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Outcome of delayed resuscitation bundle achievement in emergency department patients with septic shock

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Abstract The aim of this study was to assess whether delayed resuscitation bundle compliance from 6 to 12 h after a diagnosis of septic shock has an impact upon 28-day mortality. A prospective observational study on consecutive adult patients with septic shock was performed in the Emergency Department (ED) of a tertiary care university-affiliated hospital between January 2010 and July 2012. Compliance with the resuscitation bundle was assessed at 6 and 12 h after a septic shock diagnosis (time 0). Patients were divided into three groups: early compliance ($\leq$6 h), delayed compliance (>6 but $\leq$12 h), and non-compliance (>12 h). The 28-day mortality was compared among the groups. A total of 332 patients were included, with an overall 28-day mortality of 17.2 %. The mean age was 63.9 years; 57.8 % were men. Early compliance was achieved in 195 patients (58.7 %), delayed compliance in 59 patients (19.8 %), and non-compliance in 78 patients (23.5 %). The groups did not differ in baseline sequential organ failure assessment illness severity. However, the non-compliance group had a significantly higher mortality (29.5 %) than the delayed-compliance (13.6 %) and early-compliance (13.3 %) groups ($p = 0.04$). Delayed compliance was associated with a lower mortality risk than non-compliance (adjusted odds ratio 0.32, 95 % confidence interval: 0.13–0.82, $p = 0.02$). In conclusion, if bundle therapy be started at the time of presentation, the outcome of delayed resuscitation bundle compliance within 12 h is same as that of early resuscitation bundle compliance within 6 h, and these are better than that of the patients who had late or no compliance.

Keywords Septic shock · Surviving Sepsis Campaign · Resuscitation bundle · Mortality

Introduction

Severe sepsis and septic shock are associated with a high mortality and cost, affecting approximately 750,000 Americans annually [1, 2]. An estimated 500,000 patients with severe sepsis are treated annually in EDs in the United States [3]. Time is one of the key factors in determining the outcome of patients with sepsis, evidence showing that early identification and management of septic shock can significantly reduce mortality [4–9]. The Surviving Sepsis Campaign recommends accomplishing the resuscitation bundle within 6 h from the onset of septic shock, and the application of adjunctive treatments within 24 h [10]. The early resuscitation bundle, including early goal-directed therapy (EGDT), improves outcomes in patients with septic shock [11–14]. However, few data are available on the impact of late completion of bundle elements, i.e., after 6 h, on outcomes [15, 16]. Furthermore, no studies have been done on the impact of delayed compliance on outcomes when bundle resuscitation is completed in more than 6 but fewer than 12 h from the time of a septic shock diagnosis, especially in ED populations. The aim of this study was to assess whether failure to comply with the resuscitation bundle within 6 h but achieving it by 12 h

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after the diagnosis of septic shock was related to an improvement in 28-day mortality.

Methods

This was a prospective observational study analyzing all consecutive adult (18 years of age or older) patients with septic shock who were treated with protocol-driven resuscitation bundle therapy including EGDT in the ED of the Asan Medical Center, a 2,800-bed, university-affiliated, tertiary referral hospital center, in Seoul, Korea between January 2010 and July 2012. This study was reviewed and approved by the Ethics Committee of Asan Medical Center.

We included patients in the ED, who met two or more criteria for systemic inflammatory response and who had refractory hypotension or a serum lactate level ≥4 mmol/L. We defined refractory hypotension as a systolic blood pressure <90 mmHg or mean arterial pressure (MAP) <60 mmHg requiring vasopressors even after an intravenous fluid challenge (20 mL/kg over 30 min) [17]. All patients with septic shock were treated with protocol-driven resuscitation bundle therapy, including EGDT, while in the ED [10]. Patients were excluded from the study if they had one of the following: pregnancy, absolute contraindication for a central venous catheter, trauma, 'do not resuscitate' status, refusal of invasive therapy, patients who transferred to other hospitals, and central venous oxygenation ($ScvO_2$) not checked at 12 h. The treatment protocol was a sepsis management program called "ED Shock Management," which was organized and implemented for treatment of severe sepsis and shock at the hospital beginning in 2007. Team members met monthly to review current patient data and to discuss ways to improve patient care. Treatment was carried out according to the standard bundle protocol for sepsis resuscitation: (1) serum lactate measurement made as soon as possible from the time of the onset of severe sepsis; (2) blood culture before antibiotic administration; (3) delivery of an initial minimum volume of 20 mL/kg crystalloid (or colloid); (4) achievement and maintenance of MAP ≥65 mmHg; (5) achievement of central venous pressure (CVP) ≥8 mmHg; and (6) achievement of $ScvO_2$ ≥70 % [17]. Outcomes were evaluated in three patient groups. The early-compliance group consisted of patients who received all six bundle elements within 6 h of diagnosis (Time 0) in the ED. The delayed-compliance group included patients who received all bundle elements within 12 h of Time 0. The non-compliance group consisted of patients who did not achieve all bundle elements within 12 h, including a MAP ≥65 mmHg, CVP ≥8 mmHg, and $ScvO_2$ ≥70 % (Fig. 1). The primary outcome was 28-day mortality following compliance with the sepsis resuscitation bundle.

Demographic and clinical data, including age, gender, symptoms, previous medical history, initial vital signs, blood results, 28-day course, and diagnosis on admission, were collected. $ScvO_2$ was checked at initial diagnosis, 6,

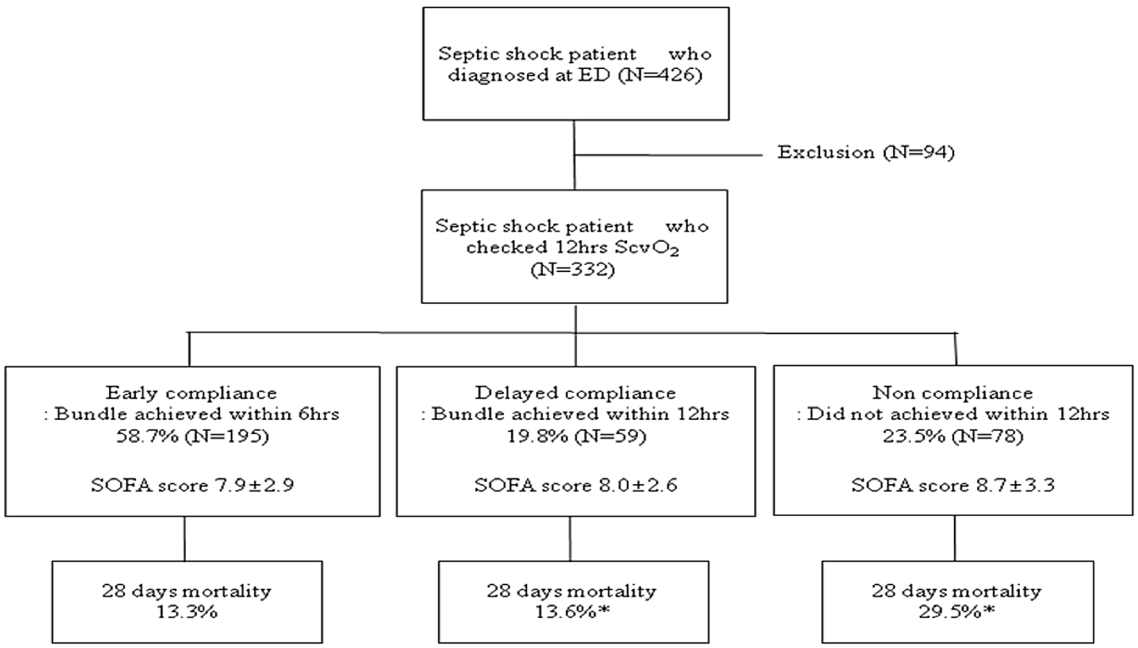

Fig. 1 Flow diagram of study selection process. *ED* emergency department, *$ScvO_2$* central venous oxygenation, *SOFA* sequential organ failure assessment. *P value = 0.04

and 12 h. The sequential organ failure assessment (SOFA) score was calculated at ED admission.

Statistical analysis

Continuous variables were expressed as means with standard deviations or medians with range if the assumption of a normal distribution was violated. Categorical variables were expressed as numbers and percentages. Differences between means were assessed for significance using Student's *t* test, the Wilcoxon rank sum test, or ANOVA. Chi Squared or Fisher's exact test was used to compare group differences for categorical variables. Multiple logistic regression models were used to evaluate the association of delayed compliance with 28-day mortality. Data were presented as odds ratios (OR) with 95 % confidence intervals (CI). A two-sided p value <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 426 adult patients were diagnosed with septic shock in the ED during the study period. Of these, we excluded 39 patients who transferred to other hospitals, 32 patients with a consent of do-not-resuscitate, 19 patients who had insufficient data, and 4 patients who refused to have invasive procedures, leaving a total of 332 patients for analysis.

The mean age of the study cohort was 63.9 years; 192 patients (57.8 %) were men. The 6-h compliance with resuscitation bundle elements was 100 % for serum lactate measurement, blood culture before antibiotic administration, and delivery of an initial minimum volume of 20 mL/kg crystalloid (or colloid). Achievement and maintenance of MAP $\geq$65 mmHg were seen in 319 patients (96.1 %); 287 patients (86.4 %) achieved CVP $\geq$8 mmHg; and 212 patients (63.9 %) had a $ScvO_2$ $\geq$70 %.

When the study cohort was evaluated for compliance with all six bundle therapy elements, early compliance ($\leq$6 h) was achieved in 195 patients (58.7 %) and delayed compliance ($\leq$12 h) in 59 patients (19.8 %). Non-compliance (>12 h) was observed in 78 patients (23.5 %). Overall, 275 patients survived and 57 patients died, for a 28-day mortality rate of 17.2 %. There were no statistically significant differences in gender, previous medical history, baseline vital signs, and laboratory test results between these groups (Table 1). The non-compliance group had a significantly higher median age (69.5 years) than the delayed-compliance (64.0 years) and early-compliance (65.0 years) groups (both $p = 0.01$). The between-group differences in variables of illness severity mostly had no significant differences (Table 2). However, the non-compliance group received a higher dose of norepinephrine treatment, more days of mechanical ventilator therapy, and renal replacement therapy than the delayed-compliance and early-compliance groups. Furthermore, the non-compliance group had a significantly higher 28-day mortality of 29.5 % than the delayed-compliance or early-compliance group (13.6 and 13.3 %, respectively, $p = 0.04$). Considering that there were no differences in baseline illness severity, delayed compliance decreased the 28-day mortality compared to non-compliance (OR 0.32, 95 % CI 0.13–0.82, $p = 0.02$).

Discussion

This study evaluated 28-day mortality in ED patients who achieved resuscitation bundle compliance within 6 h of septic shock diagnosis, more than 6 but fewer than 12 h, and patients who did not achieve compliance within 12 h. Our findings show that delayed compliance with the resuscitation bundle in patients diagnosed with septic shock in the ED has a significantly lower 28-day mortality (13.6 %) than non-compliance (29.5 %), and a better overall mortality (OR 0.32, 95 % CI 0.13–0.82, $p = 0.02$).

In 2001, Rivers et al. [4] reported that EGDT for severe sepsis and septic shock reduced mortality when begun in the ED before intensive care unit admission. Previous studies that assessed performance of the resuscitation bundle [9, 11–13] primarily addressed outcomes when compliance was achieved within the first 6 h of septic shock presentation. Consequently, the impact on mortality of those patients who completed the protocol beyond that time is unknown. Our results provide additional data on the resuscitation bundle for preventing septic shock-associated mortality. The data indicate that the period to complete the protocol may be extended beyond the time limit proposed by the Surviving Sepsis Campaign. However, treatment should start at the time of shock presentation, with a goal of achieving compliance as early as possible.

In our results, compliance was achieved in 58.7 % of patients within the initial 6-h target. This is much higher than the 31.3 % reported by the international guideline-based performance improvement results of the Surviving Sepsis Campaign [8], and could help account for the low 17.2 % mortality in this study. Furthermore, we studied a cohort including only ED patients, rather than patients presenting from a variety of settings, and likely receiving various methods of initial resuscitation. Our overall mortality rate was consistent with other studies of ED patients receiving bundle resuscitation [11–13]. In this study, delayed compliance until 12 h was seen in 23.5 % of

Table 1 Demographic and baseline characteristics of patients with septic shock

	Early compliance ($n = 195$)	Delayed compliance ($n = 59$)	Non-compliance ($n = 78$)	p
Age (years)	65.0 (57.0–72.0)	64.0 (55.0–71.0)	69.5 (60.8–76.3)	0.01
Sex, male	115 (59.0)	32 (54.2)	45 (57.7)	0.81
Pre-existing diseases				
Congestive heart failure	7 (3.6)	2 (3.4)	5 (6.4)	0.55
Chronic renal failure	12 (6.2)	4 (6.8)	4 (5.1)	0.90
Chronic pulmonary disease	10 (5.1)	5 (8.5)	6 (7.7)	0.47
Chronic liver disease	21 (10.8)	10 (16.9)	3 (3.8)	0.05
Diabetes mellitus	43 (22.1)	10 (16.9)	13 (16.7)	0.50
Cancer with metastasis	63 (32.3)	16 (27.1)	22 (22.2)	0.67
Initial vital signs				
Systolic BP (mmHg)	84.4 ± 16.9	84.3 ± 20.4	82.7 ± 19.5	0.32
Diastolic BP (mmHg)	52.1 ± 12.6	52.9 ± 18.6	51.5 ± 15.1	0.30
PR (beats per minute)	107.5 ± 20.2	101.9 ± 24.2	105.0 ± 25.4	0.33
RR (breaths per minute)	22.6 ± 4.5	22.1 ± 5.0	23.9 ± 6.8	0.04
Laboratory findings				
WBC ($\times 10^3/\mu L$)	11.4 ± 9.2	11.8 ± 8.8	13.6 ± 13.2	0.88
Platelets ($\times 10^3/\mu L$)	165.5 ± 108.6	160.2 ± 100.6	172.3 ± 112.3	0.82
Creatinine (mg/dL)	1.8 ± 1.6	1.7 ± 1.6	2.1 ± 1.7	0.49
Total bilirubin (mg/dL)	2.5 ± 3.6	3.8 ± 6.4	2.0 ± 2.1	0.48
CRP (mg/dL)	14.7 ± 11.4	20.2 ± 36.2	16.9 ± 12.1	0.37
D-Dimer (μg/mL)	8.6 ± 17.6	6.1 ± 9.2	17.8 ± 57.9	0.50
Procalcitonin (ng/mL)	28.8 ± 47.3	20.1 ± 27.8	35.8 ± 54.9	0.66
Troponin-I (ng/mL)	0.7 ± 3.8	3.5 ± 17.5	0.5 ± 1.6	0.65
BNP (pg/mL)	469.5 ± 708.4	594.5 ± 1,201.4	597.4 ± 932.2	0.41

Values are expressed as mean ± standard deviation or median with interquartile range and n (%)

BP blood pressure, *PR* pulse rate, *RR* respiration rate, *WBC* white blood cell, *CRP* C-reactive protein, *BNP* B-type natriuretic peptide

Table 2 Illness severity and outcomes of patients with septic shock

	Early compliance ($n = 195$)	Delayed compliance ($n = 59$)	Non-compliance ($n = 78$)	p
Illness severity				
Lactic acid (mmol/L)	3.8 ± 3.1	3.2 ± 2.6	4.6 ± 3.9	0.20
PaO_2/FiO_2 ratio	348 (266–428)	352 (304–460)	318 (241–402)	0.65
Glasgow coma scale	14.2 ± 2.5	13.9 ± 3.4	13.8 ± 3.4	0.56
Urine output <0.5 L/h	79 (49.0)	25 (43.1)	30 (22.4)	0.89
Norepinephrine (mcg/kg/min)	0.17 (0.08–0.32)	0.18 (0.08–0.40)	0.28 (0.08–0.53)	0.01
Duration of vasopressor use (days)	2.0 (1.0–3.3)	2.0 (2.0–4.0)	2.0 (2.0–4.0)	0.95
SOFA score	7.9 ± 2.9	8.0 ± 2.5	8.7 ± 3.3	0.19
Interventions				
Mechanical ventilation	45 (23.1)	10 (16.9)	32 (41.0)	<0.01
CRRT	19 (9.7)	2 (3.4)	17 (21.8)	<0.01
28-day mortality	26 (13.3)	8 (13.6)	23 (29.5)	<0.01

Values are expressed as mean ± standard deviation or median with interquartile range and n (%)

SOFA sequential organ failure assessment, *CRRT* continuous renal replacement therapy

patients. As such, failure to comply might be the failure to reach the target despite the clinician's attempt because all of the patients in the current study received the same early recognition and aggressive treatment protocol. The failure to achieve a target may be indicative of greater severity, so compliance with the attempt alone may produce the false impression that compliance is associated with reduced mortality. Therefore, attention to adjustment for severity of patient illness at the time of enrollment should be taken into account. The difference in baseline SOFA illness severity between delayed compliance and non-compliant patients was not statistically significant (19.8 vs. 23.5 %,

$p = 0.28$), also in the comorbidities, lactic acid level, PaO_2/FiO_2 ratio, decreased urine output, and duration of vasopressor use. However, age could have affected the greater mortality in the non-compliance group. Taking this into consideration, delayed compliance still has the benefit of decreased 28-day mortality compared to non-compliance as defined here.

To the best of our knowledge, results regarding the impact on mortality of resuscitation bundle completion within 12 h in an ED population have not been reported previously. In a recent study, Coba et al. [16] evaluated the impact of quality improvement of sepsis bundle therapy on mortality, and report the effectiveness of therapy when completed within 18 h. Compliance at 18 h has a hospital mortality of 37.1 %, which is 10.2 % lower than non-compliance at 18 h ($p < 0.03$). They conclude that when bundle completion is extended from 6 to 18 h, the mortality reduction remains significant. Although their study included all intensive care unit patients, and early compliance with the 6 h bundle target was only 12.9 %, their results are consistent with our findings that late is better than never. However, importantly, we do not suggest extending the time limit of achievement of bundle target to 12 h, but that delayed compliance might be an extra benefit of the improvement in the process of sepsis care compared to what is achieved when sepsis recognition and application of the resuscitation bundle are early and aggressive.

This study has several limitations that should be considered. We did not assess the timing of antibiotic administration, which may affect mortality and the achievement of management bundle, or other treatments such as low-dose steroid administration, or glucose control. This study is from a single institution, which limits the generalization of the findings to other institutions or patient populations. In addition, the sample size is relatively small.

In conclusion, if sepsis bundle therapy is started at the time of presentation, the outcome of delayed resuscitation bundle compliance within 12 h is the same as that of early resuscitation bundle compliance within 6 h, and these are better than that of the patients in whom bundle compliance goals cannot be met.

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References

1. Angus D, Linde-Zwirble W, Lidicker J, Clermont G, Carcillo J, Pinsky M (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 29(7):1303–1310
2. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL (2007) Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Crit Care Med 35(5):1244–1250
3. Wang HE, Shapiro NI, Angus DC, Yealy DM (2007) National estimates of severe sepsis in United States emergency departments. Crit Care Med 35(8):1928–1936
4. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345(19):1368–1377
5. Nguyen HB, Corbett SW, Steele R, Banta J, Clark RT, Hayes SR, Edwards J, Cho TW, Wittlake WA (2007) Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. Crit Care Med 35(4):1105–1112
6. Micek ST, Roubinian N, Heuring T, Bode M, Williams J, Harrison C, Murphy T, Prentice D, Ruoff BE, Kollef MH (2006) Before-after study of a standardized hospital order set for the management of septic shock. Crit Care Med 34(11):2707–2713
7. Ferrer R, Artigas A, Levy MM, Blanco J, González-Díaz G, Garnacho-Montero J, Ibáñez J, Palencia E, Quintana M, de la Torre-Prados MV, Edusepsis Study Group (2008) Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. JAMA 299(19):2294–2303. doi:10.1001/jama.299.19.2294
8. Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, Schorr C, Artigas A, Ramsay G, Beale R, Parker MM, Gerlach H, Reinhart K, Silva E, Harvey M, Regan S, Angus DC, Surviving Sepsis Campaign (2010) The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Intensive Care Med 36(2):222–231. doi:10.1007/s00134-009-1738-3
9. Cardoso T, Carneiro AH, Ribeiro O, Teixeira-Pinto A, Costa-Pereira A (2010) Reducing mortality in severe sepsis with the implementation of a core 6-hour bundle: results from the Portuguese Community-Acquired Sepsis Study (SACiUCI Study). Crit Care 14(3):R83. doi:10.1186/cc9008
10. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL, International Surviving Sepsis Campaign Guidelines Committee, American Association of Critical-Care Nurses, American College of Chest Physicians, American College of Emergency Physicians, Canadian Critical Care Society, European Society of Clinical Microbiology and Infectious Diseases, European Society of Intensive Care Medicine, European Respiratory Society, International Sepsis Forum, Japanese Association for Acute Medicine, Japanese Society of Intensive Care Medicine, Society of Critical Care Medicine, Society of Hospital Medicine, Surgical Infection Society, World Federation of Societies of Intensive and Critical Care Medicine (2008) Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock. Crit Care Med 36(1):296–327
11. Jones AE, Focht A, Horton JM, Kline JA (2007) Prospective external validation of the clinical effectiveness of an emergency department-based early goal directed therapy protocol for severe sepsis and septic shock. Chest 132(2):425–432
12. Trzeciak S, Dellinger RP, Abata NL, Cowan RM, Stauss M, Kilgannon JH, Zanotti S, Parrillo JE (2006) Translating research to clinical practice: a 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. Chest 129(2):225–232

13. Shapiro NI, Howell MD, Talmor D, Lahey D, Ngo L, Buras J, Wolfe RE, Weiss JW, Lisbon A (2006) Implementation and outcomes of the multiple urgent sepsis therapies (MUST) protocol. Crit Care Med 34(4):1025–1032
14. Huang DT, Clermont G, Dremsizov TT, Angus DC (2007) Implementation of early goal-directed therapy for severe septic shock: a decision analysis. Crit Care Med 35(9):2090–2100
15. Castellanos-Ortega Á, Suberviola B, García-Astudillo LA, Ortiz F, Llorca J, Delgado-Rodríguez M (2011) Late compliance with the sepsis resuscitation bundle: impact on mortality. Shock 36(6):542–547. doi:10.1097/SHK.0b013e3182360f7c
16. Coba V, Whitmill M, Mooney R, Horst HM, Brandt MM, Digiovine B, Mlynarek M, McLellan B, Boleski G, Yang J, Conway W, Jordon J (2011) Resuscitation bundle compliance in severe sepsis and septic shock: improves survival, is better late than never. J Intensive Care Med 26(5):304–313. doi:10.1177/0885066610392499
17. Bone R, Balk R, Cerra F, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ, ACCP/SCCM Consensus Conference Committee (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 101(6):1644–1655