SEP-1: The Lactate Myth and Other Fairytales*

Paul E. Marik, MD, FCCM
Division of Pulmonary and Critical Care Medicine
Eastern Virginia Medical School
Norfolk, VA

In 2015, the Centers for Medicare and Medicaid Services instituted the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) and began to monitor its compliance by all hospitals in the United States (1). The SEP-1 bundle requires lactate measurements, blood cultures, and broad-spectrum antibiotics within 3 hours of sepsis onset, with repeat lactate measurements within 6 hours if the initial lactate is greater than 2.0 mmol/L. The septic shock bundle requires 30 cc/kg of IV fluids within 3 hours and vasopressors within 6 hours for persistent hypotension. All elements of the bundled are afforded equal weight, and all qualifying elements must be met to pass the bundle. Recognizing that sepsis is a common, costly, and deadly disease (2), the presumed goal of this "quality measure" was to improve the outcome of patients with sepsis and septic shock. Unfortunately, apart from the timely administration of antibiotics, none of the other elements of the bundle are supported by any scientific data, nor have they been demonstrated to improve patient outcomes (3, 4); the reason for their inclusion in the SEP-1 "quality measure" is therefore quite mysterious. In this issue of *Critical Care Medicine*, Rhee et al (5) performed a retrospective study of data from seven U.S. hospitals comparing the outcomes of sepsis patients that passed versus failed the SEP-1 measure during the first 2 years after the measure was implemented. As in previous studies, these authors demonstrated that delays of greater than 3 hours until the administration of antibiotics were significantly associated with death, whereas failing SEP-1 for any other reason was not. The most common reason for failing the measure was omission of the 3- and 6-hour lactate measurement. This is an important observation because meeting the lactate requirement is resource intensive and failure to measure lactate was not associated with a worse outcome. This finding is not surprising because the interpretation of a serum lactate level in patients with sepsis is shrouded in myth (6, 7).

It is widely regarded that in the setting of sepsis, an increased serum lactate is a marker of impaired microcirculatory flow with tissue hypoxia (6, 7). There are, however, scant data that tissue hypoxia occurs in patients with sepsis. Multiple experimental models have failed to demonstrate cellular hypoxia in sepsis (8, 9). Increasing oxygen delivery in patients with sepsis does not increase oxygen consumption (10). This approach has universally failed to improve the outcome of critically ill patients; Gattinoni et al (11) demonstrated this over 20 years ago. Clinical and experimental data suggest that in patients with sepsis increased β_2-adrenergic activation (as part of the stress response) increases glycogenolysis with increased production of glucose (stress hyperglycemia) (10). The glucose is then metabolized to pyruvate at a rate that exceeds its metabolic conversion in the Krebs cycle and pyruvate is then shunted toward lactate production. The serum lactate is therefore an indication of the degree of activation of the stress response and a marker of disease severity. This phenomenon is likely compounded by thiamine deficiency and cytokine-mediated down-regulation of the pyruvate dehydrogenase complex (12). Thiamine pyrophosphate is a critical coenzyme for the pyruvate dehydrogenase complex, the rate-limiting step in the Krebs cycle (13). Thiamine deficiency is common among septic patients, with a range in prevalence between 20% and 70% (14–16). In a pilot randomized controlled trial, Donnino et al (16) randomized 88 patients with septic shock to receive 200 mg thiamine bid for 7 days. In the predefined subgroup of patients with thiamine deficiency, those in the thiamine treatment group had statistically significantly lower lactate levels at 24 hours and a lower mortality at 30 days. The only intervention that I am aware of that can actually decrease blood lactate level (and improve patient outcome) is the administration of thiamine, hence its inclusion in the Hydrocortisone, Ascorbic Acid, Thiamine protocol (17). Furthermore, by attenuating the proinflammatory response, it is likely that the combination of hydrocortisone and vitamin C may restore pyruvate dehydrogenase activity. Attempting to "titrate" hemodynamic management to a lactate level is an absurd concept (18). Equally as absurd, is the concept promoted by the SEP-1 mandate that the mere act of measuring a blood lactate level will improve patient outcome. The study by Rhee et al (5) provides additional supportive evidence that it is now time to retire the SEP-1 "quality" initiative. A second take home message from this study is that reporting of national mortality rates without severity and covariate adjustment will lead to erroneous and misleading conclusions.

***See also p. 1585.**

Key Words: Centers for Medicare and Medicaid Services; lactate; quality measures; SEP-1; sepsis; septic shock

Dr. Marik disclosed off-label product use of thiamine, as it is U.S. Food and Drug Administration-approved under the category "generally regarded as safe," but it is not specifically approved for the treatment of sepsis.

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The Changing Paradigm of Sepsis: Early Diagnosis, Early Antibiotics, Early Pressors, and Early Adjuvant Treatment*

Paul E. Marik, MD, FCCM
Division of Pulmonary and Critical Care Medicine
Eastern Virginia Medical School
Norfolk, VA

Joshua D. Farkas, MD
Division of Pulmonary and Critical Care Medicine
Larner College of Medicine at the University of Vermont
Burlington, VT

The global burden of sepsis is substantial with an estimated 32 million cases and 5.3 million deaths per year (1). In 2013, over 1.3 million patients were hospitalized in the United States with a diagnosis of sepsis of whom over 300,000 died (2). In addition to short-term mortality, septic patients suffer from numerous long-term complications with a reduced quality of life. The early detection and timely administration of appropriate antibiotics are likely the most important factors in improving the outcome of patients with sepsis. However, the initial signs and symptoms of sepsis are frequently nonspecific, leading to a delay in diagnosis. In this issue of *Critical Care Medicine*, Filbin et al (3) report that over a one third of patients with septic shock presented to the emergency department (ED) with vague symptoms that were not specific for infection. The diagnosis of sepsis and the administration of antibiotics were delayed in these patients. Most importantly, patients presenting with vague symptoms were twice as likely to die. The most common vague symptoms included malaise, fatigue, shortness of breath, and altered mental status. As sepsis is largely a disease of the elderly (age, > 60 yr), clinicians should have a high degree of suspicion of sepsis in elderly patients presenting to the ED with these vague symptoms. A blood count with differential, chest radiograph, and urinalysis are essential in these patients. Early signs of sepsis may include tachycardia, hypotension, abnormal temperature, tachypnea with a respiratory alkalosis, abnormal leukocyte count (with left shift), bandemia, thrombocytopenia, or elevated lactate level (4). An elevated procalcitonin would further support the diagnosis of sepsis (5). In addition, the trajectory of the procalcitonin level is useful in monitoring the response to treatment and in decisions regarding stopping antibiotics (6).

The timely diagnosis of sepsis is critical particularly once hypotension develops. The delayed administration of antibiotics in hypotensive patients is associated with an increased risk of death (7). However, we do not agree with enforcing

*See also p. 1592.

Key Words: fever; sepsis; septic shock; vasopressors

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Compliance With the National SEP-1 Quality Measure and Association With Sepsis Outcomes: A Multicenter Retrospective Cohort Study*

Chanu Rhee, MD, MPH[1,2]; Michael R. Filbin, MD, MSc[3]; Anthony F. Massaro, MD[2]; Amy L. Bulger, RN, MPH[4]; Donna McEachern, RN, ALM[4]; Kathleen A. Tobin, RN[5]; Barrett T. Kitch, MD[6]; Bert Thurlo-Walsh, RN, MM[7]; Aran Kadar, MD[8]; Alexandra Koffman, RN[9]; Anupam Pande, MD, MPH[10]; Yasir Hamad, MD[10]; David K. Warren, MD, MPH[10]; Travis M. Jones, PharmD[11]; Cara O'Brien, MD[12]; Deverick J. Anderson, MD, MPH[11]; Rui Wang, PhD[1]; Michael Klompas, MD, MPH[1,2]; for the Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program

*See also p. 1689.

[1]Department of Population Medicine, Harvard Medical School/Harvard Pilgrim Health Care Institute, Boston, MA.

[2]Department of Medicine, Brigham and Women's Hospital, Boston, MA.

[3]Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA.

[4]Department of Quality and Safety, Brigham and Women's Hospital, Boston, MA.

[5]Lawrence Center for Quality and Safety, Massachusetts General Hospital, Boston, MA.

[6]Department of Medicine, North Shore Medical Center, Salem, MA.

[7]Office of Quality, Patient Safety & Experience, Newton-Wellesley Hospital, Newton, MA.

[8]Department of Medicine, Newton-Wellesley Hospital, Newton, MA.

[9]Department of Quality, Brigham and Women's Faulkner Hospital, Boston, MA.

[10]Department of Medicine, Washington University School of Medicine, St. Louis, MO.

[11]Duke Center for Antimicrobial Stewardship and Infection Prevention, Durham, NC.

[12]Department of Medicine, Duke University Medical Center, Durham, NC.

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For information regarding this article, E-mail: crhee@bwh.harvard.edu

Objectives: Many septic patients receive care that fails the Centers for Medicare and Medicaid Services' SEP-1 measure, but it is unclear whether this reflects meaningful lapses in care, differences in clinical characteristics, or excessive rigidity of the "all-or-nothing" measure. We compared outcomes in cases that passed versus failed SEP-1 during the first 2 years after the measure was implemented.

Design: Retrospective cohort study.

Setting: Seven U.S. hospitals.

Patients: Adult patients included in SEP-1 reporting between October 2015 and September 2017.

Interventions: None.

Measurements and Main Results: Of 851 sepsis cases in the cohort, 281 (33%) passed SEP-1 and 570 (67%) failed. SEP-1 failures had higher rates of septic shock (20% vs 9%; $p < 0.001$), hospital-onset sepsis (11% vs 4%; $p = 0.001$), and vague presenting symptoms (46% vs 30%; $p < 0.001$). The most common reasons for failure

were omission of 3- and 6-hour lactate measurements (228/570 failures, 40%). Only 86 of 570 failures (15.1%) had greater than 3-hour delays until broad-spectrum antibiotics. Cases that failed SEP-1 had higher in-hospital mortality rates (18.4% vs 11.0%; odds ratio, 1.82; 95% CI, 1.19–2.80; $p = 0.006$), but this association was no longer significant after adjusting for differences in clinical characteristics and severity of illness (adjusted odds ratio, 1.36; 95% CI, 0.85–2.18; $p = 0.205$). Delays of greater than 3 hours until antibiotics were significantly associated with death (adjusted odds ratio, 1.94; 95% CI, 1.04–3.62; $p = 0.038$), whereas failing SEP-1 for any other reason was not (adjusted odds ratio, 1.10; 95% CI, 0.70–1.72; $p = 0.674$).

Conclusions: Crude mortality rates were higher in sepsis cases that failed versus passed SEP-1, but there was no difference after adjusting for clinical characteristics and severity of illness. Delays in antibiotic administration were associated with higher mortality but only accounted for a small fraction of SEP-1 failures. SEP-1 may not clearly differentiate between high- and low-quality care, and detailed risk adjustment is necessary to properly interpret associations between SEP-1 compliance and mortality. (*Crit Care Med* 2018; 46:1585–1591)

Key Words: quality measures; sepsis; sepsis bundles; septic shock; SEP-1

In October 2015, the Centers for Medicare and Medicaid Services (CMS) began requiring U.S. hospitals to report compliance rates with the "SEP-1" core sepsis measure. The severe sepsis bundle requires lactate measurements, blood cultures, and broad-spectrum antibiotics within 3 hours of sepsis onset, with repeat lactate measurements within 6 hours if the initial lactate is greater than 2.0 mmol/L (1). The septic shock bundle also requires 30 cc/kg of IV fluids within 3 hours, vasopressors within 6 hours for persistent hypotension, and a repeat volume assessment examination within 6 hours (1).

Preliminary data from CMS indicate that the majority of SEP-1 cases nationally fail the measure, and cases that fail have higher mortality rates than cases that pass (2). It is unclear, however, whether failures are due to clinically meaningful lapses in care or whether the measure is overly prescriptive. CMS imposes very strict conditions to pass SEP-1, including detailed documentation of volume status, repeat lactate measurements regardless of patients' clinical appearance, and little flexibility to accommodate relative contraindications to aggressive fluid resuscitation (3, 4). It is also unclear if higher mortality rates for cases that fail SEP-1 are due to inferior care or higher severity of illness. For example, SEP-1 has more requirements for septic shock compared with severe sepsis alone, which may make SEP-1 failure more likely and inflate its apparent impact on mortality (5).

In addition, the evidence supporting each of the components included in SEP-1 is variable. Some measures, such as time to antibiotic administration, are relatively well supported whereas lactate measurements, volume reassessments, and how much fluids to give patients are more controversial (6–11). As an "all-or-nothing measure" that requires perfect performance to pass, SEP-1 gives equal weight to all of these components.

Given the substantial resources being devoted by hospitals to SEP-1 compliance and reporting, we evaluated the association between SEP-1 compliance and patient outcomes taking into account patients' clinical characteristics. We examined sepsis cases reported by seven academic and community hospitals to CMS during the first 2 years after SEP-1 implementation.

METHODS

Study Design, Patients, and Setting

This was a retrospective cohort study of sepsis cases submitted by seven hospitals to CMS for the SEP-1 measure from October 1, 2015—when SEP-1 went into effect—to September 31, 2017. SEP-1 adherence was measured by quality staff at each hospital who reviewed 20 randomly selected cases per month with discharge *International Classification of Diseases*, 10th Edition (ICD-10), codes for sepsis, as per CMS requirements. Quality staff assessed whether patients met CMS criteria for severe sepsis (i.e., documentation of suspected infection, greater than or equal to 2 systemic inflammatory response syndrome criteria, and organ dysfunction), when "time zero" occurred, and whether sepsis bundles were completed (1) (for a summary of SEP-1 criteria, see **Appendix A and B, Online Supplement**, Supplemental Digital Content 1, http://links.lww.com/CCM/D752). CMS exclusion criteria included transfer from outside facilities, documented goals of care precluding sepsis care, or hospital length of stay greater than 120 days. We also excluded cases transferred out of study hospitals to other acute care hospitals since their vital status at final discharge could not be ascertained.

The primary study sites included two academic referral hospitals in Boston, MA (Massachusetts General Hospital and Brigham and Women's Hospital), and three community hospitals in Eastern Massachusetts (Brigham and Women's Faulkner Hospital, North Shore Medical Center, and Newton-Wellesley Hospital). In addition, Barnes-Jewish Hospital in St. Louis, MO, and Duke University Hospital in Durham, NC (both academic referral hospitals), each contributed 30 randomly selected cases from quarters 3 or 4 of 2016 that met inclusion criteria. The study was approved by the Institutional Review Boards at Harvard Pilgrim Health Care Institute, Partners Healthcare, Washington University School of Medicine, and Duke University Health System.

Outcome and Variables

The primary outcome was in-hospital mortality. The primary exposure was failing SEP-1 (on any bundle component). Covariates from SEP-1 reporting included age, sex, race, specialty of discharging physician (medical, surgical, or other), and presence of septic shock (defined by initial lactate ≥ 4 mmol/L or persistent hypotension despite a fluid bolus of ≥ 30 cc/kg, as per CMS criteria [1]). Study investigators also reviewed medical records to assess organ dysfunction at severe sepsis time zero, body site of infection (pulmonary, urinary, intra-abdominal, or other), positive blood cultures (within ± 48 hr of time zero, excluding common skin contaminants),

and ICU admission and discharge dates. We calculated comorbidities and a weighted comorbidity score using the Elixhauser method for ICD-10 revision, discharge diagnosis codes (12–14). Hospital-onset sepsis was defined as time zero occurring more than 48 hours after admission.

SEP-1 reporting requirements allow abstractors to stop once any bundle component is determined to be noncompliant; for example, if a patient failed an initial lactate check, hospital quality officers did not routinely assess whether care teams passed or failed all subsequent components. Study investigators manually reviewed all cases, however, to identify the time of administration of IV broad-spectrum antibiotics. "Broad-spectrum" antibiotics were defined per CMS SEP-1 criteria, which require monotherapy with broad-spectrum β-lactams or fluoroquinolones, or combination therapy with two narrow-spectrum antibiotics (1).

We also reviewed medical records for documentation of "explicit infectious symptoms" versus "vague symptoms" at the time of presentation to the emergency department for sepsis present-on-admission or within the 24 hours before hospital-onset sepsis, since certain symptoms may increase the likelihood that clinicians recognize and treat sepsis (15). Explicit infectious symptoms were defined as fever (including fever at triage), sweats, chills, rigors, productive cough, dysuria, overt skin/soft tissue changes (e.g., unilateral limb erythema, abscess, or draining wound), or referral from an outside provider for documented infection (e.g., positive blood cultures), whereas vague infectious symptoms included altered mental status, weakness, fatigue, malaise, focal neurologic symptoms, abdominal pain, nausea, vomiting, diarrhea, hypotension, shortness of breath, dry cough, hypoxemia, or unexplained laboratory abnormalities without explicit infectious symptoms (15).

Statistical Analysis

We compared characteristics of cases that passed versus failed SEP-1 using the Wilcoxon rank sum test for continuous variables and the chi-square statistic for categorical variables. We used univariate logistic regression to assess associations between individual covariates and in-hospital death. We included the year of hospitalization (year 2 vs 1 of the study) as a covariate to account for possible temporal changes in SEP-1 compliance and minor specification changes that CMS introduced after the first year. Multivariate logistic regression was used to assess associations between SEP-1 failure and death. Age, sex, and race were included in the multivariable model a priori given their known association with sepsis outcomes (16, 17). Additional variables were chosen by first including all covariates with univariate p values less than or equal to 0.20. We then removed all covariates with adjusted p values greater than 0.10 from the multivariate model. The C-statistic was calculated to assess the discriminatory performance of the final multivariate model.

Time to antibiotics was not included as a separate covariate due to collinearity with the SEP-1 measure. In a sensitivity analysis, however, we replaced SEP-1 failure with one variable for time to antibiotics greater than 3 hours (which was assessed for all study patients, including those that failed SEP-1 earlier in the bundle pathway) and one variable for SEP-1 failure due to any reason other than time to antibiotics. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). We considered p value less than 0.05 to be statistically significant and used two-tailed tests.

RESULTS

Patient Characteristics and Reasons for SEP-1 Failure

A flowchart demonstrating the study cohort derivation and exclusions is shown in **Figure 1**. Of the 851 sepsis patients available for analysis, 281 (33.0%) passed SEP-1, whereas 570 (67.0%) failed. SEP-1 compliance rates were higher in the second year of the study versus the first (36.2% vs 29.6%; $p = 0.002$).

Cases that failed SEP-1 were similar to those that passed in terms of age, sex, race, and comorbidity burden but were significantly different with respect to other clinical characteristics (**Table 1**). Notably, SEP-1 failures were more likely to have septic shock, hospital-onset sepsis, vague rather than explicit infectious symptoms, and nonpulmonary infections compared with cases that passed.

The reasons that cases failed SEP-1 are shown in **Table 2**. Failure to draw an initial lactate or repeat lactate within 6 hours accounted for 40% of failures. Among all 570 cases that failed (including those that failed to have initial lactate or blood cultures drawn), only 86 patients (15.1%) had delays of greater than 3 hours until broad-spectrum antibiotic administration.

SEP-1 Compliance and Mortality

Of the 851 sepsis patients, 136 (16.0%) died in hospital. Sepsis mortality was similar in the first versus second year of the study (68/415, 16.4% vs 68/368, 15.6%; $p = 0.441$). The results of the univariate screen and multivariate analysis are shown in **Table 3**. Unadjusted mortality rates were higher for SEP-1 failures (18.4% vs 11.0%; odds ratio [OR], 1.82; 95% CI, 1.19–2.80; $p = 0.006$), but this difference was no longer significant after adjusting for patients' clinical characteristics (adjusted OR, 1.36; 95% CI, 0.85–2.18; $p = 0.205$). Variables significantly associated with an increased odds of death on multivariate analysis included age, non-white race, higher Elixhauser score, hospital-onset sepsis, septic shock, nonurinary source of infection, and vague presenting symptoms. The model's C-statistic was 0.79.

On sensitivity analysis, time to antibiotics of greater than 3 hours was significantly associated with death (adjusted OR, 1.94; 95% CI, 1.04–3.62; $p = 0.038$), whereas failing SEP-1 for any reason other than time to antibiotics was not (adjusted OR, 1.10; 95% CI, 0.70–1.72; $p = 0.674$). Findings were consistent for patients with severe sepsis alone versus those with septic shock and patients with community- versus hospital-onset sepsis; however, both SEP-1 failure and greater than 3-hour delays

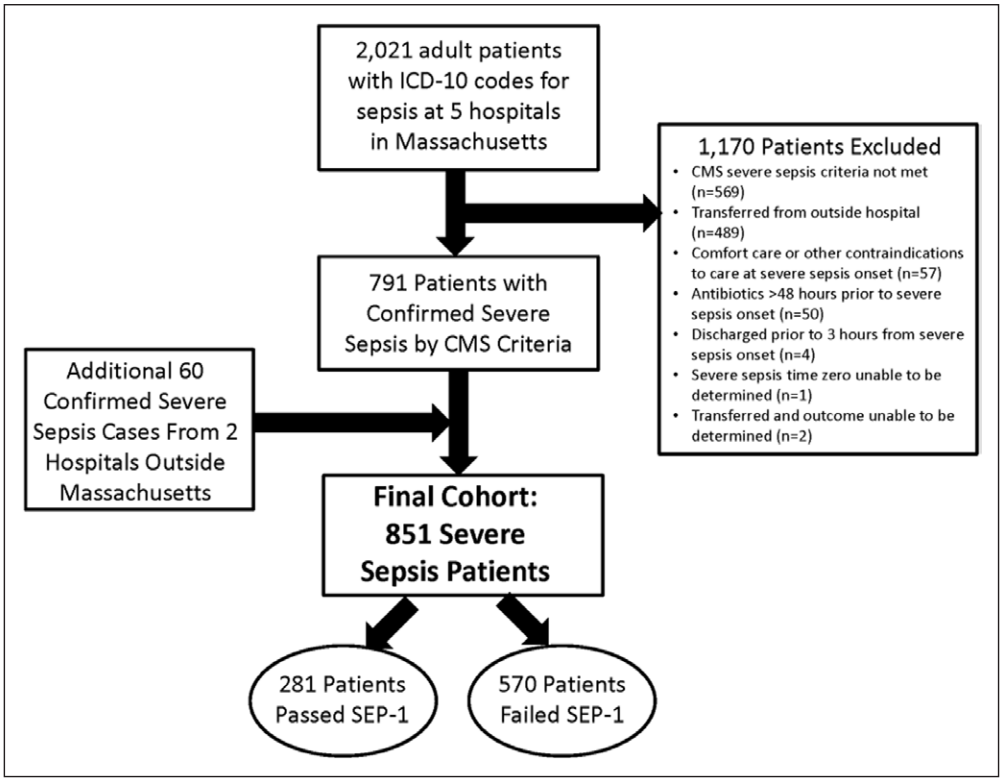

Figure 1. Flowchart for study cohort derivation and exclusions. CMS = Centers for Medicare and Medicaid Services, ICD-10 = *International Classification of Diseases*, 10th Edition.

in antibiotics were associated with higher mortality in patients with explicit infectious signs but not those with vague presenting complaints (**eTable**, Online Supplement, Supplemental Digital Content 1, http://links.lww.com/CCM/D752).

DISCUSSION

Most sepsis patients in this multicenter cohort received care that was noncompliant with the national SEP-1 measure. Mortality rates were higher in cases that failed SEP-1 compared with those that passed, but SEP-1 failures were more likely to have septic shock, hospital-onset sepsis, and vague infectious presenting symptoms. There was no significant difference in mortality between SEP-1 passes and failures after adjusting for these differences. Delays in broad-spectrum antibiotics were associated with higher mortality rates but only accounted for a fraction of SEP-1 failures.

Our findings of similar adjusted outcomes in cases that failed versus passed SEP-1 may reflect the overly rigid nature of the measure rather than ineffectiveness of timely sepsis care. In particular, SEP-1 does not allow partial credit for completing some bundle components nor does it prioritize any bundle components over others. The most common reasons for failure in our cohort were not measuring initial or repeat lactate levels. Although lactate levels may help risk stratify patients (18–20), there is limited evidence that measuring lactate improves patient outcomes (10). Many cases also failed because clinicians administered inadequate volumes of crystalloid fluids or neglected to document a repeat volume assessment examination. Only 15% of failures were due to delays greater than 3 hours in administering antibiotics, the one bundle component that was associated with higher mortality on multivariate analysis. This mortality association is consistent with prior studies suggesting that timely antibiotics are the most important component of sepsis bundles, particularly in patients with septic shock (7, 8, 21–23). In contrast, there is little evidence to support the fluid bundle component or the other SEP-1 hemodynamic interventions (7, 11).

In our cohort, SEP-1 failures were more common among patients with septic shock, presumably because this requires more steps to be performed and documented to pass. SEP-1 failures were also more common in hospital-onset sepsis, which tends to occur in more severely ill patients and is associated with worse outcomes than community-onset sepsis (24). Previous studies have also demonstrated that delays in sepsis recognition and management occur more often on hospital wards compared with emergency departments, where sepsis awareness and protocolized care tend to be more common (5, 25, 26).

We found that explicit infectious symptoms were strongly associated with SEP-1 compliance, timely antibiotics, and survival rates. Previous studies have documented that fever is associated with faster sepsis recognition (27–29), but this study and a companion analysis (15) extend this observation to include other obvious signs of infection. Our findings also suggest that presenting symptoms may be an important unmeasured confounder in other observational studies that have suggested lower mortality rates with rapid sepsis bundle application (15, 30–35). Conversely, patients with vague presenting symptoms may suffer worse outcomes because of delays in recognition and care or more frequent comorbid conditions. In addition, the lack of benefit of sepsis bundles and timely antibiotics in patients with vague symptoms may be because true infections are less common in this population.

Our study has several limitations. First, our findings may not be generalizable to other healthcare systems. However, our rate of SEP-1 compliance is similar to what has been reported nationwide (2), and our hospitals included both academic and community hospitals from three different states. Second, it is possible that our study was underpowered to detect a statistically significant association of failing SEP-1 with mortality. However, our sensitivity analyses demonstrated the

TABLE 1. Characteristics and Outcomes of Sepsis Patients Who Passed Versus Failed SEP-1

Clinical Characteristics	Pass (*n* = 281)	Fail (*n* = 570)	*p*
Median age (IQR)	68 (57–81)	67 (57–80)	0.319
Male sex, *n* (%)	155 (55.2)	303 (53.2)	0.582
White race, *n* (%)	223 (79.4)	446 (78.3)	0.710
Median Elixhauser score (IQR)	11 (5–16)	11 (5–17)	0.608
Academic vs community hospital, *n* (%)	144 (51.3)	301 (52.8)	0.668
Discharged in study year 2 (vs year 1), *n* (%)	158 (56.2)	278 (48.8)	0.041[a]
Discharging service, *n* (%)			
Medical	206 (73.3)	407 (71.4)	0.560
Surgical	4 (1.4)	37 (6.5)	0.001[a]
Other	71 (25.3)	125 (21.9)	0.277
Sepsis onset in emergency department, *n* (%)	232 (82.6)	421 (73.9)	0.005[a]
Hospital-onset sepsis (> 48 hr from presentation), *n* (%)	12 (4.3)	63 (11.1)	0.001[a]
Initial sepsis organ dysfunction, *n* (%)			
Hypotension	87 (31.0)	189 (33.2)	0.520
Lactate > 2 and < 4	80 (28.5)	138 (24.2)	0.181
Lactate ≥ 4	18 (6.4)	72 (12.6)	0.006[a]
Respiratory failure	13 (4.6)	37 (6.5)	0.277
Creatinine > 2	20 (7.1)	36 (6.3)	0.658
Bilirubin > 2	8 (2.9)	13 (2.3)	0.617
Platelets < 100	10 (3.6)	15 (2.6)	0.452
International normalized ratio > 1.5 or partial thromboplastin time > 60	4 (1.4)	9 (1.6)	0.862
Physician/provider documentation of severe sepsis/ septic shock	41 (14.6)	61 (10.7)	0.101
Septic shock (persistent hypotension or lactate ≥ 4), *n* (%)	25 (8.9)	112 (19.7)	<0.001[a]
Positive blood cultures, *n* (%)	75 (26.7)	160 (28.1)	0.672
Explicit infectious symptoms at presentation, *n* (%)	197 (70.1)	310 (54.4)	<0.001[a]
Body site source of infection, *n* (%)			
Pneumonia	113 (40.2)	188 (33.0)	0.038[a]
Urinary tract infection	66 (23.5)	137 (24.0)	0.860
Intra-abdominal infection	50 (17.8)	105 (18.4)	0.824
Other	52 (18.5)	140 (24.6)	0.047[a]
Outcomes			
Required ICU stay, *n* (%)	142 (50.5)	299 (52.5)	0.598
Median ICU LOS (IQR)	3 (2–6)	4 (2–9)	0.030[a]
Median hospital LOS (IQR)	7 (5–12)	8 (5–13)	0.132
In-hospital death, *n* (%)	31 (11.0)	105 (18.4)	0.006[a]

IQR = interquartile range, LOS = length of stay.

[a]Statistically significant variables at $p < 0.05$.

TABLE 2. Reasons for SEP-1 Failure

Bundle Failure Reason	No. of Failures (%)[a] (Total $n = 570$)
Initial lactate not drawn within 3 hr	112 (19.7)
Blood cultures within 3 hr (not drawn, or drawn after antibiotics)	86 (15.1)
Antibiotics within 3 hr	
Not given	77 (13.5)
Inappropriate selection	12 (2.1)
Repeat lactate not drawn within 6 hr	116 (20.4)
Crystalloids (inadequate amount or not given within 3 hr)	104 (18.3)
Persistent hypotension not assessed after crystalloid fluids	4 (0.7)
Vasopressors not given within 6 hr of persistent hypotension	8 (1.4)
Volume assessment not done within 6 hr of septic shock	42 (7.4)

[a]The distribution includes only the first component of the SEP-1 bundle that failed in each case.

significance of time to antibiotics, and the effect estimate was close to one for all SEP-1 component failures other than timely antibiotics. Third, as with all observational studies, we cannot rule out the possibility of residual confounding. Fourth, CMS introduced minor changes in the SEP-1 specification in the second year of SEP-1. However, study year had no influence in our model. Last, aside from antibiotic administration time, we were unable to measure the relative contributions of different components of the SEP-1 bundle or percentage of total bundle compliance to patients' outcomes, since data on each component were not available in patients who failed the measure. This also means that our reported failure rates for individual SEP-1 bundle components may underestimate their true failure rates.

In conclusion, our early experience with SEP-1 demonstrates a high rate of SEP-1 failures and higher crude mortality rates in sepsis cases that failed versus passed, but no difference in mortality after adjusting for clinical characteristics and severity of illness. The all-or-nothing nature of SEP-1 fails to differentiate between vital factors, such as early antibiotic administration, versus secondary factors, such as measuring lactates and documenting volume status. In addition, sophisticated risk adjustment is necessary to interpret differences in

TABLE 3. Univariate and Multivariate Models Examining Factors Associated With Death

Covariates	Univariate Screen		Multivariate Model	
Age (continuous)[a]	1.01 (1.00–1.02)	0.057	1.02 (1.00–1.03)	0.016
Male sex[a]	1.03 (0.71–1.49)	0.880	0.78 (0.52–1.19)	0.256
White race[a]	0.78 (0.51–1.20)	0.263	0.60 (0.37–0.96)	0.035
Elixhauser score[a] (continuous)	1.06 (1.04–1.09)	< 0.001	1.05 (1.03–1.08)	< 0.001
Academic hospital (vs community)[a]	1.64 (1.13–2.40)	0.010	–	–
Study year 2 vs year 1	0.94 (0.65–1.36)	0.754	–	–
Discharging service		0.239		–
Medical	Reference		–	
Surgical	1.41 (0.63–3.15)		–	
Other	1.40 (0.92–2.13)		–	
Hospital-onset sepsis[a]	5.13 (3.11–8.47)	< 0.001	4.61 (2.62–8.10)	< 0.001
Hypotension at sepsis onset	1.21 (0.83–1.78)	0.329	–	–
Septic shock (persistent hypotension or lactate ≥ 4 mmol/L)[a]	1.70 (1.08–2.66)	0.022	1.89 (1.14–3.12)	0.014
Respiratory failure at sepsis onset[a]	2.95 (1.59–5.47)	< 0.001	2.00 (0.98–4.06)	0.056
Vague symptoms[a]	3.16 (2.16–4.64)	< 0.001	2.36 (1.53–3.62)	< 0.001
Body site of infection[a]		< 0.001		< 0.001
Urinary	Reference		Reference	
Pulmonary	3.49 (1.86–6.55)		3.23 (1.64–6.38)	
Abdominal	2.55 (1.25–5.21)		2.24 (1.04–4.84)	
Other	4.09 (2.12–7.90)		4.20 (2.06–8.58)	
Positive blood cultures	1.11 (0.74–1.66)	0.609	–	–
Failing SEP-1 (all-or-nothing)	1.82 (1.19–2.80)	0.006	1.36 (0.85–2.18)	0.205

[a]Variables that were included in the multivariate model, based on significance at $p < 0.20$ on univariate screen or a priori decision to include (age, sex, race, and failing SEP-1). Academic hospital was dropped in the intermediate model because its p value was > 0.10.

Dashes indicate variables that were dropped in the final multivariate model.

outcomes between SEP-1 passes and failures. These findings call into question the utility of SEP-1 as currently structured and suggest possible ways to improve the measure.

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