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Evaluation of the Recommended 30 cc/kg Fluid Dose for Patients With Septic Shock and Hypoperfusion With Lactate Greater Than 4 mmol/L

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OBJECTIVES: The Surviving Sepsis Campaign Guidelines recommend fluid administration of 30 cc/kg ideal body weight (IBW) for patients with sepsis and lactate greater than 4 mmol/L within 3 hours of identification. In this study, we explore the impact of fluid dose on lactate normalization, treatment cost, length of stay, and mortality in patients with lactate greater than 4.

DESIGN: Multicenter retrospective observational study.

SETTING: Eight-hospital urban healthcare system in Northeastern United States.

PATIENTS: Patients with sepsis, initial lactate value greater than 4 mmol/L, and received appropriate antibiotics within 3 hours.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We stratified patients into five groups based on the dose of fluid administered within 3 hours after sepsis identification. The groupings were less than 15 cc/kg IBW, 15.1–25 cc/kg IBW, 25.1–35 cc/kg IBW, 35.1–50 cc/kg IBW, and greater than 50 cc/kg IBW. We used the group that received a fluid dose of 25.1–35 cc/kg IBW, as a reference group. The mean age was 66 years, and 56% were male. Three hundred seventy-one (25%) received less than 15 cc/kg of IBW of crystalloid fluid, 278 (17%) received 15–25 cc/kg of IBW, 316 (21%) received 25.1–35 cc/kg of IBW, 319 (21%) received 35.1–50 cc/kg of IBW, and 207 (14%) received greater than 50 cc/kg of IBW. After multilinear regression, there was no significant difference in lactate normalization between the reference group and any of the other fluid groups. We also found no statistically significant difference in the observed/expected cost, or observed/expected length of stay, between the reference group and any of the other fluid groups. Mortality was higher among patients who received greater than 50 cc/kg IBW when compared to the recommended dose.

CONCLUSIONS: In patients with sepsis and lactate value greater than 4 mmol/L, high or low fluid doses were not associated with better lactate clearance or patient outcomes. Greater than 50 cc/kg IBW dose of fluids within 3 hours is associated with higher mortality.

KEY WORDS: fluid administration; lactate normalization; outcomes; resuscitation; septic shock

Sepsis, a life-threatening condition that results from the bodies' abnormal response to infection (1), affects millions each year leading to high morbidity and enormous burden on the healthcare system (2–4). Septic shock, a more severe form of sepsis, causes circulatory, cellular, and metabolic abnormalities profound enough to substantially increase mortality. Septic shock is associated with mortality of up to 25%. The benefit of early goal-directed therapy

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KEY POINTS

Question: Does the dose of crystalloid fluids administered impact lactate normalization or patient outcomes in patients with sepsis with a lactate greater than 4 who received appropriate antibiotics within 3 hours of sepsis onset.

Findings: When compared to patients who received fluid dose of 25–35 cc/kg ideal body weight (IBW), higher or lower doses of fluids were not associated with higher rate of lactate normalization. Patients who received fluid dose of greater than 50 cc/kg IBW had a higher mortality.

Meanings: The Surviving Sepsis Campaign recommended dose of 30 cc/kg IBW of fluid administration needs to be validated with randomized controlled trials. Fluid dose greater than 50 cc/kg IBW should be avoided as it leads to an increase in mortality.

for septic shock has undergone reevaluation in recent years in the setting of multiple randomized controlled trials failing to show a mortality benefit (5).

The Surviving Sepsis Campaign (SSC), which serves as an important cornerstone for establishing and updating guidelines for sepsis management, recommends that an initial dose of 30 cc/kg crystalloid fluid be administered within the first 3 hours of septic shock diagnosis (3).

At most hospitals in the United States, practice patterns for the management of sepsis and septic shock are guided by the Centers for Medicare and Medicaid Services (CMS) Inpatient Quality Reporting Metric mandate, the Severe Sepsis and Septic Shock Management Bundle (SEP-1). SEP-1 Sepsis Core Measure also mandates the administration of 30 cc/kg of fluids for patients with lactate value greater than 4 mmol/L, within 3 hours of identification (6) (**Fig. 1**).

Both the SSC and SEP-1 recommendations on fluid administration in septic shock are based on observational data and lack definitive evidence. This guidance has been challenged by several papers in the literature, which have linked excess fluid administration to increased mortality through edema and organ dysfunction (7–9).

Three randomized controlled trials on septic shock treatment, A Randomized Trial of Protocol-Based Care for Early Septic Shock, The Australasian Resuscitation in Sepsis Evaluation, and Protocolized Management In Sepsis, did not study impact of fluid dose, as patients in all arms were administered 4–5 L prior to randomization (10).

In 2020, the SSC published areas of research priorities in fluid resuscitation and vasopressor therapy. The article identified the following two questions as research priorities among others: 1) what are the ideal endpoints for volume resuscitation and how should volume resuscitation be titrated and 2) what is the optimal fluid volume for sepsis resuscitation (11).

In this article, we evaluate the impact of different fluid dose ranges in patients with septic shock, defined by lactate level greater than 4 mmol/L, on lactate normalization and patient outcomes.

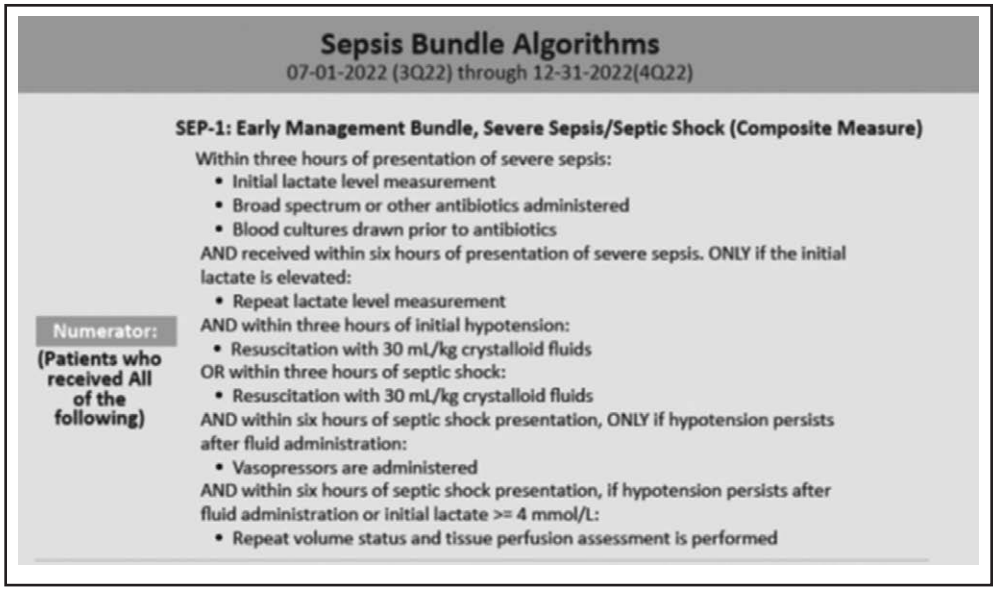

Figure 1. The Severe Sepsis and Septic Shock Management Bundle (SEP-1) 3- and 6-hr sepsis bundle.

METHODS

Setting

We conducted a multicenter retrospective observational study of an eight-hospital urban healthcare system in Northeastern United States. The hospital system adopted the CMS SEP-1 bundle as the standard of care for septic shock in 2015. Performance improvement teams were organized

centrally and at each hospital that was responsible for implementing and measuring SEP-1 bundle compliance. Each hospital was responsible for developing its own implementation workflow. As part of the quality improvement effort, a database was developed with data from all eight hospitals to monitor SEP-1 compliance and patient outcomes.

A sepsis Early Warning System (EWS), called St John's Alert (Cerner Corporation, Kansas City, MO), was embedded in the electronic health record at all hospitals (12). The EWS uses the American College of Chest Physicians/Society of Critical Care Medicine Sepsis 2 definition from 2001 to screen patients at risk for sepsis using systemic inflammatory response syndrome criteria and markers of end-organ dysfunction (13).

Data Collection and Definitions

We pulled data from the sepsis quality improvement database at all hospitals. Data elements pulled included demographics, time of sepsis alert (onset), initial and subsequent lactate levels within 6 hours, discharge diagnosis, and administration times for each SEP-1 bundle element including type and dose of fluids administered.

We collected data on cost of care, outcome, and severity of illness from the Vizient Clinical Database/Resource Manager (used by permission of Vizient, Tx, all rights reserved). Vizient is an alliance of 117 U.S. academic medical centers and 300 of their affiliated hospitals. Members that participate in the clinical database/resource manager submit demographic data, medication data, and up to 99 *International Classification of Diseases* diagnosis and procedure codes per encounter for all inpatient and outpatient encounters. Vizient performs rigorous quality assessments of submitted data before the data are loaded into the clinical database/resource manager. Vizient also calculates a severity-of-illness score, which accounts for demographic variables, hospital diagnoses, and comorbid conditions that were present upon hospital admission. The Vizient dataset has been used in a range of scientific studies and quality improvement initiatives, us, and others have published previously using the Vizient severity of illness metrics (14–16).

Patient Selection

Patients who were admitted to one of the eight hospitals in the network between January 1, 2016, and January 31, 2020, were evaluated for the study. Our inclusion criteria were: 1) patients with a primary or secondary discharge diagnosis of sepsis by Diagnosis-Related Groups code (870–872); 2) sepsis onset time was documented by the sepsis EWS, "Alert"; 3) a lactate value drawn 60 minutes before or 180 minutes after the Alert was greater than 4 mmol/L; and 4) patient received appropriate broad spectrum antibiotics within 3 hours after the Alert, which met CMS SEP-1 criteria. Exclusion criteria were age below 18 years.

The start time of the study was selected due to the start of data availability in the database. The end of the study period was selected to analyze outcomes before the onset of the COVID-19 pandemic in the region as hospital and ICU capacity were impacted thereafter by the pandemic.

Study Design

We stratified patients into five groupings based on the dose of fluid administered within 3 hours after the "Alert." The groupings were less than 15 cc/kg ideal body weight (IBW), 15.1–25 cc/kg IBW, 25.1–35 cc/kg IBW, 35.1–50 cc/kg IBW, and greater than 50 cc/kg IBW. We included all crystalloids administered including normal saline, lactated ringers, and balanced solutions. We used the group that received a fluid dose of 25.1–35 cc/kg IBW, "Recommended Dose," as a reference group given the SSCs fluid dose recommendation for septic shock and sepsis induced hypoperfusion with lactate greater than 4 mmol/L. We compared outcomes against the recommended dose group. Time of St John's Sepsis Alert was defined as the time of onset of sepsis.

Our primary outcome was lactate normalization within 6 hours. Lactate normalization was defined as a lactate result less than 2 mmol/L within 3–6 hours after identification of sepsis-induced hypoperfusion. Our secondary outcomes were hospital cost (observed/expected ratio), hospital length of stay (observed/expected ratio), and hospital mortality or hospice transfer. For length of stay analysis, patients who died or were transferred to hospice were assigned a length of stay at 95% of the longest length of stay among study patients to correlate with a poor outcome. Patients who died or were transferred to hospice were also assigned a cost at the highest 95% among study patients.

Statistical Analysis

Comparison of baseline characteristics was performed using Fisher exact test for categorical variables, analysis of variance for continuous variables with normal distribution and the Kruskal-Wallis test for continuous variables with non-normal distribution. Logistic regression model was used to assess effect of fluid dosage on lactate normalization. All groups were compared with the group that received 25.1–35 cc/kg IBW fluid per current guidelines. Multivariable linear regression analysis was performed and adjusted odds ratios were calculated accounting for baseline characteristics, which were significantly different between each of the fluid dose grouping.

The test for secondary outcomes variables of continuous measures was conducted using Kruskal-Wallis test and using Fisher exact test for categorical outcomes. Ratio of observed versus expected length of stay and observed versus expected direct cost were calculated. Multivariable linear regression analysis was conducted for the ratio of observed versus expected length of stay and direct cost. Both were log transformed to reduce skewness in the data. Multivariable logistic regression was conducted for mortality/hospice. All models were adjusted using the same variables used to adjust the primary outcome.

The study was submitted to MedStar Health Research Institute Institutional Review Board (IRB) under the title "Dose and Timing of Fluid Administration and Outcomes for Severe Sepsis and Septic Shock." The board provided study approval and waiver for informed consent on April 13, 2020, under IRB Identification STUDY00002158 in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

RESULTS

Across the eight hospital centers, 2,300 patients met all four inclusion criteria and were evaluated for the study. Of these, 254 patients were excluded because a second lactate level was not measured within 6 hours of Sepsis Alert, and 555 patients were excluded because a fluid bolus was not administered within 3 hours after the Alert. Subsequently, 1,491 were included into the final analysis (**Fig. 2**).

Among the 1,491 patients, 371 (25%) received less than 15 cc/kg of IBW of crystalloid fluid, 278 (17%) received 15–25 cc/kg of IBW, 316 (21%) received 25.1–35 cc/kg of IBW, 319 (21%) received 35.1–50 cc/kg of IBW, and 207 (14%) received greater than 50 cc/kg of IBW.

As shown in **Supplemental Table 1** (http://links.lww.com/CCX/B207), the majority of patients were male (56%), with a mean age of 66 ± 15.96 years. Over half of the patients were African American in all treatment groups, and more than 95% of all patients were of non-Hispanic ethnicity. More than 64 % of patients had Medicare insurance. There were no statistically significant differences in age, gender, race, ethnicity, year of admission, or type of insurance between the five treatment groups. As hospital sizes differed in bed capacity, the majority of patients were admitted to the larger hospitals. Sepsis was present at the time of admission in more than 93% of the cases, with higher occurrence of sepsis at admission in the higher fluid dose groups. Between 4% and 37% of patients

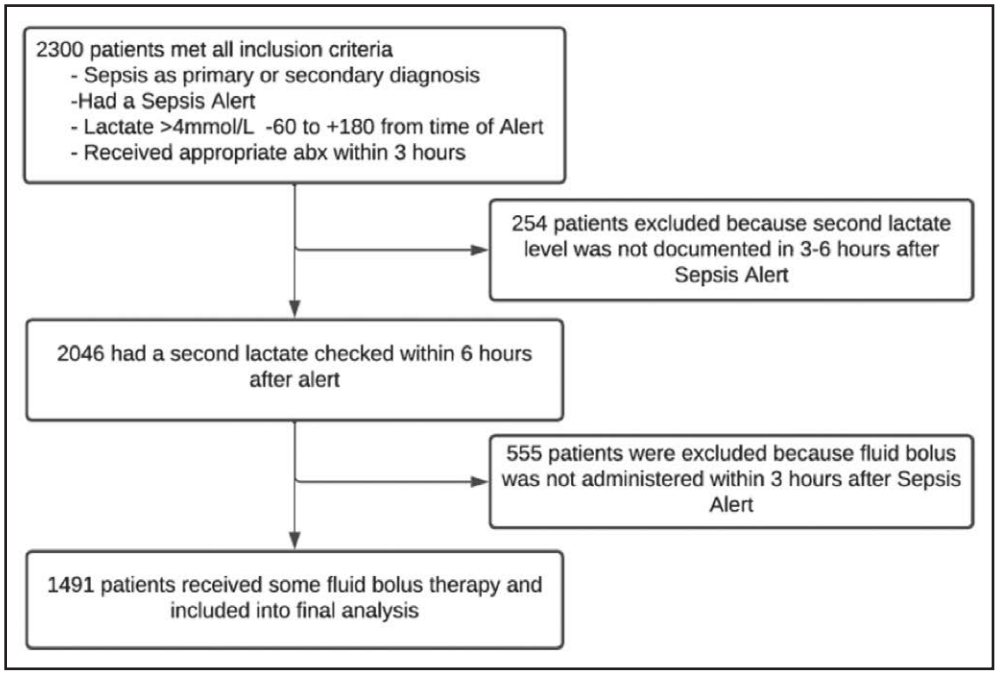

Figure 2. Patient enrollment. abx = antibiotics.

had sepsis diagnosed on the hospital wards for each group, while the majority of cases were diagnosed in the emergency department or an observation area. Patients were significantly more likely to be identified with sepsis in an inpatient unit in the groups that received either less than 15 cc/kg IBW or 15–25 cc/kg IBW than the higher dose groups ($p < 0.001$). Vizient based severity of illness was highest in the lowest fluid and highest fluid administered groups, which was statistically significant (Supplemental Table 1, http://links.lww.com/CCX/B207).

In primary analysis, lactate normalization was observed in only 14.5% of all patients. Multilinear regression was performed adjusting for baseline characteristics, which were significantly different between groups (i.e., the hospital, sepsis presence at admission, time to antibiotics, and severity of illness). After adjustments, when compared with the reference group that received 25–35 cc/kg IBW fluid bolus, there were no significant differences in lactate normalization in lower or higher fluid administration groups (**Table 1**).

In secondary analysis, the median overall length of stay was 15 days, median observed/expected length of stay was 1.67 days, and the median unadjusted cost for all patients was $19,061.50. After adjusting for the variables that were significantly different between the baseline groups, there were no statistically significant differences in the observed/expected length of stay, or observed/expected direct cost between the recommended fluid dose group and any of the lower or higher fluid dose groups.

Mortality was 35% among all patients. After adjusting for baseline characteristics that showed a statistically significant difference between the groups, mortality was highest among patients who received greater than 50 cc/kg IBW when compared with the recommended dose. However, there was no difference in mortality rates among the other fluid administration groups and the recommended fluid group (**Table 2**).

TABLE 1.
Primary Outcomes

Fluid Dose Administered	Lactate Normalization, *n* (%)			
	No	Yes	OR	*p*
All	1,275 (85.5)	216 (14.5)		
< 15 cc/kg IBW	325 (87.6)	46 (12.4)	0.969	0.268
15–25 cc/kg IBW	243 (87.4)	35 (12.6)	0.955	0.121
Reference: 25.1–35 cc/kg IBW	258 (81.6)	58 (18.4)	–	–
35.1–50 cc/kg IBW	265 (83.1)	54 (16.9)	0.993	0.813
> 50 cc/kg IBW	184 (88.9)	23 (11.1)	0.939	0.054

IBW = ideal body weight, OR = odds ratio.
Lactate clearance within 6 hr.
Dashes indicate statistical significance of $p = 0.05$.

DISCUSSION

In this multicenter observational study, we explored the impact of fluid dose in patients with septic shock and sepsis induced hypoperfusion with a serum lactate greater than 4 mmol/L, on lactate normalization, cost, length of stay, and mortality. Our analysis showed that very high fluid dose (> 50 cc/kg IBW) is independently associated with higher mortality when compared with the recommended fluid dose of 25–35 cc/kg IBW. However, we found no differences between recommended fluid dose (25–35 cc/kg IBW) and lower or slightly higher fluid doses in any of our primary or secondary outcomes.

Our findings are consistent with several studies that have raised concerns about a fluid dose recommendation that is not supported by well-designed randomized controlled trials. In a smaller prospective study, Antal et al (17) have recently reported that there was no difference in urine output outcome at 24 hours or 28-day mortality between patients that received the SSC recommended dose of fluid and those that did not. An earlier study in 2016, done in different population with malaria in a resource poor setting, showed that total fluid balance at discharge greater than 10 L was an independent predictor of ICU mortality, hospital mortality, and new organ dysfunction at discharge (9). To that end, Marik and Bellomo (18) have argued that sepsis is primarily not a volume-depleted state and most septic patients are poorly responsive to fluids. They have postulated that administered fluid is sequestered in the tissues, resulting in severe edema in vital organs and, thereby, increasing the risk of organ dysfunction. Our data further provides evidence of significant increase in mortality for septic patients receiving a high dose of administered fluid (> 50 cc/kg IBW).

TABLE 2.
Secondary Outcomes After Multilinear Regression Adjustment

Fluid Dose in cc/kg IBW	Overall	< 15 cc/kg IBW	15–25 cc/kg IBW	25.1–35 cc/kg IBW ([a]Reference)	35.1–50 cc/kg IBW	> 50.1 cc/kg IBW
n	1,491	316	371	278	319	207
LOS						
Expected LOS, d, median (IQR)	6.81 (5.30–11.03)	6.53 (5.18–10.92)	7.67 (5.59–12.71)	6.89 (5.39–10.51)	6.37 (5.18–10.00)	6.89 (5.30–10.83)
Observed LOS, d, median (IQR)	15.00 (7.00–34.50)	22.00 (8.00–34.50)	16.50 (6.00–34.50)	13.00 (6.00–34.50)	13.00 (6.00–34.50)	17.00 (7.00–34.50)
Observed/expected ratio, median (IQR)	1.67 (0.91–3.90)	1.99 (0.97–4.04)	1.66 (0.89–4.36)	1.56 (0.86–3.32)	1.52 (0.86–3.50)	1.73 (1.01–4.28)
% change from reference	–	−4.5	−5.9	1.43	−2.2	−1.6
p	–	0.302	0.194	0.044	0.660	0.833
Cost						
Expected direct cost, dollars, median (IQR)	9,784.50 (6,738.25–17,447.25)	8,485.00 (6,125.50–16,877.00)	11,943.00 (7,584.75–21,318.25)	9,497.00 (6,622.25–15,544.25)	8,722.50 (6,401.00–15,181.50)	10,046.50 (7,130.50–17,957.00)
Observed direct cost, dollars, median (IQR)	19,061.50 (7,806.50–52,470.65)	34,265.00 (11,017.25–52,470.65)	20,033.00 (7,603.00–52,470.65)	14,703.50 (6,604.50–52,470.65)	14,234.00 (6,913.00–52,470.65)	23,680.00 (8,390.00–52,470.65)
Direct cost observed/expected ratio, median (IQR)	1.38 (0.78–3.66)	1.49 (0.86–3.80)	1.48 (0.79–4.25)	1.30 (0.74–2.85)	1.32 (0.70–3.19)	1.43 (0.79–3.75)
Change from reference, %	–	0.5	7.9	1.24	2.0	15.6
p	–	0.937	0.284	0.443	0.767	0.061
Mortality and hospice						
Expired or hospice[b] (%)	35.3	28.8	41.0	37.1	30.7	39.6
Odds ratio (95% CI)	–	1.026 (0.959–1.098)	1.064 (0.991–1.1441)	–	1.016 (0.95–1.088)	1.104 (1.023–1.192)
p	–	0.461	0.086	–	0.636	0.011

IBW = ideal body weight, IQR = interquartile range, LOS = length of stay.

[a]The group with fluid dose 25.1–35 cc/kg group was used as the reference group.

[b]Values for expired/hospice LOS and direct cost were replaced with the 95th percentile highest value for the group.

Dashes indicate statistical significance of $p = 0.05$.

Additionally, recent studies have recommended a transition to an earlier vasopressor initiation in septic shock. One prospective study that looked at initiating vasopressors, even without completing the initial fluid loading, resulted in less resuscitation fluids within 8 hours with a significant reduction in risk of death at day 28 (19). Of course, we are not suggesting vasopressors for elevated lactate only as that study was implemented for hypotension.

The literature has demonstrated that lactate clearance is associated with improved outcomes (20, 21). In our study, only a very small percent achieved lactate normalization within 6 hours regardless of fluid dose. Surprisingly, higher doses of fluids were not associated with higher lactate normalization. This finding is corroborated by the explanation that lactate elevation is not only due hypoperfusion but also due to microcirculatory and mitochondrial hypoxia (22).

Lactate normalization is indeed not always achieved within 6 hours but lactate improvement is often seen after fluid resuscitation. In our study, we selected lactate normalization as a primary outcome based on the study by Ryoo et al (23), which compared lactate clearance at less than 10%, less than 20%, and less than 30% versus lactate improvement to 2, 3, or 4 mmol/L within 6 hours. It showed that lactate value greater than 2 mmol/L had the greatest sensitivity (85%) in predicting mortality. While fluid administration may result in other favorable outcomes such as need for vasopressors, duration of vasopressors, or others, we selected our outcomes to be predictive of mortality because CMS SEP-1 reporting is based on mortality.

Our main takeaway from this study is that there is likely not a one size fits all fluid dose for normalization of elevated lactate in septic patients and that higher fluid doses contribute to poor patient outcomes and increased mortality rates. Both the SSC and CMS recommend assessment of tissue perfusion and volume responsiveness after the initial 30 cc/kg of fluid administration. We believe that this individualized approach is best used earlier to identify those that are fluid responders from the nonresponders. Further randomized controlled trials are needed that focus on early antibiotics, early initiation of vasopressors for hypotension, and an earlier assessment of fluid responsiveness with capitation beyond certain weight-based targets. We also believe that the recommendation for a universal weight based fluid administration should be reconsidered toward an early assessment of responsiveness and reversal of hypotension.

In contrast to our findings, other studies have shown the benefits of fluid administration. Kuttab et al (24) have demonstrated that in a population that presented with sepsis to a tertiary hospital, not achieving 30 cc/kg of fluid was associated with increased odds of in-hospital mortality.

Our study has several limitations. Even though we controlled for variations in patient demographics, treatments, hospital, as well as the severity of illness, the retrospective nature of the study can be affected by other confounding factors that were not controlled for. We did not exclude patients that had an exception to the "recommended dose" of fluids due to congestive heart failure or other reasons. However, this is less likely to impact our results as we found no additional benefit of higher doses of fluid administration.

We excluded 254 patients from analysis because a second lactate value was not available. It is possible that this group may represent a sicker or even healthier group. However, the 17% of patients without a second lactate within 6 hours is about where our second lactate compliance usually is reported at our hospitals. This is mostly due to the logistical challenges of completing elements of the bundle within the 6-hour window. We also excluded 555 patients because there was no fluid bolus administered within 3 hours. We felt this group represented a different variable than patients that received some fluid bolus. We wanted all patients included to have gone through a clinical evaluation where a provider felt some bolus of fluid was necessary within the 3-hour window. However, it is also possible that some in this group did not receive any fluid bolus because they were sicker or healthier. Both of these groups could impact the ability to identify mortality differences, as bundled treatments have been shown to be associated with improved outcomes.

Finally, it is quite plausible that there are patients that may benefit from higher or lower dose than the standard group, but our study was not powered to tease out those differences. We selected give dosing groups to investigate if there is an incremental value to fluid dosing. However, the binning of the fluid doses was not evidence-based and may force a loss of information in the boundaries. But our goal in this study was not to recommend a fluid dose, it was to investigate the

outcome benefits of the SSC fluid dose recommendation for this group (23).

The strength of our study is that it represents a real-world scenario with 15–25% of patients having received one of the five fluid dose groupings, indicating the variability in current practice. In addition, since the data are gathered from a single hospital system with a dedicated electronic dataset across all hospitals, it is likely to have minimal variations in data collection. The hospitals have also adopted the same treatment algorithm for sepsis thus leading to a reduction in variability of antibiotics administered or other factors of treatment. We have tried to control for treatment variations, including the hour of antibiotic administration. We have also used a digitally recorded alert as time of onset of sepsis thereby taking out the variability of response time as a variability in care.

CONCLUSIONS

In this study, we explored two questions that were identified by the SSC as future directions for sepsis research (11). We found that a "recommended dose" of fluids at 25–35 cc/kg of fluid/IBW for lactate elevation greater than 4 mmol/L is not better than lower or higher doses in improving lactate normalization, hospital length of stay, cost, or mortality. We also demonstrated that fluid dose greater than 50 cc/kg IBW is associated with worse patient outcomes. Given these findings, we believe fluid administration for lactate elevation to be geared toward early reversal of hypotension by using a combination of early vasopressors and response based administration of fluids. Randomized controlled trials are needed to reduce variability in care and answer this very important question.

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All authors performed work for this project from their home base institution.

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