Prognostic Value of Timing of Antibiotic Administration in Patients With Septic Shock Treated With Early Quantitative Resuscitation

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Abstract: *Background:* The Surviving Sepsis Campaign recommends initiating broad-spectrum antibiotic treatment within 1 hour of septic shock recognition. However, there is controversy regarding this owing to contradictory studies. This study investigated the relationship between the antibiotic administration interval and 28-day mortality in septic shock patients treated with an early quantitative resuscitation protocol in an emergency department (ED). *Methods:* 715 consecutive septic shock patients were prospectively collected from January 2010 to December 2012. Of these, 426 patients developed shock at or after initial assessment, and the time of initial antibiotic administration was recorded. The primary outcome was 28-day mortality. *Results:* The median antibiotic administration interval was 91.5 (47.0–158.0) minutes, and the 28-day mortality was 20.0%. Mortality did not change with hourly delays in antibiotic administration up to 5 hours after shock recognition: 1 hour (odds ratio [OR]: 0.81, 95% confidence interval [CI]: 0.45–1.45), 2 hours (OR: 0.72, 95% CI: 0.40–1.29) and 3 hours (OR: 0.61, 95% CI: 0.30–1.25). However, inability to achieve early resuscitation goals (OR: 1.94, 95% CI: 1.07–3.51), sequential organ failure assessment score (OR: 1.30, 95% CI: 1.17–1.44) and lactic acid concentration (OR: 1.66, 95% CI: 1.11–2.49) were significantly associated with an increased risk of 28-day mortality. *Conclusions:* Among septic shock patients who underwent early quantitative resuscitation in an ED, mortality did not increase with hourly delays in antibiotic administration. These data call into question the strength of the association between hourly delays in antibiotic administration and mortality in septic shock patients.

Key Indexing Terms: Sepsis; Antibiotics; Mortality. **[Am J Med Sci 2015;349(4):328–333.]**

Severe sepsis and septic shock are associated with high mortality and high costs and affect approximately 750,000 Americans annually.[1,2] It was estimated that 1 patient presents to an emergency department (ED) in the United States with severe sepsis or septic shock every minute, and mortality ranges from 20% to 40%.[3–6] Antibiotic therapy has long been a mainstay of the treatment of such patients. The international guidelines of the Surviving Sepsis Campaign for the management of severe sepsis and septic shock recommend administering broad-spectrum antimicrobial therapy within 1 hour of septic shock recognition.[7,8] These recommendations are based on a retrospective landmark study conducted by Kumar et al[9] in an intensive care unit (ICU), which reported that each 1-hour delay in initiating effective antibiotic therapy after the onset of hypotension was associated with a decrease in survival of 7.6%. However, there is great controversy surrounding this issue owing to recent contradictory studies of septic shock patients treated with an early quantitative resuscitation protocol in EDs.[5,6,10,11] Thus, the optimal timing of antibiotic administration and its impact on patient outcome remain unclear in the early treatment of septic shock.

The objective of this study was to evaluate whether the shock recognition-to-antibiotic administration interval is associated with 28-day mortality in septic shock patients treated with a standardized resuscitation algorithm, including early quantitative resuscitation, in EDs.

METHODS

Patients

This retrospective cohort study of prospectively collected data was performed at an urban academic adult ED at a tertiary referral center with an annual census of more than 100,000 patients. The study was approved by the Research Ethics Committee of the hospital. A total of 715 consecutive septic shock adult patients (≥18 years old) who fulfilled the septic shock criteria were prospectively added to the septic shock registry from January 2010 to December 2012. From this registry, we retrospectively identified patients who developed shock at or after initial assessment and 1st received antibiotics after shock recognition. Diagnosis of septic shock was defined as refractory hypotension, specifically, systolic blood pressure <90 mm Hg or mean arterial pressure <70 mm Hg requiring vasopressors despite adequate fluid therapy, or a blood lactate concentration of at least 4 mmol/L.[4] All consecutive patients with septic shock received protocol-driven resuscitation bundle therapy, including early quantitative resuscitation, according to the Surviving Sepsis Campaign.[12] The achievement of early resuscitation goals was defined as the accomplishment of all 3 bundle elements within 6 hours as follows: (1) mean arterial pressure ≥65 mm Hg, (2) central venous pressure ≥8 mm Hg and (3) central venous oxygenation ≥70%.

There was guidance on initial empiric antibiotic selection to minimize the percentage of patients who received inappropriate antibiotics in the ED. Recommendations were based on the presumed source of infection: ceftriaxone with azithromycin or piperacillin-tazobactam with levofloxacin for pneumonia, cefotaxime with metronidazole for intra-abdominal infections, piperacillin-tazobactam with vancomycin for neutropenia, carbapenem for recent infection of extended spectrum beta-lactamase releasing pathogen and piperacillin-tazobactam with ciprofloxacin for unknown infection sources.

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Patients were excluded if they fulfilled one of the following criteria: had a "do not attempt resuscitation" status, received antibiotics before shock recognition or were transferred from another hospital after initial resuscitation. The primary outcome was the 28-day mortality rate.

Data Collection

Demographic and clinical data, including age, gender, symptoms, medical history, initial vital signs and laboratory findings, were retrieved from electronic hospital records. Sequential organ failure assessment (SOFA) scores were calculated based on the worst variables recorded during the first 24 hours after ED admission.[13] The interval between shock recognition and antibiotic intravenous injection was calculated. Shock recognition was defined as when the patient developed 2 or more systemic inflammatory response criteria and either a systolic blood pressure of <90 mm Hg after a minimum of 20 mL/kg rapid volume challenge or a blood lactate concentration of at least 4 mmol/L. We compared the outcomes of subjects who received an initial dose of antibiotics after versus before each hourly increment after shock recognition, up to a maximum of 5 hours.

Statistical Analysis

Continuous variables are expressed as mean and standard deviation or as median and interquartile range if the assumption of a normal distribution was violated. Categorical variables are expressed as number and percentage. The primary analysis compared patients who were still alive at 28 days and those who were not. All variables were subjected to the Kolmogorov-Smirnov test to determine whether they had a normal distribution. The Student's *t* test was used to compare the means of normally distributed continuous variables, whereas the Mann-Whitney's *U*-test was used to compare noncontinuous variables. The χ^2 or Fisher's exact test was used to compare categorical variables. Unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) are also provided for demographic and clinical characteristics. To attempt to control for potential confounders, we constructed a multivariate logistic regression model using the 28-day mortality as the dependent variable. Candidate variables were compared using the Kruskal-Wallis test to assess for differences in patients who received antibiotics within each hourly interval versus all the rest of the cohort. Multivariate logistic regression was conducted by backward elimination with all variables that had a P value <0.05 in univariate analysis and the interval between shock recognition and antibiotic injection. The results of multivariate analysis are reported as OR and 95% CI. A 2-sided P value <0.05 was considered to be statistically significant. Model performance was assessed by C statistics and the Hosmer-Lemeshow test. All statistical analyses were performed using SPSS for Windows version 18.0 (SPSS Inc, Chicago, IL).

RESULTS

Of the 715 adult patients with severe sepsis and septic shock who were enrolled in the registry, we excluded 212 patients who were transferred from another hospital, 39 patients who received antibiotics before shock recognition and 38 patients who had a "do not attempt resuscitation" status, leaving 426 patients for analysis. The mean age of these patients was 62.9 years, and 260 patients (61.0%) were male. Overall, 340 patients survived and 86 patients expired, yielding a 28-day mortality rate of 20.2%. The baseline characteristics of the patients who were alive at 28 days (survived group) and those who were not (expired group) are shown in Table 1. Failure to achieve early resuscitation goals (70.5% versus 53.7%), mechanical ventilation (64.0% versus 21.2%), continuous renal replacement therapy (36.0% versus 8.5%) and underlying heart failure (8.1% versus 2.4%) were more frequent in the expired group than in the survived group. In addition, patients in the expired group had a significantly higher pulse rate, respiratory rate, procalcitonin level, initial lactic acid level and SOFA score and a significantly lower pulse oxygen saturation level and platelet count than patients in the survived group ($P < 0.05$ each; Table 1).

Bacteria were identified in 62.7% of blood, urine and sputum cultures, and the choice of empiric antibiotics was appropriate for the bacteria in 91.8% of cases. According to the guidance, the empirical antibiotic choice was reasonable in 98.0% of cases. The most common infection site was the abdomen (42.7%), followed by the lung (33.1%), urinary tract (9.6%) and musculoskeletal system (4.0%). The primary infection site was unknown in 10.1% of cases.

The median interval between shock recognition and antibiotic administration was 91.5 (47.0–158.0) minutes. Figure 1 shows the interval between shock recognition and initial antibiotic administration in the entire cohort, stratified by 28-day mortality. The median interval between shock recognition and antibiotic administration was shorter in the survived group than in the expired group, but this was not statistically significant (82.0 [47.0–149.3] minutes versus 100.0 [46.0–143.3] minutes, $P = 0.87$).

The relative mortality and OR according to the number of hours between shock recognition and antibiotic administration are summarized in Table 2. Mortality was not associated with hourly delays in antibiotic administration, up to 5 hours after shock recognition. Furthermore, the interval between ED triage and antibiotic administration was not associated with mortality: 1 hour (OR: 0.68, 95% CI: 0.28–1.63), 2 hours (OR: 0.92, 95% CI: 0.51–1.66), 3 hours (OR: 0.64, 95% CI: 0.35–1.16), 4 hours (OR: 0.82, 95% CI: 0.43–1.56) and 5 hours (OR: 0.78, 95% CI: 0.37–1.63). However, failure to achieve resuscitation goals (OR: 1.94, 95% CI: 1.07–3.51), SOFA score (OR: 1.30, 95% CI: 1.17–1.44) and lactic acid concentration (OR: 1.66, 95% CI: 1.11–2.49) were significantly associated with an increased risk of 28-day mortality (Table 3).

DISCUSSION

The optimal timing of antibiotic administration and its impact on patient outcome remain unclear. Our results showed that there was no significant association between the shock recognition-to-initial antibiotic administration interval and 28-day mortality in septic shock patients treated with an early quantitative resuscitation protocol in an ED. The illness severity and achievement of resuscitation goals were the most important determinants of outcome in these patients.

Management of septic shock patients is no longer confined to ICUs. Recent advances in the recognition and early management of severe sepsis and septic shock focused on the critical first 24 hours of patient care, which is often initiated in EDs.[8,14–16] Early quantitative resuscitation and early administration of antimicrobial therapy are 2 key components of the "sepsis bundle." Although evidence of the benefit of early antibiotic therapy initiation is well established in the ICU setting, it needs to be verified in the ED setting.[9,17,18]

A recent article by Gaieski et al,[5] which evaluated a cohort of septic shock patients in whom early quantitative resuscitation was initiated in EDs, raises interesting questions