

# Effectiveness of Treatments for Severe Sepsis

## A Prospective, Multicenter, Observational Study

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**Rationale:** Several Surviving Sepsis Campaign Guidelines recommendations are reevaluated.

**Objectives:** To analyze the effectiveness of treatments recommended in the sepsis guidelines.

**Methods:** In a prospective observational study, we studied all adult patients with severe sepsis from 77 intensive care units. We recorded compliance with four therapeutic goals (central venous pressure 8 mm Hg or greater for persistent hypotension despite fluid resuscitation and/or lactate greater than 36 mg/dl, central venous oxygen saturation 70% or greater for persistent hypotension despite fluid resuscitation and/or lactate greater than 36 mg/dl, blood glucose greater than or equal to the lower limit of normal but less than 150 mg/dl, and inspiratory plateau pressure less than 30 cm H<sub>2</sub>O for mechanically ventilated patients) and four treatments (early broad-spectrum antibiotics, fluid challenge in the event of hypotension and/or lactate greater than 36 mg/dl, low-dose steroids for septic shock, drotrecogin alfa [activated] for multiorgan failure). The primary outcome measure was hospital mortality. The effectiveness of each treatment was estimated using propensity scores.

**Measurements and Main Results:** Of 2,796 patients, 41.6% died before hospital discharge. Treatments associated with lower hospital mortality were early broad-spectrum antibiotic treatment (treatment within 1 hour vs. no treatment within first 6 hours of diagnosis; odds ratio, 0.67; 95% confidence interval, 0.50–0.90;  $P = 0.008$ ) and drotrecogin alfa (activated) (odds ratio, 0.59; 95% confidence interval, 0.41–0.84;  $P = 0.004$ ). Fluid challenge and low-dose steroids showed no benefits.

**Conclusions:** In severe sepsis, early administration of broad-spectrum antibiotics in all patients and administration of drotrecogin alfa (activated) in the most severe patients reduce mortality.

**Keywords:** intensive care unit; guidelines; mortality; propensity scores

Severe sepsis and septic shock are major healthcare problems, affecting millions of individuals around the world each year (1, 2). Severe sepsis and septic shock are among the main causes of death among hospitalized patients, with a mortality rate of 20 to 54% (3–5).

Early appropriate antibiotic therapy (6–8), early goal-directed therapy (EGDT) (9), corticosteroids (10), recombinant human activated protein C or drotrecogin alfa (activated) (11),

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### AT A GLANCE COMMENTARY

#### Scientific Knowledge on the Subject

Early appropriate antibiotic therapy, early goal-directed therapy, corticosteroids, recombinant human-activated protein C, tight glucose control, and lung protective strategies have been associated with survival benefits in patients with severe sepsis.

#### What This Study Adds to the Field

In a large cohort of ICU patients with severe sepsis, we found that two of the four treatments recommended in the Surviving Sepsis Campaign care bundles, i.e., early administration of broad-spectrum antibiotics and administration of drotrecogin alfa (activated), were independently associated with lower hospital mortality after adjusting for several independent clinical predictors of death.

tight glucose control (12), and lung protective strategies (13) have been associated with survival benefits. These and other therapeutic advances led to the development of the Surviving Sepsis Campaign (SSC) guidelines (14, 15) as part of a plan to reduce mortality due to severe sepsis by 25% by 2009.

To improve care for sepsis, the SSC and the Institute for Healthcare Improvement recommend implementing a 6-hour resuscitation bundle including lactate determination, early cultures and antibiotics, and EGDT, as well as a 24-hour management bundle including optimization of glycemic control and respiratory inspiratory plateau pressure and determination of the need for corticosteroids or drotrecogin alfa (activated). The negative results of recent trials, such as the CORTICUS study (16) and the NICE SUGAR study (17), have made some of these recommendations controversial and are being reevaluated.

In a previous prospective before-and-after study, we demonstrated that it is possible to improve compliance with the SSC guidelines and to improve outcome through a multicenter educational program based on the SSC bundles (Edusepsis study) (18). The main objective of the present study was to analyze the impact of treatments for severe sepsis on hospital mortality in all patients included in the three periods of the Edusepsis study (preeducational period, posteducational period, and long-term follow-up). Some preliminary results of this study were reported in the form of an abstract at the Society of Critical Care Medicine Conference in 2007 (19).

### METHODS

#### Subjects and Design

We included all adult patients with severe sepsis or septic shock from the 77 intensive care units (ICU) participating in the Edusepsis study (18), an

observational study with three inclusion periods: a 2-month period before the implementation of an educational program (November–December 2005), a 4-month period after its implementation (March–June 2006), and a 2-month, long-term follow-up period 1 year later (May–June 2007).

All ICU admissions from the emergency department or from wards and all ICU patients were actively screened daily for the presence of severe sepsis or septic shock. We excluded patients in whom the onset of severe sepsis could not be determined.

Severe sepsis was defined as sepsis associated with organ dysfunction unexplained by other causes. A diagnosis of sepsis was made based on the following findings: respiratory dysfunction (bilateral pulmonary infiltrates with  $\text{PaO}_2/\text{FiO}_2 < 300$ ), renal dysfunction (urine output  $< 0.5$  ml/kg/hr for at least 2 hours or creatinine  $> 2.0$  mg/dl), coagulation abnormalities (International Normalized Ratio [INR]  $> 1.5$  or a partial thromboplastin time [PTT]  $> 60$  seconds), thrombocytopenia (platelet count  $< 100,000 \mu\text{l}^{-1}$ ), hyperbilirubinemia (total plasma bilirubin  $> 2.0$  mg/dl), hypoperfusion (lactate  $> 18$  mg/dl), or hypotension (systolic blood pressure  $< 90$  mm Hg, mean arterial pressure  $< 65$  mm Hg, or a reduction in systolic blood pressure  $> 40$  mm Hg from baseline measurements). Septic shock was defined as acute circulatory failure (systolic blood pressure  $< 90$  mm Hg, mean arterial pressure  $< 65$  mm Hg, or a reduction in systolic blood pressure  $> 40$  mm Hg from baseline) despite adequate volume resuscitation.

### Clinical and Outcome Variables

The following clinical variables were recorded: age, sex, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, patient location at sepsis diagnosis, origin of infection, baseline lactate level, organ dysfunction at sepsis diagnosis, and hospital mortality. During the first 24 hours after sepsis, we recorded the four therapeutic goals and the four treatments included in the SSC care bundles. Therapeutic goals were (1) central venous pressure (CVP) at least 8 mm Hg in the event of persistent hypotension despite fluid resuscitation and/or lactate greater than 36 mg/dl, (2) central venous oxygen saturation ( $\text{ScvO}_2$ ) at least 70% in the event of persistent hypotension despite fluid resuscitation and/or lactate greater than 36 mg/dl, (3) blood glucose greater than or equal to the lower limit of normal but less than 150 mg/dl, and (4) inspiratory plateau pressure less than 30 cm  $\text{H}_2\text{O}$  for mechanically ventilated patients. Treatments were (1) early administration of broad-spectrum antibiotics (time from severe sepsis presentation to antibiotic administration: first hour, 1 to 3 hours, 3 to 6 hours, previous antibiotic, or no antibiotic administered in the first 6 hours), (2) fluid challenge of a minimum of 20 ml/kg of crystalloid (or colloid equivalent) in the event of hypotension and/or lactate greater than 36 mg/dl, (3) low-dose steroids in the event of persistent hypotension despite fluid resuscitation and/or lactate greater than 36 mg/dl, and (4) drotrecogin alfa (activated) for multiorgan failure. The primary outcome measure was hospital mortality.

### Data Collection and Quality Control

Data were collected prospectively daily using preprinted case report forms. Completed data forms were mailed to the coordinating center and registered in the database by a research nurse with experience in sepsis trials. Errors or blank fields generated queries that were returned to each center for correction.

For quality assurance purposes, data were checked for completeness, accuracy, and uniformity. A random sample of 10% of patients was reevaluated, and interrater reliability for the variables was assessed in this sample. A reliability of 96.5% of all variables per case report form was observed.

### Statistical Analysis

Frequencies and percentages or means and standard deviations were used where appropriate to describe patient characteristics for the entire group and for survivors and nonsurvivors. Student's *t* tests and  $\chi^2$  tests were used to compare survivors and nonsurvivors when appropriate.

The effectiveness of each treatment was estimated using propensity scores in the subsample where it was indicated. Propensity scores were estimated by fitting a multinomial logistic regression for time-to-administration of broad-spectrum antibiotics and binary logistic regressions for the other three treatments. The covariates included in the propensity

score models were all clinical variables (Table 1) except lactate (because it was poorly determined) and the therapeutic goals that showed a statistically significant association with mortality (Table 2) along with the three remaining treatments except the one being modeled (Table 3). We derived propensity score quintiles and assessed the validity of the propensity scores in three ways. First, to assess the balancing of covariates between treated and untreated groups in each propensity score quintile, we compared all the covariates for the treated and untreated groups within each quintile. Second, we drew box plots of the estimated propensity scores for treated and untreated patients within each quintile of the propensity scores (20). Third, the area under the curve for the propensity score models was derived. For each assessed treatment, to take into account potential residual imbalances in the final model in addition to treatment and the propensity score quintiles, we included all the covariates that showed a statistically significant difference between treated and untreated groups in any quintile and APACHE II scores in the logistic regression model for mortality (21).

To assess the robustness of our results, we conducted several sensitivity analyses. First, we refitted the propensity score models including only treatment and the associated propensity score quintiles in the logistic models for mortality. Second, we fitted "classical" multivariable logistic regression models for each treatment including as covariates the ones used to estimate the propensity scores. Third, to assess the presence of immortal bias for treatments showing a statistically significant reduction in mortality, we refitted the propensity score models excluding patients who died within the time recommended for administering the treatment in the SSC (6 hours for antibiotics and fluids and 24 hours for steroids and drotrecogin alfa). In addition, we fitted time-varying Cox proportional hazards models where the treatment was included as a time-dependent covariate, and the covariates used to estimate the propensity scores were included as nontime-varying covariates (22).

Two-tailed *P* values less than 0.05 were considered statistically significant. All analyses were conducted using SPSS version 17.0 (SPSS, Chicago, IL).

### Ethical Issues

Each participating center's Research and Ethical Review Board approved the study, and patients remained anonymous. The need for informed consent was waived in view of the anonymous nature of the study and because all interventions had been tested and published in previous trials (23).

## RESULTS

### Demographic and Clinical Characteristics

A total of 2,804 ICU patients with severe sepsis or septic shock were recruited during the three study periods. Eight patients were excluded because the time of onset of sepsis could not be determined. Thus, 2,796 patients were included, and 1,164 (41.6%) of these died before hospital discharge (Table 1). Mean age was 62.2 years, mean APACHE II score was 21.2, 61.4% were male, and 62.2% had medical septic conditions. Pneumonia (36.5%) was the most common infection, followed by abdominal infections (29.8%). Most patients were admitted to the ICU with severe sepsis from the emergency department (41.1%) or ward (44%), and only 14.9% first presented sepsis in the ICU. At severe sepsis diagnosis, the mean number of organ failures was 3.0, with hemodynamic, respiratory, and renal failure being the most common. The mean initial lactate level was 32.9 mg/dl; however, lactate level was only determined in 54.1% of cases.

### Clinical Risks Factors for Mortality

The univariate analysis revealed significant differences between survivors and nonsurvivors (Table 1). Nonsurvivors were older and predominantly male. Nosocomial (ward or ICU) presentation of severe sepsis was more common in nonsurvivors. Severity at sepsis presentation was greater in nonsurvivors:

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS

Variable	All patients (n = 2,796)	Nonsurvivors (n = 1,164)	Survivors (n = 1,632)	P Value
Age, mean ± SD	62.2 ± 16.3	65.3 ± 14.9	60.0 ± 16.8	<0.001
Male, n (%)	1,717 (61.4)	754 (64.8)	963 (59.0)	0.002
Diagnosis on ICU admission, n (%)				0.492
Medical	1,738 (62.2)	713 (61.5)	1,025 (63.2)	
Surgical urgent	817 (29.2)	345 (29.7)	472 (29.1)	
Surgical nonurgent	157 (5.6)	74 (6.4)	83 (5.1)	
Trauma	70 (2.5)	28 (2.4)	42 (2.6)	
Patient location at sepsis diagnosis, n (%)				<0.001
Emergency department	1,149 (41.1)	381 (32.7)	768 (47.1)	
Ward	1,230 (44.0)	564 (48.5)	666 (40.8)	
ICU	417 (14.9)	219 (18.8)	198 (12.1)	
Origin of infection, n (%)				<0.001
Pneumonia	1,020 (36.5)	486 (41.8)	534 (32.7)	
Acute abdominal infection	833 (29.8)	354 (30.4)	479 (29.4)	
Urinary tract infection	299 (10.7)	69 (5.9)	230 (14.1)	
Meningitis	81 (2.9)	20 (1.7)	61 (3.7)	
Soft-tissue infection	107 (3.8)	36 (3.1)	71 (4.4)	
Catheter-related bacteremia	60 (2.1)	20 (1.7)	40 (2.5)	
Other	317 (11.3)	140 (12.0)	177 (10.8)	
Multiple infection sites	79 (2.8)	39 (3.4)	40 (2.5)	
APACHE II, mean ± SD	21.2 ± 7.7	24.2 ± 7.6	19.1 ± 6.9	<0.001
Lactate (mg/dl), mean ± SD	32.9 ± 26.1	39.3 ± 31.1	28.4 ± 20.8	<0.001
Organ dysfunction criteria at sepsis presentation, n (%)				
Hypotension	2,308 (82.5)	992 (85.2)	1,316 (80.6)	0.002
Respiratory	1,814 (64.9)	854 (73.4)	960 (58.8)	<0.001
Renal	2,016 (72.1)	921 (79.1)	1,095 (67.1)	<0.001
Hyperbilirubinemia	509 (18.2)	261 (22.4)	248 (15.2)	<0.001
Thrombocytopenia	681 (24.4)	362 (31.1)	319 (19.5)	<0.001
Coagulation	952 (34.0)	481 (41.3)	471 (28.9)	<0.001
Number organ failure, mean ± SD	3.0 ± 1.2	3.3 ± 1.3	2.7 ± 1.1	<0.001

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit.

Nonsurvivors had higher APACHE II scores, higher baseline lactate levels, and more organ failures at sepsis diagnosis.

### Therapeutic Interventions for Severe Sepsis

Therapeutic goals are listed in Table 2. For persistent hypotension despite fluid resuscitation and/or lactate greater than 36 mg/dl, a CVP value of at least 8 mm Hg was achieved in 79.7%, and a ScvO<sub>2</sub> value of at least 70% was achieved in 34.8%. Blood glucose levels were maintained below 150 mg/dl without hypoglycemia in 48.2% of patients, and inspiratory plateau pressure was kept below 30 cm H<sub>2</sub>O in 84.7% of mechanically ventilated patients. All therapeutic goals except a CVP value of at least 8 mm Hg were achieved more often in survivors than in nonsurvivors (*P* < 0.01 in all cases).

Broad-spectrum antibiotics were administered in the first 3 hours to 39% of the patients (Table 3). A fluid challenge was given to 91.1% of patients with persistent hypotension and/or lactate greater than 36 mg/dl. Low-dose steroids were administered to 53.0% of patients with persistent hypotension despite fluid resuscitation and/or lactate greater than 36 mg/dl, and

drotrecogin alfa (activated) was administered to 6.5% of patients with multiorgan failure.

The propensity score analysis (Table 4) showed that two recommended measures were associated with lower hospital mortality: administering broad-spectrum antibiotic treatment in the first hour of severe sepsis versus no antibiotic in the first 6 hours (odds ratio [OR], 0.67; 95% confidence interval [CI], 0.50–0.90; *P* = 0.008) and administering drotrecogin alfa (activated) in multiorgan failure (OR, 0.59; 95% CI, 0.41–0.84; *P* = 0.004). Fluid challenge and low-dose steroids did not show benefit.

### Validation of Propensity Scores and Sensitivity Analyses

Regarding the validity of the propensity scores, the distribution of the propensity scores for treated and untreated patients within each propensity score quintile were generally similar, although there were some exceptions, suggesting some residual imbalance (see Figures E1–E7 in the online supplement). These results were in agreement with the comparison of the covariates for treated and untreated patients within each propensity score

TABLE 2. THERAPEUTIC GOALS FOR SEVERE SEPSIS IN SURVIVORS AND NONSURVIVORS

Variable	All patients (n = 2,796)	Nonsurvivors (n = 1,164)	Survivors (n = 1,632)	P Value
CVP ≥8 mm Hg for persistent hypotension despite fluid resuscitation and/or lactate >36 mg/dl (n = 1,878), n (%)	1,496 (79.7)	676 (78.7)	820 (80.5)	0.341
ScvO <sub>2</sub> ≥70% for persistent hypotension despite fluid resuscitation and/or lactate >36 mg/dl (n = 1,878), n (%)	654 (34.8)	272 (31.7)	382 (37.5)	0.008
Blood glucose: lower limit of normal but <150 mg/dl (n = 2,796), n (%)	1,347 (48.2)	495 (42.5)	852 (52.2)	<0.001
IPP <30 cm H <sub>2</sub> O for mechanically ventilated patients (n = 1,642), n (%)	1,391 (84.7)	697 (82.0)	694 (87.6)	0.002

Definition of abbreviations: CVP = central venous pressure; IPP = inspiratory plateau pressure; ScvO<sub>2</sub> = central venous oxygen saturation.

TABLE 3. TREATMENTS FOR SEVERE SEPSIS IN SURVIVORS AND NONSURVIVORS

Variable	All patients (n = 2,796)	Nonsurvivors (n = 1,164)	Survivors (n = 1,632)	P Value
Broad-spectrum antibiotics (n = 2,776), n (%):				0.001
0–1 h	510 (18.4)	175 (15.1)	335 (20.7)	
1–3 h	572 (20.6)	228 (19.7)	344 (21.2)	
3–6 h	290 (10.4)	123 (10.6)	167 (10.3)	
Previous antibiotic	989 (35.6)	441 (38.1)	548 (33.8)	
No antibiotic in the first 6 h	415 (14.9)	189 (16.3)	226 (14.0)	
Fluid challenge in the event of hypotension and/or lactate >36 mg/dl (n = 2,316), n (%)	2,109 (91.1)	918 (91.3)	1,191 (90.9)	0.778
Low-dose steroids for persistent hypotension despite fluid resuscitation and/or lactate >36 mg/dl (n = 1,878), n (%)	995 (53.0)	480 (55.9)	515 (50.5)	0.021
Drotrecogin alfa (activated) in multiorgan failure (n = 2,545), n (%)	165 (6.5)	66 (6.0)	99 (6.9)	0.365

quintile; in general, overlapping was good, although some statistically significant differences were found for some covariates in some quintiles (see Tables E1–E7 in the online supplement). Similarly, the AUCs for all the propensity score models were below the threshold of 0.8 (range, 0.60–0.77), suggesting good overlapping of the propensity scores between groups. Nonetheless, the covariates showing statistically significant differences between treated and treated patients in some propensity score quintile were included in the final propensity score models to take possible residual imbalances into account.

The results of the sensitivity analyses that involved refitting the final models to include only the treatment assessed and the associated propensity score quintiles and the results of the sensitivity analysis that involved fitting “classical” multivariable logistic regression models were highly consistent with the results obtained in the original propensity score analysis (Tables E8 and E9). For the two treatments associated with reductions in mortality, the results of the analysis, excluding patients who died within the time recommended for the treatments in the SSC, were similar to the overall results including these patients (Table E10). Furthermore, the results from the time-varying Cox regressions were highly consistent (data not shown); hence, there was no evidence of immortal bias in our results. Finally, because there was only one patient in the first propensity score quintile for patients treated with drotrecogin alfa (activated), we examined the results of refitting the final model for drotrecogin alfa (activated), excluding patients in the first propensity score quintile. Again, the results were highly consistent with the overall results including the first propensity score quintile (OR, 0.60; 95% CI, 0.42–0.86;  $P = 0.005$ ).

## DISCUSSION

This is the first study to use propensity scores to analyze the effectiveness of all treatments for severe sepsis included in the SSC care bundles in a nonexperimental clinical setting. In a large cohort of ICU patients with severe sepsis, we found that two of the four treatments recommended in the SSC care

bundles were independently associated with lower hospital mortality after adjusting for several independent clinical predictors of death.

In our study, early administration of broad-spectrum antibiotics was associated with better survival. Our results are concordant with those of other investigators, who have also reported a relationship between delays in administering broad-spectrum antibiotics in critically ill septic patients and outcome (7, 24). However, we have no data about the appropriateness of the empiric antibiotic treatment; it is likely that the effect of time to antibiotic treatment on outcome would be even more evident in the subset of patients with appropriate antibiotic treatment.

The administration of drotrecogin alfa (activated) in patients with multiorgan failure was associated with lower risk of death in our study. The indication of drotrecogin alfa (activated) has been controversial since the publication of the negative trial in patients with low risk of death (25), the negative pediatric study (26), and the most recent negative phase II trial in acute lung injury (27). In fact, the clinical use of drotrecogin alfa (activated) in Europe is low (28) and similar to our rate (6.5%). Nevertheless, our results are similar to recently published observational studies (29–32). However, because data about comorbidities are lacking, we cannot exclude a selection bias due to the possibility of patients with contraindications to drotrecogin alfa (activated) or therapeutic limitations in the untreated population. A confirmatory study of drotrecogin alfa (activated) in patients with severe sepsis and vasopressor-dependent hypotension is underway (33) and should help to define the utility of this agent in critically ill patients.

Although fluid administration has been shown to be effective in severe sepsis (34), we found no therapeutic benefit of fluid challenge. This discrepancy is probably related to the severity of our patients. Our population included a high percentage of septic shock patients, who are characterized by a low response to fluids. The small number of patients in our population without septic shock does not allow us to test the effectiveness of fluid management. Moreover, by including only patients

TABLE 4. PROPENSITY-ADJUSTED LOGISTIC REGRESSION MODELS FOR THE IMPACT OF THERAPEUTIC INTERVENTIONS FOR SEVERE SEPSIS ON HOSPITAL MORTALITY

Variable	Odds Ratio	95% Confidence Interval	P Value
Broad-spectrum antibiotics			
0–1 h	0.67	0.50–0.90	0.008
1–3 h	0.80	0.60–1.06	0.127
3–6 h	0.87	0.62–1.22	0.419
Previous antibiotic	0.89	0.69–1.15	0.383
No antibiotic in the first 6 h	1		
Fluid challenge in the event of hypotension and/or lactate >36 mg/dl	1.01	0.73–1.39	0.966
Low-dose steroids for persistent hypotension despite fluid resuscitation and/or lactate >36 mg/dl	1.04	0.85–1.28	0.688
Drotrecogin alfa (activated) in multiorgan failure	0.59	0.41–0.84	0.004

admitted to the ICU, we probably selected patients who did not improve with initial treatment. Thus, we might be underestimating the effect of fluids. This selection bias probably also applies to antibiotic treatment. To avoid this bias, a new prospective observational study including all patients with severe sepsis (whether admitted to the ICU or not) should be conducted.

We found no association between the administration of low-dose steroids in septic shock and death. These results are in conflict with those reported by Annane and coworkers (10) but agree with the findings of the recently published Corticus randomized controlled trial (16). Our study does not support the use of steroids in septic shock.

A recent analysis of the pivotal trials in severe sepsis using Bayesian methodology reached similar results, showing beneficial results with drotrecogin alfa (activated) trials but not with low-dose steroids and EGDT trials (35).

In the univariate analyses, achievement of each of the therapeutic goals (except CVP  $\geq 8$  mm Hg) was associated with better survival. However, we did not record the therapies used in attempts to meet the therapeutic goals, and we decided not to analyze the therapeutic goals as treatments because it is impossible to ascertain to what extent attaining the therapeutic goals is due to the treatment.

Our study is limited by its observational design, which cannot exclude the possibility of our results being confounded by case-mix heterogeneity or secular trends. However, although a prospective, controlled, randomized clinical trial is the optimal means of demonstrating causality, appropriately designed observational studies with the right analytical strategies can provide valuable information on treatment effectiveness (36). Suarez and colleagues showed that, when analyzed with propensity score methodology, the results obtained in prospective observational studies might be similar to those obtained in randomized controlled trials (37). Moreover, observational studies maximize external validity (38). In addition, recent simulation research showed that propensity score methods generally gave treatment effect estimates that were closer to the true treatment effect than logistic regression models in which all confounders were modeled (39), and this reinforces our choice for propensity scores as the main analysis. Finally, our results are strengthened by the results of several sensitivity analyses, which were highly consistent with the results of the propensity score analyses and preclude the presence of immortal bias (22).

We did not evaluate source control and other important measures not included in the SSC care bundles. The heterogeneity of source control techniques makes it difficult to evaluate their effectiveness in observational studies.

In conclusion, early administration of broad-spectrum antibiotics is imperative in all patients with severe sepsis, and strategies to shorten the time to antibiotic treatment should be implemented in all hospitals. In addition, the administration of drotrecogin alfa (activated) reduces mortality in the most severe patients.

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