ORIGINAL REPORT

Effect of Door-to-Antibiotic Time on Mortality of Patients with Sepsis in Emergency Department: A Prospective Cohort Study

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Abstract- Sepsis constitutes an important cause of hospital admission with a high mortality rate. Appropriate antibiotic therapy is the cornerstone of therapy in patients with sepsis. Although numerous studies have recommended early antibiotic initiation in severe sepsis or septic shock stages of sepsis syndrome, its role in treatment of patients with sepsis who have not entered these stages remains to be investigated. The purpose of this study is to investigate the effect of door-to-antibiotic time in sepsis patients with various degrees of severity. This is a longitudinal prospective cohort study on adult patients admitted with sepsis to the emergency department. Sepsis was defined as presence of at least two criteria of systemic inflammatory response syndrome and procalcitonin levels ≥ 2μg/l. Severity of sepsis was determined using the APACHE II (Acute Physiology and Chronic Health Evaluation II) scoring system. Time to antibiotic administration was recorded and its relationship with mortality was assessed. A total of 145 patients were eligible for enrollment. The mean age was 60.4 years and the mean APACHE score was 13.7. The overall in-hospital mortality was 21.4%, and the mean length of stay in hospital was 211.9 hours. The mean door-to-antibiotic time for our patients was 104.4 minutes. Antibiotic administration time and mortality in patients with APACHE scores of 21 or higher (P=0.05) were significantly related; whereas such a relationship was not observed for patients with APACHE scores of 11- 20 (P=0.46). We observed early antibiotic initiation for patients in sepsis phase with higher severity scores was associated with significant improvement in survival rate.

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Keywords: APACHE II; Door-to-antibiotic time; Mortality; Sepsis

Introduction

Sepsis is defined as the state of systemic inflammatory response syndrome (SIRS) combined with a known or probable infectious etiology (1). Sepsis constitutes an important cause of hospital admissions, as well as being a common culprit for death. In spite of strike advances in diagnosis and treatment, it is associated with a mortality rate of 20-50% (1,2). A limited number of therapies have been proposed for sepsis, among which early goal-directed therapy (EGDT) is a noteworthy method of the last decade (3). Thus, it is essential to diagnose sepsis in the shortest time possible, and begin therapy immediately (3). Recently, numerous inflammatory markers (namely, interleukins 6 and 8, C-reactive protein, neopterin, and procalcitonin) have been suggested for early diagnosis of this clinical syndrome (4). Serum levels of procalcitonin have proved beneficial in early diagnosis of sepsis, and consequently expedite the appropriate therapy (5). Furthermore, it has been found that appropriate antibiotic therapy in patients with septic shock and severe sepsis is associated with better prognosis, and conversely, patients with infection of any source who are deprived from appropriate antibiotic therapy will have poorer prognosis (6,7). In addition, the time of initiating antibiotic for patients with septic shock or severe sepsis affects prognosis. A study by Kumar *et al.* indicated that each hour of delay in initiating therapy following hypotension increases mortality by 7.6% (8). Another study by Gaieski *et al.*

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reported better prognosis for patients with septic shock or severe sepsis who had received antibiotic therapy during the first 2 hours of admission to emergency department (ED) (3). However, some other studies have failed to indicate a relationship between time of initiation of therapy and hospital admission and mortality rate (9,10). Moreover, the present data regarding the role that time of antibiotic initiation may play in sepsis patients who are not in severe sepsis or septic shock is far from complete and this question remains. In this study, we investigated the interval between the patient`s arrival to ED and initiation of antibiotic therapy (door-to-antibiotic), length of hospital stay and mortality rate of patients with sepsis.

Materials and Methods

Study design

This is a longitudinal prospective cohort study conducted on sepsis patients admitted to the ED of our hospital from March 2007 through June 2009.

Considering the fact that our study did not involve any intervention or cost for patients, the Institutional Review Board exempted the study from obtaining informed consent from the patients.

Study setting and population

The hospital is a tertiary care center with 700 patient beds. The 24-hour ED is run by emergency medicine specialists (all board certified) and residents of emergency medicine, visiting an average of 40,000 patients annually.

In our study, patients were included if they had at least 2 out of 4 criteria for SIRS combined with high levels of serum procalcitonin. The following exclusion criteria were applied: age below 12 years, mechanical trauma, surgical trauma, heat stroke, thyroid tumors, squamous cell carcinoma, and severe burns. Our approach included prompt initiation of appropriate antibiotic therapy based on clinical diagnosis. Our empirical therapy consisted of at least one effective antibiotic (as confirmed by a specialist in infectious diseases department) administered within 24 hours of patient entry to the emergency department administered according to the standard dose and pattern. The door-to-antibiotic time was defined as the interval between patient`s arrival to the emergency department and the administration of the first dose of antibiotic. The time of antibiotic prescription was defined as the precise time of antibiotic prescription by physician as recorded in the medical file, and the time of antibiotic administration was defined as the precise time of antibiotic administration by the nursing staff. The hospital stay was defined as the number of hours spanning from entry to discharge.

Study protocol

Serum level of procalcitonin was measured for all patients who met 2 SIRS criteria in preliminary examinations. The BRAHMS PCT-Q kit (Hennigsdorf, Germany) was used for measurements. Those patients with positive serum levels (above 2µg/l) and without the exclusion criteria entered the study. The severity of the patient`s condition was determined according to the APACHE II (Acute Physiology and Chronic Health Evaluation II) criteria. All patients diagnosed with sepsis received appropriate antibiotic therapy (according to the algorithm of American College of Chest Physician/Society of Critical Care Medicine Consensus Conference Committee); the therapy was evaluated based on the data acquired from repeated physical examinations and laboratory data (e.g. blood/urine cultures) and modified, if deemed necessary. All patients were visited by specialists of infectious disease and the antibiotic regimens were confirmed by them. Furthermore, all necessary supportive therapies were provided according to the EGDT protocol (measuring and correcting central venous pressure, mean arterial pressure and central venous oxygen saturation (ScvO2) at the very early phase of the disease) immediately after admission as dictated by the patient`s condition.

The entire process of diagnosis and treatment was conducted under supervision of the attending physician of the emergency medicine department. All patients were followed up to discharge or demise, whether in the emergency department or after being transferred to other wards.

Measurements

All the data including age, gender, past medical history, time of entering the emergency department, clinical observations and physical examinations, the probable source of infection based on history and physical examinations, time of antibiotic prescription, time of antibiotic administration, laboratory data, the clinical course, and time of hospital stay were extracted from the medical files by one of the authors (H.B), recorded in special forms and analyzed. The primary outcome was defined as sepsis-related death or discharge, and length of hospital stay was considered as the secondary outcome.

Statistical analysis

Chi-square and Fisher's exact test was used to compare categorical variables and Student's t-test was used for parametric variables. For all the analyses, a two-tailed *P*-value of 0.05 was considered statistically significant. The statistical analysis was performed using SPSS version 15 (SPSS Inc., Chicago, IL).

Results

This study was conducted on 164 patients admitted with a diagnosis of sepsis who met our inclusion criteria and lacked the exclusion criteria. Of these 164 patients, 19 were excluded from the study including those for whom a follow-up was not feasible (remote rural residency, patients possibly intending to travel abroad) and those who left the hospital prematurely on their own decision. The mean age of the remaining 145 (63 female and 82 male) patients, who were enrolled to the study, was 60.4±16.4 years. Table 1 summarizes the demographic features of our patients.

We evaluated the clinical presentations as well as the laboratory and imaging data. Table 2 demonstrates the diagnoses considered.

Thirty one (21.4%) out of 145 patients died during their hospital stay. Among 144 patients whose accurate antibiotic administration data was available, 18.0%, 55.6% and 26.4% of patients received antibiotics within an hour, between the first and second hour and after 2 hours of admission respectively. Statistical analysis of these data indicates a significant relationship between door-to-antibiotic time and patient survival (*P*=0.005) (Table 3).

Using the APACHE II scoring system, we divided our patients in three groups. Group 1, patients with APACHE scores of lower than 10, consisted of 55 patients without any cases of mortality. Group 2, APACHE scores of 11-20, included 62 patients with 7 cases of mortality (11.3%). In group 3, where patients with APACHE scores of 21 or higher were categorized, 24 out of 27 (88.9%) patients died.

Table 1. Baseline demographic characteristics of patients.

	Number of Patients	Mean±SD
Temperature (^{o}C)	145	38.3±0.9
Consciousness (GCS†)	144	13.9±0.9
White blood cells (× 10^{9}/l)	144	11.8±6.6
Hemoglobin (g/dl)	145	11.92.1
Hematocrit (%)	144	36.4±6.3
Serum bicarbonate (mEq/l)	143	24.8±5.1
Serum pH	144	7.4±0.1
Sodium (mEq/l)	144	139.5±6.2
Potassium (mEq/l)	144	4.2±0.7
Serum creatinine (mg/dl)	143	1.5±0.8
FIO_2 (%)	138	36.4±18.8
Door-to-antibiotic time (minutes)	144	104.4±61.0
Length of hospital stay (hours)	144	211.9±181.2
APACHE II score	145	13.7±7.2

SD: Standard Deviation, GCS: Glasgow Coma Scale, FIO_2: Fraction of Inspired Oxygen;
APACHE: Acute Physiology and Chronic Health Evaluation.

Table 2. Sources of infection in study patients (N=145).

Underlying Disease	No. (%)
Pneumonia	30 (20.7)
Urinary tract infection	19 (13.1)
Digestive tract infection	22 (15.2)
Soft tissue infection	25 (17.2)
Meningitis	6 (4.1)
Spontaneous bacterial peritonitis	3 (2.1)
Orchitis	2 (1.4)
Unknown	38 (26.2)

Table 3. Analysis of outcome in relation to time from triage to administration of appropriate antibiotic.

Outcome of therapy	Door-to-antibiotic time			Total
	< 60 minutes	60 -120 minutes	> 60 minutes	
Resolution	25	64	24	113
Death	1	16	14	31
Total	26	80	38	144

P=0.005

Table 4. Analysis of outcome in relation to severity of sepsis based on APACHE II score.

APACHE score	Outcome	Door-to-antibiotic time			Total
		< 60 minutes	60-120 minutes	> 120 minutes	
≤10	Resolution	13	30	12	55
	Death	0	0	0	0
	Total	13	30	12	55
11-20	Resolution	11	32	12	55
	Death	0	6	1	7
	Total	11	38	13	62
≥21	Resolution	1	2	0	3
	Death	1	10	13	24
	Total	2	12	13	27

Patients with APACHE scores of 21 or higher were evaluated for their door-to-antibiotic time; the findings indicate a significant relationship between antibiotic time and mortality in this group of patients (*P*=0.05); whereas such a relationship is not observed for the second group consisting of patients with APACHE scores of 11-20 (*P*=0.46) (Table 4).

Discussion

In this study, we found that early initiation of antibiotic therapy for sepsis patients is associated with increased survival, particularly in patients with more severe disease, based on the APACHE II score (*P*=0.05 for APACHE>21 *vs*. *P*=0.46 for APACHE score of 11-20).

Similar to previous studies, in the present study APACHE II scoring system was shown to be directly related to mortality rate and may be used as a reliable indicator of prognosis, as well as the earlier and more aggressive therapy initiation (8,11,12).

To the best of our knowledge, no other study has considered the impact of antibiotic initiation time on the outcome of patients in the sepsis stage specifically. Most studies have dealt with the impact of antibiotic time in certain groups of patients in terms of source of infection, sepsis patients with particular strains of infective microorganisms, patients in the phase of severe sepsis, septic shock or bacteremia (3,8,13-26). In the well-known study by Kumar *et al.* on 2154 patients with septic shock, every hour of delay in administering the right antibiotic during the first 6 hours of diagnosis increased mortality by 7.6% (8). Based on that and other studies, the Surviving Sepsis Campaign recommended broads-spectrum antibiotic to be administered during the first hour after diagnosis in patients with severe sepsis or septic shock (27).

Similarly, Gaieski *et al*. conducted a study on 261 patients with severe sepsis or septic shock under EGDT therapy to discover that the time lapse from triage and qualification for EGDT until receiving appropriate antibiotic determines mortality for patients (*P*=0.02 and *P*=0.03 respectively); thus, they recommended antibiotic therapy to initiate during the first hour after qualification for EGDT (3). Except for the stage of the disease, our findings corroborate the results of that study. In Gaieski *et al*. study, the median duration of time from triage to administration of the appropriate antibiotic was 127 minutes, while it is 104.4 minutes in our study. In Gaieski *et al.* study, a significant relationship was observed between the appropriate antibiotic time in less than an hour and patient mortality (*P*=0.02). Similarly in our study, patients who had received appropriate antibiotic in less than an hour had the lowest mortality (3.8%, *P*=0.005).

Another issue covered in several studies is the appropriateness and adequacy of antibiotic therapy

(12,18,19,24,25,28-31). Most studies have emphasized the detrimental impact of inadequate antibiotic therapy on the outcome of patients in different stages of sepsis. Montero *et al.* conducted a study on 224 patients in various stages of sepsis and indicated delayed initiation of adequate antibiotic therapy alongside APACHE II score to be two major independent predictors of in-hospital mortality (12). However, another prospective observational study by Ferrer *et al.* on 2796 patients with severe sepsis and septic shock, two treatments were reported to entail significantly reduced mortality: First, administration of broad-spectrum antibiotics during the first hour of diagnosis; and second, administration of drotrecogin (23). The researchers stated that since they did not have access to the data necessary for determining antibiotic appropriateness, it may be hypothesized that time is the main factor influencing patient outcome.

In any case, as explained earlier, antibiotic appropriateness and adequacy were established in our study and thus we may have better judgment of the impact of antibiotic time on patient survival. Positive SIRS cases may be caused by non-infectious etiologies; however, confirming sepsis with microbiologic studies is time-consuming and relying on them for antibiotic initiation may aggravate prognosis in patients. On the other hand, unjustified antibiotic therapy for these patients may result in adverse reactions and increased resistance of microorganisms to antibiotics. Thus, initiating antibiotics for these patients poses a dilemma. Based on the findings of our study, it appears that patients with higher APACHE II scores (APACHE score>20) benefit more from early antibiotic therapy and it may be justifiable to initiate empirical antibiotics for them as soon as possible, whereas considering the small influence of early antibiotic therapy on survival in patients with lower APACHE scores (APACHE score <20), it is advisable to start the appropriate antibiotic regimen after due studies.

Our study has limitations of its own. The observational nature of the study, as well as its small sample size and lack of a control group may render it vulnerable to confounding factors. Nonetheless, it is impossible to conduct a clinical trial of this type due to ethical considerations. Owing to the time-consuming and sometimes expensive nature of microbiologic studies, patients who fulfilled two of the SIRS criteria plus a procalcitonin level of higher than 2 were considered sepsis patients and the false positive cases of these criteria may be a confounding factor for our study.

In conclusion, sepsis claims about 2% of cases of hospital admissions and its annual incidence has risen to 1.5% (32,33). Consequently, the number patients who enter the phases of severe sepsis, septic shock and organ dysfunction due to delayed therapy is on the rise. Previous studies have indicated the relationship between early antibiotic initiation and reduced mortality in patients with septic shock and severe sepsis, resulting in recommendations for early antibiotic therapy for these patients. However, the impact of early antibiotic therapy on patients who have not entered these stages of sepsis remains to be known. Keeping in mind the fact that treating patients in early stages of sepsis and preventing their progression to the severe stages of sepsis and septic shock may reduce their mortality rates considerably, our study indicates that early antibiotic initiation for patients with high APACHE scores may improve their survival rates. Nevertheless, antibiotics are apparently initiated with delay for these patients and development of a unified protocol may contribute to improve the present situation. In any case, future studies with larger sample sizes and an added control group are necessary to corroborate our findings.

References

1. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. 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 1992;101(6):1644–55.
2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29(7):1303–10.
3. Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, Shofer FS, Goyal M. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med 2010;38(4):1045-53.
4. Sorbera LA. Procalcitonin as an effective biomarker for the diagnosis and prognosis of severe sepsis. Highlights from the 25th International Symposium on Intensive Care and Emergency Medicine. March 21-25, 2005, Brussels, Belgium. Drugs Today (Barc) 2005;41(5):253-6.
5. Liu XL, Du B, Pan JQ, Xu Y, Hua BL. Role of procalcitonin in the differentiation and surveillance of systemic inflammatory response syndrome. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2005;27(1):48-52.

6. Sibbald WJ, Vincent JL. Round table conference on clinical trials for the treatment of sepsis. Crit Care Med 1995;23(2):394.
7. Vallés J, Rello J, Ochagavía A, Garnacho J, Alcalá MA. Community-acquired bloodstream infection in critically ill adult patients: impact of shock and inappropriate antibiotic therapy on survival. Chest 2003;123(5):1615-24.
8. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34(6):1589-96.
9. Osih RB, McGregor JC, Rich SE, Moore AC, Furuno JP, Perencevich EN, Harris AD. Impact of Empiric Antibiotic Therapy on Outcomes in Patients with Pseudomonas aeruginosa Bacteremia. Antimicrob Agents Chemother 2007;51(3):839–44.
10. Ostman H, Sharma VK, Djekidel K, Haber A. Time to Antibiotic Administration and Outcome in Severe Sepsis and Septic Shock.
    Chest. 2007; 132(4_MeetingAbstracts):495 a
    http://journal.publications.chestnet.org/article.aspx?articleid=1093525
11. Fulda GJ, Zubrow M, Dahanayake T, Mahoney D, Ellicott A, Seckel M. Time to Antibiotic Administration and Outcome in Severe Sepsis and Septic Shock. Chest 2007;132(4_Meeting Abstracts): 495
    http://journal.publications.chestnet.org/article.aspx?articleid=1093524
12. Garnacho-Montero J, Aldabo-Pallas T, Garnacho-Montero C, Cayuela A, Jiménez R, Barroso S, Ortiz-Leyba C. Timing of adequate antibiotic therapy is a greater determinant of outcome than are TNF and IL-10 polymorphisms in patients with sepsis. Crit Care 2006;10(4):R111.
13. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med 2004;164(6):637-44.
14. Battleman DS, Callahan M, Thaler HT. Rapid antibiotic delivery and appropriate antibiotic selection reduce length of hospital stay of patients with community-acquired pneumonia: link between quality of care and resource utilization. Arch Intern Med 2002;162(6):682-8.
15. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH.. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 2002;122(1):262-8.
16. Miner JR, Heegaard W, Mapes A, Biros M. Presentation, time to antibiotics, and mortality of patients with bacterial meningitis at an urban county medical center. J Emerg Med 2001;21(4):387-92.
17. Lepur D, Barsić B. Community-acquired bacterial meningitis in adults: antibiotic timing in disease course and outcome. Infection 2007;35(4):225-31.
18. Kim SH, Park WB, Lee CS, Kang CI, Bang JW, Kim HB, Kim NJ, Kim EC, Oh MD, Choe KW. Outcome of inappropriate empirical antibiotic therapy in patients with Staphylococcus aureus bacteraemia: analytical strategy using propensity scores. Clin Microbiol Infect 2006;12(1):13-21.
19. Marschall J, Agniel D, Fraser VJ, Doherty J, Warren DK. Gram-negative bacteraemia in non ICU patients: factors associated with inadequate antibiotic therapy and impact on outcomes. J Antimicrob Chemother 2008;61(6):1376-83.
20. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother 2005;49(9):3640-5.
21. Lodise TP, McKinnon PS, Swiderski L, Rybak MJ. Outcomes analysis of delayed antibiotic treatment for hospital-acquired Staphylococcus aureus bacteremia. Clin Infect Dis 2003;36(11):1418-23.
22. Varpula M, Karlsson S, Parviainen I, Ruokonen E, Pettilä V; Finnsepsis Study Group. Community-acquired septic shock: early management and outcome in a nationwide study in Finland. Acta Anaesthesiol Scand 2007;51(10):1320-6.
23. Ferrer R, Artigas A, Suarez D, Palencia E, Levy MM, Arenzana A, Pérez XL, Sirvent JM; Edusepsis Study Group. Effectiveness of treatments for severe sepsis: a prospective, multicenter, observational study. Am J Respir Crit Care Med 2009; 180(9):861-6.
24. Zaragoza R, Artero A, Camarena JJ, Sancho S, González R, Nogueira JM. The influence of inadequate empirical antimicrobial treatment on patients with bloodstream infections in an intensive care unit. Clin Microbiol Infect 2003;9(5):412-8.
25. Lin MY, Weinstein RA, Hota B. Delay of active antimicrobial therapy and mortality among patients with bacteremia: impact of severe neutropenia. Antimicrob Agents Chemother 2008;52(9):3188-94.
26. Corona A, Bertolini G, Lipman J, Wilson AP, Singer M. Antibiotic use and impact on outcome from bacteraemic critical illness: the Bacteraemia Study in Intensive Care (BASIC). J Antimicrob Chemother 2010; 65(6):1276-85.

27. 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. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 2008;34(1):17-60.
28. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 2003;31(12):2742-51.
29. Garnacho-Montero J, Ortiz-Leyba C, Herrera-Melero I, Aldabó-Pallás T, Cayuela-Dominguez A, Marquez-Vacaro JA, Carbajal-Guerrero J, Garcia-Garmendia JL. Mortality and morbidity attributable to inadequate empirical antimicrobial therapy in patients admitted to the ICU with sepsis: a matched cohort study. J Antimicrob Chemother 2008;61(2):436-41.
30. Artero A, Zaragoza R, Camarena JJ, Sancho S, González R, Nogueira JM. Prognostic factors of mortality in patients with community-acquired bloodstream infection with severe sepsis and septic shock. J Crit Care 2010;25(2):276-81.
31. MacArthur RD, Miller M, Albertson T, Panacek E, Johnson D, Teoh L, Barchuk W. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. Clin Infect Dis 2004;38(2):284-8.
32. Annane D, Bellissant E, Cavaillon JM. Septic shock. Lancet. 2005;365(9453):63-78.
33. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348(16):1546-54.