RESUSCITATIVE FLUIDS IN SEPSIS AND SEPTIC SHOCK: A SYSTEMATIC REVIEW, NETWORK META-ANALYSIS AND PILOT STUDY PROTOCOL

BY: BRAM ROCHWERG, BSc, MD, FRCPC

A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfillment of the Requirements

for the Degree of Master of Science

McMaster University

© Copyright by Bram Rochwerg, July 2015

TITLE: Resuscitative fluids in sepsis and septic shock: a systematic review, network meta-analysis and pilot study protocol.

AUTHOR: Bram Rochwerg, BSc (Western University), MD

(The University of Ottawa)

SUPERVISORS: Dr. Jan Brozek, Dr. Gordon Guyatt, Dr. Roman Jaeschke

EXTERNAL REVIEWER: Dr. Francois Lamontagne (University of Sherbrooke)

**ABSTRACT**

This thesis consists of two related studies presented as three separate manuscripts (all three have been published in peer-reviewed journals) and a study protocol that has been submitted for peer-reviewed funding. The over-arching theme of this thesis was to better characterize the efficacy of different intravenous fluids used for the resuscitation of intensive care unit (ICU) patients with severe sepsis or septic shock.

We performed an extensive search including multiple databases which found 20 randomized controlled trials (RCTs) that examined the effects of different intravenous fluids used in septic patients and met our *a priori* inclusion and exclusion criteria. In the first manuscript, we described in detail the composition of the 19 unique fluid products that were used in the various studies. This description included the fluid type, trade name, osmolality, tonicity, electrolyte content, molecular composition, pH, and manufacturer. We reviewed manufacturer’s websites, product monographs, and emailed industry representatives or study authors for more information regarding the fluids as required. The results of this study and systematic review led us to the second and third manuscripts which reported on a Bayesian network meta-analysis (NMA) of all fluid type comparisons.

Despite multiple well-done RCTs, comparative data regarding the clinical effect of different resuscitative fluids when used for sepsis was incomplete. Most RCTs used 0.9% saline (normal saline) as control fluid and very few studies compared colloids directly. The advantage of using an NMA model in this setting was the ability to include indirect data into the overall point estimates. Data was abstracted from the 14 studies which focused on adult ICU patients and analyzed examining the outcomes of mortality (manuscript #2) and the use of renal replacement therapy (RRT) (manuscript #3). Certainty of evidence was evaluated for both outcomes using the GRADE approach.

Results of the analysis clearly document the harm of starch-based fluids when used in septic patients. Albumin containing fluids and crystalloids (such as normal saline and Ringer’s Lactate) are better options. Lower chloride solutions, such as Ringer’s Lactate, showed a signal towards decreased mortality and a decreased use of renal replacement therapy when compared to higher chloride fluids, such as normal saline, however this was based on indirect data, not statistically significant, and warrants direct comparison trials.

The final component of this thesis is a pilot study protocol for a study assessing the feasibility of a larger RCT examining the effect of low chloride versus high chloride fluids for resuscitation in patients with sepsis and septic shock. This protocol has been submitted as part of a peer-reviewed grant with the hopes of addressing this clinically important and timely question.

**ACKNOWLEDGEMENTS**

I would like to express my sincerest gratitude to my thesis committee. Roman Jaeschke epitomizes a true mentor, supervisor and friend. His guidance and encouragement through these early stages of my career have been invaluable. I am lucky to have been the recipient of his wisdom and sage counsel. Gordon Guyatt, since our early encounters on the clinical teaching unit, has been incredibly supportive of my research aspirations and been instrumental in advancing my career goals. Despite his international reputation and incredibly busy schedule, I know I can email him with any question or concern and will receive a very helpful and articulate early morning response. Jan Brozek, as my lead supervisor, has advocated on my behalf multiple times and continues to supply me with integral hands-on advice and research opportunities. I am truly fortunate to have had such a group of individuals on my Master’s committee. Importantly, I would also like to recognize my other research supporters and mentors who were not formally a part of my committee including Deborah Cook, Maureen Meade, Waleed Alhazzani, Alison Fox-Robichaud, Azim Gangji, Peter Margetts, Christine Ribic, and Holger Schunemann.

To my clinical colleagues, especially Tim Karachi, your contributions, supportive comments and collaborative attitudes are always appreciated.

Rachel, you are incredibly understanding. Your support, in good times and bad, is what keeps me going. Thanks for putting up with the research meetings, conferences and time I spend away. There is nothing more important to me then you and the boys. I can’t imagine spending my life with anyone else. To my sons, Nate and Leo, your dad is finally going to be done school! (maybe)

**TABLE OF CONTENTS**

Abstract…………………………………………………………………………………….…3

Acknowledgements…………………………………………………………………………...4

Table of Contents………………………………………………………………………….….5

Declaration of Academic Achievement……………………………………………….……...6

Introduction…………………………………………………………………………….……..7

Manuscript #1 – Fluid resuscitation in severe sepsis and septic shock: systematic

description of fluids used in randomized trials for researchers and clinicians…….....10

Manuscript #2 – Fluid resuscitation in sepsis: a systematic review and network

meta-analysis………………………………………………………………………....22

Manuscript #3 – Fluid type and the use of renal replacement therapy in sepsis: a

systematic review and network meta-analysis……………………………………….54

Study Protocol – Fluids in sepsis and septic shock (FISSH): a pilot randomized

controlled trial………………………………………………………………………..81

Methodological Issues and Thesis Conclusions……………………………………………...94

References……………………………………………………………………………………97

**DECLARATION OF ACADEMIC ACHIEVEMENT**

This thesis is submitted in partial fulfillment of the requirements for the Master of

Science program in Health Research Methodology. The work takes the form of a sandwich thesis, consisting of three separate, but related manuscripts and a related pilot study protocol which will be submitted for peer-reviewed funding.

Bram Rochwerg is the first author of all three manuscripts and the principle investigator of the pilot grant submission. Anees Sindi and Roman Jaeschke developed the protocol for the systematic review and meta-analysis at which point it became Bram’s project. Bram was involved with title and abstract review, case report form generation, data abstraction, analysis and GRADE application. Diane Heels-Ansdell, our statistician, ran the Bayesian network meta-analysis for the two outcomes of interest. Funding for the statistical analysis was provided by Hamilton Chapter of The Canadian Intensive Care Foundation, the Critical Care Medicine Residency Program and the Critical Care Division Alternate Funding Plan both at McMaster University, Hamilton, Ontario. Bram wrote the first draft of each manuscript prior to group revisions.

Bram developed the pilot study protocol under the mentorship of his committee, Deborah Cook and Maureen Meade, who helped to prepare it for grant submission.

**INTRODUCTION**

***Sepsis is common condition with a high mortality rate.***

Sepsis is a common problem with an annual incidence of approximately 200 to 300 cases per 100,000[[1](#_ENREF_1)]. Sepsis includes the presence of the systemic inflammatory response syndrome (SIRS) in addition to a clinical suspicion of infection as a likely etiology. In patients with septic shock (sepsis in addition to signs or symptoms of organ hypo-perfusion), mortality rates range from 20% to 40%[[2](#_ENREF_2)]. Septic shock is unique compared to many other shock syndromes (eg. cardiogenic, obstructive, hypovolemic) in that the vascular endothelium becomes porous or leaky in response to inflammatory cytokines. A resultant shift of fluid from the intravascular space to the interstitium occurs, described as a ‘distributive shock’. This pathophysiologic mechanism differentiates septic shock and may necessitate a specific treatment plan compared to other shock etiologies.

***Intravenous fluids are crucial to the management of sepsis.***

Hypotension has a profound deleterious effect on organ function. At the vascular endothelial level, pathogen-mediated molecules, for example the endotoxin lipopolysaccharide in gram-negative bacteria, initiate an inflammatory cascade associated with cytokine release and monocyte/lymphocyte aggregation[[3](#_ENREF_3)]. The smooth muscle cells respond to these inflammatory signals by vaso-dilating and the endothelial cells by contracting resulting in leakage of leukocytes and proteins into the extravascular space[[4](#_ENREF_4)]. The consequence of this response is systemic hypo-perfusion secondary to a loss of vascular tone and extravasation of intravascular fluid. In addition to antimicrobials, the replacement of intravascular fluid is the mainstay of treatment for sepsis to combat this complication of the host response and to maintain organ perfusion and oxygen delivery.

An RCT by *Rivers et al* in 2001 evaluated the concept of early goal-directed therapy (EGDT), and showed that patients with sepsis who were randomized to protocolized care, which included high volumes of intravascular fluid replacement in the first 6 hours after presentation, had lower mortality compared to those receiving standard care and less fluid (RR 0.58, 95% CI 0.38-0.87) [[5](#_ENREF_5)]. More recently, two large RCTs examined EGDT versus standard care during the first 6 golden hours of sepsis resuscitation. The first showed no mortality benefit associated with protocolized fluid administration for sepsis (risk difference -0.3, 95% CI -4.1 to 3.6, p=0.90), however both the intervention arm and usual care arm received large amounts of fluid in the initial 6 hours after presentation (1964 mls versus 1713 mls) [[6](#_ENREF_6), [7](#_ENREF_7)]. Similarly, the second recent RCT examining EGDT found no benefit in mortality, need for organ support or length of stay for those receiving protocolized care [[7](#_ENREF_7)]. It has been hypothesized that this discrepancy in results between the original trial in 2001 that suggested a benefit of EGDT and the 2 recent trials that showed no benefit of EGDT can be explained by shifting clinical practice and standard of care. Mostly as a result of the first trial, clinicians now better appreciate the importance of early and rapid volume infusion in patients with sepsis. This is evident given that patients enrolled in the more recent studies received similar amounts of fluid within the first 6 hours whether they were randomized to the protocolized or standard care arms.

***Different formulations of intravenous fluids are available for use in sepsis***

Several fluid solutions, categorized as either crystalloids or colloids, are available for resuscitation. Each fluid has unique properties, including tonicity, pH, and osmolality depending on its specific electrolyte and molecular composition[[8](#_ENREF_8)].

Crystalloids are divided primarily based on tonicity into hypertonic, isotonic and hypotonic solutions. Isotonic crystalloids function as volume expanders having a tonicity similar to that of plasma, thereby preventing significant fluid shifts across the vascular membrane. Even isotonic fluids will, however, eventually redistribute throughout cellular compartments with up to two-thirds eventually reaching the extravascular space. The most commonly used isotonic crystalloid worldwide is 0.9% normal saline (saline) which contains a supra-physiologic concentration of chloride [[9](#_ENREF_9)]. Some other isotonic crystalloid solutions contain an organic anion (eg. lactate, maleate, acetate) and therefore have a lower chloride content more closely resembling that of human plasma (eg. Ringer’s Lactate, and Ringer’s Acetate). These solutions with a more physiologic chloride content are termed “balanced crystalloids”. Hypertonic solutions can be effective as volume expanders but are associated with deleterious effects such as hypernatremia and irreversible cerebral damage when used in large amounts. Hypotonic crystalloids are ineffective volume expanders due to their rapid shift out of the vascular space via osmosis.

Colloids, in contrast, contain large-molecular weight compounds that remain in the intravascular space for a prolonged period of time. The net result is an oncotic gradient that draws fluid from the extracellular space into the vasculature. The theoretical benefit is resuscitation using a smaller volume of intravenous fluid. Examples of colloids used for resuscitation in sepsis include albumin, hydroy-ethyl starches (HES) (both low and high molecular weight), dextran and gelatin solutions.

***Randomized trial data guiding the use of resuscitation fluids in sepsis provide few definitive results***

One meta-analysis addressing optimal fluid choice included 74 trials in critically ill patients (not just those with sepsis) and found no difference in mortality between those resuscitated with crystalloid compared to albumin (RR 1.01, 95% CI 0.93-1.10), HES (RR 1.10, 95% CI 0.91-1.32), gelatin (RR 0.91, 95% CI 0.49-1.72) or dextran (RR 1.24, 95% CI 0.94-1.65) [[10](#_ENREF_10)].

In contrast to these results, a number of recent large-scale RCTs have shown worse outcomes when using HES for resuscitation in patients with sepsis [[11-13](#_ENREF_11)]. A meta-analysis of 9 trials comparing HES versus other fluids for resuscitation in sepsis found an increased mortality (RR 1.11, 95% CI 1.00-1.23) and an increased use of renal replacement therapy (RRT) (RR 1.36, 95% CI 1.08-1.72) in patients receiving HES[[14](#_ENREF_14)]. This has led to an FDA warning[[15](#_ENREF_15)] against their use in septic patients and has limited their use to stable outpatients in the operating room setting.

Other than HES, albumin is the best studied of the colloid solutions. In the SAFE trial 6,997 critically ill patients (again not just those with sepsis) requiring fluid resuscitation were randomized to receive resuscitation with a 4% albumin solution or normal saline, a commonly used crystalloid solution[[16](#_ENREF_16)]. No significant difference was observed between albumin and saline on 30-day mortality (relative risk (RR) 0.99; 95% confidence interval (CI) 0.91-1.09). Of note patients in the saline arm required 1.4 times more fluid to achieve the same hemodynamic endpoints as those in the albumin arm. A more recent meta-analysis focusing only on resuscitation in patients with sepsis included 17 studies and 1977 patients comparing albumin versus crystalloids and demonstrated the potential benefit of albumin in terms of mortality (OR 0.82, 95% CI 0.67-1.0, p = 0.047) [[17](#_ENREF_17)].

***Observational studies and small RCTs suggest that fluids composed of supra-physiologic chloride concentrations may be harmful.***

Compared with balanced crystalloid solutions, normal saline predisposes patients to hyper-chloremic metabolic acidosis, decreased renal blood flow to the glomerulus, and impaired smooth muscle contractility [[18](#_ENREF_18)]. Whether this translates into inferior patient-important outcomes remains, however, questionable. Indeed, some have hypothesized that a small degree of acidosis may be protective against hypoxic stress[[19](#_ENREF_19)].

An observational study of 9,799 ICU patients in a large US teaching hospital found no association between hyper-chloremic acidosis and risk of death [[20](#_ENREF_20)]. Another cohort study included 53,448 septic patients from 360 US hospitals [[21](#_ENREF_21)]. Overall, 3,396 (6.4%) of the patients received a balanced crystalloid fluid by the second ICU day. After propensity matching, patients receiving balanced crystalloid had improved hospital survival (RR 0.86, 95% CI 0.78-0.94) but the frequency of acute renal failure or length of ICU stay did not differ [[21](#_ENREF_21)]. A single center study of 760 patients in Australia compared balanced and unbalanced crystalloids administration in the ICU using a before-and-after observational cohort design [[22](#_ENREF_22)]. Balanced fluid solutions were 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.

Two intra-operative studies have directly compared the use of balanced versus unbalanced fluids in stable, non-hypotensive patients. The first randomized 66 patients undergoing elective abdominal aortic aneurysm repair to receive either normal saline or Ringer’s lactate throughout their operation[[23](#_ENREF_23)]. Patients randomized to receive normal saline had increased rates of hyperchloremic acidosis requiring more bicarbonate therapy in addition to an increased need for blood product transfusion. The authors hypothesized that the acidosis may have affected the clotting cascade leading to increased rates of bleeding in the normal saline group.

The second intraoperative study randomized 51 patients undergoing renal transplantation to receive either normal saline or Ringer’s lactate[[24](#_ENREF_24)]. Although enrolment was planned for 200 patients, this study was stopped early due to harm observed in the normal saline arm. Five patients in the normal saline arm (compared to zero in the Ringer’s arm) developed hyperkalemia (p = 0.05) and 8 patients in the saline arm (compared to zero in the Ringer’s arm) developed acidosis (p=0.004). Although Ringer’s Lactate contains a small amount of potassium, it’s possible the metabolic acidosis precipitated by the high chloride in the saline was responsible for the hyperkalemia in the saline arm.

A potentially crucial factor rarely considered in trial designs involving colloids is the electrolyte content of the crystalloid in which a specific colloid is dissolved. This property may have contributed to the observed harmful effect of HES in one RCT in which the colloid was dissolved in normal saline and compared to a balanced crystalloid solution[[11](#_ENREF_11)].

In summary, observational studies and physiological findings from small RCTs are consistent with the hypothesis that using balanced crystalloid as the resuscitation fluid results in lower mortality than use of normal saline.

***Indirect RCT evidence suggests a potential benefit of low chloride versus normal chloride intravenous fluids in septic patients.***

Our group recently performed a network meta-analysis (NMA) of all fluid types used for resuscitation in patients with septic shock [[25](#_ENREF_25)]. The NMA model combines direct and indirect estimates of effect in order to calculate the overall relative effectiveness of an intervention. In other words, if an NMA is addressing treatments A, B, and C, for the A–B comparison, the direct estimates will come from all RCTs that compare A vs. B, and the indirect estimates will come from RCTs comparing A vs. C and B vs. C, which allow to make an inference of the estimate of A vs. B, through C [[26](#_ENREF_26)]. This allows for comparison of interventions even in situations where no head-to-head trials exist (relying only on indirect evidence). Also, in situations where direct and indirect evidence are available, pooling may increase the precision of the effect estimate.

For our NMA, a systematic review of the literature produced 14 RCTs that examined mortality[[11-13](#_ENREF_11), [16](#_ENREF_16), [27-36](#_ENREF_27)] and 10 that examined the use of RRT [[11-13](#_ENREF_11), [16](#_ENREF_16), [27-29](#_ENREF_27), [33](#_ENREF_33), [35](#_ENREF_35), [36](#_ENREF_36)]. Appendix Table 1 presents a summary of the included trials. Analysis divided crystalloids into balanced or unbalanced solutions. Results suggested that albumin is superior to saline (NMA OR 0.82; 95% Credible Interval (CrI) 0.65-1.04). Using the GRADE approach to evidence-based clinical recommendations [[37](#_ENREF_37)], we considered this comparison to provide moderate quality of evidence. Results suggested mortality did not differ between albumin and balanced crystalloid (NMA OR 0.95; 95% CrI 0.65-1.38, very low quality of evidence). Most relevant to the current proposal, results suggested balanced crystalloid may be superior to saline (NMA OR 0.78; 95% CrI 0.58-1.05); however, this was based on indirect evidence only, yielding low quality of evidence.

Regarding the use of RRT, balanced crystalloid proved superior to both light (NMA OR 0.70; 95% CrI 0.49-0.99, high quality of evidence) and heavy starch (NMA OR 0.50, 95% CrI 0.34-0.74, moderate quality of evidence) [[38](#_ENREF_38)]. Confidence intervals around the difference in the need for RRT associated with the use of balanced crystalloid in comparison to saline were very wide (NMA OR 0.85; 95% CrI 0.56-1.30, low quality of evidence).

In summary, indirect comparisons from randomized trials in septic patients are consistent with the hypothesis that using balanced crystalloid as the resuscitation fluid results in lower mortality than use of normal saline.

***Summary***

Based upon the research described above, the 2013 update to the Surviving Sepsis Campaign Guidelines recommend that crystalloid solutions be used as first-line intravenous fluid for patients with septic shock (GRADE 1B) but do not make any suggestion as to which crystalloid solution to use [[1](#_ENREF_1)]. Albumin is suggested for those requiring large fluid volumes (GRADE 2C); electrolyte content is, however, not mentioned.

Despite the evidence we have summarized of the physiologic benefits and possible lower mortality associated with balanced solutions, normal saline remains the most widely used fluid in the world. Given uncertainty about the impact of lower chloride versus higher chloride solutions on mortality, it is unlikely clinical practice will change without new and direct RCT evidence. Editorials published in leading critical care journals have called for RCTs to address this important clinical question [[19](#_ENREF_19), [39-44](#_ENREF_39)].

**Manuscript #1 - Fluid Resuscitation in severe sepsis and septic shock: systematic description of fluids used in randomized trials for researchers and clinicians.**

**Objective Manuscript #1:** Based on the systematic review, we composed a comprehensive summary of all fluids used in RCTs examining the resuscitation of ICU patients with sepsis.

**Reference:** [Rochwerg B](http://www.ncbi.nlm.nih.gov/pubmed?term=Rochwerg%20B%5BAuthor%5D&cauthor=true&cauthor_uid=24185099), [Włudarczyk A](http://www.ncbi.nlm.nih.gov/pubmed?term=W%C5%82udarczyk%20A%5BAuthor%5D&cauthor=true&cauthor_uid=24185099), [Szczeklik W](http://www.ncbi.nlm.nih.gov/pubmed?term=Szczeklik%20W%5BAuthor%5D&cauthor=true&cauthor_uid=24185099), [Alhazzani W](http://www.ncbi.nlm.nih.gov/pubmed?term=Alhazzani%20W%5BAuthor%5D&cauthor=true&cauthor_uid=24185099), [Sindi A](http://www.ncbi.nlm.nih.gov/pubmed?term=Sindi%20A%5BAuthor%5D&cauthor=true&cauthor_uid=24185099), [Alshamsi F](http://www.ncbi.nlm.nih.gov/pubmed?term=Alshamsi%20F%5BAuthor%5D&cauthor=true&cauthor_uid=24185099), [Ip WC](http://www.ncbi.nlm.nih.gov/pubmed?term=Ip%20WC%5BAuthor%5D&cauthor=true&cauthor_uid=24185099), [Wang M](http://www.ncbi.nlm.nih.gov/pubmed?term=Wang%20M%5BAuthor%5D&cauthor=true&cauthor_uid=24185099), [Altayyar S](http://www.ncbi.nlm.nih.gov/pubmed?term=Altayyar%20S%5BAuthor%5D&cauthor=true&cauthor_uid=24185099), Li G, [Fox-Robichaud A](http://www.ncbi.nlm.nih.gov/pubmed?term=Fox-Robichaud%20A%5BAuthor%5D&cauthor=true&cauthor_uid=24185099), [Guyatt G](http://www.ncbi.nlm.nih.gov/pubmed?term=Guyatt%20G%5BAuthor%5D&cauthor=true&cauthor_uid=24185099), Jaeschke R; [FISSH group](http://www.ncbi.nlm.nih.gov/pubmed?term=FISSH%20group%5BCorporate%20Author%5D). Fluid resuscitation in severe sepsis and septic shock: systematic description of fluids used in randomized trials. [Pol Arch Med Wewn.](http://www.ncbi.nlm.nih.gov/pubmed/24185099) 2013 Nov 29;123(11):603-8.

**Fluid Resuscitation in severe sepsis and septic shock: systematic description of fluids used in randomized trials for researchers and clinicians.**

Rochwerg B1, Włudarczyk A2, Szczeklik W2, Alhazzani W1, 3, Sindi A4, Guyatt G1,5, Jaeschke R1,5 for FISSH\* group

\* FISSH group (Fluids In Sepsis and Septic Shock): Alhazzani W1, Alshamsi F1, Altayyar S1, Annane D6, Cook DJ1,5, Fox-Robichaud A1, Guyatt G1,5, Heels-Ansdell D5, Ip W1, Jaeschke R1,5 , Li G5, Mbuagbaw L5, Rochwerg B1, Sindi A4, Szczeklik W2, Thabane L5, Wang M1, Włudarczyk A2, Zhou Q5

1Department of Medicine, McMaster University, Hamilton, Ontario

2 Department of Medicine, Jagiellonian University Medical College

3 Department of Critical Care, Prince Sultan Military Medical City, Riyadh, Saudi Arabia

4 Department of Anaesthesia & Critical Care, King Abdulaziz University, Jeddah, Saudi Arabia

5 Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario

6 Department of Medicine, University of Versailles, Versailles, France

The authors of this paper do not report any conflict of interest.

Corresponding Author: Roman Jaeschke, jaeschke@mcmaster.ca

**Abstract**

**Introduction & Objectives:** Fluid therapy is one of the cornerstones of initial management of sepsis. The choice of fluids used for resuscitation is controversial. While trying to determine the effects of alternative fluidsused in sepsis resuscitation randomized controlled trials (RCTs) we found that the precise description of those fluids was frequently not available. This report presents the result of our efforts to provide their characteristics to both researchers and clinicians.

**Methods:** We searched the following electronic databases CENTRAL, MEDLINE, EMBASE, CINAHL, ACPJC and examined the reference lists of recently published meta-analyses of fluid therapies in the critically ill. These databases were searched from inception until August 2013. The data abstraction stage included determination of: fluid composition, pH, chloride concentration and presence or absence of buffers. We relied on the original articles as well as on manufacturers’ web sites, contact with authors and contact with experts in the field.

**Results**: Our original search yielded 7002 articles; in consecutive stages we reduced it to 20. The types of fluids varied widely, including chloride content (from 110 to 154 mmol/l) and presence or absence of buffering substances in colloid solutions. Those characteristics were frequently not presented and always not emphasized in the original articles.

**Conclusions:** Thebasic characteristics of fluids used in the fluid therapy trials are often not easily available, yet of increasingly recognized clinical importance. We provide the information concerning composition of fluids used in RCTs which will be useful not only to future investigators and systematic reviewers but also to clinicians using those fluids in regular clinical practice.

**Keywords:** buffer, colloid, crystalloid, fluids, osmolality, resuscitation, sepsis, shock, starch, tonicity

**Background**

Sepsis is a common health problem around the world with an annual incidence of approximately 200 to 300 cases per 100,000 inhabitants. Sepsis still carries a mortality rate of approximately 20% and even up to 40% in patients with septic shock.[[1](#_ENREF_1)] Fluid therapy is one of the cornerstones of initial management of sepsis, and systemic blood pressure response to fluid therapy helps to discriminate patients with sepsis and severe sepsis from those with septic shock. The choice of fluids used for resuscitation (defined in principle as the administration of a bolus of intravenous fluid over and above that required for maintenance or replacement fluids) is both important and controversial.

Multiple large-scale randomized controlled trials (RCTs)[[11-13](#_ENREF_11), [16](#_ENREF_16), [35](#_ENREF_35)] as well as meta-analyses[[10](#_ENREF_10), [17](#_ENREF_17), [45](#_ENREF_45), [46](#_ENREF_46)] have compared different types of crystalloid and colloid solutions in the resuscitation of critically ill patients. Taking into account newly emerging evidence, as well as some suggestion of the importance of chloride content in the fluids[[22](#_ENREF_22)], we are performing a multiple-comparison meta-analysis (network meta-analysis)[[47](#_ENREF_47)] examining both direct and indirect comparisons. Our question is: What are the comparative effects (in terms of mortality and need for renal replacement therapy) of different resuscitation fluids for patients with severe sepsis and septic shock.

While addressing this question we had to characterize and classify a variety of fluids. This included the division of crystalloids versus colloids, but also the subdivision of different types of colloids (i.e. HES, albumin, gelatins, dextrans), and fluids of varying chloride content and buffering substances (i.e. lactate or acetate). We found significant knowledge gaps regarding fluid chloride content and buffering potential and therefore set about to collect the relevant information. Obtaining the information proved challenging and time consuming. The goal of this work is to characterize fluids used in sepsis resuscitation RCTs over the course of the last few decades.

**Methods summary**

We examined parallel-group randomized controlled trials (RCTs) including patients with sepsis syndromes undergoing fluid resuscitation. Studies examining post-operative elective surgical patients were excluded and the minimum duration of observation was the length of ICU stay or hospital stay. We compared any fluid (or fluid strategy) used for resuscitation against another fluid (fluid strategy). Our outcomes were mortality and the need for renal replacement therapy.

We have searched the following electronic databases: CENTRAL (Cochrane Central Register of Controlled Trials), MEDLINE, EMBASE (Excerpta Medica Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature) and ACPJC (American College Physicians Journal Club) and examined the reference lists of the recently published meta-analyses of fluid therapies in critically ill. The search was performed in December 2012 and then updated in August 2013. Working in pairs, the number of reports identified during original wide searches was reduced in two stages – by reviewing titles and, as required, abstracts to delete records that were obviously not relevant (stage 1), then by reviewing full texts of publications selected in stage 1 to determine eligibility and abstract the data (stage 2).

The data abstraction stage included determination of fluid composition, including its pH, chloride concentration and presence or absence of buffers. This information was frequently not provided in the original publications. To find it we used data available publicly on-line, contacted manufacturers, or contacted the authors of the original studies. On occasion we relied on input from expert researchers in this field.

For the purposes of categorization, buffered solution is defined as any solution containing buffer (such as lactate, acetate, gluconate, pyruvate, malate, octanoate (=caprylate), bicarbonates, tryptophanate) and with Cl ion concentration of no more than 128mmol/L[[41](#_ENREF_41)].

**Results**

Our original search yielded 7002 articles, in consecutive stages we reduced it to 185 (through titles & abstracts review) and finally to 20 articles (through full text review). Fourteen involving adults (>15 years of age)[[11-13](#_ENREF_11), [16](#_ENREF_16), [27-36](#_ENREF_27)] and 6 involved a pediatric population[[48-53](#_ENREF_48)]. We then embarked on the process of characterizing the fluids used in identified studies.

The main findings of this process are presented in Table 1. This table lists studies fulfilling our criteria and describes the main characteristics of the fluids used, including their mineral content with attention to the presence of buffering solutions and chloride level. The chloride content in fluids considered isotonic ranged from 110 to 154 mmol/l and its content in buffered Ringer’s solutions varied from 110 to 127 mmol/l (in un-buffered Ringer’s solution up to 156 mmol/l; however, this was not used in RCTs). Such differences are probably of clinical relevance11, yet usually not considered of major importance by the authors of the original papers. The presence or absence of buffering substances was also not a major consideration in most reports. The source of the included information is presented; some of the additional data was extracted from manufacturers or government websites (<http://www.bbraun.com/>, <http://www.fresenius-kabi.com/>, <http://www.baxter.com>, <http://dailymed.nlm.nih.gov/>, <http://www.csl.com.au/>, <http://www.medicines.org.uk/>) or obtained through personal communication from authors of original studies or experts in the field (see acknowledgments).

**Discussion**

Our ultimate goal was to investigate the effects of different fluids used in resuscitation of patients with severe sepsis and septic shock and this is the subject of a separate manuscript. However, categorizing these fluids according to their composition proved to be a critical first step. We hypothesized that fluids’ effects may be influenced by some of their properties: crystalloid versus colloid structure, higher versus lower molecular weight for the hydroxyl-ethyl-starches, or the presence of buffering solutions. In a number of cases the information concerning pH, chloride concentration or presence of buffers was not readily available in relevant papers or publically available product descriptions. We believe this is likely related to a low degree of importance ascribed to these characteristics at the time of original publications and mirrors generally low awareness of those properties among practicing physicians. This manuscript provides the relevant information we were able to collect from a variety of sources and which could be of use for investigators and systematic reviewers involved in future research on this topic as well as for clinicians using those fluids currently.

The strength of this manuscript includes a careful search for and evaluation of studies which examined fluids used in septic shock trials. In our attempts to characterize fluids we contacted a number of authors and manufacturers. We provide a number of resources which those interested may use to obtain more information. The weaknesses include not only the fact that on occasion we were unsuccessful in fully identifying a specific fluid used, but mostly the fact that the clinical relevance of identified fluid differences is not clear. The presence of buffering or stabilizing substances, pH and especially chloride content of commonly used fluids is recognized as potentially important11 but high quality patient-important evidence in this respect is still missing.

Until such evidence is available we encourage readers to review the values in Table 1, especially those describing chloride content. Even though as seen in the recently published CRISTAL study[[27](#_ENREF_27)] normal saline is by far the most commonly used crystalloid for resuscitation we believe this practice needs to be reassessed or at least formally investigated.[[44](#_ENREF_44)] A similar comment applies to colloid solutions suspended in fluids with high chloride concentration. In our own practice increasing awareness of observational evidence suggesting the harmful effect of chloride rich solutions[[22](#_ENREF_22)] has led some of us to limit their high-volume use.

**Acknowledgments:**

We would like to acknowledge the following clinicians for providing us with information regarding fluids used in several studies: Dr. JL Vincent [[30](#_ENREF_30), [34](#_ENREF_34)], Dr. JL Falk [[30](#_ENREF_30), [34](#_ENREF_34)], Dr. LA McIntyre[[33](#_ENREF_33)], Dr. K Maitland[[48](#_ENREF_48), [50-52](#_ENREF_50)]. We acknowledge librarians Lois Cottrell and Jean Maragno for their invaluable help with structuring and performing our search. We also acknowledge financial support from the Canadian Intensive Care Foundation and from the Critical Care Medicine Residency Program, McMaster University, Hamilton, Ontario.

Table 1. Characteristics of fluids used in RCTs examining the resuscitation strategies of patients with sepsis syndromes.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of Fluid** | **Fluid Name (Generic)** | **Trade Name/Manufacturer** | | **Osmolarity \*** | **Tonicity \*\*** | **ELECTROLYTES (mEq/L)** | | | | | **BUFFER (mEq/L)** | | | **Balanced\*\*\*** | **pH** | **Study** |
| **Na+** | **Cl-** | **K+** | **Ca2+** | **Mg2+** | **Lactate** | **Acetate** | **Other** |
| **High molecular weight hydrohyethyl starch (HES) (200 000 – 600 000 Da)** | 6 % HES (200/0,5) | Haes Steril - Fresenius, Hemohes - B.Braun, HES – Baxter | | 308 | Iso | 154 | 154 | 0 | 0 | 0 | 0 | 0 |  | No | 3,5-7,0 | [[[35](#_ENREF_35), [53](#_ENREF_53)]±] [e1-3] |
| 10% HES (200/0,5) | [[[11](#_ENREF_11), [33](#_ENREF_33)]±] [e1-3] |
| 6% HES (600/0,75) | Hespan – B.Braun | | 309 | Iso | 154 | 154 | 0 | 0 | 0 | 0 | 0 |  | No | 5,9 | [[[30](#_ENREF_30), [34](#_ENREF_34)]] [e3] |
| Hypertonic salnie HES | HyperHAES – Fresenius | | 2464 | Hyper | 1232 | 1232 | 0 | 0 | 0 | 0 | 0 |  | No | 3,5-6,0 | [[[31](#_ENREF_31)]±]  [e1] |
| Pentastarch | Pentaspan – Bristol-Myers | | 326 | Iso | 154 | 154 | 0 | 0 | 0 | 0 | 0 |  | No | 5 | [[[34](#_ENREF_34)]] [e4] |
| **Low molecular weight hydrohyethyl starch (HES) (130 000 Da)** | 6% HES (130/0,4) | Voluven – Fresenius, Venofundin - B.Braun | | 308 | Iso | 154 | 154 | 0 | 0 | 0 | 0 | 0 |  | No | 4,0-5,5 | [[[12](#_ENREF_12), [28](#_ENREF_28), [29](#_ENREF_29), [32](#_ENREF_32)]±] [e1,e3] |
| 6% HES (130/0,42) in balanced solution | Tetraspan 60mg/ml – B.Braun | | 297 | Iso | 140 | 118 | 4 | 5 | 2 | 0 | 24 | Malate | Yes | 5,6-6,4 | [[[13](#_ENREF_13)]] [e3] |
| **Dextrans** | 6% Dextran 70 000 | Dextran 70 – Fresenius, B.Braun, Baxter | | 310 | Iso | 154 | 154 | 0 | 0 | 0 | 0 | 0 |  | No | NA | [[[53](#_ENREF_53)]±] [e2] |
| **Gelatins** | succinylated gelatin | Plasmagel – Fresenius | | NA |  | 120 | NA | 0 | 0 | 0 | 0 | 0 |  | No | NA | [[[35](#_ENREF_35)]] |
| **Human**  **Albumins** |  | Buminate 5% - Baxter | | NA |  | 145 | NA | NA | 0 | 0 | 0 | 0 | Caprylate 4 mmol/l; tryptohanate 4; bicarbonate (conc. not clear) | Yes | NA | [[[50](#_ENREF_50)]] [e2] |
|  | 4,5% Zenalb - Bio Products Laboratory UK | | NA |  | 100-160 | NA | 0 | 0 | 0 | 0 | 0 |  | No | NA | [[[48](#_ENREF_48), [51](#_ENREF_51), [52](#_ENREF_52)]] [e5] |
|  | 4% Albumex – CSL | | NA |  | 140 | 128 | 0 | 0 | 0 | 0 | 0 | Octanoate 6.4 mmol/L | Yes | NA | [[[16](#_ENREF_16)]] [e6] |
|  | 5% Albumin – Cutter | | NA |  | 154 | 154 | 0 | 0 | 0 | 0 | 0 |  | No | NA | [[[30](#_ENREF_30), [34](#_ENREF_34)]] |
| **CRYSTALOIDS** | Normal Saline | 0,9% NaCl | | 308 | Iso | 154 | 154 | 0 | 0 | 0 | 0 | 0 |  | No | 4,5-7,0 | [e7] |
| Hypertonic Saline | 3% NaCl | | 1030 | Hyper | 513 | 513 | 0 | 0 | 0 | 0 | 0 |  | No | 4,5-7,0 | [[[49](#_ENREF_49)]] [e2] |
| Lactated Ringer |  | | 275 | Iso | 130 | 110 | 4 | 3 | 0 | 28 | 0 |  | Yes | 6,0-7,5 | [[[53](#_ENREF_53)]] [e7] |
| Modified Ringer | Sterofundin ISO (Ringer's Acetate) | B.Braun | 309 | Iso | 145 | 127 | 4 | 5 | 2 | 0 | 24 | Malate | Yes | 5,1-5,9 | [[[13](#_ENREF_13)]] [e3] |
| Sterofundin | 299 | Iso | 140 | 106 | 4 | 5 | 2 | 45 | 0 |  | Yes | 4,5-7,5 | [[[11](#_ENREF_11)]] [e3] |
| Half Strength Darrow's Solution with 5% dextrose |  | | NA | Hypo | 61 | 51 | 18 | 0 | 0 | 27 | 0 | Possible: Bicarbonate | Yes | NA | [[[48](#_ENREF_48)]] [e8] |

NA: not available; Iso: iso-osmolar; Hypo: hypo-osmolar; Hyper: hyper-osmolar.

\*Osmolarity of a solution is the number of osmoles of solute per liter of solution - independent of any membrane

\*\*Tonicity - effective osmolality - equal to the sum of the concentrations of the solutes which have the capacity to exert the osmotic force across a particular membrane (those which do not travel easily through the membrane). For the purpose of our report we assumed a fluid is isotonic, when its osmolarity was close to plasma (270-310mOsm/l) in case of absence of additional glucose and with Na close to plasma level (130-155mEq/L)

\*\*\*Balanced fluid – we have defined it as any solution containing buffer (such as lactate, acetate, gluconate, pyruvate, malate, octanoate (=caprylate), bicarbonates, tryptophanate) and with Cl ion concentration of no more than 128mmol/L [[41](#_ENREF_41)]

± - no exact name of the fluid used in the study given, but described content is similar to this presented in the table

1. http://www.fresenius-kabi.com/, http://www.fresenius-kabi.pl/
2. http://www.baxter.com/ ; http://www.baxter.com.pl
3. http://www.bbraun.com/; http://www.bbraun.co.uk/;
4. http://www.bmscanada.ca
5. http://www.bpl.co.uk/
6. http://www.csl.com.au/
7. http://dailymed.nlm.nih.gov/dailymed/
8. http:// www.who.int

**Manuscript #2 –** Fluid Resuscitation in Sepsis: A Systematic Review and Network Meta-analysis.

**Objective Manuscript #2:** Bayesian network meta-anlaysis including direct and indirect evidence assessing the effect of resuscitative fluid on the outcome of mortality in septic ICU patients.

**Reference:** Rochwerg B**,** Alhazzani W, Sindhi A, Al-Shamsi F, Sultan R, Ip W, Li G, Mbuagbaw L, Wang M, Cook DJ, Guyatt G, Thabane L, Heels-Ansdell D, Jaeschke R, Annane D. Fluid Resuscitation in Sepsis, a systematic review and multiple treatment analysis (A Network Meta-analysis). Ann Intern Med. 2014 Sep 2;161(5):347-55. doi: 10.7326/M14-0178.

**Fluid Resuscitation in Sepsis: A systematic review and network meta-analysis.**

Rochwerg B MD1, Alhazzani W MD1,2 , Sindi A MD3, Heels-Ansdell D MSc4,

Thabane L PhD4, Fox-Robichaud A MD1, Mbuagbaw L MSc4, Szczeklik W MD5, Alshamsi F MD1, Altayyar S MD1, Ip W MD1, Li G MSc4, Wang M MD1,

Włudarczyk A MD5, Zhou Q PhD4, Guyatt GH MD1,4, Cook DJ MD1,4, Jaeschke R MD1,4 and Annane D MD, PhD6 for the FISSH\* Group (Fluids in Sepsis & Septic Shock)

1 Department of Medicine, McMaster University, Hamilton, Ontario

2 Department of Critical Care, Prince Sultan Military Medical City, Riyadh, Saudi Arabia

3Department of Anaesthesia & Critical Care, King Abdulaziz University, Jeddah, Saudi Arabia

4 Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario

5 Department of Medicine, Jagiellonian University Medical College

6 Department of Critical Care, University of Versailles SQY, Garches, France

We also acknowledge financial support from the Hamilton Chapter of The Canadian Intensive Care Foundation, the Critical Care Medicine Residency Program and the Critical Care Division Alternate Funding Plan both at McMaster University, Hamilton, Ontario.

The authors declare no relevant financial conflict of interest. Dr D. Cook is a Research Chair of the Canadian Institutes of Health Research. Dr. D. Cook coauthored a fluid trial cited herein. Dr. D. Annane was principal investigator of a fluid trial cited herein.

Corresponding Author and Reprint Requests:

Dr. Deborah Cook

Academic Chair, Critical Care Medicine

Room D176 St Joseph's Healthcare

50 Charlton Avenue East

Hamilton, Ontario, Canada

Email: [debcook@mcmaster.ca](mailto:djillali.annane@rpc.aphp.fr" \t "_blank)

Word Count: 2,892

Abstract Word Count: 270

**Abstract**

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

*Purpose*: Our objective was to perform a network meta-analysis (NMA), including direct and indirect comparisons. We examined the effect of different resuscitative fluids on mortality in patients with sepsis.

*Data Sources*: MEDLINE, EMBASE, ACPJC, CINAHL and Cochrane Central Register up to March 2014.

*Study Selection*: Eligible studies included randomized trials which evaluated different resuscitative fluids in adult patients with sepsis or septic shock and mortality. No language restrictions were applied.

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

*Data Synthesis*: Fourteen studies (18,916 patients) were included with a total of 15 direct comparisons. NMA at 4-node level showed higher mortality with starch compared to crystalloid (high confidence) and lower mortality with albumin compared with crystalloid (moderate confidence) or starch (moderate confidence). NMA at the 6-node level showed lower mortality of albumin compared to saline (moderate confidence) and light starch (low confidence). Lower mortality was also observed in patients receiving balanced crystalloid compared to saline (low confidence), heavy starch (moderate confidence), and light starch (moderate confidence).

*Limitations:* These trials are heterogeneous with respect to 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 crystalloid or albumin compared to other fluids appears to be associated with reduced mortality.

*Primary Funding Sources:* the Hamilton Chapter of The Canadian Intensive Care Foundation, the Critical Care Medicine Residency Program and the Critical Care Division Alternate Funding Plan both at McMaster University, Hamilton, Ontario.

**INTRODUCTION**

Resuscitation with crystalloids compared to colloid solutions for critically ill patients has been evaluated in large randomized controlled trials [[11-13](#_ENREF_11), [16](#_ENREF_16), [29](#_ENREF_29), [36](#_ENREF_36)] and meta-analyses [[10](#_ENREF_10), [14](#_ENREF_14), [17](#_ENREF_17), [45](#_ENREF_45), [46](#_ENREF_46), [54](#_ENREF_54), [55](#_ENREF_55)]. One meta-analysis [[10](#_ENREF_10)] including 74 trials reported no difference in mortality between critically ill patients resuscitated with crystalloid compared to albumin (relative risk [RR] 1.01, 95% CI 0.93-1.10), hydroxyl-ethyl starch (HES) (RR 1.10, 95% CI 0.91-1.32), gelatin (RR 0.91, 95% CI 0.49-1.72) or dextran (RR 1.24, 95% CI 0.94-1.65). Another meta-analysis [[17](#_ENREF_17)] reported that resuscitation with an albumin-containing solution in sepsis may decrease mortality compared to solutions containing no albumin (RR 0.82, 95% CI 0.67-1.00). Recent evidence suggests that starches, compared to other fluids and regardless of molecular weight, may be associated with acute kidney injury, both in the general population of critically ill patients, and in those with sepsis[[14](#_ENREF_14), [46](#_ENREF_46), [56-58](#_ENREF_56)]. A recent large pragmatic trial comparing colloids (mostly starches) to crystalloids (mostly 0.9% saline) suggested a possible mortality benefit of colloids at 90 days (RR 0.92, 95% CI 0.86-0.99)[[27](#_ENREF_27)].

Crystalloids can be characterized based on tonicity and electrolyte content. The presence of an organic anion (e.g., lactate, acetate, or gluconate) and correspondingly lower chloride content, more closely resembling the composition of plasma, suggest that a crystalloid is ‘balanced’ (e.g. Ringer’s Lactate and Ringer’s Acetate)[[19](#_ENREF_19)]. The most commonly used crystalloid, normal saline (0.9% sodium chloride), is far from ‘normal’ with a pH well below 7 and a supra-physiologic chloride content of 154mmol/L [[22](#_ENREF_22), [43](#_ENREF_43)]. Compared to a balanced crystalloid solution, normal saline predisposes patients to hyper-chloremic metabolic acidosis, decreased glomerular renal blood flow, and decreased smooth muscle contractility [[18](#_ENREF_18)]. Although investigators have not conducted randomized clinical trials (RCTs) comparing balanced to unbalanced crystalloids, in one large before-after study of critically ill patients, a balanced vs an unbalanced fluid solution was associated with a lower incidence of acute kidney injury (8.4% vs. 14%, p<0.01) and renal replacement therapy (RRT) (6.3% vs 10%, p=0.05) but no differences in hospital mortality [[22](#_ENREF_22)].

Colloids include natural compounds such as albumin, and synthetic compounds of HES, gelatin, or dextran. Plasma volume expansion increases in proportion to the osmotic or oncotic potential, and colloids theoretically require less volume than crystalloids to achieve equivalent hemodynamic effect[[43](#_ENREF_43)]. Limitations of colloids include development of acute kidney injury and coagulation disorders with starch[[57](#_ENREF_57)] and the risk of blood product exposure with albumin[[43](#_ENREF_43)]. 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 from 154 mmol/L (Voluven, Fresenius Kabi, Germany) to 118 mmol/L (Tetraspan, B. Braun Medical, Netherlands)[[8](#_ENREF_8)].

Whether any of the foregoing 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 sepsis management [[5](#_ENREF_5)]. However, fluid management in patients with sepsis is reflected in wide practice variation[[27](#_ENREF_27), [59](#_ENREF_59), [60](#_ENREF_60)]. Prior meta-analyses of fluid resuscitation have been limited by not focusing on patients with sepsis[[10](#_ENREF_10), [45](#_ENREF_45), [54](#_ENREF_54)], not considering electrolyte composition[[10](#_ENREF_10), [14](#_ENREF_14), [17](#_ENREF_17), [46](#_ENREF_46)], considering only 2 or 3 categories of fluid[[61](#_ENREF_61)], not including direct and indirect comparisons in the same model, and omission of recent large RCTs[[12](#_ENREF_12), [13](#_ENREF_13), [27](#_ENREF_27), [36](#_ENREF_36)]. Therefore, we performed a network meta-analysis considering both direct and indirect comparisons of all types of fluid resuscitation tested in randomized trials in patients with severe sepsis and septic shock focusing on their effect on mortality.

**METHODS**

**Data Sources & Searches:**

This review was conducted using a predefined protocol. Initially, we conducted a search of MEDLINE (1948 to December 2012), EMBASE (1980 to December 2012), ACPJC (1991 to December 2012), Cochrane (CENTRAL) database, and CINAHL. We updated the MEDLINE and EMBASE searches in August 2013 and in March 2014. We screened previously published meta-analyses for relevant citations. The Appendix presents search terms used. Six reviewers working in three pairs screened the titles and abstracts to determine potential eligibility and entries identified by any reviewer proceeded to the full-text eligibility review. Pre-tested eligibility forms were used for full text review, which was also performed in duplicate, with a third adjudicator helping to reach consensus in situations of disagreement.

**Study Selection:**

*Types of Studies*: We included parallel-group RCTs, including factorial designs, but excluded quasi-randomized and cross-over trials. We excluded all studies published by Dr. J Boldt due to suspected fraud [[62](#_ENREF_62), [63](#_ENREF_63)]. No language or publication date restrictions were applied.

*Population:* Studies that involved adult (≥16 years of age) 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 over and above that required for maintenance or replacement fluids) were included. Studies with mixed critically ill populations were included whenever separate data for patients with sepsis were available. Studies in which the majority of patients had Systemic Inflammatory Response Syndrome clearly secondary to other causes (e.g., burn, pancreatitis, and trauma) without a clear sepsis subgroup, and studies focusing on post-operative elective surgical patients were excluded.

*Intervention*: Any fluid or fluid strategy used for resuscitation compared to another fluid or fluid strategy. We excluded studies in which the primary goal was to assess short-term hemodynamic response.

*Outcome:* Our outcome was 90-day mortality or, if not available, the longest available of 30-day, ICU or hospital mortality.

**Data Extraction and Risk of Bias Assessment:**

*Data Extraction:* Pairs from the same six reviewers performed data abstraction in duplicate. Another clinician reviewed disagreements and consensus was reached by discussion. Authors of primary publications were contacted for missing or unclear information.

*Risk of Bias:*Independently and in duplicate, reviewers assessed risk of bias (RoB) using a tool modified from that recommended by the Cochrane Collaboration [[64](#_ENREF_64)] [[65](#_ENREF_65)]. For each included study we provided a judgment of ‘low RoB, probably low RoB, probably high RoB or high RoB’ for each of the following items: randomization sequence generation, randomization concealment, blinding, incomplete data, selective reporting, and free of other bias (including intention-to-treat analysis). The overall rating of RoB for each individual study was the lowest of the ratings for any of the RoB criteria.

**Data Synthesis and Analysis:**

Our analysis included division of fluids into following categories and subcategories: crystalloids (divided into balanced and unbalanced solutions) and colloids (divided into albumin, gelatin, light molecular weight HES and heavy molecular HES (threshold molecular weight 150,000 kDa)). We considered fluid as balanced if it contained an anion of a weak acid (buffer) and if its chloride content was correspondingly lower than in 0.9% sodium chloride [[8](#_ENREF_8)]. The relevant analyses included: a four nodes network meta-analysis (crystalloids vs. albumin vs. HES vs. gelatin), a six nodes network meta-analysis (above four nodes with crystalloids divided into balanced/unbalanced and HES divided into lower/higher molecular weight), and a conventional direct frequentist fixed-effect meta-analytic comparison of crystalloids vs. colloids.

To calculate direct estimates of treatment effect for each pair of treatments within the four and six-node networks, we performed a frequentist fixed-effects meta-analysis. The results are reported as odds ratios [OR] and their corresponding 95% confidence intervals (CI). Heterogeneity was evaluated by estimating the variance between studies (Chi squared test and I2)[[66](#_ENREF_66), [67](#_ENREF_67)].

Using a Bayesian framework, we carried out two fixed effects network meta-analyses (four nodes and six nodes), one for each of the treatment categorizations described. The results are reported as odds ratios [OR] and their corresponding 95% credibility intervals (CrI), which are the Bayesian analog of the 95% confidence intervals[[68](#_ENREF_68)]. 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. A random SEED and vague priors were used. Non-convergence was assessed based on Brooks Gelman Rubin plots[[69](#_ENREF_69)].

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 direct, indirect and final network meta-analysis estimates [[70](#_ENREF_70)]. Our confidence assessment addressed the following: risk of bias, incoherence, imprecision, inconsistency, indirectness, and publication bias.

The starting point for confidence in both direct and indirect estimates was ‘high’. Indirect estimates were, however, potentially rated down for intransivity (that is, differences in the patients, co-interventions or setting that could lead to effect modification and thus a misleading comparison of fluid management strategies). Confidence in indirect estimates was inferred from examination of 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 instance, consider a comparison of A vs. B that is informed by A vs. C and B vs. C. If A vs. C was rated as high confidence and B vs. C as moderate confidence, the overall indirect confidence rating was initially based on the B vs. C comparison and was then potentially rated down to low for indirectness. The judgment of precision was based on the credible interval around the point estimate from the indirect comparison.

The overall network meta-analysis confidence rating was the higher of the 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 one level for incoherence if there was no significant overlap in the credible intervals between the direct and indirect estimates. The approach we used here was consistent with preliminary GRADE guidance as well as GRADE methods for direct comparisons [[37](#_ENREF_37), [71](#_ENREF_71)].

The Bayesian analysis for the network meta-analysis was conducted using WinBUGS 1.4.3 [http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml] and all frequentist analysis using Review Manager 5.2.3 (Revman; <http://ims.cochrane.org/revman/download>).

**RESULTS**

Of 9,548 titles identified during the primary search (7,002 after de-duplication) (Figure I), 6819 were judged as ineligible on the basis of titles and abstracts, leaving 185 studies for full text review. This included 2 unpublished studies, one found through screening titles included in previous meta-analysis [[36](#_ENREF_36)], and another (since published) found through author correspondence [[27](#_ENREF_27)]. Of these 185 RCTs, 171 proved ineligible leaving 14 eligible RCTs[[11-13](#_ENREF_11), [16](#_ENREF_16), [27-36](#_ENREF_27)]. Table I summarizes the characteristics of 14 trials involving 18,916 adults available for analysis. In four of the included trials [[12](#_ENREF_12), [16](#_ENREF_16), [27](#_ENREF_27), [30](#_ENREF_30)] septic patients were a subgroup of all patients enrolled, and only one of the four studies [[27](#_ENREF_27)] stratified randomization based on the diagnosis of sepsis. Through contact with primary authors or authors of previous reviews we obtained relevant data for 10 of 14 studies (see Acknowledgements). No additional data were needed for the other 4 studies.

The majority of included studies employed a definition for sepsis consistent with international consensus [[72](#_ENREF_72)]. Five studies reported APACHE II scores in which the mean ranged from 17-20.6 while another four studies reported SOFA scores with median values of 7-8.5. The fluid intervention period lasted between 24 hours and 90 days. The observation period for outcome assessment varied between 30 days to 1 year.

Appendix Figure I & II present network nodes illustrating direct and indirect comparisons as well as number of studies available for comparisons. Table II indicates the contribution of individual studies and the sub-classification of each fluid at each level of analysis.

*Four-node analysis:* The results suggest the possibility of higher mortality associated with starch compared to crystalloid (NMA OR 1.13; 95% CrI 0.99-1.30, high confidence) and lower mortality with albumin compared to crystalloid (NMA OR 0.83; 95% CrI 0.65 – 1.04, moderate confidence) and compared to starch (NMA OR 0.73; 95% CrI 0.56-0.95, moderate confidence) (Table III).

*Six-node analysis*: Table IV presents this analysis. Evidence suggests the superiority of albumin to saline (NMA OR 0.82; 95% CrI 0.65-1.04, moderate confidence) and to light starch (NMA OR 0.79; 95% CrI 0.59-1.06, low confidence). Evidence suggests the superiority of balanced crystalloid compared to saline (NMA OR 0.78; 95% CrI 0.58-1.05, low confidence), heavy starch (NMA OR 0.82; 95% CrI 0.60–1.13, moderate confidence) and light starch (NMA OR 0.75; 95% CrI 0.58-0.97, moderate confidence).

*Post-hoc Sensitivity Analysis*: Two sensitivity analyses were performed at the request of reviewers and are included in the Appendix (Appendix Table 2). The first (analysis #1) incorporates the recently published ALBIOS trial [[73](#_ENREF_73)]. Given that the aim of fluid administration in this trial was not clearly resuscitative, we had initially excluded it from our review. Inclusion of ALBIOS in this post-hoc analysis had no effect on our results. The second (analysis #2) was performed to investigate the effect of excluding the two older studies by Haupt et al in 1982 and Rackow et al in 1989, both with low event rates and a small number of patients. This requested post-hoc analysis did not impact our results either.

*Crystalloid vs Colloid:* There was no evidence for difference in mortality in the crude analysis of colloids vs. crystalloids for fluid resuscitation in adult patients (Appendix Figure III) (OR 0.99; 95% CI 0.89-1.10; p = 0.85; Chi2 = 23.20, I2 = 53%; confidence moderate because of inconsistency).

**DISCUSSION**

The results of this network meta-analysis highlight potentially important differences in mortality between different crystalloid solutions. Our findings suggest a possible advantage of balanced crystalloids vs saline (low confidence), and balanced crystalloids vs light or heavy starches (moderate confidence), with similar mortality for balanced crystalloids vs albumin (very low confidence) (Table IV). These differences were not detectable using a standard meta-analytic approach directly comparing 'any crystalloids vs any colloids', results of which are consistent with previous meta-analyses[[10](#_ENREF_10), [45](#_ENREF_45)] and a recent large RCT[[27](#_ENREF_27)].

Biological rationale is consistent with the findings of lower mortality for balanced crystalloid solutions in contrast to saline, as balanced fluids mimic homeostatic body fluid composition to a greater extent than do unbalanced fluids [[19](#_ENREF_19), [22](#_ENREF_22)]. It is unclear which component of balanced solutions - the pH, the electrolyte composition, or the presence of a buffer contributes to this potential benefit. These results raise concerns about whether the practice of using mostly unbalanced crystalloids in the acute resuscitation of septic patients is optimal. Our findings may partially explain the higher 90-day mortality rates observed in the crystalloid compared to the colloid arm of a recent trial in which 86% of the patients randomized to the crystalloid arm received normal saline[[27](#_ENREF_27)].

We found that different colloids may also vary in their effects, with albumin appearing equivalent or superior to all other alternatives. Starches, regardless of molecular weight, appear inferior to alternative resuscitation fluids (i.e., albumin and balanced crystalloids). Data regarding gelatin are markedly less robust. Gelatin is associated with increased mortality relative to some other resuscitation fluids; however, only one small trial contributes directly to this analysis. The heterogeneity of effects observed across different types of colloids renders crude 'colloid vs crystalloid' comparisons uninformative (see Appendix Figure III).

The strengths of this review include a precise clinical question restricted to patients with sepsis rather than all critically ill patients, focusing on resuscitation rather than maintenance fluid, distinguishing balanced from unbalanced crystalloids and distinguishing among starches of different molecular weight. We conducted a comprehensive search and risk of bias assessment, with both processes involving duplicate review and third party adjudication. Using rigorous network meta-analysis methods[[68](#_ENREF_68)] we incorporated both direct and indirect evidence. The GRADE approach, seldom previously applied to network meta-analysis, allowed reporting of confidence in estimates of effect when interpreting 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, there was also some heterogeneity in fluid protocols with varying amounts of fluid administered and durations of the fluid intervention periods. Some observed results may be related to the interplay of different fluid properties, in particular the differential presence of chloride in each colloid. For instance, the albumin used in the largest albumin study[[16](#_ENREF_16)] was dissolved in a crystalloid solution containing >6mmol/L of caprylate and a chloride content of 128 mmol/L, and suggested a trend towards benefit compared with saline (154 mmol/L of chloride) in the sepsis subgroup[[74](#_ENREF_74)]. Given our network meta-analysis 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. Similarly, one starch study[[11](#_ENREF_11)] found statistically significant benefit of balanced crystalloid that contained 45 mmol/L of lactate and 106 mmol/L of chloride compared with starch dissolved in saline (chloride content 154 mmol/L). The mortality difference may in part be due to the balanced vs. unbalanced nature of the solutions.

This analysis provides a current, comprehensive summary of the impact of resuscitation fluids on mortality in patients with sepsis. The presence of buffering substances and chloride content is often over-looked when choosing resuscitative fluids in the clinical setting, and is rarely transparently reported in clinical trials, which should no longer be the case. Our analyses suggest that if crystalloid is used, balanced solutions may be preferable to unbalanced solutions. These results also suggest that in sepsis, albumin may be a reasonable alternative to other resuscitation fluids. Relative to balanced crystalloids, however, albumin confers a small risk associated with blood product transfusion, and markedly increased cost.

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

**Acknowledgments:**

We would like to acknowledge the following clinicians for providing us with information contributing to this paper: Dr. JL Vincent[[30](#_ENREF_30), [34](#_ENREF_34)], Dr. L Jie[[32](#_ENREF_32)], Dr. S. Finfer[[16](#_ENREF_16)], Dr. K Reinhart[[11](#_ENREF_11)], Dr. A Chopra, Dr. JL Falk [[30](#_ENREF_30), [34](#_ENREF_34)], Dr. F Shortgen[[35](#_ENREF_35)], Dr. B Wills, Dr. N Haase[[29](#_ENREF_29), [36](#_ENREF_36)], Dr. LL McIntyre[[33](#_ENREF_33)], Dr. K Maitland and Dr J Myburgh[[12](#_ENREF_12)]. We acknowledge librarians Lois Cottrell and Jean Maragno for their invaluable help with structuring and performing our search.

**Grant Support:** None

**Reprint Requests:** Dr. Deborah Cook

Academic Chair, Critical Care Medicine

Room D176 St Joseph's Healthcare

50 Charlton Avenue East

Hamilton, Ontario, Canada

Email: [debcook@mcmaster.ca](mailto:djillali.annane@rpc.aphp.fr" \t "_blank)

Table I. Study characteristics.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Number of Randomized Patients** | **Sepsis according to International Sepsis Definition (or similar)i** | **Mean APACHE II Score** | **Interventions** | **Blood Products**  **Transfused** | **Cumulative Dose** | **Intervention Period (Mortality Observation Period)** | **Overall ROB** | **Mortality** | **Industry Sponsor** |
| **Haupt**  **1982** | Single Center  USA  N = 17 | Not stated | Not reported | NS  AL  HES-H | Not reported | NS 6371 ml (mean)  AL 3134 ml (mean)  HES 4466 ml (mean) | 24 hours (hospital stay) | Probably Low | NS 3/4  AL 5/7  HES 3/6 | Cutter |
| **Rackow 1989** | Single Center  USA, N = 20 | Yes | Not reported | AL  HES-H | Not reported | AL 975 ml  HES 900 ml | <24 hours (hospital stay) | Probably Low | AL 5/10  HES 5/10 | Dupont Critical Care  Cutter |
| **Shortgen 2001** | Multicenter (3)  France  N = 129 | Yes | Not reported | GL  HES-H | Not reported | GL 43 ml/kg  HES 31 ml/kg | HES 4 days (ICU stay)  GL until ICU discharge (ICU stay) | Low | GL 29/64  HES 28/65 | Not Reported |
| **SAFE**  **2004** | Multicenter (16)  Australia & NZ  N = 6997 | Yes | 18.9 | NS  AL | Not reported | NS >3000 ml  AL >2000 ml | 28 days (31 days) | Low | NS 217/615  AL 185/603 | CSL Behring |
| **Brunkhorst 2008** | Multicenter (18)  Germany, N = 537 | Yes | 20 | RL  HES-H | RL 189/275 (68.7%)  HES 199/262 (76%) | RL 1.32x HES dose  HES 70.4ml/kg | 21 days (90 days) | Low± | RL 93/274  HES 107/261 | B. Braun  Novo Nordisk  HemoCue |
| **Li**  **2008** | Single Center  China, N = 60 | Yes | 18 | HES/HS  HES  HS  NS | Not reported | Not reported | <24 hours (31 days) | Probably Low± | HES/HS 5/15  HES 9/15  HS 10/15  NS 10/15 | None Reported |
| **McIntyre 2008** | Multicenter (4)  NZ & Canada  N = 40 | Yes | 20.6 | NS  HES-H | NS 5/19 (26%)  HES 10/21 (48%) | NS 2100 ml  HES 1900ml | <24 hours (hospital stay) | Low | NS 7/19  HES 9/21 | Bristol Meyer Squibb  Edward Life Sciences |
| **Dubin**  **2010** | Multicenter (2)  Argentina, N = 25 | Yes | Not reported (mean SOFA score 8.5) | NS  HES-L | NS 18%  HES 22% | NS 6254 ml  HES 2610 ml | 24 hours (31 days) | Probably Low± | NS 7/13  HES 3/12 | Not Reported |
| **BaSES**  **2011** | Single Center  Switzerland  N = 241 | Not reported | Not included | NS  HES-L | Not reported | NS not reported  HES 3775 ml (median) | 5 days (1 year) | Low | NS 50/124  HES 44/117 | Fresenius AG |
| **Guidet**  **2012** | Multicenter (24)  France & Germany  N = 196 | Yes | Not reported (mean SOFA score 8.5) | NS  HES-L | NS 20/96 (21%)  HES 29/100 (29%) | NS 2788 ml  HES 2615 ml | 4 days (90 days) | Low | NS 32/95  HES 40/99 | Fresenius Kabi |
| **Lu**  **2012** | Single Center  China, N = 42 | Not reported | Not reported | RL  HES-L | Not reported | RL 3460 ml  HES 2770 ml | Not clear (ICU stay) | Probably Low± | RL 12/20  HES 7/22 | Not Reported |
| **Myburgh 2012** | Multicenter (32)  Australia & NZ  N = 7000 | Not | 17 | NS  HES-L | Not reported | Study fluid for enrolled over first 4 days: NS 2456 ml  HES 2104 ml | 90 days (90 days) | Low | NS 224/945  HES 248/976 | Fresenius Kabi |
| **Perner**  **2012** | Multicenter (26)  Scandanavia, N = 804 | Yes | Not reported  (mean SOFA score 7) | RA  HES-L | RA 204/380 (54%)  HES 243/376 (65%) | RA 3000 ml (mean)  HES 3000 ml (mean) | 90 days (90 days) | Low | RA 173/400  HES 202/398 | B. Braun Medical |
| **CRISTAL 2013** | Multicenter (57)  Worldwide, N = 2857 | Yes | Not reported (mean SOFA score 8) | Cry  Col | Cry 358/1443 (24.8%)  Col 377/1414 (26.7%) | Cry 3000 ml in 7 days  Col 2000 ml in 7 days | Until ICU discharge (90 days) | Low | Cry 286/779  Col 252/774 | None |

RL: ringer’s lactate, RA: ringer’s acetate, NS: normal saline, HS: hypertonic saline, HES: hydroxyl-ethyl starch,

AL: albumin, DX: dextran, GL: gelatin, Cry: crystalloid, Col: colloid, H: heavy, L: light, ICU: intensive care unit, RoB: risk of bias, N: number, APACHE II: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment score

± intervention in this study was unblinded, t = reference [Crit Care Med.](http://www.ncbi.nlm.nih.gov/pubmed/?term=CCM+2003%3B31(4)%3A1250-6) 2003 Apr;31(4):1250-6.

Table II. Contribution of individual studies to each level of analysis.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study Name** | **Fluid Name** | **Trade Name** | **Crystalloid vs Colloid** | **4-Node Analysis** | **6-Node Analysis** |
| **Haupt**  **1982** | Normal Saline  5% Albumin  6% HES | Saline  Albumin  Hespan | Crystalloid  Colloid  Colloid | Crystalloid  Albumin  HES | Saline  Albumin  Heavy HES |
| **Rackow 1989** | 5% Albumin  10% HES | Albumin  Pentastarch | Colloid  Colloid | Albumin  HES | Albumin  Heavy HES |
| **Shortgen 2001** | 3% Gelatin  6% HES | Plasmagel  Haes-Steril | Colloid  Colloid | Gelatin  HES | Gelatin  Heavy HES |
| **SAFE**  **2004** | Normal Saline  4% Albumin | Saline  Albumex | Crystalloid  Colloid | Crystalloid  Albumin | Saline  Albumin |
| **Brunkhorst 2008** | Ringer’s Lactate  10% HES | RL  Pentastarch | Crystalloid  Colloid | RL  HES | Balanced Crystalloid  Heavy HES |
| **Li**  **2008** | HES in Hypertonic Saline  HES  Hypertonic Saline  Normal Saline | Not reported | Colloid  Colloid  Crystalloid  Crystalloid | HES  HES  Crystalloid  Crystalloid | Heavy HES  Heavy HES  Saline  Saline |
| **McIntyre 2008** | Normal Saline  10% HES | Saline  Pentastarch | Crystalloid  Colloid | Crystalloid  HES | Saline  Heavy HES |
| **Dubin**  **2010** | Normal Saline  6% HES | Saline  Voluven | Crystalloid  Colloid | Crystalloid  HES | Saline  Light HES |
| **BaSES**  **2011** | Normal Saline  6% HES | Saline  Voluven | Crystalloid  Colloid | Crystalloid  HES | Saline  Light HES |
| **Guidet**  **2012** | Normal Saline  6% HES | Saline  Voluven | Crystalloid  Colloid | Crystalloid  HES | Saline  Light HES |
| **Lu**  **2012** | Ringer’s Lactate  6% HES | RL  Voluven | Crystalloid  Colloid | Crystalloid  HES | Balanced Crystalloid  Light HES |
| **Myburgh 2012** | Normal Saline  6% HES | Saline  Voluven | Crystalloid  Colloid | Crystalloid  HES | Saline  Light HES |
| **Perner**  **2012** | Ringer’s Acetate  6% HES | RA  Tetraspan | Crystalloid  Colloid | Crystalloid  HES | Balanced Crystalloid  Light HES |
| **CRISTAL 2013** | Any Crystalloid  Any Colloid | N/A | Crystalloid  Colloid | Not included in analysis | Not included in analysis |

Table III. NMA results of 4-node analysis including confidence assessments.

| **Comparison** | **Number of trials with direct comparisons** | **Direct estimate**  **(95% CI)** | **Indirect estimate**  **(95% CrI)** | **NMA estimate (95% CrI) (higher of direct or indirect confidence)** |
| --- | --- | --- | --- | --- |
| Starch vs Crystalloid | 10 | 1.14 (0.99, 1.30) H | 0.81 (0.13, 5.14) VL1,2 | 1.13 (0.99, 1.30) H |
| Albumin vs Crystalloid | 2 | 0.81 (0.64, 1.03) M3 | 1.13 (0.18, 7.32) VL1,2 | 0.83 (0.65, 1.04) M |
| Gelatin vs Crystalloid | 0 | - | 1.24 (0.61, 2.55) VL1,3 | 1.24 (0.61, 2.55) VL |
| Albumin vs Starch | 2 | 1.40 (0.35, 5.56) L2 | 0.71 (0.54, 0.94) M1 | 0.73 (0.56, 0.95) M |
| Gelatin vs Starch | 1 | 1.09 (0.55, 2.19) L2 | - | 1.10 (0.54, 2.22) L |
| Gelatin vs Albumin | 0 | - | 1.51 (0.71, 3.20) VL1,2 | 1.51 (0.71, 3.20) VL |

CI = Confidence Interval, CrI = Credibility Interval, QoE = H – high, M – moderate, L – low, VL – very low

1 – rated down for indirectness , 2 – rated down 2 levels for imprecision, 3 – rated down for imprecision

Table IV. NMA results of 6-node analysis including confidence assessments.

| **Comparison** | **Number of trials with direct comparisons** | **Direct estimate**  **(95% CI)** | **Indirect estimate**  **(95% CrI)** | **NMA estimate (95% CrI) (higher of direct or indirect confidence)** |
| --- | --- | --- | --- | --- |
| Light Starch vs Saline | 4 | 1.07 (0.89, 1.29) M1 | 0.59 (0.25, 1.35) VL1,2,3 | 1.04 (0.87, 1.25) M |
| Heavy Starch vs Saline | 3 | 0.64 (0.30, 1.37) M1 | 1.13 (0.71, 1.80) VL1,2 | 0.95 (0.64, 1.41) M |
| Albumin vs Saline | 2 | 0.81 (0.64, 1.03) M1 | 0.96 (0.14, 6.31) VL2,4 | 0.82 (0.65, 1.04) M |
| Balanced Crystalloid vs Saline | 0 | - | 0.78 (0.58, 1.05) L1,2 | 0.78 (0.58, 1.05) L |
| Gelatin vs Saline | 0 | - | 1.04 (0.46, 2.32) VL1,2 | 1.04 (0.46, 2.32) VL |
| Heavy Starch vs Light Starch | 0 | - | 0.91 (0.63, 1.33) L1,2 | 0.91 (0.63, 1.33) L |
| Albumin vs Light Starch | 0 | - | 0.79 (0.59, 1.06) L1,2 | 0.79 (0.59, 1.06) L |
| Balanced Crystalloid vs Light Starch | 2 | 0.80 (0.61, 1.04) M3 | 0.44 (0.19, 0.97) M2 | 0.75 (0.58, 0.97) M |
| Gelatin vs Light Starch | 0 | - | 1.00 (0.44, 2.21) VL1,2 | 1.00 (0.44, 2.21) VL |
| Albumin vs Heavy Starch | 2 | 1.40 (0.35, 5.56) L4 | 0.83 (0.52, 1.33) L1,2 | 0.87 (0.55, 1.36) L |
| Balanced Crystalloid vs Heavy Starch | 1 | 0.74 (0.52, 1.05) M1 | 1.35 (0.63, 2.92) VL2,4 | 0.82 (0.60, 1.13) M |
| Gelatin vs Heavy Starch | 1 | 1.09 (0.55, 2.19) L4 | - | 1.10 (0.54, 2.21) L |
| Balanced Crystalloid vs Albumin | 0 | - | 0.95 (0.65, 1.38) VL1,2 | 0.95 (0.65, 1.38) VL |
| Gelatin vs Albumin | 0 | - | 1.26 (0.55, 2.90) VL2,4 | 1.26 (0.55, 2.90) VL |
| Gelatin vs Balanced Crystalloid | 0 | - | 1.34 (0.61, 2.89) VL2,4 | 1.34 (0.61, 2.89) VL |

CI = Confidence Interval, CrI = Credible Interval, QoE = H – high, M – moderate, L – low, VL – very low

1 – rated down for imprecision, 2 – rated down for indirectness, 3 – rated down for inconsistency (I2 = 80%, p = 0.03 for heterogeneity), 4 - rated down 2 levels for imprecision

Figure I. Flow chart of search results.

Full-text articles assessed for eligibility  
(n = 183) + studies identified from previous meta-analysis (n = 1) + studies not yet published (n = 1)

Records screened  
(n = 7,329)

Records after duplicates removed  
(n = 7,329)

Records excluded  
(n = 7,146)

Records identified through database searching:

MEDLINE: 3,132

EMBASE: 3,182

CENTRAL: 1,457

HEALTHSTAR: 2,046

ACP JOURNAL CLUB: 34

CINAHL: 22

AMED: 2

(n = 9,875)

Studies included in quantitative synthesis (meta-analysis)  
(n = 14 adults)

Full-text articles excluded   
(n = 171)

Septic subgroup not included or not separately analyzed (n = 58)

Duplicate Publication (n = 43)

Non RCT (n = 20)

Short-term Follow-Up (n = 9)

Not Resuscitation (n = 8)

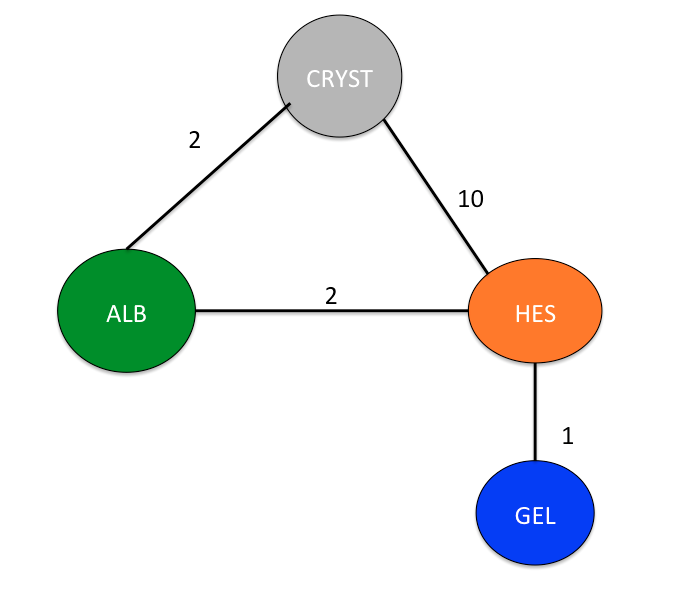
Review/Letter (n = 7)

Pediatric Population (n = 6)

Not Human (n = 3)

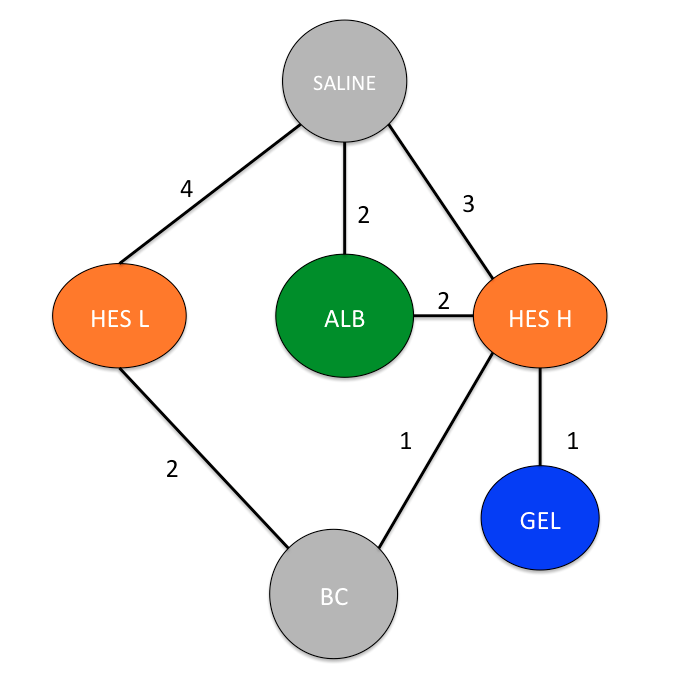
Others (n = 17)

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



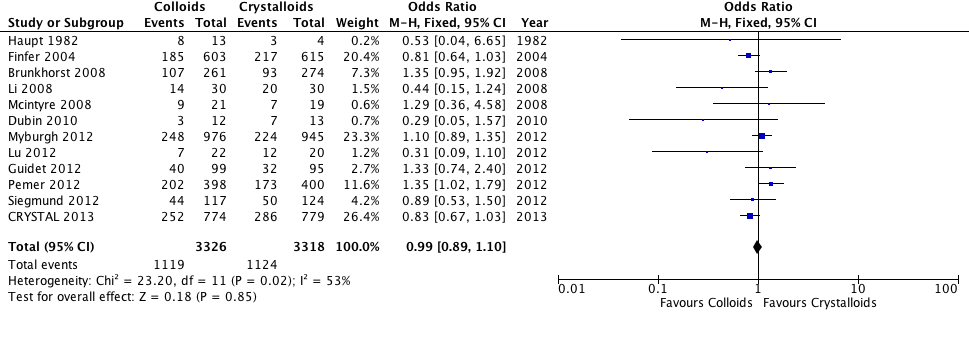
ALB – albumin, CRYST – crystalloid, HES – hydroxyl-ethyl starch, GEL – gelatin

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



HES L – light hydroxyl-ethyl starch, ALB – albumin, BC – balanced crystalloid, HES H – heavy hydroxyl-ethyl starch, GEL – gelatin

**Appendix Figure III.** Forrest plot for mortality in direct comparisons of all crystalloids versus all colloids



**Appendix Figure IV.** WinBUGS code for network meta-analysis

# Binomial likelihood, logit link, MTC

# Fixed effect model

model{ # \*\*\* PROGRAM STARTS

for(i in 1:ns){ # LOOP THROUGH STUDIES

mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines

for (k in 1:na[i]) { # LOOP THROUGH ARMS

r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood

logit(p[i,k]) <- mu[i] + d[t[i,k]]-d[t[i,1]] # model for linear predictor

rhat[i,k] <- p[i,k] \* n[i,k] # expected value of the numerators

dev[i,k] <- 2 \* (r[i,k] \* (log(r[i,k])-log(rhat[i,k])) #Deviance contribution

+ (n[i,k]-r[i,k]) \* (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

}

resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial

}

totresdev <- sum(resdev[]) #Total Residual Deviance

d[1]<- 0 # treatment effect is zero for reference treatment

for (k in 2:nt) { d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects

# pairwise ORs and LORs for all possible pair-wise comparisons

for (c in 1:(nt-1)) { for (k in (c+1):nt) {

or[c,k] <- exp(d[k] - d[c])

lor[c,k] <- (d[k]-d[c])

}

}

} # \*\*\* PROGRAM ENDS

**Appendix Figure V**. GRADE confidence explanations for all point estimates

For all analysis the final NMA confidence assessment was the higher confidence of the indirect or direct evidence.

**4-node analysis**

Starch vs Crystalloid

*Direct estimate*: high confidence

*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via albumin (the first order loop includes the direct comparisons of starch vs albumin (low confidence) and albumin vs crystalloid (moderate confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (low). Due to very wide confidence intervals in the indirect estimate we lowered a further 2 levels for imprecision. This resulted in our final confidence assessment which was very low.

Albumin vs Crystalloid

*Direct estimate:* rated down one level to moderate for imprecision given wide confidence intervals which cross 1

*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via starch (the first order loop includes the direct comparisons of albumin vs starch (low confidence) and starch vs crystalloid (high confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (low). Due to very wide confidence intervals in the indirect estimate we lowered 2 further levels for imprecision. This resulted in our final confidence assessment which was very low.

Gelatin vs Crystalloid

*Direct estimate*: none

*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via starch (the first order loop includes the direct comparisons of gelatin vs starch (low confidence) and starch vs crystalloid (high confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (low). Due to wide confidence intervals in the indirect estimate we lowered one further level for imprecision. This resulted in our final confidence assessment which was very low.

Albumin vs Starch

*Direct estimate:* due to very wide confidence intervals was lowered by 2 levels to low confidence

*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via crystalloid (the first order loop includes the direct comparisons of albumin vs crystalloid (moderate confidence) and crystalloid vs starch (high confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (moderate). Therefore our final confidence assessment was moderate.

Gelatin vs Starch

*Direct estimate*: due to very wide confidence intervals was lowered by 2 levels to low confidence

*Indirect estimate*: none

Gelatin vs Albumin

*Direct estimate:* none

*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via starch (the first order loop includes the direct comparisons of gelatin vs starch (low confidence) and starch vs albumin (low confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (low). Due to very wide confidence intervals in the indirect estimate we lowered 2 further levels for imprecision. This resulted in our final confidence assessment which was very low.

**6-node analysis**

Light Starch vs Saline

*Direct estimate:* rated down one level to moderate for imprecision given wide confidence intervals which cross 1

*Indirect estimate*: the indirect evidence for this comparison goes through a second-order loop via balanced crystalloid and heavy starch (the second order loop includes the direct comparisons of light starch vs balanced crystalloid (moderate confidence), balanced crystalloid vs heavy starch (moderate confidence) and heavy starch vs saline (moderate confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (moderate). Due to wide confidence intervals in the indirect estimate we lowered one level for imprecision. Finally we lowered one further level for inconsistency given that there was significant heterogeneity in the direct comparison of light starch vs balanced crystalloid. This resulted in our final confidence assessment which was very low.

Heavy Starch vs Saline

*Direct estimate*: rated down one level to moderate for imprecision given wide confidence intervals which cross 1

*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via albumin (the first order loop includes the direct comparisons of heavy starch vs albumin (low confidence) and albumin vs saline (moderate confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (low). Due to wide confidence intervals in the indirect estimate we lowered one further level for imprecision. This resulted in our final confidence assessment which was very low.

Albumin vs Saline

*Direct estimate*: rated down one level to moderate for imprecision given wide confidence intervals which cross 1

*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via heavy starch (the first order loop includes the direct comparisons of albumin vs heavy starch (low confidence) and heavy starch vs saline (moderate confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (low). Due to very wide confidence intervals in the indirect estimate we lowered 2 further levels for imprecision. This resulted in our final confidence assessment which was very low.

Balanced Crystalloid vs Saline

*Direct estimate*: none

*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via heavy starch (the first order loop includes the direct comparisons of balanced crystalloid vs heavy starch (moderate confidence) and heavy starch vs saline (moderate confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (moderate). Due to wide confidence intervals in the indirect estimate we lowered one further level for imprecision. This resulted in our final confidence assessment which was low.

Gelatin vs Saline

*Direct estimate*: none

*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via heavy starch (the first order loop includes the direct comparisons of gelatin vs heavy starch (low confidence) and heavy starch vs saline (moderate confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (low). Due to wide confidence intervals in the indirect estimate we lowered one further level for imprecision. This resulted in our final confidence assessment which was very low.

Heavy Starch vs Light Starch

*Direct estimate*: none

*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via saline (the first order loop includes the direct comparisons of heavy starch vs saline (moderate confidence) and saline vs light starch (moderate confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (moderate). Due to wide confidence intervals in the indirect estimate we lowered one further level for imprecision. This resulted in our final confidence assessment which was low.

Albumin vs Light Starch

*Direct estimate*: none

*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via saline (the first order loop includes the direct comparisons of albumin vs saline (moderate confidence) and saline vs light starch (moderate confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (moderate). Due to wide confidence intervals in the indirect estimate we lowered one further level for imprecision. This resulted in our final confidence assessment which was low.

Balanced Crystalloid vs Light Starch

*Direct estimate*: rated down 1 level for inconsistency due to heterogeneity in this direct meta-analysis (I2 = 80%)

*Indirect estimate*: the indirect evidence for this comparison goes through a second-order loop via heavy starch and saline (the second order loop includes the direct comparisons of balanced crystalloid vs heavy starch (moderate confidence), heavy starch vs saline (moderate confidence) and saline vs light starch (moderate confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (moderate). This resulted in our final confidence assessment which was moderate.

Gelatin vs Light Starch

*Direct estimate*: none

*Indirect estimate:* the indirect evidence for this comparison goes through a second-order loop via heavy starch and saline (the second order loop includes the direct comparisons of gelatin vs heavy starch (low confidence), heavy starch vs saline (moderate confidence) and saline vs light starch (moderate confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (low). Due to wide confidence intervals in the indirect estimate we lowered one further level for imprecision. This resulted in our final confidence assessment which was very low.

Albumin vs Heavy Starch

*Direct estimate:* rated down two levels to low for imprecision given very wide confidence intervals

*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via saline (the first order loop includes the direct comparisons of albumin vs saline (moderate confidence) and saline vs heavy starch (moderate confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (moderate). Due to wide confidence intervals in the indirect estimate we lowered one further level for imprecision. This resulted in our final confidence assessment which was low.

Balanced Crystalloid vs Heavy Starch

*Direct estimate*: rated down one level to moderate for imprecision given wide confidence intervals which cross 1

*Indirect estimate*: the indirect evidence for this comparison goes through a second-order loop via light starch and saline (the second order loop includes the direct comparisons of balanced crystalloid vs light starch (moderate confidence), light starch vs saline (moderate confidence) and saline vs heavy starch (moderate confidence). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (moderate)). Due to very wide confidence intervals in the indirect estimate we lowered 2 further levels for imprecision. This resulted in our final confidence assessment which was very low.

Gelatin vs Heavy Starch

*Direct estimate*: rated down two levels to low for imprecision given very wide confidence intervals.

*Indirect estimate*: none

Balanced Crystalloid vs Albumin

*Direct estimate*: none

*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via heavy starch (the first order loop includes the direct comparisons of balanced crystalloid vs heavy starch (moderate confidence) and heavy starch vs albumin (low confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (low). Due to wide confidence intervals in the indirect estimate we lowered one further level for imprecision. This resulted in our final confidence assessment which was very low.

Gelatin vs Albumin

*Direct estimate*: none

*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via heavy starch (the first order loop includes the direct comparisons of gelatin vs heavy starch (low confidence) and heavy starch vs albumin (low confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (low). Due to very wide confidence intervals in the indirect estimate we lowered 2 further levels for imprecision. This resulted in our final confidence assessment which was very low.

Gelatin vs Balanced Crystalloid

*Direct estimate*: none

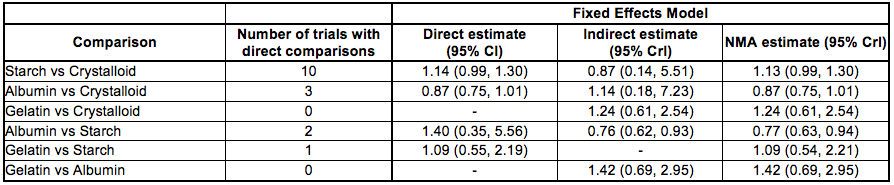
*Indirect estimate*: the indirect evidence for this comparison goes through a first-order loop via heavy starch (the first order loop includes the direct comparisons of gelatin vs heavy starch (low confidence) and heavy starch vs balanced crystalloid (moderate confidence)). Here we use the lowest of the confidence from the direct comparisons that make up the indirect comparison (low). Due to very wide confidence intervals in the indirect estimate we lowered 2 further levels for imprecision. This resulted in our final confidence assessment which was very low.

**Appendix Table 1.** Individual study risk of bias

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author,Year** | **ROB - randomization - sequence generation** | **ROB - randomization - concealment** | **ROB - Blinding** | **ROB - incomplete data** | **ROB - selective reporting** | **ROB - other (include ITT)** | **overall ROB for mortality** |
| Myburgh 2012 (Chest) | low ROB | Low ROB | Low ROB | low ROB | Low ROB | Low ROB | Low ROB |
| Guidet 2012 - CRYSTMAS | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |
| Perner 2012 (6S) | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |
| Haupt, 1982 | Probably Low ROB | Probably Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Probably Low ROB |
| Rackow, 1989 | Probably Low ROB | Probably Low ROB | Probably Low ROB | Low ROB | Low ROB | Low ROB | Probably Low ROB |
| Brunkhorst 2008 (VISEP) | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |
| Dubin 2010 | Low ROB | Probably Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Probably Low ROB |
| Li 2008 | Probably Low ROB | Probably Low ROB | Probably Low ROB | Probably Low ROB | Probably Low ROB | Probably Low ROB | Probably Low ROB |
| Lu, 2012 | Probably Low ROB | Probably Low ROB | Probably Low ROB | Probably Low ROB | Probably Low ROB | Probably Low ROB | Probably Low ROB |
| McIntyre 2008 (FINESS) | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |
| SAFE, 2004 | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |
| CRISTAL 2013 | Low ROB | Probably Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Probably Low ROB |
| BASES 2012 | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |
| Shortgen 2001 | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |

**Appendix Table 2.** Post hoc sensitivity analysis performed at the request of reviewers/editors.

The ALBIOS study was recently published in the NEJM ([N Engl J Med.](http://www.ncbi.nlm.nih.gov/pubmed/?term=ALBIOS++NEJM) 2014 Apr 10;370(15):1412-21). We had come across this study during our systematic review however it was deemed ineligible based mostly on the fact that it did not focus on resuscitation. Despite our assessment that this study is too indirect to inform our clinical question, we recognize that others may differ in this assessment. Therefore, we have conducted a sensitivity analysis including ALBIOS. In the control arm the ALBIOS protocol did not differentiate between balanced crystalloid or saline and therefore we could not include this study in our 6-node analysis. The 4-node analysis is included below:



The inclusion of ALBIOS had no effect on our results and given the concerns stated above, we have not included this study in our manuscript.

**Manuscript #3 –** Fluid Type and the use of Renal Replacement Therapy in Sepsis: A systematic review and Network Meta-analysis.

**Objective Manuscript #2:** Bayesian network meta-anlaysis including direct and indirect evidence assessing the effect of resuscitative fluid on the outcome of use of renal replacement therapy in septic ICU patients.

**Reference:** [Rochwerg B](http://www.ncbi.nlm.nih.gov/pubmed/?term=Rochwerg%20B%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Alhazzani W](http://www.ncbi.nlm.nih.gov/pubmed/?term=Alhazzani%20W%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Gibson A](http://www.ncbi.nlm.nih.gov/pubmed/?term=Gibson%20A%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Ribic CM](http://www.ncbi.nlm.nih.gov/pubmed/?term=Ribic%20CM%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Sindi A](http://www.ncbi.nlm.nih.gov/pubmed/?term=Sindi%20A%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Heels-Ansdell D](http://www.ncbi.nlm.nih.gov/pubmed/?term=Heels-Ansdell%20D%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Thabane L](http://www.ncbi.nlm.nih.gov/pubmed/?term=Thabane%20L%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Fox-Robichaud A](http://www.ncbi.nlm.nih.gov/pubmed/?term=Fox-Robichaud%20A%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Mbuagbaw L](http://www.ncbi.nlm.nih.gov/pubmed/?term=Mbuagbaw%20L%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Szczeklik W](http://www.ncbi.nlm.nih.gov/pubmed/?term=Szczeklik%20W%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Alshamsi F](http://www.ncbi.nlm.nih.gov/pubmed/?term=Alshamsi%20F%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Altayyar S](http://www.ncbi.nlm.nih.gov/pubmed/?term=Altayyar%20S%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Ip W](http://www.ncbi.nlm.nih.gov/pubmed/?term=Ip%20W%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Li G](http://www.ncbi.nlm.nih.gov/pubmed/?term=Li%20G%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Wang M](http://www.ncbi.nlm.nih.gov/pubmed/?term=Wang%20M%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Włudarczyk A](http://www.ncbi.nlm.nih.gov/pubmed/?term=W%C5%82udarczyk%20A%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Zhou Q](http://www.ncbi.nlm.nih.gov/pubmed/?term=Zhou%20Q%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Annane D](http://www.ncbi.nlm.nih.gov/pubmed/?term=Annane%20D%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Cook DJ](http://www.ncbi.nlm.nih.gov/pubmed/?term=Cook%20DJ%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Jaeschke R](http://www.ncbi.nlm.nih.gov/pubmed/?term=Jaeschke%20R%5BAuthor%5D&cauthor=true&cauthor_uid=25904181), [Guyatt GH](http://www.ncbi.nlm.nih.gov/pubmed/?term=Guyatt%20GH%5BAuthor%5D&cauthor=true&cauthor_uid=25904181); [FISSH Group (Fluids in Sepsis and Septic Shock)](http://www.ncbi.nlm.nih.gov/pubmed/?term=FISSH%20Group%20(Fluids%20in%20Sepsis%20and%20Septic%20Shock)%5BCorporate%20Author%5D). Fluid type and the use of renal replacement therapy in sepsis: a systematic review and network meta-analysis. [Intensive Care Med.](http://www.ncbi.nlm.nih.gov/pubmed/25904181) 2015 Apr 23. [Epub ahead of print]

d estencefidencel have no clude **Fluid Type and the use of Renal Replacement Therapy in Sepsis: A Systematic Review and Network Meta-analysis.**

Rochwerg B MD1, Alhazzani W MD1,2 , Gibson A MD1, Ribic CM MD1, Sindi A MD3, Heels-Ansdell D MSc4, Thabane L PhD4, Fox-Robichaud A MD, PhD1, Mbuagbaw L PhD4, Szczeklik W MD5, Alshamsi F MD1, Altayyar S MD1, Ip W MD1, Li G MSc4, Wang M MD1,

Włudarczyk A MD5, Zhou Q PhD4, Annane D MD, PhD6, Cook DJ MD1,4, Jaeschke R MD1,4 and Guyatt GH MD1,4 for the FISSH\* Group (Fluids in Sepsis & Septic Shock)

1 Department of Medicine, McMaster University, Hamilton, Ontario

2 Department of Critical Care, Prince Sultan Military Medical City, Riyadh, Saudi Arabia

3Department of Anaesthesia & Critical Care, King Abdulaziz University, Jeddah, Saudi Arabia

4 Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario

5 Department of Medicine, Jagiellonian University Medical College

6 Department of Critical Care, University of Versailles SQY, Garches, France

We also acknowledge financial support from the Hamilton Chapter of The Canadian Intensive Care Foundation, the Critical Care Medicine Residency Program and the Critical Care Division Alternate Funding Plan both at McMaster University, Hamilton, Ontario.

The authors declare no relevant financial conflict of interest. Dr. D. Cook is a Research Chair of the Canadian Institutes of Health Research. Dr. D. Cook coauthored a fluid trial cited herein. Dr. D. Annane was principal investigator of a fluid trial cited herein.

Corresponding Author and Reprint Requests:

Bram Rochwerg

Department of Medicine

Division of Critical Care

McMaster University

1200 Main St W

Hamilton ON

L8S 4L8

bram.rochwerg@medportal.ca

Keywords: sepsis, renal replacement therapy, fluids, resuscitation, network meta-analysis

**Abstract**

*Background*: Fluid resuscitation is the cornerstone of treatment for patients with sepsis. However, whether balanced or unbalanced crystalloids, or natural or synthetic colloids impact on requirements for renal replacement therapy (RRT) remains unclear.

*Objective*: We performed a network meta-analysis (NMA), including direct and indirect comparisons that addressed the effect of different resuscitative fluids on the use of RRT in patients with sepsis.

*Data Sources*: MEDLINE, EMBASE, ACPJC, CINAHL and Cochrane Central Register up to March 2014.

*Study Selection*: Eligible studies included randomized trials reported in any language that enrolled adult patients with sepsis or septic shock and addressed the use of RRT associated with alternative resuscitative fluids.

*Data Extraction*: Two reviewers extracted data on study characteristics, methods and outcomes. We assessed the risk of bias for individual studies and the overall certainty of the evidence.

*Data Synthesis*: Ten eligible studies (6,664 patients) included a total of 9 direct comparisons. NMA at the 4-node level showed an increased risk of receiving RRT associated with starch compared to crystalloid (OR 1.39, 95% CrI 1.17-1.66, high certainty). Data suggested no difference between albumin and crystalloid (OR 1.04, 95% CrI 0.78-1.38, moderate certainty) or starch (OR 0.74, 95% CrI 0.53-1.04, low certainty). NMA at the 6-node level showed decreased risk of receiving RRT with balanced crystalloid compared to heavy starch (OR 0.50, 95% CrI 0.34-0.74, moderate certainty) or light starch (OR 0.70, 95% CrI 0.49-0.99, high certainty). There was no significant difference with balanced crystalloid compared to saline (OR 0.85, 95% CrI 0.56-1.30, low certainty) or albumin (OR 0.82, 95% CrI 0.49-1.37, low certainty).

*Limitations:* These trials vary with respect to case mix, fluids evaluated, duration of fluid exposure and risk of bias. Imprecise estimates contribute to low confidence in most estimates of effect.

*Conclusion*: Among patients with sepsis, resuscitation with crystalloids compared to starch results in reduced use of RRT; the same may be true for albumin versus starch.

**INTRODUCTION**

Acute kidney injury (AKI) is common in patients who are admitted to the intensive care unit (ICU) with sepsis[[75](#_ENREF_75)]. The cause of AKI in sepsis is multifactorial, including vasodilatation, hypotension, volume depletion, the effect of circulating inflammatory cytokines, and medication toxicity. Approximately 45-70% of all AKI in the ICU occurs in the setting of sepsis[[76](#_ENREF_76), [77](#_ENREF_77)] which may be further associated with need for long-term dialysis and increased mortality [[78](#_ENREF_78)].

Fluid resuscitation, in addition to antibiotics, is the cornerstone of the initial management of patients with sepsis[[5](#_ENREF_5)], improving end-organ perfusion and renal hemodynamics[[79](#_ENREF_79)]. Whether specific fluids contribute to the risk of AKI when used for resuscitation in sepsis remains, however, uncertain.

A large randomized controlled trial (RCT) in critically ill patients found no difference in renal replacement therapy (RRT) rates between those receiving colloids versus those receiving crystalloids for fluid resuscitation (relative risk (RR) 0.93, 95% CI 0.83-1.03)[[27](#_ENREF_27)]. The division of fluids into these broad categories, however, ignores the possibility that individual crystalloid or colloid solutions differ in their impact on renal function.

Several RCTs have suggested an increased risk of AKI and a higher use of RRT following resuscitation of patients with sepsis using hydroxyethyl starch (HES), regardless of molecular weight[[12](#_ENREF_12), [13](#_ENREF_13), [29](#_ENREF_29)]. Meta-analysis of 31 RCTs including heterogeneous critically ill patients randomized to either HES or crystalloid solution showed an increased risk of AKI (RR 1.27, 95% CI 1.09-1.47) and use of RRT (RR 1.32, 95% CI 1.15-1.50) in those receiving HES for fluid resuscitation[[46](#_ENREF_46)]. These results prompted an FDA warning against the use of HES in critically ill adults[[58](#_ENREF_58)].

Less data are available addressing the effect of resuscitation using albumin or gelatin colloid solutions on the risk for AKI. The largest RCT comparing albumin versus saline in the resuscitation of critically ill patients found no difference in RRT rates[[16](#_ENREF_16)]. The only study to examine renal outcomes when directly comparing two different colloids in the resuscitation of sepsis showed no difference in the risk of AKI with a high molecular weight HES compared with a gelatin (RR 1.32, 95% CI 0.55-3.18) [[35](#_ENREF_35)].

Crystalloids can be subdivided based on tonicity and electrolyte composition[[8](#_ENREF_8)]. Balanced solutions contain an organic anion (e.g., lactate, acetate) and have a chloride concentration that more closely resembles that of plasma[[19](#_ENREF_19)]. Normal saline (0.9% sodium chloride), the mostly widely used resuscitative fluid worldwide, has both a pH well below 7.0 and a supra-physiologic chloride concentration, and appears nephrotoxic in animal models [[18](#_ENREF_18)].

No direct RCT evidence exists comparing different crystalloids used for resuscitation and the risk for AKI. One large before-after study of critically ill patients showed the use of a balanced versus an unbalanced fluid solution was associated with a lower incidence of AKI (8.4% vs. 14%, p<0.01) and RRT (6.3% vs 10%, p=0.05)[[22](#_ENREF_22)]. A retrospective cohort study of 53,448 septic ICU patients using propensity matching found a significantly decreased risk of death (RR 0.86, 95% CI 0.78-0.94) using balanced crystalloid solutions with no significant effect on AKI (RR 0.95, 95% CI 0.78-1.15) or RRT rates (RR 0.95, 95% CI 0.76-1.19)[[21](#_ENREF_21)].

Although these data provide compelling evidence that HES increases AKI and RRT, the relative merit of other resuscitation fluids remains unclear, contributing to large variation in practice [[59](#_ENREF_59), [60](#_ENREF_60)]. Prior meta-analyses have failed to focus on patients with sepsis, to consider the electrolyte composition of fluids studied, to include direct and indirect comparisons in the same model, and have not included data from recent large RCTs[[12](#_ENREF_12), [13](#_ENREF_13), [27](#_ENREF_27), [36](#_ENREF_36)]. Our group has previously reported the effect of resuscitation fluid on mortality using a network meta-analysis (NMA) approach incorporating both direct and indirect comparisons[[25](#_ENREF_25)]. We have now applied NMA of RCT data to examine the effect of all types of fluids used for resuscitation on the use of RRT in patients with severe sepsis and septic shock.

**MATERIAL AND METHODS**

**Data Sources & Searches:**

A previous publication presented the detailed methods for this systematic review and NMA[[25](#_ENREF_25)]. Here, we summarize the current methods, highlighting differences from the previous report[[25](#_ENREF_25)]. We conducted a search in March of 2014 of MEDLINE, EMBASE, ACPJC, Cochrane (CENTRAL) database, and CINAHL. We screened previously published meta-analyses for relevant citations. Six reviewers working in three pairs reviewed the titles and abstracts; any potentially eligible article proceeded to the full-text review. We used pre-tested eligibility forms for full text review, which was also performed in duplicate, with a third adjudicator resolving disagreement.

**Study Selection:**

*Types of Studies*: We included parallel-group RCTs, including factorial designs, without language or publication date restrictions, but excluded quasi-randomized and cross-over trials. We excluded all studies published by Dr. J Boldt due to suspected fraud[[62](#_ENREF_62)].

*Population:* Eligible studies enrolled adult (≥16 years of age) critically ill patients with severe sepsis or septic shock as defined by the investigators who required fluid resuscitation (defined as the administration of a bolus of intravenous fluid over and above that required for maintenance or replacement fluids). Eligible studies included those with mixed critically ill populations whenever separate data for patients with sepsis were available.

*Intervention*: Any fluid or fluid strategy used for resuscitation compared to another fluid or fluid strategy. We excluded studies in which the primary goal was to assess short-term hemodynamic response.

*Outcome:* This report focuses on the use of RRT during hospital admission.

**Data Extraction and Risk of Bias Assessment:**

The same six reviewers, working in pairs, performed data abstraction in duplicate. A third reviewer resolved disagreements. Risk of bias was assessed independently and in duplicate, using modification of the Cochrane Collaboration risk of bias instrument[[64](#_ENREF_64), [65](#_ENREF_65)]. The overall rating of risk of bias for each individual study was the lowest of the ratings for any of the risk of bias criteria.

**Data Synthesis and Analysis:**

Our analysis included division of fluids into the following categories and subcategories: crystalloids (divided into balanced and unbalanced solutions) and colloids (divided into albumin, gelatin, light molecular weight HES and heavy molecular HES – light HES had a molecular weight of 130,000 kDa and heavy HES had a molecular weight greater than 130,000 kDa). We considered fluid as balanced if it contained an anion of a weak acid (buffer) and if its chloride content was lower than in 0.9% sodium chloride [[8](#_ENREF_8)]. The relevant analyses included: a four node NMA (crystalloids vs. albumin vs. HES vs. gelatin), a six node NMA (above four nodes with crystalloids divided into balanced/unbalanced and HES divided into lower/higher molecular weight), and a conventional direct frequentist fixed-effect meta-analytic comparison of crystalloids vs. colloids.

To calculate direct estimates of treatment effect for each pair of treatments within the four and six-node networks, we performed a frequentist fixed-effects meta-analysis, reporting results as odds ratios [OR] and their corresponding 95% confidence intervals (CI). Heterogeneity was evaluated using Chi squared test and I2[[66](#_ENREF_66), [67](#_ENREF_67)].

Using a Bayesian framework, we conducted two fixed effects network meta-analyses (four nodes and six nodes), one for each of the treatment categorizations described. The results are reported as odds ratios [OR] and their corresponding 95% credibility intervals (CrI), which are the Bayesian equivalent of the 95% confidence intervals[[68](#_ENREF_68)]. 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. A random SEED and vague priors were used. Non-convergence was assessed based on Brooks Gelman Rubin plots[[69](#_ENREF_69)].

We used the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach to assess certainty in estimates of effect (quality of or confidence in evidence) associated with specific comparisons, including direct, indirect and final NMA estimates [[70](#_ENREF_70)]. The first step was assessing coherence between the direct and indirect estimates by ensuring sufficient overlap of their associated confidence intervals. Our certainty assessment also addressed the following domains: risk of bias, imprecision, inconsistency, indirectness, publication bias and intransitivity (for indirect estimates only).

The overall NMA confidence rating was the higher of the certainty in the direct and indirect comparisons with the possibility of rating up further for gains in precision with pooling of direct and indirect comparisons. The approach we used here was consistent with GRADE guidance as well as GRADE methods for direct comparisons [[37](#_ENREF_37), [80](#_ENREF_80)].

The Bayesian analysis for the NMA was conducted using WinBUGS 1.4.3 [http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml] and all frequentist analysis using Review Manager 5.2.3 (Revman; <http://ims.cochrane.org/revman/download>).

**RESULTS**

Of 9,548 titles identified during the primary search (7,002 after de-duplication) (Figure I), 6819 were judged as ineligible on the basis of titles and abstracts, leaving 185 studies for full text review. These included 2 unpublished studies, one found through screening titles included in previous meta-analysis [[36](#_ENREF_36)], and another (since published) found through author correspondence [[27](#_ENREF_27)]. Of these 185 RCTs, 175 proved ineligible leaving 10 eligible RCTs[[11-13](#_ENREF_11), [16](#_ENREF_16), [27-29](#_ENREF_27), [33](#_ENREF_33), [35](#_ENREF_35), [36](#_ENREF_36)]. Table I summarizes the characteristics of the 10 trials including 6,664 adults available for analysis. In three of the included trials [[12](#_ENREF_12), [16](#_ENREF_16), [27](#_ENREF_27)] only the subgroup of patients with sepsis were included in the analysis. Through contact with primary authors or authors of previous reviews we obtained relevant data for the 7 studies in which required data were incomplete (see Acknowledgements).

One of the studies [[27](#_ENREF_27)] did not provide results based on the individual fluid used and only divided fluids into crystalloid or colloid; therefore, it could not be included in the four-node or six-node analysis. Eight of the eligible RCTs employed a definition for sepsis consistent with international consensus [[72](#_ENREF_72)]. Four studies reported APACHE II scores in which the mean ranged from 17-20.6 [[11](#_ENREF_11), [12](#_ENREF_12), [16](#_ENREF_16), [33](#_ENREF_33)] while another four studies reported SOFA scores with median values of 7-8.5 [[13](#_ENREF_13), [27-29](#_ENREF_27)]. The fluid intervention period lasted between 24 hours and 90 days. The observation period for outcome in all studies was hospital stay.

Supplemental Digital Content - Appendix Figure I & II present network graphs illustrating direct and indirect comparisons as well as the number of studies available for each comparison. Table II indicates the contribution of individual studies and the sub-classification of each fluid at each level of analysis.

*Four-node analysis:* The results of this statistical analysis did not reveal any instances where the direct and indirect estimates were incoherent. Results show an increased risk of receiving RRT associated with starch compared to crystalloid (NMA OR 1.39; 95% CrI 1.17-1.66, high certainty) and a potentially decreased risk of receiving RRT with albumin compared to starch (NMA OR 0.74; 95% CrI 0.53-1.04, low certainty, rated down for imprecision and indirectness). Results suggested no difference in the use of RRT with albumin versus crystalloid (NMA OR 1.04; 95% CrI 0.78-1.38, moderate certainty, rated down for imprecision) (Table III).

*Six-node analysis*: Similar to the four-node analysis, we encountered no instances of statistical incoherence between the direct and indirect estimates. Balanced crystalloid proved superior to both light (NMA OR 0.70; 95% CrI 0.49-0.99, high certainty) and heavy starch (NMA OR 0.50, 95% CrI 0.34-0.74, moderate certainty, rated down for individual study risk of bias). Evidence suggests no significant difference in the need for RRT associated with the use of balanced crystalloid in comparison to saline (NMA OR 0.85; 95% CrI 0.56-1.30, low certainty, rated down for imprecision and indirectness) or albumin (NMA OR 0.82; 95% CrI 0.49-1.37, low certainty, rated down for imprecision and indirectness). Evidence also suggests no significant difference in the use of RRT with albumin compared to light starch (NMA OR 0.86; 95% CrI 0.59-1.25, low certainty, rated down for imprecision and indirectness) or heavy starch (NMA OR 0.61; 95% CrI 0.32–1.15, very low certainty, rated down for imprecision and indirectness). Results suggested similar use of RRT with albumin versus saline (NMA OR 1.04; 95% CrI 0.78-1.38, moderate certainty, rated down for imprecision). Light starch (NMA OR 1.21; 95% CrI 0.96-1.54, moderate certainty, rated down for imprecision) and heavy starch (NMA OR 1.70; 95% CrI 0.97-3.00, low certainty, rated down two levels for imprecision) both potentially increase the risk of RRT when compared with saline. (Table IV)

*Crystalloid vs Colloid:* There was a significant increase in the use of RRT using colloids compared with crystalloids for fluid resuscitation in adult patients (Supplemental Digital Content - Appendix Figure III) (OR 1.26; 95% CI 1.10-1.45; p = 0.001; Chi2 = 11.60, I2 = 22%; high certainty in estimate).

**DISCUSSION**

The results of this NMA suggest that the choice of resuscitative fluid used in sepsis influences the use of RRT in the ICU. Crystalloid unequivocally lowers the rates of RRT when compared to starches, irrespective of molecular weight. For all other comparisons, results are based on low or very low certainty and inferences are therefore weak. When grouped together, colloids were associated with greater use of RRT than crystalloids; however, this was driven by the inclusion of HES studies in the colloid category (see Supplemental Digital Content - Appendix for Forrest plot with subgroup analysis). The results presented here are consistent with previously reported mortality data from these studies[[25](#_ENREF_25)].

It is increasingly clear that starches relative to crytalloids, when used in critically ill patients, lead to increased mortality and organ dysfunction. The effects of albumin and gelatin are more uncertain. Albumin may be beneficial when compared to starches, but appears similar to saline in terms of RRT use (Table IV).

An important, often overlooked, consideration when using colloids is the crystalloid in which they are dissolved. The largest albumin study included in this review compared albumin dissolved in a chloride poor solution (128mmol/L) with saline (chloride concentration 154mmol/L)[[16](#_ENREF_16)]. A possible explanation for the similar results with albumin and saline is that albumin was harmful but the adverse effect was mitigated by the use of solvent balanced solution.

Biologic rationale exists to support the conclusion that chloride-rich, unbalanced solutions may be harmful to renal hemodynamics, especially in the setting of systemic hypoperfusion. The use of normal saline in ICU patients compared with balanced solutions such as Ringer’s Lactate or PlasmaLyte leads to worsened metabolic acidosis and acidemia as documented in a large before-and-after observational study[[81](#_ENREF_81)]. Low pH and high chloride concentrations can decrease glomerular blood flow worsening renal perfusion[[18](#_ENREF_18)]. Although human data are limited, animal models have shown decreased organ dysfunction, including renal failure, in hypotensive rats who received Ringer’s Maleate compared with saline[[82](#_ENREF_82)]. Our results, while not inconsistent with a reduced need for RRT in balanced solutions, provide little support for the hypothesis (OR 0.85; 95% CrI 0.56-1.30, low certainty).

The strengths of this review include a clear clinical question. We focused on patients receiving resuscitative fluids, above maintenance rate, in the setting of sepsis or septic shock. By focusing strictly on resuscitation we excluded two large recently completed trials (ALBIOS [[73](#_ENREF_73)] & EARSS [[83](#_ENREF_83)]) in which fluid was administered on a scheduled basis as dictated by serum albumin levels and not based on hemodynamic indices. We differentiated between balanced and unbalanced fluids and older (higher molecular weight) and newer (low molecular weight starches). Our search was comprehensive, and we assessed risk of bias carefully using duplicate review and third party adjudication. Using rigorous NMA methods[[68](#_ENREF_68)] we incorporated both direct and indirect evidence. The GRADE approach, seldom previously applied to NMAs, allowed reporting of certainty in estimates of effect when interpreting each fluid comparison.

The limitations of our review include the small number of studies relative to the number of comparisons, resulting in low certainty in estimates for many comparisons. Although all studies focused on fluid for resuscitation, there was variability in fluid protocols with varying amounts of fluid administered and durations of the fluid intervention periods. Some observed results may be related to the interplay of different fluid properties, in particular the differential presence of chloride in each colloid. We also analyzed the use of RRT as reported in individual trials, using this as a marker for clinically relevant AKI. In this regard, we are likely capturing the most severe AKI, albeit influenced by variable thresholds for starting dialysis, but missing potentially important events which don’t result in the use of RRT.

The results of this comprehensive review summarize the impact of resuscitative fluids on the need for RRT in septic ICU patients. When used in sepsis, crystalloid solutions are certainly superior to HES. There is no difference in need for RRT between using crystalloid or albumin solutions for resuscitation. If clinicians wish to use a colloid in septic patients, it should not be a starch-containing solution. When using any colloid, it may be advisable for clinicians to consider the electrolyte content and pH of the solution in which the colloid is dissolved. No RCT has directly compared a balanced versus unbalanced solution of similar composition for resuscitation, leaving only low certainty in the relative merits of balanced versus unbalanced resuscitation fluids, and underscoring the need for large, rigorous RCTs addressing this issue.

**Acknowledgments:**

We would like to acknowledge the following clinicians for providing us with information contributing to this paper: Dr. S. Finfer[[16](#_ENREF_16)], Dr. K Reinhart[[11](#_ENREF_11)], Dr. A Chopra, Dr. F Shortgen[[35](#_ENREF_35)], Dr. B Wills, Dr. N Haase[[29](#_ENREF_29), [36](#_ENREF_36)], Dr. LL McIntyre[[33](#_ENREF_33)], Dr. K Maitland and Dr J Myburgh[[12](#_ENREF_12)]. We acknowledge librarians Lois Cottrell and Jean Maragno for their invaluable help with structuring and performing our search.

Table I. Study characteristics.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Number of Randomized Patients** | **Sepsis according to International Sepsis Definition (or similar)i** | **Mean APACHE II Score** | **Interventions** | **Blood Products**  **Transfused** | **Cumulative Dose** | **Intervention Period** | **Overall ROB** | **RRT** | **Industry Sponsor** |
| **Shortgen 2001** | Multicenter (3)  France  N = 129 | Yes | Not reported | GL  HES-H | Not reported | GL 43 ml/kg  HES 31 ml/kg | HES 4 days  GL until ICU discharge) | Probably Low± | GL 11/64  HES 14/65 | Not Reported |
| **SAFE**  **2004** | Multicenter (16)  Australia & NZ  N = 6997 | Yes | 18.9 | NS  AL | Not reported | NS >3000 ml  AL >2000 ml | 28 days | Low | NS 112/615  AL 113/603 | CSL Behring |
| **Brunkhorst 2008** | Multicenter (18)  Germany, N = 537 | Yes | 20 | RL  HES-H | RL 189/275 (68.7%)  HES 199/262 (76%) | RL 1.32x HES dose  HES 70.4ml/kg | 21 days | Probably Low± | RL 51/272  HES 81/261 | B. Braun  Novo Nordisk  HemoCue |
| **McIntyre 2008** | Multicenter (4)  NZ & Canada  N = 40 | Yes | 20.6 | NS  HES-H | NS 5/19 (26%)  HES 10/21 (48%) | NS 2100 ml  HES 1900ml | <24 hours | Low | NS 1/19  HES 3/21 | Bristol Meyer Squibb  Edward Life Sciences |
| **Dubin**  **2010** | Multicenter (2)  Argentina, N = 25 | Yes | Not reported (mean SOFA score 8.5) | NS  HES-L | NS 18%  HES 22% | NS 6254 ml  HES 2610 ml | 24 hours | Probably Low± | NS 2/11  HES 0/9 | Not Reported |
| **BaSES**  **2011** | Single Center  Switzerland  N = 241 | Not reported | Not included | NS  HES-L | Not reported | NS not reported  HES 3775 ml (median) | 5 days | Low | NS 23/124  HES 28/117 | Fresenius AG |
| **Guidet**  **2012** | Multicenter (24)  France & Germany  N = 196 | Yes | Not reported (mean SOFA score 8.5) | NS  HES-L | NS 20/96 (21%)  HES 29/100 (29%) | NS 2788 ml  HES 2615 ml | 4 days | Low | NS 11/96  HES 21/100 | Fresenius Kabi |
| **Myburgh 2012** | Multicenter (32)  Australia & NZ  N = 7000 | Not | 17 | NS  HES-L | Not reported | Study fluid for enrolled over first 4 days: NS 2456 ml  HES 2104 ml | 90 days | Low | NS 110/957  HES 124/979 | Fresenius Kabi |
| **Perner**  **2012** | Multicenter (26)  Scandanavia, N = 804 | Yes | Not reported  (mean SOFA score 7) | RA  HES-L | RA 204/380 (54%)  HES 243/376 (65%) | RA 3000 ml (mean)  HES 3000 ml (mean) | 90 days | Low | RA 65/400  HES 87/398 | B. Braun Medical |
| **CRISTAL 2013** | Multicenter (57)  Worldwide, N = 2857 | Yes | Not reported (mean SOFA score 8) | Cry  Col | Cry 358/1443 (24.8%)  Col 377/1414 (26.7%) | Cry 3000 ml in 7 days  Col 2000 ml in 7 days | Until ICU discharge | Low | Cry 35/779  Col 35/774 | None |

RL: ringer’s lactate, RA: ringer’s acetate, NS: normal saline, HES: hydroxyl-ethyl starch,

AL: albumin, GL: gelatin, Cry: crystalloid, Col: colloid, H: heavy, L: light, ICU: intensive care unit, RoB: risk of bias, N: number, APACHE II: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment score

± intervention in this study was unblinded, t = reference [Crit Care Med.](http://www.ncbi.nlm.nih.gov/pubmed/?term=CCM+2003%3B31(4)%3A1250-6) 2003 Apr;31(4):1250-6.

Table II. Contribution of individual studies to each level of analysis.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study Name** | **Fluid Name** | **Trade Name** | **Crystalloid vs Colloid** | **4-Node Analysis** | **6-Node Analysis** |
| **Shortgen 2001** | 3% Gelatin  6% HES | Plasmagel  Haes-Steril | Colloid  Colloid | Gelatin  HES | Gelatin  Heavy HES |
| **SAFE**  **2004** | Normal Saline  4% Albumin | Saline  Albumex | Crystalloid  Colloid | Crystalloid  Albumin | Saline  Albumin |
| **Brunkhorst 2008** | Ringer’s Lactate  10% HES | RL  Pentastarch | Crystalloid  Colloid | RL  HES | Balanced Crystalloid  Heavy HES |
| **McIntyre 2008** | Normal Saline  10% HES | Saline  Pentastarch | Crystalloid  Colloid | Crystalloid  HES | Saline  Heavy HES |
| **Dubin**  **2010** | Normal Saline  6% HES | Saline  Voluven | Crystalloid  Colloid | Crystalloid  HES | Saline  Light HES |
| **BaSES**  **2011** | Normal Saline  6% HES | Saline  Voluven | Crystalloid  Colloid | Crystalloid  HES | Saline  Light HES |
| **Guidet**  **2012** | Normal Saline  6% HES | Saline  Voluven | Crystalloid  Colloid | Crystalloid  HES | Saline  Light HES |
| **Myburgh 2012** | Normal Saline  6% HES | Saline  Voluven | Crystalloid  Colloid | Crystalloid  HES | Saline  Light HES |
| **Perner**  **2012** | Ringer’s Acetate  6% HES | RA  Tetraspan | Crystalloid  Colloid | Crystalloid  HES | Balanced Crystalloid  Light HES |
| **CRISTAL 2013** | Any Crystalloid  Any Colloid | N/A | Crystalloid  Colloid | Not included in analysis | Not included in analysis |

Table III. NMA results of 4-node analysis including confidence assessments.

| **Comparison** | **Number of trials with direct comparisons** | **Direct estimate**  **(95% CI)** | **Indirect estimate**  **(95% CrI)** | **NMA estimate (95% CrI) (higher of direct or indirect confidence)** |
| --- | --- | --- | --- | --- |
| Starch vs Crystalloid | 7 | 1.39 (1.17, 1.66) H | - | 1.39 (1.17, 1.66) H |
| Albumin vs Crystalloid | 1 | 1.04 (0.78, 1.38) M1 | - | 1.04 (0.78, 1.38) M |
| Gelatin vs Crystalloid | 0 | - | 1.05 (0.42, 2.56) VL2 | 1.05 (0.42, 2.56) VL |
| Albumin vs Starch | 0 | - | 0.74 (0.53, 1.04) L3 | 0.74 (0.53, 1.04) L |
| Gelatin vs Starch | 1 | 0.76 (0.31, 1.82) L1,4 | - | 0.75 (0.30, 1.81) L |
| Gelatin vs Albumin | 0 | - | 1.01 (0.38, 2.60) VL3 | 1.01 (0.38, 2.60) VL |

CI = Confidence Interval, CrI = Credibility Interval, H = High Certainty, M = Moderate Certainty, L = Low Certainty, VL = Very Low Certainty

1 – rated down for imprecision, 2 – started as low (due to evidence making up loops) and rated down for imprecision, 3 – started as moderate (due to evidence making up loops) and rated down for imprecision, 4 – rated down for risk of bias

Table IV. NMA results of 6-node analysis including confidence assessments.

| **Comparison** | **Number of trials with direct comparisons** | **Direct estimate**  **(95% CI)** | **Indirect estimate**  **(95% CrI)** | **NMA estimate (95% CrI) (higher of direct or indirect confidence)** |
| --- | --- | --- | --- | --- |
| Light Starch vs Saline | 4 | 1.20 (0.95, 1.52) M1 | 2.92 (0.26, 100.10) VL2 | 1.21 (0.96, 1.54) M |
| Heavy Starch vs Saline | 1 | 3.00 (0.28, 31.63) L3 | 1.64 (0.90, 2.95) L | 1.70 (0.97, 3.00) L |
| Albumin vs Saline | 1 | 1.04 (0.78, 1.38) M4 | - | 1.04 (0.78, 1.38) M |
| Balanced Crystalloid vs Saline | 0 | - | 0.85 (0.56, 1.30) L4 | 0.85 (0.56, 1.30) L |
| Gelatin vs Saline | 0 | - | 1.27 (0.44, 3.64) VL2 | 1.27 (0.44, 3.64) VL |
| Heavy Starch vs Light Starch | 0 | - | 1.40 (0.83, 2.37) L4 | 1.40 (0.83, 2.37) L |
| Albumin vs Light Starch | 0 | - | 0.86 (0.59, 1.25) L4 | 0.86 (0.59, 1.25) L |
| Balanced Crystalloid vs Light Starch | 1 | 0.69 (0.49, 0.99) H | 1.68 (0.15, 52.26) VL2 | 0.70 (0.49, 0.999) H |
| Gelatin vs Light Starch | 0 | - | 1.05 (0.37, 2.94) VL2 | 1.05 (0.37, 2.94) VL |
| Albumin vs Heavy Starch | 0 | - | 0.61 (0.32, 1.15) VL2 | 0.61 (0.32, 1.15) VL |
| Balanced Crystalloid vs Heavy Starch | 1 | 0.51 (0.34, 0.77) M5 | 0.21 (0.01, 2.33) VL2 | 0.50 (0.34, 0.74) M |
| Gelatin vs Heavy Starch | 1 | 0.76 (0.31, 1.82) L1,5 | - | 0.75 (0.30, 1.81) L |
| Balanced Crystalloid vs Albumin | 0 | - | 0.82 (0.49, 1.37) L4 | 0.82 (0.49, 1.37) L |
| Gelatin vs Albumin | 0 | - | 1.23 (0.41, 3.67) VL2 | 1.23 (0.41, 3.67) VL |
| Gelatin vs Balanced Crystalloid | 0 | - | 1.50 (0.56, 3.96) VL2 | 1.50 (0.56, 3.96) VL |

CI = Confidence Interval, CrI = Credibility Interval, H = High Certainty, M = Moderate Certainty, L = Low Certainty, VL = Very Low Certainty

1 – rated down for imprecision, 2 – started as low (due to evidence making up loops) and rated down for imprecision, 3 – rated down 2 levels for imprecision, 4 – started as moderate (due to evidence making up loops) and rated down for imprecision, 5 - rated down for risk of bias

Figure I. Flow chart of search results.

Full-text articles assessed for eligibility  
(n = 183) + studies identified from previous meta-analysis (n = 1) + studies not yet published (n = 1)

Records screened  
(n = 7,329)

Records after duplicates removed  
(n = 7,329)

Records excluded  
(n = 7,146)

Full-text articles excluded   
(n = 175)

Septic subgroup not included or not separately analyzed (n = 58)

Duplicate Publication (n = 43)

Non RCT (n = 20)

Short-term Follow-Up (n = 9)

Not Resuscitation (n = 8)

Review/Letter (n = 7)

Pediatric Population (n = 6)

No RRT data (n = 4)

Not Human (n = 3)

Others (n = 17)

Records identified through database searching:

MEDLINE: 3,132

EMBASE: 3,182

CENTRAL: 1,457

HEALTHSTAR: 2,046

ACP JOURNAL CLUB: 34

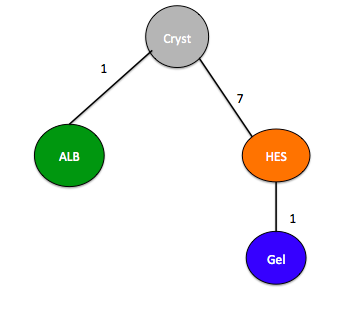
CINAHL: 22

AMED: 2

(n = 9,875)

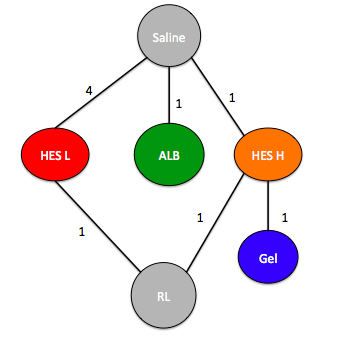
Studies included in quantitative synthesis (meta-analysis)  
(n = 10 adults)

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



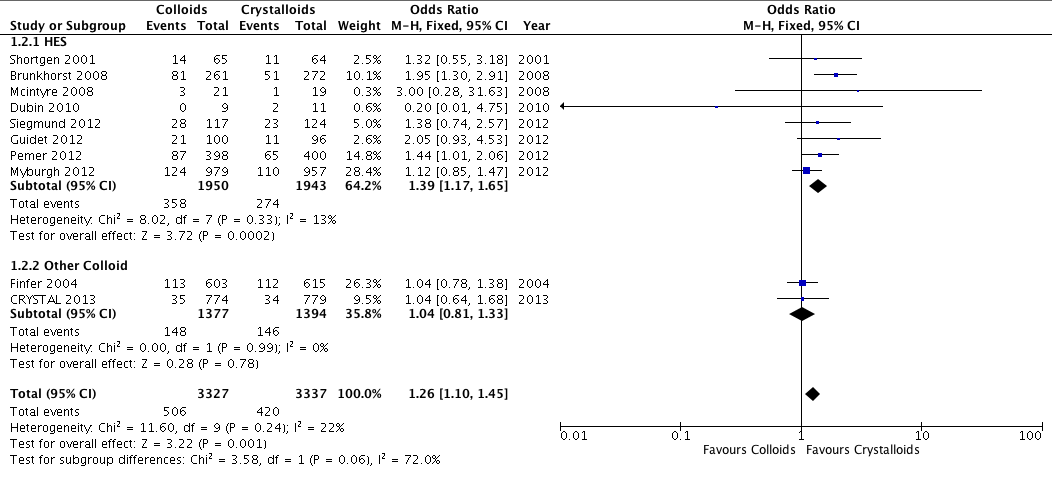
ALB – albumin, CRYST – crystalloid, HES – hydroxyl-ethyl starch, GEL – gelatin

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



HES L – light hydroxyl-ethyl starch, ALB – albumin, BC – balanced crystalloid, HES H – heavy hydroxyl-ethyl starch, GEL – gelatin

**Appendix Figure III.** Forrest plot of need for RRT outcome in direct comparisons of all crystalloids versus all colloids



**Appendix Figure IV.** WinBUGS code for network meta-analysis

# Binomial likelihood, logit link, MTC

# Fixed effect model

model{ # \*\*\* PROGRAM STARTS

for(i in 1:ns){ # LOOP THROUGH STUDIES

mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines

for (k in 1:na[i]) { # LOOP THROUGH ARMS

r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood

logit(p[i,k]) <- mu[i] + d[t[i,k]]-d[t[i,1]] # model for linear predictor

rhat[i,k] <- p[i,k] \* n[i,k] # expected value of the numerators

dev[i,k] <- 2 \* (r[i,k] \* (log(r[i,k])-log(rhat[i,k])) #Deviancecontribution

+ (n[i,k]-r[i,k]) \* (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

}

resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial

}

totresdev<- sum(resdev[]) #Total Residual Deviance

d[1]<- 0 # treatment effect is zero for reference treatment

for (k in 2:nt) { d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects

# pairwise ORs and LORs for all possible pair-wise comparisons

for (c in 1:(nt-1)) { for (k in (c+1):nt) {

or[c,k] <- exp(d[k] - d[c])

lor[c,k] <- (d[k]-d[c])

}

}

} # \*\*\* PROGRAM ENDS

**Appendix Table 1.** Individual study risk of bias

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author,Year** | **ROB - randomization - sequence generation** | **ROB - randomization - concealment** | **ROB - Blinding** | **ROB - incomplete data** | **ROB - selective reporting** | **ROB - other (include ITT)** | **overall ROB for RRT** |
| Myburgh 2012 (Chest) | low ROB | Low ROB | Low ROB | low ROB | Low ROB | Low ROB | Low ROB |
| Guidet 2012 - CRYSTMAS | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |
| Perner 2012 (6S) | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |
| Brunkhorst 2008 (VISEP) | Low ROB | Low ROB | Probably Low ROB | Low ROB | Low ROB | Low ROB | Probably Low ROB |
| Dubin 2010 | Low ROB | Probably Low ROB | Probably Low ROB | Low ROB | Low ROB | Low ROB | Probably Low ROB |
| McIntyre 2008 (FINESS) | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |
| SAFE, 2004 | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |
| CRISTAL 2013 | Low ROB | Probably Low ROB | Probably Low ROB | Low ROB | Low ROB | Low ROB | Probably Low ROB |
| BASES 2012 | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |
| Shortgen 2001 | Low ROB | Low ROB | Probably Low ROB | Low ROB | Low ROB | Low ROB | Probably Low ROB |

**Appendix.** Certainty in Estimates of Effect

**4 Node Analysis:**

Albumin vs Crystalloid

*Direct estimate:* rated down one level to moderate certainty for imprecision due to wide confidence interval

*Indirect estimate:* none

Crystalloid vs Starch

*Direct estimate:* high certainty

*Indirect estimate:* none

Starch vs Gelatin

*Direct estimate:* rated down two levels to low certainty; once for risk of bias (in the only included study the allocation was unblinded), and once for imprecision

*Indirect estimate:* none

Crystalloid vs Gelatin

*Direct estimate:* none

*Indirect estimate:* the evidence for this comparison goes through a first-order loop via starch (the first-order loop includes the direct comparisons of crystalloid vs starch (high certainty) and starch vs gelatin (low certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparisons (low). We rated down an additional level for imprecision due to a very wide confidence interval, resulting in a final certainty assessment of very low.

Albumin vs Starch

*Direct estimate:* none

*Indirect estimate:* the evidence for this comparison goes through a first-order loop via crystalloid (the first-order loop inclues the direct comparisons of albumin vs crystalloid (moderate certainty) and crystalloid vs starch (high certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparisons (moderate). We rated down an additional level for imprecision due to a wide confidence interval in the indirect estimate which resulted in our final certainty assessment of low.

Albumin vs Gelatin

*Direct estimate:* none

*Indirect estimate:* the evidence for this comparison goes through a second-order loop via crystalloid and starch (the second-order loop includes the direct comparisons of albumin vs crystalloid (moderate certainty), crystalloid vs starch (high certainty) and starch vs gelatin (low certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparison (low). We rated down an additional level for imprecision due to a wide confidence interval in the indirect comparison, for a final certainty assessment of very low.

**6 Node Analysis**

Light Starch vs Saline

*Direct estimate:* rated down one level to moderate certainty due to imprecision for wide confidence interval crossing one

*Indirect estimate:* the evidence for this comparison goes through a second-order loop via balanced crystalloid and heavy starch (the second-order loop includes the direct comparisons of light starch vs balanced crystalloid (high certainty), balanced crystalloid vs heavy starch (moderate certainty) and heavy starch vs saline (low certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparison (low). We rated down an additional level for imprecision due to a wide confidence interval in the indirect comparison, for a final certainty assessment of very low.

Heavy Starch vs Saline

*Direct estimate:* rated down two levels to low certainty due to imprecision for very wide confidence interval crossing one

*Indirect estimate:* the evidence for this comparison goes through a second-order loop via balanced crystalloid and light starch (the second-order loop includes the direct comparisons of heavy starch vs balanced crystalloid (moderate certainty), balanced crystalloid vs light starch (high certainty) and light starch vs saline (moderate certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparison (moderate). We rated down an additional level for imprecision due to a wide confidence interval in the indirect comparison, for a final certainty assessment of low.

Albumin vs Saline

*Direct estimate:* rated down one level for imprecision to moderate certainty due to a wide confidence interval in the direct assessment that crossed one

*Indirect estimate:* none

Balanced Crystalloid vs Saline

*Direct estimate:* none

*Indirect estimate:* the evidence for this comparison goes through a first-order loop via light starch (the first-order loop includes the direct comparisons of balanced crystalloid vs light starch (high certainty) and light starch vs saline (moderate certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparison (moderate). We rated down an additional level for imprecision due to a wide confidence interval in the indirect comparison, for a final certainty assessment of low.

Gelatin vs Saline

*Direct estimate:* none

*Indirect estimate:* the evidence for this comparison goes through a first-order loop via heavy starch (the first-order loop includes the direct comparisons of gelatin vs heavy starch (low certainty) and heavy starch vs saline (low certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparison (low). We rated down an additional two levels for imprecision due to a very wide confidence interval in the indirect comparison, for a final certainty assessment of very low.

Heavy Starch vs Light Starch

*Direct estimate:* none

*Indirect estimate:* the evidence for this comparison goes through a first-order loop via balanced crystalloid (the first-order loop includes the direct comparisons of heavy starch vs balanced crystalloid (moderate certainty) and balanced crystalloid versus light starch (high certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparison (moderate). We rated down an additional level for imprecision due to a wide confidence interval in the indirect comparison, for a final certainty assessment of low.

Albumin vs Light Starch

*Direct estimate:* none

*Indirect estimate:* the evidence for this comparison goes through a first-order loop via saline (the first-order loop includes the direct comparisons of albumin vs saline (moderate certainty) and saline vs light starch (moderate certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparison (moderate). We rated down an additional level for imprecision due to a wide confidence interval in the indirect comparison, for a final certainty assessment of low.

Balanced Crystalloid vs Light Starch

*Direct estimate:* high confidence

*Indirect estimate:* the evidence for this comparison goes through a second-order loop via heavy starch and saline (the second-order loop includes the direct comparisons of balanced crystalloid vs heavy starch (moderate certainty), heavy starch vs saline (low certainty) and saline vs light starch (moderate certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparison (low). We rated down an additional two levels for imprecision due to a very wide confidence interval in the indirect comparison, for a final certainty assessment of very low.

Gelatin vs Light Starch

*Direct estimate:* none

*Indirect estimate:* the evidence for this comparison goes through a second-order loop via heavy starch and balanced crystalloid (the second-order loop includes the direct comparisons of gelatin vs heavy starch (low certainty), heavy starch vs balanced crystalloid (moderate certainty) and balanced crystalloid vs light starch (high certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparison (low). We rated down an additional level for imprecision due to a wide confidence interval in the indirect comparison, for a final certainty assessment of very low.

Albumin vs Heavy Starch

*Direct estimate:* none

*Indirect estimate:* the evidence for this comparison goes through a first-order loop via saline (the first-order loop includes the direct comparisons of albumin vs saline (moderate certainty) and saline vs heavy starch (certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparison (low). We rated down an additional level for imprecision due to a wide confidence interval in the indirect comparison, for a final certainty assessment of very low.

Balanced Crystalloid vs Heavy Starch

*Direct estimate:* rated down one level to moderate certainty due to potential risk of bias (unblinded intervention) found in one of the included studies

*Indirect estimate:* the evidence for this comparison goes through a second-order loop via light starch and saline (the second-order loop includes the direct comparisons of balanced crystalloid vs light starch (high certainty), light starch vs saline (moderate certainty) and saline versus heavy starch (low certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparison (low). We rated down an additional level for imprecision due to a wide confidence interval in the indirect comparison, for a final certainty assessment of very low.

Gelatin vs Heavy Starch

*Direct estimate:* rated down two levels to low certainty for potential risk of bias (unblinded intervention in the one included study) and imprecision (wide confidence interval)

*Indirect estimate:* none

Balanced crystalloid vs Albumin

*Direct estimate:* none

*Indirect estimate:* the evidence for this comparison goes through a second-order loop via light starch and saline (the second-order loop includes the direct comparisons of balanced crystalloid vs light starch (high certainty), light starch vs saline (moderate certainty) and saline vs albumin (moderate certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparison (moderate). We rated down an additional level for imprecision due to a wide confidence interval in the indirect comparison, for a final certainty assessment of low.

Gelatin vs Albumin

*Direct estimate:* none

*Indirect estimate:* the evidence for this comparison goes through a second-order loop via heavy starch and saline (the second -order loop includes the direct comparisons of gelatin vs heavy starch (low certainty), heavy starch vs saline (low certainty) and saline versus albumin (moderate certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparison (low). We rated down an additional two levels for imprecision due to a wide confidence interval in the indirect comparison, for a final certainty assessment of very low.

Gelatin vs Balanced crystalloid

*Direct estimate:* none

*Indirect estimate:* the evidence for this comparison goes through a first-order loop via heavy starch (the first-order loop includes the direct comparisons of gelatin vs heavy starch (low certainty) and heavy starch vs balanced crystalloid (moderate certainty)). Here we use the lowest certainty assessment of the direct comparisons that make up the indirect comparison (low). We rated down an additional two levels for imprecision due to a wide confidence interval in the indirect comparison, for a final certainty assessment of very low.

**Pilot Study Protocol –** Fluids in Sepsis and Septic Shock (FISSH): a pilot randomized controlled trial.

**Objective of Pilot Study:** Is it feasible to perform a large randomized controlled trial (RCT) in critically ill patients with severe sepsis or septic shock to investigate whether the administration of normal chloride concentration versus low chloride concentration fluids for hemodynamic resuscitation improves survival and other patient important outcomes?

**Project Design, Methodology & Analysis**

***Research question for the FISSH Pilot RCT***

Is it feasible to perform a large RCT in critically ill patients with severe sepsis or septic shock to investigate whether the administration of higher chloride versus lower chloride fluids for hemodynamic resuscitation improves survival and other patient important outcomes?

***PICOT Question for Pilot***

Population: Adults 18 years old or greater in the ICU with severe sepsis or septic shock.

Intervention: Administration of only fluids with a lower chloride concentration while in the ICU (this includes crystalloids or albumin)

Control: Administration of only fluids with a higher chloride concentration while in the ICU (this includes crystalloids or albumin)

Outcomes: For the pilot RCT, the main outcomes are feasibility (consent rate, recruitment, protocol adherence). We will also examine all the clinical outcomes relevant for the larger RCT.

Type of study: Randomized, concealed, blinded, parallel-group feasibility pilot RCT.

***Research Question for the Main FISSH RCT***

In patients with septic shock, does the administration of solutions with a lower chloride content compared to using solutions with a higher chloride content lead to improved patient important outcomes (eg. hospital mortality)?

***PICOT Question for Main FISSH RCT***

Population: Adults 18 years old or greater in the ICU with severe sepsis or septic shock.

Intervention: Administration of only fluids with a lower chloride concentration while in the ICU (this includes crystalloids or albumin)

Control: Administration of only fluids with a higher chloride concentration while in the ICU (this includes crystalloids or albumin)

Outcomes: hospital mortality, 30-day mortality, use of RRT, rates of AKI, ICU length of stay, hospital length of stay, ventilator-free days, persistent organ dysfunction (POD) [[84](#_ENREF_84)], the rates of acidosis, hyperkalemia and hyperchloremia.

***Pilot Study Design & Study Centers***

This is a pragmatic multi-centre stratified concealed parallel-group pilot randomized controlled blinded trial. The primary outcome for this pilot trial will be feasibility as assessed by 3 outcomes of consent rate, recruitment parameters and protocol adherence. We plan to enrol patients at 3 study centers. These all will be at academic teaching hospitals associated with McMaster University in Hamilton, Ontario (St Joseph’s Hospital, Juravinski Hospital and the Hamilton General Hospital). The study is supported by the Canadian Critical Care Trials Group (CCCTG), which is a network of intensive care physicians and research co-ordinators across Canada who support investigator-driven research projects and help facilitate multi-centred ICU research in Canada. The principle investigator and many of the co-investigators of this study are members of the CCCTG.

***Patients***

All patients will be screened for study eligibility at the time of ICU admission. A dedicated research co-ordinator will be physically present in the ICU and will screen every admission for potential inclusion. On weekends or after-hours ICU clinical staff will perform screening as availability allows. A screening log will be kept at each study center with all patients reviewed and reasons for study exclusion documented. All study centers have ICUs with at least 15 funded ICU beds providing considerable capacity and potential patients.

***Inclusion criteria***

All adult patients (at least 18 years of age) who require fluid resuscitation for hypotension and/or organ hypo-perfusion and fulfill the criteria for severe sepsis or septic shock will be included. The definition of severe sepsis includes a suspected source of infection, meeting 2 of 4 systemic inflammatory response syndrome (SIRS) criteria and at least one organ failure (Sepsis-related Organ Failure Assessment score >2 in organ in question – see Appendix Table 2). SIRS criteria include: temperature >38oC or <36oC, heart rate >90 bpm, respiratory rate >20 or pCO2 <32 mmHg, white blood cell count >12,000/uL, <4,000/uL or >10% band forms.

***Exclusion criteria***

Patients are excluded if they:

* have received >5L of resuscitative fluid in the 24 hours prior to randomization (to limit contamination)
* have had an intracranial bleed or intracranial hypertension during this hospital admission
* have an acute burn injury (>10% body surface area)
* are not expected to survive >72 hours from the time of study eligibility, or if they have a palliative care plan already in place
* were previously enrolled in the FISSH study or a confounding trial

***Informed Consent***

Given the emergency nature of the intervention, the fact that most patients will not able to consent for themselves at the time of study entry, and that both the trial intervention and control are both currently considered the standard of care, we will use a deferred consent model. Patients will be enrolled in the study and consent will be obtained from the SDM or the patient themselves, or both, in a timely manner. Precedent exists for using a deferred consent model in another study examining the use of emergency resuscitative fluids in Canadian centres in which a few members of our trial’s steering committee were involved [[85](#_ENREF_85)].

***Allocation & Randomization***

Once the research coordinator has identified an eligible patient, s/he will log into our centralized data centre. Once connected, computerized prompts will be given for preliminary identifying data. If eligibility criteria are confirmed the patient will be randomly allocated in a 1:1 schedule to either the lower chloride fluids group or the higher chloride fluids group.

Allocation will be concealed so the research coordinator will be provided with identifying letters/numbers found on the bags of intravenous fluid in the ICU. Randomization will use undisclosed variable blocks sizes and stratified based on study centre and presence of CKD (AKIN stage 3 or higher).

***Experimental & Control*** ***Interventions***

The allocated fluid will be administered immediately. The allocated fluid type is to be used throughout the ICU stay or up until 30 days after enrolment (hereafter referred to as in the ICU), or whichever comes first. The allocated fluid type will be used for both resuscitation and maintenance. Blood products and fluids used for medication infusions are exempt due to drug-fluid compatibility issues.

After 30 days in ICU or upon discharge from the ICU, open-label fluid may be used at the discretion of the treating physician. While in the ICU, the treating physician will be able to decide on the type of fluid, as in usual practice (albumin or crystalloid) to be infused as clinically indicated, but will be blinded to the chloride status. Given that most fluids administered to patients with septic shock within the first few hours, are crystalloids, infusion bags of study crystalloid fluids will be readily available in relevant patient care areas. We plan to have pre-prepared carts of study crystalloid available in participating ICUs. Once a patient is randomized, the cart containing crystalloids consistent with their allocated group will be brought into the patient’s room or left just outside to facilitate the bedside nurse’s easy administration (especially in an emergency situation).

If the physician prescribes albumin, this request will be processed and the fluid distributed from the hospital blood bank as per usual in all study centers. The blood bank at each center will be provided with a list of enrolled patients and their allocation, allowing for the distribution of the proper solution for each patient. This list will be updated each time a new patient is enrolled. The albumin solution, blinded in appearance to chloride content, will then be supplied to the patient care area for infusion. We have confirmed collaboration with CSL Boehring (hopefully will have letter of support attached) as they manufacture a low chloride albumin solution which previously has gained Health Canada approval for patient use and is available at most Ontario hospitals. Grifols Canada distributes a higher chloride albumin which is already predominantly used at Hamilton hospitals and will be used in patients randomized to our higher chloride arm.

***Open Label Fluids***

Patients will not be permitted to receive open label crystalloid or albumin products in the ICU except for the following situations:

* Patients will be permitted to receive open label Dextrose (10% in water only) run at a maximum rate of 50ml/hr and only for documented hypoglycaemia (serum or capillary blood glucose level <4mmol/L)
* Patients with a serum sodium level >150mmol/L
* Patients with a pH <7.10 and a serum chloride level >115mmol/L

If any of these conditions are met then the study fluid may be held and open label fluid may be administered at the discretion of the treating physician, for a period of 24 hours.

After the 24 hours, as long as the patient is no longer meeting the criteria above, the allocated fluid type (as per protocol above) will restart. If the patient still meets the holding criteria after 24 hours, another 24 hours of open label fluids would be permitted. This would continue until the criteria are no longer met, at which point the study fluid would resume.

Protocol violations and open-label fluid use for the indications mentioned above will be closely documented with reasons for non-adherence. Adjudication will be used in situations where uncertainty exists regarding qualification of protocol violations. We are sufficiently concerned about compliance that protocol adherence is one of our main feasibility objectives.

All other aspects of patient care, other than fluid chloride content, will be left at the discretion of the treating physician. Study fluids are only to be administered in the ICU, not on the ward or step-down units. If a study patient is discharged from ICU and re-admitted within the 30-day intervention period then they will receive all fluids based on their allocated group while in the ICU until they reach 30 days from the original randomization date or until they are again discharged from the unit. Patients transferred to another hospital’s ICU will stop receiving the study fluid, unless the new ICU is also an active trial center. If a patient is transferred to another trial participating center, the Methods Center will be informed and the new center will be provided with serial numbers corresponding with fluids to be used at the new center. In either case, patients transferred to another hospital’s ICU will be included in the final analysis.

***Blinding***

Patients, nurses, allied health providers, and physicians will be blinded to study allocation. All study fluids, whether containing a lower or higher chloride concentration will be identical in appearance, consistency and packaging except for the identifying serial number found on the individual label.

Individual center pharmacists and blood bank employees will need to help ensure patients receive their allocated fluid type and thus, will not be blinded. While central hospital pharmacists will not be blinded, ICU pharmacists will be. Importantly, although crystalloid solutions will look different from albumin, this is not the comparison of interest for this trial. Throughout this trial, clinicians and patients will be blinded to chloride content (the randomization variable), which does not alter the appearance of fluids.

If ongoing concerns persist in that clinicians are able to identify allocated fluids based on appearance, then opaque intravenous bags and tubing will be used rather than the traditional transparent type as was used successfully in the SAFE Trial [[16](#_ENREF_16)]. At periodic intervals, the fluid labeling process will be audited by the Methods Center to confirm its accuracy and to ensure that blinding is maintained. This will be part of a quality control sub-study that will be nested within the pilot trial. Bedside physicians and other clinical members of the ICU team will be intermittently surveyed at each study center regarding the effectiveness of blinding and to assess their certainty regarding individual patient allocation. This information will be useful to better understand whether blinding, and the resources required to ensure it’s done properly, are worth the investment for the larger RCT.

It is possible that clinicians involved in the FISSH study may be able to surmise allocated group after a few days of study intervention based on readily available bloodwork values (eg. sodium or chloride levels). Despite this, the benefits of blinding in this study outweigh the added complexity and costs that will be encountered. Blinding will limit the potential for bias and co-interventions in the initial time period and for some patients with more ambiguous lab values potentially throughout the study period.

We will also ensure blinding of research assistants, site investigators, data collectors, outcome adjudicators, and data analysts. An emergency phone number to the 24-hour Methods Center, will be available at all centers should emergent unblinding be required. Emergent unblinding will only be allowed if the treating physician is sure that the results will change the clinical management of the patient.

***Outcomes***

***Pilot Study Primary Feasibility Outcomes***

Our primary outcome for the FISSH Pilot Trial is feasibility, judged by 3 outcomes of consent rate, recruitment parameters and protocol adherence.

*Consent Rate* – A successful consent rate will be defined as greater than 75% of SDMs or patients when approached for consent choose to participate or continue in the study. This will be calculated as the overall proportion of consented patients of those SDMs or patients approached. Given our plan for deferred consent, there will be some lag time between study enrolment and consent. If a patient or SDM chooses to withdraw from the study but allows for the data that had been collected up until that point to be used for analysis, they will still be counted as not providing consent. Reasons for withdrawal will be recorded. The consent rate will be reviewed weekly by the study steering committee, and if necessary, barriers will be discussed and interventions undertaken mid-study in order to improve the consent process. This outcome is crucial for assessing the acceptability of the study to patients and their family members.

*Recruitment* – Successful recruitment will be defined as achieving enrolment of 50 patients over the 12 months study period. This works out to approximately 3 patients/center every 2 months. Once the pilot trial begins, the screening logs will be reviewed at all 3 study centers by the study steering committee on a monthly basis. We will record exclusions and reasons for physician refusals. Excluded patients and eligible non-randomized patients will be reviewed to determine whether any modifications to the protocol might be warranted, or to address implementation challenges. Barriers to enrolment will be discussed, and if necessary, strategies to improve enrolment will be operationalized. This metric will be crucial in deciding on feasibility for a larger RCT.

*Protocol Adherence* – Successful adherence will be defined as patients receiving at least 75% study fluid of all intravenous fluid that is administered in the ICU excluding blood products and medication infusions. Understanding this may be a significant barrier in this pilot trial, strategies will be employed *a priori* in order to facilitate compliance. As described above, crystalloid study carts will be prepared, stocked regularly and left in a convenient location for nurses and physicians. These will be designed in a very user-friendly manner with input from bedside clinical staff regarding issues such as location. Albumin distribution is controlled from the hospital blood bank so we hope there is less opportunity for non-adherence. Pre-study education sessions and routine clinical reminders (including posters, bedside clinical cards and indicators for patient’s charts) will be supplied to help improve study compliance. Research Co-ordinators will document all the fluid that study patients receive including protocol violations. Reasons for violation will be documented, if available, in order to distinguish deviations for clinical reasons from true protocol violations. Protocol adherence will be evaluated on a monthly basis by the steering committee. If necessary, further behavioural strategies will be employed to improve adherence.

***Pilot Study Secondary Clinical Outcomes***

In the main FISSH trial, we will aim to determine whether the use of lower chloride compared to higher chloride fluids in septic ICU patients has any impact on patient-important outcomes. These outcomes will be captured in this pilot study but we will not have a sufficient number of patients to make conclusions related to them. Outcomes for the full trial will include:

* Hospital mortality
* RRT use during 90-day period post randomization (including peritoneal dialysis, continuous renal replacement therapy or conventional hemodialysis or ultrafiltration)
* 30-day mortality
* ICU length of stay (censored at 90 days)
* Hospital length of stay (censored at 90 days)
* Ventilator-free days in the first 90 days post randomization
* Safety outcomes:
  + The development of acidosis (any pH <7.10 in the ICU post-randomization)
  + Hyperkalemia (any K > 5.5 in the ICU post-randomization)

***Pilot Study Adjudication & Subgroups***

An adjudication committee will be formed for this pilot trial including ICU clinicians. The primary role of this committee will be to adjudicate situations in which uncertainty exists regarding protocol violations (our primary feasibility outcome). These situations will be identified by the steering committee or the individual site research co-ordinators. Clinical charts will be reviewed in order to better clarify whether violations occurred.

No subgroup analysis is planned for the feasibility pilot trial. An *a priori* subgroup assessment will be done for all outcomes of the larger trial, comparing patients without baseline renal dysfunction to those with documented pre-existing chronic renal failure (AKIN CKD stage 3 or higher).

***Pilot Study Data Collection***

Data collection will be done by trained staff at each study centre (usually the research coordinator or delegate). Paper case report forms (CRFs) will be completed and then transcribed into web-based e-CRFs (REDCap – <http://www.project-redcap.org>) which are encrypted and password-protected. All CRFs will be pre-tested and sufficiently edited for clarity and ease-of-use prior to the study initiation. The online database we plan to use fully complies with FDA and Health Canada rules for electronic data management. Initially collected data will include eligibility criteria, baseline demographic data, admitting diagnosis and APACHE II admission prognosis score (see appendix 3 for details). No data that could lead to study patient identification will be entered. While in the ICU, daily data collection will include parameters around organ dysfunction, ventilator requirements, hemodynamics, all fluid administered (including study, non-study and blood products), use of renal replacement therapy, and daily relevant bloodwork values (see appendix 4 for daily data collection CRF). Co-interventions will also be captured including but not limited to bicarbonate requirements, vasopressor/inotrope use, corticosteroid use, and diuretic use. Vital status will also be documented when relevant during the 90-day followup period (discharge, readmission, death).

The web-based CRF will allow for data validation, consistency checks and frequent audits of entered data to ensure they are complete and accurate. The paper CRFs will always be available as backup or to check potential errors against. The centralized data center will be responsible for managing the database and quality assurance using anomaly searches and logic checks. Real-time data entry will ensure missing data is identified quickly and issues are resolved in a timely manner. Inquiries will be made to study centres that are slow to enter data or enter inconsistent data with helpful remediation recommendations offered. records and CRFs will be kept for the duration as required by local regulatory bodies.

A screening log will be maintained at each study center to record both eligible and ineligible patients with reasons for exclusion clearly documented. Ineligible patients or eligible patients who are not enrolled will have absolutely no personal information entered, as they will not be approached for consent. The screening log will also be transcribed to the e-CRF on a daily basis to ensure it is consistent with the information at the centralized data center.

***Statistical Analysis***

***FISSH Pilot Sample Size***

Sample size for the pilot was calculated using a 95% confidence interval approach examining protocol adherence. Protocol adherence is defined as the percent of total volume as prescribed by the treating clinician that corresponds to the allocated fluid type (excluding allowed open label fluid use and medication infusions as described above). The lower bound for the confidence interval was set at the threshold for feasibility (75%) and an expected adherence rate (95%) was chosen based on previously published RCTs examining fluid use in the ICU [[12](#_ENREF_12), [13](#_ENREF_13), [27](#_ENREF_27)]. Using a power of 80%, the required sample size is at least 47 patients. To be conservative we will plan for 50 patients (approximately 25 per study arm). Similar calculations could be performed for the outcome of consent rate using a feasibility threshold of 75% and an expected consent rate of 95% leading to an identical sample size number. This number of patients will allow us to assess the 3 feasibility objectives according to our *a priori* feasibility outcomes in a cost-effective manner.

***FISSH Pilot Study Analysis***

Calculation of the 3 feasibility outcomes for the FISSH trial are noted in the outcomes section above. No interim analysis are planned for the pilot study due to the short duration.

***Full FISSH Study Analysis***

All analysis will be conducted based on intention-to-treat basis by a blinded statistician team. The baseline characteristics comparing balanced fluid and unbalanced fluid groups will be reported using means (and standard deviations), medians (and inter-quartile ranges) or proportions as indicated. Comparison of baseline characteristics will be done using chi-squared or Fisher’s exact test for proportions or unpaired t-tests for means.

Dichotomous outcomes will be reported using odds ratio and 95% confidence intervals and calculated using logistic regression. Non-parametric testing, the Mantzel-Cox log rank test, will be used for the continuous outcomes of ICU length of stay, hospital length of stay and ventilator-free days given when the data is not normally distributed. These continuous variables will be sanctioned (or censored) at 90 days. An independent t-test will be used to compare the means of the safety outcomes (serum K, serum pH) between the 2 groups and mean difference with 95% confidence intervals and p-values will be reported. A p-value of <0.05 will be considered statistically significant for all outcomes.

***Pilot Study Data & Safety Monitoring***

An independent data safety and monitoring board (DSMB) will be formed for this pilot trial. It will be composed of clinical experts in the field and a statistician, all of whom are not involved with this study in any way. Although no interim analysis is planned, the DSMB will be responsible for reviewing any identified severe adverse events (SAEs). Ideally the same DSMB would carry over to the larger FISSH trial.

***Pilot Study Trial Administration***

The principle investigator for this trial is Dr. Bram Rochwerg. A steering committee (SC) will be formed including senior and experienced ICU trialists, the study co-ordinator, the head biostatistician, a nursing representative, the lead data manager from the centralized data center and other local and international experts in ICU research methodology and fluid resuscitation. Dr. Deborah Cook, Dr. Maureen Meade, Dr. Gordon Guyatt and Dr. Francois Lamontagne have committed to being part of the SC. Dr. Cook and Dr. Meade are internationally recognized as ICU trialists and both have led several large multinational CIHR funded studies. Dr. Cook has also provided mentorship for 2 other trials of fluid resuscitation [[33](#_ENREF_33), [85](#_ENREF_85)] amongst many others. Dr. Gordon Guyatt is an internationally acclaimed methodologist with extensive RCT expertise. Dr. Francois Lamontagne is an early-career clinician-investigator with experience running pilot RCTs in the area of resuscitative medicine.

Bimonthly meetings of the steering committee will occur either in person or via teleconference. The steering committee will be responsible for monitoring study recruitment and targets, monitoring issues with data collection and missing data, and making decisions on new center recruitment in the larger trial. Dr. Rochwerg will meet with the study co-ordinator weekly, and will be responsible for overall start-up and study management.

Local principle investigators (PIs) will be identified at each center and they will be responsible for all local procedures in conjunction with Dr. Rochwerg. This includes local REB approval, hospital approval, ensuring pharmacy and blood bank cooperation and ensuring all parties are properly trained. The steering committee and central Methods Center staff will closely support local PIs. At the time of center initiation all relevant paperwork and standard operating procedures (SOPs) will be supplied to the local PI. Dr. Rochwerg and the study co-ordinator will provide on-site training sessions for the local PIs and study co-ordinators in terms of study protocols and data collection procedures. Educational material will be offerred to the local PI and research staff to facilitate education of other clinicians at participating hospitals.

Quarterly research meetings with all research staff from all centers will be planned with relevant study updates, recruitment numbers and motivational messages. Dr. Rochwerg, or a steering committee delegate, will be available 24 hours a day, 7 days a week if a specific center has problems or questions. The FISSH pilot trial will be registered on clinicaltrials.gov.

***Pilot Trial Feasibility & Funding***

Dr. Rochwerg has been involved as the junior co-principle investigator for a multi-center observational study that examined the use of bioelectric impedance to assess volume status in the ICU (submitted for publication). In addition to this prospective research, he has led systematic reviews and meta-analyses, some of which examined the role of fluids in resuscitation (see Appendix). He is a research fellow, practicing intensive care clinician and has significant protected research time to dedicate to completing this trial. He has completed a Master’s degree in Health Research Methodology at McMaster University with a focus on RCTs, meta-analyses and clinical practice guideline methodology.

Also, the co-investigators, who will be part of the steering committee, include very established ICU trialists with extensive experience conducting pilot RCTs of this type[[33](#_ENREF_33), [85-87](#_ENREF_85)]. They will act as mentors and provide guidance to the principle investigator throughout the trial lead-in and study period.

The centers which we plan to recruit to participate in FISSH have all previously participated in trials administered by members of the steering committee and have established research infrastructure and teams. Our centralized data center has collaborated on many similar ICU trials including ones studying resuscitative fluids in septic patients. We have extensive experience using REDCaps e-CRFs and will work with our statisticians and data analysts in developing and pre-testing e-CRFs specific to this study.

***Ethical Considerations***

The trial will adhere to the Helsinki Declaration and all local and national laws for each participating centre. Center enrolment will only begin after approval by each local REB. The vast majority of patients will be unable to provide consent at the time of enrolment. Patients will be enrolled using deferred consent; however, patients will only be continued in the trial if they or a suitable SDM provides consent in a timely manner. If consent is not obtained then the patient will be removed from the trial, although data will be retained up until this point. Given that most patients will be unconscious at the time of enrolment they represent a potentially vulnerable population. This trial could not be performed in conscious patients and excluding these patients from studies would have a deleterious effect on our ability to treat this condition at a population level.

***Knowledge Translation***

The knowledge translation (KT) plan for the FISSH trial includes both integrated and end-of-grant KT. From an integrated KT standpoint, multi-disciplinary groups at all participating centers (physicians, pharmacists, nurses, etc) will be engaged through email and presentation of research rounds on the importance of this topic and the details of the study planned. A structured abstract and information poster will be circulated to all participating centers for distribution and posting throughout their center. Practicing clinicians at participating centers will be surveyed prior to study initiation to better assess current state of knowledge regarding chloride content of resuscitation fluids and prescribing practices. Clinician focus groups will be planned to understand motivators for using certain fluids as opposed to others.

In terms of end-of-grant KT, the steering committee will be responsible for the production of a manuscript summarizing the results and we will disseminate this via a high impact peer-reviewed scientific journal. If deemed feasible, the pilot trial will inform a large-scale RCT designed to inform clinical practice. FISSH investigators will present the results at relevant ICU, anaesthesia, emergency, surgical and medical rounds and conferences. Social media is quickly gaining traction as a vehicle for knowledge translation and we will use avenues such as twitter ([www.twitter.com](http://www.twitter.com)) and online medical education blogs in order to increase uptake of the results.

**METHODOLOGICAL ISSUES AND THESIS CONCLUSIONS**

Manuscript #1

Clinicians often overlook the chemical composition of intravenous fluids. The properties of these fluids, including electrolyte concentration, pH and the presence or absence of a buffer may have significant effects on the clinical course of patients in whom they are administered. In this manuscript we have provided a detailed description of the composition of all fluids used in RCTs that examined the resuscitation of patients with sepsis. This first step was necessary to help organize the analysis for our systematic review and we are hopeful that the information will be useful for bedside clinicians as well.

There were some methodological challenges encountered while performing this systematic review and summary. The sheer number of titles and abstracts that required review (n = 9875) necessitated multiple reviewers. The review was done in two stages, first titles and abstracts, then PDF review, with each step performed in duplicate. Three pairs of reviewers performed the screening with very good agreement between reviewers (pair #1 kappa = 0.81 95% CI 0.74-0.88, pair #2 kappa = 0.90 95% CI 0.84-0.96, pair #3 kappa = 0.91 95% CI 0.81-0.97).

Many of the studies identified for inclusion lacked integral information regarding composition of the fluids used. To overcome this limitation we emailed study authors, fluid experts and reviewed industry websites and product monographs. Ultimately, we were able to locate most necessary summary data. Although the data presented in this manuscript are potentially useful, it remains unclear the importance of these fluid features on the clinical course of septic patients. This assessment is further complicated by the fact that most fluid types have never been compared in head-to-head trials.

Manuscript #2

The chemical features of different resuscitative fluids were summarized in manuscript #1 however uncertainty persists in regards to the effect of these components on patient-important outcomes. Balanced fluids, or those containing a physiologic chloride concentration more closely resembling that of plasma, have been hypothesized to be beneficial compared to unbalanced fluids however this has never been tested in prospective RCTs.

Direct comparison and traditional meta-analytic techniques are limited in this situation by multiple potential comparisons and the lack of head-to-head trials. We decided to use a network meta-analysis approach which includes both direct and indirect evidence. For example, let’s say we are hoping to look at the effect of treatment A compared to treatment C and these interventions had never been compared directly in previous trials but both had been studied against a common comparator called treatment B. Treatment effects for the A vs C comparison can be generated via indirect evidence from A vs B and B vs C. Even in situations where direct evidence is available, indirect evidence can be added potentially improving the confidence in our point estimate (assuming coherence).

Manuscript #2 focused on different IV fluids used for resuscitation in sepsis, specifically in terms of the effect on mortality. After including all available evidence (direct and indirect), some conclusions emerged. Starches were found to be harmful compared to albumin and crystalloid solutions. This observation is consistent with previous reviews and has led to black-box warnings against using starch-based fluids in patients with sepsis. Interestingly, a signal showing the potential benefit of balanced crystalloid compared to unbalanced crystalloid however the confidence interval failed to exclude the possibility of no effect (OR 0.78, 95% CI 0.58-1.05). This point is one of significant interest and deserves further investigation by way of prospective clinical trials of direct comparison.

Manuscript #2 also had significant methodological issues. Having included many different clinically relevant interventions and comparisons with a relatively small number of trials (n=14), many point estimates had wide confidence intervals. We used the GRADE approach to assess the quality of evidence for direct evidence, indirect evidence and the resulting combined network evidence. GRADE application to NMA quality of evidence is a very new concept and the methodology is in its infancy. We worked with members of the GRADE working group in order to properly apply the new approach and provided a detailed summary in the appendix for those interested in the detailed analysis.

Manuscript #3

This manuscript is very similar to Manuscript #2 but instead focuses on the outcome “use of renal replacement therapy”. Again both direct and indirect evidence were incorporated in order to best estimate the effect of different fluid interventions when compared to each other in ICU patients with sepsis. Similar to Manuscript #2, starches were found to be harmful when compared with albumin or crystalloid containing solutions. This is also consistent with previous reviews.

Although the point estimate and confidence interval did not rule out a beneficial effect of balanced crystalloid when compared to unbalanced crystalloid the confidence intervals were sufficiently wide (OR 0.85, 95% CI 0.56-1.30). Overall, the quality of evidence for this outcome was lower as a reflection of fewer primary publications which reported on RRT use and subsequently less available evidence to guide estimates of effect.

In addition to the lower quality of evidence, another methodological issue encountered in this manuscript related to the outcome. Use of RRT is a subjective decision made by clinicians based on a myriad of clinical parameters and influenced by institutional practice and personal experience. Many of the included studies did not pre-specify indicators for RRT initiation and the decision was left to individual clinicians. Obviously this could lead to a potential for bias. Again for this manuscript we used the GRADE approach to assess the NMA quality of evidence and a detailed description of the process was included in the appendix.

FISSH Pilot Protocol

Having performed the aforementioned systematic review, having summarized the composition of currently available resuscitative fluids and having assessed the current state of knowledge via network meta-analysis including direct and indirect evidence we are left with some important unresolved clinical questions. The most pressing one, as assessed by our research team, pertains to the potential effect of chloride concentration of resuscitation fluids on patients with sepsis. Although our review illustrates that the use of balanced solutions may lead to improved survival and less use of RRT, no direct head-to-head RCT has been done in any patient population other than the perioperative setting.

Understanding this, we have presented here a protocol for a pilot RCT addressing this question, specifically in patients with sepsis or septic shock. The pilot is planned as a first step to demonstrate feasibility with the hopes of a larger, more definitive RCT in the future. This pilot proposal will be submitted for peer-reviewed funding in the spring of 2015.

We have had to address significant methodological issues in regards to producing this protocol. Some of these are presented here:

1. Feasibility Design – we have chosen a primary outcome of feasibility for this pilot study. Feasibility will be assessed through the three outcomes of recruitment rate, protocol adherence and consent rate. Given that balanced and unbalanced fluids have never been compared to one another in the ICU setting we felt it important to prove feasibility before moving on to a large scale RCT. Also, given the current funding climate in Canada, we felt we would have a much better chance getting funded initially for a feasibility pilot and then using this data to help in applying for the larger study.
2. Protocol Adherence – some ICU physicians have long-held beliefs of what fluids are best for resuscitation, and despite the pragmatic design of this study protocol, violations are a significant concern. We will closely monitor all fluids that study patients receive in order to document when violations occur. Prior to initiating our study at a specific site we will discuss the project with the attending physicians to ensure equipoise exists. We are planning for in-grant knowledge translation to educate practitioners and ensure study compliance and understanding. We will ensure study fluids are readily available, easy accessible and that study protocols are not onerous to help ensure they are closely followed. Specific safety criteria are built into the protocol that allow for open label fluid administration for a 24-hour period if triggered by biochemical criteria.
3. Knowledge Translation – it will obviously be very important to disseminate the results of the larger study (if feasible) to practitioners worldwide. We plan for a comprehensive approach including both in-grant and end-of-grant KT strategies. Uniquely from an end-of-grant KT perspective we plan to capitalize on social media and disseminate our message via twitter ([www.twitter.com](http://www.twitter.com)) and other similar platforms. This would be in addition to more traditional avenues including manuscript publication in a high-impact journal and presentation at relevant international conferences.

Final Conclusions

This objective of this thesis was to better understand the role of different resuscitative fluids in sepsis. Our approach was comprehensive and started with summarizing the current state of knowledge utilizing unique statistical methods which incorporated both direct and indirect evidence. The results from this analysis led us to an interesting research question concerning the role of balanced versus unbalanced fluids and their effect on patient-important outcomes such as mortality and acute kidney injury. Herein, we propose a pilot study that will investigate the feasibility of a larger RCT attempting to address this important clinical question.

**REFERENCES**

**1. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R *et al*: Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical care medicine* 2013, 41(2):580-637.**

**2. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL: Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Critical care medicine* 2007, 35(5):1244-1250.**

**3. Salomao R, Brunialti MK, Rapozo MM, Baggio-Zappia GL, Galanos C, Freudenberg M: Bacterial sensing, cell signaling, and modulation of the immune response during sepsis. *Shock (Augusta, Ga)* 2012, 38(3):227-242.**

**4. King EG, Bauza GJ, Mella JR, Remick DG: Pathophysiologic mechanisms in septic shock. *Laboratory investigation; a journal of technical methods and pathology* 2014, 94(1):4-12.**

**5. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *The New England journal of medicine* 2001, 345(19):1368-1377.**

**6. Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, Higgins AM, Holdgate A, Howe BD, Webb SA *et al*: Goal-directed resuscitation for patients with early septic shock. *The New England journal of medicine* 2014, 371(16):1496-1506.**

**7. Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F *et al*: A randomized trial of protocol-based care for early septic shock. *The New England journal of medicine* 2014, 370(18):1683-1693.**

**8. Rochwerg B, Wludarczyk A, Szczeklik W, Alhazzani W, Sindi A, Alshamsi F, Ip WC, Wang M, Altayyar S, Li G *et al*: Fluid resuscitation in severe sepsis and septic shock: systematic description of fluids used in randomized trials. *Polskie Archiwum Medycyny Wewnetrznej* 2013, 123(11):603-608.**

**9. Bellomo R, Naka T, Baldwin I: Intravenous fluids and acid-base balance. *Contributions to nephrology* 2004, 144:105-118.**

**10. Perel P, Roberts I, Ker K: Colloids versus crystalloids for fluid resuscitation in critically ill patients. *The Cochrane database of systematic reviews* 2013, 2:CD000567.**

**11. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S *et al*: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *The New England journal of medicine* 2008, 358(2):125-139.**

**12. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C *et al*: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *The New England journal of medicine* 2012, 367(20):1901-1911.**

**13. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, Madsen KR, Moller MH, Elkjaer JM, Poulsen LM *et al*: Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *The New England journal of medicine* 2012, 367(2):124-134.**

**14. Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M, Wetterslev J: Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. *Bmj* 2013, 346:f839.**

**15. FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings. In*.* Edited by Administration UFaD. Online; 2013.**

**16. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *The New England journal of medicine* 2004, 350(22):2247-2256.**

**17. 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. *Critical care medicine* 2011, 39(2):386-391.**

**18. Lobo DN: Intravenous 0.9% saline and general surgical patients: a problem, not a solution. *Annals of surgery* 2012, 255(5):830-832.**

**19. Morgan TJ: The ideal crystalloid - what is 'balanced'? *Current opinion in critical care* 2013, 19(4):299-307.**

**20. Gunnerson KJ, Saul M, He S, Kellum JA: Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. *Critical care (London, England)* 2006, 10(1):R22.**

**21. Raghunathan K, Shaw A, Nathanson B, Sturmer T, Brookhart A, Stefan MS, Setoguchi S, Beadles C, Lindenauer PK: Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis\*. *Critical care medicine* 2014, 42(7):1585-1591.**

**22. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M: Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA : the journal of the American Medical Association* 2012, 308(15):1566-1572.**

**23. Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR: Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. *Anesthesia and analgesia* 2001, 93(4):817-822.**

**24. O'Malley CM, Frumento RJ, Hardy MA, Benvenisty AI, Brentjens TE, Mercer JS, Bennett-Guerrero E: A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. *Anesthesia and analgesia* 2005, 100(5):1518-1524, table of contents.**

**25. Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, Mbuagbaw L, Szczeklik W, Alshamsi F, Altayyar S *et al*: Fluid Resuscitation in Sepsis: A Systematic Review and Network Meta-analysis. *Annals of internal medicine* 2014, 161(5):347-355.**

**26. Brignardello-Petersen R, Rochwerg B, Guyatt GH: What is a network meta-analysis and how can we use it to inform clinical practice? *Polskie Archiwum Medycyny Wewnetrznej* 2014, 124(12):659-660.**

**27. Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declere AD, Preiser JC, Outin H, Troche G, Charpentier C *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 : the journal of the American Medical Association* 2013.**

**28. Dubin A, Pozo MO, Casabella CA, Murias G, Palizas F, Jr., Moseinco MC, Kanoore Edul VS, Palizas F, Estenssoro E, Ince C: Comparison of 6% hydroxyethyl starch 130/0.4 and saline solution for resuscitation of the microcirculation during the early goal-directed therapy of septic patients. *Journal of critical care* 2010, 25(4):659 e651-658.**

**29. Guidet B, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, Forceville X, Feissel M, Hasselmann M, Heininger A *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. *Critical care (London, England)* 2012, 16(3):R94.**

**30. Haupt MT, Rackow EC: Colloid osmotic pressure and fluid resuscitation with hetastarch, albumin, and saline solutions. *Critical care medicine* 1982, 10(3):159-162.**

**31. Li F, Sun H, Han XD: [The effect of different fluids on early fluid resuscitation in septic shock]. *Zhongguo wei zhong bing ji jiu yi xue = Chinese critical care medicine = Zhongguo weizhongbing jijiuyixue* 2008, 20(8):472-475.**

**32. Lv J, Zhao HY, Liu F, An YZ: [The influence of lactate Ringer solution versus hydroxyethyl starch on coagulation and fibrinolytic system in patients with septic shock]. *Zhongguo wei zhong bing ji jiu yi xue = Chinese critical care medicine = Zhongguo weizhongbing jijiuyixue* 2012, 24(1):38-41.**

**33. McIntyre LA, Fergusson D, Cook DJ, Rankin N, Dhingra V, Granton J, Magder S, Stiell I, Taljaard M, Hebert PC: Fluid resuscitation in the management of early septic shock (FINESS): a randomized controlled feasibility trial. *Canadian journal of anaesthesia = Journal canadien d'anesthesie* 2008, 55(12):819-826.**

**34. Rackow EC, Mecher C, Astiz ME, Griffel M, Falk JL, Weil MH: Effects of pentastarch and albumin infusion on cardiorespiratory function and coagulation in patients with severe sepsis and systemic hypoperfusion. *Critical care medicine* 1989, 17(5):394-398.**

**35. Schortgen F, Lacherade J-C, Bruneel F, Cattaneo I, Hemery F, Lemaire F, Brochard L: Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study. *The Lancet* 2001, 357(9260):911-916.**

**36. Siegemund M: Basel Study for Evaluation of Starch (130;0.4) Infusion in Septic Patients: BaSES (130;0.4) Trial. In*.*; 2011.**

**37. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Bmj* 2008, 336(7650):924-926.**

**38. Rochwerg B, Alhazzani W, Gibson A, Ribic CM, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, Mbuagbaw L, Szczeklik W *et al*: Fluid type and the use of renal replacement therapy in sepsis: a systematic review and network meta-analysis. *Intensive care medicine* 2015.**

**39. Kadri SS, Danner RL: ACP Journal Club: review: in sepsis, the effect of resuscitation with crystalloid and colloid fluids on mortality varies. *Annals of internal medicine* 2014, 161(10):JC12.**

**40. Dellinger RP: Crystalloids for fluid resuscitation in sepsis: where is the balance? *Annals of internal medicine* 2014, 161(5):372-373.**

**41. Guidet B, Soni N, Della Rocca G, Kozek S, Vallet B, Annane D, James M: A balanced view of balanced solutions. *Critical care (London, England)* 2010, 14(5):325.**

**42. Myburgh J: Advances in fluid resuscitation in critically ill patients: implications for clinical practice. *Current opinion in critical care* 2013, 19(4):279-281.**

**43. Myburgh JA, Mythen MG: Resuscitation fluids. *The New England journal of medicine* 2013, 369(13):1243-1251.**

**44. Seymour CW, Angus DC: Making a Pragmatic Choice for Fluid Resuscitation in Critically Ill Patients. *JAMA : the journal of the American Medical Association* 2013.**

**45. Bunn F, Trivedi D: Colloid solutions for fluid resuscitation. *The Cochrane database of systematic reviews* 2012, 7:CD001319.**

**46. Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, Fergusson DA: 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 : the journal of the American Medical Association* 2013, 309(7):678-688.**

**47. Brignardello-Petersen R, Guyatt GH: beta-Blockers in heart failure--are all created equal? *Polskie Archiwum Medycyny Wewnetrznej* 2013, 123(5):204-205.**

**48. Akech SO, Karisa J, Nakamya P, Boga M, Maitland K: Phase II trial of isotonic fluid resuscitation in Kenyan children with severe malnutrition and hypovolaemia. *BMC pediatrics* 2010, 10:71.**

**49. Chopra A, Kumar V, Dutta A: Hypertonic versus normal saline as initial fluid bolus in pediatric septic shock. *Indian journal of pediatrics* 2011, 78(7):833-837.**

**50. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, Nyeko R, Mtove G, Reyburn H, Lang T *et al*: Mortality after fluid bolus in African children with severe infection. *The New England journal of medicine* 2011, 364(26):2483-2495.**

**51. Maitland K, Pamba A, English M, Peshu N, Levin M, Marsh K, Newton CR: Pre-transfusion management of children with severe malarial anaemia: a randomised controlled trial of intravascular volume expansion. *British journal of haematology* 2005, 128(3):393-400.**

**52. Maitland K, Pamba A, English M, Peshu N, Marsh K, Newton C, Levin M: Randomized trial of volume expansion with albumin or saline in children with severe malaria: preliminary evidence of albumin benefit. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2005, 40(4):538-545.**

**53. Wills BA, Nguyen MD, Ha TL, Dong TH, Tran TN, Le TT, Tran VD, Nguyen TH, Nguyen VC, Stepniewska K *et al*: Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *The New England journal of medicine* 2005, 353(9):877-889.**

**54. Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S, Committee CM: Fluid resuscitation with 6% hydroxyethyl starch (130/0.4) in acutely ill patients: an updated systematic review and meta-analysis. *Anesthesia and analgesia* 2012, 114(1):159-169.**

**55. Wilkes MM, Navickis RJ: Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. *Annals of internal medicine* 2001, 135(3):149-164.**

**56. Bellomo R, Prowle JR, Echeverri JE, Ligabo V, Ronco C: Fluid management in septic acute kidney injury and cardiorenal syndromes. *Contributions to nephrology* 2010, 165:206-218.**

**57. Haase N, Perner A: Hydroxyethyl starch for resuscitation. *Current opinion in critical care* 2013, 19(4):321-325.**

**58. Administration UFaD: FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings. In*.*** <http://www.fda.gov/biologicsbloodvaccines/safetyavailability/ucm358271.htm;> **2013.**

**59. Jiwaji Z, Brady S, McIntyre LA, Gray A, Walsh TS: Emergency department management of early sepsis: a national survey of emergency medicine and intensive care consultants. *Emergency medicine journal : EMJ* 2013.**

**60. Jones D, McEvoy S, Merz TM, Higgins A, Bellomo R, Cooper JD, Hollis S, McArthur C, Myburgh JA, Taylor C *et al*: International albumin use: 1995 to 2006. *Anaesthesia and intensive care* 2010, 38(2):266-273.**

**61. Bansal M, Farrugia A, Balboni S, Martin G: Relative Survival Benefit and Morbidity with Fluids in Severe Sepsis-A Network Meta-Analysis of Alternative Therapies. *Current drug safety* 2013.**

**62. Miller DR: Update to readers and authors on ethical and scientific misconduct: retraction of the "Boldt articles". *Canadian journal of anaesthesia = Journal canadien d'anesthesie* 2011, 58(9):777-779, 779-781.**

**63. Reilly C: Retraction. Notice of formal retraction of articles by Dr. Joachim Boldt. *British journal of anaesthesia* 2011, 107(1):116-117.**

**64. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011, 343:d5928.**

**65. Evidence Partners [**<http://distillercer.com/resources/methodological-resources/risk-of-bias-commentary/>**]**

**66. Jansen JP, Cope S: Meta-regression models to address heterogeneity and inconsistency in network meta-analysis of survival outcomes. *BMC medical research methodology* 2012, 12:152.**

**67. Jansen JP, Naci H: Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. *BMC medicine* 2013, 11:159.**

**68. Mills EJ, Ioannidis JP, Thorlund K, Schunemann HJ, Puhan MA, Guyatt GH: How to use an article reporting a multiple treatment comparison meta-analysis. *JAMA : the journal of the American Medical Association* 2012, 308(12):1246-1253.**

**69. Gelman A RD: Inferences from iterative simulation using multiple sequences. *Statistical Science* 1992, 7:457-472.**

**70. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S *et al*: GRADE guidelines: 3. Rating the quality of evidence. *Journal of clinical epidemiology* 2011, 64(4):401-406.**

**71. Guyatt GH, Rennie D: Users' guides to the medical literature. *JAMA : the journal of the American Medical Association* 1993, 270(17):2096-2097.**

**72. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Critical care medicine* 2003, 31(4):1250-1256.**

**73. Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, Fanizza C, Caspani L, Faenza S, Grasselli G *et al*: Albumin replacement in patients with severe sepsis or septic shock. *The New England journal of medicine* 2014, 370(15):1412-1421.**

**74. Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, Norton R: Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive care medicine* 2011, 37(1):86-96.**

**75. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E *et al*: Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA : the journal of the American Medical Association* 2005, 294(7):813-818.**

**76. Bagshaw SM, Laupland KB, Doig CJ, Mortis G, Fick GH, Mucenski M, Godinez-Luna T, Svenson LW, Rosenal T: Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. *Critical care (London, England)* 2005, 9(6):R700-709.**

**77. Neveu H, Kleinknecht D, Brivet F, Loirat P, Landais P: Prognostic factors in acute renal failure due to sepsis. Results of a prospective multicentre study. The French Study Group on Acute Renal Failure. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 1996, 11(2):293-299.**

**78. Wald R, Quinn RR, Adhikari NK, Burns KE, Friedrich JO, Garg AX, Harel Z, Hladunewich MA, Luo J, Mamdani M *et al*: Risk of chronic dialysis and death following acute kidney injury. *The American journal of medicine* 2012, 125(6):585-593.**

**79. Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R: Fluid balance and acute kidney injury. *Nature reviews Nephrology* 2010, 6(2):107-115.**

**80. Puhan MA, Schunemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, Kessels AG, Guyatt GH: A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *Bmj* 2014, 349:g5630.**

**81. Yunos NM, Kim IB, Bellomo R, Bailey M, Ho L, Story D, Gutteridge GA, Hart GK: The biochemical effects of restricting chloride-rich fluids in intensive care. *Critical care medicine* 2011, 39(11):2419-2424.**

**82. Dai ZL, Wu J, Meng C, Zeng F, Yang Y, Yao SL: Ringer's malate solution protects against the multiple organ injury and dysfunction caused by hemorrhagic shock in rats. *Shock (Augusta, Ga)* 2012, 38(3):268-274.**

**83. Mira J-P: Early Albumin Resuscitation During Septic Shock. In*.* https://clinicaltrials.gov/ct2/show/NCT00327704; 2014.**

**84. Heyland DK, Muscedere J, Drover J, Jiang X, Day AG: Persistent organ dysfunction plus death: a novel, composite outcome measure for critical care trials. *Critical care (London, England)* 2011, 15(2):R98.**

**85. McIntyre LA, Fergusson DA, Cook DJ, Rowe BH, Bagshaw SM, Easton D, Emond M, Finfer S, Fox-Robichaud A, Gaudert C *et al*: Fluid Resuscitation with 5% albumin versus Normal Saline in Early Septic Shock: a pilot randomized, controlled trial. *Journal of critical care* 2012, 27(3):317 e311-316.**

**86. Christian MD, Hamielec C, Lazar NM, Wax RS, Griffith L, Herridge MS, Lee D, Cook DJ: A retrospective cohort pilot study to evaluate a triage tool for use in a pandemic. *Critical care (London, England)* 2009, 13(5):R170.**

**87. Duffett M, Choong K, Foster J, Cheng J, Meade MO, Menon K, Cook DJ: Clonidine in the sedation of mechanically ventilated children: a pilot randomized trial. *Journal of critical care* 2014, 29(5):758-763.**