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ORIGINAL

Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database

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Abstract

Purpose: The optimal strategy of fluid resuscitation in the early hours of severe sepsis and septic shock is controversial, with both an aggressive and conservative approach being recommended.

Methods: We used the 2013 Premier Hospital Discharge database to analyse the administration of fluids on the first ICU day, in 23,513 patients with severe sepsis and septic shock, who were admitted to an ICU from the emergency department. Day 1 fluid was grouped into categories 1 L wide, starting with 1–1.99 L up to ≥9 L, to examine the effect of day 1 fluids on patient mortality. We built binary response models for hospital mortality and the propensity for receiving more than 5 L of fluids on day 1, using patient age and acute conditions present on admission. Patients were grouped by the requirement for mechanical ventilation and the presence or absence of shock. We assessed trends in the difference between actual and expected mortality, in the low fluid range (1–5 L day 1 fluids) and the high fluid range (5 to ≥9 L day 1 fluids) categories, using weighted linear regression controlling for the effects of sample size and variation within the day 1 fluid category.

Results: Day 1 fluid administration averaged 4.4 L being lowest in the group with no mechanical ventilation and no shock (3.6 L) and highest (5.4 L) in the group receiving mechanical ventilation and in shock. The administration of day 1 fluids was remarkably consistent on the basis of hospital size, teaching status, rural/urban location, and region of the country. The hospital mortality in the entire cohort was 25.8%, with a mean ICU and hospital length of stay of 5.1 and 9.1 days, respectively. In the entire cohort, low volume resuscitation (1–4.99 L) was associated with a small but significant reduction in mortality, of −0.7% per litre (95% CI −1.0%, −0.4%; $p = 0.02$). However, in patients receiving high

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Take-home message: In patients with severe sepsis and septic shock, the administration of more than 5 L of fluid on the first hospital day is associated with a significantly increased risk of death and significantly higher hospital costs. Low-volume resuscitation (1–4.99 L) is associated with a small but significant reduction in mortality.

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volume resuscitation (5 to ≥9 L), the mortality increased by 2.3% (95% CI 2.0, 2.5%; $p = 0.0003$) for each additional litre above 5 L. Total hospital cost increased by $999 for each litre of fluid above 5 L (adjusted $R^2 = 92.7\%$, $p = 0.005$).

Conclusion: The mean amount of fluid administered to patients with severe sepsis and septic shock in the USA during the first ICU day is less than that recommended by the Surviving Sepsis Campaign guidelines. The administration of more than 5 L of fluid during the first ICU day is associated with a significantly increased risk of death and significantly higher hospital costs.

Keywords: Sepsis, Septic shock, Fluid administration, Mortality, National database

Introduction

Traditional teaching suggests that aggressive fluid resuscitation is the best initial approach for the cardiovascular instability of sepsis. In the Rivers' Early Goal Directed Therapy (EGDT) study, 4.9 L of crystalloid was given in the first 6 h and 13.4 L in the first 72 h [1]. The Surviving Sepsis Campaign recommends "aggressive fluid resuscitation during the first 24 h" of management [2]. These guidelines require patients with hypotension or a lactate concentration >4 mmol/L, to receive a 30 ml/kg bolus of crystalloid within 3 h of triage, with repeated boluses to achieve a central venous pressure of 8–15 cmH_2O [3]. Consequently, large volumes of fluid are administered to septic patients during the first day of ICU admission.

The only reason to give a patient a fluid challenge, is to increase stroke volume and cardiac output. Yet, multiple studies have reproducibly demonstrated that only about 50% of hemodynamically unstable patients will respond to a fluid challenge [4, 5]. Furthermore, the hemodynamic benefit of a fluid bolus in terms of cardiac output and blood pressure is short lived, lasting less than an hour [6–8]. On the basis of this data, we have suggested a conservative strategy regarding fluid resuscitation in patients with sepsis [9–12]. This approach differs significantly from the Surviving Sepsis Campaign protocol. The Premier Hospital Discharge Database is a comprehensive databank representing current in-hospital practice in the USA. An analysis of this database gave us the opportunity to analyse the prescription of intravenous fluid for patients with sepsis, within the first day of ICU admission, and to evaluate the association between the volume of fluid administered and the outcome. We hypothesized that large volume fluid resuscitation (>5 L) during the first ICU day would be associated with an increased risk of severity-adjusted mortality.

Methods

Data source

We constructed the study cohort using the 2013 Premier Hospital Discharge Database with 6,186,940 discharges from 500 hospitals in the USA. The Premier database (Premier Inc., Charlotte, NC, USA) includes patient demographic data, ICD-9-CM diagnoses including present on admission information, ICD-9-CM procedures with procedure day, and a date-stamped log of all invoiced items, including medications, laboratory orders, diagnostic and therapeutic services, and other details including the quantity, cost, and charge for each item.

Case selection

We selected all discharges for those 18 years of age and older that met the following criteria: a diagnosis of severe sepsis (995.92) or septic shock (785.52) present on admission; admitted through the emergency department; admitted to the intensive care unit (ICU) with parenteral antibiotics on day 1, and were non-surgical patients. Because not all institutions uniformly invoiced to the same level of detail, we excluded hospitals where the 25th percentile for recorded fluid on day 1 was below 1 L. Additionally, because only the day of the hospitalization is recorded and not the time of day, we captured fluid use for the day and not for a 24 h period. To compensate for this, we further excluded any cases where there was less than 1 L of fluid on day 1. To investigate how similar our final cohort was to those reported in current practice, we compared the patient characteristics and outcomes of this study to those in the Protocolized Care for Early Septic Shock (ProCESS) trial as well as the Australasian Resuscitation in Sepsis Evaluation (ARISE) and Protocolized Management in Sepsis (ProMISe) trials [13–15].

Definitions

We organized patient data by use of mechanical ventilation on day 1 of the hospitalization and by the presence of septic shock (use of parenteral vasopressors on day 1 or day 2). Patients were further characterized by acute organ dysfunctions present at admission (see Supplementary Table 1) [16] and by Charleson-Deyo comorbidities [17]. Day 1 fluid was grouped into categories 1 L wide starting with 1–1.99 L up to ≥9 L to examine the effect of day 1 fluids on patient outcomes. Hospitals were characterized by size (<200, 200–399, ≥400 beds), teaching status, urban/rural location, and geographic region (Midwest, Northeast, South, and West). Day 1 fluid included fluids

administered in the emergency department. The primary outcome of interest was hospital mortality but we also examined hospital length of stay (LOS), ICU LOS, duration of mechanical ventilation, and total cost.

Case mix adjustment

We built binary response models for hospital mortality and the propensity for receiving more than 5 L of fluids on day 1, using patient age, acute conditions present on admission including acute organ dysfunctions, anaemia (280.0, 281.0, 282.0–0.3, 287.7, 283, 284.9, 285.0, 285.1, 285.2, 285.8), and a number of chronic conditions: heart failure (398.91, 402.91, 425.4–0.9, 428); chronic renal failure; end-stage renal disease; neoplasm of digestive, bone, genitourinary tract, and lymphoma (150–159, 170–171, 179–189, 200–208); pulmonary and central nervous system neoplasm (160–165, 191–192); metastatic neoplasm (196–199); dysrhythmias and conduction disorders (426.0–0.1, 427.3–0.4, 785.0, 996.01, 996.04); hypertensive kidney disease (403.01, 403.11, 403.91, 404.01–0.03, 404.11–0.13, 404.91–0.93) and complex liver disease (456.0, 570, 571.1, 572.2–0.8). The 5 L day 1 fluid intake cut-off was predefined on the basis of prognostic thresholds in previous studies [18–21]. A factor indicating whether a patient was in the upper half of the propensity range was included in the hospital mortality model to assess the interplay of severity and propensity for greater fluid use. The models used a generalized logistic link function and fit was assessed using likelihood *r*-square, Chi square dispersion, area under the ROC curve, and the Hosmer–Lemeshow *C* statistic.

Statistical analysis

We compared continuous data by Mann–Whitney *U* test and categorical data by Chi square or Fisher's exact test as appropriate. We assessed trends in the difference between actual and expected mortality in the low fluid range (1–5 L day 1 fluids) and the high fluid range (5 to ≥9 L day 1 fluids) categories using weighted linear regression controlling for the effects of sample size and variation within the day 1 fluid categories. We constructed the databases in FoxPro 9.0 (Microsoft Corp., Redmond WA, USA) and conducted analyses in Data Desk 6.3 (Data Description, Ithaca NY, USA).

Results

During the year 2013, 35,135 patients with a diagnosis of severe sepsis or septic shock were admitted to an ICU in one of the 500 participating hospitals with a hospital mortality rate of 26.53%. There were 156 hospitals that had a 25th percentile of day 1 fluid use below 1 L. These 156 hospitals were excluded from all further analyses. The excluded hospitals had a similar hospital mortality (27.7% vs. 26.0%) but had a mean recorded day 1 fluid use of almost one quarter that of the other hospitals. The comparison of the excluded hospitals with the remaining hospitals is shown in Supplementary Table 2. We further excluded 195 cases where there was less than 1 L day 1 fluid recorded, which may have been from very late in the day admission or poor coding for the case (see Supplementary Table 3). The final cohort had 344 hospitals and 23,513 discharges with a mean day 1 fluid use of 4.407 L, a 25th percentile of 2.5 L, and a hospital mortality rate of 25.8%. The demographic and clinical data of the final cohort of patients grouped by the requirement for mechanical ventilation and the presence or absence of shock is listed in Table 1. The day 1 fluid administration and outcomes are provided in Table 2. The mean day 1 fluid administration by hospital characteristic is provided in Supplementary Table 4. The patient characteristics and outcomes of this study as compared to those in the ProCESS trial are presented in Supplementary Table 5. A total of 753 subjects died on the first day in the hospital (3.2% of the cohort); as a result of the small sample size, no adjustment was made for these cases.

The ability of the prognostic model to predict mortality based on the admission severity model is presented in Fig. 1. The model performed moderately well with an AUC of 0.73, Likelihood *r*-square of 45.196, Chi squared dispersion of 1.104, and a Hosmer–Lemeshow *C* statistic of 7.8 (8 *df*, $p = 0.02$). The actual vs. predicted mortality for all patients grouped by decile of day 1 fluid administration is illustrated in Fig. 2 (bars indicate 95% CI; the difference between actual and predicted mortality is significant when 95% CI bars do not cross the line for predicted mortality). The actual vs. predicted mortality by day 1 fluid administration across day 1 mechanical ventilation and shock categories, is presented in Fig. 3. The statistical association between the trend of low volume (1–5 L), and that for high volume resuscitation (5 to ≥9 L) across the categories of mechanical ventilation and shock, is presented in Table 3. While the volume of fluid administered on the first ICU day increased with increasing disease severity, patients who received more than 5 L had a significantly increased risk-adjusted likelihood of death in each fluid category, except those not mechanically ventilated and in those without shock. In the entire cohort, low volume resuscitation (1–4.99 L) was associated with a small but significant reduction in mortality of −0.7% per litre (95% CI −1.0%, −0.4%; $p = 0.02$). However, in patients receiving high volume resuscitation (5 to ≥9 L) the mortality increased by 2.3% (95% CI 2.0, 2.5%; $p = 0.0003$) for each additional litre above 5 L. There was no association between day 1 fluid administration and ICU and hospital length of stay (LOS) and the duration of mechanical ventilation

Table 1 Cohort characteristics

	No MV, no shock	MV, no shock	No MV, shock	MV & shock	All
Cases count (%)	6970 (29.6%)	2012 (8.6%)	8583 (36.5%)	5948 (25.3%)	23,513
Age mean [median]	67.5 [69]	65.3 [67]	68.5 [70]	66.3 [67]	67.4 [69]
Male	50.3%	50.1%	48.8%	54.0%	50.6%
Race (%) white	70.8%	64.9%	71.3%	65.4%	69.1%
Black	12.9%	17.7%	12.4%	16.2%	13.9%
Other	16.3%	17.3%	16.4%	18.5%	17.0%
Admission organ failures respiratory	0.0%	100.0%	0.0%	100.0%	33.9%
Hematologic	16.4%	14.8%	20.9%	22.2%	19.4%
CNS	20.8%	29.8%	19.1%	28.9%	23.0%
Cardiac	0.0%	0.0%	100.0%	100.0%	61.8%
Renal	58.4%	50.5%	62.2%	61.8%	60.0%
Hepatic	2.8%	4.5%	4.7%	10.7%	5.6%
Average per case	1.0	2.0	2.1	3.2	2.0
Co-morbidities diabetes	36.5%	36.7%	35.0%	35.8%	35.8%
Chronic pulmonary disease	15.1%	17.6%	16.0%	17.0%	16.1%
Cerebrovascular disease	0.1%	0.1%	0.1%	0.2%	0.1%
Dementia	1.7%	1.8%	1.3%	1.5%	1.5%
Non-metastatic neoplasm	11.7%	8.5%	13.4%	10.5%	11.7%
Metastatic neoplasm	5.6%	4.1%	5.9%	4.6%	5.3%
Para- and quadriplegia	2.2%	2.7%	2.0%	2.1%	2.2%
Peripheral vascular disease	8.2%	6.7%	8.3%	7.5%	7.9%
Rheumatic disease	4.8%	4.1%	4.9%	3.3%	4.4%
Chronic renal disease	30.6%	26.9%	32.4%	28.2%	30.4%
Mild liver disease	4.3%	4.1%	6.0%	6.0%	5.3%
Major liver disease	3.4%	3.0%	4.3%	4.7%	4.0%

MV mechanical ventilation

Table 2 Day 1 fluid use and outcomes

	No MV, no shock	MV, no shock	No MV, shock	MV & shock	All
Cases count (%)	6970 (29.6%)	2012 (8.6%)	8583 (36.5%)	5948 (25.3%)	23,513
Day 1 fluids mean (ml)	3618	3889	4440	5459	4407
10th percentile	1250	1400	1650	2000	1510
25th percentile	2100	2195	2650	3250	2500
Median	3250	3500	4250	5145	4050
75th percentile	5000	5250	5850	7000	5800
90th percentile	6150	6757	7250	9288	7500
Hospital mortality	12.7%	22.6%	23.6%	45.5%	25.8%
LOS mean (median)	8.3 (6)	11.2 (9)	8.4 (6)	10.3 (7)	9.1 (7)
ICU LOS Mean (median)	3.8 (2)	7.0 (5)	4.5 (3)	7.0 (5)	5.1 (3)
MV days mean (median)	–	6.9 (5)	–	6.9 (4)	3.1 (0)
Mean cost	$20,038	$32,123	$21,393	$31,199	$24,390

(Supplementary Table 6). Total cost, however, did have an association with day 1 fluid administration (adjusted $R^2 = 92.7\%$, $p = 0.005$), with greater than 5 L having on average an added cost of $999 for each litre of fluid above 5 L (see Supplementary Fig. 1).

Discussion

Our study represents the largest study to date to investigate the association between fluid administration with the outcome of patients with severe sepsis and septic shock. The patients included in our analysis are broadly

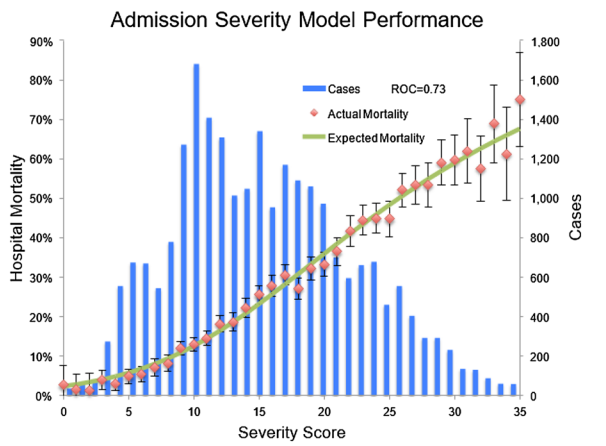

Fig. 1 Admission Severity Model

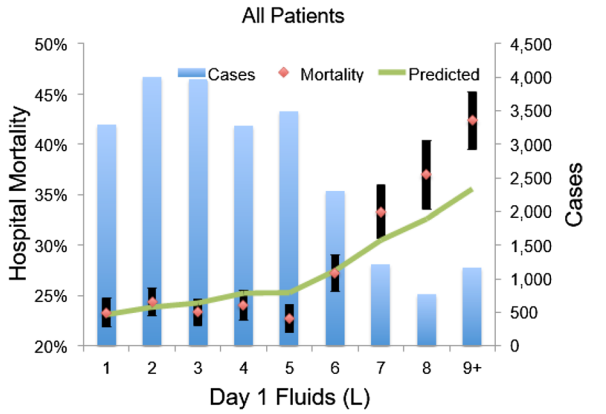

Fig. 2 Actual and expected hospital mortality, by day 1 fluid groups

representative of patients treated for sepsis and septic shock in the USA and reflect real-world practice. An additional strength of our study, is that we developed a model to accurately predict mortality, based on numerous clinical indicators. Previous studies have been criticized because they did not control for severity of illness, which is likely a major confounding factor affecting the volume of fluid administered, i.e., sicker patients are likely to receive more fluid and are more likely to die because they are sicker [20, 22]. Indeed, we noted that the predicted mortality increased almost linearly with increasing fluid administration (see Fig. 2); this finding provides further validity to the consistency and reliability of the data and the predictive model. Our study provides information on two very important issues, namely the average volume of fluid administered to septic patients in the USA during the critical first day of ICU care and the association between of the volume of fluid administered and patient mortality.

The mean volume of crystalloid administered during the first day of ICU admission, averaged 4.4 L. The volume of fluid administered was higher (5.4 L) in patients receiving mechanical ventilation and in shock, compared to those with neither of these characteristics (3.6 L). The mean amount of fluid administered was remarkably consistent regarding hospital size, teaching status, rural/urban location, and region of the country. This volume is less than that recommend by the EGDT protocol and the Surviving Sepsis Campaign [1, 23]. The guidelines for hemodynamic support of sepsis published by the American College of Critical Care Medicine, state that "large fluid deficits exist in patients with septic shock. Up to 6–10 L of crystalloid solutions may be required for initial resuscitation in the first 24 h". The EGDT protocol and the Surviving Sepsis Campaign guidelines recommend targeting a central venous pressure (CVP) between 8–12 and 12–15 mmHg for patients receiving mechanical ventilation. We have previously demonstrated a very strong correlation ($R^2 = 0.84$) between the amount of fluid administered in the first 6 h of the EGDT protocol and the target CVP [12]. In this analysis, targeting a CVP of 15 mmHg will result in the administration of approximately 5 L of fluid within 6 h [12]. It is noteworthy that in the Australian Resuscitation in Sepsis Evaluation (ARISE) trial, patients in both arms of the study received on average 4.4 L of fluid from the time of hospital admission to 6 h after enrolment in the study [14]. In the ARISE study, the CVP in both the EGDT arm and the "usual care" arm at 6 h, was approximately 12 mmHg. These findings suggest that the EGDT protocol has influenced "usual care", in that physicians seem compelled to target a CVP of 12 mmHg in patients with sepsis, regardless of their hemodynamic profile. Such an approach will predictably lead to volume overload. Kelm and colleagues evaluated the fluid status of 405 patients with severe sepsis and septic shock, who were resuscitated according to the EGDT approach [21]. In this study, 67% of patients had clinical evidence of fluid overload at 24 h, with fluid overload being an independent predictor of mortality.

The second important finding of our analysis was that the severity-adjusted mortality was significantly increased in patients who received more than 5 L of fluid on the first ICU day (see Fig. 2; Table 3). This applied to the entire cohort as well as all patient groups except those who did not require mechanical ventilation and were not in shock (see Fig. 3). In addition, there was a significant increase in hospital costs for those patients receiving greater than 5 L of fluid on the first ICU day (see Supplementary Fig. 1). It is noteworthy, that in the entire cohort low volume resuscitation (1–4.99 L) was associated with a small but significant reduction in mortality. This finding contradicts the well-established dogma that

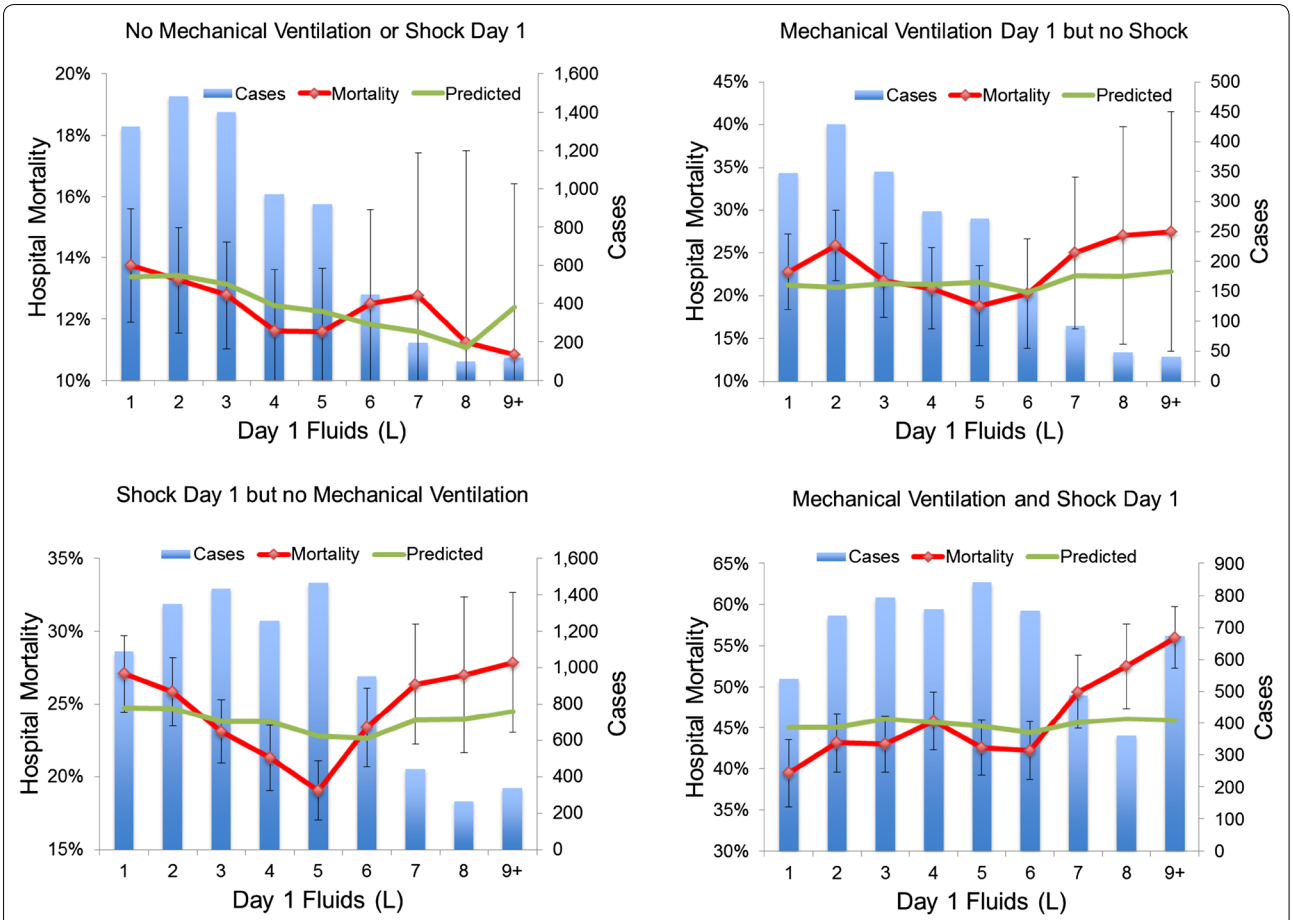

Fig. 3 Hospital mortality by day 1 fluid groups, across day 1 mechanical ventilation and shock categories

Table 3 Low volume and high volume fluid resuscitation by day 1 fluid administered

	No mv, no shock	MV, no shock	No mv, shock	MV & shock	All
Count	6970	2012	8583	5948	23,513
%	29.6%	8.6%	36.5%	25.3%	
Low volume resuscitation (1–5 L)					
Mortality effect per added litre	−0.3%	−1.4%	−1.5%	0.8%	−0.7%
95% CI	[−0.4%, −0.1%]	[−2.5%, 0.2%]	[−1.6%,−1.4%]	[−0.4%, 1.9%]	[−1.0%, −0.4%]
R^2	70	51	99	12	81
p	0.0490*	0.1080	0.0002*	0.2997	0.0234*
High volume resuscitation (5 to ≥9 L)					
Mortality effect per added litre	−0.2%	2.0%	1.7%	3.4%	2.3%
95% CI	[−0.9%, 0.5%]	[1.4%, 2.7%]	[0.7%, 2.7%]	[2.6%, 4.2%]	[2.0%, 2.5%]
R^2	10	90	74	95	99
p	0.6086	0.0087*	0.0397	0.0036*	0.0003*

* indicates statistical significance

under-resuscitation increases the risk of organ failure and death [23, 24]. Those patients not mechanically ventilated and without shock had no indication of over-resuscitation (there was no trend for higher than expected mortality as day 1 fluid increased past 5 L). In this group, there was no significant effect on the high end largely because there

were very few patients getting larger day 1 volumes. On the lower fluid use end of this population, there is a small decrease in mortality of 0.3% for each litre of fluid up to five, which would be at most a 1.5% mortality benefit of less day 1 fluid. Those mechanically ventilated (two of the subgroups) have no under-resuscitation effect but an over-resuscitation signal, which was much larger for those with shock. Important here is that the incremental effect is present even with moderately higher fluid use beyond 5 L. Those with shock but without mechanical ventilation have strong signals for both over- and under-resuscitation. The finding that day 1 fluid administration in excess of 5 L is associated with an increased risk of death is supported by multiple studies, which have demonstrated an independent association between increasing fluid balance and mortality [20, 22, 25–30]. However, unlike previous studies, we used mathematical modelling to compare expected with actual mortality, thereby correcting for illness severity and studied subgroups according to the use of mechanical ventilation and the presence or absence of shock. Acheampong and Vincent demonstrated that the daily fluid balance was more than twice as large in the non-survivors as in the survivors and that persistence of a positive fluid balance over time was associated with increased mortality [20]. In patients resuscitated using the EGDT protocol, Sadaka et al. reported that a more positive fluid balance at 24 h was associated with an increased risk of death [19]. The most compelling data that fluid loading in sepsis is harmful comes from the landmark "Fluid Expansion as Supportive Therapy (FEAST)" study performed in 3141 sub-Saharan children with severe sepsis. In this randomized study, aggressive fluid loading was associated with a significantly increased risk of death [31]. A number of studies have recently evaluated a conservative fluid or deresuscitative strategy following the initial resuscitation phase of critical illness [32, 33]. The CLASSIC study randomized 150 patients with septic shock to a fluid restrictive or standard care protocol after initial resuscitation in the ICU [32]. While the incidence of worsening kidney function was significantly less in the fluid restrictive group there was no significant difference in 90-day mortality. Silversides et al. performed a meta-analysis of 11 randomized trials comparing a conservative to a more liberal fluid strategy in 2015 patients with sepsis or acute respiratory distress syndrome (ARDS) [33]. These authors demonstrated a non-significant trend towards a reduced mortality in patients treated with a conservative as compared to a liberal strategy or usual care; however, the ICU LOS was significantly reduced and the number of ventilator-free days was significantly greater in the patients treated with the conservative fluid strategy. While the results of these studies are consistent with the findings of our current study, they are limited by the small sample size [32, 33] and significant patient and study heterogeneity [33].

Our study has several limitations, which should be acknowledged. Since administered fluid is reported by day (rather than 24 h intervals) the total amount of fluids administered may be underestimated. The study examined fluid administration during the first day only; inferences regarding the impact of cumulative fluid balance or the impact of subsequent fluid management on outcome, cannot be determined. Septic patients who were given fluids in the Emergency Department and did not require ICU admission were not captured in our database. This may be important as Emergency Department fluid resuscitation practice may prevent some patients from requiring ICU admission, and be an important consideration in deciding whether conservative or liberal practice is most appropriate. Furthermore, we did not evaluate the effect of different proportions of Ringers lactate and Normal Saline on the interaction between the volume of fluid administered and outcomes [34]. We evaluated the absolute volume of fluid used rather than the relative volume corrected for body weight (i.e. ml/Kg). However, in the real-world fluid is usually administered per bag (i.e. 1 L bags) rather than per body weight. Our study reflects only 1 year of practice in the USA, which preceded publication of the ProCESS, ARISE and ProMISe trials [13–15]; the impact of these trials on current practice remains unknown. However, the patient characteristics, outcomes and three-day fluid use in our cohort was very similar to the three arms of the ProCESS trial as well as the ARISE and ProMISe trials, suggesting our final cohort is likely representative of current practice (see Supplementary Table 5). It is important to emphasize that our model does not adjust for physiological derangements that are the markers of illness severity and are likely to influence clinical decisions to administer fluid. It is plausible that the higher fluid volume reflects more deranged physiology at the time fluid therapy is administered and that this is the explanation for the increased risk of death observed with large volume resuscitation. Finally, it is important to characterize the results of this study as descriptive and not causal and the findings require validation in an independent database.

In conclusion, we have demonstrated the average day 1 fluid administration in patients with severe sepsis and septic shock, treated in a broad spectrum of hospitals in the USA, averages about 4.4 L, which is considerably less than that currently recommended. Furthermore, patients receiving more than 5 L of fluid during this time, regardless of illness severity, have an increased risk of death and higher hospital costs.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4675-y) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

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Conflicts of interest
Doctors Marik, Linde-Zwirble and Bittner have no conflicts to declare. Dr. Hansell and Ms. Sahatjian are employees of Cheetah Medical, the manufacturer of the NICOM hemodynamic device.

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