



Adherence to fluid resuscitation guidelines and outcomes in patients with septic shock: Reassessing the “one-size-fits-all” approach☆

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ABSTRACT

Objective: The Surviving Sepsis Campaign and Centers for Medicare and Medicaid Services (CMS) Severe Sepsis and Septic Shock Management Bundle (SEP-1) recommend rapid crystalloid infusion (≥ 30 mL/kg) for patients with sepsis-induced hypoperfusion or septic shock. We aimed to assess compliance with this recommendation, factors associated with non-compliance, and how compliance relates to mortality.

Design: Retrospective, observational study.

Setting: 1136-bed academic and 235-bed community hospital (January 2015–June 2016).

Patients: Patients with septic shock.

Interventions: Crystalloid infusion (≥ 30 mL/kg) within 6 h of identification of septic shock as required by CMS.

Measurements: Associations with compliance and how compliance associates with mortality; odds ratios (OR) and 95% confidence intervals (CI) reported.

Main results: Overall, 1027 septic shock patients were included. Of these, 486 (47.3%) met the 6-hour 30 mL/kg fluid requirement. Compliance was lower in patients with congestive heart failure (CHF) (40.9%), chronic kidney disease (CKD) (42.3%) or chronic liver disease (38.5%) and among those that were identified in the inpatient setting (35.4%) rather than in the emergency department (51.7%). When adjusting for relevant covariates, compliance (compared to non-compliance) was not associated with in-hospital mortality; OR 1.03 CI 0.76–1.41.

Conclusions: These findings question a “one-size-fits-all” approach to fluid administration and performance measures for patients with sepsis.

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1. Introduction

Hospitals in New York State (NYS) are accountable to the NYSDOH and the Centers for Medicare and Medicaid Services (CMS) for the diagnosis and management of sepsis patients. In 2013, the NYSDOH began requiring hospitals to follow protocols for early diagnosis, treatment and subsequently reporting of performance measures in patients with sepsis [1]. In 2015, CMS enacted the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) performance measure and began to monitor hospital reporting of these measures [2–4]. Rapid fluid infusion (30 mL/kg) is recommended by both entities in the initial resuscitation phase for septic patients with persistent hypotension despite fluid resuscitation requiring vasopressors, or with an initial lactate ≥ 4 mmol/L [1,5–7]. This requirement is based on

early studies demonstrating a mortality benefit associated with compliance with a sepsis bundle, which included fluid administration [8,9].

There have been no definitive studies demonstrating the unequivocal benefit of fluid resuscitation as an independent intervention and the available evidence is mixed. In an observational cohort, Leisman et al. found that earlier initiation of fluid resuscitation was associated with decreased mortality but did not address the volume of resuscitation [10]. A 2017 randomized trial showed that early resuscitation with fluids and vasopressors increased in-hospital mortality compared to usual care [11]. In addition, a recent study of New York State data on 49,331 sepsis patients found that time to completion of rapid fluid infusion was not associated with sepsis mortality [12]. Given the lack of clear evidence, it is imperative to evaluate the application of these guideline recommendations in real-world clinical practice and to reassess the benefit of a ‘one-size-fits-all’ fluid resuscitation recommendation adopted by regulatory bodies.

The Mount Sinai Hospital (a large urban academic center) and Mount Sinai Queens Hospital (a community hospital) utilize a robust process based on an electronic medical record (EMR)-embedded sepsis

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screening protocol. All cases suspected of sepsis are clinically assessed and treated in real-time, and cases are retrospectively adjudicated by trained clinicians. This protocol provides a unique opportunity to assess the impact of treatment relative to clinical characteristics for patients with sepsis. We aimed to assess whether non-compliance is associated with increased mortality and study the factors associated with non-compliance with the rapid fluid infusion requirement. We hypothesized that non-compliance is not associated with mortality and clinically relevant factors contribute to non-compliance.

2. Methods

2.1. Data source and study design

In this retrospective observational study we used data from June 2014 to June 2016 from a robust process based on an automated, EMR-based sepsis screening program at a 1171-bed academic hospital and a 235-bed community hospital (see Fig. 1 for the decision algorithm). When ≥ 2 vital signs meet certain criteria, a 3-part screening questionnaire is generated in the EMR for the nurse to complete. When a patient meets ≥ 3 criteria, the EMR prompts the nurse to inform the patient's primary team and the Rapid Response Team, who then assess and treat the patient. Detailed diagnostic, treatment, and outcome data are collected prospectively as part of the institution's Sepsis Program. All cases are rigorously adjudicated retrospectively by an expert committee of trained nurses and physicians for the presence of sepsis. Patients are clinically adjudicated as severe sepsis [sepsis with hypotension (systolic blood pressure < 90 mmHg) and/or lactate ≥ 4 mmol/L] and septic shock (sepsis with hypotension not responsive to the recommended amount of fluids and requiring vasopressors). Patients were observed from time of sepsis diagnosis to either mortality or hospital discharge (median 8.1 days) and included in the study and analysis if they met the septic shock criteria (sepsis with initial lactate > 4 mmol/L and/or hypotension not responsive to fluid requiring vasopressor) [4–6].

2.2. Study intervention and variables of interest

Elements of the 3-hour and 6-hour CMS bundles are recorded. The 3-hour bundle includes blood cultures before antibiotic administration,

serum lactate, and administration of broad-spectrum antibiotics. The 6-hour bundle includes administration of a bolus of 30 mL/kg of intravenous fluids in septic shock patients, vasopressors for refractory hypotension, and a repeat serum lactate measurement.

The intervention of interest was the proportion of patients receiving 30 mL/kg of intravenous fluids during the 6-hour bundle period [T0 to T+6], defined as 'compliant' according to CMS criteria while also recognizing that clinically valid reasons (including concerns for pulmonary complications) may exist for those deemed 'non-compliant'. The primary outcome was in-hospital mortality. This outcome was chosen over intermediate outcomes (such as pulmonary and renal complications) as this is specifically captured for reporting purposes. Covariates examined were patient demographics, comorbidities (CHF, CKD, chronic liver disease, and the Charlson comorbidity index), insurance type, source of admission (home, nursing home/sub-acute rehabilitation admission, transfer, other), characteristics at time of positive screen (serum lactate, vital signs, time from admission in hours, and service [inpatient, emergency department (ED) or intensive care unit (ICU)]), compliance with 3-hour antibiotic requirement, site of infection, length of stay, and fluid resuscitation volume in three time windows (12 h before positive screen until positive screen [T-12 to T0], the 6-hour bundle time window [T0 to T+6] and the following 12 h [T+6 to T+18]).

To assess potential clinical reasons for non-compliance with the rapid fluid infusion requirement we determined the prevalence of CHF, CKD, and chronic liver disease. In addition, we assessed the fluid resuscitation volume in the T-12 to T0 and T+6 to T+18 time windows to identify potential indicators of concern for volume overload.

2.3. Sample size and statistical analyses

No a priori sample size calculation was performed. Based on an estimated overall mortality risk of 37.7% in septic shock [13], our sample size had $>99\%$ power to detect a 25% relative difference in mortality between the fluid compliant and fluid non-compliant arms; using a more conservative relative effect estimate, our sample size had 97% power to detect a 15% relative mortality difference between groups. Univariable associations between compliance with the rapid fluid infusion requirement and study variables were analyzed using the Chi-square test for categorical and the *t*-test for continuous variables; given the skewed

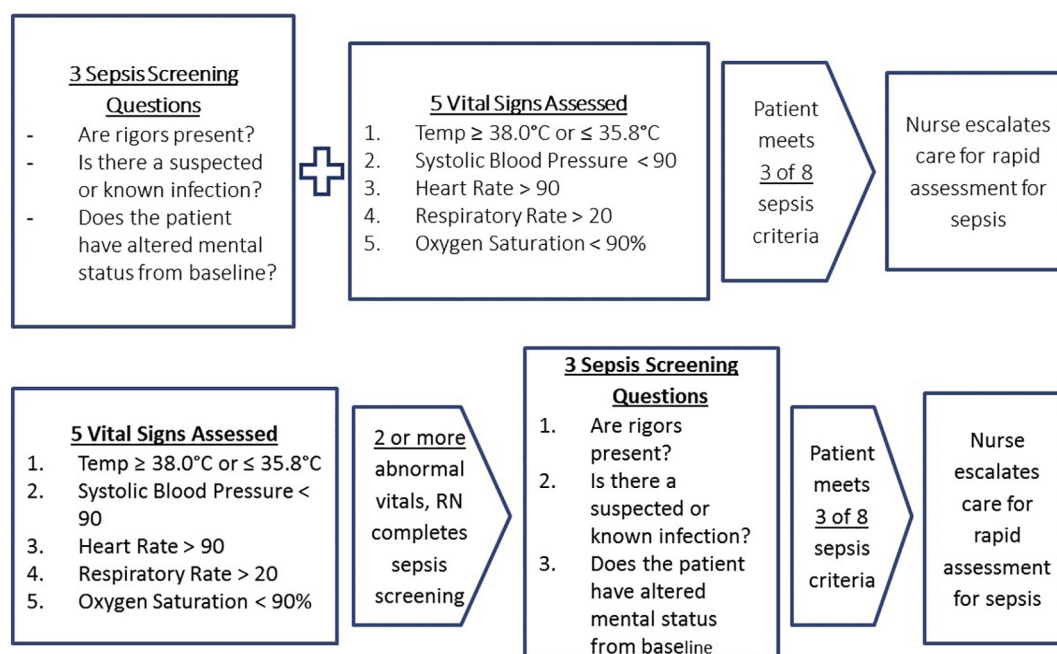


Fig. 1. Decision algorithm of the Mount Sinai EMR-based sepsis screening program.

distribution of continuous variables of interest we report medians and interquartile ranges. A multivariable logistic regression model was developed to measure the association between the rapid fluid infusion requirement compliance and in-hospital mortality. Multivariable models were adjusted for variables based on clinical and/or univariable importance at the $P < .15$ level. Odds ratios (OR) and 95% confidence intervals (CI) are reported. Analyses were performed using SAS v9.4 statistical software (SAS Institute, Cary, NC).

3. Results

Overall, 1858 patients were clinical adjudicated as having severe sepsis or septic shock. Of these, 1027 patients met the septic shock definition and were included in the analysis.

486 (47.3%) cases of septic shock were defined as compliant while 541 (52.7%) were non-compliant with the rapid fluid infusion requirement. Tables 1 and 2 show study variables by compliance. Compliance was significantly higher for patients with sepsis diagnosed in the ICU (57.5%) while significantly lower compliance was observed in patients with CHF (40.9%), CKD (42.3%), and chronic liver disease (38.5%); all $P < .05$. Compliance was also noted to be significantly lower with increasing comorbidity burden. Sepsis occurring in the inpatient setting was associated with significantly lower compliance (35.4%) compared to those screened positive in the ED (51.7%); this is consistent with the shorter median time from admission to meeting the sepsis criteria for compliant (3.5 h) compared to non-compliant (16.7 h) cases. Median fluid resuscitation volume in the T-12 to T0 window was higher in the non-compliant group, suggestive of a potential driver of decision-making regarding fluid resuscitation in the T0 to T + 6 time window.

Table 3 shows results from the multivariable model. When adjusting for relevant covariates, compliance with the fluid metric was not significantly associated with in-hospital mortality for patients with septic shock (OR 1.03 CI 0.76–1.41). Higher adjusted odds for mortality were seen for cases that screened positive in the ICU setting, patients with a respiratory source of infection and those with chronic kidney or liver diseases. The corresponding model c-statistic was 0.79, indicating

Table 1
Demographics and comorbidities by compliance with the fluid metric.

	Septic shock compliance with fluid metric				P-value ^b
	Yes (n = 486)		No (n = 541)		
	n	%	n	%	
Cohort					
Septic shock	486	47.3%	541	52.7%	–
Demographics					
Median age ^a	68	58–80	66	56–77	0.1082
Gender					0.0095
Female	245	51.7%	229	48.3%	
Male	241	43.6%	312	56.4%	
Race					0.7514
White	178	48.0%	193	52.0%	
Non-White	308	47.0%	348	53.0%	
Insurance type					0.4682
Commercial	147	48.0%	159	52.0%	
Medicaid	72	45.3%	87	54.7%	
Medicare	186	45.6%	222	54.4%	
Other	81	52.6%	73	47.4%	
Comorbidities					
Congestive heart failure	110	40.9%	159	59.1%	0.0140
Chronic kidney disease	143	42.3%	195	57.7%	0.0242
Chronic liver disease	80	38.5%	128	61.5%	0.0042
Charlson comorbidity index					0.0006
0	95	61.7%	59	38.3%	
1	100	57.8%	73	42.2%	
2	109	53.7%	94	46.3%	
≥2	629	47.4%	699	52.6%	

^a Median and interquartile range instead of N and %.

^b Chi2-test for categorical variables; t-test for continuous variables.

Table 2

Episode related characteristics by compliance with the fluid metric.

	Compliance with fluid metric				P-value ^b
	Yes (n = 486)		No (n = 541)		
	n	%	n	%	
Episode related					
Source of admission					0.0265
Home	290	45.0%	354	55.0%	
Nursing home/SAR admission	131	56.0%	103	44.0%	
Transfer	61	43.6%	79	56.4%	
Other	4	44.4%	5	55.6%	
At time of positive screen (T0)					
Median serum lactate value ^a	4.1	2.0–5.9	4.7	4.0–6.1	<0.0001
Median systolic blood pressure ^a	96	83–117	96	82–122	0.5580
Median heart rate ^a	96	83–117	96	64–100	0.5706
Median time from admission (hours) ^a	3.5	0.4–101.3	16.7	2.1–169.1	<0.0001
Service					<0.0001
Inpatient	123	35.4%	224	64.6%	
Emergency Department	252	51.7%	235	48.3%	
ICU	111	57.5%	82	42.5%	
Compliance with 3-hr antibiotic requirement	350	52.1%	322	47.9%	<0.0001
Site of infection					0.5518
Respiratory	192	48.5%	204	51.5%	
Urinary	73	51.8%	68	48.2%	
Gastrointestinal	113	47.5%	125	52.5%	
Skin	30	42.3%	41	57.7%	
Central nervous system	2	28.6%	5	71.4%	
Other/Unknown	76	43.7%	98	56.3%	
Median length of stay ^a	11	5–24	12	6–25	0.1912
Discharge status					0.7378
Home	129	49.2%	133	50.8%	
Hospice	40	51.3%	38	48.7%	
Died during hospitalization	179	46.3%	208	53.7%	
Other	138	46.0%	162	54.0%	
Median fluid resuscitation (mL) ^a					
T-12 to T0	1000	1000–2000	2000	1000–2500	0.0281
T0 to T+6	3000	1500–4000	1000	0–1500	<0.0001
T+6 to T+18	0	0–1000	0	0–1000	0.0063

^a Median and interquartile range instead of N and %.

^b Chi2-test for categorical variables; t-test for continuous variables.

adequate model discrimination. Of note, patient casemix differences between the two hospitals (slightly healthier patients in the community hospital) were adjusted for in the multivariable analysis thus limiting its effect.

4. Discussion

Using data from an academic hospital and a community hospital, we evaluated real-world application of guideline recommendations regarding fluid resuscitation in sepsis patients. We found that despite current guidelines and hospital-based protocols, less than one-half of patients with septic shock received the CMS recommended fluid volume during the 6-hour bundle period. Non-compliance with the rapid fluid infusion requirement was more common for patients with CHF, CKD, chronic liver disease and those with a higher comorbidity burden, suggesting that concern for volume overload may have been a driver of non-compliance. In addition, patients labeled as non-compliant screened positive for sepsis at a later point during hospitalization and received a higher volume of fluids before T0, further suggestive of concerns for volume overload. Importantly, independent of these group differences, compliance with the fluid metric was not significantly associated with in-hospital mortality.

Table 3

Multivariable model demonstrating the association between fluid metric compliance (and additionally selected key variables) and in-hospital mortality.

	Septic shock	
	OR	95% CI
Compliance with fluid metric	1.03	0.76–1.41
Compliance with antibiotic metric	0.90	0.65–1.23
Comorbidities		
Congestive heart failure	1.00	0.70–1.42
Chronic kidney disease	1.80*	1.28–2.54
Chronic liver disease	2.02*	1.38–2.96
Episode related		
Source of admission		
Home	REF	–
Nursing home / SAR admission	1.38	0.95–2.00
Transfer	1.41	0.89–2.23
Other	0.35	0.06–1.92
Service at time of positive screen (T0)		
Emergency Department	REF	–
Inpatient	1.18	0.79–1.77
ICU	1.68*	1.06–2.66
Site of infection		
Respiratory	REF	–
Urinary	0.33*	0.20–0.54
Gastrointestinal	0.81	0.54–1.20
Skin	0.49*	0.26–0.92
Central nervous system	1.70	0.33–8.85
Other/Unknown	0.83	0.54–1.28

REF: reference.

Models adjusted for: age, gender, race, Charlson comorbidities, payer, lactate value, systolic blood pressure, heart rate, time from admission, length of stay, and fluid resuscitation before T0 (T–12 to T0).

* $P < .05$.

The fluid compliance rate in our cohort was slightly lower than the 56% previously reported for patients with severe sepsis or septic shock diagnosed in the ED or ICU [8] and similar to the 51% compliance rate from the New York State Department of Health data [14]. Few studies have focused on the reasons behind suboptimal compliance with the fluid metric in sepsis patients. Potential causes may be lack of knowledge of the guideline or protocol, inadequate systems to promote compliance, in response to a lack of substantial high-quality evidence supporting the fluid requirement in sepsis, or clinical judgment necessitating a deviation from the protocol due to concerns for fluid overload. We suspect that clinicians' individualized treatment decision based on a patient's clinical performance is common. For example, if patients are at risk for or are showing signs of pulmonary complications or are hemodynamically improved with less than the recommended amount of fluid, clinicians may be hesitant to give additional fluid to fulfil the core measure. To date, there has only been observational data based on bundle compliance to support the fluid measure [8,9,15]. Prior studies have shown that septic patients with a positive fluid balance have increased fluid-related pulmonary complications and required more interventions to decrease the fluid burden, which may support a clinical decision to administer less fluids than the amount recommended by guidelines [16,17]. The lack of an association of fluid compliance with mortality in our study is consistent with findings by Seymour et al., who found no association between the timing of fluid administration and mortality [12]. Finally, a recent systematic review by Pepper et al. concluded that there is no high- or moderate-level evidence to support improved survival in adult with sepsis regarding SEP-1 hemodynamic interventions [18]. Importantly, this discussion is ongoing and has recently shifted towards the potential for harm [19,20].

Our finding that non-compliance was more common for patients with CHF, CKD, chronic liver disease and those with a higher comorbidity burden suggests that clinicians are making individualized decisions on fluid resuscitation based on unique patient characteristics. The difference between the CMS and NYSDOH fluid recommendations is that the

NYSDOH allows for exemption based on a clinician's assessment that the recommended amount of fluid is not clinically indicated. The lower compliance in the above groups of patients likely reflects this difference. Septic patients are often hypovolemic due to decreased intake and increased losses, and sepsis-induced vasoplegia and venodilation lead to reduced cardiac preload and cardiac output [21]. The rationale for fluid resuscitation is to restore preload and optimize cardiac function. However, patients with CHF and CKD may be volume-overloaded, and therefore may not be fluid responsive [21]. Moreover, prior evidence suggests that a positive fluid balance in septic patients with renal disease increases mortality [17,22] and that a positive fluid balance is associated with acute lung injury and increased hospital mortality in patients with sepsis [23]. Future research should focus on the role of the concern for fluid overload in decision-making surrounding sepsis care.

We found that compliance with the fluid requirement was less likely when sepsis was identified in the inpatient setting relative to the emergency department (ED). This finding suggests that clinicians may be recognizing a clinical distinction between hospital-onset and community-onset sepsis [24]. Differences in management may be due to factors associated with sepsis pathophysiology, patient characteristics, and environmental resources. First, inpatient-diagnosed sepsis may be more complex than those diagnosed in the ED as hospital-onset sepsis patients may have more comorbidities and may be more severely ill than patients diagnosed with sepsis in the ED [24]. Second, sepsis presentation is often insidious such that defining the exact time of disease onset is often difficult. An attention-rich environment like the ED may be better equipped at diagnosing and treating sepsis earlier compared to the inpatient setting. Lastly, it is plausible that differences in clinical focus are responsible for differences between community-onset and hospital-onset sepsis. For example, ED physicians may be more comfortable with aggressive fluid administration than physicians in the inpatient setting. Despite the differences in community-onset and hospital-onset sepsis, current sepsis diagnosis and treatment guidelines make no distinction between these groups of patients. Most studies have focused on sepsis diagnosed in the ED or ICU [9,25,26], resulting in a knowledge gap of the characteristics of hospital-onset sepsis on inpatient wards. This distinction is crucial as these patients account for approximately 30% of overall sepsis cases [12].

Our study has several limitations. First, as an observational study there may have been unmeasured confounding variables contributing to the lack of benefit for fluid compliance. For example detailed clinical information on sequential organ failure assessment (SOFA) scores, vasopressor use or parameters for stopping fluids was not available as it is not part of the CMS sepsis bundle. However, we were able to minimize this limitation through the robustness of data collection and multivariable analyses, which allowed for control for numerous covariates. Second, it is possible that non-compliant cases did not receive the recommended fluid amount due to a lower severity of illness, which would lead to lower mortality and bias our findings towards the null. However, the non-compliant cases had higher Charlson comorbidity scores and had higher median lactate, suggesting these patients were at least as ill as the compliant cases. Third, though our analysis revealed possible drivers for fluid non-compliance, we were not able to identify exact reasons on clinical decision-making given the retrospective nature of our study. Qualitative studies on physician decision-making in sepsis treatment could explore this further. Fourth, though sepsis cases were clinically adjudicated, we used administrative data to identify comorbidities, which may underestimate their actual prevalence. However, we expect this underestimation to be independent of the treatment groups. Finally, though we found no overall association of fluid compliance with mortality, it is plausible that fluid administration may differentially mitigate mortality risk for certain subgroups. Follow-up studies examining whether there are patient subgroups more likely to benefit from rapid fluid administration and those where there is greater potential for harm may provide crucial information on the overall value of widespread implementation of sepsis bundles.

In conclusion, using data from a large academic hospital and a community hospital we found that fewer than one-half of patients with septic shock received the recommended amount of fluids. Non-compliance was more common in patients diagnosed in the inpatient setting and in those with CHF, CKD, chronic liver disease and higher comorbidity burden, suggesting that concern for volume overload may be a key driver of non-compliance. Compliance was not significantly associated with mortality, suggesting that the fluid requirement may be unnecessary for some patients. In the current climate of performance measures and mandatory reporting, and the potential negative consequences on hospital reimbursement and public ranking, it is crucial to ensure that measures accurately assess the quality of care that is being delivered. Most importantly, requirements within clinical bundles and measures should translate to improved patient outcomes while not encouraging care that may be clinically harmful. Our study suggests that clinical protocols and performance measures mandating a “one-size-fits-all” approach to fluid management in sepsis may not be appropriate and needs to be re-evaluated.

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