

Literature Grading

What is the Preferred Resuscitation Fluid for Patients with Severe Sepsis and Septic Shock?

Search Results

Tier 1

- A. Keywords used in search: sepsis OR severe sepsis OR septic shock OR systemic inflammatory response syndrome OR sepsis syndrome AND intravenous fluid OR fluid resuscitation OR normal saline OR balanced solution OR albumin OR colloid AND systematic [sb]
- B. Database Searched: Pubmed
- C. Dates Searched: From 2011 to 2016 with references: 639
- D. Limits Applied
 - Limit: Human
 - Limit: Adult
 - Limit: English
- E. Final Search Results with # of references: 136

Tier 2

- A. Keywords used in search: sepsis OR severe sepsis OR septic shock OR systemic inflammatory response syndrome OR sepsis syndrome AND intravenous fluid OR fluid resuscitation OR normal saline OR balanced solution OR albumin OR colloid
- B. Database Searched: Pubmed
- C. Dates Searched: From 2011 to 2016
- D. Limits Applied
 - a. Limit: Human
 - b. Limit: Adult
 - c. Limit: English
 - d. Limit: Randomized Controlled Trial
- E. Final Search Results with # of references: 1300

Tier 3

- A. Keywords used in search: sepsis OR severe sepsis OR septic shock OR systemic inflammatory response syndrome OR sepsis syndrome AND intravenous fluid OR fluid resuscitation OR normal saline OR balanced solution OR albumin OR colloid
- B. Database Searched: Pubmed
- C. Dates Searched: From 2011 to 2016
- D. Limits Applied
 - a. Limit: Human
 - b. Limit: Adult
 - c. Limit: English
 - d. Limit: Clinical Trial
- E. Final Search Results with # of references: 1805

Tier 4

- A. Keywords used in search: sepsis OR severe sepsis OR septic shock OR systemic inflammatory response syndrome OR sepsis syndrome AND intravenous fluid OR fluid resuscitation OR normal saline OR balanced solution OR albumin OR colloid
- B. Database Searched: Pubmed
- C. Dates Searched: From 2011 to 2016
- D. Limits Applied
 - a. Limit: Human
 - b. Limit: Adult

- c. Limit: English
 E. Final Search Results with # of references: 9062

Systematic Reviews

1. Patel A, Laffan MA, Waheed U, Brett SJ. Randomised trials of human albumin for adults with sepsis: review and meta-analysis with trial sequential analysis of all-cause mortality. *BMJ*. 2014; 349:g4561.
2. Rochwerf B, Alhazzani W, Sindi A, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. *Ann Intern Med*. 2014; 161:347-355.
3. Xu JY, Chen QH, Xie JF, et al. Comparison of the effects of albumin and crystalloid on mortality in adult patients with severe sepsis and septic shock: a meta-analysis of randomized clinical trials. *Crit Care*. 2014;18:702.
4. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation a systematic review and meta-analysis. *JAMA*. 2013; 309:678-88.
5. Gattas DJ, Dan A, Myburgh J, et al. Fluid resuscitation with 6% hydroxyethyl starch (130/0.4 and 130/042) in acutely ill patients: systematic review of effects on mortality and treatment with renal replacement therapy. *Intensive Care Med*. 2013; 39:558-68.
6. Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. *Crit Care Med*. 2011; 39:386-91.

Original Research

1. Müller RB, Haase N, Lange T, Wetterslev J, Perner A. Acute kidney injury with hydroxyethyl starch 130/0.42 in severe sepsis. *Acta Anaesthesiol Scand*. 2015 Mar;59(3):329-36.
2. Raghunathan K, Shaw A, Nathanson B, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill patients with sepsis. *Crit Care Med*. 2014; 42:1585-91.
3. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *NEJM*. 2014; 370: 1412-21.
4. Waechter J, Kumar A, Lapinsky SE, et al. Interaction between fluids and vasoactive agent on mortality in septic shock: a multicenter, observational study. *Crit Care Med*. 2014; 42:158-68.
5. Perner A, Haase N, Winkel P, et al. Long-term outcomes in patients with severe sepsis randomised to resuscitation with hydroxyethyl starch 130/0.42 or Ringer's acetate. *Intensive Care Med*. 2014;40(7):927-34.
6. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. *JAMA*. 2013; 310:1809-17.
7. Perner A, Haase N, Guttormsen AB, et al. Hydroxethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *NEJM*. 2012; 367:124-34.
8. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *NEJM*. 2012; 367:1901-11.
9. Guidet B, Martinet O, Boulain T, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study. *Crit Care*. 2012; 16:R94.
10. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA*. 2012; 308:1566-72.
11. Finfer S, McEvoy S, Bellomo R, et al. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive Care Med*. 2011; 37:86-96.

Publications	Grade	Quality	Comments
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<p>Patel A, Laffan MA, Waheed U, Brett SJ. <i>BMJ</i> 2014; 349:g4561.</p>	<p>A</p>	<p>Good</p>	<ul style="list-style-type: none"> • 16 RCTs • 4190 patients • 3 primary trials were multicenter and designed to investigate the endpoint of all-cause mortality in 3820 randomized patients with severe sepsis and septic shock. • Comparison fluids were crystalloids (0.9% NS, Ringer's lactate) and colloids (HES, gelatin) • All-cause mortality <ul style="list-style-type: none"> ○ Statistically similar between two fluid groups; no publication bias ○ Exclusion of studies at high risk of bias left 6 studies in 3942 patients; not statistically significant benefit • Albumin compared with crystalloid fluids <ul style="list-style-type: none"> ○ 7 clinical trials randomized 3878 patients ○ Mortality similar for both fluid groups ○ Publication bias was not detected ○ Statistical heterogeneity was not present • Mortality in adults with sepsis, severe sepsis, septic shock was not significantly reduced or increased by the use of human albumin products as part of fluid expansion or resuscitation in intensive or critical care settings.
<p>Rochweg B, Ahazzani W, Sindi A, et al. <i>Ann Intern Med</i> 2014; 161:347-355.</p>	<p>A</p>	<p>Good</p>	<ul style="list-style-type: none"> • 14 RCTs included • 4-Node Analysis <ul style="list-style-type: none"> ○ Higher mortality with starches than crystalloids ○ Lower mortality with albumin than with crystalloids and starches • 6-Node Analysis

			<ul style="list-style-type: none"> ○ Balanced crystalloids are superior to saline OR 0.78 (CI 0.58 to 1.05; low confidence)
Xu JY, Chen QH, Xie JF, et al. <i>Crit Care</i> . 2014 Dec 15;18:702.	A	Adequate	<ul style="list-style-type: none"> ● 5 studies – 3658 severe sepsis; 2180 septic shock <ul style="list-style-type: none"> ○ 3 studies used 4% or 5% albumin; 1 used 20%; 1 used both concentrations ○ Normal saline used in 2 trials; Ringer's lactate in 1; the remaining 2 used varying fluids ● Mortality <ul style="list-style-type: none"> ○ Severe sepsis: trend towards reduced mortality (OR 0.88) but not statistically significant ○ Septic shock: decreased mortality (OR 0.81)
Zarychanski R, Abou-Setta AM, Turgeon AF, et al. <i>JAMA</i> 2013; 309:678-88.	B	Good	<ul style="list-style-type: none"> ● 38 trials <ul style="list-style-type: none"> ○ 10,880 patients ○ No significant difference in mortality or AKI ● When 7 trials by Boldt et al removed – HES was significant associated with increased death (RR 1.09) ● Incidence of AKI significantly higher in patients receiving HES (RR 1.27)
Gattas DJ, Dan A, Myburgh J, et al. <i>Intensive Care Med</i> 2013; 39:558-68.	B	Adequate	<ul style="list-style-type: none"> ● 35 studies; 25 of which reported on mortality ● 3 studies had low risk of bias – all published in year preceding this review and comprised majority of numbers ● Mortality: RR 1.08 (CI 1.00-1.17) ● RRT: RR 1.25 (CI 1.08-1.44)
Delaney AP, Dan A, McCaffrey J, Finfer S. <i>Crit Care Med</i> 2011.	A	Poor	<ul style="list-style-type: none"> ● 17 studies – 1977 patients ● 8 studies in septic patients ● 9 studies where septic patients were subgroup

			<ul style="list-style-type: none"> • Use of albumin associated with reduction in mortality (OR 0.82, CI 0.67-1.0) • 6 studies from Boldt et al.
Müller RB, Haase N, Lange T, Wetterslev J, Perner A. <i>Acta Anaesthesiol Scand</i> . 2015 Mar;59(3):329-36.	E	Adequate	<ul style="list-style-type: none"> • Post-hoc analysis of 6S study (Perner et al, NEJM 2012) to determine effect of HES on AKI and its association with mortality • 798 patients • 26 ICUs in Scandinavia • Randomized to fluid resuscitation with 130/0.42 HES or Ringer's acetate • IVF given at discretion of treating clinician • AKI: 28% in HES, 22% in Ringer's acetate group • AKI more severe and RRT initiated earlier in first 5 days of patients who got HES • Original trial not powered to investigate AKI
Raghunathan K, Shaw A, Nathanson B, et al. <i>Crit Care Med</i> 2014; 42:1585-91	D	Poor	<ul style="list-style-type: none"> • Retrospective cohort • 360 hospitals of healthcare alliance • Included adult patients with principal or secondary diagnosis of sepsis who were receiving vasopressors by day 2 and needed to receive at least 2L of crystalloid by day 2 • Categorized into No Balanced IVF Group and Balanced Group • 53,448 patients • 3,396 patients got some form of balanced fluids • Most received < 40% • Predominant fluid was LR • Absolute in-hospital mortality for balanced group 19.6% vs. 22.8% for No Balanced group
Caironi P, Tognoni G, Masson S, et al. <i>NEJM</i> 2014; 370: 1412-21.	A	Outstanding	<ul style="list-style-type: none"> • Multicenter, open-label RCT • 100 ICUs in Italy • Adult patients who met clinical criteria for severe sepsis within previous 24 hours of ICU stay

			<ul style="list-style-type: none"> • Goal was to investigate effects of albumin + crystalloid to crystalloid alone in severe sepsis • Patients given 20% albumin+ crystalloid to maintain serum albumin level of 30 g/L • 1818 patients • 28-day mortality 31.8% in albumin group and 32% in crystalloid group • No difference in newly developed organ failure scores or SOFA scores
Perner A, Haase N, Winkel P, et al. <i>Intensive Care Med.</i> 2014; 40(7):927-34.	E	Adequate	<ul style="list-style-type: none"> • Protocolized long-term follow-up of the 6S study • Long-term mortality <ul style="list-style-type: none"> ○ 6 months: 53.3% HES vs. 47.5% in Ringer's acetate ○ 1 year: 56% HES vs. 51.5% Ringer's acetate (not significant) ○ Longest follow up: 59.8% HES vs. 56.3% Ringer's acetate (not significant) • 6S trial not powered for mortality after 90 days
Annane D, Siami S, Jaber S, et al. <i>JAMA</i> 2013; 310:1809-17	B	Poor	<ul style="list-style-type: none"> • Multicenter, randomized, parallel-group trial • 57 ICUs in France, Belgium, Canada, Algeria, Tunisia • Included patients with no prior IVF resuscitation during their ICU stay that now needed IVFS for hypovolemia • Randomized 1:1 stratified by center and admission diagnosis (sepsis, trauma, other) • 2857 patients: 1443 in crystalloid group, 1414 in colloid group • Severe sepsis main diagnosis • 28-day Mortality: 25.4% in colloid group; 27% in crystalloid group • 90-day mortality: 30% in colloid group, 34% in crystalloid group – statistically significant

			<ul style="list-style-type: none"> • Protocol violations in 20% of colloid group, took 9 years to recruit, non-blinded
Perner A, Haase N, Guttormsen AB, et al. <i>NEJM</i> 2012; 367:124-34.	A	Outstanding	<ul style="list-style-type: none"> • Multicenter, parallel-group, blinded trial • 26 ICUs in Scandinavia • Randomized patients with 6% HES 130/0.42 or Ringer's acetate at a dose of up to 33 ml/kg IBW • Primary outcome: death or end-stage kidney failure at 90 days • 804 patients with severe sepsis • HES <ul style="list-style-type: none"> ○ Higher 90-day mortality (51 vs. 43%) ○ Increased risk of RRT (22 vs. 16%) ○ More RBC transfusion (58 vs. 46%)
Myburgh JA, Finfer S, Bellomo R, et al. <i>NEJM</i> 2012; 367:1901-11.	B	Outstanding	<ul style="list-style-type: none"> • Multicenter, randomized, prospective trial • 32 medical-surgical ICU in Australia and New Zealand • Patients eligible if treating physician felt they needed fluid therapy • Patients randomized to 6% HES (130/0.4) or 0.9% saline • Primary outcome 90-day all-cause mortality • 7000 patients; approx. 28% had sepsis • No difference found in 90-day all-cause mortality (18% HES, 17% saline) • More patients in HES group required RRT (7% vs. 5.8%) • HES associated with increased risk of adverse events (5.3% vs. 2.8%)
Guidet B, Martinet O, Boulain T, et al. <i>Crit Care</i> 2012; 16:R94.	A	Adequate	<ul style="list-style-type: none"> • Prospective, multicenter, active-controlled, double-blind, randomized trial • 24 centers in France and Germany • Adult patients with severe sepsis

			<ul style="list-style-type: none"> • HES 130/0.4 vs. NS • Primary outcome was amount of IVF required to reach hemodynamic stability; • 196 patients in the ICU • Most patients got fluids and catecholamines prior to randomization • Number of patients reaching hemodynamic stability in 48 hours similar in both groups • Less volume used in HES group • Mortality 31% HES vs. 25.3% saline (not statistically different) • ARF or RRT not significantly different: 24.5% HES vs. 20% saline • Study not powered for mortality or effects on kidney function
Yunos NM, Bellomo R, Hegarty C, et al. <i>JAMA</i> 2012; 308:1566-72.	C	Poor	<ul style="list-style-type: none"> • Prospective, open-label, before-and-after study • 22-bed multidisciplinary ICU in Melbourne Australia • Determine if a chloride-restrictive IVF strategy might be associated with a decreased incidence of AKI • 1533 patients: 760 in control, 773 in intervention) • Severe sepsis in 7%-10% of patients • Significantly lower increase in serum creatinine during ICU stay during intervention period • Decreased incidence of renal injury and failure • No change in mortality • Limitations: not blinded RCT, subject to observation bias; lots of different solutions used
Finfer S, McEvoy S, Bellomo R, et al. <i>Intensive Care Med</i> 2011; 37:86-96.	E	Poor	<ul style="list-style-type: none"> • Detailed publication of the cohort of 1218 patients in the SAFE trial with severe sepsis at the time of randomization • SAFE trial was a blinded, randomized, controlled trial that reported no overall difference in risk of death for heterogeneous

			<p>population of patients who received albumin or saline in the ICU</p> <ul style="list-style-type: none"> • 16 hospitals in Australia and New Zealand • 1218 patients: 603 assigned to albumin, 615 assigned to saline • No significant difference between groups in the SOFA scores for cardiovascular, respiratory, renal, or coagulation systems during first 7 days • Number of patients receiving RRT was the same • Mortality: 30.7% for albumin vs. 35.3% for saline (not significant) • After adjustment for potential confounding variables, albumin independently associated with decreased odds of death at 28 days (OR 0.71; CI 0.52-0.97; p=0.03) • Subgroup analysis – sample size not predetermined, trial not designed to examine albumin and saline in sepsis; not all patients included in the multivariate analysis
<p>Shaw AD, Raghunathan K, Peyerl FW, et al. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. <i>Intensive Care Med</i> 2014; 40:1897-905.</p>	<p>D</p>	<p>Outstanding</p>	<ul style="list-style-type: none"> • Retrospective analysis of a prospectively collected HER database of 109,836 adult patients with SIRS from 124 hospitals • Examined change in serum chloride, fluid volume and chloride administration • Lowest mortality (2.6%) when volume adjusted chloride load was 105-115 mmol/L • In-hospital mortality was lowest among patients with baseline chloride concentrations of 100–110 mmol/L (3.4 %) and highest among patients with 130–140 mmol/L baseline concentrations (31.1 %) • Larger positive shifts in serum chloride from baseline were

			<p>associated with increased in-hospital mortality</p> <ul style="list-style-type: none">• Patients with the smallest increase in serum chloride concentration (0–10 mmol/L) had the lowest observed in-hospital mortality (3.7 %), and mortality increased significantly as the change in serum chloride increased.• Mortality rate was 7.2 % in patients with shifts of 10–20 mmol/L, 9.2 % in patients with shifts of 20–30 mmol/L and 9.7 % in patients with shifts of 30–40 mmol/L (P = 0.001)
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