Reports of Original Investigations

Resuscitating patients with early severe sepsis: a Canadian multicentre observational study

[Réanimation des patients en début de sepsie sévère : une étude observationnelle multi-centrique canadienne]

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Background: Fluid resuscitation is a key factor in restoring hemodynamic stability and tissue perfusion in patients with severe sepsis. We sought to examine associations of the quantity and type of fluid administered in the first six hours after identification of severe sepsis and hospital mortality, intensive care unit (ICU) mortality, and organ failure.

Methods: A retrospective, multicentre cohort study was undertaken at five Canadian tertiary care ICUs. We identified patients with severe sepsis admitted to the ICU between July 1, 2000, and June 30, 2002, using both administrative and clinical databases. Patients were included if they were hypotensive, had an infectious source, and at least two systemic inflammatory response syndrome criteria. We recorded total quantity and type of fluid administered for the first six hours after severe sepsis was identified. The first episode of hypotension defined the starting point for collection of fluid data. Multivariable regression analyses were performed to examine associations between quantity and type of fluid administered and hospital/ICU mortality, and organ failure.

Results: Of 2,026 potentially eligible patient charts identified, 496 patients met eligibility criteria. The mean age and Acute Physiology and Chronic Health Evaluation score (APACHE II) were 61.8 ± 16.5 yr and 29.0 ± 8.0, respectively. No associations between quantity or type of fluid administered and hospital mortality or ICU mortality were identified, and there were no statistically significant associations between quantity or type of fluid administered and organ failure. However, more fluid resuscitation was associated with an increased risk of cardiovascular failure [odds ratio (OR) and 95% confidence interval (CI)] for 2–4 L 1.67 (1.03–2.70) and > 4 L 2.34 (1.23–4.44) and a reduced risk of renal failure [OR, 95% CI for 2–4 L 0.48 (0.28–0.83) and > 4 L 0.45 (0.22–0.92)] in the first 24 hr of severe sepsis. Administration of colloid and crystalloid fluid as compared to crystalloid fluid alone was associated with a lower risk of renal failure [OR, 95% CI 0.45 (0.26 to 0.76)].

Conclusion: An association between hospital mortality and quantity or type of fluid administered in the first six hours after the diagnosis of severe sepsis was not identifiable. These findings should be considered as hypothesis-generating and warrant confirmation or refutation by randomized controlled trials.

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Contexte *: La réanimation liquidienne est un facteur crucial pour restaurer la stabilité hémodynamique et la perfusion tissulaire chez les patients en septicémie sévère. Nous avons cherché à examiner les liens entre la quantité et le type de liquide administré durant les six premières heures suivant le diagnostic d'une septicémie sévère et la mortalité hospitalière, la mortalité aux soins intensifs et la défaillance systémique.*

Méthode *: Une étude de cohorte rétrospective et multi-centrique a été entreprise dans cinq unités de soins intensifs de soins*

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tertiaires au Canada. Nous avons identifié les patients atteints de septicémie sévère admis aux soins intensifs entre le 1er juillet 2000 et le 30 juin 2002, en se fondant sur des bases de données administratives et cliniques. Les critères d'inclusion comprenaient : l'hypotension, la présence d'une source infectieuse, et au minimum deux critères du syndrome de réponse inflammatoire systémique. Nous avons enregistré la quantité totale et le type de liquide administré durant les six premières heures suivant le diagnostic d'une septicémie sévère. Le premier épisode d'hypotension a défini le point de départ pour la récolte des données concernant les liquides administrés. Des analyses de régression multivariées ont été menées afin d'examiner les liens entre la quantité et le type de liquide administré et la mortalité à l'hôpital/aux soins intensifs, ainsi que la défaillance systémique.

***Résultats** : Parmi les 2 026 dossiers de patients potentiellement éligibles, 496 patients ont présenté les critères d'admissibilité. L'âge moyen et le score APACHE II (Acute Physiology and Chronic Health Evaluation) étaient de 61,8 ± 16,5 ans et 29,0 ± 8,0, respectivement. Aucun lien entre la quantité ou le type de liquide administré et la mortalité à l'hôpital ou aux soins intensifs n'a été identifié, et nous n'avons pas trouvé de liens statistiquement significatifs entre la quantité ou le type de liquide administré et la défaillance systémique. Toutefois, davantage de réanimation liquidienne a été associée à un risque accru de défaillance cardiovasculaire [rapport de cote (OR) et intervalle de confiance (CI) de 95 %] pour 2–4 L 1,67 (1,03–2,70) et > 4 L 2,34 (1,23–4,44) ainsi qu'un risque réduit de défaillance rénale [OR, CI 95 % pour 2–4 L 0,48 (0,28–0,83) et > 4 L 0,45 (0,22–0,92)] durant les premières 24 h de septicémie sévère. L'administration simultanée de colloïde et cristalloïde, comparativement à du cristalloïde seul, a été associée à un risque moindre de défaillance rénale [OR, CI 95 % 0,45 (0,26 à 0,76)].*

***Conclusion** : Aucune association entre la mortalité à l'hôpital et la quantité ou le type de liquide administré durant les six premières heures suivant le diagnostic d'une septicémie sévère n'a pu être identifiée. Ces données devraient être considérées comme génératrices d'hypothèses et exigent leur confirmation ou, au contraire, leur réfutation, par des études randomisées contrôlées.*

SEVERE sepsis accounts for approximately 2.9% of admissions to hospital, 10% of admissions to the intensive care unit (ICU), and is the tenth leading cause of death in the ICU.[1,2] Despite several decades of intense therapeutic investigation, the mortality from severe sepsis and septic shock remains between 30 and 60%.[3,4]

Fluid resuscitation is an integral component of early treatment, as several litres of fluid may be administered in the first hours of severe sepsis and septic shock.[5] In a landmark randomized controlled trial of goal directed therapy in early septic shock, the goal directed group received more intravenous fluid, red blood cells, and dobutamine as compared to the standard therapy group.[6] However, it is unclear whether the difference in quantity or type of fluid administered between the groups influenced the favourable survival outcome observed in the goal directed group, since this arm was comprised of many different interventions. Furthermore, the superiority of colloid as compared to crystalloid solutions for resuscitation in specific groups of critically ill patients also remains a hypothesized but contentious issue.[7–14] A very large, well conducted multicentre randomized controlled trial of 6,997 heterogeneous critically ill patients in need of volume resuscitation compared 4% albumin to normal saline and found no difference in 28-day mortality between the two groups.[15] However, there was a trend towards lower mortality in a severe sepsis subgroup receiving albumin [relative risk ratio of 0.87 and 95% confidence intervals (CI) from 0.74–1.02].

Given that intravenous fluids are an integral component in the resuscitation of patients with severe sepsis and septic shock, and the suggestion that the type and amount of fluid may influence outcomes, our objective was to evaluate whether the quantity and type of fluid administered within the first six hours after the identification of severe sepsis were associated with mortality and organ failure.

Methods

Design

This study was approved by the Research Ethics Boards of all participating hospitals. We conducted a retrospective multicentre cohort study at five tertiary care hospitals in Canada representing six ICUs. We identified consecutive patients admitted to the ICU with the diagnosis of severe sepsis from July 1, 2000, to June 30, 2002, using ICU and medical records database searches. Chart reviews were undertaken to confirm the diagnosis of severe sepsis. The following were required to be eligible for the study: 1) presence of infection; 2) two or more of the systemic inflammatory response syndrome criteria; and 3) hypotension defined as the first documented systolic blood pressure of less than or equal to 90 mmHg, a mean arterial blood pressure less than or equal to 65 mmHg, or a decrease in systolic blood pressure of greater than or equal to 40 mmHg from baseline values (identification of severe sepsis).[16] The time of the first hypotensive event defined the beginning of data collection, as this cardinal sign prompts the beginning of fluid resuscitation. Exclusion criteria included: 1) withdrawal of treatment within the first six hours after severe sepsis was identified; 2) development of severe

sepsis after the first 24 hr following ICU admission or after seven days of hospitalization; and 3) no index admission for severe sepsis in the study period.

Data collection

We collected data on demographics, severity of illness, co-morbid illnesses, infection characteristics, intravenous fluids administered (quantity and type) in the first six hours after identification of severe sepsis, ICU and hospital mortality, ICU and hospital length of stay, and development of organ failure within the first 24 hr after identification of severe sepsis.

The total amount of fluids administered included all crystalloid (normal saline, Ringer's lactate, 1/2 normal saline, dextrose 5% in 1/2 normal saline, 2/3 and 1/3 solutions, and dextrose 5% and 10%) and colloid (pentastarch, 5% and 25% albumin) fluid boluses and infusions, and cellular blood components (red blood cells, platelets, fresh frozen plasma), a method similar to that used in the Rivers' trial[6] to quantity fluids. The total fluid administered was quantified into three categories: 0–2, 2–4, and greater than 4 L administered.

The types of administered fluids were categorized into either a crystalloid-based resuscitation (defined in quantity of fluid section) or a combined crystalloid and colloid-based resuscitation. In Canada, the main two primary colloid fluids used in the resuscitation of critically ill patients are albumin (5% and 25%) and pentastarch (Pentaspan).

The primary outcome was all cause hospital mortality. Secondary outcomes were all cause ICU mortality and the development of organ failure within the first 24 hr after identification of severe sepsis. The worst values for individual organs were quantified according to the Sequential Organ Failure Assessment (SOFA) score.[16] The SOFA score includes six organ failures from the cardiovascular, pulmonary, gastrointestinal, renal, neurological, and hematological systems. The scores for each organ range from 0 (normal) to 4 (severe organ failure). Individual organs were considered to have failed if a SOFA score of 3 or greater was present in the first 24 hr after identification of severe sepsis. For gastrointestinal organ failure, a SOFA score of ≥ 2 (n = 96) defined that organ failure, as there were too few observations for SOFA ≥ 3 (n = 19). The composite outcome organ failure was defined by two or more failed organs in the first 24 hr after identification of severe sepsis.

At the co-ordinating centre (The Ottawa Hospital), 100 potentially eligible patient charts were screened in duplicate by a second data abstractor to ensure that the included patients were correctly classified with severe sepsis. These charts were also examined for correct recording of the first episode of hypotension, and the total volume of fluids administered during the first six hours of care. All errors were reviewed with the principal investigator (L.M.). No excluded charts were screened in duplicate.

All data abstractors underwent a two-week training session with experienced ICU research nurses and the site principal investigator, after which the abstractors communicated with the principal investigator on a weekly basis. Data collection was monitored extensively for the first five to ten charts at each of the participating sites. A data dictionary and instruction manual were created in order to ensure accurate and efficient data collection. Data were entered manually or directly into the computer using a Teleform application. Logic and range checks were built into Teleform to ensure accurate data collection.

Data analyses

Baseline characteristics were calculated for all patients and then according to quantity and type of fluid administered. We described continuous variables [age and Acute Physiology and Chronic Health Evaluation (APACHE II) score], with means and standard deviations and categorical variables (sex, type of admission, co-morbid disease, infectious source, hospital location) using proportions (%) and 95% CI. Lengths of stay in ICU and hospital were summarized using medians and interquartile ranges (IQR; 25th and 75th percentile).

The association between quantity of fluid and the primary outcome, hospital mortality (alive *vs* dead) was examined using multivariable logistic regression. The association between quantity of fluid and secondary outcomes - ICU mortality (alive *vs* dead), organ failure (≥ 2 *vs* < 2 organ failures), and individual organ failures (SOFA score ≥ 3 *vs* < 3) were established *a priori* and were examined using multivariable logistic regression. An analogous approach was used to examine the association between type of fluid administered and all outcomes.

We expressed the adjusted effect of quantity and type of fluid administered on all dichotomous outcomes using odds ratios (OR) and 95% CI. The reference category for all quantity of fluid analyses was 0–2 L. The crystalloid fluid group represented the reference category for all type of fluid analyses. The reference category for the analysis of organ failure was zero to one failed organ, and for individual organ failures, a SOFA score of ≤ 2. An OR less than one favoured the treatment as compared to the reference group, while an OR greater than one favoured the reference

TABLE I Baseline characteristics

	Entire cohort	*Quantity of fluid (n = 496)*			**Type of Fluid (n = 493)*	
	(n = 496)	*0 – 2 L (n = 210)*	*2 – 4L (n = 186)*	*> 4L (n = 100)*	*Crystalloid (n = 235)*	***Colloid + Crystalloid (n = 258)*
Age mean (SD)	61.8 (16.5)	64.5 (15.7)	60.9 (16.6)	58.0 (17.4)	61.5 (17.3)	62.3 (15.9)
APACHE II** mean (SD)	29.0 (8.0)	28.1 (7.9)	29.2 (8.2)	30.7 (7.6)	28.8 (8.1)	29.2 (7.9)
Sex - females (%, 95% CI)	44.0 (39.5, 48.5)	43.3 (36.5, 50.3)	46.8 (39.4, 54.2)	40.0 (30.3, 50.3)	44.7 (38.2, 51.3)	42.6 (36.5, 48.9)
Type of admission (%, 95% CI)						
Medical	76.1 (72.0, 79.7)	84.8 (79.2, 89.3)	75.3 (68.4, 81.3)	59.0 (48.7, 68.7)	84.3 (79.0, 88.7)	68.2 (62.2, 73.8)
Emergent postoperative	18.3 (15.0, 22.0)	8.6 (5.2, 13.2)	17.7 (12.5, 24.0)	40.0 (30.3, 50.3)	10.6 (7.0, 15.3)	25.6 (20.4, 31.4)
Elective postoperative	5.7 (3.8, 8.1)	6.7 (3.7, 10.9)	7.0 (3.8, 11.7)	1.0 (.03, 5.4)	5.1 (2.7, 8.7)	6.2 (3.6, 9.9)
# Co-morbid diseases (%, 95% CI)						
0	21.6 (18.0, 25.5)	15.2 (10.7, 20.8)	22.6 (16.8, 29.3)	33.0 (23.9, 43.1)	23.0 (17.8, 28.9)	20.5 (15.8, 26.0)
1 – 2	51.2 (46.7, 55.7)	49.1 (42.1, 56.0)	53.2 (45.8, 60.6)	52.0 (41.8, 62.1)	46.8 (40.3, 53.4)	55.0 (48.7, 61.2)
≥ 3	27.2 (23.4, 31.4)	35.7 (29.2, 42.6)	24.2 (18.2, 31.0)	15.0 (8.7, 23.5)	30.2 (24.4, 36.5)	24.4 (19.3, 30.1)
Infectious source (%, 95% CI)						
Pulmonary	37.9 (33.6, 42.3)	47.1 (40.2, 54.1)	35.5 (29.6, 42.8)	23.0 (15.2, 32.5)	39.2 (32.9, 45.7)	37.2 (31.3, 43.4)
Intra-abdominal	30.8 (26.8, 35.1)	23.3 (17.8, 29.7)	29.6 (23.1, 36.7)	49.0 (38.9, 59.2)	21.3 (16.2, 27.1)	39.1 (33.1, 45.4)
Urinary tract	12.1 (10.1, 16.2)	11.4 (7.5, 16.5)	16.7 (11.6, 22.8)	9.0 (4.2, 16.4)	17.4 (12.8, 22.9)	8.9 (5.7, 13.1)
Soft tissue	6.2 (4.3, 8.7)	6.7 (3.7, 11.0)	5.4 (2.6, 9.7)	7.0 (2.9, 13.9)	8.5 (5.3, 12.8)	4.3 (2.1, 7.5)
Other	12.1 (9.4, 15.3)	11.4 (7.5, 16.5)	12.9 (8.5, 18.6)	12.0 (6.4, 20.0)	13.6 (9.5, 18.7)	10.5 (7.0, 14.9)
Vital signs, mean (SD)						
Mean arterial pressure (mmHg)	56.9 (10.2)	58.6 (9.1)	57.0 (8.0)	55.3 (9.3)	57.4 (9.1)	56.0 (11.0)
Heart rate (beats·min^{-1})	107.7 (24.0)	103.5 (25.5)	109.9 (20.6)	112.4 (25.5)	104.3 (23.9)	111.0 (23.7)
Respiratory rate (breaths·min^{-1})	24.2 (9.1)	23.4 (8.7)	24.8 (9.8)	25.0 (8.6)	24.5 (9.0)	24.1 (9.3)
Temperature (degrees Celsius)	37.4 (1.5)	37.4 (1.3)	37.4 (1.6)	37.2 (1.7)	37.2 (1.6)	37.5 (1.3)
Glasgow coma scale score	12.6 (3.4)	12.4 (3.2)	12.9 (3.1)	12.5 (3.4)	12.6 (3.1)	12.5 (3.3)
Place in hospital (%, 95% CI)						
ICU	28.6 (24.9, 32.8)	41.4 (34.7, 48.4)	25.3 (19.2, 32.1)	8.0 (3.5, 15.2)	23.0 (17.8, 28.9)	34.1 (28.3, 40.2)
ER	32.7 (28.6, 37.0)	28.1 (22.1, 34.7)	33.3 (26.6, 40.6)	41.0 (31.2, 51.3)	32.3 (26.4, 38.7)	33.3 (27.6, 39.4)
Hospital ward	16.3 (13.2, 20.0)	16.7 (11.9, 22.4)	18.3 (13.0, 24.6)	12.0 (6.4, 20.0)	16.6 (12.1, 22.0)	15.1 (11.0, 20.1)
OR/PACU	7.1 (5.0, 9.7)	1.4 (0.3, 4.1)	7.5 (4.2, 12.3)	18.0 (11.0, 26.9)	3.0 (1.2, 6.0)	10.8 (7.3, 15.3)
Peripheral hospital	15.3 (12.3, 18.8)	12.4 (8.2, 17.6)	15.6 (10.7, 21.6)	21.0 (13.5, 30.3)	25.1 (19.7, 31.2)	6.6 (3.9, 10.3)
# Days in hospital (before Identification of severe sepsis) Median (IQR)	0 (0, 2)	1 (0, 3)	0 (0, 2)	0 (0, 1)	0 (0, 2)	1 (0, 3)

CI = confidence interval; ICU = intensive care unit; ER = emergency room; OR = operating room; PACU = postoperative care unit; # = number; IQR = interquartile range. *Three patients received no fluid in the first six hours of care; **All colloid use = pentastarch.

TABLE II Fluid data

	Entire cohort	*Quantity of fluid (n = 496)*			**Type of Fluid (n = 493)*	
	(n = 496)	*0 – 2 L (n = 210)*	*2 – 4L (n = 186)*	*> 4L (n = 100)*	*Crystalloid (n = 235)*	***Colloid + Crystalloid (n = 258)*
Total fluid (L) median (IQR)	2.4 (1.4, 3.7)					
Type of fluid (%, 95% CI)						
No fluid	0.6 (0.1, 1.8)	1.4 (0.3, 4.1)	0	0		
Crystalloid alone	47.4 (42.9, 51.9)	58.6 (51.6, 65.3)	44.6 (37.3, 52.1)	29.0 (20.4, 39.0)		
Colloid alone	0	0	0	0		
**Colloid and Crystalloid	52.0 (47.5, 56.5)	40.0 (33.3, 47.0)	55.4 (47.9, 62.6)	71.0 (61.1, 79.6)		
RBC transfusions (%, 95% CI)	12.7 (9.9, 16.0)	6.2 (3.3, 10.3)	11.3 (7.1, 16.7)	29 (20.4, 38.9)	8.5 (5.3, 12.8)	16.7 (12.3, 21.8)
Fresh frozen plasma (%, 95% CI)	0.8 (0.2, 2.0)	0	1.1 (0.1, 3.8)	2.0 (0.2, 7.0)	0.4 (0.0, 2.3)	1.2 (0.0, 3.4)
Platelets (%, 95% CI)	0	0	0	0	0	0

IQR = interquartile range; CI = confidence interval; RBC = red blood cells. *Three patients received no fluid in the first six hours of care; **All colloid use = pentastarch.

TABLE III Outcomes

	Entire cohort	*Quantity of fluid (n = 496)*			**Type of Fluid (n = 493)*	
	(n = 496)	*0 – 2 L (n = 210)*	*2 – 4L (n = 186)*	*> 4L (n = 100)*	*Crystalloid (n = 235)*	***Colloid + Crystalloid (n = 258)*
Hospital mortality (%, 95% CI)	45.2 (40.7, 49.7)	46.2 (39.3, 53.2)	44.1 (36.8, 51.5)	45.0 (35.0, 55.3)	43.0 (36.6, 49.6)	46.9 (40.7, 53.2)
ICU mortality (%, 95% CI)	34.9 (30.7, 39.2)	31.4 (25.2, 38.2)	35.5 (28.6, 42.8)	41.0 (31.3, 51.3)	30.6 (24.8, 37.0)	38.4 (32.4, 44.6)
Hospital length of stay median (IQR)	14.0 (6.0, 27.0)	14.0 (8.0, 28.0)	13.5 (6.0, 26.0)	17.0 (6.0, 28.0)	13.0 (7.0, 27.0)	15.0 (6.0, 26.0)
ICU length of stay median (IQR)	6.0 (2.0, 12.0)	6.0 (2.0, 11.0)	5.0 (2.0, 12.0)	6.0 (2.0, 12.0)	5.0 (2.0, 11.0)	6.0 (3.0, 12.0)
Organ failure (%, 95% CI) ≥ 2 failed organs	35.3 (31.1, 39.7)	32.4 (26.1, 39.2)	38.2 (31.2, 45.6)	36.0 (26.6, 45.4)	34.9 (28.8, 41.4)	35.66 (29.8, 41.8)

CI = confidence interval; IQR = interquartile range; SOFA = sequential organ failure assessment score. *Three patients required no fluid in the first six hours of care; **All colloid use = pentastarch.

group. Baseline covariates that were considered to be clinically or biologically relevant were forced into the model to adjust for the effect of quantity and type of fluid on all outcomes. Covariates included age (increments of ten years), APACHE II score (increments of 10), sex, source of infection (pulmonary, intra-abdominal, urinary tract, soft tissue, other), number of co-morbid illnesses (0, 1–2, ≥ 3), type of admission (medical, emergent/elective postoperative), hospital site, and hospital location (emergency room, ICU, hospital ward, operating room/postoperative care unit, peripheral hospital) at the time that severe sepsis was identified.

Missing dependent (outcome) variables were considered to not have the adverse outcome in the multivariable analyses. Missing independent (explanatory) variables that were continuous in nature were imputed using the group mean. Missing categorical data were imputed from existing data with missing values randomly assigned to the categories in the same proportion as the observed proportions.

Results

We identified 2,026 charts for screening using the medical records and ICU databases. After the chart review process, 1,643 charts did not meet the inclusion, leaving a total of 496 eligible patients in our cohort.

Pilot inter-rater reliability

Of 100 charts that were screened in duplicate, seven patients were excluded after a second review because they were ineligible. In 97 of 100 charts, abstractors agreed on the first episode of hypotension (identification of severe sepsis crude agreement 97%); for three patients, this time was revised. In 95 of 100 charts, abstractors agreed on the total amount of fluids recorded in the first six hours after severe sepsis (crude agreement 95%); for five patients, the total infusion was corrected.

Baseline characteristics

Patients were 61.8 (± SD 16.5) yr of age with an APACHE II score of 29.0 (± SD 8.0); 44.0% were female. Medical admissions comprised 76.1% of this cohort and 51.2% of patients had at least one co-morbid illness. Patients were hypotensive [56.9 (± SD 10.2)], tachycardic [107.2 (± SD 24.0)], tachypneic [24.2 (± SD 9.1)], and had abnormal Glasgow coma scale scores [12.6 (± SD 3.4)]. Median length of stay in hospital prior to admission to ICU for severe sepsis was 0 days (IQR zero to two days) (Table I). When baseline characteristics were categorized according to their fluid exposure variables, there were imbalances among the groups (Table I). For example, the age for patients who received 0–2 L of fluid was 64.5 yr (± SD 15.7) as compared to 58.0 yr (± SD 17.4) for those who received greater than 4 L of fluid; 15.2%

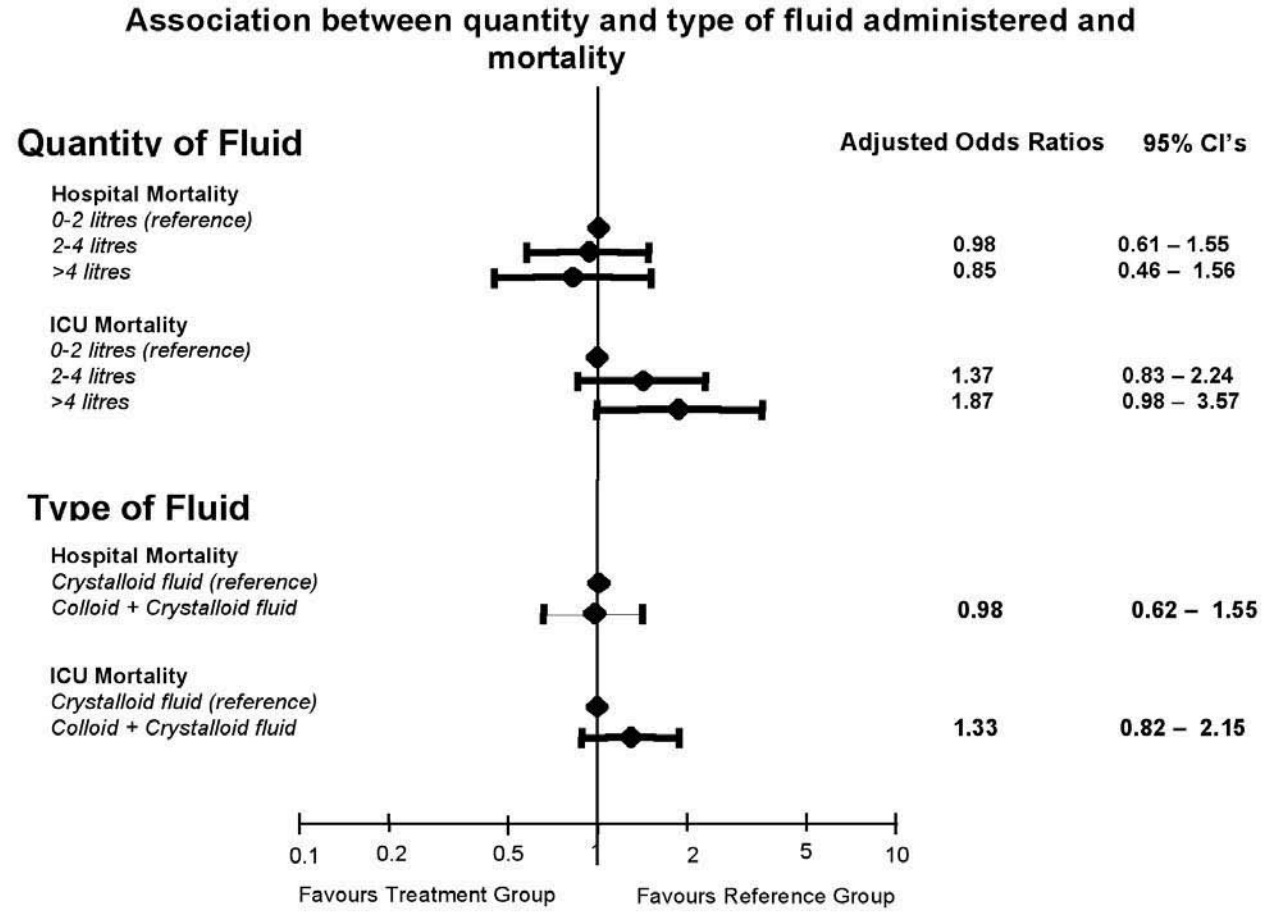

FIGURE Reference group for quantity of fluid = 0–2 L, treatment group = 2–4 and > 4 L. Reference group for type of fluid = crystalloid fluid. Treatment group = colloid and crystalloid fluid. Adjusted odds ratios were generated using multivariable logistic regression that incorporated variables age, sex, Acute Physiology and Chronic Health Evaluation (APACHE II) score, type of admission, infectious source, number of co-morbidities, hospital site, and place in hospital.

of patients in the 0–2 as compared to 33.0% in the greater than 4 L group had no co-morbid illnesses.

The median amount of fluid delivered was 2.4 L (IQR 1.4 to 3.7 L). Three patients received no fluid in the first six hours after the identification of severe sepsis (Table II). A combination of colloid and crystalloid fluids were administered to 52.0% of patients. No patient received colloid solutions only, and none received the colloid agent albumin in the first six hours of care. Pentastarch was the only colloid solution used for resuscitation of these patients in the first six hours of care.

Overall ICU mortality was 34.9% and hospital mortality was 45.2%. Median length of stay in ICU was 6.0 days (IQR 2.0 to 12.0 days), and in hospital was 14.0 days (IQR 6.0 to 27.0 days). At least two organs failed in the first 24 hr after severe sepsis was identified in 35.3% of patients.

Primary analysis

The adjusted odds of hospital mortality according to quantity of fluid administered was not statistically significant (Figure). The quantity of fluid administered was not associated with statistically significant differences in the odds of death in ICU or organ failure. Increased quantity of fluid was associated with a significantly increased risk of cardiovascular organ failure (OR 1.67, 95% CI 1.03 to 2.70 for 2–4 L and OR 2.34, 95% CI 1.23 to 4.44 for greater than 4 L as compared to the 0–2 L group) and a reduced risk of renal failure in the first 24 hr after severe sepsis was identified (OR 0.48, 95% CI 0.28 to 0.83 for 2–4 L, and OR 0.45, 95% CI 0.22 to 0.92 for the greater than 4 L fluid groups respectively).

Secondary analysis

The adjusted odds of hospital mortality, ICU mortality, and organ failure for the colloid and crystalloid fluid group in comparison to crystalloid fluid group alone did not reveal any statistically significant differences between groups. The administration of colloid and crystalloid fluid as compared to crystalloid fluid alone was associated with a significant reduction in the risk of renal failure in the first 24 hr after severe sepsis was identified (OR 0.45, 95% CI 0.26 to 0.76).

Discussion

Rapid and early administration of large quantities of fluid for patients with severe sepsis and septic shock is a key aspect of initial resuscitation to restore and maintain hemodynamic stability and hence tissue perfusion.[17,18] Six to 10 L of fluid may be administered in the first 24 hr of management.[5] Indeed, in the Rivers' goal directed resuscitation trial of septic shock, patients in the goal directed group received a mean of 5.0 (± SD 3.0) as compared to 3.5 (± SD 2.4) L of fluid in the standard therapy arm in just the first six hours of care.[6] In this study, we did not observe an association between quantity of fluid administered and hospital mortality. Several reasons may account for the inability to detect this association. It is possible that patients who received more fluid were also more severely ill. Patients in the higher quantity of fluid group appeared to have lower blood pressure, faster heart rates, and higher APACHE II scores at baseline. However, patients who received greater quantities of fluids also had fewer co-morbid illnesses. Further, both the APACHE II score and co-morbid illnesses were controlled for in the multivariable analysis. It is also possible that excess fluid administration could have led to morbid events. In a multicentre randomized controlled trial, Wiedemann *et al.*[19] compared liberal *vs* restrictive strategies for fluid management in 1,000 critically ill patients with acute lung injury. Although there was no difference in death at 60 days between the study groups (25.5% for restrictive *vs* 28.4% for liberal, $P = 0.3$), the restrictive fluid strategy group was associated with improvements in lung function, an increase in ventilator-free days, and a reduced ICU length of stay. However, patients in the trial were randomized into the study an average of 43 hr after ICU admission as compared to the Rivers' study that enrolled patients within two hours of their arrival to the emergency room.[19,20] Hence, findings from the Wiedemann study may not apply to patients in the early phases of severe sepsis or septic shock. In addition, the median amount of fluid administered in our study was 2.4 L as compared to an average of 5.0 L delivered in Rivers' study.[6] Finally, due to our retrospective study design, we were unable to record details of fluid resuscitation such as whether the fluid was delivered with rapid and repeated fluid challenges, and whether the fluids were administered with resuscitation algorithms and according to physiological goals.[6,21–25] The inability to control for potential imbalances in these factors limits our ability to identify possible associations between hospital mortality and increased quantity of fluid.

We were also unable to detect an association between the administration of colloid and crystalloid fluid *vs* crystalloid fluid alone and hospital mortality. Despite decades of research, there is still a lack of evidence in specific critically ill patient populations to help guide the clinician as to the optimal choice of resuscitation fluid.[18] Results of the SAFE trial have resolved some of the colloid-crystalloid controversy

because investigators found no difference in 28-day mortality between the 4% albumin and normal saline study groups.[15] However, a severe sepsis subgroup analysis of 1,219 patients found a trend toward a reduction in 28-day mortality for the albumin as compared to normal saline group (relative risk ratio of 0.87, 95% CI 0.74 to 1.02)[15] suggesting the possibility for benefit in this specific critically ill patient population. In our study, the administration of crystalloid and colloidal fluid as compared to crystalloid fluid alone was not associated with a reduction in hospital mortality. However, in light of the sample size in the SAFE severe sepsis subgroup analysis, it is likely that we would have required a larger study to detect small but clinically important treatment differences between the fluids administered. The efficacy of colloid *vs* crystalloid fluid in the setting of sepsis is still unanswered and authors from the SAFE trial as well as an editorial have highlighted the need for further fluid resuscitation research in this patient population.[26]

Another controversial topic related to the administration of colloid fluids, and specifically hydroxyethyl starches (HES), is the issue of acute renal failure in the critically ill.[27] A randomized controlled trial of 129 patients with septic shock compared the administration of a HES *vs* a gelatin resuscitation fluid and found an increase in renal insufficiency (defined by peak serum creatinine) in the HES group.[28] More recently, a multicentre randomized controlled trial from Germany compared the effect of 10% HES *vs* Ringer's lactate in a severe sepsis and septic shock patient populations and found a significant increase in the need for renal replacement therapy in the HES group (31% 10% HES *vs* 18.8% Ringer's lactate, $P = 0.001$).[29] Our study found that a resuscitation strategy including both colloid (pentastarch) and crystalloid fluid as compared to crystalloid fluid alone was associated with a significant reduction in the risk of renal failure in the first 24 hr of care. Although our results contrast the findings of these two randomized controlled trials,[28,29] it is important to consider our results as hypothesis generating. Our study was retrospective and observational in nature, not a randomized controlled trial. Importantly, we were able to identify the presence of renal failure at only one time point, within the first 24 hr after the identification of severe sepsis. Multiple assessments for renal dysfunction throughout the ICU stay would have strengthened the design.

Our study had several limitations. These include potential for selection bias, information bias, confounding, and residual confounding. We made efforts to reduce selection bias by identifying all patients in a consecutive manner who were admitted to the ICU with severe sepsis during the study period, and by having minimal exclusion criteria. However, as we limited our search to ICU patients, it is possible that we missed patients with severe sepsis who were never admitted to the ICU. In an effort to reduce information bias, all data collectors received a two-week training session and an ongoing review of the data collection process with the principal investigator. Further, the accuracy of three important data points were evaluated by duplicate data collection for 100 included charts. Although we attempted to control for important confounding variables in the multivariable analysis, it is still possible that residual confounding variables may have influenced our results. Importantly, our study may have been insufficiently powered to exclude clinically important benefits or adverse effects associated with quantity or type of fluid. The results of this observational study should be considered hypothesis-generating.

Conclusion

Resuscitation fluids remain a cornerstone of management for the hemodynamically unstable patient. The effect of colloid *vs* crystalloid resuscitation fluid on outcome in the severe sepsis and septic shock patient populations still requires a definitive answer. A well designed and adequately powered randomized controlled trial with clinically important endpoints is required to address this important question.

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