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Outcomes of Unbalanced versus Balanced Crystalloids in Sepsis: A Systematic Review

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PA599 - Directed Study

Augsburg University

## **Abstract**

This systematic review attempts to examine current literature regarding the outcomes of septic patients who receive fluid resuscitation with balanced versus unbalanced crystalloids. Inclusion criteria were randomized controlled trials (RCTs), retrospective cohort studies, and clinical trials that presented either pediatric or adult patients who were admitted to the hospital in critically ill condition and received either 0.9% normal saline or any type of balanced crystalloid, with the presence of at least one out of three primary outcomes: comparative rates of mortality, renal dysfunction, or metabolic acidosis. Reports were excluded if they did not contain information regarding any primary outcome measure, had a mixed age population, or did not include septic patients. Pubmed was the database in which this systematic review was conducted, which took place from inception until July 2023. The included studies were summarized in the results section of this systematic review which includes the dates, patient population, interventions, primary outcomes, results, and overall conclusions of the authors. The total number of included studies was 11, with 107,921 total participants. 71,983 patients received normal saline, 17,846 received balanced crystalloids, and 7,054 received some combination of both. Results of the majority of studies point to balanced crystalloids as a better option for fluid resuscitation than normal saline, showing decreases in overall mortality as well as renal dysfunction and metabolic acidosis. The implications of this finding further support the weak recommendation made by the current Surviving Sepsis Campaign Guidelines, arguing for the preference of balanced over unbalanced crystalloids in initial management of sepsis.

## Introduction

Sepsis has been regularly cited as a major cause of mortality worldwide and a global health issue. Sepsis is defined as “a life-threatening organ dysfunction caused by a dysregulated host response to infection,” while septic shock is defined as “a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a higher risk of mortality than sepsis alone” (Moschopoulos et al., 2023).<sup>12</sup> The diagnosis and management of sepsis has been primarily standardized, with the current guidelines suggesting the use of early intravenous antibiotics and fluids. As such, resuscitation therapy with intravenous fluids is a hallmark of sepsis management, however there is much debate over the type of fluids to give. While current guidelines emphasize the importance of early intravascular volume expansion with crystalloids as opposed to colloids, they only give a weak recommendation with low quality evidence regarding the preferential crystalloid type in fluid resuscitation of septic patients.

Previously, fluid resuscitation revolved around the Starling principle, which described a semi-permeable membrane separating the interstitial and intravascular fluid spaces, and movement of fluid between these two compartments as dependent on both the hydrostatic and oncotic pressure gradient between them.<sup>3</sup> This principle was later revised and began to incorporate the endothelial glycocalyx layer (EGL). The EGL is a matrix of glycoproteins and proteoglycans that are membrane-bound and project inward from the luminal surface of endothelial cells. This glycocalyx serves as the direct interface between intravascular blood and blood vessels, and greatly helps to regulate filtration of fluid from the intravascular space to the interstitial space.<sup>3</sup> During sepsis, the glycocalyx appears to be disrupted via an oxidative stress mechanism with accompanying endothelial injury. Disruption of the EGL results in the leakage of fluid and protein into the extravascular space. Concurrently, the host response to infection

induces the release of a significant amount of inflammatory mediators which act on endothelial cells, causing systemic vasodilation.<sup>12</sup> These processes combine to lead to extravascular rapid fluid loss, hypovolemia, and hypotension requiring fluid resuscitation.<sup>3</sup>

According to the Surviving Sepsis Campaign Guidelines, patients who are septic and show signs of tissue hypoperfusion, hypotension, or hypovolemia must receive an initial fluid bolus with 30mL/kg of body weight with crystalloids.<sup>6</sup> Included in the initial treatment algorithm of sepsis are crystalloids, vasopressors, inotropes, and red blood cell transfusions in addition to antibiotic therapy. It is important to note that administering the correct type and amount of fluids early in the setting of sepsis can alone result in full resuscitation of many patients. Newer guidelines do recommend the administration of balanced crystalloids instead of normal saline, however this recommendation is very weak and has low quality evidence.<sup>12</sup> There are multiple types of crystalloids, and therefore it is imperative to provide strong evidence concerning which type of crystalloid is associated with better outcomes in the management of sepsis.

Crystalloid solutions contain both water and electrolytes, and are sub-grouped into either balanced or unbalanced crystalloids. The most commonly used crystalloid in the world is 0.9% sodium chloride, otherwise known as normal saline (NS).<sup>3</sup> Normal saline is an unbalanced solution and is technically classified as isotonic, however it has a higher osmolarity than human plasma with 154 mmol/L of both Na<sup>+</sup> and Cl<sup>-</sup> (the most prevalent cation and anion in the body), whereas human plasma only contains about 140 mmol/L of Na<sup>+</sup> and 102 mmol/L of Cl<sup>-</sup> respectively.<sup>15</sup> While NS may be the most commonly used crystalloid, it has an unclear origin which does not seem to be rooted in scientific inquiry. The widespread use of 0.9% saline appears to be related to the incorrect conclusion of Dutch physiologist Hartog Jakob Hamburger, who assumed that the physiologic concentration of sodium chloride in the body is 0.9%.<sup>3</sup>

However, it is unclear whether he intended for this conclusion to be the basis for rationale behind utilizing intravenous salt solutions.<sup>3</sup> Recently, there has been some controversy on the use of normal saline. Data from both experimental and clinical trials have shown that 0.9% normal saline leads to a hyperchloremic metabolic acidosis, has detrimental effects on the kidneys, induces coagulopathy, and is also correlated with increased inflammatory markers.<sup>3,5</sup>

Due to the increased [Cl<sup>-</sup>] in 0.9% normal saline relative to human plasma, it has been shown to lead to hyperchloremia. Hyperchloremia leads to increased chloride delivery to the distal nephrons of the kidneys, which promotes constriction of the afferent renal arterioles. This leads to compromised blood flow to the kidneys, lowering glomerular filtration rate and overall kidney function. Not only has this been associated with acute kidney injury and decreased urine output, but several physiological mechanisms then lead to metabolic acidosis. This is because 0.9% normal saline contains equal amounts of Na<sup>+</sup> and Cl<sup>-</sup>, creating a strong ion difference (SID) of zero. During resuscitation, when serum chloride concentrations increase, the overall positive charge of the plasma (SID) is reduced. This is responded to by compensatory mechanisms which increase the positive charge of the plasma by increasing the hydrogen ion concentration. Increased concentrations of hydrogen ions decreases blood pH, leading to a hyperchloremic metabolic acidosis.<sup>5</sup> Lastly, NS has a pH range of 4.5-7.0, which is significantly more acidic than physiologically normal human plasma (7.35-7.45).<sup>15</sup> Administration of an acidic intravenous fluid (0.9% NS) to a septic patient combined with increasing chloride concentrations only serves to exacerbate the known side effect of sepsis which is lactic acidosis.<sup>15</sup>

Balanced solutions, on the other hand, contain components that more closely mimic what is naturally present in human plasma. Balanced crystalloids contain lower concentrations of Cl<sup>-</sup> and also contain buffers, such as lactate, acetate, gluconate, or malate. The most frequently used

balanced crystalloid worldwide is Lactated Ringer's solution (LR), which contains 130 mmol/L of  $\text{Na}^+$  and 109 mmol/L of  $\text{Cl}^-$ , as well as potassium, calcium, and sodium lactate. LR has a pH range of 6.0-7.5, which more closely mimics the physiologically normal pH of human plasma (7.35-7.45) than normal saline. Another frequently used balanced solution is Plasma-Lyte, which is unique in that it does not contain calcium, but otherwise has similar components to LR.<sup>20</sup>

Proposed benefits of administration of LR include not only intravascular volume resuscitation with reduced risk of AKI, but also decreased cellular death from ischemia.<sup>10,20</sup> LR provides the body with sodium lactate.<sup>20</sup> The compensatory base of lactic acid is lactate, which is constantly made in the human body during anaerobic metabolism. Normal aerobic metabolism of glucose leads to the production of pyruvate into cellular respiration.<sup>20</sup> At the same time, small amounts of anaerobic metabolism are always taking place. This process involves pyruvate reacting with NADH to form  $\text{NAD}^+$ , eventually leading to the production of lactate as a byproduct from the enzyme LDH. The purpose of this reaction is to preserve  $\text{NAD}^+$  levels in order to allow metabolism of glucose to continue even in the absence of oxygen.<sup>20</sup> Thus, the sodium lactate given in Lactated Ringer's solution is a metabolic fuel that the human body metabolizes under ischemic conditions. This allows for metabolism to persist, resulting in the continued production of ATP, water ( $\text{H}_2\text{O}$ ), and carbon dioxide ( $\text{CO}_2$ ), decreasing overall cellular death in the presence of ischemia.<sup>20</sup>

There is a general caution when discussing administration of LR as it has historically been thought to cause hyperkalemia and worsen lactic acidosis. This is due to LR's  $[\text{K}^+]$  of 4mEq/L, and concern comes from the idea that giving a patient LR with hyperkalemia would only cause their  $[\text{K}^+]$  to increase. This has been proven to be a false concern, and should not be a deterrent to considering Lactated Ringer's solution.<sup>20</sup> The volume of distribution of potassium in

the human body is larger than extracellular compartments, and equilibrates between the intracellular and extracellular spaces.<sup>20</sup> When giving LR, which has a concentration of potassium in the normal range of human plasma (4mEq/L vs 3.5-5.0mEq/L), it will trend the serum potassium toward 4mEq/L. This is to say that giving the [K<sup>+</sup>] in LR is not an additive effect, but a dilutional effect wherein it would be theoretically impossible to cause the serum concentration of potassium to increase past 4mEq/L. In addition, Lactated Ringer's has not been associated with causing acidosis like Normal Saline has, something that would theoretically increase serum potassium concentration by promoting extracellular shifting of K<sup>+</sup> into the bloodstream. Instead, as discussed previously, LR contains sodium lactate which is used as a metabolic fuel by the body. This is not to be confused with lactic acid, which is known to become elevated during sepsis and is a marker for severe sepsis.<sup>20</sup>

In summary, balanced crystalloids theoretically have advantages over unbalanced crystalloids, namely normal saline. However, there is not an adequate amount of evidence to support the adoption of balanced crystalloids as first-line resuscitation for sepsis. In order to answer the research

question of “Does fluid resuscitation with normal saline or balanced crystalloids have better outcomes in sepsis?”—this systematic review will examine current literature surrounding the use

Table 1: Comparing Crystalloids based on Composition

	Human Plasma	NS	LR	Plasma-Lyte
<b>Sodium</b>	140 ± 5	154	130	140-141
<b>Chloride</b>	102 ± 8	154	109	98
<b>Potassium</b>	4.5 ± 1	0	4	5
<b>Calcium</b>	2.4 ± 0.2	0	1.4	0
<b>Magnesium</b>	0.9 ± 0.1	0	0	1.5
<b>Bicarbonate</b>	28 ± 4	0	0	0
<b>Lactate</b>	<2	0	28	0
<b>Gluconate</b>	0	0	0	23
<b>Acetate</b>	0	0	0	27
<b>Malate</b>	0	0	0	0
<b>Osmolarity</b>	285 ± 10	308	273	295
<b>pH</b>	7.4 ± 0.02	4.5-7.0	6.0-7.5	6.5-8.0
<b>SID</b>	40 ± 2	0	27	50
<b>Na/Cl ratio</b>	1.21-1.54	1	1.19	1.43

All variables have units in mmol/L, except for osmolarity (mosm/L) and pH.  
Information from San Geroto et al. (15) was summarized to create this table.

and outcomes of normal saline and balanced crystalloids. After a comprehensive discussion regarding the findings, a proposal for future research and next steps will be given.

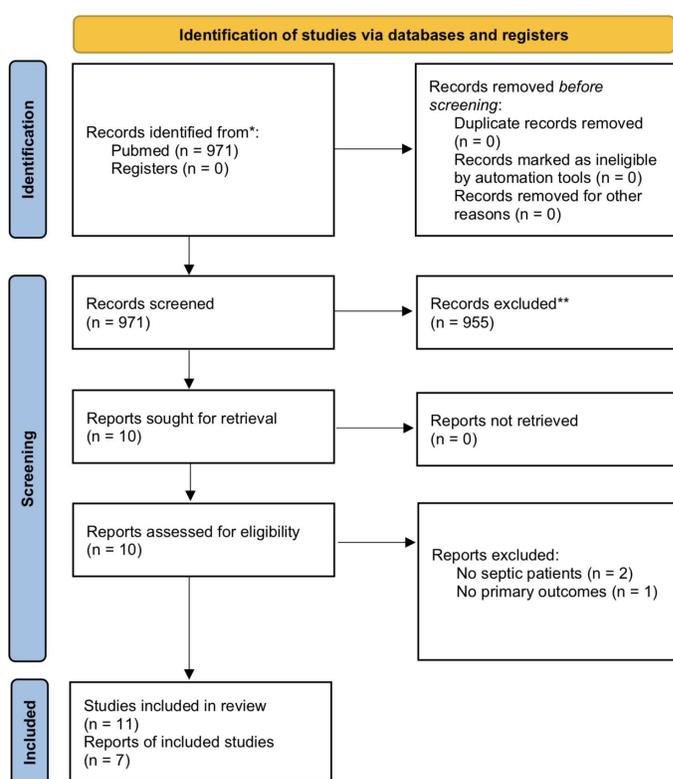
## **Methods**

A systematic review of the current literature was conducted utilizing the PubMed database which occurred from inception until July 2023. Strategies for search terms included patient condition, type of crystalloid administered, and patient outcomes. Included were randomized controlled trials (RCTs), retrospective cohort studies, and clinical trials. Primary outcomes included comparative rates of mortality, renal dysfunction, and metabolic acidosis between those who received balanced and unbalanced crystalloids, or a combination of both. Reports that were included presented either pediatric or adult patients who were admitted to the hospital in critically ill condition and received either 0.9% normal saline, any type of balanced crystalloid, or a combination of both, and also presented any of the primary outcomes. Reports were excluded if they did not contain information regarding any primary outcome measure, had a mixed age population, or did not include septic patients. One non-randomized clinical trial was included which used septic animal models in the setting of fluid resuscitation. One secondary analysis of a large RCT was included, as well as a concurrent ancillary analysis. Search terms were “sepsis fluid management OR septic shock resuscitation OR septic shock fluid choice OR septic shock fluid management OR sepsis outcomes OR crystalloid type OR acute kidney injury sepsis OR renal dysfunction sepsis OR renal outcomes sepsis OR pediatric sepsis OR pediatric sepsis outcomes OR crystalloid pediatric sepsis OR sepsis resuscitation OR sepsis fluid type. Filters used were “Free full text”, “Clinical Trial”, “Randomized Controlled Trial”, “Review”, and “from 2015 - 3000/12/12”. A single author (Gus R. Whittington) screened the studies independently for inclusion and exclusion criteria, and also individually collected data from the

reports. No automation tools were used in the process. There were no required extra steps in order to prepare the data for presentation or synthesis, such as data conversion or handling of missing summary statistics.

## Results

Records were identified from the PubMed database. N=971 records were initially identified. No duplicates were found. No automation tools were used. No records were initially removed for other reasons. N=971 records were initially screened. N=955 records were excluded, leaving



n=10 reports sought for retrieval. N=10 reports were retrieved and assessed for eligibility. N=2 reports were excluded as they did not contain data from patients who were diagnosed with either sepsis, severe sepsis, or septic shock.<sup>16,17</sup> N=1 report was excluded because it lacked inclusion of any of the three primary outcomes.<sup>7</sup>

### *Clinical Evidence of Outcomes*

Raghunathan et al. performed a retrospective cohort study from

2006-2010, with the goal of assessing the outcomes of different intravenous fluid mixtures on initial fluid resuscitation in severe sepsis.<sup>14</sup> There were 60,734 adult patient participants admitted to 360 different ICUs throughout the United States. Participants were patients with severe sepsis who were categorized into one of four exposure categories: those receiving only isotonic saline

(“Sal” n=44,347), those receiving saline in addition to balanced crystalloids (“Sal + Bal” n=3,651), saline in addition to colloids (“Sal + Col” n=11,038), and those receiving all three fluid types (“Sal + Bal + Col” n=1,698).<sup>14</sup> Lactated Ringer’s was the predominant balanced crystalloid used, while albumin was the predominant colloid used. The researchers restricted exposure to the intravenous fluids received within the first two days of hospital stay. The primary outcome was in-hospital mortality, while secondary outcomes were length of stay and cost per day. Results showed that in-hospital mortality was lowest in the Sal + Bal group (17.7%), intermediate in the Sal alone group (20.2%) and Sal + Bal + Col group (19.2%), and highest in the Sal + Col group (24.2%).<sup>14</sup> Length of stay and cost per day were significantly higher with coadministration of colloids when compared to the Sal or Sal + Bal groups.<sup>14</sup>

In 2015 there was a double-blind, double-crossover study that was cluster randomized comparing the effectiveness of NS vs Plasma-Lyte in critically ill patients in the ICU.<sup>12</sup> This study took place in New Zealand over the course of 7 months, and was called the SPLIT trial (Saline vs Plasma-Lyte 148 for ICU fluid Therapy). The sample size was 2262 patients. 1110 patients received NS and 1152 patients received Plasma-Lyte. Patients in both groups received a median volume of 2000mL of intravenous fluid. The primary outcome of this study was to determine rates of acute kidney injury (AKI). The results showed that there was no significant difference in the rates of AKI among those patients who received either NS or Plasma-Lyte, however only 4% of the patients included in the trial were diagnosed with sepsis.<sup>12</sup>

In contrast, the SALT (isotonic Solution Administration Logistical Testing) trial in 2017 showed more significant findings.<sup>19</sup> The SALT trial was a cluster-randomized, multiple crossover trial that had 974 participants, and examined the outcomes of critically ill adult patients in the ICU who received Balanced Solutions (BSs) versus NS. Crystalloid solutions were alternated

monthly from BSs (LR or Plasma-Lyte) to NS. 520 patients received BSs with a median fluid volume of 1617mL. 454 patients received NS with a median fluid volume of 1424mL. The primary outcome of this trial was the difference between the proportion of crystalloid given that was normal saline in either group. Secondary outcomes included rates of major kidney events and AKI. All patients (n=974) who were admitted to the ICU were enrolled in the trial, regardless of diagnosis or prognosis. The most frequent admitting diagnoses were sepsis and respiratory failure. Approximately 28.6% of the patients who received BSs were septic, while 25% of patients who received NS were septic. Results showed that there was a positive correlation between patients who received larger volumes of NS and more frequent major renal complications. However, the rates of stage II or greater acute kidney injury and new renal replacement therapy was not different between either group. The highest serum chloride concentrations were found in the group who received NS, while it was more common to see abnormal serum potassium values ( $>5\text{mmol/L}$  and  $<3\text{mmol/L}$ ) in the BSs group.<sup>19</sup>

More significant outcomes with NS and BSs were found in the SMART trial (isotonic Solutions and Major Adverse Renal Events Trial).<sup>18</sup> This single-center cluster-randomized controlled trial was conducted in 2018 across five adult ICUs. This was a relatively large study, including 15,802 adult ICU patients who were randomized to either receive fluid resuscitation with balanced solutions (LR or Plasma-Lyte, n=7942) or 0.9% Normal Saline (n=7860).<sup>18</sup> Contraindications to receiving balanced crystalloids were hyperkalemia or brain injury, in which case NS rather than BSs was administered. Researchers compared primary outcomes of mortality, new renal replacement therapy, or persistent renal dysfunction. Outcomes were all censored after 30 days or hospital discharge, whichever came first. Results of the SMART trial showed that fluid resuscitation with either LR or Plasma-Lyte, when compared to NS, were

associated with lower mortality rates (10.3% vs 11.1%), lower rates of renal dysfunction (14.3% vs 15.4%), and less need for renal replacement therapy (2.5% vs 2.9%).<sup>18</sup> Among the patients included in this trial, it was found that the benefit of BSs over NS was greatest in those who were admitted to the ICU with a diagnosis of either sepsis or septic shock. Researchers found that the number-needed-to-treat (NNT) with BSs among septic or septic shock patients in order to prevent death, new renal replacement therapy, or persistent renal dysfunction was approximately 20 patients.<sup>15</sup>

In 2021 a secondary analysis of the SMART trial was performed. Researchers focused solely on those patients who were diagnosed with sepsis, as well as on the fluid choice in the setting of the ICU or the ED. During the first 7 months of the SMART trial the fluid choice was controlled only in the ICU, while in the latter 15 months the choice of fluid was coordinated between the ED and ICU.<sup>9</sup> Researchers assessed 30-day in hospital mortality between groups who received BSs or NS, and also between groups whose fluid choice was controlled in different settings. There were 1641 patients total who were diagnosed with sepsis. 824 patients received either Lactated Ringer's or Plasma-Lyte, with a mean fluid volume of 2967mL. 817 patients received Normal Saline with a mean volume of 3454mL.<sup>12</sup> Results not only showed a lower 30-day in hospital mortality rate in those who received BSs rather than NS, they also showed that the beneficial effects of balanced solutions were greater in those whose fluid choice was controlled starting in the ED versus starting in the ICU.<sup>9</sup>

There was also an ancillary analysis of the SMART trial performed in 2016 with published results in 2021. The primary outcome was assessing the rates of acute kidney injury (AKI) after resuscitation with BSs versus NS, measured via early urinary biomarkers for AKI.<sup>8</sup> 261 patients who were consecutively-enrolled and admitted to the ICU were the participants in

this ancillary study. Urinary levels of neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) were taken at  $36\pm 12$  hours after admission, and compared between the 131 patients who were given balanced crystalloids and the 130 patients who were given normal saline.<sup>8</sup> Results of this study showed that urinary NGAL levels were markedly lower in the group who received balanced crystalloids compared to those who received normal saline. However, KIM-1 levels were not significantly different between either group. Researchers concluded that the use of balanced crystalloids leads to a modest reduction of early biomarkers of AKI when compared to the use of normal saline in the fluid resuscitation of critically ill adult patients.<sup>8</sup>

In 2021 the large RCT Balanced Solution in Intensive Care Study (BaSICS) was published, which compared the outcomes of Plasma-Lyte vs NS on 90 day survival in critically ill patients admitted to the ICU.<sup>12</sup> There were 10520 patients total. 5230 patients received Plasma-Lyte while 5290 patients received NS, with both groups receiving a median fluid volume of 1500mL. The results of the BaSICS trial did not show a significant reduction in mortality between either group. However, there was a significant finding in the subgroup of patients who were septic and solely received balanced crystalloids prior to enrolling in the trial. These patients did have a significantly higher 90-day survival rate, compared to those patients who received either NS alone or NS with BSs prior to enrollment.<sup>12</sup>

In contrast to most previous studies, the PLUS trial (Plasma-Lyte 148 versus Saline Study) showed no significant difference between the two crystalloid types.<sup>12</sup> This trial took place in 2022 with 5037 adult ICU patients. 2515 patients received Plasma-Lyte 148 with a median volume of 3900mL, while 2522 patients received NS with a median fluid volume of 3700mL. The primary outcomes of this study were rates of AKI and mortality after 90 days. No significant

difference was found. Interestingly, 42.3% of the patients included in this trial were diagnosed with sepsis, yet still there was no difference in primary outcome between the two groups.<sup>12</sup>

In addition to adult populations, there is even more scarce evidence in the pediatric population on the preferred fluid type in sepsis management. In 2017 Weiss et al. performed a matched retrospective cohort analysis of 12,529 septic pediatric patients and assessed outcomes after initial resuscitation with and without LR. Pediatric patients were admitted to 382 hospitals in the United States with a diagnosis of either severe sepsis or septic shock between 2000 and 2013. In the first three days of hospital admission, 10,379 patients received only NS (NS group) while 2,150 patients received LR. The latter group included patients who received any LR at all (LR-only group, n=1691) as well as 459 patients who only received LR (LR-only group).<sup>23</sup> The median volume of total fluids received was approximately 24mL/kg. The primary outcome was 30-day in-hospital mortality. Secondary outcomes were rates of AKI, new dialysis, and length of stay. Results did not show a significant difference in mortality between the NS and LR groups (7.2% vs 7.9%). The only significant difference in secondary outcomes was a longer length of hospital stay in the LR-any group when compared to other groups. There were no differences in rates of AKI or new dialysis.<sup>23</sup>

Trepatchayakorn et al. recently performed a randomized controlled trial with 42 septic pediatric patients assessing outcomes after resuscitation with BSs or NS.<sup>22</sup> 42 patients were admitted to King Chulalongkorn Memorial Hospital from November 2016 to November 2019. Patients were randomized into three groups to receive either Normal Saline solution, Lactated Ringer's solution, or Sterofundin (another balanced crystalloid). Patients received a median fluid dose of 30mL/kg. Data from initial, 2 hour, 6 hour, and 24 hour fluid boluses were collected which included electrolytes, kidney function, and coagulation studies. Researchers also measured

levels of urinary neutrophil gelatinase-associated lipocalin (uNGAL), an early biomarker for acute kidney injury (AKI).<sup>22</sup> Results showed no difference in outcomes between any of the groups. However, patients who received fluid boluses of LR larger than 30mL/kg had decreased levels of uNGAL biomarkers after 2 hours of resuscitative therapy when compared to the other groups.<sup>22</sup>

Aside from human clinical trials, there have been multiple trials on animal subjects as well. One such trial was conducted in 2016 by Orbegozo et al. These researchers performed a randomized trial on adult sheep after induction of experimental abdominal sepsis, randomizing the sheep into receiving either LR, Plasma-Lyte, or NS.<sup>13</sup> This experiment involved sedating adult sheep and placing them on a mechanical ventilator. They then induced peritonitis by intra-abdominally injecting autologous feces in 21 subjects and performed baseline measurements. Thereafter, subjects were randomized into groups of seven to either receive fluid resuscitation with LR, Plasma-Lyte, or NS. Each group received a 10ml/kg IV bolus given over 15 minutes prior to a 3mL/kg/h continuous infusion of their randomized crystalloid. Sidestream dark field videomicroscopy was used to measure sublingual microcirculation, while near-infrared spectroscopy was utilized to measure oxygen saturation in muscle tissues. Results showed that resuscitation with NS was associated with hyperchloremic metabolic acidosis as opposed to other groups. Subjects given NS had a lower cardiac index and left ventricular output, lower MAP, and decreased vessel perfusion than those treated with LR. Oxygen saturation of muscle tissue was lower in the NS treated group compared to groups treated with LR and Plasma-Lyte. Subjects given NS had a lower survival time than those given LR, but a survival time similar to those given Plasma-Lyte.<sup>13</sup>

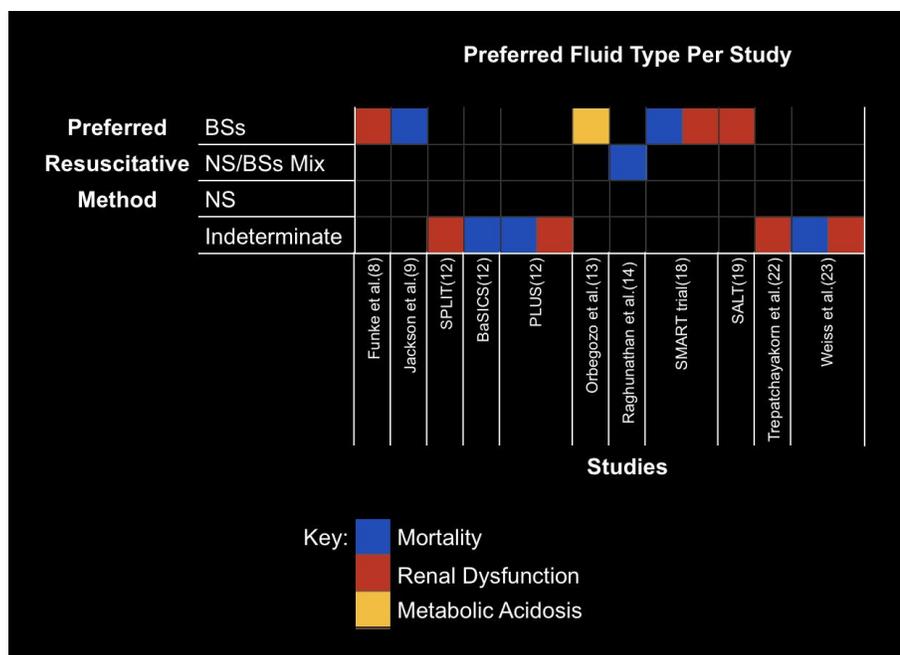
## **Discussion**

Overall, six out of the eleven above studies report a statistically significant benefit in critically ill patients when given some form of balanced crystalloids over normal saline. Most studies that support balanced crystalloids highlight the overall decrease in mortality and renal dysfunction, with one study confirming the association between NS and metabolic acidosis.

The remaining five studies have indeterminate results, showing no significant difference between any of the groups. It should be noted that none of the included studies show better outcomes in those who were preferentially given normal saline as opposed to balanced crystalloids, highlighting the fact that there may be no drawback to utilizing balanced crystalloids almost every time.

The primary outcomes of this systematic review are determining rates of mortality, renal dysfunction, and metabolic acidosis in septic patients who are given either 0.9% normal saline (NS) or balanced crystalloids (BSs). There were eleven studies included in this systematic review. Six studies report outcomes on mortality rates, seven studies report outcomes on renal dysfunction, and one study reports an outcome of metabolic acidosis.

This summary table explains the findings of the studies in this systematic review. The x-axis denotes each study with the primary author(s) and reference number. The y-axis represents



the preferred method of resuscitation concluded by the authors of each study. Some studies have multiple variables, signifying that there were multiple outcomes in a study, denoted by the color key. Each outcome is plotted against the method with which the best results were obtained. For example, in study 8, balanced solutions (BSs) yielded the best outcomes on rates of renal dysfunction.

#### *Comparing outcomes of Mortality*

Three out of six studies show a significant decrease in mortality with BSs compared to NS. Those studies will be discussed first, followed by the three studies that show no difference. One of the latter studies, while finding no difference between outcomes during the study, did find that fluids administered before being enrolled in the trial affected patient outcomes.

The retrospective cohort study performed by Raghunathan et al. was the largest study in terms of patient population included in this systematic review. Results showed that those given a combination of NS+BSs had significantly lower in-hospital mortality rates than other groups. It should be noted that no patients in this study received BSs alone. All other groups received either NS alone or combined with other fluid types.<sup>14</sup> The main limitation of this study was the non-randomization of patients into exposure categories, as this was not an RCT but a retrospective cohort study. As such, it can be inferred that clinician preference was the primary factor in deciding which fluid mixture patients received. Pros of this study are that it was a multi-year, multi-center study with a very large patient population who were all admitted with severe sepsis. Findings of this study indicate that even in combination with normal saline, balanced crystalloids are correlated with lower rates of in-hospital mortality in severely septic patients.

Perhaps the most significant study included in this systematic review is the SMART trial conducted by Semler et al. which directly compared the outcomes of BSs versus NS alone.<sup>18</sup> Results showed that resuscitation with BSs was associated with a lower mortality rate than NS. In addition, it was shown that the benefit of using BSs over NS was greatest in those who had a diagnosis of sepsis or septic shock, further supporting the use of BSs in sepsis. Limitations of this study include that the outcomes of patients who received BSs were grouped together regardless of whether patients received LR or Plasma-Lyte, as well as the fact that hyperkalemia was a contraindication to BSs when it has been shown that BSs may in fact be preferable to NS in the setting of hyperkalemia. Pros of this study are that it was a large patient population, patients were randomized into exposure categories, and outcomes were directly measured between BSs and NS. These findings indicate that balanced crystalloids are essential in reducing the mortality rate of septic patients.

Next is the secondary analysis of the SMART trial, performed by Jackson et al.<sup>9</sup> This secondary analysis focused on only the septic patients in the SMART trial, making it a more specific study. Researchers found that patients given BSs had a lower 30-day in-hospital mortality than those given NS. In addition, they found that the benefits of BSs were greater in those who received them earlier in their clinical course. The primary limitation of this study was that it was a small patient population. Pros of this study include that patients were randomized and it was a specific patient population in terms of age and diagnosis. Findings of this study not only correlate BSs with lower mortality, but also correlate better outcomes with earlier administration of BSs.<sup>9</sup>

The BaSICS study measured 90 day survival in adult ICU patients when given Plasma-Lyte versus NS.<sup>12</sup> Limitations of this study were that patients in both groups only

received a median fluid volume of 1500mL, as opposed to other studies with larger fluid volume administrations. Pros of this study are the large number of enrolled patients as well as the direct comparison between NS and a specific balanced crystalloid, Plasma-Lyte. Results did not show a difference in mortality between either group. However, researchers found that septic patients actually had better mortality outcomes when they received only BSs prior to being enrolled in the trial, as opposed to NS or other fluid mixtures. These findings, while not significant for distinguishing outcomes between groups in the ICU, do indicate that reduced mortality is directly related to earlier administration of BSs in septic patients.

Conversely, two studies found absolutely no significant difference in rates of mortality between groups who received BSs and NS at all, with no contradicting evidence like the BaSICS study mentioned above. The first is the PLUS trial, which found no difference in rates of 90-day mortality between adult ICU patients who received Plasma-Lyte or NS.<sup>12</sup> Pros of this study were that patients received large volumes of both fluid types (median of 3900mL in the Plasma-Lyte 148 arm and 3700mL in the NS arm), a significant portion of the enrolled patients were septic (42.3%), and the study directly compared Plasma-Lyte vs NS alone. The primary limitation was the comparatively smaller patient population than other studies (n=5037).

The second study reporting absolutely no mortality differences is the retrospective cohort analysis conducted by Weiss et al., which found no differences in mortality between septic pediatric patients receiving LR or NS.<sup>23</sup> Limitations of this study were that patients were not randomized into fluid exposure categories, and therefore clinical preference was most likely the deciding factor in what fluid patients received. In addition, only about 17% of patients received LR while almost 83% of patients received NS, creating an unequal distribution of fluids and thus possibly skewing results. Pros of this study are that it was a multi-center (n=382 hospitals) study

directly comparing a single balanced crystalloid (LR) with NS. Findings of both this study as well as the PLUS trial mentioned above seem to indicate that crystalloid type does not matter when assessing risk of mortality in septic patients.

#### *Comparing outcomes of Renal Dysfunction*

Four out of seven studies concluded that BSs are associated with fewer instances of renal dysfunction, and will be discussed first. The remaining four studies found no difference between groups and will be discussed last.

The SALT trial had two main limitations which were the low fluid administration volumes (median fluid volume of 1617mL of BSs and 1424mL of NS) and small patient population. Pros of the SALT trial were that a significant proportion of the patients were septic (28.6% who received BSs and 25% who received NS) and there was no bias in enrolling patients into the trial as all 970 ICU patients in-a-row were enrolled regardless of the admitting diagnosis or comorbidities. Findings slightly point toward a benefit with BSs, as there was a positive correlation between patients who received large volumes of NS and more frequent major renal complications. Although, there were no differences found in rates of stage II or greater AKI or new renal replacement therapy (RRT). These findings seem to correlate NS with renal complications, while the main limitation of this study being small fluid volumes could have contributed to the lack of development of AKI or RRT.

While previously discussed above when comparing rates of mortality, the SMART trial also included outcomes on persistent renal dysfunction and new RRT.<sup>18</sup> As a reminder, this study compared BSs vs NS on adult ICU patients. Researchers found that patients who were resuscitated with BSs had lower rates of renal dysfunction as well as a decreased need for RRT than those given NS.

Not yet discussed was the ancillary analysis of the SMART trial, which examined rates of AKI between groups by measuring urinary biomarkers for AKI (NGAL and KIM-1).<sup>8</sup> The limitation of this study was the comparatively small sample size of 261 patients. However, these patients were all consecutively enrolled after ICU admission and were also randomized into exposure categories, limiting treatment bias by clinicians. Researchers found a markedly decreased level of NGAL in those who received BSs than in those who received NS, while KIM-1 levels did not change significantly. Instead of directly measuring the rates of AKI, which depend more on patient presentation and volume of fluid administered, the measurement of AKI biomarkers allowed for researchers to predict those at risk for AKI with smaller fluid volumes. This process highlights the detrimental effects of large volume administration of NS on the renal circulatory system.

Lastly, there was the RCT of pediatric septic patients performed by Trepatchayakorn et al. which compared outcomes on groups receiving NS, LR, or a balanced crystalloid called Stereofundin.<sup>22</sup> Limitations were the small sample size (n=42). Pros of this study are that all patients were septic and it was specific to the pediatric population. There were ultimately no differences in rates of AKI, electrolytes, or coagulation studies between groups. However, uNGAL levels (an early urinary biomarker for AKI) were also measured between groups. It was found that patients who received LR fluid boluses >30mL/kg had lower urinary concentrations of uNGAL than other groups. Again, while there were no differences in rates of AKI, this study shows that NS is once again associated with worse effects on the kidneys than BSs.

In contrast, three studies showed no difference in outcomes of renal dysfunction. The SPLIT trial compared NS vs Plasma-Lyte in adult ICU patients.<sup>12</sup> Limitations of this study are that it has a low sample size (n=2262) and only 4% of the enrolled patients were diagnosed with

sepsis. Pros include that patients were randomized into exposure categories where the study directly compared one fluid (NS) against another (Plasma-Lyte). Researchers found no difference in rates of AKI between the two groups. The PLUS trial, discussed above, did not show differences in rates of AKI between those who were given Plasma-Lyte or NS.<sup>12</sup> In addition, the retrospective cohort analysis conducted by Weiss et al. showed no significant differences in rates of AKI or new dialysis.<sup>23</sup> However, it should be noted that the vast majority of patients in this study received NS (83%) instead of BSs, in addition to the fact that clinician preference was most likely the deciding factor in fluid selection.

#### *Comparing outcomes of Metabolic Acidosis*

There was only one study included in this systematic review which compared a primary outcome of metabolic acidosis. The trial on animal subjects conducted in 2016 by Orbegozo et al. compared outcomes of fluid types on septic adult sheep.<sup>13</sup> A limitation of this study is that it was performed on sheep, while the differences in sepsis and fluid administration between sheep and humans has not been extensively researched. Regardless, pros were that sheep were randomized into fluid exposure category and each sheep was given the same amount of intravenous fluid. Some subjects who were given NS were found to enter into a state of hyperchloremic metabolic acidosis, while subjects in other groups did not. This is important for clinical practice as inducing a state of metabolic acidosis in a septic patient only serves to worsen their condition, pointing toward BSs as a safer alternative.

#### *Summary*

Overall, the studies analyzed in this systematic review either present one of two results: in the setting of sepsis, balanced crystalloids result in better outcomes than normal saline, or outcomes are not different and fluid choice does not matter. Take note that no conclusions were

made inferring that NS has better outcomes than BSs. The majority of studies concluded that BSs do in fact offer a safer alternative, one that is more physiologically compatible with human plasma and thus makes more sense to use. Not only is there a positive correlation between NS and death, but also renal dysfunction and metabolic acidosis. Among the more shocking facts concluded in the research, the SMART study found that the number needed to treat (NNT) with BSs instead of NS among septic or septic shock patients in order to prevent death, new renal replacement therapy, or persistent renal dysfunction was approximately 20 patients.<sup>15</sup> This indicates that up to 5% of septic patients will greatly benefit from balanced solutions. This, in combination with the evidence presented above, points to a shift in future practice for clinicians managing sepsis. However, more thorough and complete research is needed to make a definitive answer.

#### *Future Research Proposal*

The author designed a single-blind study to evaluate the safety, efficacy, and outcomes of balanced versus unbalanced crystalloid administration in septic patients. In the ideal setting, this study would include over 50,000 adult patients of any sex or demographic who are randomized into exposure categories. The primary outcomes of this study are to contrast and compare rates of 90-day mortality, renal dysfunction, and metabolic acidosis. Secondary outcomes are electrolyte abnormalities, length of hospital stay, and cost per day. The goal of this study is to determine which type of crystalloid should be the first-line resuscitation agent in the setting of sepsis, for which there is little current evidence.

Inclusion and exclusion criteria of this study are as follows: 1. Patients must have a suspected/documentated bacterial infection and meet 2/4 SIRS criteria at the time of enrollment. 2. Patients must be between the ages of 18-65 years. 3. Patients may not have any known

contraindications to balanced crystalloids, including moderate neurologic injury. Hyperkalemia, cirrhosis or hepatic injury will not be considered contraindications to balanced crystalloids.

Patients will consent to enrollment in the trial at the time of sepsis diagnosis. They will then be randomized into one of three exposure categories: 0.9% Normal Saline, Lactated Ringer's, or Plasma-Lyte. Patients will then receive an agreed-upon fluid volume of their randomized fluid type, in addition to other diagnostic and therapeutic interventions (antibiotic therapy, vasopressors, inotropes, etc). Patients will be followed during the course of their treatment for a total of 90 days or upon hospital discharge, whichever comes first. Rates of 90-day mortality, renal dysfunction, metabolic acidosis, electrolyte abnormalities, length of hospital stay, and cost per day will all be monitored and evaluated.

### **Conclusion**

As discussed above, the current Surviving Sepsis Campaign Guidelines do give a recommendation of administering BSs over NS, however as stated this is a weak recommendation with low quality evidence.<sup>6</sup> There is still much debate about the best type of fluid for certain situations, which makes tailoring fluid choice to the patient all the more difficult. The results from this systematic review give more evidence to the claim that balanced crystalloids are the better option in the setting of sepsis, as they are more commonly associated with reduced rates of mortality, renal dysfunction, and metabolic acidosis than is normal saline.

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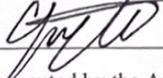
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