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Are Fluid Resuscitation Strategies Associated with Hospital Mortality in Severely Septic Patients?
A Retrospective Cohort Study

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Are Fluid Resuscitation Strategies Associated with Hospital Mortality in Severely Septic Patients?

A Retrospective Cohort Study

By

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Abstract

Background: Fluid resuscitation is the foundation of severe sepsis management as it is a key factor for optimizing cardiac output, and hence restoring hemodynamic stability and perfusion to the tissues.

Objective: To examine for the association between quantity (primary), type (secondary) and method (secondary) of fluid administered in the first six hours after the identification of severe sepsis and hospital mortality.

Design: Retrospective cohort study.

Setting: The Ottawa Hospital (General Campus), Ottawa, Ontario

Methods: Patients with severe sepsis admitted to the Ottawa Hospital, General Campus between July 1, 2000 and June 30, 2002 were identified using ICU database and medical records search strategies. Inclusion criteria were: 1) hypotension (SBP $\leq$ 90 mm Hg/MAP 65 $\leq$ mm Hg or a drop in SBP $\geq$ 40 mm Hg from baseline); 2) infectious source; 3) $\geq$ 2 systemic inflammatory responses syndrome (SIRS) criteria. Total quantity of fluid, type of fluid, and method of fluid administered was recorded over the first 6 hours after severe sepsis was identified. The first episode of hypotension defined the starting point for collection of fluid data. Adjusted and unadjusted logistic regression analyses were performed to examine for the association between quantity, type, and method of fluid administered in the first six hours after severe sepsis was identified and hospital mortality.

Results: 1080 charts were screened and 282 patients were included in the chart review. Overall, the mean age and Acute Physiology and Chronic Health Evaluation Score (APACHE II) were 63±14 years and 28±8 respectively. Females comprised 48% of the cohort. For the quantity of fluid administered analysis, the adjusted odds of death and 95% confidence intervals for the "2 – 4" L and "greater than 4" liter groups were 0.99 (0.51 to 1.94) and 1.02 (0.39 to 2.57) as compared to the "0 – 2" liter fluid group respectively. For the type of fluid administered analysis, the adjusted odds of death and 95% confidence intervals for the colloid and crystalloid fluid group was 1.02 (0.55 to 1.89) as compared to the crystalloid fluid group. For the method of fluid administered analysis, the adjusted odds of death and 95% confidence intervals for the fluid bolus and fluid infusion group was 0.42 (0.15 to 1.15) as compared to the fluid infusion group alone.

Conclusion: In this retrospective cohort study, quantity and type of fluid administered in the first six hours after the identification of severe sepsis were not associated with hospital mortality. However, there was a trend toward a reduction in hospital mortality for the group that received fluid boluses and fluid infusions as compared to fluid infusions alone. Future research is required to determine optimal fluid resuscitation practices for patients with severe sepsis.

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Table of Contents

List of Tables

List of Figures and Illustrations

List of Appendices

1.0: BACKGROUND AND REVIEW OF THE LITERATURE

1.1 Statement of the Problem

Severe sepsis imposes a significant burden to the health care system in terms of both high mortality as well as cost. Sepsis accounts for approximately 2.9% of admissions to hospital, 10% of admissions to the intensive care unit (ICU), and is the 10th leading cause of death in ICU's[1;2]. Despite over several decades of intense therapeutic investigation, the mortality from severe sepsis and septic shock remains between 30 and 60%[3;4].

The infectious pathogen followed by the host response is primarily responsible for the initiation and then malignant release of both the inflammatory and coagulation cascades. It is the interaction between these cascades that result in reduced oxygen delivery, end organ ischemia, and hypoperfusion to the tissues with the final pathway of multiple organ failure and death[3]. Novel pharmacological treatments and resuscitation strategies for severe sepsis and septic shock have recently been shown to reduce morality from this devastating illness. Pharmacological treatments include the administration of anticoagulants and corticosteroids[5;6]. Both of these therapies are targeted either directly or indirectly at modulating the inflammatory and coagulation response.

Early identification and rapid resuscitation for patients with severe sepsis and septic shock is crucial[7-11]. The administration of resuscitation fluids are a key factor in the early resuscitation of these patients because all patients are hypovolemic secondary to intravascular and interstitial fluid volume deficits. Sepsis itself causes a vasodilatory state, thus contributing to hypovolemia. Persistent hypovolemia, vasodilatation, and myocardial suppression associated with sepsis result in inadequate cardiac output, hemodynamic instability manifested by hypotension, and hypoperfusion of the tissues[12]. Fluid resuscitation, especially in the early phases of this illness is considered to be a central factor for restoring optimal cardiac output and hemodynamic stability because for the heart to pump maximally, it requires adequate volume loading[13]. Maximizing cardiac output serves to optimize oxygen delivery and perfusion to the tissues[14] and may also serve to modulate the inflammatory and coagulation response[14-18], and endothelial cell injury[15;16;19], all mechanisms that may contribute to the development of multiple organ failure and death.

In support of the importance of an early and aggressive fluid resuscitation strategy, recent evidence from a randomized controlled clinical trial found that hospital mortality was reduced to a significant extent when an early and aggressive resuscitation strategy was used for patients with severe sepsis and septic shock[20]. This resuscitation strategy included the aggressive administration of fluids in the first six hours of care[20].

Given that intravenous fluids are an integral component in the resuscitation of patients with severe sepsis and septic shock, the primary objective of this thesis was to understand if the total quantity of fluid administered within the first six hours after the identification of severe sepsis was associated with hospital mortality[21]. Secondary study objectives of this thesis were to understand if the type and method of fluids administered within the first six hours after the identification of severe sepsis were associated with hospital mortality.

1.2 Sepsis Definitions

In 1992, an expert panel at the American College of Chest Physicians/Society of Critical Care Medicine consensus conference developed more standard criteria to define sepsis and its subgroups (severe sepsis and septic shock) in an effort to improve the conduct of clinical trials and epidemiological studies in the field of sepsis[22](Table 1). From this consensus process, sepsis was defined by the combination of a confirmed or clinically suspected infection in addition to two or more criteria of the systemic inflammatory response syndrome[22]. The systemic inflammatory response syndrome (SIRS) may be evoked by the host in response to a variety of insults, including an infectious pathogen. Prospective randomized controlled trials in severe sepsis and septic shock included SIRS as eligibility criteria because it is a sensitive, but not specific method that aids in the identification of these patients[5;20;23]. SIRS is composed of four criteria: heart rate > 90 beats per minute, respiratory rate > 20 breathes per minute, temperature > 38° or < 36° Celsius, and a white blood cell count >12,000 mm^3 or < 4,000 mm^3 or > 10% bands.

Severe sepsis is an increasingly severe form of sepsis. The definition for severe sepsis includes the criteria listed above (infectious source and SIRS) in addition to the development of at least one of the following: organ dysfunction, organ hypoperfusion, or sepsis induced hypotension. Examples of organ dysfunction include abnormalities of the central nervous system, cardiovascular, respiratory, renal, hematological, and gastrointestinal systems. Examples of organ hypoperfusion include lactic acidosis, oliguria, and alteration in mental status.

Septic shock is the most severe form of sepsis. The definition for septic shock includes all of the criteria listed above (infectious source, SIRS, and organ dysfunction, or organ hypoperfusion, or sepsis induced hypotension), in addition to the presence of persistent hemodynamic instability despite adequate fluid resuscitation. Hemodynamic instability is manifested by hypotension and is defined by the need for vasopressor agent support to maintain an adequate blood pressure (Table 1).

1. 3 Epidemiology of Sepsis

A recently published epidemiological study involving approximately 10 million episodes of sepsis, and representing data from 500 hospitals across the USA for the years 1979 to 2000, found that the incidence of sepsis has doubled over the last 22 years[2]. More specifically, the incidence of sepsis went from 82.7 cases per 100, 000 population, to 240.4 cases per 100,000 population in 2000, for an annualized increase of 8.7% (Figure 1)[2]. This doubling in incidence has several plausible explanations including more standard definitions for and adoption of these diagnoses in major databases, as well as increased numbers of patients with a compromised immune status from conditions such as malignancy, solid organ transplantation, HIV, and their associated treatments. Other factors include the increased detection of malnutrition, alcoholism and diabetes, increased use of invasive procedures, emergence of resistant pathogens, and an aging population[24].

Sepsis is associated with a mortality exceeding 30%, as well as important short and long term morbidity[3;4;25-27]. The development of multiple organ failure contributes in a cumulative manner to this high mortality[2]. For example, Martin and colleagues reported a 15% mortality for septic patients without any organ failure in contrast to a 70% mortality for patients with three or more organs failing. The average annual cost for treating severe sepsis is estimated to be $16.7 billion nationally in the USA[28]. Costs of care may continue to increase with the advent of new recombinant therapies such as the Activated Protein C molecule that is now an established treatment for severe sepsis and septic shock[29].

1.4 Sepsis Pathophysiology

Any infection from bacteria, viruses, parasites, or fungi can initiate a chain of events that lead to the development of multiple organ failure and death from severe sepsis and septic shock. Although the host response to infection is ultimately intended to combat and overcome the infection, specific elements of the host's response may in fact propagate a malignant release of mediators that are ultimately responsible for the development of multiple organ failure and death[30]. This chain of events involves a complex release and then interaction between the inflammatory and complement cascades, coagulation cascades, and dysfunction of endocrine pathways[3;30-32].

The release of inflammatory mediators such as cytokines, interleukins, and arachadonic acid metabolites from white blood cells as well as endothelial and epithelial cells, and the activation of complement pathways all cause release of reactive oxygen species[30;33;34]. These reactive oxygen species, although critical for killing of the infectious pathogen, are also capable of inducing increased capillary membrane permeability with endothelial cell leak from the vessels and capillary shunting in tissue beds, all leading to the development of tissue damage and organ injury[3;33]. In addition, reduced oxygen delivery to the tissues secondary to hypovolemia and a vasodilated state, in combination with the release of these mediators, may act to induce mitochondrial dysfunction, otherwise termed cytopathic hypoxia, at the cellular level[35-38]. The infectious pathogen in connection with the inflammatory response leads to activation of coagulation cascades including the activation of platelet activating factor, enhanced tissue factor expression, a reduction in endogenous activated protein C and anti-thrombin III, and reduced fibrinolysis[3;31;39]. Activation of coagulation leads to a hypercoagulable state that is a set up for widespread microvascular thrombosis in different tissue beds[3]. In addition to activation of inflammation and coagulation, severe sepsis and septic shock are also associated with dysfunction of the neuroendocrine system[40]. For example, severe sepsis and septic shock are associated with a relative deficiency in endogenous corticosteroids, termed relative adrenal insufficiency[41], in conjunction with hyperglycemia and a state of insulin resistance[3;23]. It is the interaction between all of these factors that are most likely responsible for the development of tissue hypoperfusion, organ ischemia, and finally multiple organ failure and death (Figure 2)[30].

1.5 Principles of Management of Severe Sepsis and Septic Shock

General principles of managing patients with severe sepsis and septic shock include the early identification as well as prompt management and transfer of these patients into an ICU or monitored setting. The initial management strategies include optimization of oxygen delivery, minimization of oxygen demand, and institution of broad spectrum antibiotics, as well as eradication of the infectious source[12].

Oxygen delivery is dependent upon cardiac output (heart rate (beats per minute) x stroke volume (mls) and oxygen content [((hemoglobin (g/L) x 1.34) x oxygen saturation (%)) + (partial pressure of arterial oxygen (mm Hg) x 0.003)] in the blood. A main determinant of cardiac output is pre – load, or volume loading of the right heart [13]. Volume loading of the right heart to optimize venous return is facilitated with the administration of repeated resuscitation fluid challenges (500 mls over 15 minutes), in addition to the administration of vasoactive agents to support the blood pressure if a patient remains hypotensive after optimal volume loading[42;43]. Other methods to increase oxygen delivery include the administration of red blood cells to optimize hemoglobin concentrations[44], and inotropes to increase contractility of the heart[43]. Interventions aimed at minimizing oxygen demand include intubation and mechanical ventilation for respiratory failure, as well as treatment of fever, pain, and anxiety or agitation with the administration of acetaminophen, analgesic medications, and sedatives respectively[45;46]. Identification of the suspected infectious source by collecting cultures, source control of the infection such as drainage of pus from an abscess, and prompt institution of broad spectrum antibiotics directed at the presumed source of sepsis guided by susceptibility patterns of microorganisms in the hospital, are all important aspects of initial sepsis management[47;48].

1.5.1 New Treatments for Severe Sepsis and Septic Shock

Therapeutic research in severe sepsis and septic shock has been conducted for several decades. Clinical sepsis trials date back to 1963 when high doses of corticosteroids were being examined in an attempt to modulate the inflammatory response[34]. However, until recently, no study has been able to demonstrate a mortality benefit and the death from this illness has remained at approximately 30 – 60%[3;4]. In the last few years, three randomized controlled trials directed at the treatment of severe sepsis and septic shock have finally demonstrated a mortality benefit[5;20;23].

The first trial focused on the coagulation cascade in severe sepsis. In this study, Bernard and colleagues randomized 1,690 patients with severe sepsis identified within 24 hours of developing their first organ failure to receive intravenous Activated Protein C or placebo for 96 hours in a blinded fashion. Twenty – eight day mortality in the Activated Protein C as compared to placebo group was 30.8% versus 24.7% (relative risk of death 0.80, 95% confidence intervals from 0.69 to 0.94, p=0.005). A pre-specified stratified analysis conducted according to patients with increasingly severe illness defined by an APACHE II score of greater than or equal to 25 suggested an even greater benefit for Activated Protein C compared to placebo (31% versus 44%, absolute reduction in mortality 13%)[49].

Annane and colleagues recently published a multi-center randomized controlled trial in a septic shock population that examined the effect of corticosteroid administration on mortality[6]. In this trial, 300 patients with septic shock were randomized to receive intravenous hydrocortisone and fludrocortisone by mouth versus placebo within the first 8 hours of septic shock diagnosis for seven days in a blinded fashion. Twenty-eight day mortality for the whole group trended toward significance (odds ratio of 0.65, 95% confidence intervals from 0.39 to 1.07, p=0.09). However, in a pre-specified analysis for those patients who had relative adrenal insufficiency according to an adreno-corticotropin hormone (ACTH) stimulation test at the time of randomization, the absolute reduction in 28-day mortality was 10% (odds ratio of 0.54, 95% confidence intervals from 0.31 to 0.97, p=0.04).

Recently, a study evaluated early and aggressive resuscitation strategies aimed at achieving optimal perfusion and delivery of oxygen to the tissues in an attempt to prevent the development of multiple organ failure and death. In this study, 263 patients with severe sepsis and septic shock were identified within 2 hours of arrival to the emergency department and randomly allocated to algorithm driven "goal – directed" therapy versus a standard therapy alone for the first six hours of care[20]. The algorithms for both groups included the administration of colloidal and crystalloid fluids and vasoactive agents. Resuscitation goals for both groups included a central venous pressure of 8 to 12 mm Hg, a mean arterial blood pressure of at least 65 mm Hg, and a urine output of at least 0.5 mls/kg/hr. The "goal-directed" therapy group had an additional resuscitation goal to achieve a central venous oxygen saturation of at least 70%. Central venous oxygen saturations provided a global marker of oxygen transport, and thus reflected the balance between oxygen delivery and oxygen demand[50]. Hospital mortality in the "goal-directed" group was decreased by an absolute difference of 16% (relative risk of 0.58 and 95% confidence intervals from 0.38 to 0.87 p=0.009). A major component of care in the Rivers study involved the aggressive administration of fluids. Indeed, the "goal – directed" group received more fluids in the first six hours of care as compared to the standard therapy group (4981 +/- 2984 mls versus 3499 +/- 2438 mls, $p<0.001$). However, when the amount of fluid was quantified over the first 72 hours of care, total quantity of fluids delivered appeared similar between the groups (13443 +/- 6390 versus 13,358 +/- 7729 mls, $p = 0.73$). Hence, institution of aggressive "goal – directed" fluid resuscitation in the early stages of severe sepsis and septic shock may have been partly responsible for the observed difference in mortality between the groups. The type of fluid used for resuscitation in the Rivers trial was left to the discretion of the physician and included the use of colloids and crystalloids.

As fluid therapy is a key factor in the resuscitation of these patients, it is reasonable to believe that the quantity, type, and method of fluids administered may impact on clinical outcome.

1.6 Colloidal versus Crystalloid Fluids for Volume Resuscitation in Severe Sepsis and Septic Shock: The Physiological Rationale

Those who favor the use of colloids argue that hypo-oncotic crystalloids leak from the plasma to excessively expand the interstitial fluid volume[51]. In contrast to crystalloid solutions, colloidal solutions are macromolecules that under normal physiologic conditions do not pass through the endothelial layer and into the interstitial space. Thus, colloids have the potential advantage of less leak of fluid into the interstitium, and hence, less volume to expand the intravascular space in comparison to crystalloids. However, in abnormal physiological states such as severe sepsis and septic shock where endothelial injury and increased capillary membrane permeability are present, this theory may not hold true. Thus, advocates of crystalloid solutions suggest that leakage of colloid into the interstitial space may also contribute to edema formation, particularly in the setting of endothelial injury[51]. Colloids trapped in the interstitial space create an osmotic gradient and pull additional water into the interstitial space. Although both of these arguments may make physiological sense, there is a lack of data from clinical studies to support either of these hypotheses.

The two crystalloid resuscitation fluids are normal saline and ringer's lactate. Normal saline is the crystalloid solution that is considered as the 'usual care' fluid, particularly in the first hours of resuscitation of patients with severe sepsis and septic shock. Although slightly hypertonic, the electrolyte components of normal saline (154 meq of sodium, 154 meq of chloride) are close to that of plasma in a healthy person (140 meq of sodium, 110 meq of chloride), and as such, may be of potential physiological benefit. However, there is some data to suggest that different crystalloid solutions may be associated with deleterious effects other than leak into the interstitial space. For example, normal saline as compared to ringer's lactate has been associated with the development of hyperchloremic metabolic acidosis[52]. Although the clinical significance of this type of acidosis is debatable, one small randomized controlled trial comparing normal saline to ringer's lactate conducted in healthy volunteers suggested that normal saline was associated with more abdominal discomfort, a longer time to urination, and subjective mental changes[53]. In addition, some preliminary research suggests that administration of both normal saline and ringer's lactate may be associated with the development of a hypercoagulable state[54-57].

In Canada, two main colloidal solutions are available, albumin (5% and 25%) and pentastarch (10%). Both of these solutions are bathed in normal saline. Although both are colloidal resuscitation fluids, it is possible that albumin and pentastarch may exert different biological actions, and hence, have different effects on clinical outcome. For example, experimental data suggests that volume resuscitation with albumin as compared to normal saline and pentastarch, may reduce myocardial depression associated with sepsis by altering nitric oxide expression and increasing contractility of myocyte cells[58]. Further, in comparison to crystalloid agents, albumin in experimental sepsis, may preserve surface area for tissue oxygen exchange[19;59;60]. However, albumin is a blood product, and hence, is associated with small but real infectious risks. Both pentastarch and albumin are considerably more expensive than normal saline or ringer's lactate crystalloid solutions (approximate cost of 500 mls of ringer's lactate/normal saline is $1.00 - $1.50; approximate cost of 500 mls of pentastarch/ albumin is $70.00). Albumin use declined significantly after the publication of two meta-analyses suggesting that it may be associated with harm[61;62]. However, results from the recently conducted multi – center randomized controlled effectiveness study comparing 4% albumin to normal saline as volume resuscitation strategies in critically ill patients found that there was no difference in 28 day mortality between the two groups (20.9% albumin vs 21.1% normal saline, relative risk of 0.99 with 95% confidence intervals from 0.91 to 1.09, p=0.87)[63]. Hence, use of albumin as a resuscitation fluid for critically ill patients may be re-considered.

In contrast to albumin, pentastarch is a synthetic colloid that is made from the starch amylopectin. Pentastarch is the only hydroxyethyly starch that is available at present for use in Canada. It has become increasingly popular as an early resuscitation fluid in severe sepsis and septic shock for several reasons. First, in comparison to albumin, the pentstarch molecule is larger and as such, the solution may be better maintained in the intravascular space[19;64], limiting the total amount of volume of fluid required to maintain hemodynamic stability. Less overall fluid administered may translate to less development of interstitial edema. Pentastarch may also possess important and distinct biological actions in sepsis. Preliminary evidence suggests that the family of hydroxyethyl starches may be superior to crystalloid fluid resuscitation as these molecules may be able to halt the processes that produce the deleterious effects of severe sepsis and septic shock. For example, in a surgical, trauma, and septic population, these molecules may either decrease the inflammatory response, reduce endothelial activation, and/or prevent endothelial injury[15;65;66], in addition to modulating neutrophil chemotaxis[17;18]. 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[19;64], and in a blunt trauma population[67]. Although not a perfect index, gastric intra-mucosal partial pressure of carbon dioxide measured using a gastric tonometer has been used in the experimental critical care setting to measure adequacy of tissue perfusion. Within this context, there is conflicting evidence regarding the efficacy of hydroxyethyl starches in improving tissue perfusion in a vascular and septic patient population respectively[68;69]. The family of hydroxyethyl starches do have potential deleterious effects as well. For example, they have been associated with the development of a coagulopathy[70;71], renal failure[72-74], anaphylactoid reactions[75-77], and severe skin rashes[78;79]. Thus, all of the administered fluids are associated with potential risks.

1.7 Colloidal versus Crystalloid Solutions for Fluid Resuscitation: A Critical Review of the Evidence

In the first 24 hours of care, patients with severe sepsis and septic shock often receive several liters of fluid including the use of colloids, crystalloids or a combination of the two[21]. Even though resuscitation with both of these fluids is an integral component in the early management of these patients, there is a lack of evidence that favors the use of one fluid over another[21]. Despite the ongoing controversy between the superiority of colloids versus crystalloids, seven published systematic reviews have not consistently demonstrated that one fluid is superior to another in terms of the development of organ dysfunction or death[62;80-85].

As background for this thesis, a systematic search to identify previous systematic reviews that compared mortality of colloidal or albumin fluid to crystalloid fluids in critically ill patient populations was conducted. A review was considered to be systematic if a comprehensive search was conducted for relevant studies, and if the studies were, "appraised and synthesized according to a predetermined and explicit method"[86].

Each systematic review was evaluated on the basis of 4 inclusion criteria: study design (systematic review); target population (critically ill patients); therapeutic intervention (colloidal versus crystalloid solution); and outcome (all cause mortality). Published systematic reviews comparing the effect of colloidal versus crystalloid solutions on clinical outcome from critical illness were identified using both electronic and manual search strategies from January 1966 to August 2003. All data was abstracted by the principal investigator (Lauralyn McIntyre) and included information on patient populations, fluids compared, and mortality at the end of follow up. Data was also collected on the methodology of each systematic review and included information on the search strategy utilized, data abstraction, methodological quality assessment, and type of analysis conducted. Two of these reviews did not outline methods used to identify studies included and were thus excluded from further review[87;88]. Hence, seven systematic reviews were included (Table 2).

1.7.1 Methodology of Systematic Reviews

Information on the search strategy, data abstraction, quality assessment, and type of analysis conducted for each systematic review are summarized in Tables 3 and 4.

1.7.2 Results of Systematic Reviews

Six of seven systematic reviews included trauma, burns, surgical, and hypovolemic patient populations (Table 2). One review focused on critically ill trauma victims only[80]. Four reviews included adult patients only, and three included adult and neonatal populations. All reviews included patients who were in need of volume resuscitation, and three included patients who were hypoproteinemic[62;81;85].

All systematic reviews included randomized controlled trials that compared the effect of albumin or plasma protein fraction solution to crystalloid solution or nothing[62;81;85] on mortality, or compared the effect of a variety of colloidal solutions (hydroxyethyl starches, gelatins, albumins, dextrans) to crystalloid solutions (normal saline, ringer's lactate, haemaccel)[82-84] on mortality. The review published by Wade and colleagues compared the effect of hypertonic saline +/- dextran to isotonic saline on mortality[80]. Wade reported results on the hypertonic saline in dextran versus isotonic saline separately. As the main objective of this analysis was to compare colloidal to crystalloid agents, only the hypertonic saline with dextran versus isotonic saline results are highlighted.

Six of seven pooled mortality estimates suggested a trend toward harm with colloids, with exception of the review published by Wade and colleagues[80] (Table 6). In the two Cochrane reviews, one examining albumin, and the other colloids, both pooled mortality estimates reached statistical significance (relative risk of 0.66, 95% confidence intervals from 0.50 to 0.85 and relative risk of 0.66, 95% confidence intervals from 0.49 to 0.93 respectively)[62;84]. However, a closer examination of subgroups, grouped either by patient population or by type of colloid administered revealed more discordant results, with some trending toward harm and others protective with colloid use. For example, in the subgroup of patients with ascites[81], non-trauma[82], and surgical patient populations[83], there was a trend toward a mortality reduction in favor of colloidal solutions, suggesting that colloidal solutions may be beneficial in different patient populations affected by different diseases with potentially different pathophysiology. Similar discordant trends were found when the studies were analyzed according to the type of colloidal solution administered[84], suggesting that not all colloidal solutions are similar. A separate subgroup analysis conducted according to a severe sepsis and septic shock patient population was not found in any of the systematic reviews likely because there were so few clinical fluid resuscitation trials comparing colloidal to crystalloid solutions in this population.

1.7.3 Discussion of Systematic Reviews

Despite the number of individual trials included in these systematic reviews, none have consistently demonstrated that one type of fluid is superior to another in terms of the development of organ dysfunction or death[62;80-85]. Several reasons may explain discordant results. Six of seven systematic reviews pooled heterogeneous patient populations and four reviews pooled different colloidal and crystalloid solutions. Individual studies in these systematic reviews had fundamentally different objectives (physiologic Vs morbidity endpoints), different resuscitation schedules (volume, rate, duration of administration), out dated fluid protocols without adequate physiologic rationale for administration of fluids, and lack of standardized co-interventions[89;90]. Finally, many of the individual studies from these reviews lacked sufficient methodological rigor to protect against bias[61](Table 4 and 5). Indeed, Wilkes[81] and Choi[82] reported blinding in 13% and 18% of included studies respectively. Three systematic reviews reported adequate allocation concealment in 11%[84], 38%[81], and 52%[62] of included trials.

For all of the above reasons, no firm conclusion with respect to the superiority of colloidal versus crystalloid solutions in reducing mortality could be made. In fact, authors of these systematic reviews suggested that large, well designed, and rigorously conducted randomized controlled trials in specific patient populations with specific fluids administered were required to resolve this uncertainty[61;81-83;85].

1.8 Colloid versus Crystalloid Studies in Sepsis

Finfer and colleagues recently conducted a very large and well designed multi-center randomized controlled fluid resuscitation trial designed to resolve some of the uncertainty about superiority of colloidal versus crystalloid fluids. In 6997 heterogeneous critically ill patients in need of volume resuscitation, Finfer and colleagues evaluated the effect of 4% albumin versus 0.9% saline on 28-day mortality (SAFE study). There was no difference in 28-day mortality between the two groups overall (relative risk of 0.99 with 95% confidence intervals from 0.91 to 1.09). However, in a pre-defined subgroup analysis of patients with severe sepsis (n=1218), there was a trend toward a reduction in death for the albumin as compared to the normal saline group (30.7% vs. 35.3% respectively with relative risk of 0.87 and 95% confidence intervals from 0.74 to 1.02)[63]. Although these results were intriguing, caution should be used when interpreting them because there may have been important imbalances between the colloid and normal saline sub groups that influenced outcome. Importantly, this subgroup of patients represented a much smaller subset than the original SAFE study with 95% confidence intervals that crossed one. Hence, the possibility of statistically or clinically important benefit or harm could not be confirmed or refuted [91].

There is little further evidence to guide the physician with regard to the optimal type of fluid to use in the resuscitation of the severely septic and septic shock patient population.

Indeed, Rackow and colleagues have conducted the only randomized controlled fluid resuscitation trial that compared colloids to crystalloids in this patient population. In this trial, 26 patients with hypovolemic (n=8) or septic shock (n=18) were randomized to receive either normal saline (n=9), 6% hetastarch (n=9), or 5% albumin (n=8) solutions. The normal saline group required two to four times the volume of fluid in order to maintain hemodynamic stability in comparison to the albumin and hetastarch group ($p<0.05$). At 24 hours post-resuscitation, pulmonary edema was more frequent in the normal saline (87.5%) as compared to the albumin (22%) and hetastarch (22%) group ($p<0.05$). Although deaths were not reported, the trial was not powered to evaluate this endpoint.

The results from the systematic reviews as well as the SAFE trial highlight the need to further examine whether colloidal resuscitation is superior to crystalloid resuscitation in patients with severe sepsis and septic shock. A randomized controlled trial comparing the effect of a colloidal versus crystalloid solution in a septic shock population will serve to answer this question definitively.

Fluid management is an absolutely integral component in the early resuscitation of patients with severe sepsis and septic shock. However, no study in a severely septic or septic shock patient population has evaluated in detail the relationship between fluid resuscitation strategies and clinical outcome. Thus, I have evaluated the relationship between the quantity, type, and method of fluid administered in the first six hours after the identification of severe sepsis and mortality at hospital discharge.

2.0: THESIS GOALS AND OBJECTIVES

The goals of this thesis were to evaluate the relationship between fluid resuscitation strategies and mortality at hospital discharge in patients who have developed severe sepsis with three objectives.

2.1 Primary Study Objective

a) To determine if the total quantity of fluid administered in the first six hours after the identification of severe sepsis time was associated with hospital mortality at the Ottawa Hospital, General Campus.

b) To determine if the total quantity of fluid administered in the first six hours after the identification of severe sepsis was associated with ICU mortality, need for mechanical ventilation within 24 hours after identification of severe sepsis, need for vasoactive agent support within 24 hours after identification of severe sepsis, and time to discharge from ICU and hospital?

2.2 Secondary Study Objectives

a) To determine if the type of fluid administered (colloid and crystalloid fluid versus crystalloid fluids) in the first six hours after the identification of severe sepsis was associated with hospital mortality at the Ottawa Hospital, General Campus.

b) To determine if the type of fluid administered in the first six hours after the identification of severe sepsis was associated with ICU mortality, need for mechanical ventilation within 24 hours after identification of severe sepsis, need for vasoactive agent support within 24 hours after identification of severe sepsis, and time to discharge from ICU and hospital?

c) To determine if the method (fluid bolus and infusions versus fluid infusion) of fluid administered in the first six hours after the identification of severe sepsis was associated with hospital mortality at the Ottawa Hospital, General Campus.

d) To determine if the method of fluid administered in the first six hours after the identification of severe sepsis was associated with ICU mortality, need for mechanical ventilation within 24 hours after identification of severe sepsis, need for vasoactive agent support within 24 hours after identification of severe sepsis, and time to discharge from ICU and hospital?

3.0: METHODS

3.1 Study Design

A retrospective cohort study designed and conducted to understand if the quantity, type, and method of fluids administered in the first six hours after the identification of severe sepsis were associated with hospital mortality (Figure 3).

3.2 Study Setting

The study was conducted at the Ottawa Hospital, General Campus. The Ottawa Hospital, General Campus is a 469 bed hospital that has approximately 21,000 admissions per year. The ICU at the Ottawa Hospital, General Campus is a 21 bed unit with approximately 1,100 admissions per year.

3.3 Study Period

The thesis proposal was conceived in January 2002 and developed from January 2002 to June 2002. Data collection was initiated in July 2002 and completed in June 2004. The study included all patients in the hospital with severe sepsis over the time period July 1, 2000, to June 30, 2002, as identified by database and chart review.

3.4 Sampling Time Frame and Sample Size

A sampling time frame of two years was chosen as it was judged long enough to generate a sample size of 411 patients that would provide reasonable ability to detect sensible treatment effects, and short enough to avoid secular trends related to changes in the patient population or treatment of severe sepsis.

To calculate the sample size for this study, 'quantification of fluids' received in the first six hours after the identification of severe sepsis was dichotomized into ≤ 3.5 liters versus ≥ 5 liters. Rationale for using the fluid cut – offs as well as for the effect size was derived from the Rivers study[20]. The following assumptions were made to calculate the sample size: 1) an effect size with an odds ratio of 0.43 benefiting those patients who were administered $\geq$ 5 liters of fluid; 2) alpha of 0.05; and 3) power of 80%. Based on these assumptions, a total sample size of 411 was required (sample size calculation with NCSS 2002 – Appendix I).

3.5 Definition of Study Population

The target population included all patients defined with severe sepsis at the Ottawa Hospital, General Campus in the time period from July 1, 2000, to June 30, 2002, as identified by a database search and chart review.

3.5.1 Inclusion Criteria

Three criteria including the presence of infection, SIRS, and hypotension defined a patient with severe sepsis.

3.5.1.1 Presence of Infection

Presence of infection was defined by either a confirmed or suspected site for infection documented from 72 hours before, and up to 24 hours following identification of severe sepsis. A confirmed infection was defined by the presence of a microorganism(s) in a normally sterile body tissue, or by the presence of positive blood cultures. A suspected infection was defined by a physician's clinical suspicion of infection, but in absence of actual microbial confirmation. A suspected source of infection was considered to be visualized when purulent fluid or fecal contamination was seen in the sterile body tissue.

3.5.1.2 Presence of the Systemic Inflammatory Response Syndrome (SIRS)

Two or more of the SIRS criteria needed to be present within 24 hours of identification of severe sepsis. These four criteria included: a) a temperature greater than 38°

Celsius or less than 36° Celsius, or b) a white blood cell count greater than 12 x 10^9 per mm^3 or less than 4 x 10^{9} per mm^3 or greater than 10% band cells on the blood count differential, or c) a respiratory rate greater than 20 breathes per minute or an arterial partial pressure of carbon dioxide of less than 32 mm Hg, or mechanical ventilation, or d) a heart rate greater than 90 beats per minute, or the heart rate controlled with use of beta blockers, calcium channel blockers, or use of a pacemaker.

3.5.1.3 Presence of Hypotension

Hypotension was defined as the first documented systolic blood pressure of less than or equal to 90 mm Hg, a mean arterial blood pressure less than or equal to 65 mm Hg, or a drop in systolic blood pressure of greater than or equal to 40 mm Hg from baseline values. Importantly, the first hypotensive event (identification of severe sepsis) defined the starting point for all data collection (refer to the instruction manual, Appendix II, pages 5 – 7 for detailed definitions of the inclusion criteria).

3.5.1.4 Justification for Inclusion Criteria

Definitions for infection in this study were a modification of standard published criteria used to define infection[92]. Positive culture results were considered to be associated with the sepsis episode if they were obtained from 72 hours before and up to and including the 24 hours following identification of severe sepsis. This time frame was chosen because cultures are not always drawn right at identification of severe sepsis. Hence, this time window provided an adequate time in order to identify an organism. In addition, it was a reasonable time frame to assume that the organism identified was related to severe sepsis.

The second criteria, presence of the systemic inflammatory response syndrome criteria needed to have been present within 24 hours of identification of severe sepsis. The systemic inflammatory response can vary between subjects, both in terms of the timing of onset, as well as its severity. Hence, this window provided a reasonable time frame in which to identify these criteria.

The third criteria to define severe sepsis can be one of sepsis induced hypotension, organ hypoperfusion, or organ system dysfunction (Table 1). For this study, sepsis induced hypotension was used as the third criteria to define severe sepsis. The rationale for choosing sepsis induced hypotension as the third criteria to define severe sepsis was as follows: 1) hypotension is associated with increased illness severity as well as mortality; 2) physicians consider hypotension to be a universal sign that denotes increasingly severe sepsis, and importantly; 3) it is the cardinal sign that triggers a clinician to start the administration of fluid resuscitation, and finally; 4) using sepsis induced hypotension as the main criteria to define severe sepsis allowed for a standard start time (identification of severe sepsis) for the collection of all fluid data.

3.5.2 Exclusion Criteria

The main exclusion criteria were: a) with drawl of care within the first six hours after severe sepsis was identified (patients who had care withdrawn in this time period included those who were pronounced brain dead, had a "Do Not Resuscitate" order in the medical record, and patients with a terminal illness documented by the attending critical care physician in the medical chart); or b) development of criteria for severe sepsis after seven days of hospitalization; or c) not an index admission for severe sepsis in the study period.

3.5.2.1 Justification for Exclusion Criteria

Patients who had care withdrawn within the first 6 hours after the identification of severe sepsis were excluded from the study as these patients and their clinical management are dramatically different from those who are undergoing active care. Specifically, when care is withdrawn, all active medications and intravenous infusions, including fluids, are typically discontinued with the exception of comfort medications in order to let the patient die. Fluid administration in these patients would not reflect an active and ongoing resuscitation attempt, and hence the rationale for their exclusion.

The development of severe sepsis needed to have occurred within the first seven days of admission to hospital for the following reasons. The pathophysiology of sepsis as well as outcome from sepsis may be very different for a patient who has been hospitalized for several weeks in comparison to a patient who has been hospitalized for several days [93]. Several explanations may account for this difference, but timing of the onset of sepsis may be one important contributor. Hence, the seven day cut off was used in an attempt to identify patients who have similar timing with respect to the onset and evolution of the pathophysiologic septic process. In addition, the identification of a hypotensive patient in a retrospective manner becomes a much more difficult task as this time point is identified through careful chart review.

For each patient, only their index admission to the hospital with severe sepsis during the study period was included so that the denominator for all analyses in this study represented all patients, not admissions, with the diagnosis of severe sepsis.

3.6 Definitions of Baseline Covariates

3.6.1 Demographics

Demographic variables included age and sex of patients with severe sepsis.

3.6.2 Severity of Illness

3.6.2.1 APACHE II Score

Severity of illness data included the Acute Physiology and Chronic Health Evaluation score (APACHE II score) as well as the presence of co-morbid illnesses. The APACHE II score is a severity of illness score that has been well validated in various groups of critically ill patients and is meant to provide a general measure of illness severity within the first 24 hours of admission to an ICU. It is well correlated with mortality[94;95]. It is an ordinal point score that ranges from 0 – 71, with higher scores positively associated with increased mortality. For example, APACHE II scores in the range of 10 – 14 and 25 - 29 correspond to mortality rates of 15% and 50% respectively[95].

The score is based upon a summation of the following: 11 physiological measures (temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, sodium, potassium, arterial PH, hematocrit, white blood cell count, and creatinine), Glasgow Coma Scale score, age, and chronic health score. The chronic health score is defined by the combination of chronic co-morbidities (chronic liver disease, pulmonary disease, heart disease, and immunocomprimised status) in addition to the type of admission to the ICU (medical, emergent post-operative, and elective post-operative). For an example APACHE II score sheet, see Appendix III. For a detailed explanation as to how the APACHE II score was calculated, refer to Appendix IV.

3.6.2.2 Co – Morbid Diseases

Co-morbid diseases included diabetes, chronic pulmonary disease, chronic renal failure, chronic liver disease, ischemic heart disease, congestive heart failure, peripheral vascular disease, cancer, and chronic immunosupressed state. For detailed definitions of each co-morbidity, refer to the instruction manual (Appendix II).

3.6.3 Type of Admission

Type of admission to the ICU was considered to be medical, emergent post – operative, or elective post – operative. Detailed definitions are given in the instruction manual (Appendix II).

3.6.4 Infection Characteristics

The infectious sources were categorized according to the: pulmonary system, abdominal cavity, urinary tract, vascular device, or the skin or soft tissue. If the infectious source was unknown or derived from another source, then the source of infection was placed in the “other” category. Further detailed definitions and examples of infectious sources are summarized in the instruction manual (Appendix II).

3.6.5 Place in Hospital at Identification of Severe Sepsis

The location of patients when severe sepsis was identified was classified as having come from the following areas: emergency room, hospital ward (medical or surgical ward), ICU, post-operative recovery unit or operating room, or the peripheral hospital (emergency room, hospital ward, or ICU).

3.7 Definition of Fluid Exposure Variables

3.7.1 Quantity of Fluid Administered

The primary purpose of this thesis was to determine if the quantity of fluid administered in the first six hours after the identification of severe sepsis was associated with hospital mortality. The total amount of fluids administered in the first six hours of care included the total amount of crystalloid solutions (normal saline, ringers lactate, ½ normal saline, dextrose

5% in ½ normal saline, 2/3 and 1/3 solutions, and dextrose 5% and 10%) and colloidal solutions (pentastarch, albumin, cellular products (red blood cells, fresh frozen plasma, platelets).

The total volume of intravenous fluid administered in the first six hours was quantified in the following way. A bolus of resuscitation fluid was defined as at least a 250 ml fluid challenge of colloid (pentastarch or albumin) or crystalloid (normal saline or ringer's lactate) administered within no longer than one hour according to the nurses charting record. Crystalloid boluses of normal saline and ringers lactate were added together so the total amount of these boluses reflects one or both of these fluids. Boluses of the colloidal fluids pentastarch and albumin were quantified separately. Intravenous infusions were summed together and included the administration of the following crystalloid solutions: normal saline, ringers lactate, ½ normal saline, dextrose 5% in normal saline, 2/3 and 1/3 solutions, dextrose 10% in water (D10W), dextrose 5% in water (D5W), and intravenous medications. Normal saline and ringers lactate were recorded in the intravenous infusion section when the fluid infused was recorded at less than 250 mls per hour. Blood products were quantified separately and these included the administration of red blood cells, fresh frozen plasma, and platelets.

The original plan was to conduct the quantity of fluid analysis with the independent variable, 'quantity of fluid' expressed as a dichotomous variable (less than or equal to 3.5 liters, and greater than or equal to 5 liters) based upon a post – hoc subgroup analysis from the Rivers trial[20]. However, there were too few patients who received greater than or equal to five liters of fluid in the first six hours of care which made it difficult to conduct a multivariable regression analysis. Importantly, in this study, the quantity of fluid received in the first six hours after the identification of severe sepsis was considered to be more in keeping with a categorical rather than a dichotomous variable. Dividing the fluid received into the categories provided a better ability to examine for the potential of a dose effect (with the hypothesis being that more fluid is better with regard to reducing mortality). Thus, for purposes of the analysis in this thesis, I made the decision to separate the quantity of fluid received into 3 categories ("0 – 2" liters versus "2 – 4" liters versus "greater than 4" liters). These fluid categories provided a different representation of the distribution of fluids among this patient population. The "0 – 2" liter group represented a group of patients who received little fluid. This amount of fluid is also in keeping with published initial fluid resuscitation guidelines for the hemodynamically unstable patient with severe sepsis[96]. The "greater than 4" liter group was meant to represent a group of patients who had received a large quantity of resuscitation fluid, and the group who received "2 – 4" liters representing a middle ground amount of fluid.

3.7.2 Type of Fluid Administered

The second objective of this thesis was to determine if the type of fluid administered over the first six hours after the identification of severe sepsis was associated with hospital mortality. The two main types of fluids that are used to resuscitate the hemodynamically unstable patient with severe sepsis are colloidal fluids and crystalloid fluids.

Colloidal fluids are protein, starch, or cellular derived fluids. These include albumin (protein), pentastarch (starch), and red blood cells, fresh frozen plasma, and platelet (cellular derived) fluids. Pentastarch and albumin are the two main colloidal resuscitation fluids that are administered with the primary purpose to regain hemodynamic stability for patients with severe sepsis. Red blood cells, fresh frozen plasma, and platelets are cellular derived colloidal fluids. They are not considered as resuscitation fluids except in the setting of acute blood loss such as a trauma patient who has hemorrhaged. In severe sepsis, red blood cells are primarily used to increase oxygen delivery by increasing oxygen content and fresh frozen plasma and platelets are used to aid in the correction of coagulopathies. For the analysis, colloidal fluids included the administration of pentastarch and albumin fluids only.

Crystalloid solutions include normal saline, ringer's lactate, ½ normal saline, 2/3 and 1/3, D5W and D10W solutions. The two main crystalloid resuscitation agents include normal saline and ringer's lactate. Although ½ normal saline, 2/3 and 1/3, D5W and D10W solutions are not considered primary resuscitation fluids, they are categorized as crystalloid fluids that are infused daily into critically ill patients. These fluids are administered as maintenance infusions, to replace sugar, salt, or water, and as a mechanism to deliver intravenous medications. For the analysis, crystalloid fluids included the sum of all crystalloid fluids. Although it would have been optimal to only include resuscitation crystalloid fluids in the analysis, this was an impossible task due to the lack of detail provided in the fluid data sheets.

For the analysis, the independent variable 'type of fluid administered' was divided into those patients who had received crystalloid fluid only, or a combination of colloidal and crystalloid solutions.

3.7.3 Method of Fluid Administered

The third objective of this thesis was to determine if the method of fluid administered over the first six hours after the identification of severe sepsis was associated with hospital mortality. Fluid can be delivered as infusions, and or, in bolus format. Rapid fluid bolusing as compared to infusions of fluid is an accepted and encouraged practice to facilitate rapid restoration and perfusion of the tissues in the critical care setting[42]. In this study, a fluid bolus with either a colloidal (pentastarch, albumin) or crystalloid agent (normal saline or ringers lactate) was defined as a minimum of 250 mls of fluid administered over no more than a one hour period. In contrast, fluid was considered to have been infused only when no bolus fluid was administered.

3.8 Definitions of Outcome Measures

3.8.1 Primary Outcome

3.8.1.1 Hospital Mortality

Hospital mortality was defined as any death that occurred after the identification of severe sepsis until discharge from the Ottawa Hospital, General Campus. Hospital mortality was selected as the primary outcome measure because was an important and frequent outcome in the critical care setting. Importantly, this outcome may be affected by insufficient, inappropriate, or delays in starting of resuscitation[7-11].

3.8.2 Secondary Outcomes

3.8.2.1 ICU Mortality

ICU mortality was defined as a death that occurred after the identification of severe sepsis until discharge from the ICU at the Ottawa Hospital, General Campus.

3.8.2.2 Time to Discharge from Hospital

Time to discharge from hospital was defined from the first day of admission to hospital until the date of discharge or death from the Ottawa Hospital, General Campus.

3.8.2.3 Time to Discharge from ICU

Time to discharge from ICU was defined from the first day of admission to the ICU until the date of discharge or death from the Ottawa Hospital, General Campus, ICU.

3.8.2.4 Need for Mechanical Ventilation Within 24 Hours After Identification of Severe Sepsis

A patient was defined as being on a mechanical ventilator if this event occurred within the first 24 hours after severe sepsis was identified. Mechanical ventilation was defined by the need for either invasive (intubation) or non-invasive (mask – continuous positive airway pressure or bi-level positive airway pressure) ventilation.

3.8.2.5 Need for Vasoactive Agent Support Within 24 Hours After Identification of Severe Sepsis

A patient was defined as needing a vasoactive agent in the first 24 hours after severe sepsis was identified if the vasoactive agent was infused for at least one hour during that 24 hour period. Vasoactive agents included the use of phenylephrine, nor-epinephrine, dopamine, epinephrine, vasopressin, milrinone, and dobutamine.

3.9 Identification of Patients with Severe Sepsis

It was important to consider all locations in the hospital in order to identify all patients with severe sepsis (emergency room, hospital wards, post-operative units, ICUs, and peripheral hospital). All patients with severe sepsis at the Ottawa Hospital, General Campus in the time period July 1, 2000, to June 30, 2002, were identified using two distinct databases: medical records (section 3.10.1), and the ICU unit database (section 3.10.2) at the Ottawa Hospital, General Campus.

3.9.1 Medical Records Search Strategy

The medical records database was queried using a series of "International Classification of Diseases, 9th Revision, Clinical Modification" codes (ICD – 9 CM) to identify patients with severe sepsis. The search strategy was recently published in the sepsis literature[28]. With use of these ICD – 9 CM codes, severe sepsis was identified when a patient had evidence of infection in addition to the presence of at least one organ failure. The search strategy is outlined in Appendix V. The medical records search identified all patients from the entire hospital classified with severe sepsis.

The medical records search was limited in that it was unable to make the temporal link between the development of organ failure and infection. For example, a patient may have developed acute renal failure during a hospital admission that was entirely unrelated to the infectious episode. Further, approximately 50% of patients develop sepsis, but the actual infectious pathogen causing the sepsis is never identified[2]. The nature of the medical records coding and search strategy required the presence of a confirmed pathogen. Thus, in order to avoid missing patients, a search of the ICU database at the Ottawa Hospital, General Campus ICU was also conducted.

3.9.2 ICU Database Search Strategy

The ICU database search assisted in the verification of the diagnosis of severe sepsis for those patients identified by the medical records search and admitted to the ICU. The ICU database at the Ottawa Hospital contained data that was collected prospectively by a trained and experienced ICU research nurse. Data were collected on a daily basis. The ICU research nurse ensured accurate collection of variables with daily questions and feedback from the ICU attending physicians.

The ICU database search strategy is outlined in Appendix VI. This list was then cross - referenced with the list that was generated from medical records search to ensure that all patients who were admitted to the ICU with severe sepsis were included. Duplicates that were generated from the medical records and ICU database search were then collated into a separate list called the "common" list. After all ICU patients were identified, a careful chart review was conducted to verify that the correct ICU patient population was indeed identified.

3.10 Data Collection

3.10.1 Development of Data Collection Instrument

A standardized case report form was developed in order to capture all information required for this study. The principal investigator (L.M.) created the first draft of the case report form. The case report form then underwent multiple iterations after receiving feedback from the thesis committee (P.H., D.F., R.N.), as well as research nursing staff (J.A., I.W., T.M.). The principal investigator pre-tested the case report form on approximately 20 hospital records. Further minor modifications to the form were made after the pre-testing was complete. The final case report form was used to collect data on all hospital charts (Appendix VII).

3.10.2 Training Steps for Collection of Data

All data collectors (L.M., S.K., N.R., R.R., D.H.) in this project had data collection training. All abstractors went through rigorous training sessions (approximately 2 weeks) with experienced ICU research nurses (J.A., I.W., T.M.). In these sessions, the ICU research nurses explained how and where to access information for variables in the chart review. In addition, the ICU nurses monitored the students' data collection on approximately 10 charts each. During this two week training session, the data collectors met with the principal investigator on a daily basis to review progress as well as answer any questions related to the data collection. After the initial 2 week training sessions were completed, the data collectors met with the principal investigator daily for the next two weeks to review progress and answer questions. Thereafter, the principal investigator met with the data collectors on a weekly basis, or when required to review progress and answer questions.

3.10.3 Data Verification Steps

The principal investigator created a data dictionary and instruction manual in order to ensure accurate and efficient data collection. All data from the patient medical charts were entered either onto a paper case report form or directly into the computer using a Teleform application. The Teleform application provided the ability to process and store data electronically. Logic and range checks were built into Teleform to help ensure accurate data collection. For example, all numerical data points had an upper and lower limit set so as to alert the data collector of any potential entry errors. If the data collector entered a numerical variable that was outside the set range, the electronic form would reject the data point. If the data was first entered onto a paper case report form, it was then manually entered into the Teleform application on the computer. All electronic information in the case report forms were then processed and verified through the Teleform application. Once verified, the data was stored in an electronic file. The principal investigator reviewed every completed case report form to further ensure the accuracy and completeness of the data collected. Paper copies for all case report were generated and stored in a locked filing cabinet.

Patient confidentiality was maintained by creating a unique study number for each patient. A list that outlines the actual hospital chart number and corresponding study number was kept in a separate and secure location.

13.11 Case Report Form – Sections A - H

The case report form consisted of eight sections encompassing three main categories of variables: patient characteristics, exposure variables, and outcome variables. See

Appendix VII for the case report form, Appendix II for the instruction manual, and Appendix VIII for a summary of the eight case report form sections

3.12 Evaluation for Sources of Information Bias

One of the experienced data collectors (DH) examined 100 of the included charts in duplicate (these charts were originally filled out by another data collector) to ensure that the included cases were correctly classified with severe sepsis. D.H. also examined these 100 charts for two important data collection items: date and time of first hypotensive event (identification of severe sepsis), and the total amount of fluids administered in the first 6 hours after the identification of severe sepsis. All data that D.H. considered to be incorrectly recorded was reviewed and verified with principal investigator (Lauralyn McIntyre). No excluded charts were screened in duplicate.

3.13 Data Analysis

3.13.1 Procedures for Verification of Data Integrity and Accuracy

Each variable that was included in this analysis was checked for missing, incorrectly entered, and potential outlier data. Frequency distributions using a tabular approach were used to identify any missing data. When data was identified as missing, the principal investigator went back to the case report form and or the hospital chart to see if data was available. If the data was available, the information was then added onto the paper case report form, as well as in the electronic database. For data that were continuous in nature, frequency distributions that were graphical in nature were used to identify any potential data in the extremes of ranges. The principal investigator (L.M.) then verified any data that appeared to be in the extreme range by examining the case report form and or the hospital chart.

3.13.2 Methods to Deal with Missing Data at Baseline

As a general rule, the decision was made to impute when less than or equal to 10% of data was missing at baseline. The following methods were used for imputation. For continuous data, I imputed using the group mean from the existing data. For categorical data, I imputed using the group proportions from existing data with missing values randomly assigned to the categories in the same proportion as the observed proportions.

3.14 Descriptive Statistics

3.14.1 Entire Cohort

The entire cohort was first described with descriptive statistics. Continuous variables were described with means and standard deviations and categorical variables with proportions.

Continuous variables included age and the APACHE II score. Categorical variables included sex (male, female), type of admission to the ICU (medical, emergent post operative, or elective post operative), infectious source (pulmonary, intra-abdominal, urinary tract, vascular device, skin/soft tissue, and other categories), presence of co-morbid diseases described individually and then quantitatively (0, 1 - 2, 3 – 4, greater than 4 co-morbid diseases), and place in hospital at the identification of severe sepsis (ICU, emergency room, hospital ward, operating room or post-operative recovery unit, or peripheral hospital location).

The fluid exposure variables were also categorized. Quantity of fluid was categorized as "0 – 2" liters, "2 – 4" liters, and "greater than 4" liters, type of fluid was categorized as crystalloid fluid (normal saline, ringer's lactate, 2/3 and 1/3 solutions, D51/2 normal saline, D5W and D10W) versus colloidal fluid (pentastarch and albumin), and the method of fluid administration was categorized as fluid infusions versus the combination of fluid infusions and fluid boluses in the first six hours after identification of severe sepsis.

Hospital and ICU mortality (dead versus alive), as well as need for mechanical ventilation (yes versus no) and vasoactive agent (yes versus no) support in the first 24 hours after the identification of severe sepsis were expressed as proportions. Lengths of stay in the hospital and ICU were expressed as medians and interquartile ranges (25^{th} and 75^{th} percentile).

3.14.2 According to Quantity, Type, and Method of Fluid Administered

After the entire cohort was described, it was broken down according to each of the fluid exposure variables (quantity, type, and method of fluid administered). Continuous variables were described with means and standard deviations and categorical variables with proportions.

3.15 Quantity of Fluid Analyses

3.15.1 Quantity of Fluid and Hospital Mortality

The association between the quantity of fluid administered (independent variable) in the first six hours after the identification of severe sepsis and hospital mortality (dependent variable) was analyzed with logistic regression models. The unadjusted and adjusted effect of quantity of fluid administered in the first six hours after the identification of severe sepsis with hospital mortality was expressed in terms of odds ratios and 95% confidence intervals.

The referent group for all quantity of fluid analyses was "0 – 2" liters. An odds ratio of less than one represented a reduction in hospital mortality for the "2 – 4" liter and or the "greater than 4" liter group in comparison to the "0 – 2" liter group. An odds ratio of greater than one represented an increase in hospital mortality for the "2 – 4" liter and or the "greater than 4" liter group in comparison to the "0 – 2" liter group.

For all multivariable analyses, baseline co-variates that were considered to be clinically or biologically relevant were entered into the model to adjust for the effect of quantity of fluid on hospital mortality. Co-variates included age and APACHE II score entered as continuous variables, and sex (male = reference group), source of infection (pulmonary = reference group), presence of co-morbid illnesses (0 co-morbidities = reference group), type of admission to the ICU (medical = reference group), and patient location at the identification of severe sepsis (ICU = reference group), that were entered as categorical variables. Increases of age and APACHE II score by 10 were entered into the logistic model as these increments were judged to represent clinically meaningful increases that would enable an understanding as to how much of an effect these variables would have on the outcome.

3.15.2 Quantity of Fluid and Secondary Outcomes

The association between the quantity of fluid administered (independent variable) in the first six hours of care after the identification of severe sepsis and the secondary outcomes (dependent variables) ICU mortality, need for mechanical ventilation within 24 hours after identification of severe sepsis, and need for vasoactive agent support within the first 24 hours after the identification of severe sepsis were analyzed with logistic regression models. The same baseline co-variates that were entered into "quantity of fluid and hospital mortality" multivariable model were entered into these models. The unadjusted and adjusted effect of quantity of fluid administered on these secondary outcomes was expressed in terms of odds ratios and 95% confidence intervals.

An odds ratio of less than one represented a reduction in ICU mortality, or need for mechanical ventilation, or need for vasoactive agent support within 24 hours of the identification of severe sepsis for the "2 – 4" liter and or the "greater than 4" liter group in comparison to the "0 – 2" liter group. An odds ratio of greater than one represented an increase in ICU mortality, or need for mechanical ventilation, or need for vasoactive agent support within 24 hours of the identification of severe sepsis for the "2 – 4" liter and or the "greater than 4" liter group in comparison to the "0 – 2" liter group.

The association between quantity of fluid (independent variable) administered in the first six hours after the identification of severe sepsis and time to discharge from ICU or hospital (dependent variables) were explored using cox-proportional hazards models as the length of stay outcomes were not normally distributed. The same baseline co-variates that were entered into the "quantity of fluid and hospital mortality" model were entered into these models. Categorical variables were entered with use of dummy variables. Patients who died at any point during hospitalization were censored on the date of their death. Each categorical variable was examined for proportionality to one another. The unadjusted and adjusted effect of quantity of fluid administered on time to discharge from ICU or hospital was expressed in terms of hazard ratios and 95% confidence intervals.

A hazard ratio of less than one was associated with a reduced time to discharge in the ICU or hospital for the "2 – 4" liter and or the "greater than 4" liter group in comparison to the "0 – 2" liter group. A hazard ratio of greater than one was associated with an increased time to discharge in the ICU or hospital for the "2 – 4" liter and or the "greater than 4" liter group in comparison to the "0 – 2" liter group.

3.15.3 Quantity of Fluid and Hospital Mortality – Sensitivity Analyses

Sensitivity analyses based on those baseline co-variates that were strong predictors of hospital mortality in the "quantity of fluid and hospital mortality" multivariable analyses were performed to determine if these variables acted as confounders in the association between the quantity of fluid administered in the first six hours after the identification of severe sepsis and hospital mortality. Co-variates were removed from the model individually to see if the direction or strength of the association between quantity of fluid and hospital mortality was affected.

An examination for the effect of new treatment strategies for severe sepsis that became available during the study was also performed. During the study period, two studies were published, both of which reduced mortality from severe sepsis The first was a treatment aimed at reducing activation of the coagulation cascade, and the second was an early and aggressive "goal – directed" resuscitation strategy[20;49]. Logistic regression analyses using the same baseline covariates were performed before and after each of these studies were published to see if the association between quantity of fluid administered in the first six hours after the identification of severe sepsis and hospital mortality was affected by the advent of these new treatments.

3.16 Type of Fluid Analyses

3.16.1 Type of Fluid and Hospital Mortality

The same analytic approach that was used to assess for associations between "quantity of fluid and hospital mortality" was used to examine for the association between the type of fluid administered (independent variable) in the first six hours of care after the identification of severe sepsis and hospital mortality (dependent variable). The referent group for the type of fluid analysis was the crystalloid group alone.

An odds ratio of less than one represented a reduction in hospital mortality for the colloid and crystalloid group in comparison to the crystalloid group alone. An odds ratio of greater than one represented an increase in hospital mortality for the colloid and crystalloid group in comparison to the crystalloid group alone.

3.16.2 Type of Fluid and Secondary Outcomes

The same analytic approaches that were used to assess for associations between "quantity of fluid and secondary outcomes" were used to examine for the association between the type of fluid administered in the first six hours after the identification of severe sepsis and secondary outcomes.

An odds ratio of less than one represented a reduction in ICU mortality, or need for mechanical ventilation within 24 hours after identification of severe sepsis, or need for vasoactive agent support within 24 hours after the identification of severe sepsis for the colloid and crystalloid group in comparison to the crystalloid group alone. An odds ratio of greater than one represented an increase in ICU mortality, or need for mechanical ventilation within 24 hours after identification of severe sepsis, or need for vasoactive agent support within 24 hours after the identification of severe sepsis for the colloid and crystalloid group in comparison to the crystalloid group alone.

3.16.3 Type of Fluid and Hospital Mortality – Sensitivity Analyses

The same sensitivity analyses that were conducted for the "quantity of fluid and hospital mortality" multivariable analyses were conducted for the type of fluid sensitivity analyses.

3.17 Method of Fluid Analyses

3.17.1 Method of Fluid and Hospital Mortality

The same analytic approach that was used to assess for associations between "quantity of fluid and hospital mortality" was used to examine for the association between the method of fluid administered (independent variable) in the first six hours of care after the identification of severe sepsis and hospital mortality (dependent variable). The referent group for the method of fluid analysis was the fluid infusion group alone.

An odds ratio of less than one represented a reduction in hospital mortality for the fluid bolus and fluid infusion group in comparison to the fluid infusion group alone. An odds ratio of greater than one represented an increase in hospital mortality for the fluid bolus and fluid infusion group in comparison to the fluid infusion group alone.

3.17.2 Method of Fluid and Secondary Outcomes

The same analytic approaches that were used to assess for associations between "quantity of fluid and secondary outcomes" were used to examine for the association between the method of fluid administered in the first six hours of care after the identification of severe sepsis and secondary outcomes.

An odds ratio of less than one represented a reduction in ICU mortality, or need for mechanical ventilation within 24 hours after identification of severe sepsis, or need for vasoactive agent support within 24 hours after the identification of severe sepsis for the fluid bolus and fluid infusion group in comparison to the fluid infusion group alone. An odds ratio of greater than one represented an increase in ICU mortality, or need for mechanical ventilation within 24 hours after identification of severe sepsis, or need for vasoactive agent support within 24 hours after the identification of severe sepsis for the fluid bolus and fluid infusion group in comparison to the fluid infusion group alone.

3.17.3 Method of Fluid and Hospital Mortality – Sensitivity Analyses

The same sensitivity analyses that were conducted for the "quantity of fluid and hospital mortality" analyses were conducted for the method of fluid sensitivity analyses.

3.18 ETHICS

The study protocol received ethics approval by the institutional ethics review board of the Ottawa Hospital prior to starting data collection (Appendix IX). All personal identifiers were kept strictly confidential and stored separately from the clinical information that was collected.

4.0: STUDY RESULTS

4.1 Flow of Inclusion of Patients

A total of 1,291 charts were identified for screening using the medical records and ICU databases (Figure 4). From this total, 211 of the charts were common to both databases. This left a total of 1,080 charts for detailed chart review: 583 charts that were unique to the medical records database, 286 that were unique to the ICU database, and the 211 charts that were common to both databases. After the chart review process, 791 of the charts were excluded: 537 from the medical records database, 156 from the ICU database, and 98 from the charts that were found to be common to both databases. Of the 791 excluded charts, 787 were excluded because these patients did not develop study criteria for severe sepsis within seven days of hospitalization. An additional four of these charts were excluded because treatment was withdrawn within six hours of the identification of severe sepsis. Hence, the screening strategy identified 289 (or 27% of the total screened) eligible patients.

4.2 Assessment for Information Bias

An experienced data collector (DH) examined 100 of the included hospital charts in duplicate to ensure that the included cases were correctly classified with severe sepsis (methods, Section 3.13). Seven hospital charts were excluded after a second review by DH: four of the charts were excluded because insufficient information was provided to calculate the total fluids administered, and three of the charts were excluded because of an error in diagnosis (misclassification errors: hypovolemia (n=2), cardiogenic shock (n=1). All seven of these hospital charts that were excluded were reviewed with the principal investigator (Lauralyn McIntyre).

Two important data points were also examined in duplicate by this data collector: date and time of first hypotensive episode (identification of severe sepsis), and the total amount of fluids administered in the first 6 hours after the identification of severe sepsis. In three of the 100 hospital charts, identification of severe sepsis was recorded incorrectly. In five of the 100 hospital charts, the total amount of fluids recorded in the first 6 hours after the identification of severe sepsis was recorded incorrectly. All errors in these hospital charts were reviewed with the principal investigator (Lauralyn McIntyre).

The goal was to achieve a sample size of approximately 400 patients for this study. However, after screening a total of 1,080 charts, a total of 282 patients were identified. Hence, the analysis was conducted on these 282 patients. Hence, a total of 282 patients were included in this study (Figure 4).

4.3 Descriptive Data

The baseline characteristics were assessed for the entire cohort and according to the following fluid exposure variables: quantity, type, and method of fluid administration.

4.3.1 Baseline Characteristics: Entire Cohort

The mean age and standard deviation for the entire cohort was 63 +/- 14 years. The mean APACHE II score and standard deviation for the entire cohort was 28+/-8. Females comprised 48% of the entire group. Medical admissions comprised 76% of this cohort. Emergency post – operative and elective post – operative admissions to the ICU were 17% and 7% respectively (Table 7).

The most common co-morbidity in this study was a diagnosis of cancer (36%). The frequency of other co-morbidities were, diabetes (26%), immune suppression (23%), chronic pulmonary disease (21%), coronary artery disease (21%), congestive heart failure (16%), chronic renal failure (13%), peripheral vascular disease (11%), and liver disease (9%). As some of these patients had more than one co-morbidity, the aggregate percent is greater than 100. Eighty-one percent of patients had at least one co-morbid illness; 56% of patients had 1 – 2 co-morbid illnesses; 22% of patients had 3 – 4 co-morbid illnesses; and 3% of patients had greater than 4 co – morbid illnesses (Table 7).

The three most frequent sources of infection were pulmonary (39%), intra-abdominal (33%), and urinary tract infections (10%). Soft tissue and vascular device infections were sited less frequently as the infectious source (6% and 3% respectively). The "other" category comprised 9% of the infectious sources and included infections from the central nervous system (n=5), the heart (endocarditis n=4), febrile neutropenia (n=4), disseminated histoplasmosis (n=1), toxic shock (n=1), and infectious source unknown (Table 7).

The majority of patients were either located in the emergency room (33%) or the ICU (34%) in the Ottawa Hospital, General Campus at identification of severe sepsis. The remaining patients were located on the hospital ward (15%), in a peripheral hospital (10%), or the post – operative care unit or operating room (8%) (Table 7).

4.4 Imputation of Missing Data

Data was missing for individual components of the APACHE II score as well as for the co – morbid disease variable (Table 7). For the APACHE II score, 53/282 (19%) patients had one or more missing data points (total 58 missing data points) (Table 8). For the co-morbid diseases variable, there was one missing data value for chronic renal failure and three missing data values for peripheral vascular disease (Table 7).

As the APACHE II score was an important baseline variable, I decided to impute with the methods described previously (Methods section 3.13.2) even though 19% of these data were missing.

4.4.1 Imputation for Continuous Data: APACHE II Continuous Variables

When both the high and low values for a continuous variable were missing (temperature, mean arterial pressure, heart rate, respiratory rate, hematocrit, Glasgow Coma Scale Score), then imputation using the worst group mean from the dataset with no missing data was used. For example, for the variable respiratory rate, there were two missing data points (Table 8). Hence the worst mean value for the high and low component was used to impute for these two missing values (high value = 29 (23); low value = 14 (5)).

4.4.2 Imputation for Categorical Data: APACHE II Chronic Health Score and Co-Morbid Disease Variables

There are two components to calculating the APACHE II chronic health score; type of admission and APACHE II co-morbidities. A score of 5 is given if a patient has at least one APACHE II co-morbidity and is either a medical or emergent post – operative admission. A score of 2 is given if a patient has at least one APACHE II co-morbidity and is an elective post – operative admission. There was no missing data for admission type. However 35 patients had missing data for the APACHE II co-morbidity (Table 8). To calculate the chronic health score for these patients (n=35), I did the following. First, I calculated the proportion of patients who had a chronic health score of 5 and 2 for the medical, emergent post – operative, and elective post-operative patients respectively using the larger dataset (n=229). For medical admissions, 90/192 (47%), had a score of 5. For urgent post-operative surgical admits, 12/39 (31%), had a score of 5. For elective post-operative surgical admits, 1/16 (6%), had a score of 2. For the 21 missing medical admission chronic health scores, 10 were randomly assigned a score of 5 (21 missing x 47% = 10). For the 10 missing emergent post operative admissions, 3 were randomly assigned a score of 5 (10 missing x 31% = 3). For the 4 missing elective post operative admissions, 0 were assigned a score of 2 (4 missing x 6% = 0).

A total of three data points were missing for the co-morbid disease variable (Table 7). Data was missing for one patient with the chronic renal failure co-morbidity, and for three patients with the peripheral vascular disease co-morbidity. The same approach used to impute for the APACHE II chronic health score was used to impute for these data.

4.4.3 Imputation of APACHE II Score

I calculated the APACHE II score with the following imputation methods to evaluate how the overall score was affected by these different methods of imputation: 1) with missing variables deleted (n=229); 2) with the missing variables recorded as normal (n=282); 3) with missing variables recorded as extreme (n=282).

The APACHE II score calculated with different methods of imputation are summarized in Table 8. The average APACHE II score was 27 with a standard deviation of 8 for the 229 patients with complete data. However, when missing data was imputed using either normal or extreme values, the average APACHE II score was 26 with a standard deviation of 8, and 30 with a standard deviation of 8 respectively. When missing data was imputed using the group mean for continuous data, and the group proportions for categorical variables, the average APACHE II score was 28 with a standard deviation of 8. Scores ranged from 26 to 30. This evaluation demonstrated that with different methods of imputation, the APACHE II score had minimal variation. Thus, for all analyses, I used the

APACHE II score that was calculated according to the group mean for continuous data, and the group proportions for categorical data.

4.5 Baseline Characteristics: According to Fluid Exposure Variables

For each of the fluid exposure variables, quantity, type, and method of fluids administered, there were imbalances in the distribution of some baseline characteristics. Thus, baseline characteristics were summarized according to each of the fluid exposure variables (Table 9).

4.5.1 Quantity of Fluid Administered

For the quantity of fluid exposure variable, baseline characteristics were categorized according to the "0 – 2", "2 – 4", and "greater than 4" liter fluid groups (Table 9). There appeared to be little variation in the mean age and APACHE II score between these three fluid groups. However, for the remaining baseline characteristics, variation was present. Medical and emergency post – operative admissions comprised 85% and 7% of patients in the "0 – 2" liter group respectively. However, in the "greater than 4" liter group, medical and emergency post-operative admissions comprised 53% and 44% of admissions respectively.

Diabetes was the only co-morbidity with little variation between the fluid groups (range: 25% to 27%). Cancer varied considerably between the fluid groups. The proportion of patients with cancer in the "0 – 2", "2 – 4", and "greater than 4" liter groups were 37% versus 40% and 24% respectively. When co-morbid illnesses were quantified according to zero, one to two, three to four, or greater than four co-morbidities, the variation in the distribution of co-morbid diseases across the quantity of fluid administered group was also evident. Twelve percent of patients in the "0 – 2" liter group, 21% in the "2 – 4" liter group, and 35% of patients in the "greater than 4" liter group had no co-morbidities. Further, 26% of patients in the "0 – 2" liter group, versus 21% in the "2 – 4" liter group, and 9% of patients in the "greater than 4" liter group had 3 to 4 co-morbidities. The two most common sources of infection, pulmonary and intra-abdominal, had the greatest amount of variation in between the fluid groups. The proportion of patients with a pulmonary infection in the "0 – 2" liter, and "greater than 4" liter groups were 50% and 16% respectively. In contrast, 22% and 53% of patients in the "0 – 2" liter and "greater than 4" liter groups had intra-abdominal infections.

Finally, the place in hospital at the identification of severe sepsis also varied between the fluid groups. The proportion of patients who were in the ICU at the identification of severe sepsis ranged from 47% to 7% for those who received "0 – 2" liters and "greater than 4" liters of fluid respectively. Similarly, the proportion of patients who were in the emergency room at the identification of severe sepsis ranged from 29% in the "0 – 2" liter group to 47% in the "greater than 4" liter group.

4.5.2 Type and Method of Fluid Administered

For the type of fluid administered exposure variable, baseline characteristics were categorized according to the crystalloid only versus colloid and crystalloid group (Table 9). For the method of fluid administered exposure variable, baseline characteristics were recorded according to the fluid infusions only versus the combination of fluid boluses with fluid infusions. Similar variability in the distribution of baseline characteristics between fluid groups for both of these fluid exposure variables was noted.

4.6 The Fluid Exposure Variable

The mean (standard deviation) total quantity of fluid administered in the first six hours after the identification of severe sepsis was 2.71 (2.09) liters (Table 10). For the analysis, the total quantity of fluid administered in the first six hours after the identification of severe sepsis was divided into the categories "0 – 2", "2 – 4", and greater than 4" liters to understand in more detail the distribution of fluid administration. When total quantity of fluid administered was divided into these categories, 47% received "0-2" liters, 37% "2 – 4" liters, and 16% of patients received "greater than 4" liters of fluid.

The two main types of fluid administered were colloidal agents (pentastarch and albumin) and crystalloid agents (normal saline, ringers lactate, ½ normal saline, Dextrose 5% in ½ normal saline, 2/3+1/3, D5W, and D10W). For the type of fluid analysis, fluids were categorized as crystalloid fluid versus colloid and crystalloid fluid. In the first six hours after the identification of severe sepsis, 1% patients received no fluid, 36% received crystalloid fluids only, and 63% received a combination of colloidal and crystalloid fluids. No patients received colloidal solutions only and none received the colloidal agent albumin. Hence, all colloidal fluid resuscitation reflected use of pentastarch.

For the method of fluid administered analysis, fluid was categorized as fluid infusions alone versus the combination of fluid boluses with fluid infusions. In the first six hours after the identification of severe sepsis, 9% of patients received fluid in the form of fluid infusions. Thus, the majority of patients received fluid as the combination of fluid infusions and fluid boluses (91%).

4.7 Outcomes: Entire Cohort

Hospital and ICU mortality for the entire cohort was 45% and 33% respectively. Median length of stay in hospital and ICU was 15 days (interquartile range 7 to 29 days) and 6 days (interquartile range 2 to 13 days) respectively. Thirty – nine percent of patients required vasopressor support and 70% required mechanical ventilation within the first 24 hours after severe sepsis was identified (Table 11).

4.8 Outcomes: According to Fluid Exposure Variables

4.8.1 Quantity of Fluid Administered

Hospital mortality for the "0 – 2", "2 – 4", and "greater than 4" liter groups were 45%, 44%, and 47% respectively. ICU mortality for the "0 – 2", "2 – 4", and "greater than 4" liter groups were 29%, 31%, and 44% respectively. Median length of stay in the ICU was the same for all fluid groups (6 days, interquartile range 2 to 13 days). Median length of stay in the hospital was also similar for all fluid groups ("0 – 2" liters: 15 days, interquartile range 9 to 30 days; "2 – 4" liters: 14 days, interquartile range 5 – 26 days; and "greater than 4" liters: 14 days, interquartile range 6 to 30 days). Twenty – six percent of patients in the "0 - 2" liter group as compared to 46% in the "2 – 4" liter and 60% in the "greater than 4" liter groups required vasoactive agents in the first 24 hours after severe sepsis was identified. Mechanical ventilation was required for 69% of patients in the "0 – 2" liter group, 70% in the "2 – 4" liter group, and 76% in the "greater than 4" liter group in the first 24 hours after severe sepsis was identified (Table 11).

4.8.2 Type of Fluid Administered

Hospital mortality for the crystalloid as compared to the colloid and crystalloid group was 40% and 47% respectively. ICU mortality for the crystalloid as compared to the colloid and crystalloid group was 25% and 36% respectively. Length of stay in hospital was 14 days (interquartile range 7 to 29 days) for the crystalloid and 16 days (interquartile range 7 to 29 days) for the colloid and crystalloid group. Length of stay in ICU for the crystalloid as compared to the colloid and crystalloid group was 6 days (interquartile range 2 to 12 days) and 7 days (interquartile range 3 to13 days) respectively. In the first 24 hours after severe sepsis was identified, vasopressor agents were required for 37% in the crystalloid and 40% of patients in the crystalloid and colloid group. Mechanical ventilation was required for 61% in the crystalloid and 76% in the crystalloid and colloid group (Table 11).

4.8.3 Method of Fluid Administered

Hospital mortality for the fluid infusion as compared to the fluid infusion and bolus group was 54% and 44% respectively. ICU mortality for the fluid infusion as compared to the fluid infusion and bolus group was 28% and 33% respectively. Length of stay in hospital for the fluid infusion group was 19 days (interquartile range 3 to 52 days) as compared to 14 days (interquartile range 7 to 75 days) for the fluid infusion and bolus. Length of stay in ICU for the fluid infusion as compared to the fluid infusion and bolus group was 10 days (interquartile range 5 to 24 days) and 14 days (interquartile range 7 to 75 days) respectively. In the first 24 hours after severe sepsis was identified, vasopressor agents were required for 23% in the fluid infusion and 41% of patients in the fluid infusion and bolus group. Mechanical ventilation was required for 81% in the fluid infusion and 70% in the fluid infusion and bolus group (Table 11).

4.9 Rationale for Choosing Covariates for Multivariable Analyses

The following variables were entered into all multivariable analyses: age, sex, APACHE II score, type of admission, number of co-morbid illnesses, infectious source, and place in hospital. Although the mean ages between the quantity of fluid groups appeared similar, age was entered into the multivariable models as it is a variable strongly associated with death[97]. In addition, although the mean APACHE II score did not appear too dissimilar between the quantity of fluid groups, it too was entered into the multivariable models as it is also a strong predictor of death in critically ill patients[94;95]. Rationale for selecting the remaining variables (sex, type of admission, number of co-morbid diseases, infectious source, and place in hospital) for entry into the logistic regression model were two fold. First, these baseline characteristics are associated with death from critical illness in the literature[97-100]. Second, the distribution of these baseline characteristics varied between the quantity of fluid groups and hence, may have confounded the estimates of effect for the fluid analyses.

4.10 Quantity of Fluid Analyses

4.10.1 Quantity of Fluid and Hospital Mortality

The crude odds of hospital mortality for the "2 – 4" and "greater than 4" liter in comparison to the "0 - 2" liter group was not statistically significant (odds ratio of 0.97 and 95% confidence intervals from 0.58 to 1.62 and odds ratio of 1.08 and 95% confidence intervals from 0.55 to 2.14 respectively) (Table 12).

After adjustment, the administration of "2 – 4" and "greater than 4" in comparison to "0 – 2" liters of fluid in the first six hours after the identification of severe sepsis were not associated with a statistically significant increase or decrease in the odds of hospital mortality (odds ratio of 0.99 and 95% confidence intervals from 0.51 to 1.94 and odds ratio of 1.02 and 95% confidence intervals from 0.39 to 2.57 respectively) (Table 13).

4.10.2 Quantity of Fluid and Secondary Outcomes/Sensitivity Analyses

The administration of "2 – 4" and "greater than 4" as compared to "0 – 2" liters of fluid in the first six hours after the identification of severe sepsis were not associated with a statistically significant increase or decrease in the crude odds of death in ICU (odds ratio of 1.12 and 95% confidence intervals from 0.63 to 2.00 and odds ratio of 1.97 and 95% confidence intervals from 0.97 to 3.99 respectively) or need for mechanical ventilation within 24 hours after the identification of severe sepsis (odds ratio of 1.03 and 95% confidence intervals from 0.59 to 1.79 and odds ratio of 1.39 and 95% confidence intervals from 0.64 to 3.02 respectively) (Table 16). The administration of "2 – 4" and "greater than 4" liters in comparison to "0 – 2" liters of fluid was associated with a statistically and clinically significant increase in the need for vasoactive agent support within the first 24 hours after the identification of severe sepsis (odds ratio of 2.43 and 95% confidence intervals from 1.40 to 4.20 and odds ratio of 4.32 and 95% confidence intervals from 2.12 to 8.12 respectively). The administration of "2 – 4" and "greater than 4" liters as compared to "0 – 2" liters of fluid was not associated with statistically significant increased or decreased time to discharge from ICU (hazard ratio of 0.95 and 95% confidence intervals from 0.61 to 1.49 and hazard ratio of 1.22 and 95% confidence intervals from 0.88 to 1.68 respectively) or hospital (hazard ratio of 1.02 and 95% confidence intervals from 0.64 to 1.62 and hazard ratio of 0.25 and 95% confidence intervals from 0.88 to 1.77 respectively) (Table 16).

After adjustment, no association between quantity of fluid administered in the first six hours after the identification of severe sepsis and ICU mortality (odds ratio of 0.97 and

95% confidence intervals from 0.46 to 2.03 and odds ratio of 1.61 and 95% confidence intervals from 0.59 to 4.41), time to discharge from ICU (hazard ratios of 1.14 and 95% confidence intervals from 0.77 to 1.69 and hazard ratios of 0.88 and 95% confidence intervals from 0.50 to 1.54), or hospital (hazard ratio of 1.17 and 95% confidence intervals from 0.77 to 1.79 and hazard ratio of 0.93 and 95% confidence intervals from 0.53 to 1.62), or need for mechanical ventilation within the first 24 hours after identification of severe sepsis were evident (odds ratio of 1.22 and 95% confidence intervals from 0.56 to 2.63 for and odds ratio of 2.17 and 95% confidence intervals from 0.73 to 6.47). The administration of "2 – 4" and "greater than 4" liters in comparison to "0 – 2" liters of fluid was associated with a statistically and clinically significant increased odds of needing vasoactive agent support within the first 24 hours after the identification of severe sepsis (odds ratio of 1.96 and 95% confidence from 1.02 to 3.78 and odds ratio of 4.16 and 95% confidence intervals from 1.63 to 10.65 respectively) (Table 17). Sensitivity analyses did not alter the association between quantity of fluid administered in the first six hours after the identification of severe sepsis and hospital mortality (Table 18).

4.11 Type of Fluid Analyses

4.11.1 Type of Fluid and Hospital Mortality

The crude odds of hospital mortality for colloidal and crystalloid fluid group in comparison to crystalloid fluid group alone were not statistically significant (odds ratio of 1.33 and 95% confidence intervals from 0.81 to 2.18) (Table 12).

After adjustment, the administration of colloidal and crystalloid fluid in comparison to crystalloid fluid alone in the first six hours after the identification of severe sepsis was not associated with a statistically significant increase or decrease in the odds of hospital mortality (odds ratio of 1.02 and 95% confidence intervals from 0.55 to 1.89) (Table 14).

4.11.2 Type of Fluid and Secondary Outcomes/Sensitivity Analyses

The administration of colloidal and crystalloid fluid in comparison to crystalloid fluid alone was not associated with statistically significant increases or decreases in the crude odds of ICU mortality (odds ratio of 1.73 and 95% confidence intervals from 0.98 to 3.06), need for vasoactive agent support within 24 hours after the identification of severe sepsis (odds ratio of 1.12 and 95% confidence intervals from 0.68 to 1.85), or time to discharge from ICU (hazard ratio of 1.08 and 95% confidence intervals from 0.79 to 1.47), and hospital (hazard ratio of 1.09 and 95% confidence intervals from 0.78 to 1.50) (Table 16). There was a statistically and clinically significant increase in the need for mechanical ventilation within 24 hours after the identification of severe sepsis for the colloidal and crystalloid fluid group as compared to crystalloid fluid group alone (odds ratio of 2.10 and 95% confidence intervals from 1.23 to 3.54) (Table 16).

After adjustment, no association between the type of fluid administered in the first six hours after the identification of severe sepsis and ICU mortality (odds ratio of 1.46 and 95% confidence intervals from 0.71 to 2.94), time to discharge from ICU (hazard ratio 1.07 and 95% confidence intervals from 0.75 to 1.52), or hospital (hazard ratio of 1.01 and 95% confidence intervals from 0.70 to 1.45), or need for vasoactive agent support within the first 24 hours after the identification of severe sepsis were evident (odds ratio of 1.48 and 95% confidence intervals from 0.79 to 2.75). After adjustment, the administration of colloid and crystalloid fluids in comparison to crystalloid fluids alone remained associated with a statistically and clinically significant increase in the need for mechanical ventilation within the first 24 hours after the identification of severe sepsis (odds ratio of 2.23 and 95% confidence intervals from 1.10 to 4.53) (Table 17). Sensitivity analyses did not alter the association between the type of fluid administered in the first six hours after the identification of severe sepsis and hospital mortality (Table 18).

4.12 Method of Fluid Administered Analyses

4.12.1 Method of Fluid and Hospital Mortality

The crude odds of hospital mortality for the combination of fluid infusions and fluid boluses in comparison to fluid infusions alone were not statistically significant (odds ratio of 0.67 and 95% confidence intervals from 0.29 to 1.50) (Table 12).

After adjustment the administration of fluid boluses and fluid infusions in comparison to fluid infusions alone were not associated with a statistically significant reduction in the odds of hospital mortality (odds ratio of 0.42 and 95% confidence intervals from 0.15 to 1.15) (Table 15).

4.12.2 Method of Fluid and Secondary Outcomes/Sensitivity Analyses

The administration of fluid boluses and fluid infusions in comparison to fluid infusions alone in the first six hours after the identification of severe sepsis were not associated with a statistically significant increase or decrease in the crude odds of death in ICU (odds ratio of 1.25 and 95% confidence intervals from 0.50 to 3.13), need for mechanical ventilation (odds ratio of 0.55 and 95% confidence intervals from 0.20 to 1.51), or need for vasoactive agent support (odds ratio of 2.27 and 95% confidence intervals from 0.88 to 5.86) within 24 hours after the identification of severe sepsis (Table 16). Time to discharge from ICU (crude hazard ratio of 0.60 and 95% confidence intervals from0.36 to 1.00) and hospital (crude hazard ratio of 0.45 and 95% confidence intervals from 0.24 to

0.84) were significantly reduced for the fluid bolus and fluid infusion group as compared to the fluid infusion group alone (Table 16).

After adjustment, time to discharge in the hospital (hazard ratio 0.40 and 95% confidence intervals from 0.20 to 0.78) and ICU (hazard ratio of 0.59 and 95% confidence intervals from 0.33 to 1.05) remained significantly reduced for the group who received the combination of fluid boluses with fluid infusions as compared to fluid infusions alone (Table 16). No associations between the method of fluids administered and ICU mortality (odds ratio of 0.90 and 95% confidence intervals from 0.28 to 2.85), need for mechanical ventilation (odds ratio of 0.41 and 95% confidence intervals from 0.10 to 1.73) or vasoactive agents (odds ratio of 2.04 and 95% confidence intervals from 0.63 to 6.56) within 24 hours of the identification of severe sepsis were evident (Table 17). Sensitivity analyses did not alter the association between method of fluids administered and hospital mortality (Table 18).

5.0: DISCUSSION

5.1 Major Findings

I demonstrated in this study that the quantity, type, and method of fluids administered in the first six hours after the identification of severe sepsis were not associated with a statistically significant reduction in hospital mortality. With regard to secondary outcomes, increased quantity of fluid administered was associated with a statistically and clinically significant increased need for vasoactive agent support within the first 24 hours after severe sepsis was identified. The administration of colloid and crystalloid fluid as compared to crystalloid fluids alone were associated with a statistically and clinically significant increase in the need for mechanical ventilation within the first 24 hours after severe sepsis was identified. There also appeared to be a trend toward a reduction in hospital mortality when patients were administered fluid boluses in combination with fluid infusions as compared to fluid infusions alone in the first six hours after identification of severe sepsis. The administration of fluid boluses with fluid infusions as compared to fluid infusions alone were associated with a significant reduction in time to discharge from hospital as well as ICU. Sensitivity analyses performed using strong predictors of hospital mortality including age (< 60 versus >= 60), APACHE II score (< 25 versus >= 25), and peripheral hospital admission did not significantly alter the associations between fluid administered and any of these outcomes. Overall, based upon the 282 patients with severe sepsis in this analysis, associations between the quantity, type, and method of intravenous fluids administered appeared to be either absent or weak.

5.1.1 Quantity of Fluid Administered

The primary study objective was to determine if there was an association between the quantity of fluid administered in the first six hours after the identification of severe sepsis and hospital mortality. This question was put forth because clinical observations have suggested that fluid administration has a major impact on acute physiology. Furthermore, a subgroup analysis from a sentinel clinical trial of early resuscitation documented an important association between the quantity of fluids administered and hospital mortality[20]. However, in my study, I was unable to detect an association between quantity of fluid administered in the first six hours of care and hospital mortality in patients with severe sepsis.

Several reasons may explain why I was unable to detect an association. The six hour time window may not have provided an adequate time frame to examine for this association. A more sensitive method would have been to record the amount of fluid delivered to these patients on an hourly basis. However, the data was not collected with this amount of detail as it would have become far too labor intensive, and hence infeasible. Rivers identified and randomized patients into the study within two hours of arrival to the emergency room. Much effort was made to identify an accurate inception of severe sepsis. However, it is possible that the initiation of the severe sepsis process occurred several hours before these patients were identified as I relied on correctly identifying the population through retrospective data collection. In addition, although vital sign charting occurs on an hourly basis in the ICU, on the hospital ward, it occurs at best every 2 to 12 hours depending on how ill the patient is. Although correctly identifying the inception of severe sepsis was an issue in my study, one could also make the same argument with the Rivers study, which was a prospective randomized controlled trial[20]. Both delayed identification of these patients and lack of detailed fluid data collection in the first few hours after the identification of severe sepsis are forms of information bias. This bias may have served to blunt the magnitude of difference ascertained between the fluid groups.

Other reasons for the inability to detect an association between quantity of fluid administered and hospital mortality may relate to inaccurately charted, or missing data. In addition, as the charting of fluid is typically done on the hour, I made the decision a priori to always calculate the total fluid delivered in the first six hours of care to the closest hour. For example, if the identification of severe sepsis occurred at 12:42 pm, the six hour recording of fluid ended at 19:00 for that patient (i.e. not at 18:42). Hence, in some patients, the fluids recorded in the first six hours of care may have in fact reflected more than six, but not as much as seven hours of resuscitation. Although these data inaccuracies represent another form of information bias, it is likely that this bias would be non-differential between the fluid groups, and hence have little effect on the overall estimate of effect.

Efforts were made to reduce as much as possible inaccurately recording of data from the data abstractors. First, I created a data collection instrument with an easy to understand instruction manual that defined all data collection variables. Second, each data abstractor had a medicine background either in the form of nursing or doctoring. Hence the medical language and interpretation of data was facilitated with ease. Finally, I put all data collectors through a two week training session followed by ongoing evaluation of data collection of every chart by the principal investigator. I also evaluated the accuracy of data collection by having a second experienced data collector review 100 of the included charts for correct classification of severe sepsis, correct identification of the first hypotensive event, and correct quantification of fluids received in the first six hours after severe sepsis was identified.

The Rivers trial only identified patients from the emergency room, not from the entire hospital as was done in this study. Hence, this study may have represented a patient population that was different from Rivers. More importantly, findings from the Rivers trial may not be generalizable to all patients with severe sepsis. In the Rivers' trial, the "goal-directed" group also received more blood transfusions (64.1% versus 18.5%, $p<0.001$) and inotropic agents (13.7% versus 0.8%, $p<0.001$) in the first six hours of care. These co-interventions may have been responsible for the reduction in mortality. Quantity of fluid administered may have represented a marker of severity of illness of these patients, rather than being responsible for the reduction in mortality.

Another potential study limitation related to the sample size. The confidence intervals were wide, and thus, the possibility of harm or benefit could not be determined ("2 – 4" liters odds ratio and 95% confidence intervals 0.99 (0.51 to 1.94) and "greater than 4" liters odds ratio and 95% confidence intervals 1.02 (0.39 to 2.57).

5.1.2 Type of Fluid Administered

In Canada, the two main colloidal agents used for resuscitation of patients with septic shock are pentastarch and albumin. The two main crystalloid agents used are normal saline and ringer's lactate. The optimal choice of fluid type in various patient populations remains a source of major debate[62;80-85]. Based upon the ongoing controversy, I explored for these potential associations in this cohort of patients. However, I was unable to detect any associations between the type of fluid administered in the first six hours after the identification of severe sepsis and hospital mortality.

Recently published practice parameters for hemodynamic support as well as an evidence based review on fluid resuscitation for severe sepsis and septic shock suggested that either colloidal or crystalloid agents may be used for fluid resuscitation as there was no evidence to support the use of one type of fluid over the other in this setting[42]. Recently, the 'Saline versus Albumin Fluid Evaluation' (SAFE) study, a 6,997 patient randomized trial, evaluated the use of 4% albumin versus normal saline in critically ill patients that required resuscitation in the ICU. Although there was no difference in 28-day mortality for the entire group, an "a priori" derived subgroup analysis of patients with severe sepsis suggested a trend toward reduction in death for the albumin as compared to normal saline group (relative risk ratio of 0.87 and 95% confidence intervals from 0.74 to 1.02). As acknowledged by the authors, these results should be considered preliminary and hypothesis generating as the trial was not designed, nor powered to answer this question specifically. Further, as these results were derived from a subgroup analysis, it is possible that there were important imbalances between the groups that may have confounded the estimate of effect between the groups[91]. The SAFE study severe sepsis subgroup results were not statistically significant and thus the possibility of benefit or harm could not be confirmed. Finally, as the SAFE severe sepsis results were derived from a subgroup, it is possible that these results may have occurred due to chance alone.

In addition to the limitations of delayed identification and inaccuracies in the identification of severe sepsis, there may be other reasons that explain the inability to detect and association between colloidal fluids and hospital mortality in this study. In this study, no patients received the colloid albumin as a resuscitation fluid in the first six hours of care. Rather, all patients received the colloid pentastarch. As these colloidal fluids may possess different biological actions[19;58-60;64-67], the lack of difference may be due to the fact that no patients received albumin as a resuscitation fluid. A lack of albumin use with the sole use of pentastarch as the colloidal resuscitation fluid in this study may be related to results published from a systematic review in the British Medical Journal in 1998 that suggested albumin may be harmful in comparison to crystalloid fluids[85]. Although these data were derived from a systematic review that included small heterogeneous studies, with heterogeneous groups of critically ill patients, and with methodological flaws, the authors from this review strongly concluded that use of albumin should be restricted to use in the context of clinical trials only. Another systematic review comparing albumin to crystalloid fluids was published in 2001 and concluded that albumin had no effect on mortality, although the confidence intervals for all analyses included the null. Hence, one could not exclude the potential for harm or benefit[81]. Editorials published from this review pointed out that the conclusions made were biased and potentially subject to influence from the pharmaceutical industry as this systematic review was sponsored by the manufacturers of albumin[89].

In this study, all crystalloid solutions were summed together. However, different crystalloid solutions may also possess different biological actions[52-57]. As I did not separately collect the total normal saline and ringers lactate fluids delivered in the first six hours of care in this study, an analysis according to type of crystalloid solution administered could not be conducted. The potential differences in biological actions for these fluids highlight the need for future fluid resuscitation research.

5.1.3 Method of Fluid Administered

In the multivariable analyses, there was not a statistically significant reduction in hospital mortality for patients who were administered the combination of fluid boluses with fluid infusions as compared to fluid infusions alone. However, there was a trend toward a reduction in hospital mortality for the group of patients who were administered fluid boluses in combination with fluid infusions as compared to fluid infusions alone (odds ratio of 0.42 and 95% confidence intervals from 0.15 to 1.15). All secondary outcomes, with exception of the need for vasoactive agent support demonstrated comparable trends.

The administration of resuscitation fluid in the form of fluid boluses was considered an essential aspect of management in the hypotensive and unstable patient. The rationale for bolusing fluid as opposed to running fluid as infusions was to replace intravascular volume rapidly, and hence, optimize oxygen delivery and tissue perfusion so that organ failure and death could be prevented. In support of this management strategy, a recently published evidence-based review on fluid resuscitation for patients with severe sepsis and septic shock sited rapid fluid challenging using clinical response as indicators for adequacy of fluid resuscitation as the optimal method to resuscitate patients with suspected inadequate arterial circulation. However, the level of evidence supporting this recommendation was grade E. Studies supporting this recommendation were either Level IV (non-randomized, historical controls and expert opinion) or level V evidence (case series, uncontrolled studies, and expert opinion)[42]. Hence, the published evidence for administering resuscitation fluids in the form of boluses was very weak.

Due to the retrospective nature of this study, I was unable to document the quantity and rapidity of each individual fluid bolus and then conduct a multivariable analysis that included a time dependent quantity of fluid covariate. Despite this, a trend toward a reduction in mortality was apparent when fluids were delivered as boluses with infusions as compared to fluid infusions alone. It is possible that this association may have occurred spuriously as I conducted many analyses and I did not make adjustments for these multiple comparisons. Further, not all analyses suggested a beneficial trend with the administration of fluid boluses and fluid infusions as compared to fluid infusions alone[91]. However, it was a study question that I posed a priori. In addition, the idea that this association was true may be supported by the strength and temporality of this association, in addition to the biologic plausibility that the administration of fluid boluses with fluid infusions are the optimal method to resuscitate these hemodynamically unstable patients[101].

Although a randomized controlled trial would have been the optimal method to evaluate this aspect of fluid resuscitation, the administration of fluid boluses was such an accepted and taught practice in critical care that it would have been considered unethical to conduct a controlled trial to address the question. Hence, in absence of other data this study provided some evidence in support of using fluid boluses in combination with fluid infusions when resuscitating patients with severe sepsis and septic shock.

5.2 Other Study Strengths and Limitations

This study was novel in that the specific associations between quantity, type, and method that fluid was administered in the first six hours of care for patients with severe sepsis and hospital mortality have never been examined in the context of primary study questions. I believe that a retrospective cohort study provided a reasonable initial study design to examine for these associations as it enabled me to collect data on a large number of patients with severe sepsis, in a relatively expedient fashion, and without excessive costs.

This study lacked sufficient power to detect an association between quantity of fluid and hospital mortality as I did not achieve the original sample size of 411 patients. With a sample size of 282 patients and using the original estimates of effect (mortality of 50% for $\leq$ 3.5 L and 30% for $\geq$ 5 L of fluid), and an alpha of 0.05, I had approximately 50% power to detect an association between quantity of fluid and hospital mortality if an association truly existed. Hence, the lack of an association found between quantity of fluid and hospital may have been due to a type II error, concluding that there was no association when indeed an association did exist.

In addition to the limitations of information bias discussed previously, there are other limitations that threatened the internal and external validity of the study findings. These included problems of selection bias, residual confounding, secular trends, and generalizability.

5.2.1 Selection Bias

I made efforts to reduce selection bias as much as possible by identifying all patients in a consecutive manner who were admitted to the Ottawa Hospital with severe sepsis during the study period, and by having minimal exclusion criteria. I did not ascertain the number of patients who may have developed criteria for severe sepsis after seven days of hospital admission as to have done so would have made this study not feasible. However, for the 282 patients who were included, 75% developed severe sepsis within two days of hospital admission. Importantly, the seven day criterion was chosen in an attempt to include patients who had similar timing with respect to the onset and evolution of their disease process. I also excluded patients who had treatment withdrawn within the first six hours after the identification of severe sepsis because resuscitation of these patients is aborted and the focus of care is on palliation in anticipation of death. Only three patients were excluded from this study for this reason.

Efforts were made to identify all patients with the diagnosis of severe sepsis (actual population) during the study period with use of two separate search strategies (medical records search with ICD – 9 codes, and an ICU database search). Despite these efforts, 1,080 charts were screened and only 26% or 282 charts met criteria for severe sepsis (study population). Correct classification of patients with the diagnosis of severe sepsis in a retrospective manner has always posed a challenge for critical care researchers. A major reason for these difficulties related to the lack of specific codes for severe sepsis and septic shock in internationally utilized medical coding systems (International Center for Disease 9 and 10 Codes). However, several reasons may explain why there were not better coding systems in place. The definitions for severe sepsis and septic shock included three and potentially four separate criteria to make the diagnosis (infectious source, two or more criteria for the systemic inflammatory response syndrome, one or more acute organ failures, and the persistence of hypotension despite adequate fluid resuscitation). Hence, one can imagine the difficulties in coding these diagnoses, especially if they are being captured in a retrospective fashion. These problems would be magnified if the person doing the coding did not possess medical expertise. As a consequence, prospective data collection by trained individuals with some medical background is the preferred but still imperfect method used to classify these patients. The Angus ICD – 9 medical records search criteria have several shortcomings. According to the Angus search criteria, to qualify for the diagnosis of severe sepsis, a patient needed to have an ICD – 9 code for infection in addition to a code for at least one organ failure. There were two problems with this search method. First, only approximately 50% of patients with severe sepsis were likely to have an identifiable blood stream infection[102]. Second, in this search, the presence of organ failure was not necessarily temporally related to the infection. Hence, a patient may have developed organ failure at an entirely different time and for a different reason during the hospitalization. After completing the chart review for this study, the Angus search criteria identified only 20% ((45 + 112)/(583 + 211)) patients correctly with severe sepsis. In contrast to the Angus search method, our ICU database contained prospectively collected data with personnel who have a medical background. Despite these potential strengths, our database identified 48% ((125 + 112)/(286 + 211)) patients correctly as having severe sepsis. Hence, although the ICU database was superior to the Angus search criteria, neither of these strategies in isolation were excellent in identifying these patients, highlighting the difficulty in identifying these patients. The seven day exclusion criteria may have exaggerated how poor these strategies were. However, this remains speculative as I did not confirm if those patients went on to develop severe sepsis at a later point in the hospitalization.

Another reason for lack of identification of patients with severe sepsis related to the dynamic nature of this problem. For example, a patient can progress from having sepsis to septic shock and then back to sepsis in a manner of hours or days. Depending on the method of data collection in these databases, a patient's progression from sepsis to severe sepsis or septic shock may not be captured. In this study, hypotension, instead of the development of any single organ failure, was used to identify patients with severe sepsis, as the main purpose of this thesis was to examine how fluid administration was associated with hospital mortality. Hypotension was the cardinal sign for a physician to start administering fluids. Although hypotension has an ICD – 9 code attached to it, in order for these data to be entered into a database, the data needed to be captured. A hypotensive episode may not have been captured in these retrospectively collected databases as this amount of detail is typically undertaken in the context of a chart review. Although all of these issues represented forms of selection bias, I believe that the bias would have been non – differential between the fluid groups, and hence had minimal impact on the estimates of effect.

5.2.2 Secular Trends

The third threat to the internal validity of this study related to the possibility of changes in treatment influencing the management of these patients over time. Two randomized controlled trials for patients with severe sepsis and septic shock were published during the study period. These included the Activated Protein C study and the "Early goal - directed" resuscitation trial published in March and November 2001 respectively[5;20]. I did not collect information on Activated Protein C, or specifics of "goal-directed" resuscitation in this study. However, to evaluate for the possibility of change in management affecting these associations, I conducted analyses before and after these trials were published. None of these sensitivity analyses affected the strength or direction of the associations.

The use of Activated Protein C would not have altered the association between fluid administration in the first six hours of care and hospital mortality because this drug was not considered as a first line treatment strategy for severe sepsis and septic shock. Rather, it was indicated for use within 48 hours after the onset of severe sepsis and septic shock. However, the publication of Rivers "goal-directed" therapy trial may have influenced the association between fluid administration and hospital mortality because "goal – directed" therapy was meant to be instituted immediately after severe sepsis and septic shock was identified. However, analyses conducted according to the date of publication of this trial did not reveal any different association between fluid administration and hospital mortality. A more sensitive method to examine for the effect of this kind of therapy would be to adjust for the amount of fluid administered over certain time windows by conducting either stratified analyses or by entering fluid over time as an independent variable into the multivariable logistic regression analysis. I did not collect this amount of detail in the chart review. Hence, this analysis was not conducted.

5.2.3 Residual Confounding

The descriptive section of the results section highlighted that there existed many imbalances among the fluid groups for variables that may have influenced the outcome of these patients. Hence, it is possible that the associations between fluid administration and hospital mortality were related to the presence of imbalances in these confounding variables among the fluid groups, rather than be true associations. However, I did attempt to control for the effect of these confounding variables by entering them into the logistic regression analyses. Another method to examine for the effect of these variables with the fluid associations would have been to conduct stratified analyses. I did conduct sensitivity analyses for three variables that were significantly associated with hospital mortality (age, APACHE II score, peripheral hospital admission). For all analyses, the confidence intervals included the null. Hence, the confounding influence of these variables could not truly be ascertained. Despite efforts to control for potential confounding variables, it is likely that there existed residual confounding that I was unable to adjust for.

A prospective observational study design with matching on important confounding variables may have reduced some of the potential problems around internal validity. However, this study design would still not have controlled for all confounding variables. In addition, accurate identification of severe sepsis would have still likely been a problem as it would have required that all patients who were admitted to or diagnosed in the hospital with suspected infection would have needed continuous recording of vital signs. Patients develop severe sepsis 24 hours a day. In order to conduct a true prospective observational study, it would mean that the data collectors would need to be in hospital 24 hours a day. These realities would have made this study design prohibitively expensive, and the study not feasible. Alternatively, a randomized controlled trial design would have taken care of these issues of bias. However, this type of study design would have also been very expensive, and taken a lengthy amount of time to complete. In light of these problems, I believe that a retrospective cohort study design represented the most reasonable design in which to conduct this study.

5.2.4 Generalizability

This study was conducted at one academic care center in Canada over a period of two years. The generalizability of these study results would be strengthened if this study was conducted in several centers both academic and community across Canada. In addition, the study may have also been strengthened if data had been collected over several years, rather than the two year period chosen. However, two years represented a reasonable time frame in which to conduct and complete this study. As highlighted already, the management of septic shock has changed in the last few years due to results of randomized controlled trials that demonstrated mortality advantages for treatment interventions. Hence, conducting this study over a longer time frame may have lead to even greater heterogeneous results due to changes in practice.

6.0: CONCLUSION

In this study, I was unable to demonstrate an association between the quantity, type and method of fluid administered over the first six hours of care for patients with severe sepsis. Although, there appeared to be a trend toward a reduction in hospital mortality when fluid was administered in the combination of boluses and infusions versus infusions alone, these results may be considered as hypothesis generating due to the many limitations of this study.

There are biologically plausible and important arguments to support why quantity, type, and method of fluids administered may be important in determining outcome. However, it is unlikely that a prospective randomized controlled trial will be conducted to evaluate the quantity and method of fluid administered questions. It is instilled in critical care physicians to administer resuscitation fluid fast, and in bolus format, to increase oxygen delivery and perfusion to the tissues and findings from the Rivers trial provided indirect support for this form of resuscitation.

Future research related to the type of fluid administered question will be conducted as there appears to be more uncertainty in the critical care community with respect to what type fluid is superior to the other. The severe sepsis subgroup analysis from the SAFE study that suggested a trend toward a reduction in 28-day mortality favoring the albumin colloid group serves to highlight the importance of answering this question. Future fluid resuscitation research as well as the fluid resuscitation research that we are conducting at the Ottawa Hospital will help determine optimal fluid resuscitation practices in this vulnerable patient population.

7.0: FUTURE DIRECTIONS

Over the last three years and with much mentorship from Dr. Paul Hébert and Dr. Dean Fergusson, I have developed a program of research focused in the area of fluid resuscitation for patients with severe sepsis and septic shock. Current studies in this program include: a retrospective severe sepsis fluid resuscitation cohort study that has formed my thesis; a survey of Canadian ICU physicians resuscitation practices in early septic shock; a septic shock fluid resuscitation randomized controlled trial entitled "Fluid Resuscitation in the Early Management of Septic Shock (FINESS)" that is aimed to understand if the type of fluid administered (pentastarch versus normal saline) affects 28-day mortality from early septic shock; and a number of laboratory based studies that are embedded within FINESS and are intended to explain some septic shock pathophysiology.

My thesis has provided me with some essential background information for future grant writing in the area of fluid resuscitation research for patients with severe sepsis and septic shock. For example, I now understand approximate quantities and types of fluid administered in this population. In addition, I now have information as to where these patients are located in the hospital at the identification of severe sepsis which is important when thinking about where to concentrate recruitment efforts for the pilot RCT.

The FINESS pilot study outcomes are mainly feasibility in terms of the ability to determine the acceptability of the fluid algorithms, ability to recruit patients, and the ability to blind the study fluids. At present, I have enrolled 22 patients into FINESS with a goal of 48. If the pilot is feasible, then I will go on to conduct a multi-center, likely multi-national trial that will be powered to evaluate 28-day mortality.

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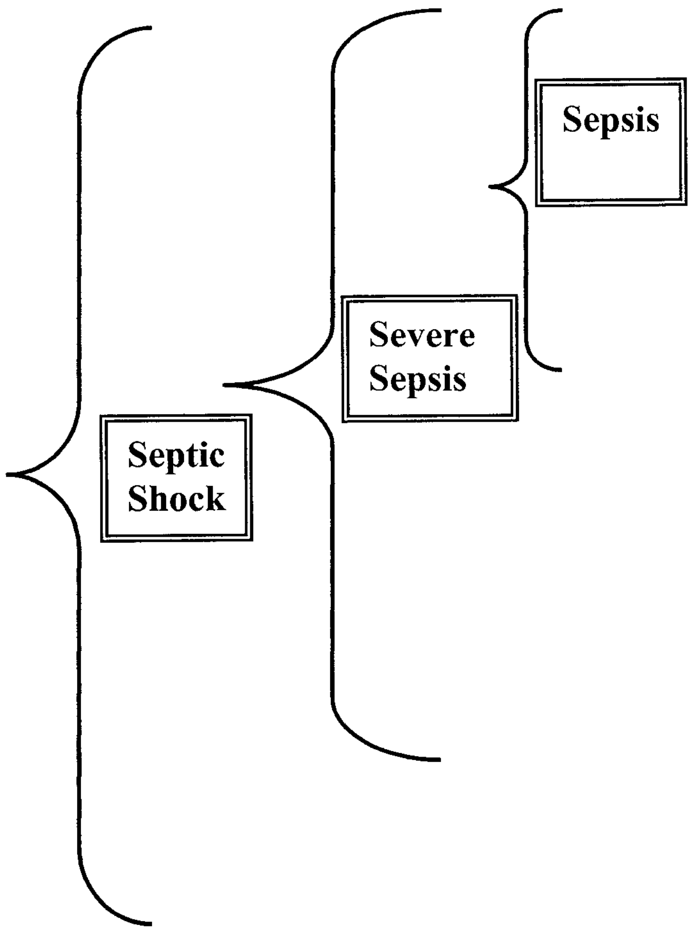
Table 1: Definitions of Sepsis, Severe Sepsis, and Septic Shock *



(A) Infection: a microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms

(B) Systemic Inflammatory Response Syndrome (need at least 2):

1) Temperature: > 38° or < 36° Celsius
2) Tachypnea: respiratory rate > 20 breathes per minute or arterial partial pressure of carbon dioxide <32 mm hg
3) Tachycardia: heart rate > 90 beats per minute
4) White Blood Cell Count: > 12,000 mm^3 or < 4,000 mm^3 or > 10% immature band cells

Severe Sepsis: In addition to (A) and (B), need at least one of:

1) Organ dysfunction**
2) Hypo-perfusion abnormality (lactic acidosis, oliguria, acute alteration in mental status)
3) Sepsis induced hypotension: a systolic blood pressure < 90 mm Hg or > 40 mm Hg decrease from baseline in absence of other causes for hypotension

<u>**Examples of organ dysfunction according to the Sequential Organ Failure Assessment Score:</u>

Central nervous system: Glasgow coma scale score 10 - 12
Hematological: Platelet count < 100 mm^3
Pulmonary: Pulmonary to inspired oxygen concentration ratio < 300 mm hg
Renal: Creatinine 171 – 299 umol/L
Gastrointestinal: Bilirubin 33 - 101 umol/L

Septic Shock:

1) Sepsis induced hypotension that persists despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction

* Definitions from American College of Chest Physicians/Society of Critical Care Medicine consensus conference[22]
** Organ dysfunction definitions according to the Sequential Organ Failure Assessment Score[103]

Table 2: Summary of Systematic Reviews

Author/Year	Inclusion Criteria	Outcomes Assessed	Sub – Groups Examined for Heterogeneity
Alderson 2002[62]	**D:** RCT's **P:** adults, neonates, critically ill – hypovolemia/ burns/ hypoproteinemia **IC:** albumin/PPF **versus** no albumin/PPF **or** crystalloid solution	Mortality end of follow-up	Hypovolemia Burns Hypoalbuminemia Allocation concealment pooled and according to sub-groups
Wilkes 2001[81]	**D:** RCT's **P:** adults, neonates - no restriction on clinical indication for albumin **IC:** albumin **versus** crystalloid	Mortality	Blinding Allocation concealment method Presence of mortality as endpoint Cross over
Roberts 1998[85]	**D:** RCT's and quasi RCT's **P:** adults, neonates, critically ill – hypovolemia from surgery/trauma/burns/hypoalbuminemia **IC:** albumin/plasma protein fraction **versus** nothing **or** crystalloid	Mortality end of follow up	Hypovolemia Burns Hypoalbuminemia Allocation concealment pooled and according to sub-groups
Alderson 2002[84]	**D:** RCT's and quasi RCT's **P:** adults, critically ill requiring volume replacement **IC:** colloids **versus** crystalloid (iso/hypertonic)	Mortality end of follow up	HES Gelatin Dextran HS + Dextran or albumin Vs HS saline or isotonic saline
Choi 1999[82]	**D:** RCT's **P:** adults requiring volume replacement **IC:** Isotonic crystalloid **versus** colloid	Mortality Hospital length of stay Pulmonary edema Physiologic parameters	Trauma versus non-trauma Double blind vs non blind - but no studies to do this analysis Randomization vs pseudorandomization Methodologic score >8 versus < 8
Schierhout 1998[83]	**D:** RCT's or pseudo RCT's **P:** adults, critically ill requiring volume replacement **IC:** colloid **versus** crystalloid	Mortality end of follow up	Trauma Burns Surgery Other (sepsis and vascular leak) Allocation concealment
Wade 1997[80]	**D:** RCT's **P:** adults with traumatic injury and SBP < 100 mm hg requiring volume replacement **IC:** HS +/- Dextran **versus** isotonic crystalloid	Mortality - 30 day or at discharge	For the hypertonic saline analysis: Deletion of studies with - Largest positive changes Larges negative changes Largest # patients

Legend: D=study design; P=study population; IC=intervention and comparison; RCT=randomized controlled trial; PPF=plasma protein fraction; SBP=systolic blood pressure; #=number

Table 3: Search Technique for Systematic Reviews

Author **Year**	Alderson 2002[62]	Wilkes 2001[81]	Roberts 1998[85]	Alderson 2002[84]	Choi 1999[82]	Schierhout 1998[83]	Wade 1997[80]
Bibliographic search:							
MEDLINE	✓	✓	✓	✓	✓	✓	x
Pubmed	✓	x	x	✓	x	x	x
BIDS	x	x	✓	x	x	✓	x
Science Citation Index	✓	x	x	✓	x	x	x
EMBASE	x	✓	✓	✓	x	✓	x
Cochrane	✓	✓	✓	✓	x	✓	x
Amnesty	✓	✓	✓	x	✓	x	x
CINAHL	x	x	x	x	x	x	x
Handsearch:							x
References of primary articles	✓	✓	✓	✓	✓	✓	x
Review articles	✓	✓	✓	✓	✓	✓	x
Top journals	✓	✓	✓	x	x	✓	x
Meetings/proceedings	✓	✓	✓	x	x	✓	✓
Contact authors/experts In field	✓	x	✓	✓	x	✓	✓
No language restriction	✓	✓	✓	x	x	✓	x

Legend: BIDS=Bath Information and Data Services; EMBASE=European Medline; CINAHL=Cumulative Index to Nursing and Allied Health Literature; x=no; √=yes

Table 4: Data Abstraction, Quality Assessment, and Analytic Method Used for Systematic Reviews

Author Year	# Reviewers who Screened Citations	# Reviewers who Assessed Studies for Inclusion	Flow Chart Inclusions/ Exclusions	# Reviewers for Data Extraction/ Quality Assessment	Quality Assessment Tool	Analysis Conducted
Alderson 2002[62]	1	2	No	2/ 2	Allocation concealment	RR and 95% CI (ITT) Heterogeneity – Chi squared test If no significant heterogeneity – fixed effects model
Wilkes 2001[81]	Not clear	Not clear	Yes	Not clear	Allocation concealment	RR and 95% CI - Mantel Haenszel Heterogeneity - DerSiminian and Laird If no significant heterogeneity – fixed effects model
Roberts 1998[85]	Not clear	Not clear	No	2/Not clear	Allocation concealment	RR and 95% CI - Mantel Haenszel (ITT) Heterogeneity – Chi squared tests If no significant heterogeneity – fixed effects model Publication bias – funnel plot asymmetry by Egger
Alderson 2002[84]	Not clear	2	No	2/Not clear	Allocation concealment	RR and 95% CI Heterogeneity – Chi squared test and visual inspection If no significant heterogeneity – fixed effects model
Choi 1999[82]	2	2	Yes	2/2	Similar to Detzky score	Agreement - Kappa Random effects model Breslow Day for difference in summary odds ratios between sub-groups
Schierhout 1998[83]	Not clear	Not clear	Yes	2/ Not clear	Allocation concealment	RR and 95% CI - Mantel Haenszel (ITT) Heterogeneity – Chi squared test If no significant heterogeneity – fixed effects model Publication bias – funnel plot asymmetry by Egger
Wade 1997[80]	Not clear	Not clear	No	Not clear	Not stated	Summary estimated odds ratio Fixed effects model Cochrane Mantel Haenszel to test for statistical significance Mean differences weighted by inverse of variance

Legend: RR=relative risk; 95% CI=95% confidence intervals; ITT=intention to treat

Table 5: Methodological Quality Assessment of Systematic Reviews

Author Year	Method of Quality Assessment	
Alderson 2002[62]	**Allocation Concealment:**	
	Adequate	13/25 (52%)
	Unclear	8/25 (32%)
	Inadequate	4/25 (16%)
Wilkes 2001[81]	**Allocation Concealment:**	
	Adequate	21/55 (38%)
	Inadequate	4/55 (7%)
	Unclear	30/55 (55%)
	Blinding:	7/55 (13%)
Roberts 1998[85]	**Allocation Concealment:**	
	Adequate	13/24 (54%)
	Unclear	7/24 (29%)
	Inadequate	4/24 (17%)
Alderson 2002[84]	**Allocation Concealment:**	
	Adequate	4/38 (11%)
	Unclear	N/R
	Inadequate	N/R
Choi 1999[82]	**Blinding:**	3/17 (18%)
	Randomization:	9/17 (53%)
Schierhout 1998[83]	**Allocation Concealment:**	
	Adequate	4/19(21%)
	Unclear	N/R
	Inadequate	N/R
Wade 1997[80]	**Blinding:**	8/8 (100%)

Legend: N/R=Not Reported

Table 6: Outcome Assessments of Systematic Reviews

Author Year	Pooled Mortality Outcome RR (95% CI's) RR < 1 Favours Crystalloids	Mortality Outcome – Clinical Subgroups RR (95% CI's) RR < 1 Favours Crystalloids		Sensitivity Analyses RR (95% CI's) RR < 1 Favours Crystalloids	
Alderson 2002[62]	0.66 (0.50 – 0.85)	Hypovolemia	0.68 (0.90 – 1.03)	Adequate AC pooled:	0.62 (0.42 – 0.92)
		Burns	0.42 (0.19 – 0.90)		
		Hypoalbuminemia	0.73 (0.49 – 1.06)	Hypovolemia	0.72 (0.42 – 1.25)
				Burns	0.41 (0.11 – 1.45)
				Hypoalbuminemia	0.59 (0.31 – 1.09)
Wilkes 2001[81]	0.90 (0.78 – 1.05)	Surgery or trauma	0.89 (0.69 – 1.18)	Adequate AC	0.89 (0.71 – 1.12)
		Burns	0.89 (0.32 – 1.18)	Inad/unclear AC	0.91 (0.75 – 1.11)
		Hypoalbuminemia	0.63 (0.36 – 1.10)		
		High risk neonates	0.84 (0.55 – 1.28)	Mort. end point	1.00 (0.85 – 1.19)
		Ascites	1.08 (0.78 – 1.49)	No mort. end point	0.67 (0.50 – 0.91)
		Other	1.10 (0.82 – 1.49)		
				No x-over	0.96 (0.82 – 1.12)
				X-over	0.70 (0.49 – 1.0)
				Blind + mort. end point	1.7 (1.0 – 2.90)
				Blind + mort. no end point	0.95 (0.45 – 2.0)
				Blind and no x-over	1.56 (0.96 – 2.5)
				Mort. end point+ no x-over	1.11 (0.92 – 1.35)
				Mort. end point + x-over	0.68 (0.46 – 0.99)
Roberts 1998[85]	0.60 (0.45 – 0.79)	Hypovolemia	0.69 (0.45 – 1.03)	AC adequate pooled:	0.62 (0.42 – 0.92)
		Burns	0.42 (0.19 – 0.90)		
		Hypoalbuminemia	0.59 (0.37 – 0.93)	AC adequate:	
				Hypovolemia	0.72 (0.42 – 1.25)
				Burns	0.41 (0.11 – 1.45)
				Hypoalbuminemia	0.59 (0.31 – 1.09)
Alderson 2002[84]	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)		
		Alb+ HS vs saline	2.00 (0.23 – 16.67)		
		D + HS vs saline	1.14 (0.95 – 1.35)		
		Colloid vs HS	0.14 (0.01 – 2.56)		

Table 6: Outcome Assessments of Systematic Reviews

Author Year	Pooled Mortality Outcome RR (95% CI's) RR < 1 Favours Crystalloids	Mortality Outcome – Clinical Subgroups RR (95% CI's) RR < 1 Favours Crystalloids		Sensitivity Analyses	
Choi 1999[82]	0.86 (0.63 – 1.17)	Trauma	0.39 (0.17 – 0.89)	For Pulmonary edema outcome:	
		Non-trauma	2.12 (0.84 – 5.34)	Randomized	0.64 (0.17 – 2.42)
		Pulmonary edema	1.2 (0.41 – 3.51)	Pseudo Randomized	3.66 (1.52 – 8.82)
				Method Score >8	0.82 (0.30 – 2.27)
				Method Score < 8	3.94 (1.60 – 9.71)
Schierhout 1998[83]	0.84 (0.69 – 1.02)	Trauma	0.77 (0.57 – 1.05)	Adequate AC	0.78 (0.57 – 1.06)
		Surgery	1.82 (0.61 – 5.56)		
		Burns	0.83 (0.60 – 1.14)		
		Other	0.93 (0.69 – 1.02)		
Wade 1997[80]	1.2 (0.94 – 1.57)			Deletion of studies with:	
				Largest positive changes:	1.15 (0.86 – 1.53)
				Larges negative changes:	1.31 (0.99 – 1.73)
				Largest # patients:	1.20 (0.89 – 1.63)

Legend : RR-relative risk; AC-allocation concealment; ARDS-acute respiratory distress syndrome; HS-hypertonic saline; CVA-cerebrovascular accident; D-dextran; mort.-mortality; x-over-cross over

Table 7: Baseline Characteristics for Entire Cohort

Baseline Characteristics	Overall (n=282)	Missing Data
Age Mean (sd)	63 (14)	0
APACHE II Score Mean (sd)	28 (8)	53
Sex (Females) No. (%)	136 (48)	0
Type of Admission No. (%)		
Medical (n=213)	213 (76)	0
Emergency Post-operative (n=49)	49 (17)	0
Elective Post-operative (n=20)	20 (7)	0
Co-Morbid Diseases No.(%)		
Diabetes (n=73)	73 (26)	0
Chronic renal failure (n=35)	35 (13)	1
Coronary Artery disease (n=59)	59 (21)	0
Congestive heart failure (n=45)	45 (16)	0
Peripheral vascular disease (n=30)	30 (11)	3
Chronic pulmonary disease (n=60)	60 (21)	0
Liver disease (n=25)	25 (9)	0
Cancer (n=102)	102 (36)	0
Immune suppression (n=65)	65 (23)	0
Number with Co-Morbid Diseases No. (%)		
0 (n=54)	54 (19)	
1-2 (n=157)	157 (56)	
3-4 (n=61)	61 (22)	
> 4 (n=10)	10 (3)	

Table 7: Baseline Characteristics for Entire Cohort

Baseline Characteristics	Overall (n=282)	Missing Data
Infectious Source No. (%)		
Pulmonary (n=109)	109 (39)	0
Intra-abdominal (n=91)	92 (33)	0
Urinary tract (n=29)	29 (10)	0
Soft tissue infection (n=16)	16 (6)	0
Vascular device (n=9)	9 (3)	0
Other (n=26)	27 (9)	0
Place in Hospital No. (%)		
Intensive Care Unit (n=94)	94 (33)	
Emergency Room (n=95)	95 (34)	
Hospital Ward (n=42)	42 (15)	
OR/PACU (n=23)	23 (8)	
Peripheral Hospital (n=28)	28 (10)	

Legend: APACHE II = Acute Physiology and Chronic Health Evaluation score; sd = standard deviation; No. (%) = number, percent

Table 8: Apache II variables – Summary Statistics for Individual Variables and Quantification of Missing APACHE II Data

APACHE II Physiology Variables	Mean (sd) High	Missing Data High	Mean (sd) Low	Missing Data Low	Missing Data (high or low)
Temperature (° Celsius)	38.17 (1.08)	4	36.27(1.65)	4	**2**
Mean Arterial Pressure (mm Hg)	n/a	n/a	51.48 (9.93)	n/a	**3** DBP's missing
Heart Rate (bpm)	121.07 (21.69)	2	78.79 (17.59)	1	**1**
Respiratory rate (bpm)	29.39 (23.14)	3	14.00 (5.0)	2	**2**
Oxygenation*					
Pa02 if Fi02<50%		n/a	90.59 (62.48)	86	86
A –a gradient		n/a	423.91 (154.07)	176	176
Serum C02		n/a	19.22 (6.88)	264	264
All 3 not present		n/a		9	**9**
Sodium	138.53 (6.12)	8	135.28 (5.71)	9	0
PH	7.37 (0.45)	30	7.26 (0.37)	35	0
Potassium	4.56 (0.77)	11	3.72 (0.65)	9	0
Hematocrit	0.32 (0.07)	9	0.26 (0.64)	9	**4**
White Blood Cell Count	17.93 (20.58)	8	11.88 (15.01)	2	0
Creatinine	216.59 (205.31)	0	167.96 (15.866)	16	0
Acute renal failure** No (%)	168 (57)				0
GCS		n/a	12.26 (3.20)	2	**2**
Age	62.44 (15.94)	n/a	n/a	n/a	0
APACHE II Co-morbidities	**No (%)**				
Respiratory	8 (3)				7
Cardiovascular	5 (2)				7
Gastrointestinal	11 (5)				56
Renal	24 (9)				6
Immunocompromised	65 (23)				0

Table 8: Apache II variables – Summary Statistics for Individual Variables and Quantification of Missing APACHE II Data

APACHE II Physiology Variables	Mean (sd) High	Missing Data High	Mean (sd) Low	Missing Data Low	Missing Data (high or low)
Chronic Health Score	**No (%)**				35
5 points	102 (41.30)				
2 points	1 (0.40)				
0 points	144 (58.30)				
Admission type	**No (%)**	**# with ≥ 1 missing APACHE II Co-morbidity**	**No (%) with Chronic Health Score *** **		
Medical	213 (75.53)	21	**Score = 5:** 90/192 (47%)	21 x 0.47 = 10	
Emergent Post - Operative	49 (17.38)	10	**Score = 5:** 12/39 (31%)	10 x 0.3 = 3	
Elective Post - Operative	20 (7.09)	4	**Score = 2:** 1/16 (6%)	4 x 0.06 = 0	
					Total Missing Data: 58

Legend: All APACHE II physiology variables (except mean arterial blood pressure, oxygenation, GCS, and age) can be abnormal in the high and low range. The high and low mean values and standard deviations are summarized for the continuous variables. For continuous variables that have a high and low component, the amount of missing data is described for each. The far right column describes the amount of missing data when both the high and low values are missing. Categorical variables are summarized with numbers and percents (acute renal failure, APACHE II co-morbidities, chronic health score, admission type).
sd=standard deviation; IQR = 25^{th} – 75^{th} percentile range; Pa02 = partial pressure of oxygen; A-a gradient = alveolar – arterial oxygen gradient; Serum C02 = serum bicarbonate;
*For calculation of oxygenation, one of three variables could have been used.
** Definition for Acute Renal Failure = a creatinine greater than 133 mmol/L and no history of know chronic renal insufficiency
*** To receive 5 chronic health points, a patient needed to have at least one co-morbidity in addition to having a non-operative or emergency post-operative admission. To receive 2 chronic health points, a patient needed to have at least one co-morbidity in addition to having an elective post-operative admission.

APACHE II Summary Score:

APACHE II Score	Mean (sd)
Missing Values Deleted (n= 229)	26.68 (8.03)
Imputation with Missing Values:	
Missing Values Normal (APACHE II score = 0)	26.00 (7.85)
Missing Values Extreme (APACHE II score = 4) (N=282)	29.72 (8.15)
Missing Values using group mean and group proportions for missing continuous and categorical data respectively (worst mean) (n=282)	27.87 (7.65)

Table 9: Baseline Characteristics by Fluid Administered

	Quantity Fluid Administered (n=282)			*Type Fluid Administered (n=280)		*Method Fluid Administered (n=280)	
Baseline Characteristics	**0 – 2 L (n=132)**	**2 – 4 L (n=105)**	**> 4 L (n=45)**	**Crystalloid (n=102)**	**Colloid + Crystalloid (n=178)**	**Infusions (n=26)**	**Infusion+Bolus (n=254)**
Age Mean (sd)	64 (15)	61 (16)	62 (18)	61 (17)	63 (15)	65 (14)	62 (16)
Apache II Score Mean (sd)	26 (7.)	29 (8)	30 (8)	27 (8)	28 (7)	25 (9)	28 (7)
Sex (Females) No (%)	63 (48)	52 (50)	21 (47)	47 (46)	87 (49)	11(42)	123 (48)
Type of Admission No (%)							
Medical (n=213)	112 (85)	77 (73)	24 (53)	86 (84)	125 (70)	21 (81)	190(75)
Emergency post – operative (n=49)	9 (7)	20 (19)	20 (45)	10 (10)	39 (22)	2 (8)	47 (18)
Elective post – operative (n=20)	11 (8)	8 (8)	1 (2)	6 (6)	14 (8)	3 (11)	17 (7)
Co-Morbid Diseases No (%)							
Diabetes (n=73)	35 (27)	26 (25)	12 (27)	28 (28)	45 (26)	7(27)	66 (26)
Chronic renal failure (n=35)	26 (20)	6 (6)	3 (7)	12 (12)	21 (12)	4 (15)	29 (12)
Coronary Artery disease (n=59)	30 (23)	23 (22)	6 (13)	20 (20)	39 (22)	6 (23)	53 (21)
Congestive heart failure (n=45)	32 (24)	10 (10)	3 (7)	19 (19)	26 (15)	3 (12)	42 (17)
Peripheral vascular disease (n=30)	19 (15)	10 (10)	1 (3)	11 (11)	19 (11)	5 (19)	25 (10)
Chronic pulmonary disease (n=60)	32 (24)	24 (23)	4 (9)	24 (24)	35 (20)	10 (39)	49 (19)
Liver disease (n=25)	14 (11)	9 (9)	2 (4)	10 (10)	14 (8)	4 (15)	20 (8)
Cancer (n=102)	49 (37)	42 (40)	11 (24)	31 (30)	71 (40)	10 (39)	92 (36)
Immune suppression (n=65)	24 (18)	34 (32)	7 (16)	19 (19)	46 (26)	2 (8)	63 (25)

Table 9: Baseline Characteristics by Fluid Administered

	Quantity Fluid Administered (n=282)			*Type Fluid Administered (n=280)		*Method Fluid Administered (n=280)	
Baseline Characteristics	**0 – 2 L (N=132)**	**2 – 4 L (N=105)**	**> 4 L (N=45)**	**Crystalloid (n=102)**	**Colloid + Crystalloid (n=178)**	**Infusions (n=26)**	**Infusion+Bolus (n=254)**
Number of Co-Morbid Diseases No (%)							
0 (n=54)	16 (12)	22 (21)	16 (35)	22 (21)	32 (18)	2 (8)	52 (20)
1 -2 (n=157)	76 (58)	56 (53)	25 (56)	57 (56)	99 (56)	17 (65)	139 (55)
3 – 4 (n=61)	35 (26)	22 (21)	4 (9)	19 (19)	41 (23)	6 (23)	54 (21)
> 4 (n=10)	5 (4)	5 (5)	0 (0)	4 (4)	6 (3)	1 (4)	9 (4)
Infectious source: No (%)							
Pulmonary (n=109)	66 (50)	36 (34)	7 (16)	46 (45)	63 (35)	14 (54)	95 (37)
Intra-abdominal (n=91)	29 (22)	39 (37)	24 (53)	22 (21)	69 (39)	4 (15)	87 (34)
Urinary Tract (n=29)	11 (8)	13 (12)	5 (11)	12 (12)	17 (10)	1 (4)	28 (11)
Soft tissue infection (n=16)	8 (6)	5 (5)	3 (7)	9 (9)	7 (4)	1 (4)	15 (6)
Vascular device (n=9)	5 (4)	3 (3)	1 (2)	3 (3)	6 (3)	0 (0)	9 (4)
Other (n=26)	13 (10)	9 (9)	5 (11)	10 (10)	16 (9)	6 (23)	20 (8)
Place in Hospital: No (%)							
Intensive Care Unit (n=94)	62 (47)	29 (28)	3 (6)	26 (26)	68 (38)	14 (54)	80 (31)
Emergency room (n=95)	38 (29)	36 (34)	21 (47)	37 (36)	58 (32)	4 (15)	91 (36)
Hospital ward (n=42)	20 (15)	18 (17)	4 (9)	17 (17)	23 (13)	5 (19)	35 (14)
OR/PACU (n=23)	2 (1)	9 (9)	12 (27)	4 (4)	19 (11)	0 (0)	23 (9)
Peripheral Hospital (n=28)	10 (8)	13 (12)	5 (11)	18 (18)	10 (6)	3 (12)	25 (10)

Legend: APACHE II = Acute Physiology and Chronic Health Evaluation score; sd = standard deviation; No (%) = number, percent
*Two patients received no fluid in the first 6 hours of care

Table 10: Fluid Administered First Six Hours after Identification of Severe Sepsis

	Mean (sd)
***Total Fluid Administered (Liters)**	2.71 (2.09)
Proportion of Total Fluid Administered	**No (%)**
0.00 – 2.00 Liters	132 (47)
2.01 – 4.00 Liters	105 (37)
> 4.01 Liters	45 (16)
Proportion Colloid and Crystalloid Administration	**No (%)**
Crystalloid only	102 (36)
**Colloid only	0 (0)
Crystalloid and Colloid	178 (63)
No fluid	2 (1)
Proportion Infusions vs Infusions and Boluses Fluid	**No (%)**
Fluid Infusions only	26 (9)
Fluid boluses and Fluid Infusions	254 (90)
No fluid	2 (1)

Legend: sd=standard deviation;
*Total fluid administered includes crystalloid fluids (normal saline, ringers lactate, ½ normal saline, D5W ½ normal saline, 2/3 and 1/3, 5% and 10% dextrose), colloid fluids (albumin 5% and 25%, pentastarch)
** Colloid = pentastarch as no patients received albumin in the first six hours of care

Table 11: Outcomes for Entire Cohort and by Fluids Administered

	Entire Cohort (n = 282)	Quantity of Fluid Administered (n = 282)			**Type of Fluid Administered (n = 280)		**Method of Fluid Administered (n = 280)	
		0 – 2 L (n=132)	2 – 4 L (n=105)	> 4 L (n = 45)	Crystalloid (n = 102)	Colloid and Crystalloid (n = 178)	Infusion (n = 26)	Bolus and Infusion (n = 254)
Primary Outcome								
Hospital Mortality No (%)	126 (45)	59 (45)	46 (44)	21 (47)	41 (40)	84 (47)	14 (54)	111 (44)
Secondary Outcomes								
ICU Mortality No (%)	86 (33)	35 (29)	31 (31)	20 (44)	22 (25)	63 (36)	7 (28)	78 (33)
ICU LOS Median (IQR)	6 (2-13)	6 (2-13)	6 (3-12)	6 (2-13)	6 (2-12)	7 (3-13)	10 (5-24)	6 (3-13)
Hospital LOS Median (IQR)	15 (7-29)	15 (9-30)	14 (5 – 26)	14 (6-30)	14 (7-29)	16 (7-29)	19 (3-52)	14 (7-75)
Vasopressors No (%)	109 (39)	34 (26)	48 (46)	27 (60)	38 (37)	71 (40)	6 (23)	103 (41)
Mechanical Ventilation No (%)	198 (70)	91 (69)	73 (70)	34 (76)	62 (61)	136 (76)	21 (81)	177 (70)

* Two patients received no fluid for first 6 hours of care

Table 12: Fluid Administered and Hospital Mortality: Univariate Analyses

	Crude Odds Ratios and 95% Confidence Intervals Hospital Mortality (n=282)
Quantity Fluid Administered	
0 – 2 L **	--
2 – 4 L	0.97 (0.58 – 1.62)
> 4 L	1.08 (0.55 – 2.14)
Type Fluid Administered	
Crystalloid **	--
Colloid and Crystalloid	1.33 (0.81 – 2.18)
Method Fluid Administered	
Infusions **	--
Infusions and boluses	0.67 (0.29 – 1.50)

Legend: ** indicates reference group

Table 13: Quantity of Fluid and Hospital Mortality: Multivariable Analyses

	Hospital Mortality	
	Adjusted Odds Ratio	95% CI's
Quantity Fluid Administered		
0 – 2 Liters *	--	--
2 – 4 Liters	0.99	0.51-1.94
> 4 Liters	1.02	0.39-2.57
Covariates to Adjust for Quantity of Fluid		
Age**	1.43	1.17-1.76
Sex (male)	0.67	0.38 – 1.18
APACHE II Score**	3.11	2.02-4.79
Type of Admission		
Medical**	--	--
Emergency post – operative	1.17	0.42 – 3.24
Elective post – operative	0.36	0.10 – 1.33
Number of Co-morbid Diseases		
0 **	--	--
1 -2	1.71	0.64 – 4.55
3 – 4	2.05	0.76 – 5.57
> 4	3.06	0.74 – 12.61
Infectious source		
Pulmonary **	--	--
Intra-abdominal	0.64	0.29-1.42
Urinary Tract	0.50	0.18-1.42
Soft tissue infection	0.96	0.27-3.43
Other	0.59	0.23-1.48
Place In Hospital at severe sepsis time 0		
Intensive Care Unit**	--	--
Emergency Room	0.67	0.32 – 1.38
Hospital Ward	0.65	0.26 – 1.64
OR/PACU	1.06	0.28 – 4.05
Peripheral Hospital	0.11	0.03 – 0.38

Legend:* indicates reference group; ** Odds ratio expressed in terms of increases in age and APACHE II scores by 10

Table 14: Type of Fluid and Hospital Mortality: Multivariable Analysis

	Hospital Mortality	
	Adjusted Odds Ratio	95% CI's
Type of Fluid Administered*		
Crystalloid**	--	--
Colloid and Crystalloid	1.02	0.55-1.89
Covariates to Adjust for Type of Fluid		
Age***	1.44	1.17-1.77
Sex (male)	0.66	0.37-1.15
APACHE II Score***	3.17	2.07-4.85
Type of Admission		
Medical ***	--	--
Emergency post – operative	1.27	0.46-3.49
Elective post – operative	0.36	0.10-1.36
Number of Co-morbid Diseases		
0 ***	--	--
1 -2	1.68	0.63-4.48
3 – 4	2.07	0.77-5.56
> 4	3.13	0.77-12.79
Infectious source		
Pulmonary ***	--	--
Intra-abdominal	0.59	0.27-1.32
Urinary Tract	0.51	0.18-1.44
Soft tissue infection	0.62	0.27-3.52
Other	0.98	0.24-1.57
Place In Hospital at Severe Sepsis Time 0:		
Intensive Care Unit ***	--	--
Emergency Room	0.67	0.33-1.37
Hospital Ward	0.59	0.23-1.50
OR/PACU	1.04	0.28-3.90
Peripheral Hospital	0.11	0.03-0.39

Legend: *2 patients did not receive any fluid in the first 6 hours of care, hence there are 280 observations in this set
** indicates reference group
*** odds ratio for age and APACHE II score expressed in terms increases by 10

Table 15: Method of Fluid and Hospital Mortality: Multivariable Analysis

	Hospital Mortality	
	Adjusted Odds Ratio	95% CI's
Method of Fluid Administered*		
Infusions **	--	--
Infusions and Boluses of fluid	0.42	0.15-1.15
Covariates to Adjust for Method of Fluid		
Age***	1.42	1.15 – 1.74
Sex (male)	0.67	0.38-1.19
APACHE II Score***	3.38	2.19-5.22
Type of Admission		
Medical ***	--	--
Emergency post – operative	1.29	0.47-3.57
Elective post – operative	0.36	0.10-1.36
Number of Co-morbid Diseases		
0 ***	--	--
1 -2	1.62	0.61-4.31
3 – 4	2.11	0.79-5.67
> 4	2.93	0.72-11.97
Infectious source		
Pulmonary ***	--	--
Intra-abdominal	0.63	0.28-1.40
Urinary Tract	0.56	0.20-1.59
Soft tissue infection	0.97	0.27-3.52
Other	0.59	0.23-1.49
Place In Hospital at Severe Sepsis Time 0		
Intensive Care Unit ***	--	--
Emergency Room	0.71	0.35-1.45
Hospital Ward	0.59	0.23-1.50
OR/PACU	1.14	0.30-4.31
Peripheral Hospital	0.11	0.03-0.38

Legend: *2 patients did not receive any fluid in the first 6 hours of care, hence there are 280 observations in this set
** indicates reference group
*** odds ratio for age and APACHE II score expressed in terms increases by 10

Table 16: Fluid Administered and Secondary Outcomes: Univariate Analyses

	Crude Odds Ratios and 95% Confidence Intervals				
Quantity Fluid Administered	**ICU Mortality** (n=265)	**Mechanical Ventilation** (n=282)	**Vasoactive Agent Support** (n=282)	****Length of Stay in Hospital** (n=282)	****Length of Stay in ICU** (n=265)
0 – 2 L *	--	--	--	--	--
2 – 4 L	1.12 (0.63 – 2.00)	1.03 (0.59-1.79)	2.43 (1.40 – 4.20)	1.02 (0.64 – 1.62)	0.95 (0.61 – 1.49)
> 4 L	1.97 (0.97 – 3.99)	1.39 (0.64-3.02)	4.32 (2.12 – 8.12)	0.25 (0.88 – 1.77)	1.22 (0.88 – 1.68)
Type Fluid Administered					
Crystalloid **	--	--	--	--	--
Colloid and Crystalloid	1.73 (0.98 – 3.06)	2.10 (1.23-3.54)	1.12 (0.68 – 1.85)	1.09 (0.78 – 1.50)	1.08 (0.79 – 1.47)
Method Fluid Administered					
Infusions **	--	--	--	--	--
Infusions and boluses	1.25 (0.50 – 3.13)	0.55 (0.20-1.51)	2.27 (0.88 – 5.86)	0.45 (0.24 – 0.84)	0.60 (0.36 – 1.00)

Legend: ICU = intensive care unit; * indicates reference group; ** Length of stay in ICU and Hospital analyses conducted with cox - proportional hazards model (estimates are expressed as hazard ratios and 95% confidence intervals.

Table 17: Fluid Administered and Secondary Outcomes: Multivariable Analyses

	Adjusted Odds Ratios and 95% Confidence Intervals				
Quantity Fluid Administered	**ICU Mortality** (n=265)	**Mechanical Ventilation** (n=282)	**Vasoactive Agent Support** (n=282)	***Length of Stay in Hospital** (n=282)	***Length of Stay in ICU** (n=265)
0 – 2 L **	--	--	--	--	--
2 – 4 L	0.97 (0.46-2.03)	1.22 (0.56-2.63)	1.96 (1.02 – 3.78)	1.17 (0.77 – 1.79)	1.14 (0.77 – 1.69)
> 4 L	1.61 (0.59 – 4.41)	2.17 (0.73-6.47)	4.16 (1.63 – 10.65)	0.93 (0.53 – 1.62)	0.88 (0.50 – 1.54)
Type Fluid Administered					
Crystalloid **	--	--	--	--	--
Colloid and Crystalloid	1.46 (0.71-2.94)	2.23 (1.10-4.53)	1.48 (0.79 – 2.75)	1.01 (0.70 – 1.45)	1.07 (0.75 – 1.52)
Method Fluid Administered					
Infusions **	--	--	--	--	--
Infusions and boluses	0.90 (0.28 – 2.85)	0.41 (0.10-1.73)	2.04 (0.63 – 6.56)	0.40 (0.20 – 0.78)	0.59 (0.33 – 1.05)

Legend: ICU = intensive care unit; * Cox proportional hazards model used for length of stay analyses – estimates expressed as hazard ratios and 95% confidence intervals
** indicates reference group

Table 18: Fluid Administered and Hospital Mortality: Multivariable Sensitivity Analyses

Baseline Characteristics	Odds Ratios and 95% CI Quantity of Fluid*		Odds Ratios and 95% CI Type of Fluid**	Odds Ratios and 95% CI Method of Fluid***
	2 – 4 Liters	> 4 Liters		
Entire Group (n = 282)				
Crude Odds Ratios	0.97 (0.58 – 1.62)	1.08 (0.55 – 2.14)	1.33 (0.81 – 2.14)	0.67 (0.29 – 1.50)
Adjusted Odds Ratios	0.99 (0.51 – 1.94)	1.02 (0.39 – 2.57)	1.02 (0.55 – 1.89)	0.42 (0.15 – 1.15)
Age (n=282)				
Removed from adjusted model	0.84 (0.44 1.56)	0.87 (0.35 – 2.15)	0.97 (0.53 – 1.78)	0.36 (0.13 – 0.96)
APACHE II Score (n=282)				
Removed from adjusted model	1.46 (0.79 – 2.68)	1.79 (0.76 – 4.22)	1.22 (0.69 – 2.14)	0.67 (0.26 – 1.70)
Peripheral Hospital (n=28)				
Removed from adjusted model	0.99 (0.50 – 1.97)	1.10 (0.42 – 2.91)	1.10 (0.58 – 2.10)	0.42 (0.14 – 1.26)
Secular Trends - APC				
July 01/00 – Mar. 31/01 (N = 93)	1.20 (0.22 – 6.66)	1.16 (0.17 – 7.93)	0.52 (0.15 – 1.89)	0.27 (0.37 – 2.01)
Apr. 01/01 – Present (N = 189)	0.92 (0.40 – 2.14)	0.85 (0.25 – 2.90)	0.98 (0.44 – 2.15)	0.40 (0.11 – 1.42)
Secular Trends - Rivers				
July 01/00 – Nov. 30/01 (N = 194)	1.25 (0.55 – 2.87)	1.14 (0.39 – 3.33)	1.11 (0.51 – 2.38)	0.23 (0.06 – 0.91)
Dec. 01/01 – Present (N = 88)	#	#	#	#

Legend: *0 – 2 liter = reference group; **Crystalloid only = reference group; ***Infusions alone = reference group; # unable to conduct multivariable analysis due to quasi-separation

Figure 1: Population Adjusted Incidence of Sepsis from 1979 – 2000[2]

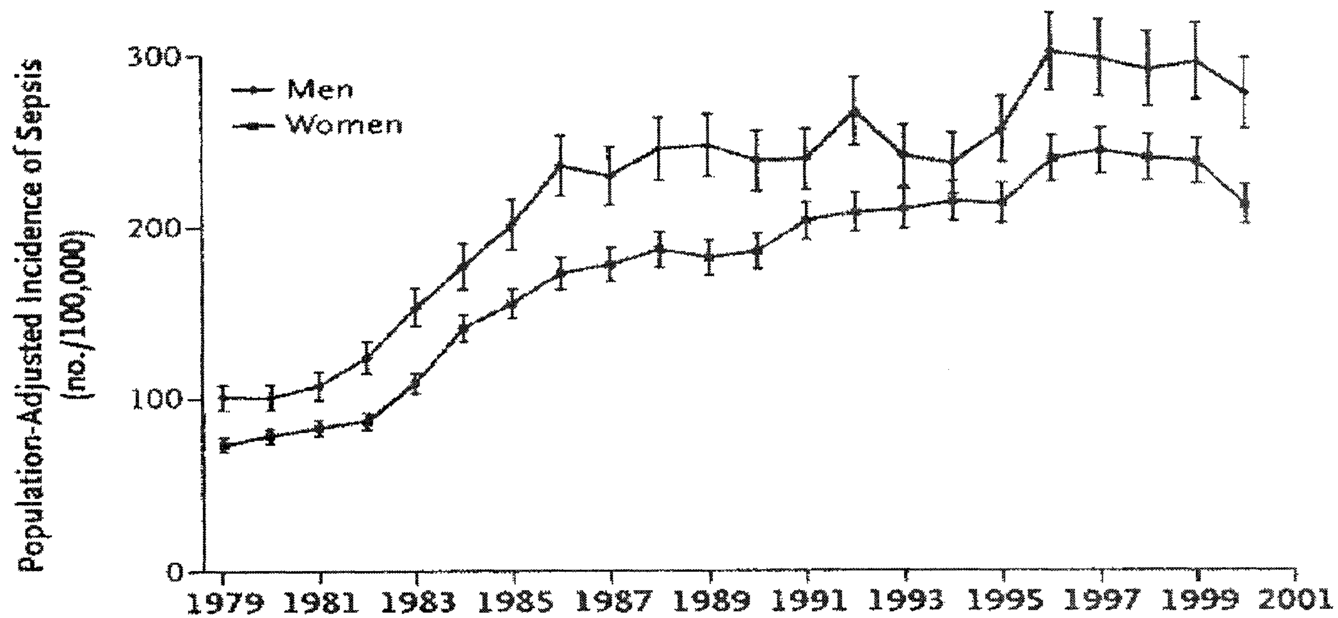
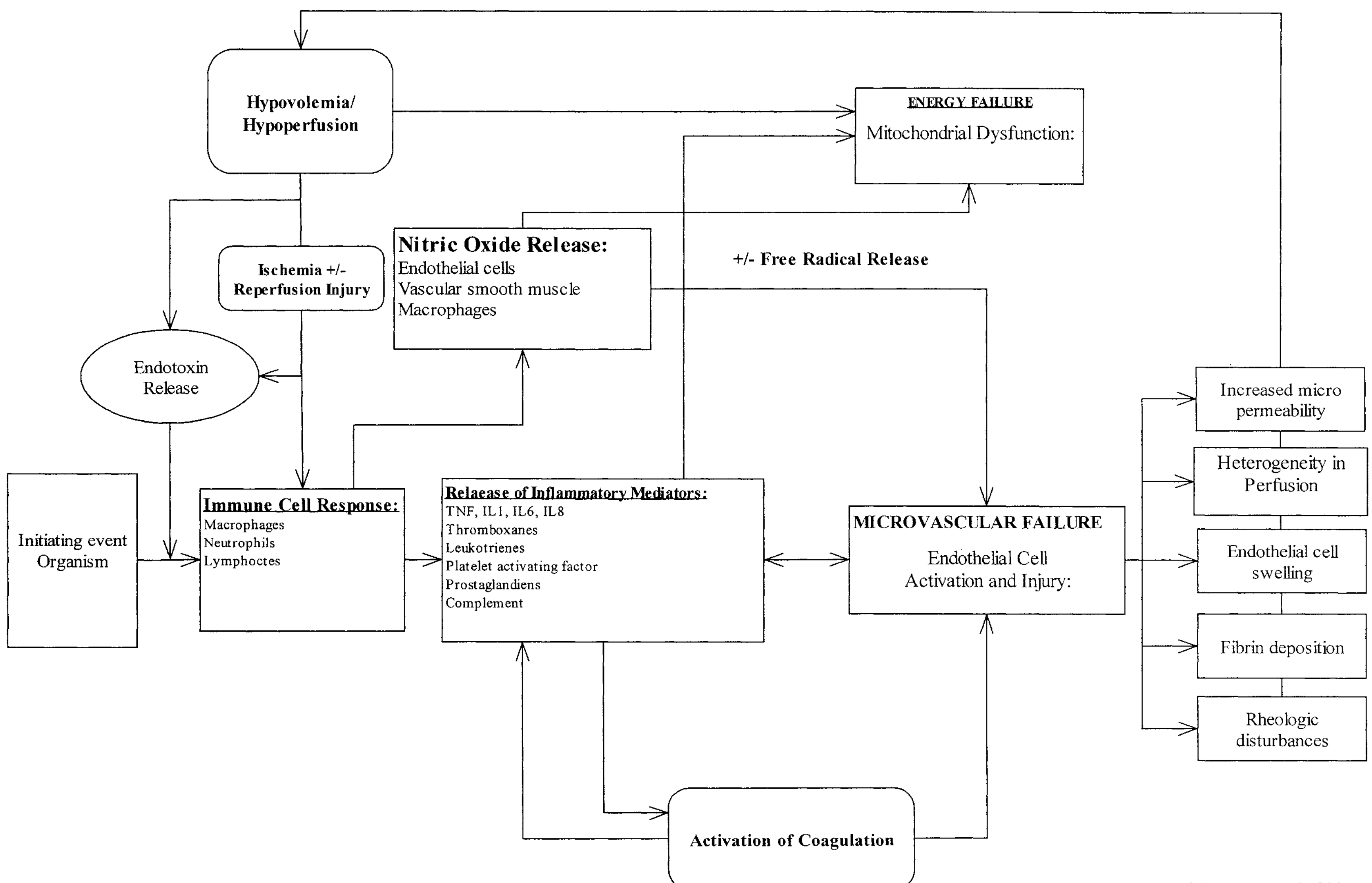


Figure 1. **Population-Adjusted Incidence of Sepsis, According to Sex, 1979–2000.** Points represent the annual incidence rate, and I bars the standard error.

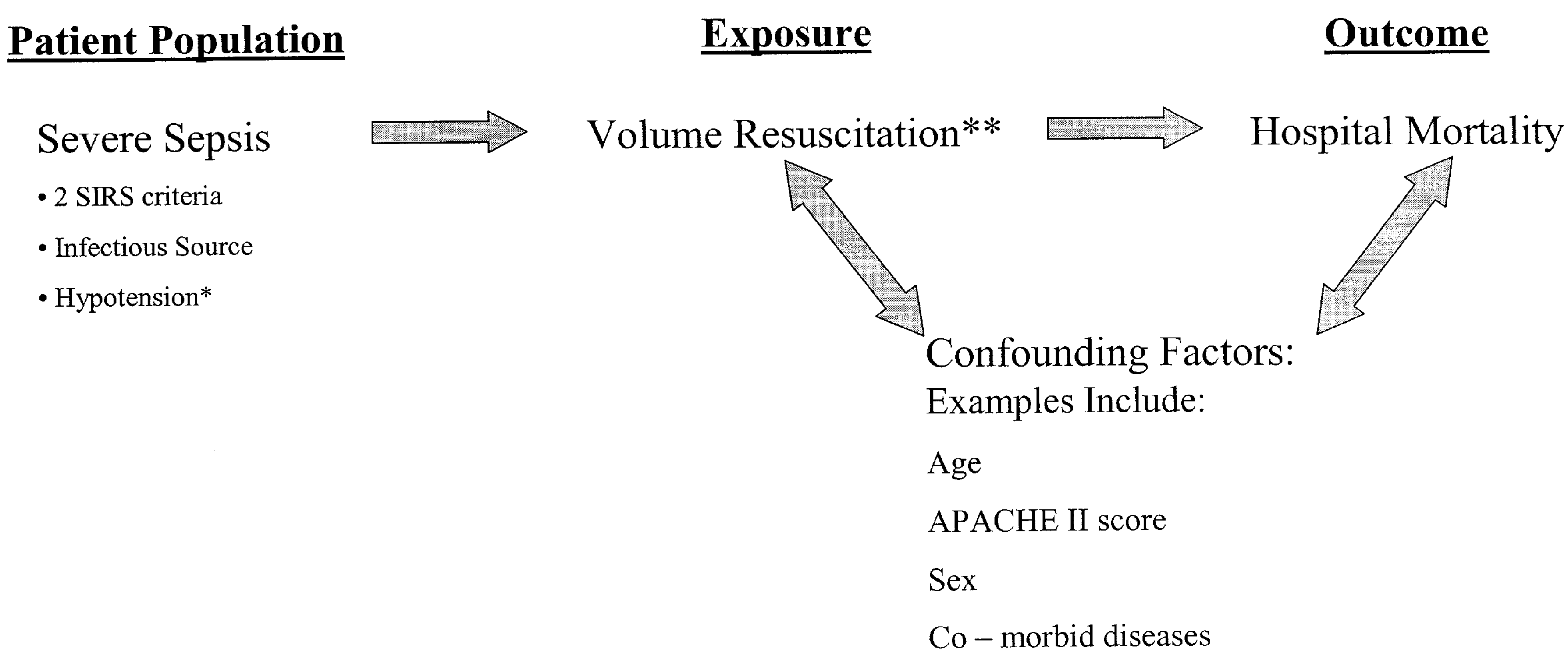
Legend: Population adjusted incidence of sepsis, according to sex from 1979 – 2000. Points represent the annual incidence rate and bars represent the standard error.

Figure 2: Sepsis Pathophysiology



L McIntyre May 30, 2004

Figure 3: Study Design



* Hypotension = "Identification of Severe Sepsis"

** Volume resuscitation for the first 6 hours after "Identification of Severe Sepsis"

Figure 4: Flow of Patients into Study