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Original Article

The Implementation of Sepsis Bundles on the Outcome of Patients with Severe Sepsis or Septic Shock in Intensive Care Units☆

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SUMMARY

Background: The goal of the study was to implement sepsis bundles and examine the effect on patients with severe sepsis or septic shock in intensive care units (ICUs).

Methods: All patients with severe sepsis or septic shock admitted to the 13-bed ICU were included. Sepsis bundles were implemented within 24 hours after admission. The implementation of sepsis bundles was categorized into preintervention (January to April 2010), education (July to October 2010), operational (November to December 2010), and postintervention (January to April 2011) phases. Comparison of bundle compliance and outcome between each phase were examined. We also found mortality predictors between preintervention and postintervention phases.

Results: There were 164 patients included in the study. Compared with the preintervention phase, the bundle compliance of each phase (education, operation, and postintervention separately) was higher (43.3%, 84.6%, and 79.2%, respectively, vs. 20.0%, $p < 0.05$), the hospital mortality was lower (10.0%, 23.1%, and 24.5%, respectively, vs. 43.6%, $p < 0.05$). Under multivariate analyses, the predictors for mortality between the preintervention and postintervention phases were: lactate at ICU (odds ratio [OR] 2.212), urinary tract infection (OR 0.026), and postintervention (OR 0.239).

Conclusion: Implementation of modified sepsis bundles was successful in changing sepsis treatment behavior and was associated with a substantial reduction in hospital mortality and trends of decreased hospital expenditure. Factors improved hospital mortality, as lower lactate levels at ICU, urinary tract infection, and postintervention. The proposed intervention is generally applicable to achieve similar improvements.

1. Introduction

Severe sepsis, defined as sepsis with one or more episodes of acute organ dysfunction, may include persistent hypotension, hypoxemia, metabolic acidosis, oliguria, thrombocytopenia, and impaired liver function. In the United States, there are approximately 750,000 new cases of sepsis each year with a mortality rate consistently higher than 25% for severe sepsis and up to 70% for septic shock[1,2]. In Taiwan the age-standardized annual incidence rate of severe sepsis increased 1.6-fold (135 per 100,000 in 1997 to 217 per 100,000 in 2006). The proportion of patients with multi-organ (≥2) dysfunction increased (11.7% in 1997 to 27.6% in 2006), but there was little change in hospital mortality, averaging 30.8%[3].

Considering the recent advances of therapeutic strategies such as early appropriate antibiotic therapy[4,5], early goal-directed therapy (EGDT)[6], low-dose steroid therapy[7], tight glucose control[8], and lung-protective strategies[9] have all been shown to be associated with survival benefits. The Surviving Sepsis Campaign (SSC) guidelines, endorsed by many professional organizations throughout the world, were developed as a plan to reduce severe sepsis mortality by 25%[10]. The development and publication of guidelines often do not lead to changes in clinical behavior[11], and the most effective means for achieving knowledge transfer remains an unanswered question across all medical disciplines. National

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efforts to promote the SSC guidelines are nonexistent in most of Asia, and are influenced by cost concerns that limit the implementation of potentially expensive bundles[12].

Bundle care has been demonstrated to improve survival using multifaceted strategies for changes in clinical behavior and quality improvement[13–15]. Although some of the recommendations are controversial, these studies suggested quality improvement efforts based on the SSC guidelines were associated with improved outcomes. Thus, an interdisciplinary team was needed to improve early recognition and process of care in patients with severe sepsis or septic shock based on SCC guidelines. The aim of the current study was to implement a modified sepsis bundle and to examine the effect of a continuous quality improvement (CQI) initiative on treated patients. It was hypothesized that improved guideline compliance would result in improved patient outcomes.

2. Materials and methods

2.1. Study design and patient selection

From January 1, 2010 to May 30, 2011, a prospective observational cohort study was conducted in a tertiary care medical center in southern Taiwan. All patients with severe sepsis or septic shock admitted to a 13-bed intensive care unit (ICU) via the emergency department were included in the study. The time of transferring such patients from the emergency department to the ICU was less than 6 hours. The ICU staff included intensivists, respiratory therapists, clinical nurse specialists, clinical dietitians, clinical pharmacists, and residents, who provided 24-hour coverage. The diagnostic criteria for severe sepsis or septic shock used in this study were adapted from the definition developed by the Consensus Panel of the American College of Chest Physicians and the Society of Critical Care Medicine (1992)[16]. Severe sepsis was defined as the presence of at least two of four criteria for systemic inflammatory response syndrome due to a proven or suspected site of infection, in association with at least one of the following sepsis-induced organ dysfunctions (Appendixes 1 and 2)[16].

Modified sepsis bundles were implemented within 24 hours after ICU admission in order to improve patient outcomes[10] (Appendix 3). Sepsis bundles were divided into four phases: preintervention (January to April 2010), education (July to October 2010), operational (November to December 2010), and postintervention (January to April 2011). During the education phases, specific training, educational materials, and CQI initiative on physicians, nurses, and residency staff in the ICU were provided, including: (1) conference lectures, bedside tutorials on the definition of sepsis, and early recognition and treatment options including decision-making algorithms; (2) a Chinese translation of the SSC guidelines in poster and pocket format; (3) a checklist focused on the early recognition and treatment of sepsis with modified sepsis bundles; and (4) a computerized physician order entry set to aid the completion of bundles. The operational phase consisted of bundle delivery in the ICU setting. Physicians and nurses used a sepsis checklist and pocket cards as daily reminders of the processes involved in bundle delivery to the staffs in the ICU and emergency department. The postintervention phase was used as a long-term follow-up at the end of study. This study was approved by Institutional Review Board of Chi Mei Medical Center.

2.2. Measurements

The following data were collected: (1) demographic and clinical variables, including age, sex, body weight, height, and body mass index (measured as body weight per square height in meters), use of a ventilator, lactate levels in the emergency department and ICU, and mean blood glucose level within 24 hours of ICU admission; (2) severity of each patient's condition as determined by clinical nurse specialists upon ICU admission using the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the Therapeutic Intervention Scoring System (TISS) scores, Glasgow Coma Scale, and the presence of acute organ dysfunction (as described in Appendix 2); (3) primary infection sites; (4) outcomes, including length of ICU and overall hospital stay, ICU and hospital mortality rate and total hospital costs; and (5) bundle compliance measurements, including individual bundles and all bundles. The primary endpoint was comparison of bundle compliance, hospital mortality, and hospital expenditure between each phase. Secondary outcome measures included predictors for hospital mortality between the preintervention and postintervention phases to avoid the possible Hawthorne effect due to intervention.

2.3. Statistical analyses

Median values, interquartile ranges, and group size were used to summarize the results for continuous variables. The differences among groups, and survival and nonsurvival groups at hospital discharge were examined by univariate analysis with a nonparametric test and a chi-square test. A p value <0.05 was considered statistically significant. Predetermined variables (as all sepsis bundles), or those significantly associated with hospital mortality in univariate analysis ($p < 0.05$), were tested for interaction with multiple logistic regression analysis. Odds ratios (OR) and 95% confidence intervals (CI) were also calculated. Statistical analysis of the data was done using SPSS 13.0 for Windows (SPSS, Inc., Chicago, IL, USA).

3. Results

There were 164 patients included in the current analysis (55 in the preintervention phase, 30 in the education phase, 26 in the operational phase, and 53 in the postintervention phase), and 42.1% were female. The median age was 74 years with a median APACHE II score, TISS score, and coma scale of 23, 27, and 9, respectively, on the day of admission to the ICU. Median body weight was 58.0 kg, with a median height of 1.6 m, and a median body mass index of 22.0 kg/m^2. There were 41 patients (25.0%) with severe sepsis, and 123 patients (75.0%) had septic shock upon admission to the ICU. The median number of acute organ dysfunctions per patient was two, the most common of which were cardiovascular failure (80.5%) and respiratory failure (46.7%). There were 125 patients (76.2%) who required intubation with ventilator support. Additional results are shown in Table 1. The major sources of infection were pneumonia (63.4%), urinary tract infection (UTI; 28.7%) and intra-abdominal infection (IAI; 8.5%), as shown in Table 2. The overall ICU and hospital mortality rates were 25.0% and 28.0%, respectively. The median duration of ICU and hospital stays was 11 and 19 days, respectively. For all patients, median hospital cost was 8.5 $\times$ 1000 US dollars (USD) (Table 3). Each group had similar baseline data, except the preintervention group had a lower lactate level in the emergency department (2.7 mmol/L) and a higher blood glucose level within 24 hours (178 mg/dL) as compared with other groups. There were also some differences on multiorgan failures between each group (hematologic, hepatic, metabolic, and respiratory failure). The completion of sepsis bundles was gradually higher after the education and operational phases (43.3% and 84.6%), and maintained a higher level (79.2%) even 1 year later during the postintervention phase as compared with the preintervention phase (20.0%, $p < 0.05$ as compared to each group), especially in broad antibiotic agents, central venous oxygen saturation ($ScvO_2$) survey, blood sugar $\leq$ 150 mg/dL (all $p < 0.05$,

Table 1
Baseline data among different patients.

Items	All (n = 164)	Preintervention	Education	Operational	Postintervention	p
		Jan–Apr 2010 (n = 55)	Jul–Oct 2010 (n = 30)	Nov–Dec 2010 (n = 26)	Jan-Apr 2011 (n = 53)	
Sex (female)	69 (42.1%)	24 (43.6%)	6 (20.0%)	15 (57.7%)	24 (45.3%)	0.863
Age	74.0 (61.0–82.0)	72.0 (57.0–85.0)	68.0 (60.0–79.0)	78.0 (71.0–83.0)	77.0 (64.0–81.0)	0.115
Body weight (kg)	58.0 (48.0–65.9)	58.0 (46.0–65.0)	64.0 (55.7–70.0)	50.0 (42.0–60.0)	55.0 (47.5–65.0)	0.189
Height (m)	1.6 (1.6–1.7)	1.6 (1.6–1.7)	1.7 (1.6–1.7)	1.6 (1.5–1.7)	1.6 (1.5–1.7)	0.537
Body mass index	22.0 (19.1–24.9)	21.3 (19.9–25.5)	23.8 (20.8–25.5)	21.7 (16.7–23.9)	21.3 (18.7–24.8)	0.172
APACHE II scores	23.0 (18.0–29.0)	18.0 (15.0–24.0)	23.0 (15.0–27.0)	26.0 (20.0–29.0)	25.0 (19.0–29.0)	0.494
Glasgow Coma Scale	9.0 (6–14)	10.0 (7.0–14.0)	10.0 (6.0–15.0)	9.0 (7.0–12.0)	10.0 (6.0–14.0)	0.538
TISS scores	27.0 (23.0-34.0)	26.0 (20.0–28.0)	30.0 (21.0–36.0)	29.0 (24.0–33.0)	30.0 (23.5–33.5)	0.181
Severe sepsis	41 (25.0%)	15 (27.3%)	8 (26.7%)	6 (23.1%)	12 (22.6%)	0.578
Septic shock	123 (75.0%)	40 (72.7%)	22 (73.3%)	20 (76.9%)	41 (77.4%)	0.628
Lactate at emergency department (mmol/L)	2.6 (1.7–4.0)	1.9 (1.5–3.7)	2.8 (1.9-6.3)	2.8 (2.0–4.0)	3.0 (2.1–4.2)	0.004
Lactate at ICU (mmol/L)	2.0 (1.6–2.9)	2.0 (1.2–3.0)	2.0 (1.5–3.9)	1.9 (1.7–2.3)	2.0 (1.7-2.8)	0.609
Blood glucose level within 24 h (mg/dL)	132.0 (112.0–162.3)	178.0 (166.0-223.0)	148.0 (108.0–194.0)	118.0 (112.0–135.0)	120.0 (110.0–136.0)	<0.001
No. of organ failures	2.0 (1.0–2.0)	2.0 (2.0–2.0)	1 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0-3.0)	0.610
Hematologic failure	21 (12.8%)	6 (10.9%)	3 (10.0%)	6 (23.1%)	12 (22.6%)	0.002
Hepatic failure	9 (5.5%)	3 (5.5%)	0 (0%)	3 (11.5%)	3 (5.7%)	0.017
Renal failure	13 (7.9%)	2 (3.6%)	5 (16.7%)	1 (3.8%)	5 (9.4%)	0.152
Metabolic failure	38 (23.2%)	9 (16.4%)	7 (23.3%)	11 (42.3%)	19 (35.8%)	<0.001
Respiratory failure	76 (46.3%)	33 (60.0%)	8 (26.7%)	5 (19.2%)	30 (56.6%)	<0.001
Cardiovascular failure	132 (80.5%)	41 (74.5%)	26 (86.7%)	21 (80.8%)	44 (83.0%)	0.535
Ventilator use	125 (76.2%)	54 (85.5%)	19 (63.3%)	18 (69.2%)	40 (75.5%)	0.994

Data are presented as median (interquartile range) or n (%).
APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; TISS = Therapeutic Intervention Scoring System.

Table 4). The education, operational, and postintervention phases also had lower hospital mortality (10.0%, 23.1%, and 24.5%, respectively), ICU stays (8, 10, and 10 days, respectively), hospital stays (15,19, and 17 days, respectively) and total hospital cost (6.3, 8.3, and 8.5 × 1000 USD) when comparison with the preintervention phase, as listed in Table 3. There were many factors that contributed to hospital mortality, including preintervention and postintervention phases (Table 5), but multivariate analyses revealed the predictors for hospital mortality were lactate levels at the ICU (OR 2.212; 95% CI, 1.305–3.759; $p = 0.003$); UTI (OR, 0.026; 95% CI, 0.02–0.370; $p = 0.007$), and postintervention (OR, 0.239; 95% CI, 0.266–0.766; $p = 0.028$).

4. Discussion

Many factors might influence the outcome of severe sepsis in a univariate study, including body weight, body mass index, condition severity (APACHE II, TISS, and Glasgow Coma Scale), IAI, and ventilator use. However, only postintervention, lower lactate levels in the ICU, and presence of a UTI were indicative of a strong prognostic effect on survival after adjustment of confounding factors. Compliance with sepsis bundles in the ICU has been reported to be associated with a reduction in mortality. Data from 15,022 patients at 165 sites revealed that improved bundle compliance decreased the hospital mortality rate from 37% to 30.8% over 2 years[13]. A similar study in Spain with 2566 patients demonstrated reduced mortality from 44.0% to 39.7% associated with increased bundle compliance 1 year later[14]. Both studies show a preintervention bundle completion rate less than 10%, which is comparable with the study from 150 ICUs of 16 Asian countries with a mortality rate of 44.5%[12]. In our study, a better bundle compliance (20.0%) at the preintervention phase, but a similar mortality rate of 43.6% was found. It is well known that adherence to new strategies is best early after implementation (after a learning curve), and that adherence decreases again after some time when no educational refreshing measures are done. In contrast, our study disclosed that the quality improvement effort was associated with a high bundle completion rate (43.3% at education phase and highest at operational phase at 84.6%), and it was maintained to almost 80% even after follow-up 1 year later at the end of the study period. Most patients had almost 100% of the bundles initiated except blood sugar control strategies (completion rate of 86.8%) at the postintervention phase, and a reduced hospital mortality was disclosed (43.6–24.5%, $p = 0.012$). A trend of lower ICU and hospital stays, ICU mortality, and hospital costs were also observed in the current study. This is supported by results from the large cohort study in Spain that found no differences in hospital or ICU admissions before and after an educational program[14]. A practice improvement program grounded in evidence-based guidelines may be responsible for the survival benefit observed in the current study. The effort on

Table 2
Infection source among different patients.

Items	All (n = 164)	Preintervention	Education	Operational	Post-intervention	p
		Jan–Apr 2010 (n = 55)	Jul–Oct 2010 (n = 30)	Nov–Dec 2010 (n = 26)	Jan-Apr 2011 (n = 53)	
Soft tissue	4 (2.4%)	2 (3.6%)	1 (3.3%)	0 (0%)	1 (1.9%)	0.765
Wound infection	7 (4.3%)	1 (1.8%)	2 (6.7%)	1 (3.8%)	3 (5.7%)	0.684
Pneumonia	104 (63.4%)	35 (63.6%)	18 (60.0%)	16 (61.5%)	35 (66.0%)	0.951
Urinary tract infection	47 (28.7%)	12 (21.8%)	9 (30.0%)	10 (38.5%)	17 (32.1%)	0.564
Intra-abdominal infection	14 (8.5%)	5 (9.1%)	3 (10.0%)	2 (7.7%)	4 (7.5%)	0.979
Central nervous system infection	6 (3.7%)	1 (1.8%)	2 (6.7%)	1 (3.8%)	2 (3.8%)	0.728
Bloodstream infection	15 (9.1%)	6 (10.9%)	0 (0%)	4 (15.4%)	5 (9.4%)	0.217
Infective endocarditis	1 (0.6%)	1 (1.8%)	0 (0%)	0 (0%)	0 (0%)	0.574

Data are presented as n (%).

Table 3
The outcomes among different patients.

Items	All ($n = 164$)	Preintervention	Education	Operational	Postintervention	p
		Jan–Apr 2010 ($n = 55$)	Jul–Oct 2010 ($n = 30$)	Nov–Dec 2010 ($n = 26$)	Jan-Apr 2011 ($n = 53$)	
ICU days	11.0 (6.0–16.0)	12.0 (7.0–16.0)	8.0 (6.0–11.0)	10.0 (6.0–16.0)	10.0 (6.0–15.0)	0.177
Hospital days	19.0 (13.0–34.0)	23.0 (13.0–35.0)	15.0 (13.0–32.0)	19.0 (11.0–34.0)	17.0 (11.0–36.0)	0.590
ICU mortality	41 (25.0%)	19 (34.5%)	3 (10.0%)	6 (23.1%)	13 (24.5%)	0.099
Hospital mortality	46 (28.0%)	24 (43.6%)	3 (10.0%)	6 (23.1%)	13 (24.5%)	0.012
Total hospital cost (×1000 USD)	8.5 (5.3–12.5)	9.1 (6.1–12.8)	6.3 (4.4–11.3)	8.3 (2.1–10.0)	8.5 (4.1–10.8)	0.645

Data are presented as median (interquartile range) or n (%).
ICU = intensive care unit; USD = US dollars.

postintervention was responsible for the reduction of hospital mortality after multivariate analysis. Applying the "plan-do-study-act" cycle via CQI is probably the best approach to sustain the effect of the educational program.

Lactate levels are frequently elevated in critically ill patients and positively correlate with disease severity. It is well accepted that elevated lactate levels are prognostic in prehospital, emergency department, and ICU settings[17,18]. Additionally, lactate clearance or lactate $\leq$ 2 mmol/L after resuscitation has been demonstrated to be an independent predictor for improved mortality[19,20]. Similarly, the current study disclosed that lower lactate levels ($\leq$2 mmol/L) at ICU admission is predictive of reduced mortality (OR 2.212, $p = 0.003$). Of note, emergency department physicians at our hospital often transfer patients to the ICU for further resuscitation within 6 hours as an alternative to EGDT at the emergency department; the lactate levels measured during admission to the ICU may also reflect the sufficiency of early sepsis resuscitation in the emergency department. In 2001, Rivers et al[6] demonstrated that EGDT upon admission to the emergency department can significantly reduce mortality in patients with severe sepsis or septic shock. Considering the achievement of $ScvO_2$ $\geq$70% in EGDT, an Australasian multicenter study reported favorable ICU and overall hospital mortality rates of 18.8% and 23.1%, respectively, without including routine, $ScvO_2$-directed resuscitation[21]. Another recent study has also shown no difference in mortality for patients with severe sepsis and septic shock who were resuscitated with a protocol of lactate clearance compared with a protocol of $ScvO_2$[22]. The current study performed resuscitation with a goal to lower lactate levels at the time of ICU admission. Furthermore, the insertion of a central venous catheter was monitored and the survey of $ScvO_2$ within 6 hours rather than $ScvO_2$ $\geq$70%. For all clinical purposes, a low $ScvO_2$ value is an important warning sign of inadequate systemic oxygen, but it does not provide guidance for the optimal therapeutic approach, as well as the reason for the oxygen inadequacy. In addition, a normal or high $ScvO_2$ value does not rule out persistent tissue hypoxia, especially in patients with sepsis caused by decreased oxygen extraction. Therefore, the $ScvO_2$ value may not be suitable to guide resuscitation in patients with severe sepsis or septic shock[23].

Consistent with published literature, the leading sources of sepsis in the current study were identified as pneumonia (63.4%), UTI (28.7%), bloodstream infection (9.1%), and IAI (8.5%)[12–15,20,22,24,25]. Levy et al[13] suggested pneumonia as the source of sepsis and predicted hospital mortality over other infections (OR, 1.37), whereas Blanco et al[24] showed that UTI was associated with lower mortality (OR, 0.1). The current results are comparable with Blanco et al[24] in that UTI as the origin of sepsis was associated with lower mortality (OR, 0.029). In contrast, no independent association of infection site with mortality after multivariate analysis was identified in a recently published large trial[25] (n = 3588). Variations may be explained by differences in the heterogeneous population and early antibiotics.

SSC was a performance improvement process, rather than a dedicated scientific evaluation of the effect of the guidelines on clinical outcomes. Thus, results must be interpreted with caution in regard to the clinical effect of bundle elements, or the protocol itself. The observation that achievement of glucose control is associated with improved outcomes is not necessarily supported by recently published data, although blood sugar control ($\leq$ 150 mg/dL) is still used as a therapeutic goal[26]. Currently, significant differences were observed between preintervention and postintervention blood sugar control (180.5 vs. 124.1 mg/dL); however, this did not translate to any mortality benefit.

The major limitation of the current study was the single center setting. The number of patients is relatively small considering the

Table 4
The completion of sepsis bundles among different groups.

Items	All ($n = 164$)	Preintervention	Education	Operational	Postintervention	p
		Jan–Apr 2010 ($n = 55$)	Jul–Oct 2010 ($n = 30$)	Nov–Dec 2010 ($n = 26$)	Jan–Apr 2011 ($n = 53$)	
Within 6 h						
Broad antibiotics	155 (94.5%)	46 (83.6%)	30 (100%)	26 (100%)	53 (100%)	<0.001
Lactate survey	161 (98.2%)	52 (94.5%)	30 (100%)	26 (100%)	53 (100%)	0.109
$ScvO_2$ survey	137 (83.5%)	30 (54.5%)	30 (100%)	26 (100%)	53 (100%)	<0.001
Blood culture before antibiotics	163 (99.4%)	54 (98.2%)	30 (100%)	26 (100%)	53 (100%)	0.574
Fluid resuscitation $\geq$ 20 mL/kg	162 (98.2%)	53 (96.4%)	30 (100%)	26 (100%)	53 (100%)	0.260
Use vasopressor on refractory hypotension	164 (100.0%)	55 (100%)	30 (100%)	26 (100%)	53 (100%)	1.000
Within 24 h						
Check cortisol before steroid use	150 (91.5%)	49 (89.1%)	29 (96.7%)	24 (92.3%)	49 (92.5%)	0.614
Low dose steroid on vasopressor use	164 (100.0%)	55 (100%)	30 (100%)	26 (100%)	53 (100%)	1.000
Blood sugar $\leq$ 150 ($\geq$ 80) mg/dL	106 (64.6%)	23 (41.8%)	14 (46.7%)	25 (96.2%)	46 (86.8%)	<0.001
Peak inspiratory pressure $\leq$ 35 (and plateau pressure $\leq$ 30) cmH_2O on ventilator	164 (100.0%)	55 (100%)	30 (100%)	26 (100%)	53 (100%)	1.000
All completion	86 (52.4%)	11 (20.0%)	13 (43.3%)	22 (84.6%)	42 (79.2%)	<0.001

Data are presented as n (%).
$ScvO_2$ = central venous oxygen saturation.

Table 5
The significant predictors of hospital mortality among preintervention and postintervention groups.

Items	Survivor ($n = 71$)	Nonsurvivor ($n = 37$)	p	OR (95% CI)	p
Body weight	55.0 (47.0–65.0)	63.5 (49.0–71.0)	0.035		
APACHE II scores	21.0 (15.0–26.0)	26.0 (19.0–34.0)	<0.001		
TISS scores	27.0 (22.0–32.0)	33.0 (24.0–38.0)	0.012		
Glasgow Coma Scale	10.0 (6.0–14.0)	6.0 (6.0–11.0)	0.003		
Lactate at ICU	1.8 (1.5–2.3)	3.0 (2.0–4.2)	<0.001	2.212 (1.305–3.759)	0.003
Urinary tract infection	26 (36.6%)	3 (8.1%)	0.001	0.026 (0.02–0.370)	0.007
Intra-abdominal infection	2 (2.8%)	7 (18.9%)	0.004		
Ventilator use	51 (71.8%)	36 (97.3%)	0.002		
Postintervention	40 (75.5%)	13 (35.1%)	0.044	0.239 (0.266–0.766)	0.028

Data are presented as median (interquartile range) or n (%).
APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; ICU = intensive care unit; OR = odds ratio; TISS = Therapeutic Intervention Scoring System.

amount of different parameters assessed. Because of nonrandomized characteristics as ethical constraints, the implementation of the bundle and quality indicators was at best associated with a mortality benefit rather than being representative of causal factors. It cannot be stated definitively that this benefit was due to some or all bundle elements, increased awareness of severe sepsis, or other unrelated factors. There may be some intrinsic bias between the preintervention and postintervention groups due to the increasing knowledge and improved medical care over time. As clinicians seek to improve treatment of patients with severe sepsis, they may choose to implement the SSC guidelines or modified bundles in their entirety, considering even the most conservative conclusion from the current report is that doing so is unlikely to cause harm. The current study did not recruit emergency department staffs to join a complete sepsis bundles. $ScvO_2$ as a resuscitation goal due to the inconvenience of continuous $ScvO_2$ insertion and the replacement of lactate measurement at ICU was monitored.

5. Conclusion

The current study demonstrates the implementation of the Surviving Sepsis Guidelines into practice using a multifaceted performance improvement initiative. This initiative was successful in changing sepsis treatment behavior as evidenced by a significant increase in compliance with sepsis bundles. Over the duration of the 1-year study, compliance was associated with a significant reduction in hospital mortality and a trend of decreased hospital costs and stays in patients with severe sepsis and septic shock. This intervention is generally applicable to other centers with a goal to achieve similar improvements in patient outcomes.

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Appendix 1
Disease diagnostic criteria (entry criteria)

The diagnostic criteria for severe sepsis used in this study are based on an adaptation of the operational definition developed by the Consensus Panel of the American College of Chest Physicians and the Society of Critical Care Medicine (Bone et al, 1992).

Proven infection: Objective identification of a pathogen by one or more methods, including culture of patient specimens, Gram stain, tissue stain, polymerase chain reaction, or other recognized methods.

Suspected infection: A highly suggestive clinical presentation. Examples include pneumonia, abdominopelvic syndromes such as cholangitis, cholecystitis, and perforated viscus, and surgical wound or other cutaneous infection, gross purulence, urosepsis, or purpura fulminans.

Appendix 2
Disease diagnostic criteria: Presence of one or more acute organ dysfunction

1. Cardiovascular (septic shock): Hypotension in the absence of additional causes other than sepsis. For example, an arterial systolic blood pressure (SBP) of $\leq$90 mmHg or a mean arterial pressure (MAP) $\leq$ 65 mmHg for at least 1 hour despite adequate fluid resuscitation; or the need for vasoactive agents (dopamine $\geq$5 μg/kg/min) to maintain SBP $\geq$90 mmHg or MAP $\geq$ 65 mmHg.

2. Respiratory: Acute lung injury due to sepsis associated with serious hypoxemia. For example, $PaO_2/FiO_2 < 250$ without pneumonia or < 200 with pneumonia.

3. Renal: Oliguria with an average urine output < 0.5 mL/kg/h for 4 hours despite adequate fluid resuscitation; or Cr $\geq$ 2 mg/dL; end-stage renal disease was excluded.

4. Hematologic: Thrombocytopenia. For example, a platelet count $< 80{,}000/mm^3$ or 50% decrease in platelet count from the highest value recorded over the past 3 days.

5. Unexplained metabolic acidosis: Defined by (1) pH $\leq$ 7.30 or base deficit $\geq$ 5.0 mEq/L and (2) a plasma lactate level $>$ 3 mmol/L. Measurement of pH or base deficit and lactate level should occur within a clinically relevant time interval such that a causal relationship exists between the measured values.

6. Hepatic: Markedly increased serum bilirubin level $\geq$ 4 mg/dL due to sepsis.

Appendix 3
Modified sepsis bundles

Within 6 hours after emergency department admission (resuscitation bundle):

1. Broad-spectrum antibiotics: from the time of presentation, broad-spectrum antibiotics administered within 1 hour of admission to the emergency department or within 3 hours at the time of ICU admission.

2. Lactate survey: serum lactate measured within 6 hours.

3. $ScvO_2$ survey: in the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate $>$ 4 mmol/L (36 mg/dL), performed central venous catheter insertion and checked central venous oxygen saturation ($ScvO_2$) at the emergency department or ICU within 6 hours.

4. Blood cultures before antibiotics: blood cultures obtained prior to antibiotic administration and performed at the emergency department or ICU within 6 hours.

5. Fluid resuscitation≥20 mL/kg: in the event of hypotension and/or lactate > 4 mmol/L (36 mg/dL), delivered an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent) within 6 hours.

6. Use vasopressor on refractory hypotension: applied vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65 mmHg within 6 hours.

Within 24 hours after emergency department admission (management bundle):

7. Check cortisol before steroid use: cortisol level checked under the suspicion of adrenal insufficiency before low-dose steroids were administered for septic shock within 24 hours.

8. Low-dose steroid on vasopressor use: low-dose steroids administered for septic shock in accordance with standardized hospital policy within 24 hours.

9. Blood sugar ≤ 150(≥ 80) mg**/dL:** glucose control maintained greater than the lower limit of normal (≥ 80 mg/dL, 4.4 mmol/L), but ≤150 mg/dL (8.3 mmol/L).

10. Ventilator strategy: keep peak inspiratory pressure ≤ 35 (and plateau pressure ≤ 30) cmH_2O on ventilator.

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