hydroxyethyl starch solution on cardiorespiratory and circulatory variables in critically ill patients. *Anesth Analg* 1996; 83:254–261
20. Boldt J, Heesen M, Welters I, et al: Does the type of volume therapy influence endothelial-related coagulation in the critically ill? *Br J Anaesth* 1995; 75:740–746
21. Boldt J, Mueller M, Menges T, et al: Influence of different volume therapy regimens on regulators of the circulation in the critically ill. *Br J Anaesth* 1996; 77:480–487
22. Boldt J, Müller M, Heesen M, et al: Influence of different volume therapies on platelet function in the critically ill. *Intensive Care Med* 1996; 22:1075–1081
23. Boldt J, Muller M, Heesen M, et al: Influence of different volume therapies and pentoxifylline infusion on circulating soluble adhesion molecules in critically ill patients. *Crit Care Med* 1996; 24:385–391
24. Boldt J, Müller M, Mentges D, et al: Volume therapy in the critically ill: Is there a difference? *Intensive Care Med* 1998; 24:28–36
25. Wang R, Lagakos SW, Ware JH, et al: Statistics in medicine–reporting of subgroup analyses in clinical trials. *N Engl J Med* 2007; 357:2189–2194
26. Akech S, Gwer S, Idro R, et al: Volume expansion with albumin compared to gelofusine in children with severe malaria: Results of a controlled trial. *PLoS Clin Trials* 2006; 1:e21
27. Dolecek M, Svoboda P, Kantorová I, et al: Therapeutic influence of 20% albumin versus 6% hydroxyethylstarch on extravascular lung water in septic patients: A randomized controlled trial. *Hepatogastroenterology* 2009; 56:1622–1628
28. Friedman G, Jankowski S, Shahla M, et al: Hemodynamic effects of 6% and 10% hydroxyethyl starch solutions versus 4% albumin solution in septic patients. *J Clin Anesth* 2008; 20:528–533
29. Maitland K, Pamba A, English M, et al: Pretransfusion management of children with severe malarial anaemia: A randomised controlled trial of intravascular volume expansion. *Br J Haematol* 2005; 128: 393–400
30. Maitland K, Pamba A, English M, et al: Randomized trial of volume expansion with albumin or saline in children with severe malaria: Preliminary evidence of albumin benefit. *Clin Infect Dis* 2005; 40:538–545
31. Metildi LA, Shackford SR, Virgilio RW, et al: Crystalloid versus colloid in fluid resuscitation of patients with severe pulmonary insufficiency. *Surg Gynecol Obstet* 1984; 158: 207–212
32. Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med* 1983; 11:839–850
33. Rackow EC, Mecher C, Astiz ME, et al: Effects of pentastarch and albumin infusion on cardiorespiratory function and coagulation in patients with severe sepsis and systemic hypoperfusion. *Crit Care Med* 1989; 17: 394–398
34. van der Heijden M, Verheij J, van Nieuw Amerongen GP, et al: Crystalloid or colloid fluid loading and pulmonary permeability, edema, and injury in septic and nonseptic critically ill patients with hypovolemia. *Crit Care Med* 2009; 37:1275–1281
35. Veneman TF, Oude Nijhuis J, Woittiez AJ: Human albumin and starch administration in critically ill patients: A prospective randomized clinical trial. *Wien Klin Wochenschr* 2004; 116:305–309
36. Lang JD Jr, Figueroa M, Chumley P, et al: Albumin and hydroxyethyl starch modulate oxidative inflammatory injury to vascular endothelium. *Anesthesiology* 2004; 100:51–58
37. Quinlan GJ, Margarson MP, Mumby S, et al: Administration of albumin to patients with sepsis syndrome: A possible beneficial role in plasma thiol repletion. *Clin Sci (Lond)* 1998; 95:459–465
38. Finfer S, Bellomo R, McEvoy S, et al: Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: Analysis of data from the saline versus albumin fluid evaluation (SAFE) study. *BMJ* 2006; 333:1044
39. LeLorier J, Grégoire G, Benhaddad A, et al: Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med* 1997; 337:536–542