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Fluid Resuscitation in the Early Management of Septic Shock

BY LAURALYN MCINTYRE, M.D.

Severe sepsis and septic shock are the most common causes of mortality in the intensive care unit (ICU), and account for approximately 10% of ICU admissions¹ and 2.9% of all hospital admissions.² In the USA, the average annual cost for treating severe sepsis amounts to \$16.7 billion nationally.² Despite over 20 years of intense therapeutic investigation, mortality has remained at approximately 50%.³ Although fluid resuscitation is an integral component in the management of severe sepsis and septic shock, evidence favouring the use of colloidal over crystalloid solutions is lacking.⁴ Indeed, despite passionate arguments in favour of either solution, no randomized controlled trial has ever demonstrated the benefit of one solution over the other. This issue of *Critical Care Rounds* presents the rationale for early aggressive volume resuscitation in septic shock and discusses the controversy over the appropriate solution.

Goals of fluid administration

In the first 24 hours of care, patients with severe sepsis or septic shock often receive several liters of fluid, including colloids, crystalloids, or a combination of the two. The goals for such aggressive administration of fluids are to expand plasma volume, maintain hemodynamic stability, and in turn, optimize perfusion and oxygen delivery to tissues.⁵ The relevance of this approach was recently emphasized by Rivers et al in a randomized controlled trial suggesting that an early aggressive resuscitation strategy, aimed at maintaining adequate oxygen delivery and tissue perfusion, improved organ dysfunction and reduced in-hospital mortality.⁶ Within 2 hours of presentation to the emergency room, the investigators randomized 263 patients with early severe sepsis and septic shock to an algorithm-driven, goal-directed, therapeutic strategy (to maintain a central venous saturation $\geq 70\%$) versus the protocol alone.⁶ Mortality in the goal-directed group was decreased by an absolute difference of 16% (46.5% versus 30.5% $p=0.009$). A major component of care involved the aggressive administration of fluids, with the goal-directed group receiving significantly more fluids in the first 6 hours (5.0 versus 3.5 liters, $p<0.001$). Unfortunately, the type of fluid used in this study was left to the discretion of the physician. Interestingly, the goal-directed arm also received a larger number of blood transfusions and their care was guided with the use of continuous monitoring central venous oxygen co-oximetry. Consequently, there are a number of plausible hypotheses that may explain the improvements in outcomes observed in this study.⁶ The importance of early aggressive resuscitation, however, likely underlines the success of the intervention



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arm of the study. In this respect, fluid administration remains critical for resuscitation in severe sepsis and septic shock. Given that several liters of fluid can be administered in response to hemodynamic instability in severe sepsis or septic shock, and recognizing that prolonged hemodynamic instability and hypoperfusion to the organs are associated with mortality, it is reasonable that the type of fluid administered may have a substantial impact on patient outcome

Colloids versus crystalloids: controversy and evidence

Two main classes of fluid serve to expand the plasma volume in the management of all acutely ill patients including patients with severe sepsis and septic shock: colloidal and crystalloid solutions. Although both solutions are used for plasma volume expansion in patients who develop severe sepsis,⁷ there is no evidence favouring the use of one fluid over the other. Those who favour the use of colloids argue that hypo-oncotic crystalloids leak from the plasma and excessively expand the interstitial fluid volume.⁸ In contrast to crystalloid solutions, colloidal solutions are macromolecules that, under normal physiologic conditions, do not pass through the endothelial layer into the interstitial space. Thus, colloids have the potential advantage of requiring much less volume to expand the intravascular space in comparison to crystalloids. However, in abnormal physiological states such as severe sepsis where endothelial injury is present, this theory may not hold true. Thus, advocates of crystalloid solutions suggest that leakage of colloids into the interstitial space may also contribute to the development of edema,⁸ particularly in the setting of endothelial injury. Colloids trapped in the interstitial space create an osmotic gradient and pull additional water into the interstitial space.

Normal saline is considered the “usual care” fluid, particularly in the first hours of resuscitation for patients with severe sepsis and septic shock. Although slightly hypertonic, the electrolyte components of normal saline are similar to plasma (154 mEq of sodium and chloride). Compared to hydroxyethyl starch molecules, normal saline:

- is considerably less expensive (\$1.08 versus \$69.32 per 500 ml bag)
- has not been associated with the development of acute renal failure or serious adverse reactions
- is not a concern with respect to clearance from the kidney
- has been used for resuscitation in this patient population for several decades.

There is limited evidence to suggest that hydroxyethyl starches may be superior, since these molecules may be able to halt the processes that produce the deleterious effects of severe sepsis and septic shock. In a trauma and septic population, these molecules may either decrease endothelial activation, and/or prevent endothelial injury,^{9,10} in addition to modulating neutrophil chemotaxis.^{11,12} These mechanisms may be critical in explaining why hydroxyethyl starches have been associated with less microvascular leakage and less tissue edema in septic animal models and in a blunt trauma population.¹³⁻¹⁵

Despite these potential benefits, colloids have also been associated with alterations in coagulation. To examine whether routinely administered colloids and crystalloids influence the hemostatic system, Innerhofer and co-workers studied 60 patients undergoing knee replacement surgery who were administered intravascular 6% hydroxyethyl starch 200/0.5 (HES) or 4% modified gelatin (GEL), in addition to a basal infusion of lactated Ringer's solution (RL), or exclusively RL.¹⁶ The authors demonstrated a significant adverse impact on platelet-mediated hemostasis and clot formation with the IV administration of fluids. Total clot strength, fibrinogen, and clot elasticity decreased significantly more in the colloid groups than in the RL group. These data suggested that the administration of colloids critically impaired fibrinogen polymerization and reduced fibrinogen concentrations early in resuscitation. The clinical relevance for these and earlier observations of the effects of colloids on hemostasis needs to be defined.

To make matters more complex, not only are there potentially relevant differences between the various starches, there may be relevant differences between the various crystalloid solutions. The development of hyperchloremic metabolic acidosis is a recognized complication of high-volume saline resuscitation. Ringer's lactate may circumvent this problem and some physicians recommend RL as the crystalloid of choice. However, the development of decreased serum osmolality (thereby increasing cerebral water) has been observed in some animal studies. This has led to recommendations for limiting RL use in neurosurgical patients.

An interesting study by Williams et al evaluated the effects of RL (50 mL/kg RL over 1 hour) or normal saline (NS) (0.9%) in 18 healthy human volunteers aged 20-48 years.¹⁷ Blood pH increased after RL, but decreased with NS. Of greater interest, subjective mental changes occurred only with NS. In addition, abdominal discomfort was more common and the time until first urination was longer with NS. The clinical relevance of these observations also requires further study.

Effects on organ perfusion

As mentioned above, the primary goal of fluid resuscitation is to ensure adequate tissue perfusion and prevent multi-system organ dysfunction. Although not a perfect index, gastric intramucosal PCO_2 , measured using a gastric tonometer has been used in experimental critical care settings to measure the adequacy of tissue perfusion. Within this context, there is conflicting evidence regarding the efficacy of hydroxyethyl starches for improving tissue perfusion in vascular and septic patient populations, respectively.^{18,19} In the latter study, Forrest et al evaluated the effect of colloid administration in 13 septic patients who were hypovolemic (wedge pressure <15 mm Hg) and had a gastric PCO_2 gradient of 25 ± 21 mm Hg. Following the administration of 250 to 1000 cc of pentastarch, there was an increase in global oxygen delivery and wedge pressure measurements. Despite these improvements, however, there was no influence of colloid administration on the gastric PCO_2 gradient. In summary, it appears there is an adequate physiologic rationale to hypothesize that pentastarch may be superior to 0.9% saline when resuscitating patients with severe sepsis and septic shock.

Despite the ongoing controversy between the superiority of colloids versus crystalloids, 7 published systematic reviews have not consistently demonstrated the superiority of one fluid over another in terms of the development of organ dysfunction or death (Table 1).²⁰⁻²⁶ However, all pooled mortality estimates do suggest a non-significant trend toward harm with colloids, with the exception of a review published by Wade and colleagues.²¹ Indeed, two Cochrane reviews (representing updated reviews previously published in the *British Medical Journal*^{20,23}) – one examining albumin, and the other colloids – reached statistical significance (relative risk 0.66 (95% CI, 0.50-0.85) and 0.66 (95% CI, 0.49-0.93). However, subgroup analyses produced more discordant results, with some demonstrating trends toward harm with colloid use, while others revealed protective trends. There are several reasons why these reviews have not been able to definitively answer the question of superiority of one fluid over the other.

- First, 6 of the 7 systematic reviews pooled heterogeneous patient populations.
- Second, 3 of the reviews pooled studies with different colloidal and crystalloid solutions.
- Third, the individual studies had fundamentally different objectives (eg, physiologic versus morbidity endpoints), different resuscitation schedules (volume, rate, duration of administration), outdated fluid protocols

without an adequate physiologic rationale for the administration of fluids, and a lack of standardized co-interventions.^{27,28}

- Finally, many studies lacked sufficient methodological rigor to protect against bias.^{24,27,28}

For these reasons, no firm conclusions can be made with respect to the superiority of one fluid over the other. Indeed, the authors of these reviews suggest that large, well-designed, and rigorously conducted, randomized, controlled trials in specific patient populations are required to resolve this uncertainty.^{20,22-24}

Clinical trials

A large, randomized, multicentre fluid resuscitation trial is underway in Australia and New Zealand (The 0.9% Saline vs. 4% Albumin Fluid Evaluation [SAFE] Study). The SAFE study includes a heterogeneous group of critically ill patients who are eligible for inclusion at *any point* during their critical illness. In this trial, fluids are administered throughout the time in the ICU and without a goal-directed or algorithm-driven protocol. The 7000th patient was enrolled on June 6th 2003 and the study was recently closed; the results are being analyzed. This study will be the largest systematic evaluation of fluid resuscitation in sepsis to date, and the intensive care community is eagerly awaiting the results.

At the University of Ottawa, Ottawa Hospital, we have developed a separate clinical trial to evaluate the effects of fluid type on the outcome during early shock since this is when the choice of fluid may have the most significant impact on outcome. The study includes patients with septic shock in the very early phases of their critical illness. Most importantly, the study administers fluids according to a goal-directed algorithm-driven protocol with the specific aim of optimizing perfusion and oxygen delivery to the tissues. In addition, the comparator solution to saline is PentaspanTM. For these reasons, we believe that this study question and design are sufficiently different from the Australian study; hence, we believe the trial is important and warranted. At present, we are in the process of validating the treatment algorithms and once this validation phase is complete, through the assistance of the Canadian Critical Care Trials Group, we anticipate starting the actual clinical trial.

Conclusion

Significant challenges remain in treating patients with septic shock. Indeed, despite how often we face patients who are septic, very basic questions remain. What goals of therapy should be used to monitor the patient? When should vasopressors be used? Which vasopressor is

Table 1: Pooled mortality and subgroup analyses of seven systematic reviews comparing colloids to crystalloids				
Author Year	Comparator	Pooled Mortality Outcome RR (95% Confidence intervals) RR < 1 favors crystalloids	Mortality Outcome – Clinical Subgroups RR (95% Confidence intervals) RR < 1 favors crystalloids	
*Alderson ²⁵ 2002 (Cochrane)	Albumin/PPF versus Crystalloid	0.66 (0.50 – 0.85)	Hypovolemia	0.68 (0.45 – 1.03)
			Burns	0.42 (0.19 – 0.90)
			Hypoalbuminemia	0.73 (0.49 – 1.06)
Wilkes ²⁴ 2001	Albumin versus Crystalloid	0.90 (0.78 – 1.05)	Surgery or trauma	0.89 (0.69 – 1.18)
			Burns	0.57 (0.32 – 1.03)
			Hypoalbuminemia	0.63 (0.36 – 1.10)
			High-risk neonates	0.84 (0.55 – 1.28)
			Ascites	1.08 (0.78 – 1.49)
			Other	1.10 (0.82 – 1.49)
The Cochrane Injuries Group ²⁰ 1998	Albumin/PPF versus Crystalloid	0.60 (0.45 – 0.79)	Hypovolemia	0.69 (0.45 – 1.03)
			Burns	0.42 (0.19 – 0.90)
			Hypoalbuminemia	0.59 (0.37 – 0.93)
*Alderson ²⁶ 2000 (Cochrane)	Colloid versus Crystalloid	0.66 (0.49 – 0.93)	HES	0.86 (0.51 – 1.47)
			Gelatin	2.00 (0.33 – 12.5)
			Dextran	0.81 (0.61 – 1.06)
			Albumin/HS vs saline	2.00 (0.23 – 16.67)
			Dextran/HS vs saline	1.14 (0.95 – 1.35)
			Colloid vs HS saline	0.14 (0.01 – 2.56)
Choi ²² 1999	Colloid versus Crystalloid	0.86 (0.63 – 1.17)	Trauma	0.39 (0.17 – 0.89)
			Non-trauma	0.98 (0.70 – 1.36)
Schierhout ²³ 1998	Colloid versus Crystalloid	0.84 (0.69 – 1.02)	Trauma	0.77 (0.57 – 1.05)
			Surgery	1.82 (0.61 – 5.56)
			Burns	0.83 (0.60 – 1.14)
			Other	0.93 (0.62 – 1.37)
***Wade ²¹ 1997	HS/Dextran versus Isotonic Saline	1.2 (0.94 – 1.57)**		

PPF = plasma protein fraction; HS = hypertonic saline; HES = hydroxyethyl starch

* Both Cochrane systematic reviews represent updated reviews that were originally published in the British Medical Journal.

** Outcome expressed as odds ratio with 95% confidence intervals

*** Results presented are only those where colloid (hypertonic saline in dextran) was compared to a crystalloid (isotonic crystalloid).

optimum? How can we assess end organ perfusion? What type of fluid should we use? Despite years of debate, there are no systematic trials to guide the answers for many of these very basic questions. The investigators of the SAFE study are to be applauded for the breadth of their trial; however, irrespective of their findings, important questions will remain, demanding further evaluation.

Lauralyn McIntyre, MD, is Clinical Scholar at the University of Ottawa. Dr. McIntyre practices critical care medicine at the Ottawa Hospital. She is developing and conducting a clinical research program focused primarily on early resuscitation in septic shock.

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Abstracts of interest

Early goal-directed therapy in the treatment of severe sepsis and septic shock.

RIVERS E, NGUYEN B, HAVSTAD S, ET AL; EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP. DETROIT, MI
BACKGROUND: Goal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit.

METHODS: We randomly assigned patients who arrived at an urban emergency department with severe sepsis or septic shock to receive either six hours of early goal-directed therapy or standard therapy (as a control) before admission to the intensive care unit. Clinicians who subsequently

assumed the care of the patients were blinded to the treatment assignment. In-hospital mortality (the primary efficacy outcome), end points with respect to resuscitation, and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were obtained serially for 72 hours and compared between the study groups.

RESULTS: Of the 263 enrolled patients, 130 were randomly assigned to early goal-directed therapy and 133 to standard therapy; there were no significant differences between the groups with respect to base-line characteristics. In-hospital mortality was 30.5 percent in the group assigned to early goal-directed therapy, as compared with 46.5 percent in the group assigned to standard therapy ($P = 0.009$). During the interval from 7 to 72 hours, the patients assigned to early goal-directed therapy had a significantly higher mean (\pm SD) central venous oxygen saturation (70.4 ± 10.7 percent vs. 65.3 ± 11.4 percent), a lower lactate concentration (3.0 ± 4.4 vs. 3.9 ± 4.4 mmol per liter), a lower base deficit (2.0 ± 6.6 vs. 5.1 ± 6.7 mmol per liter), and a higher pH (7.40 ± 0.12 vs. 7.36 ± 0.12) than the patients assigned to standard therapy ($P < \text{or} = 0.02$ for all comparisons). During the same period, mean APACHE II scores were significantly lower, indicating less severe organ dysfunction, in the patients assigned to early goal-directed therapy than in those assigned to standard therapy (13.0 ± 6.3 vs. 15.9 ± 6.4 , $P < 0.001$).

CONCLUSIONS: Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock.

N Engl J Med 2001;345(19):1368-77.

Are delays in the recognition and initial management of patients with severe sepsis associated with hospital mortality?

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Introduction: A landmark publication has demonstrated that early and aggressive resuscitation reduces mortality from severe sepsis (SS) and septic shock.

HYPOTHESIS: Our objective is to understand if delays in the recognition and initial management of patients with severe sepsis are associated with hospital mortality from severe sepsis.

METHODS: Design/Setting: Retrospective observational study at a Canadian tertiary care intensive care unit (Ottawa Hospital, Ottawa, Ontario).

Patient population: 329 patients with severe sepsis admitted to ICU July 1, 2000, to June 30, 2001 were identified using two criteria: ICU database and ICD-9 codes from medical records. Inclusion criteria were: 1) hypotension – SBP ≤ 90 mm Hg or a drop in the SBP ≥ 40 mm Hg from baseline, or a MAP ≤ 65 mm Hg; 2) confirmed or suspected infection; 3) two or more SIRS criteria. Data was collected by trained data abstractors.

RESULTS: Of 329 charts screened, 91 patients met criteria for severe sepsis. Of the 91 included patients, mean age was 62 (17.1) and 40% were women. Mean APACHE II scores were 19.1 (5.9) and 29.1 (7.5) for survivors and non-survivors respectively. Time

to first fluid challenge from SS time 0 was shorter for survivors as compared to non-survivors [2.2 (4.6) hours versus 4.8 (7.2) hours]. Time to ICU admission from SS time 0 was also shorter for survivors as compared to non-survivors [8.5 (6.8) versus 10.6 (8.1)].

CONCLUSIONS: Early and accurate identification, and prompt transfer of patients with severe sepsis to a critical care setting may be essential to improve outcome.

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