Multicenter Implementation of a Severe Sepsis and Septic Shock Treatment Bundle

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Rationale: Severe sepsis and septic shock are leading causes of intensive care unit (ICU) admission, morbidity, and mortality. The effect of compliance with sepsis management guidelines on outcomes is unclear.

Objectives: To assess the effect on mortality of compliance with a severe sepsis and septic shock management bundle.

Methods: Observational study of a severe sepsis and septic shock bundle as part of a quality improvement project in 18 ICUs in 11 hospitals in Utah and Idaho.

Measurements and Main Results: Among 4,329 adult subjects with severe sepsis or septic shock admitted to study ICUs from the emergency department between January 2004 and December 2010, hospital mortality was 12.1%, declining from 21.2% in 2004 to 8.7% in 2010. All-or-none total bundle compliance increased from 4.9–73.4% simultaneously. Mortality declined from 21.7% in 2004 to 9.7% in 2010 among subjects noncompliant with one or more bundle element. Regression models adjusting for age, severity of illness, and comorbidities identified an association between mortality and compliance with each of inotropes and red cell transfusions, glucocorticoids, and lung-protective ventilation. Compliance with early resuscitation elements during the first 3 hours after emergency department admission caused ineligibility, through lower subsequent severity of illness, for these later bundle elements.

Conclusions: Total severe sepsis and septic shock bundle compliances increased substantially and were associated with a marked reduction in hospital mortality after adjustment for age, severity of illness, and comorbidities in a multicenter ICU cohort. Early resuscitation bundle element compliance predicted ineligibility for subsequent bundle elements.

Keywords: mortality; septicemia; outcome studies; quality improvement

Severe sepsis and septic shock (henceforth septic shock) are leading causes of morbidity and mortality in the intensive care unit (ICU) (1, 2). Published in-hospital mortality caused by septic shock ranges from 25–70% (3–5). Building on strategies to diminish morbidity and mortality, including early goal-directed

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Severe sepsis and septic shock are leading causes of intensive care unit admission, morbidity, and mortality. The effect of compliance with bundled elements of sepsis management guidelines on outcomes is unclear.

What This Study Adds to the Field

Total severe sepsis and septic shock bundle compliances increased substantially and were associated with a marked reduction in hospital mortality after adjustment for age, severity of illness, and comorbidities over 7 years in a multicenter intensive care unit cohort. Early resuscitation bundle element compliance predicted ineligibility, through lower subsequent severity of illness, for later bundle elements.

therapy (6), the Surviving Sepsis Campaign in 2004 and 2008 has promoted bundling appropriate elements of care from the emergency department (ED) and ICU into two bundles, a resuscitation and a maintenance bundle (7, 8). Bundled care processes standardize interventions to reduce unintended variation among clinicians and within a single clinician from patient to patient (9–13) by establishing a shared clinical baseline on which further care can be built. Additionally, bundled care elements can be measured and compared against pertinent clinical outcomes. Implementation of Surviving Sepsis Campaign guidelines has suffered from an unclear relationship among individual bundle elements and outcomes (14). In particular, it is unclear whether compliance with the earliest bundle elements may lead to a lessening of severity of illness and hence less need for later bundle elements (e.g., rapid resolution of shock as a result of prompt, appropriate identification of septic shock and administration of antibiotics obviates the need for red cell transfusions). We conducted a multihospital quality improvement study to (1) implement a septic shock bundle, (2) evaluate resulting changes in mortality, and (3) determine the significance of individual bundle elements in predicting mortality. We hypothesized that compliance with the bundle would be associated with lower mortality and that compliance with early resuscitation bundle elements would cause ineligibility, through decreased severity of illness, for later bundle elements. Some of these results have been previously reported in abstract form (15, 16).

METHODS

Study Design

We conducted a quality improvement intervention among patients with severe sepsis and septic shock admitted directly from the ED to the ICU. Patients were enrolled from 18 Intermountain Healthcare ICUs in 11

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hospitals in Utah and Idaho between January 1, 2004 and December 31, 2010. Following local adaptation of Surviving Sepsis Campaign bundle recommendations into a bundle of care processes (see Table E1 in the online supplement), the study was conducted in three stages based on ICU admission date: (1) baseline and bundle development stage, January 1, 2004 to December 31, 2004; (2) implementation stage, January 1, 2005 to December 31, 2007; and (3) tracking stage, January 1, 2008 to December 31, 2010. The first stage represented a period of identifying bundle elements and eligibility and coordinating a data collection process. The second stage involved large-scale education about elements and intent of the bundle. The last stage reflected a period when Intermountain Healthcare made compliance with sepsis bundles a corporate initiative. The Intermountain Healthcare Institutional Review Board granted approval for waiver of consent for this quality improvement study.

Data Collection and Definitions

All subjects admitted to a participating ICU from the ED, either directly or by the operating room, were screened. Subjects not admitted to the ICU from the ED directly or from the ED by the operating room were excluded to diminish potential confounding from care delivered on the ward or at an outside hospital. The bundle was specifically designed for ED to ICU resuscitation of subjects with septic shock further necessitating exclusion of other admission sources. Subjects younger than 18 years old were excluded, as were those in which initial screening data were incomplete.

After identification of subjects (see the online supplement), trained study coordinators reviewed each subject's medical record and judged the data against standard criteria for sepsis, which includes a presumed or known source of infection along with at least two systemic inflammatory response syndrome criteria (17). Subjects were then classified as having either severe sepsis or septic shock in the first 24 hours. Severe sepsis meant sepsis plus evidence of end-organ dysfunction (e.g., altered mentation, renal insufficiency) or lactate greater than or equal to 2 mmol/L (18). Septic shock included severe sepsis plus either hypotension despite adequate fluid resuscitation or serum lactate greater than or equal to 4 mmol/L. Subjects identified as either severe sepsis or septic shock underwent study coordinator review of individual bundle elements using a combination of paper chart, direct communication with clinicians, and electronic health record review to record compliance. Demographic data, including age, sex, race or ethnicity, severity of sepsis as either severe sepsis or septic shock, Acute Physiology Score (APS), Charlson Comorbidity Index score (CCIS), and in-hospital mortality were recorded.

We divided the total bundle of 11 individual elements temporally into a seven-element resuscitation bundle and a four-element maintenance bundle (see Table E1). The first three resuscitation elements, which applied to all subjects regardless of disease severity, were to be completed within 3 hours of ED admission. The next four resuscitation elements were to be completed within 6 hours of ED admission. For hypothesis testing of the role of bundle element ineligibility on mortality, we evaluated bundle elements 4–11 as “later” bundle elements. Bundle elements 4–11 were deemed later bundle elements because they were invoked only if the subject met *a priori* definitions of severity of illness. Compliance with bundle elements 1–3 and 8 (glucose) was classified as “eligible and compliant” or “eligible and noncompliant” because all subjects were deemed eligible for these criteria. Compliance with bundle elements 4–7 and 9–11 was noted as “eligible and compliant,” “eligible and noncompliant,” or “ineligible” because not all subjects were deemed eligible for these treatments. “Ineligible” refers to subjects who are less ill and therefore did not require advanced therapies. For example, subjects who did not require high doses of vasopressors were considered ineligible for glucocorticoids. Bundle compliances were defined as all-or-none at 24 hours from ED admission: noncompliance with any single element was interpreted as noncompliance with the bundle. Individual bundle element compliance occurred when the subject was either “eligible and compliant” or “ineligible.”

Statistical Analysis

Descriptive statistics summarized subject characteristics (age, sex, and race) and compliance with the sepsis bundle over the three study stages:

baseline (January 1, 2004 to December 31, 2004); implementation (January 1, 2005 to December 31, 2007); and tracking stage (January 1, 2008 to December 31, 2010) (see Table E2 for additional details about study ICUs.) The mean and SD or median and interquartile range (IQR) were used to describe continuous measures, where appropriate. A chi-square test compared mortality over the study periods. Changes in the median number of compliant elements over time were evaluated with the Kruskal-Wallis statistic. A statistical process control chart (p-chart) was generated to illustrate total bundle compliance and mortality over time. Generalized linear mixed model for conditional logistic regression analysis with random intercepts was performed to examine the association between inpatient mortality and independent variables (age, sex, race, severity of sepsis, and sepsis bundle elements) while controlling for CCIS and APS. We considered study hospital to be the random effect. We assessed for multicollinearity using tolerance and variance inflation factor statistics. Any variable with a variance inflation factor greater than 2.5 was removed from the model (19). A stepwise, backward selection method was used for feature selection for the final model. Interactions between lactate and septic shock, fluid resuscitation and septic shock, and glucocorticoids and septic shock were evaluated for effect modification based on severity of sepsis. Finally, we created regression models using compliance with early bundle elements 1, 2, and 3 to predict ineligibility for later elements that had been identified as associated with mortality in the final, multivariate regression model. Because of potential bias in the estimated effect of early bundle compliance on later bundle element ineligibility in this observational study, two propensity score adjustment methods (stratification and matching) were used to validate the hypothesis that early bundle element compliance caused later element ineligibility. Study period, severity of sepsis, age, APS, and CCIS were included in the propensity score model of early bundle element compliance. A random 1:1 matching without replacement selection method was implemented for the propensity score with matching, and caliper width was 0.2. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC). Two-tailed statistical significance level, α , was defined at 0.05.

RESULTS

Of 4,379 subjects who met inclusion criteria over 7 years, 1.1% ($n = 50$) were excluded (Figure 1). Among the remaining 4,329 subjects, baseline demographics, APS, CCIS, and severity of sepsis are noted in Table 1 by survival and in Table E3 by study period. Central tendencies of initial ED serum lactate level, initial ED systolic blood pressure, and ED length of stay were unchanged from 2004–2010 (data not shown). Mortality was 12.1% for the overall cohort, including 17.0% among subjects with septic shock and 8.9% among subjects with severe sepsis (Table 1). Concomitant with a 68.5% absolute increase in all-or-none total bundle compliance from 4.9% at baseline to 73.4% in 2010, relative mortality declined 59.0% from 21.2% at baseline to 8.7% for 2010 ($P < 0.0001$) (Figure 2). Compliances with resuscitation and maintenance bundles were similarly associated with improved mortality (data not shown).

Mortality among subjects noncompliant with the total bundle decreased 55.3% over the study period from 21.7% at baseline to 9.7% for 2010 (see Table E5 for results by hospital). Concomitantly, the median number of noncompliant total bundle elements among noncompliant subjects fell over time ($P < 0.0001$ for trend) from 4 (IQR, 2–5; max 11) in 2004 to 2 (IQR, 1–3; max 10) for 2005–2007 and then 1 (IQR, 1–2; max 8) for 2008–2010.

Age, severity of sepsis, and most bundle elements were associated with mortality after adjustment for APS and CCIS (Table 2). In the final multivariate model age and compliance with inotropes and red cell transfusions, steroid administration, and use of a lung-protective ventilation strategy were associated with improved mortality after adjustment for APS and CCIS (Table 2). Of note, there was no interaction between glucocorticoids, lactate, or fluid resuscitation and presence of septic

Figure 1. Flow diagram of subjects by study period.

shock versus severe sepsis (data not shown). A sensitivity analysis restricted to subjects with septic shock (as opposed to severe sepsis) yielded the same results as the overall multivariate model that included patients with severe sepsis and septic shock. Only 18 subjects were admitted to the ICU from the ED by way of the operating room, of which 2 died ($P = 0.89$ for comparison of mortality in this cohort with mortality among subjects admitted directly to the ICU from the ED).

The percent of subjects ineligible for later bundle elements consistently increased over time ($P < 0.01$ for each) (see Table E6). Subjects were, by definition, always deemed eligible for element 8, glucose control. After adjustment for age, APS, and CCIS, compliance with early resuscitation elements (all in the first 3 h after ED admission) was associated with increased odds of ineligibility for inotropes and red cell transfusions, glucocorticoids, and use of a lung protective ventilation strategy in a regression model. Specifically, compliance with lactate measurement predicted ineligibility for all three of these later bundle elements (all $P < 0.001$), as did compliance with obtaining blood cultures (all $P < 0.0001$) and compliance with antibiotic administration before blood cultures (all $P < 0.01$). Matching 2,084 subjects in propensity score analysis (1,042 who were not compliant with the first three elements matched to 1,042 who were compliant with the first three elements) yielded the same findings. Compliance with the first three elements predicted

ineligibility for inotropes and red cell transfusions (odds ratio [OR], 1.40; 95% confidence interval [CI], 1.10–1.79); glucocorticoids (OR, 1.30; 95% CI, 1.06–1.60); and lung-protective ventilation (OR, 1.48; 95% CI, 1.14–1.91). Findings from propensity score analysis using stratification also were the same. For these three later elements, eligible and compliant subjects were as likely to die as eligible and noncompliant subjects (all $P = \text{NS}$). Subjects ineligible for each of the three later elements were significantly less likely to die than eligible subjects across all study periods (all $P < 0.0001$).

DISCUSSION

In a multicenter investigation after development and implementation of a septic shock bundle, absolute compliance with the total bundle increased 68.5% (from 4.9–73.4%) from 2004–2010. Total bundle compliance was significantly associated with a 59% relative reduction in hospital mortality after adjustment for age, severity of illness, and comorbidities. Compliance with early resuscitation elements (completed within the first 3 h after ED admission) also predicted greater ineligibility for inotropes and red cell transfusions, glucocorticoids, and lung-protective ventilation. The latter finding is compatible with lower rates of progression to more severe disease in the first 24 hours when early bundle elements were performed.

TABLE 1. COMPARISON OF STUDY SUBJECTS BY SURVIVAL, 2004–2010

Characteristic	Died (n = 526)	Survived (n = 3,803)	Overall (n = 4,329)	P Value
Mean (SD) age, yr	68.9 (15.2)	61.9 (17.3)	62.7 (17.2)	<0.0001
Mean (SD) Acute Physiology Score	23.5 (10.2)	15.3 (7.6)	16.3 (8.4)	<0.0001
Mean (SD) Charlson Comorbidity Index Score	5.8 (3.6)	4.9 (3.6)	5.0 (3.6)	<0.0001
Female, n (%)	264 (50.2)	1,901 (50.0)	2,165 (50.0)	0.93
Race or ethnicity, n (%)				0.29
White, non-Hispanic	474 (90.1)	3,364 (88.5)	3,838 (88.7)	
Black, non-Hispanic	4 (0.8)	42 (1.1)	46 (1.1)	
Hispanic	26 (4.9)	209 (5.5)	235 (5.4)	
Other	22 (4.2)	188 (4.9)	207 (4.8)	
Severity of sepsis, n (%)*				<0.0001
Septic shock in first 24 h	242 (50.7)	1,184 (32.9)	1,426 (34.9)	
Severe sepsis in first 24 h	235 (49.3)	2,420 (67.1)	2,655 (65.1)	

* There were 49 subjects who died and 199 who survived for which severity of sepsis could not be determined because of missing data. Percentages listed are for nonmissing data only. Among all subjects with septic shock (n = 1,426), 1,184 (83.0%) survived. Among all subjects with severe sepsis (n = 2,655), 2,420 (91.1%) survived.

Figure 2. P-chart of total bundle compliance and mortality, 2004–2010. (A) Among all subjects, mortality (circles) decreased while all-or-none total bundle compliance (squares) increased over time. The 95% statistical process control limits are represented by dashed lines. (B) Among only subjects with septic shock, mortality (circles) also decreased while all-or-none total bundle compliance (squares) increased over time. The 95% statistical process control limits are represented by dashed lines.

There are several strengths of the current investigation above and beyond previously published data. First, although the Surviving Sepsis Campaign reported a 6.2% reduction in unadjusted mortality from 37.0–30.8% over 2 years (14), we witnessed a larger 12.5% absolute reduction, a much larger relative decline (59.0%), and to a much lower mortality over 7 years. Similarly, we observed a larger reduction to a lower mortality than that described by Ferrer and colleagues throughout ICUs in Spain (20). These findings may be related to secular changes over the longer period of study (e.g., unmeasured changes in clinical practice, adoption of admission order sets for patients with sepsis, and increased early recognition of sepsis). The difference in our results may also reflect unmeasured differences between the study populations, given the absence of APS or CCIS in Surviving Sepsis Campaign data. We also achieved a higher rate of total bundle compliance (from 26–74% all-or-none total bundle compliance from 2005–2010) than Surviving Sepsis Campaign hospitals (from 11–31% over 2 yr in the resuscitation bundle and from 18–36% over 2 yr in the maintenance bundle) and Spanish ICUs (20). Importantly, even the number of individual noncompliant elements fell significantly over time (from a median of 4 to a median of 1) and with less variation. The bundle required significant collaboration between the ED and ICU, both of which bore responsibility for its completion. Second, we adjusted our multivariate analyses

for severity of illness (APS) and comorbidities (CCIS) using standard scores. Our work confirms the findings of a much smaller, single-center study from Brazil. In a study of septic shock bundle implementation in a single hospital ICU, Shiramizo and coworkers (21) noted that compliance with glucocorticoids and with lung-protective ventilation (plateau pressure < 30 cm H₂O rather than 6 ml/kg tidal volume) was associated with improved survival.

Third, we identified three elements of the bundle associated with improved survival: (1) inotropes and red cell transfusions, (2) glucocorticoids, and (3) lung-protective ventilation. The findings may be taken as supportive of Levy and coworker's (22) original “sepsis change bundle” focused on avoiding refractory hypotension (here, reflected by glucocorticoids), hypoperfusion (inotropes and red cell transfusions), and organ dysfunction (lung-protective ventilation). Inotropes and red cell transfusions for septic shock date back more than 40 years (23) and are part of early goal-directed therapy (6). Although improving oxygen delivery in the first 6 hours seemed to improve mortality in early goal-directed therapy with a special catheter in the ED environment (6), optimizing oxygen delivery during the first 24 hours of established septic shock has not held up in randomized clinical trials (24, 25). Lung-protective ventilation improves survival in acute respiratory distress syndrome (26). Patients with sepsis frequently have concomitant lung injury, although specific evaluation of lung-protective ventilation in a cohort of subjects with sepsis does not exist. Glucocorticoids, however, represent an intriguing finding in our investigation. Significant debate over the safety and benefits of glucocorticoids for sepsis persists (27, 28). In a recent review of the literature, Patel and Balk (29) poignantly concluded that “bedside clinical judgment with expert opinion” guide use of glucocorticoids in septic shock.

Fourth, we investigated why bundle elements beyond the first 3 hours of care were associated with mortality in the multivariate model. Prior investigators (14, 21) have not described the implication of ineligibility for later bundle elements in their analyses. Later bundle elements (inotropes and red cell transfusions, glucocorticoids, and lung-protective ventilation) may be associated with mortality because the overall severity of illness of our cohort decreased over time or because compliance with early resuscitation bundle elements is beneficial in decreasing the number of subjects progressing to septic shock with worsening organ failure over the first 24 hours. The former is not supported by our data. The latter is supported by two observations: the magnitude of decrease in eligible and compliant subjects over time is mostly reflected by an increase in ineligible subjects; and ineligible subjects had higher survival at all times than eligible subjects. Early resuscitation bundle compliance in the cohort predicts ineligibility of (less severity of illness in) subjects at 24 hours after ED admission. We believe the association of glucocorticoids with mortality, for example, likely reflects a statistical finding in the setting of fewer eligible subjects as a result of increasing early resuscitation compliance. Even if the specific physiologic interventions may not be beneficial in isolation, they seem to improve mortality as markers of an integrated bundle of all-or-none interventions (22, 30, 31). Prospective study is necessary to determine whether early identification of an elevated lactate, for example, might alert the ED physician to the appropriate diagnosis sooner, prompt more aggressive fluid resuscitation, increase the likelihood of ICU admission, or heighten clinical suspicion for severe disease, thereby enhancing quality of care and driving improved mortality.

Our study suffers from important limitations. First, as a largely retrospective cohort, the study may suffer from unintended selection or measurement biases. Of note, the number of cases increased markedly between the second and third study periods. We acknowledge three possible contributors to this increase:

TABLE 2. LOGISTIC REGRESSION MODELS OF HOSPITAL MORTALITY

Variable	Value	Trivariate Model		Final Multivariate Model	
		OR (95% CI)	P Value	OR (95% CI)	P Value
Age*	Per year	1.03 (1.02–1.03)	<0.0001	1.03 (1.03–1.04)	<0.0001
Acute Physiology Score†	Per point	1.11 (1.10–1.12)	<0.0001	1.12 (1.11–1.14)	<0.0001
Charlson Comorbidity Index Score†	Per point	1.06 (1.04–1.09)	<0.0001	1.05 (1.02–1.08)	<0.001
Inotropes and packed red blood cells*	Compliant‡	Referent			
	Noncompliant‡	2.31 (1.72–3.11)	<0.0001	1.62 (1.12–2.33)	<0.01
Glucocorticoids*	Compliant‡	Referent			
	Noncompliant‡	2.06 (1.62–2.62)	<0.0001	1.76 (1.32–2.37)	<0.001
Use of low tidal volume ventilation, if mechanically ventilated*	Compliant‡	Referent			
	Noncompliant‡	2.77 (1.98–3.87)	<0.0001	1.84 (1.24–2.73)	<0.01
Sex	Male	Referent			
	Female	1.00 (0.84–1.21)	0.97		
Severity of sepsis*	Severe sepsis	Referent			
	Septic shock	2.08 (1.71–2.53)	<0.0001		
Serum lactate measured*	Compliant‡	Referent			
	Noncompliant‡	1.22 (0.92–1.61)	0.17		
Blood cultures before antibiotics*	Compliant‡	Referent			
	Noncompliant‡	1.55 (1.14–2.11)	<0.01		
Broad-spectrum antibiotics*	Compliant‡	Referent			
	Noncompliant‡	1.26 (0.97–1.65)	0.09		
Fluid resuscitation*	Compliant‡	Referent			
	Noncompliant‡	1.27 (0.86–1.89)	0.23		
Vasopressors	Compliant‡	Referent			
	Noncompliant‡	0.94 (0.63–1.41)	0.77		
Central venous pressure and ScvO ₂ *	Compliant‡	Referent			
	Noncompliant‡	1.71 (1.32–2.19)	<0.0001		
Glucose control*	Compliant‡	Referent			
	Noncompliant‡	1.38 (1.08–1.76)	<0.01		
Glucocorticoids*	Compliant‡	Referent			
	Noncompliant‡	2.06 (1.62–2.62)	<0.0001	1.76 (1.32–2.37)	<0.001
Drotrecogin alfa eligibility assessed*	Compliant‡	Referent			
	Noncompliant‡	2.56 (1.87–3.49)	<0.0001		
Use of low tidal volume ventilation, if mechanically ventilated*	Compliant‡	Referent			
	Noncompliant‡	2.77 (1.98–3.87)	<0.0001	1.84 (1.24–2.73)	<0.01
Total resuscitation bundle	Compliant§	Referent			
	Noncompliant§	1.46 (1.21–1.76)	<0.0001		
Total maintenance bundle	Compliant§	Referent			
	Noncompliant§	1.80 (1.42–2.18)	<0.0001		
Total bundle	Compliant§	Referent			
	Noncompliant§	1.48 (1.22–1.79)	<0.0001		

Definition of abbreviations: CI = confidence interval; ED = emergency department; OR = odds ratio; ScvO₂ = central venous oxygen saturation.

* Potential predictors for the final model ($P < 0.25$ on trivariate analysis).

† Covariates for trivariate and multivariate models.

‡ Compliant = eligible and compliant or ineligible for that single bundle element. Noncompliant = eligible and noncompliant for that single bundle element.

§ Compliant = eligible and compliant or ineligible for all elements in that bundle. Noncompliant = eligible and noncompliant for any one element in that bundle.

(1) up to a 160% increase in severe sepsis (32) during this time nationally; (2) an increased local emphasis identifying subjects with sepsis (i.e., increased ascertainment); and (3) the opening of a new, large trauma and tertiary care hospital in October 2007, which markedly increased the catchment area and also increased ICU bed capacity. The number of available ICU beds increased 41% from 2004–2010, after the opening of a new quaternary care medical center and the addition of three hospitals with electronic records. Also, although data coordinators confirmed that all 4,329 subjects met criteria for severe sepsis or septic shock, the use of an administrative database and data coordinator review to identify subjects for screening may have introduced selection bias. Another possible source of measurement bias was higher missingness for severity of sepsis in the first phase compared with later phases (25% vs. 2.2%, respectively). If the percentage of all subjects in 2004 with septic shock were truly 76%, as found among those with nonmissing severity of sepsis, the fall in percentage of subjects with septic shock could contribute to the fall in mortality observed. Importantly, severity of sepsis was not included in the regression models because of high collinearity with other variables (e.g., APS).

Second, we cannot exclude a change over time either in unmeasured confounders or in subjects' severity of illness. We used initial ED systolic blood pressure, initial serum lactate level, and CCIS to confirm that there was not an important shift in ED admission severity of illness over time. Instead, APS, which is measured using worst physiologic values across the first 24 hours of admission, increased from 2005–2007 to 2008–2010 simultaneous with declining mortality. We suspect increasing compliance with early resuscitation elements near the time of admission may have led to a decrease in a subject's subsequent illness severity.

Third, the lower absolute mortality in our study compared with others (14, 21) may reflect that we had a less severely ill population. Four possible reasons for a less severely ill study population include (1) we excluded subjects transferred from outside, non-Intermountain Healthcare hospitals; (2) our ICU cohort had fewer or less severe baseline comorbidities than prior studies; (3) we excluded subjects who became septic while in the hospital or ICU; and (4) we only included 18 subjects who went to the OR before arrival in the ICU. Further study of only subjects with septic shock may be useful in clarifying whether our low mortality reflects local admission factors or effects of

the treatment bundle. Fourth, racial homogeneity may limit the external validity of these findings (33). Fifth, the decline in mortality among noncompliant subjects mirrors the decline among compliant subjects, suggesting that total bundle compliance alone may not have been the primary driver of decreased mortality. Subjects who did not meet criteria for total bundle compliance nevertheless had fewer noncompliant elements over time, an effect that likely contributed to the overall decrease in mortality. In addition to a decrease in the median number of noncompliant elements, variance also decreased, suggesting decreased variation in practice over time.

In a large cohort of critically ill patients with septic shock admitted from the ED to an ICU, compliance with bundle elements was associated with increased survival. Compliance with therapy to increase oxygen delivery, glucocorticoids, and lung-protective ventilation was associated with lower mortality. Compliance with early resuscitation bundle elements (first 3 h) was associated with a lower probability of being eligible for later resuscitation and maintenance bundle elements. Bundling care processes for patients with severe sepsis and septic shock seems beneficial in this multicenter cohort.

Author disclosures are available with the text of this article at www.atsjournals.org.

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