OBSERVATIONAL STUDY

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Resuscitation in the First 3 Hours of Sepsis-Induced Hypotension Varies by Patient and Hospital Factors

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IMPORTANCE: Patient and hospital factors affects how we resuscitate patients in the first 3 hours of sepsis-induced hypotension.

OBJECTIVES: To evaluate variability in compliance to the 3-hour surviving sepsis campaign (SSC) bundle and explore the association of early compliance with subsequent shock and in-hospital mortality.

DESIGN: Retrospective cohort study between September 2017 and February 2018.

SETTING: Thirty-four academic medical centers.

PARTICIPANTS: A subgroup sepsis-induced hypotensive patients from a larger shock cohort study.

MAIN OUTCOMES AND MEASURES: Compliance to SSC bundle that was defined as receiving appropriate antibiotics, 30 mL/kg of crystalloid or initiation of vasopressors, and lactate, obtained in the first 3 hours following sepsis-induced hypotension.

RESULTS: We included 977 patients with septic-induced hypotension. Bundle compliance was 43.8%, with the lowest compliance to fluid or vasopressor components (56%). Patients with high Sequential Organ Failure Assessment scores and physiologic assessments were more likely to receive compliant care, as were patients with sepsis-induced hypotension onset in the emergency department (ED) or admitted to mixed medical-surgical ICUs. SSC compliance was not associated with in-hospital mortality (adjusted odds ratio, 0.72; 95% CI, 0.47–1.10). The site-to-site variability contributed to SSC compliance (intraclass correlation coefficient [ICC], 0.15; 95% CI, 0.07–0.3) but not in-hospital mortality (ICC, 0.02; 95% CI, 0.001–0.24). Most patients remained in shock after 3 hours of resuscitation (SSC compliant 81.1% and noncompliant 53.7%). Mortality was higher among patients who were persistently hypotensive after 3 hours of resuscitation for both the SSC compliant (persistent hypotension 37% vs not hypotensive 27.2%; $p = 0.094$) and noncompliant (30.1% vs 18.2%; $p = 0.001$, respectively).

CONCLUSIONS AND RELEVANCE: Patients with a higher severity of illness and sepsis-induced hypotension identified in the ED were more likely to receive SSC-compliant care. SSC compliance was not associated with in-hospital mortality after adjusting for patient- and hospital-level differences. Higher mortality is seen among those who remain in shock after initial resuscitation, regardless of SSC compliance.

KEY WORDS: practice variation; resuscitation; sepsis; septic shock; surviving sepsis campaign; under-resuscitation

The surviving sepsis campaign (SSC) offers treatment guidelines and sets the standard of care in managing patients with sepsis and septic shock. Fluid resuscitation with 30 cc/kg and targeting a mean arterial pressure

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KEY POINTS

Question: What factors affect compliance with surviving sepsis campaign recommendations and clinical outcomes?

Finding: In this retrospective analysis of a cohort of patients with sepsis-induced hypotension, it was found that patients with higher severity of illness, hypotension diagnosed in the emergency department, or managed in a medical-surgical ICU were more likely to receive antibiotics, lactic acid monitoring, and 30 mL/kg of crystalloid or vasopressor for shock within the first 3 hours of hypotension onset. While there was substantial site-to-site variation in resuscitation practices, this did not influence in-hospital mortality. Regardless of surviving sepsis campaign compliance status, a substantial number of patients remained hypotensive after the first 3 hours of resuscitation and had higher in-hospital mortality.

Meaning: Site-to-site variation accounts for the different practices in sepsis-induced hypotension resuscitation; however, this variation does not correlate with in-hospital mortality. Underresuscitation after the first 3 hours from sepsis-induced hypotension is associated with higher in-hospital mortality.

greater than or equal to 65 mm Hg are recommended and suggested in the 2016 and 2021 SSC guidelines, respectively, highlighting the central role of fluids and vasopressors in managing this population (1, 2). Studies on compliance with SSC recommendations have highly variable results (3, 4). Large cohorts have shown that higher compliance with the bundle delineated by the SSC guidelines was associated with improved mortality in sepsis, but other studies show no association between SSC guideline compliance and mortality (5–8).

Compliance with the fluid and vasopressor components of the SSC guidelines and its relationship with mortality is among one of the more controversial aspects of the bundle. The guideline recommends targeting a mean arterial pressure of greater than or equal to 65 mm Hg in resuscitation but does not make a specific recommendation on the timing of initiation of vasopressors (2). Exploring factors affecting compliance to SSC guidelines would help understand how to promote compliance and why there is an inconsistent association between adherence to SSC guidelines and sepsis mortality.

In the post hoc analysis of a multicenter cohort of patients with sepsis-induced hypotension, we aim to understand variability in compliance to 3-hour SSC guidelines and identify hospital and patient factors contributing to noncompliance. We also aim to explore the effect of the guideline compliance on subsequent fluid and vasopressor administration after the initial 3 hours, early resolution of hypotension, and subsequent hospital mortality.

METHODS

Observation of variation in fluids administered and characterization of vasopressor requirements in shock (VOLUME-CHASERS) was a multicenter prospective cohort study conducted through the Discovery Network, the Society of Critical Care Medicine's research network (ClinicalTrials.gov NCT03190408) (9). The VOLUME-CHASERS study included adult patients with shock intended for ICU admissions between September 1, 2017, and February 1, 2018. Shock was defined as mean arterial blood pressure (MAP) less than or equal to 65 mm Hg, systolic blood pressure (SBP) less than or equal to 90 mm Hg, or requirement of vasopressor to maintain normotension. Patients were excluded for 1) previous enrollment into this study, 2) shock occurring during surgery in the operating room, 3) cardiac surgery with primary cardiogenic shock, and 4) transfer from another hospital to the study hospital. Sites screened for all consecutive patients for a 2- to 4-week period during the study period. The institutional review board at Albert Einstein College approved this study at each participating site for waiver of informed consent (VOLUME-CHASER Study, Review Board Number 2017-7860, approval date December 26, 2019). The study procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975. De-identified site data was uploaded into a secure online Research Electronic Data Capture data form (Nashville, TN). No external funding was provided for this study.

For this substudy, we only included patients from the VOLUME-CHASERS cohort (n = 1,637) with sepsis as the primary etiology of hypotension (n = 977), which was defined as SBP less than 90 mm Hg,

MAP less than 65 mm Hg, or need for a vasopressor to maintain SBP greater than or equal to 90 mm Hg, MAP greater than or equal to 65 mm Hg and infection as primary suspected etiology for hypotension by documentation, consistent with Sepsis-3 guidelines (1).

Data Collection

We collected baseline demographics, medical history, location at the time of sepsis-induced hypotension onset, and types of ICU. Acute Physiology and Chronic Health Evaluation (APACHE) III and Sequential Organ Failure Assessment (SOFA) scores were calculated 12 hours prior and 12 hours following hypotension onset. We collected data on fluid and vasopressor administration during periods following hypotension (hours 0–3, hours 3–6, hours 6–12, and hours 12–24). We calculated vasopressor doses in norepinephrine equivalent (NEQ, mg) (10–12) and recorded the use of physiologic assessments. The need for mechanical ventilation and renal replacement therapy was also collected. We followed each patient until hospital discharge or death within the hospital.

Surviving Sepsis Campaign Compliance

This study was conducted in 2017–2018, so we used the SSC 2016 recommendations to assess guideline compliance. We defined compliance to the SSC 3-hour bundle as administration of 30 mL/kg of fluid or initiation of vasopressors, lactic acid measurement within 12 hours of hypotension, and the administration of appropriate antibiotics for hypotension (1, 5). When patients' lactate levels before hypotension were greater than or equal to 2 mmol/L, we included the fluids administered 12 hours before hypotension and 3 hours after hypotension onset in determining fluid administration for bundle compliance. Patients who were started on vasopressors to maintain normotension within 3 hours of hypotension were also considered compliant with the bundle, even if 30 mL/kg of fluid had not been administered. Our rationale was to assess the typical clinical situation where the treating clinician chose to add vasopressors if hypotension is severe or ongoing despite fluid administration or concerns about fluid responsiveness or overload, reflecting real-world practice (13).

We performed an exploratory analysis on resuscitation status after hypotension onset. After the initial 3 hours of resuscitation, we determined persistent hypotension was present if SBP and MAP were lower than 90 and 65 mm Hg, respectively; or if they required vasopressors in the hours 3 to 24 time period after initial hypotension onset. In patients with persistent hypotension, we further categorized them as having resolving shock if the average vasopressor dose in hours 3 to 24 was lower than in hours 0 to 3 and having worsening shock if the average vasopressor dose at hours 3 to 24 was equal to or greater than the average dose rate in first 3 hours after the initial shock.

Statistical Analysis

We presented baseline values in mean and SD or median and interquartile range (IQR) or number (percentage), where appropriate. For unadjusted comparison, we used Student *t* test, Mann-Whitney *U* test, or Kruskal-Wallis test for continuous variables and Fisher exact test for categorical variables.

We used a mixed-effect logistic regression model with hospital sites as a random effect to determine the variables associated with SSC compliance. We chose baseline variables as clinically relevant independent variables such as age, sex, race, APACHE III, SOFA score, sepsis-induced hypotension onset location, types of ICU admission, and hours in the hospital before hypotension onset a priori in the models. We included secondary shock contributors (cardiac dysfunction, hypovolemia, trauma, and intoxication) and past medical history (hypertension, cancer, diabetes, congestive heart failure, end-stage renal disease [ESRD], chronic kidney disease, HIV/AIDS, immune suppression, liver disease, and cirrhosis) to determine the association with SSC compliance ($p < 0.05$) and assessed the confounding relationship if there was a beta coefficient by 10% in backward elimination. The model with the lowest Akaike information criterion was selected. Intraclass correlation coefficients (ICCs) estimated between-site variability. We determined the association of fluid administration and vasopressor with SSC using the mixed-effect linear regression model described above. Fluid volume was log-transformed to satisfy the assumption of normality. We used mixed-effects logistic regression to examine the association between SSC compliance and in-hospital mortality. The use of physiologic assessment in the 24 hours following hypotension onset, total fluid administered, vasopressors, and mechanical ventilator was included

in the model. We included the use of dynamic (stroke volume variation, pulse pressure variation), static (central venous pressure, pulmonary arterial occlusion pressure), and point-of-care ultrasound to determine fluid responsiveness as a physiologic assessment (9). We tested for interactions between SSC compliance, fluid, and vasopressor administration 24 hours following sepsis-induced hypotension onset. We calculated the standardized ratio of surviving sepsis compliance and in-hospital mortality by taking the observed event over the expected event in each site with more than 10 patients enrolled (14). We used STATA (Stata Statistical Software, Version 15.0, StataCorp LLC., College Station, TX) for all data analysis.

RESULTS

Patient Characteristics and SSC Compliance

From the 1,639 patients with shock from the VOLUME-CHASERS study, 977 had sepsis as their primary etiology of hypotension, and their baseline characteristics are shown in **Table 1**. Sepsis-induced hypotension onset occurred mostly in the ICU (n = 418 [42.8%]) and the emergency department (ED) (n = 379 [38.8%]). Most of the sepsis-induced hypotensive patients were managed in the medical and medical/surgical ICU (Table 1).

In this cohort of sepsis-induced hypotensive patients, only 56% either received 30 mL/kg of fluid or were initiated on vasopressor by hour 3 after the onset of hypotension, 75.8% had lactate level monitored, and 92.1% received appropriate antibiotics (**Supplemental Fig. 1,** http://links.lww.com/CCX/B135). Only 43.8% (n = 428) of the cohort was compliant with all aspects of the SSC bundle. There was no difference between the SSC compliant group and the noncompliant group regarding age, gender, race, and secondary contributors of hypotension (Table 1). However, the compliant group tended to be sicker with higher APACHE III and SOFA scores at 24 hours, as well as higher lactate levels (Table 1). In addition, most patients who received compliant care had hypotension in the ED (44.6%), and patients who received noncompliant care were first diagnosed with hypotension in the ICU (47.7%; Table 1).

Most of the fluid administered in sepsis was early, within the first 3 hours of hypotension (1,000 mL; IQR, 315–2,000). The amount of fluid administered varied substantially across each time interval (hours 0–3, 3–6, 6–12, and 12–24) (**Supplemental Fig. 2*A*,** http://links.lww.com/CCX/B135). Approximately half of the sepsis-induced hypotensive patients received vasopressors in the 24 hours following hypotension, and the median dose of vasopressor in NEQ was 10 μg/min (IQR, 5–22 μg/min) (**Supplemental Fig. 2*B*,** http://links.lww.com/CCX/B135). The SSC compliant group received 85% more fluid in the first 3 hours and 39% more cumulative fluid by 24 hours for their hypotension. SSC compliant patients were more likely to receive vasopressors at higher doses at all time points (**Supplemental Fig. 2, *C*** and ***D*,** http://links.lww.com/CCX/B135; **Supplemental Fig. 3,** http://links.lww.com/CCX/B135; and **Supplemental Table 1,** http://links.lww.com/CCX/B135).

In adjusted mixed-effect regression, SSC compliance was associated with higher SOFA scores at the time of hypotension (adjusted odds ratio [OR], 1.17; 95% CI, 1.10–1.23), the use of physiologic assessments (adjusted OR, 1.53; 95% CI, 1.11–2.11), sepsis-induced hypotension onset in the ED (vs ICU, adjusted OR, 1.68; 95% CI, 1.16–2.43), and admission to mix medical-surgical ICU (vs medical ICU, adjusted OR, 1.95; 95% CI, 1.20–3.16) (**Table 2**). Medical history of ESRD was associated with a lower likelihood of SSC compliant care (adjusted OR, 0.55; 95% CI, 0.31–0.95). A 15% within-site correlation contributed to the site-to-site variations with SSC compliance (ICC, 0.15; 95% CI, 0.07–0.30; **Fig. 1*A***).

SSC Compliance and Clinical Outcomes

Overall, 29.6% (n = 283) septic patients died during the hospitalization (**Table 3**). The SSC compliant group had a higher proportion of in-hospital mortality (35.7% vs 24.8%; unadjusted OR, 1.61; 95% CI, 1.21–2.14) (Table 3; and **Supplemental Table 2,** http://links.lww.com/CCX/B135). The SSC compliant group had higher median lactate at 24 to 48 hours after initial sepsis-induced hypotension (Table 3). The compliant group also had fewer 7-day vasopressor-free days and fewer 28-day ventilator-free days and was more likely to require mechanical ventilation (Table 3). The overall hospital and ICU length of stay did not differ between the two groups.

TABLE 1.
Cohort Characteristics

Variables	Total, *n* = 977	Compliance With 3-hr Bundle		*p*-value
		Compliant, *n* = 428	Not Compliant, *n* = 549	
Baseline characteristics				
Age, yr, mean ± SD	62.6 ± 16.2	63.0 ± 16.1	62.3 ± 16.3	0.51
Race, *n* (%)				0.86
White	589 (60.3)	257 (60.0)	332 (60.5)	
Black	169 (17.3)	77 (18.0)	92 (16.8)	
Other	219 (22.4)	94 (22.0)	125 (22.8)	
Sex, *n* (%)				
Male	532 (54.5)	246 (57.5)	286 (52.1)	0.11
Female	445 (45.6)	182 (45.5)	263 (47.9)	
Acute Physiology and Chronic Health Evaluation III, mean ± SD	90.7 ± 28	98.7 ± 28.2	84.6 ± 26.2	< 0.001
Sequential Organ Failure Assessment, median (IQR)	8 (5–11)	9.0 (7.0–12.0)	7.0 (5.0–9.0)	< 0.001
Lactate level, mg/dL, median (IQR)	2.5 (1.6–4.6)	3.0 (1.8–5.6)	2.2 (1.4–3.9)	< 0.001
12 hr before shock	2.2 (1.4–3.6)	2.5 (1.6–4.2)	2 (1.3–3.1)	0.0001
12 hr following shock	2.4 (1.4–4.4)	2.6 (1.5–5.4)	2.2 (1.4–3.9)	0.0032
Past medical history, *n* (%)				
AIDS	18 (1.8)	7 (1.6)	11 (2.0)	0.81
Cancer	228 (23.3)	103 (24.1)	125 (22.8)	0.65
Immune suppression	143 (14.6)	74 (17.3)	69 (12.6)	0.045
Liver disease	97 (9.9)	47 (11.0)	50 (9.1)	0.334
Renal dysfunction				
Chronic kidney disease, not on hemodialysis	117 (12.0)	51 (11.9)	66 (12.0)	1
End-stage renal disease on hemodialysis	80 (8.2)	28 (6.5)	52 (9.5)	0.1
Congestive heart failure	127 (13.0)	53 (12.4)	74 (13.5)	0.63
Sepsis-induced hypotension onset locations, *n* (%)				
Emergency department	379 (38.8)	191 (44.6)	188 (34.2)	0.001
Wards	151 (15.5)	65 (15.2)	86 (15.7)	0.86
ICU	418 (42.8)	156 (36.4)	262 (47.7)	< 0.001
Post-anesthesia care unit	10 (1.0)	5 (1.2)	5 (0.9)	0.76
Other	19 (1.9)	11 (2.6)	8 (1.5)	0.25
ICU types, *n* (%)				
Medical	573 (58.8)	236 (55.1)	337 (61.4)	0.05
Surgical	94 (9.7)	39 (9.1)	55 (10.0)	0.66
Mixed medical-surgical	187 (19.2)	109 (25.5)	78 (14.2)	< 0.001
Cardiothoracic ICU	48 (4.9)	18 (4.2)	30 (5.5)	0.46
Other	72 (7.4)	25 (5.8)	47 (8.6)	0.11

(*Continued*)

TABLE 1. (*Continued*).
Cohort Characteristics

Variables	Total, *n* = 977	Compliance With 3-hr Bundle		*p*-value
		Compliant, *n* = 428	Not Compliant, *n* = 549	
Secondary contributors of shock, *n* (%)				
Hypovolemia	207 (21.2)	96 (22.4)	111 (20.2)	0.43
Cardiac dysfunction	180 (18.4)	78 (18.2)	102 (18.6)	0.93
Neurologic	51 (5.2)	22 (5.1)	29 (5.3)	1
Trauma	10 (1.0)	5 (1.2)	5 (0.9)	0.76
Intoxication	29 (2.97)	16 (3.7)	13 (2.4)	0.25
Metabolic	96 (9.8)	50 (11.7)	46 (8.4)	0.1
Use of physiologic assessment, *n* (%)	408 (41.8)	202 (48.9)	196 (36.4)	< 0.0001

IQR = interquartile range.

After adjusting for patient-level differences, we did not find an association between SSC compliance with in-hospital mortality (adjusted OR, 0.72; 95% CI, 0.47–1.10) (Supplemental Table 2, http://links.lww.com/CCX/B135). In-hospital mortality was associated with higher APACHE III scores, highest lactate level in the first 24 hours of hypotension, history of cancer, vasopressor use, and mechanical ventilation. The total fluid administered following hypotension onset was not associated with in-hospital mortality. There was slight site-to-site variation with in-hospital mortality after adjusting for patient-level differences. There was low within-site correlation, suggesting there was low site-to-site variation in mortality (ICC, 0.02; 95% CI, 0.001–0.24) (**Fig. 1*B***; and Supplemental Table 2, http://links.lww.com/CCX/B135).

Three-Hour SSC Compliance and Resolution of Hypotension

After the first 3 hours of resuscitation, 81.1% of the compliant group was still hypotensive, compared with 53.7% of the noncompliant group ($p < 0.001$) (**Table 4**). However, among those patients who were in persistent hypotension after the initial 3-hour resuscitation, most of the patients in the noncompliant group required equal or higher vasopressor requirements at hours 3–24 (92.9%), compared with 74.6% of the compliant group, who were sicker by APACHE III, SOFA, and lactate acid initially ($p < 0.001$). In addition, mortality was higher among patients who were persistently hypotensive after the initial 3 hours of resuscitation for both the compliant (37% in persistently hypotensive vs 27.2% in the no longer hypotensive patients; $p = 0.094$) and noncompliant group (30.1% vs 18.2%; $p = 0.001$, respectively).

DISCUSSION

We did not find an association between SSC compliance and in-hospital mortality after adjusting for patient- and hospital-level differences. Both hospital-level and patient-level factors that influence the likelihood of compliance to SSC guidelines. Patients receiving dialysis and those who were less severely ill were less likely to be managed in compliance with the 3-hour SSC bundle. Nevertheless, there was still significant site variation in compliance that was not associated with mortality. We found this may be due to the inclusion of less severely ill patients who were successfully resuscitated with smaller fluid volumes than the suggested 30 mL/kg in the noncompliant group. However, a majority (54%) of patients in the noncompliant group were still hypotensive after the first 3 hours of resuscitation, and of these, most progressed to worsening shock (93%).

In our study, compliance to the SSC 3-hour bundle differed mainly by the resuscitation component (volume of fluid or vasopressor) within the first 3 hours. We denoted as compliant the use of vasopressors within the first 3 hours of resuscitation, which is consistent with the updated 2021 SSC guidelines (2) and reflects common clinical scenarios when hypotension is severe and persistent during fluid administration, or

TABLE 2.
Variables Associated With Surviving Sepsis Campaign Compliance

Surviving Sepsis Campaign Compliance	Unadjusted OR	Adjusted OR*
Use of physiologic assessment	1.68 (1.29–2.17)	1.53 (1.11–2.11)
Age	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Male gender	1.24 (0.96–1.60)	1.25 (0.92–1.69)
Race (vs White)		
Black	1.08 (0.77–1.52)	0.94 (0.59–1.48)
Other	0.97 (0.71–1.33)	0.93 (0.62–1.41)
Acute Physiology and Chronic Health Evaluation III score	1.02 (1.01–1.02)	1.01 (1.00–1.01)
Sequential Organ Failure Assessment score	1.18 (1.13–1.22)	1.17 (1.10–1.23)
Time spent in hospital before sepsis-induced hypotension (hr)	1.00 (0.98–1.00)	1.00 (1.00–1.00)
Sepsis-induced hypotension onset location (vs ICU)		
Emergency department	1.71 (1.29–2.26)	1.68 (1.16–2.43)
Ward	1.27 (0.87–1.85)	0.99 (0.62–1.58)
Post-anesthesia care unit	1.68 (0.48–5.89)	5.83 (1.27–26.72)
Other location	2.31 (0.91–5.86)	1.79 (0.55–5.83)
ICU type (vs medical ICU)		
Surgical ICU	1.01 (0.65–1.58)	1.04 (0.61–1.78)
Medical surgical ICU	2.00 (1.43–2.79)	1.95 (1.20–3.16)
Cardiothoracic ICU	0.86 (0.47–1.57)	1.01 (0.49–2.10)
Other ICU	0.76 (0.45–1.27)	0.64 (0.33–1.25)
Comorbidities		
End-stage renal disease on dialysis	0.67 (0.41–1.08)	0.55 (0.31–0.95)
Immune suppression	1.45 (1.02–2.08)	1.22 (0.78–1.88)
History of liver disease	1.23 (0.81–1.87)	0.64 (0.38–1.10)
Site-to-site variation (intraclass correlation coefficient)		0.15 (0.07–0.30)

OR = odds ratio.

[a]Logistic regression, parsimonious model. Adjusted for age, gender, race, hours in hospital prior to sepsis-induced hypotension, sepsis-induced hypotension onset location, ICU types, and past medical history.

when the clinicians thought that the patient was adequately fluid resuscitated or needed inotropic support early based upon other clinical factors (13, 15). This may contribute to why compliance was higher among those with more organ failure and greater severity of illness.

Variable compliance to the SSC bundle has been repeatedly demonstrated (3, 4). Indeed, in this multicenter observational study, we found significant site variation in adherence to the 3-hour bundle as reflected by the high intra-class correlation in our adjusted model. The overall noncompliance rate of 56.2% is comparable to the 19% to 82.5% found in other reports (3, 5, 7, 16, 17). Almost all of our study patients reportedly received appropriate antibiotics (92.1%), which is an improvement compared with the 64.4% found in the International Multicentre PREvalence Study on Sepsis (The IMPreSS) Study (5). We found significant hospital-level contributors to variation in compliance to the 3-hour bundle. We saw that the ED as the site of onset of sepsis-induced hypotension was more likely to be compliant than when shock onset occurred in the ICU. This reflects the substantial efforts to improve sepsis recognition and implementation of the SSC bundle in the ED (7, 16, 17) and the greater prevalence of protocolized sepsis management (7, 18). Also, patients in the ICU are more likely to have multiple organ failure, making clinicians more

TABLE 3.
Cohort Outcome

Variables	Total, *n* = 977	Compliance With 3-hr Bundle		*p*
		Compliant *n* = 428	Not Compliant, *n* = 549	
Clinical outcomes				
In-hospital mortality, *n* (%)	289 (29.6)	153 (35.7)	136 (24.8)	< 0.001
Highest lactate in hours 24–48 from shock, mg/dL, median (IQR)[a]	2.1 (1.5–3.7)	2.4 (1.5–4.3)	1.9 (1.3–3.2)	0.007
Sequential Organ Failure Assessment score in hours 24–48 from shock, median (IQR)	6 (3–10)	8 (4–11)	5 (3–8)	< 0.0001
Mechanical ventilation during hospitalization, *n* (%)	609 (62.3)	306 (71.5)	303 (55.2)	< 0.001
Renal replacement therapy, *n* (%)	214 (21.9)	104 (24.3)	110 (20)	0.12
Hospital length of stay, d, median (IQR)	12 (7–22)	12 (7–22)	12 (7–22)	0.91
Survivors	12 (8–22)	12 (8–22)	12 (7–21)	
Nonsurvivors	12 (5–22)	11 (5–20)	13 (6–22)	
ICU length of stay, d, median (IQR)	5 (3–11)	5 (3–11)	5 (3–11)	0.13
Survivors	5 (3–10)	6 (3–10)	5 (3–10)	
Nonsurvivors	5 (3–12)	6.5 (3–12)	6 (3–13)	
Vntilator-free days 28 (of those vented), d, median (IQR)	25 (0–28)	23 (0–28)	27 (12–28)	< 0.0001
Vasopressor-free day (7) shock-free days, d, median (IQR)	5 (2–7)	4 (0–6)	6 (4–7)	< 0.0001

IQR = interquartile range.

[a]Post resuscitation Sequential Organ Failure Assessment available in 541 participants (compliant *n* = 290, not compliant *n* = 251).

cautious about rapid fluid administration, especially if they have acute respiratory distress syndrome or renal failure. It is also possible that ICU providers may be more comfortable than those in other units in tolerating lower blood pressure in patients with chronically low blood pressure, such as those with ESRD. While we found significant site contribution to the variation in compliance to the 3-hour SSC guidelines, there was less site contribution to mortality in sepsis and no significant association between compliance to SSC and hospital mortality after adjusting baseline severity of illness, covariates, and sites.

The 2021 updated SSC guidelines changed the 30 mL/kg of fluid recommendation from strong to weak. It allows for more personalization of fluid resuscitation according to other factors, like dynamic physiologic assessment, capillary refill, and lactate (2). Indeed, we found this reflects what clinicians were already doing, for example, we noted that patients with ESRD on dialysis were less likely to receive 30 mL/kg fluid. More severely ill patients with more significant organ impairment, as judged by SOFA score, were more likely to receive 30 mL/kg fluid and/or vasopressors. Patients on dialysis may reflect the clinician's caution in rapid fluid resuscitation at 30 mL/kg because of the risk for fluid overload and the assumption of lower baseline blood pressure. Septic shock may be more readily recognized in patients with a higher severity of illness, for whom clinicians are compelled to institute rapid resuscitation with higher volumes of fluids and earlier use of vasopressors. Physiologic assessments like ultrasound and passive leg raises are often used to personalize fluid resuscitation in shock. Clinicians often use these assessments to continue to bolus fluids while avoiding fluid overload. We found that physiologic assessment was associated with increased compliance with 30 mL/kg fluid or vasopressor use during initial resuscitation.

We found lower compliance to 30 mL/kg fluid resuscitation or vasopressor among less severely ill patients.

TABLE 4.
Shock and Perfusion Status at Hours 3–24 After Sepsis-Induced Hypotension Onset

Compliance With SSC 3-hr Bundle		SSC Compliant, *n* = 428				SSC Noncompliant, *n* = 549			
Resuscitation status at hours 3–24	Total Cohort, N = 977	All	Survivors, *n* (%), *n* = 275 (64.3)	Nonsurvivors, *n* (%), *n* = 153 (35.7)	*p*	All	Survivors, *n* (%), *n* = 413 (75.3)	Nonsurvivors, *n* (%), *n* = 136 (24.7)	*p*
No longer hypotensive, *n* (%)	335 (34.3)	81 (18.9)	59 (72.8)	22 (27.2)	0.094	254 (46.3)	208 (81.9)	46 (18.2)	0.001
Persistent hypotensive[a], *n* (%)	642 (65.7)	347 (81.1)	216 (62.3)	131 (37.8)		295 (53.7)	205 (69.5)	90 (30.1)	
Resolving shock[b], *n* (%)	109 (17)	88 (25.4)	62 (28.7)	26 (20)	0.075	21 (7.1)	16 (7.8)	5 (5.6)	0.63
Worsening shock on pressor[c], *n* (%)	533 (83)	259 (74.6)	154 (71.3)	105 (80.2)		274 (92.9)	189 (92.2)	85 (94.4)	

SSC = surviving sepsis campaign.
[a]Persistent hypotensive is defined as systolic blood pressure < 90, mean arterial blood pressure < 65, or use of vasopressor.
[b]Resolving hypotension is defined as a lower average vasopressor dose rate at hours 3–24 compare to hours 0–3 in patients with remained hypotensive at hours 3–24.
[c]Worsening shock on pressor is defined as greater or equal average vasopressor dose rate at hours 3–24 compare to hours 0–3 in patients who remained hypotensive in our 3–24.

We postulated that clinicians may not have started vasopressor or administered 30 mL/kg of fluid if they believed the patient to be resuscitated if their hypotension resolved after 1–2 L of the fluid bolus. Indeed, we found that a higher percentage of patients in the noncompliant group had resolution of hypotension after the first 3 hours of resuscitation than patients in the compliant group (46.3% vs 18.9%; $p < 0.001$, respectively). But the majority of patients in the noncompliance group (53.7%) still had a persistent hypotension after resuscitation. The majority of these patients (92.9%) had worsening shock in the 3–24 hours after hypotension initiation by vasopressor dose rate compared with the 75% of patients who received resuscitation in compliance with the 3-hour SSC guidelines ($p < 0.001$). This would suggest that most patients were under-resuscitated even as they were less sick. This has important implications for how compliance with the updated SSC guidelines should be measured and reported. New York State currently requires sites to report the percentage of patients with septic shock compliant with antibiotics and lactate measurement in the first 3 hours of sepsis and 30 mL/kg fluid resuscitation within the first 6 hours of sepsis-induced hypotension (19). But the updated SSC 2021 guidelines now allow more personalization of resuscitation so that patients may receive less than 30 mL/kg of fluid. Many patients in this study who were not resuscitated with 30 mL/kg fluid or vasopressor within the first 3 hours of sepsis-induced hypotension experienced worsening shock with higher mortality. Monitoring compliance in patients who remain hypotensive or in worsening shock after the first 3 hours of resuscitation may be more accurate for individual prognostication and hospital site performance than monitoring compliance with 30 mL/kg of fluid administration or vasopressor alone among all patients.

There are limitations to our study. First, as an observational study, there are unaccounted confounders. We did not capture the clinical reason or rationale for why clinicians deviated from the SSC recommendation. We examined only hypotension and vasopressor dose after the initial 3-hour resuscitation and did not include repeat lactate acid measurements, revealing a higher number of under-resuscitated patients. Without knowing the lactate trend, we cannot say that patients were truly under-resuscitated and hypoperfused. Second, we relied on the data that was available from the original cohort study to determine the compliance SSC. Our definition for SSC

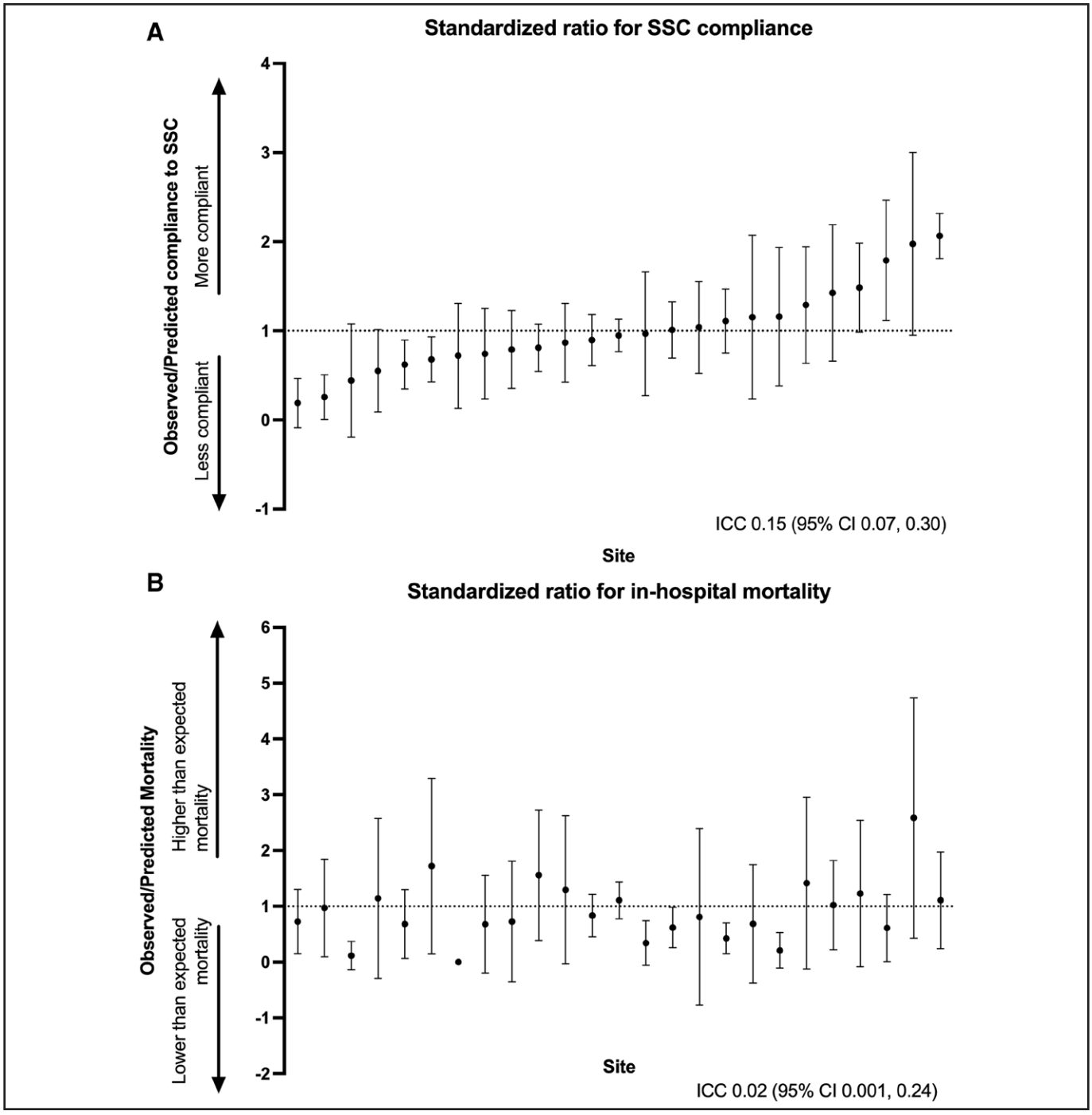

Figure 1. Standardized ratio for surviving sepsis campaign (SSC) compliance and in-hospital mortality. **A**, Standardized ratio for SSC compliance, adjusted for age, gender, race, hours in hospital prior to sepsis-induced hypotension onset, sepsis-induced hypotension onset location, ICU types, and past medical history. **B**, Standardized ratio for in-hospital mortality, adjusted for age, sex, race, Acute Physiology and Chronic Health Evaluation III, Sequential Organ Failure Assessment score, highest lactate, hours in hospital prior to sepsis-induced hypotension onset, sepsis-induced hypotension onset location, ICU types, secondary contributors of hypotension, cumulative fluid, use of any vasopressor, and use of mechanical ventilation in the 24 hr following shock onset. ICC = intra-class correlation.

compliance was quite liberal. We used lactate collected within 12 hours before and after shock, allowing concomitant fluid resuscitation at 30 mL/kg and vasopressor use in the first 3 hours of hypotension and appropriate antibiotics determined by study sites. Despite our liberal definition, we still found under-resuscitation in patients with sepsis-induced hypotension.

In conclusion, we have identified patient and hospital factors contributing to 30 mL/kg fluid and vasopressor resuscitation within the first 3 hours of shock. In line with

the updated 2021 SSC guidelines, clinicians personalize fluid resuscitation in sicker patients with shock. While compliance with SSC guidelines was not associated with in-hospital mortality, a majority of patients who did not receive 30 mL/kg fluid or vasopressors remained hypotensive or in persistent shock after the first 3 hours of resuscitation and had higher hospital mortality even as they were less severely ill, initially suggesting that significant under-resuscitation may still occur.

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REFERENCES

1. Rhodes A, Evans LE, Alhazzani W, et al: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017; 45:486–552
2. Evans L, Rhodes A, Alhazzani W, et al: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021; 49:e1063–e1143
3. Machado FR, Ferreira EM, Schippers P, et al: Implementation of sepsis bundles in public hospitals in Brazil: A prospective study with heterogeneous results. *Crit Care* 2017; 21:268
4. Pepper DJ, Sun J, Cui X, et al: Antibiotic- and fluid-focused bundles potentially improve sepsis management, but high-quality evidence is lacking for the specificity required in the Centers for Medicare and Medicaid Service's Sepsis Bundle (SEP-1). *Crit Care Med* 2019; 47:1290–1300
5. Rhodes A, Phillips G, Beale R, et al: The surviving sepsis campaign bundles and outcome: Results from the international multicentre prevalence study on sepsis (the IMPreSS study). *Intensive Care Med* 2015; 41:1620–1628
6. Pruinelli L, Westra BL, Yadav P, et al: Delay within the 3-hour surviving sepsis campaign guideline on mortality for patients with severe sepsis and septic shock. *Crit Care Med* 2018; 46:500–505
7. Levy MM, Rhodes A, Phillips GS, et al: Surviving sepsis campaign: Association between performance metrics and outcomes in a 7.5-year study. *Crit Care Med* 2015; 43:3–12
8. Ranzani OT, Monteiro MB, Besen B, et al: Association of sepsis diagnosis at daytime and on weekdays with compliance with the 3-hour sepsis treatment bundles. A multicenter cohort study. *Ann Am Thorac Soc* 2020; 17:980–987
9. Chen JT, Roberts R, Fazzari MJ, et al: Variation in fluid and vasopressor use in shock with and without physiologic assessment: A multicenter observational study. *Crit Care Med* 2020; 48:1436–1444
10. Gutsche JT, Mikkelsen ME, McCarthy FH, et al: Veno-venous extracorporeal life support in hemodynamically unstable patients with ARDS. *Anesth Analg* 2017; 124:846–848
11. Russell JA, Walley KR, Singer J, et al: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–887
12. Lee DW, Gardner R, Porter DL, et al: Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014; 124:188–195
13. Self WH, Semler MW, Bellomo R, et al: Liberal versus restrictive intravenous fluid therapy for early septic shock: Rationale for a randomized trial. *Ann Emerg Med* 2018; 72:457–466
14. May TL, Lary CW, Riker RR, et al: Variability in functional outcome and treatment practices by treatment center after out-of-hospital cardiac arrest: Analysis of International Cardiac Arrest Registry. *Intensive Care Med* 2019; 45:637–646
15. Levy MM, Evans LE, Rhodes A: The surviving sepsis campaign bundle: 2018 update. *Crit Care Med* 2018; 46:997–1000
16. Miller RR 3rd, Dong L, Nelson NC, et al: Multicenter implementation of a severe sepsis and septic shock treatment bundle. *Am J Respir Crit Care Med* 2013; 188:77–82
17. Seymour CW, Gesten F, Prescott HC, et al: Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med* 2017; 376:2235–2244
18. Milano PK, Desai SA, Eiting EA, et al: Sepsis bundle adherence is associated with improved survival in severe sepsis or septic shock. *West J Emerg Med* 2018; 19:774–781
19. Levy MM, Gesten FC, Phillips GS, et al: Mortality changes associated with mandated public reporting for sepsis. The results of the New York state initiative. *Am J Respir Crit Care Med* 2018; 198:1406–1412