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CRYSTALLOIDS OR COLLOIDS… WHAT'S IN YOUR IV? Determining Fluid Type for Septic Shock Resuscitation

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Determining Fluid Type for Septic Shock Resuscitation

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Abstract

Objective: To compare the efficacy of crystalloid versus colloid solutions, specifically normal saline versus albumin, in decreasing mortality among patients with septic shock requiring resuscitation fluids in the intensive care unit (ICU) setting. **Design:** Systematic literature review. **Methods:** Research was conducted in PubMed and UpToDate, utilizing the search terms sepsis, septic shock, fluid resuscitation, colloids and crystalloids. Specifically, in PubMed, the following limits and terms were used: randomized control trial, human subjects, English, and within the last 7 years. **Results:** The Annane et al study found no significant difference in colloid fluid resuscitation versus crystalloid fluid resuscitation in the decreasing 28-day mortality in hypovolemic shock patients specifically in the ICU setting. The Finfer et al study found no significant difference between albumin and normal saline when assessing 28-day mortality and morbidity for patients in the ICU with severe sepsis. The Caironi et al study found no significant difference in albumin and crystalloids co-administration compared to crystalloids alone in 28-day mortality and morbidity outcomes for those with septic shock admitted to the ICU. **Conclusion:** The choice of fluid in aggressive resuscitation has no significant effect on patient mortality in those with septic shock in the intensive care unit (ICU).

Introduction

Sepsis is defined as a severe infection that has spread from one site, into the systemic circulation and has the potential become life threatening in the event of septic shock. It is estimated that 1 out of every 3 patients that die while in the hospital have sepsis [1]. A complication of sepsis occurs when chemicals, commonly known as bacterial exotoxins, are released from live bacteria into the bloodstream. The body's response to these exotoxins is a heightened inflammatory response, which is meant to fight the infection, but instead can lead to vasodilation and subsequent distributive shock[2]. The hallmarks of septic shock are hypotension, tachypnea, oliguria, mental status changes, metabolic acidosis and elevated lactate levels due to increased cell damage[2]. Typically, the offending organism or source of infection is unknown at the time of arrival to the emergency department (ED) with suspected septic shock[2]. Sepsis and shock are clinical diagnoses, therefore there is no diagnostic test to be performed on arrival[3]. The cornerstone of emergent intervention is aimed at mitigating hypovolemia by maintaining perfusion to all organs with aggressive fluid resuscitation and beginning empiric antibiotic therapy[3]. The initial assessment of a suspected shock patient who presents to the ED is to protect the airway if indicated, assess oxygen saturation, draw blood cultures, and establish IV access to rapidly administer antibiotics and fluids[3]. Additionally, while the patient is being stabilized, a tool known as "systemic inflammatory response syndrome (SIRS) criteria", outlined in Table 1, is used to assess if the patient meets the criterion for a sepsis diagnosis, which can aid in determining treatment protocols[4]. If the patient meets SIRS criteria, they are typically admitted to the intensive care unit (ICU) for continuous fluid maintenance and observation with serial hematologic lab studies, chemistries and ABG's[3]. While in the ICU, the patient's work up continues to determine the source of infection in order to tailor antibiotic therapy and determine if further intervention such as intubation, dialysis, or surgery is necessary.

In the current literature, there continues to be an ongoing debate about the optimal choice of fluid for intravenous resuscitation in those diagnosed with sepsis or septic shock. When considering the proper resuscitation fluid, determining the extent of fluid loss and presence of electrolyte abnormalities is a key prognostic factor and must be addressed in this patient population[3]. Two types of fluids most commonly used in resuscitation of sepsis or shock patients are crystalloid and colloid containing solutions[5]. An example of a crystalloid solution is isotonic (normal) saline, which by definition is meant to mimic the normal serum sodium concentration and thus, help keep fluid in the intravascular space[5]. Colloid fluids, in comparison, are solutions like albumin, which mimic proteins made by the liver and aid in holding fluid in the intravascular space via increasing the serum osmolality[5]. When a patient presents with marked hypotension, both crystalloid and colloid solutions are options to use when attempting to replace lost extracellular fluid[5]. Typically, the fluid most commonly used is normal saline since it is plentiful, inexpensive, and leads to good outcomes in patients with severe volume depletion not due to bleeding[5]. Despite these benefits, 1.5 to 3 times more saline, as compared to a colloid solution, is needed in order to expand the plasma volume when loss is due to third spacing[5]. This is disadvantageous because it increases the potential for fluid overload, which in turn could negatively impact patient outcomes[5]. Therefore, some clinicians prefer the use of albumin over normal saline in patients with sepsis or septic shock because of its rapid plasma volume expansion, its low risk for dilutional hypoalbuminemia, and its ability to rapidly stabilize patients without increasing the risk of pulmonary edema[5]. In this paper, we will examine mortality rate of sepsis and septic shock patients who receive crystalloid fluid resuscitation versus those patients who receive colloid fluid resuscitation. Our research goal is to determine the best choice for fluid resuscitation that will result in good patient outcomes and overall decreased patient mortality in the setting of sepsis and septic shock in the ICU.

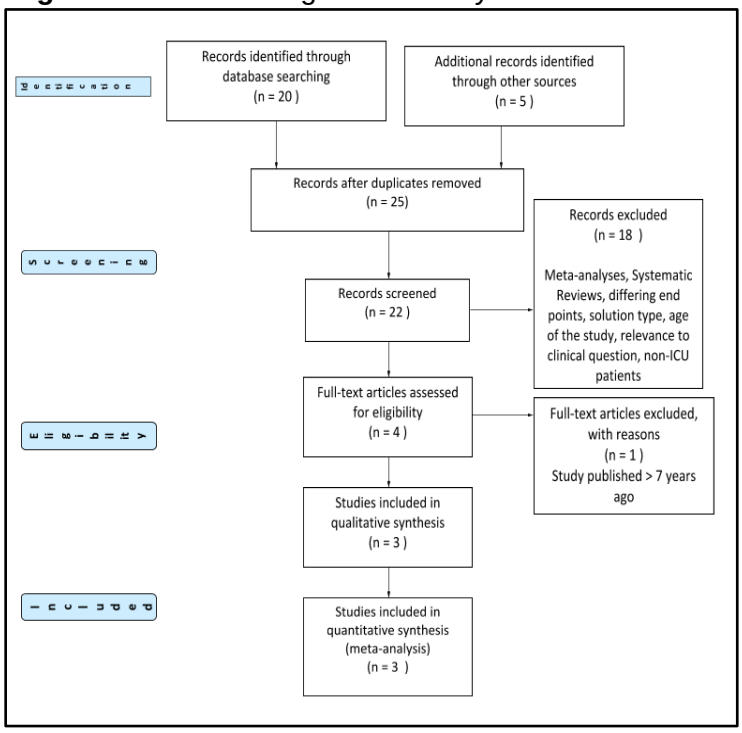
Table 1. Systemic inflammatory response syndrome criteria used in diagnosis of shock[4]

Systemic Inflammatory Response Syndrome (SIRS) Criteria 2 or more of the following variables:
Fever more than 38°C (100.4°F) or less than 36°C (98.6°F)
Heart rate of more than 90 beats per minute
Respiratory rate more than 20 breaths per minute or arterial carbon dioxide tension ($PaCO_2$) of less than 32 mm Hg
Abnormal white blood count (>12,000/mL or <4,000/mL or >10% immature (bands) forms)

Methods

A PubMed search was conducted in September 2018 using the terms sepsis, septic shock, fluid resuscitation, colloids and crystalloids. This search yielded 20 studies with pertinent subject matter to our clinical question. To further narrow our PubMed finds, we limited our search to include only randomized control trials with human subjects, published in English within the last 7 years. In addition to PubMed, 5 additional resources were gathered by assessing primary research articles cited by UptoDate in the "related articles" section of texts discussing choice of IV fluid resuscitation in shock patients and defining sepsis, severe sepsis and septic shock and the management thereof. No duplicate articles were discovered when combining the articles from our PubMed and UptoDate searches. In total 22 articles were screened and 18 articles that were meta-analyses, systematic reviews, and secondary subgroup analyses were excluded. In addition, articles that did not reflect our clinical question were excluded. Such articles did not fit our research question because of differing endpoints, various types of solutions, conduction of studies in non-ICU settings and pilot studies that were analyzing the function and potential success of a larger, future study. Lastly one full text article was excluded since it was published more than 7 years ago resulting in 3 sufficient articles for assessing the fluid choice in the setting of aggressive resuscitation in septic shock patients.

Figure 1. PRISMA diagram in this systematic review.



Results

Study 1: *Effects of Fluid Resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock*[6]

Objective: To compare colloid fluid resuscitation versus crystalloid fluid resuscitation in altering 28-day mortality in hypovolemic shock patients specifically in the ICU setting.

Study Design

This study is a multicenter, randomized control trial conducted in ICU's based in France, Belgium, North Africa and Canada. The study was conducted over 9 years from February 2003 to August 2012. 2857 patients were divided into 2 different treatment groups, 1414 patients receiving colloid fluids and 1443 patients receiving crystalloid fluids, via blinded computer-generated permuted block randomization algorithm. Consent was obtained from participants or legally authorized surrogates. Inclusion and exclusion criteria are represented in Table 2. The study defines acceptable crystalloid fluids as isotonic or hypertonic saline or lactated ringers and

the acceptable colloid solutions include gelatins, dextrans, hydroxyethyl starches, or 4% or 20% of albumin. Patients were stratified according to admission diagnoses that defined the cause of their states of shock: trauma, sepsis or other. The time and amount of therapy was up to the discretion of the investigator under the condition that the daily dose of hydroxyethyl starch (colloid solution) did not exceed 30 mL/kg and the investigators strictly followed any local regulatory agency recommendations that governed use of resuscitative fluids. The trial was discontinued when there was enough information to make a conclusion. This primary endpoint was said to be achieved when there was a 5% difference in the number of deaths between the two treatment groups at 28 days. Other outcomes being studied were mortality at 90 days, days without renal replacement, presence of organ failure (using Sequential Organ Failure Assessment (SOFA) scores), ICU and hospital-free days, days alive without mechanical ventilation, and days without use of vasopressors.

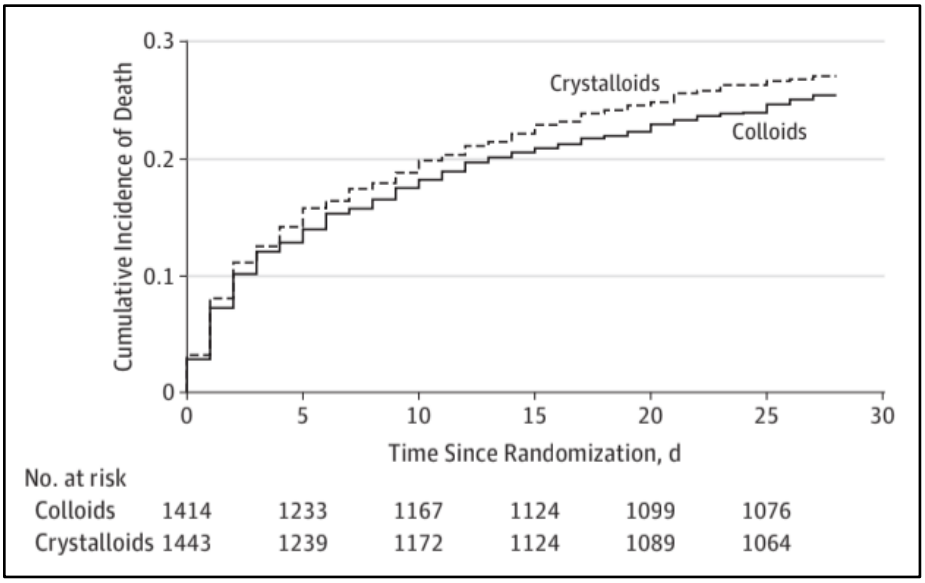
Table 2. Inclusion and exclusion criteria for Study 1.

Inclusion Criteria	**Exclusion Criteria**
1. Admission to ICU	1. Advanced chronic liver disease
2. No prior fluid resuscitation while in ICU	2. Anesthesia related hypotension
3. Hypotension: < 90/<60 with orthostatic hypotension (20 mmHg change) or delta pressure of 13%	3. Acute anaphylactic reaction
4. Evidence of low cardiac index & low filling pressures	4. Pregnancy
5. Signs tissue hypoperfusion:	5. Inherited coagulopathy
- GCS < 12	6. Burn > 20% BSA
- Mottled skin	7. Allergy to study drug
- Capillary refill ≥ 3 sec	8. Refused consent
- Arterial lactate levels > 2 mmol/L	9. Dehydrated
- BUN > 56 mg/dL	10. Brain dead
- Urinary output < 25 mL/hr	11. Organ donor
- Fractional excretion of sodium < 1%	12. Renal failure

Study Results

When the primary endpoint of mortality in 28 days was achieved, there were 359 deaths in the colloids group and 390 deaths in the crystalloid group (RR: 0.96, 95% confidence interval (CI) 0.88 to 1.04; p = 0.26). A value of less than 0.05 is considered statistically significant. In the first 7 days of treatment in the ICU, the median amount of colloid fluid used per patient was 2000 mL [IQR: 1000-3502 mL] and in the crystalloid group, a median of 3000 mL [IQR: 500-5200 mL].

Figure 2. Incidence of death within the first 28 days after randomization



Study Critique

The study is large and based on primary data which, in itself a source of strength. The reliability of data and conduction of the study is strong as evidenced by the auditing of each successive part of the trial. Inspection of the validity of informed consent, compliance to good clinical practice, validity of patient chart information, compliance to protocol, and accuracy of reporting adverse events at random times throughout the study, produced reliable data. Conduction of this study was overseen and funded by the French Ministry of Health, which is yet another positive aspect of this study as that entity is an unbiased governing party. Despite two conflicts of interest, the relationship and exchanges were explicitly stated in the study. The random allocation of patients by a blinded permuted block structure is the gold standard in quality randomized clinical trials and speaks to the validity of the study. However, the blinding of the investigators administering fluids was only hidden until the fluid bag was opened. This can be seen as a potential flaw in study design by creating performance bias but was deemed inevitable by the researchers. To offset the lack of complete blinding, investigators who were fully blinded throughout the duration of the trial were the individuals collecting and interpreting data. One finding that weakens the study is the administration of supplemental albumin alone to 237 patients in the crystalloid group. Although this was not deemed an exclusionary criterion in this study, future studies may add this criterion since it could have skewed the data collected and the conclusions made in this paper.

Study 2: *Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis*[7]

Objective: To determine which fluid, albumin or normal saline, is more effective for acute resuscitation by assessing 28-day mortality and morbidity in patients in the ICU with severe sepsis.

Study Design

This is a subgroup analysis study used to further the research done by a larger randomized control trial conducted in the intensive care unit (ICU) of 16 hospitals throughout Australia and New Zealand between November 2001 and June 2003. The initial goal of the study was to determine which fluid, albumin or normal saline, was more effective for resuscitation in those presenting with severe sepsis. Much like the initial study, this study took place in the ICU of multiple hospitals throughout Australia and New Zealand and looked at the effectiveness of fluid resuscitation in those with sepsis at baseline. The study design used in this subgroup trial was a double-blinded, randomized control trial that involved 1218 patients, all of which presented initially with severe sepsis. The source of sepsis was derived from the ICU admission diagnosis. When the admission diagnosis did not specify the source of sepsis, it was determined by retrospective analysis of medical records. Adult patients were randomly assigned to 4% albumin or 0.9% sodium chloride for all fluid resuscitation needs while being treated in the ICU for severe sepsis. After randomization was completed, 603 patients had been assigned 4% albumin and 615 patients that had been assigned 0.9% normal saline as the primary method of resuscitation while in the ICU. Fluid therapy was continued in the ICU until death, discharge, or 28 days after randomization, whichever occurred first. Inclusion and exclusion criteria for the selection of participants are presented in table 3. The primary outcome followed throughout the study was mortality within the first 28 days of randomization. Other outcomes being followed included, length of ICU stay, length of hospital stay, duration of mechanical ventilation, and duration of renal replacement therapy.

Table 3. Inclusion and exclusion criteria for Study 2.

Inclusion Criteria	**Exclusion Criteria**
Patients in the ICU with sepsis (two of the following)	Admitted to the ICU status post
- a core temperature ≥ 38° C o ≤ 36° C	- Cardiac surgery
- a heart rate ≥ 90 beats/min	- Liver transplant
- a respiratory rate ≥ 20 breaths/min or PaCO2 ≤ 32 mmHg or use of mechanical ventilation for an acute process	- Severe burns
- a white blood cell count ≥ 12000/ml or ≤ 4000/ml or immature neutrophils > 10%	

Study Results

Of 1218 patients enrolled, 185 assigned to albumin died, and 217 assigned to normal saline died (odds ratio 0.87; 95% confidence interval 0.74–1.02; p = 0.09). A value of less than 0.05 is considered statistically significant. Of these, 121 patients in the albumin group and 138 patients in the normal saline group died within 7 days of administration. 151 in the albumin group and 177 in the saline group died while in the ICU. Of those that died elsewhere in the hospital, 34 patients were assigned albumin and 40 were assigned normal saline. Furthermore, during the 28-day follow-up period, no patients who presented with severe sepsis died following hospital discharge.

Table 4. Primary and Secondary Outcomes for those with sepsis.

Outcome	Albumin group	Saline group	Odds ratio (95% CI)	Absolute difference (95% CI)	*p* value
Severe sepsis at baseline	(*n* = 603)	(*n* = 615)			
Status at 28 days: no. (%)					
Dead	185 (30.7)	217 (35.3)	0.87 (0.74–1.02)		0.09
Alive in ICU	36 (8.6)	26 (6.5)	1.35 (0.80–2.28)		0.26
Alive in hospital	135 (35.3)	142 (38.2)	0.88 (0.66–1.19)		0.42
Duration of stay in ICU (days)	8.2 ± 7.5	7.5 ± 6.7		−0.69 (−1.49 to 0.11)	0.09
Duration of hospital stay (days)	16.1 ± 9.7	15.6 ± 9.9		−0.47 (−1.58 to 0.63)	0.40
Duration of mechanical ventilation (days[a])	6.0 ± 7.2	5.4 ± 6.2		−0.56 (−1.31 to 0.20)	0.15
Duration of renal replacement therapy (days[a])	1.2 ± 3.6	1.0 ± 3.1		−0.28 (−0.66 to 0.09)	0.14

Study Critique

In this study, data was derived from a subgroup of a large blinded, randomized clinical trial (RCT) which is a strength because RCT is the gold standard for evidence-based medicine. A weakness of this study was it was a subgroup of a larger trial; therefore, the sample size was not predetermined. Additionally, the trial was not primarily designed to examine the relative benefits of albumin and normal saline in severe sepsis, which in turn might be considered a weakness. Moreover, in the study, researchers were unable to collect detailed microbiological or associated treatment data for each patient, leading to a potential imbalance in associated treatments. The imbalance may favor those assigned to albumin and in turn could have influenced the results. Additionally, another weakness of the study was that not all patients were included in the multivariate analysis because some were missing primary evaluation data. In the study, fluid resuscitation was not delayed to collect non-routine samples for laboratory data nor was it delayed to measure parameters such as the CVP, which were used for assessment. By not including all participants involved in the trial, that could have introduced selection bias or further decreased the sample size, leading to type two error. Finally, another weakness to the study was that Sequential Organ Failure Assessment (SOFA) scores were not collected after patients were discharged from the ICU, which in turn weakens the inferences drawn from this data.

Study 3: *Albumin Replacement in Patients with Severe Sepsis or Septic Shock*[8]
Objective: To determine if albumin and crystalloid fluid compared to crystalloid fluid alone results in better 28-day mortality and morbidity outcomes for those with septic shock admitted to the ICU.

Study Design
This study was a randomized control trial initiated in 100 intensive care units (ICU) in Italy, from August 2008 to February 2012. The study contained 1818 patients who were randomly assigned to either 20% albumin and 0.9 % normal saline or 0.9% normal saline alone for fluid replacement while in the ICU. Inclusion and exclusion criteria used in the selection of participants are presented in table 5. Randomization was stratified according to the participating ICU and the interval of time between which the patient met the clinical criteria for severe sepsis and randomization. A total of 8 patients were excluded from the analysis. 2 patients in the albumin group were excluded due to withdrawal of consent. 5 patients in the albumin group were excluded due to a randomization error. 1 patient in the crystalloid group was excluded due to a randomization error. Length of fluid therapy in the ICU was based on early goal directed therapy and was measured from the time of randomization until 28 days, death, or discharge, whichever came first. Directly after randomization was completed, patients in the albumin group received 300 mL of 20% albumin solution, whereas the crystalloid group received nothing. Furthermore, from day 1 to day 28 or prior to discharge, whichever came first, 20% albumin was administered on a daily basis, to maintain a serum albumin level of 30 g per liter or more. Crystalloids were only administered whenever it was clinically indicated by the attending physician managing the patient. Moreover, in this study there were two outcomes that were being measured. The first outcome, the primary outcome, was death from all-cause mortality at 28 days after randomization. The second, the secondary outcome, was death from all-cause mortality at 90 days after randomization. Other outcomes being followed included number of patients with organ dysfunction, the degree of dysfunction, and the length of stay in the ICU and hospital. In the study, the severity of systemic illness was assessed using the Simplified Acute Physiology Score, ranging from 0, meaning low severity, to 163 indicating the highest level of severity. Finally, organ function was assessed daily using the Sequential Organ Failure Assessment (SOFA) score. SOFA scores were composed of five components: respiratory, coagulation, liver, cardiovascular, and renal, and were graded on a scale of 0-4. The higher the score the more organ dysfunction was indicated.

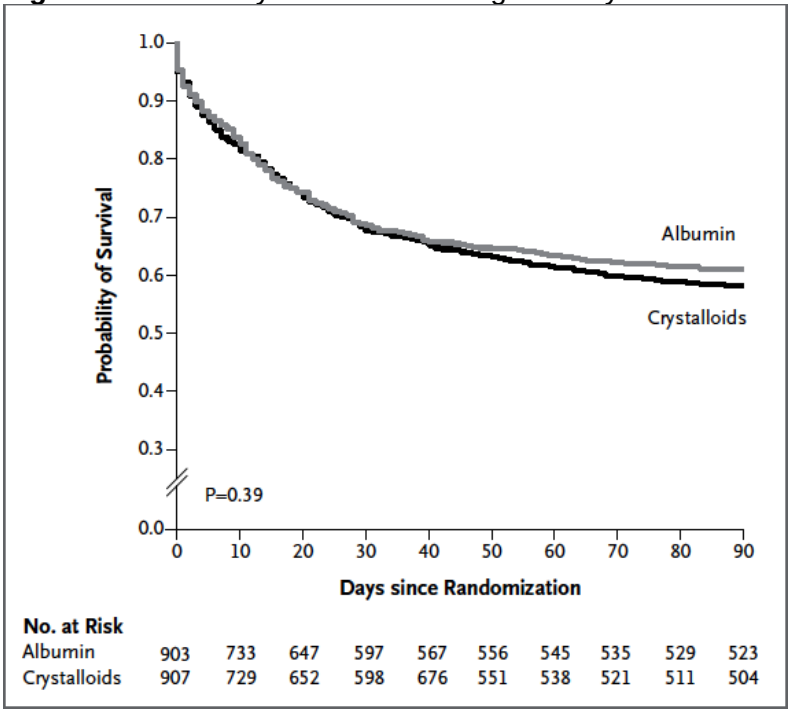
Table 5. Inclusion and exclusion criteria for Study 3.

Inclusion Criteria	Exclusion Criteria
1. Age 18 years or older	1. Age below 18 years
2. Met the clinical criteria for sepsis within 24 of ICU admission (two or more of the following)	2. Terminal state
- a core temperature ≥ 38° C o ≤ 36° C	3. Known adverse reaction to albumin administration
- a heart rate ≥ 90 beats/min	4. Severe sepsis or septic shock in patients after proved or suspected head injury, clinically active
- a respiratory rate ≥ 20 breaths/min or PaCO2 ≤ 32 mmHg or use of mechanical ventilation for an acute process	5. Congestive heart failure (New York Heart Association class of 3 or 4)
- a white blood cell count ≥ 12000/ml or ≤ 4000/ml or immature neutrophils > 10%	6. Pathological conditions in which albumin administration is clinically indicated (hepatic cirrhosis with ascites, intestinal malabsorption syndrome, nephrotic syndrome, burns)
	7. More than 24 hours since inclusion criteria were met
	8. Religious objection to the administration of human blood products
	9. Inclusion in other experimental studies

Study Results

At 28 days after randomization, 285 of 895 patients in the albumin group and 288 of 900 in the crystalloid group had died (relative risk in the albumin group, 1.00; 95% confidence interval [CI], 0.87 to 1.14; p = 0.94). At 90 days of follow-up, 365 of 888 patients (41.1%) in the albumin group and 389 of 893 (43.6%) in the crystalloid group had died (relative risk, 0.94; 95% CI, 0.85 to 1.05; p = 0.29). A value of less than 0.05 is considered statistically significant. Total daily amount of administered fluids in the first 7 days for the albumin group was 3738 ml [interquartile range, 3174 to 4437] and in the crystalloid group was 3825 ml [interquartile range, 3205 to 4533], respectively; p = 0.10).

Figure 3. Probability of Survival through 90 days



Study Critique

The trial was funded by the Italian Medicines Agency, which had no role in the conduction of the study, the reporting of the data, or the supply of study fluids. This is a strength because there was no introduction of bias or push for outcomes as might be seen in a funded study. Furthermore, the trial was overseen by the data and safety monitoring board, which is a strength because it made sure that trial was conducted within protocol and that the results could be extrapolated to the general population once collected. A limitation to this study was that it included the use of albumin solutions that were of greater concentration than those used in previous studies (20% compared to 4% used in most studies), making it difficult to know if percentage of albumin could lead to different outcomes. Furthermore, another limitation to this study was that the method in which albumin was administered differed from that of the crystalloid solution. In this study albumin was given daily to maintain an albumin level greater than 30g per liter whereas, the crystalloid solution was only given when the attending physician managing the patient deemed it clinically necessary. In addition, the volume of albumin solution that was administered in the study was markedly lower than previous studies due to the fact that investigators were not trying to replace intravascular volume. Instead, investigators treatment goal was to correct hypoalbuminemia, which could make the comparison of the results to other studies difficult. Finally, another limitation to this study was that mortality at 28 days was less than what was originally expected, which investigators believe could be linked to the study being underpowered. A study that is underpowered is problematic because it increases the risk for type 2 error.

Discussion

Shock is a life-threatening complication of severe sepsis that can be corrected with the use of aggressive fluid resuscitation in conjunction with empiric antibiotic therapy. Fluid resuscitation is aimed at stabilizing the patient by lowering tachycardia, improving blood pressure, normalizing depleted electrolytes, and increasing perfusion to vital organs to prevent complications such as organ dysfunction and death. The most common method of fluid resuscitation used in ED and ICU protocols is the administration of either crystalloid solutions (normal saline, lactated ringers) or colloid solutions (hydroxyethyl starch, albumin) to bolster intravascular volume. In our research, there was no significant difference in 28-day mortality of shock patients when treated with colloid based fluids versus crystalloid based fluids during aggressive resuscitation. The only major difference we found, between crystalloid and colloid solutions, was related to total amount of fluid administered. For example, in studies 1 and 3, the median amount of total normal saline (crystalloid) administered was much larger, as compared to the total amount of albumin (colloid) given. However, the total amount of fluid had no significant impact on patient mortality.

Since aggressive fluid resuscitation in the ED and ICU is currently the mainstay of intervention in the patient population with sepsis and septic shock, and has been found to be effective, there is not much new research being conducted on this topic. Therefore, of the older and smaller studies we found, many variables and outcomes were heterogeneous and hard to synthesize, making gathering a concise conclusion about the research challenging. Despite the same primary endpoint in all studies that were analyzed, there were other variables that were not congruent between the trials. Firstly, there were a variety of solutions with different solute concentrations and different molecules being used in each of the three studies, which takes away from the strength of our review. In addition, the statistical analyses performed in each study were not easily comparable because two were analyzed using relative risk of randomized control trials and the other looked at odds ratio of a subgroup analysis. Although no study outcome was statistically significant, the heterogeneity of the studies as a whole weakens our systematic review.

One of the strengths of our review was that all studies we included marked their endpoint for assessment of mortality at 28 days. This commonality across all studies was helpful in deciding which studies to include in our research. However, we believe this evaluation period was not long enough to determine if the use of fluids alone significantly reduced mortality rates. In our research, secondary endpoints such as vitals, hemodynamic markers, organ perfusion status and other therapeutic intervention data were recorded and analyzed. We feel that these endpoints are more clinically relevant and reliable in determining the effectiveness of intervention with different fluid solutions rather than mortality, in days, alone. We feel that assessing only mortality as the primary endpoint may not properly assess the initial and full effect of fluid choice in initial aggressive resuscitation and that other clinically relevant endpoints may show one fluid type to be a better choice than another. Furthermore, the method in which albumin was administered in study 3 differed significantly from the other two studies. In study 3, albumin was given daily to maintain an albumin level greater than 30g per liter whereas, in the other studies, albumin was administered via bolus doses in order to resuscitate patients in septic shock. This inconsistency in administration and treatment goal, contributed to

heterogeneity of our review since patient parameters for daily albumin, compared to bolus dosing, might affect clinical outcomes and have skewed the results. A further limitation to this research is the acute nature of the condition. For example, in study 3, patients who met criteria for the study were subsequently excluded from analysis if they required immediate resuscitation prior to ICU admission. By excluding these patients, the investigators might have missed important clinical outcomes, which may have altered the results of the study. Finally, a more obvious limitation to these studies is size and therefore, power. One of the studies was a subgroup analysis which by nature analyzed a smaller population size of a larger randomized study. This has potential to weaken our review by introducing type two error.

Table 6. Comparison of Studies Analyzed

Author	Year Published	Type of Study	Primary Outcome	Fluid(s) analyzed		P-Value
				Colloid	Crystalloid	
Annane et al	2013	RCT	28-day mortality	- Gelatins - Dextrans - Hydroxyethyl starches - 4% or 20% Albumin	- Isotonic Normal Saline - Hypotonic Normal Saline -Lactated Ringer's	0.26
Finfer et al	2009	Subgroup analysis of larger RCT	28-day mortality	- 4% Albumin	- 0.9% Normal Saline	0.09
Caironi et al	2014	RCT	28-day mortality	20% Albumin and 0.9 % Normal Saline	- 0.9% Normal Saline alone	0.94

Conclusion

To date, there is no evidence that a significant benefit exists in choosing crystalloid versus colloid for aggressive fluid resuscitation in the acute setting of sepsis and septic shock. Knowledge is lacking as to why one type of fluid is not superior to the other in the setting of septic shock. Is it the pathophysiology behind sepsis and septic shock that makes fluid administration choice inconclusive? Or is it the properties of the specific fluid groups and how they work to resuscitate patients during sepsis and septic shock that makes fluid choice ambiguous? Despite this gap in knowledge and questions surrounding fluid choice during sepsis and shock, there are practical considerations that should be taken into account when choosing what fluids to administer. These considerations include total amount used, possible adverse outcomes, and cost of fluid solution. These three variables are just as important to a patient's overall outcome and represent an area for future research. Other recommendations for future research are: primary data with larger sample sizes, role of fluid choice in renal replacement therapy in the ICU, and the efficacy in setting specific shock protocols in the ED and ICU in order to standardize fluid administration within the study.

Works Cited

1. CDC. “Data and Reports.” Centers for Disease Control and Prevention, 19 Sept. 2018, https://www.cdc.gov/sepsis/datareports/index.html.

2. UpToDate.https://www.uptodate.com/contents/sepsis-syndromes-in-adults-epidemiology-definitions-clinical-presentation-diagnosis-and-prognosis. Accessed 27 Sept. 2018.

3. UpToDate.https://www.uptodate.com/contents/evaluation-and-management-of-suspected-sepsis-and-septic-shock-in-adults. Accessed 27 Sept. 2018.

4. Systemic Inflammatory Response Syndrome: Background, Pathophysiology, Etiology. May 2018. eMedicine, https://emedicine.medscape.com/article/168943-overview.

5. UpToDate.https://www.uptodate.com/contents/treatment-of-hypovolemia-or-hypovolemic-shock-in-adults. Accessed 27 Sept. 2018.

6. Annane, Djillali. “Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock: The CRISTAL Randomized Trial.” JAMA, vol. 310, no. 17, Nov. 2013, p. 1809. Crossref, doi:10.1001/jama.2013.280502.

7. 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*. 2010;37(1):86-96. doi:10.1007/s00134-010-2039-6

8. Caironi P, Tognoni G, Masson S, et al. Albumin Replacement in Patients with Severe Sepsis or Septic Shock. *New England Journal of Medicine*. 2014;370(15):1412-1421. doi:10.1056/NEJMoa1305727