Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol*

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Objective: **We sought to determine the association between time to initial antibiotics and mortality of patients with septic shock treated with an emergency department-based early resuscitation protocol.**

Design: **Preplanned analysis of a multicenter randomized controlled trial of early sepsis resuscitation.**

Setting: **Three urban U.S. emergency departments.**

Patients: **Adult patients with septic shock.**

Interventions: **A quantitative resuscitation protocol in the emergency department targeting three physiological variables: central venous pressure, mean arterial pressure, and either central venous oxygen saturation or lactate clearance. The study protocol was continued until all end points were achieved or a maximum of 6 hrs.**

Measurements and Main Results: **Data on patients who received an initial dose of antibiotics after presentation to the emergency department were categorized based on both time from triage and time from shock recognition to initiation of antibiotics. The primary outcome was inhospital mortality. Of 291 included patients, mortality did not change with hourly delays in antibiotic administration up to 6 hrs after triage: 1 hr (odds ratio [OR], 1.2; 0.6–2.5), 2 hrs (OR, 0.71; 0.4–1.3), 3 hrs (OR, 0.59; 0.3–1.3). Mortality was significantly increased in patients who received initial antibiotics after shock recognition (n = 172 [59%]) compared with before shock recognition (OR, 2.4; 1.1–4.5); however, among patients who received antibiotics after shock recognition, mortality did not change with hourly delays in antibiotic administration.**

Conclusion: **In this large, prospective study of emergency department patients with septic shock, we found no increase in mortality with each hour delay to administration of antibiotics after triage. However, delay in antibiotics until after shock recognition was associated with increased mortality. (Crit Care Med 2011; 39:2066–2071)**

KEY WORDS: antibiotics; emergency medicine; sepsis; septic shock

Severe sepsis hospitalizations have doubled over the last decade resulting in at least 750,000 persons affected annually in the United States (1, 2). Estimates suggest that 500,000 patients with severe sepsis are treated annually in U.S. emergency departments (EDs) (3). The Surviving Sepsis Campaign international consensus guidelines recommend initiating broad-spectrum antibiotic coverage within the first hour of recognizing severe sepsis and septic shock (4). These recommendations are based largely on one large retrospective study (5) and expert consensus. Despite these guidelines, a recent large cohort of 165 hospitals treating >15,000 patients with septic shock from the Surviving Sepsis Campaign registry demonstrated that only 68% of patients received broad-spectrum antibiotics within 3 hrs of ED presentation (6) demonstrating the difficulty of achieving antibiotic administration within current guidelines in routine clinical practice.

To date, no prospective study has examined the timing of antibiotic administration and its association with mortality in ED patients with sepsis treated with an early quantitative resuscitation protocol. Thus, the optimal timing of antibiotic administration and its impact on outcome remain unclear in the early treatment of severe sepsis and septic shock. The aim of this study was to evaluate if the timing of antibiotic administration in relation to both triage time and time of shock recognition was associated with inhospital mortality among a group of consecutive, prospectively enrolled patients presenting to three US EDs with septic

***See also p. 2184.**

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shock and treated with an early quantitative resuscitation protocol.

METHODS

Study Design. We conducted a preplanned analysis of a recently completed prospective, parallel-group, nonblinded randomized clinical trial designed to assess the noninferiority of lactate clearance vs. central venous oxygen saturation as the protocol end point that evaluated the adequacy of oxygen delivery during ED-based early quantitative resuscitation of sepsis (7).

The trial took place from January 2007 to January 2009 at Carolinas Medical Center, Charlotte, NC; Beth Israel Deaconess Medical Center, Boston, MA; and Cooper University Hospital, Camden, NJ, all of which are large, urban, tertiary care hospitals staffed by emergency medicine resident physicians supervised by board-certified emergency medicine attending physicians. The study was approved by the institutional review board at each institution and all participants or their surrogate provided written informed consent for participation. The trial was registered on Clinicatrials.gov identifier NCT00372502.

The detailed methods of the study have been described (7). In brief, consecutive patients presenting to one of the participating EDs were eligible for enrollment if they were >17 yrs, had confirmed or suspected infection, two or more systemic inflammatory response criteria (8), and hypoperfusion evidenced by hypotension after fluid challenge or a blood lactate concentration of at least 4 mmol/L. After enrollment, patients were randomly assigned to one of two groups. Each group received structured quantitative resuscitation while in the ED. The study protocol was continued until all end points were achieved or a maximum of 6 hrs. The published results of this study showed a 6% (95% confidence interval, −3 to 14%) inhospital mortality difference between the two study groups, confirming the primary hypothesis of noninferiority between the two resuscitation end points (7).

As part of the protocol, all patients received broad-spectrum antibiotic coverage according to local hospital guidelines. The online supplement provides an example of one of the antibiotic guidelines (see Supplemental Digital Content 1, http://links.lww.com/CCM/A258). The only requirement for antibiotic administration was that they be administered as early as possible after recognition of sepsis.

Data Analysis and Outcomes. The primary outcome was inhospital mortality. We compared the outcomes of subjects who received an initial dose of antibiotics after compared with before each hourly increment up to a maximum of 6 hrs after ED triage. We also compared outcomes of patients receiving initial antibiotics after compared with before each hourly increment after shock recognition. Shock recognition was defined as the time that the patient developed two or more systemic inflammatory response syndrome criteria and either a systolic blood pressure <90 mm Hg after a minimum of 20-mL/kg rapid volume challenge or a blood lactate concentration of at least 4 mmol/L. Recognizing that some patients would receive antibiotics before shock recognition, we analyzed outcomes of patients who received antibiotics before compared with after recognition of shock; however, if patients received antibiotics before shock recognition, they were excluded from the hourly incremental analysis.

One infectious disease specialist reviewed the blood culture and clinical data from all subjects. We followed our previously published criteria for determining positive blood cultures (9). A positive blood culture required that a bacterial or fungal pathogen be isolated by routine culture in the blood. *Staphylococcus epidermidis* was uniformly considered a contaminant and other coagulase-negative staphylococci were similarly considered to be unlikely to cause septic shock and were considered contaminants unless the patient had a pre-existing indwelling venous catheter. Antibiotic administration was considered appropriate if the patient received an initial antimicrobial to which the cultured bacteria had *in vitro* sensitivity. In the case of negative cultures, antibiotics were considered appropriate if they were given in accordance with local guidelines and were extended spectrum antibiotics.

Categorical data are presented as proportions with 95% confidence intervals (CIs). Continuous data are presented as means and SDs or medians and interquartile ranges. Results were compared using chi-squared, Fisher's exact, Mann-Whitney, or Kruskal-Wallis tests as appropriate. To attempt to control for potential confounders, we constructed a multivariate logistic regression model using inhospital death as the dependent variable. Candidate variables were compared using the Kruskal-Wallis test to assess for differences in hourly intervals vs. the entire cohort and were added to the multivariate model if $p < .10$ to maintain the event (death) per independent variable ratio of approximately 8–10:1 that is necessary for multivariate modeling (10). The model was refined using reverse stepwise elimination. Model fit was determined with Hosmer and Lemeshow's goodness-of-fit test. All statistical tests were two-sided with $p < .05$ considered significant. Data were analyzed using commercially available statistical software (StatsDirect 2.7.7, Cheshire, UK; and STATA 10.0, College Station, TX).

RESULTS

Of 300 patients enrolled in the study, 291 received a first dose of antibiotics after presentation to the hospital. The remaining nine patients had received antibiotics before hospital arrival (seven from another outpatient facility, two from a rehabilitation/chronic nursing facility) and were excluded from subsequent analysis. Fifty-nine percent (172 of 291) of patients received the initial dose of antibiotics after recognition of shock. Baseline characteristics of the entire cohort are shown in Table 1 and the various sources of infection are shown in Table 2. Overall mortality was 55 of 291 (18.9%).

Table 1. Patient demographics and clinical characteristics

Variable (n = 291)	Value
Age, yrs (IQR)	62 (50–73)
Race (%)	
White	158 (54)
Black	101 (34)
Hispanic	27 (9)
Other	5 (2)
Sex, %	
Male	156 (53)
Female	135 (46)
Eligibility criteria (IQR)	
Temperature, °F	99 (97–101)
Heart rate, beats/min	102 (85–112)
Respiratory rate, breaths/min	22 (18–27)
White blood count, cells per mm^3	12.4 (7.7–17.5)
Systolic blood pressure, mm Hg	86 (77–98)
Lactate, mmol/L	3.3 (1.8–5.8)
Baseline laboratory values (IQR)	
Platelets per mm^3	214 (135–294)
Hemoglobin, mg/dL	11.4 (9.8–13.4)
Creatinine, mg/dL	1.7 (1.1–3.0)
Total bilirubin, mg/dL	1.0 (0.6–1.6)
HCO_3, mg/dL	21 (17–24)
International normalized ratio	1.3 (1.1–1.7)
Disease severity (IQR)[a]	
Simple Acute Physiology Score II	42 (30–55)
Sequential Organ Failure Assessment score	6 (4,9)
Mortality in Emergency Department Sepsis score	11 (8–14)

IQR, interquartile range.
[a]At 0 hrs.

Positive blood cultures for pathologic organisms were obtained in 100 of 291 (34.4%) patients. The organisms isolated from the blood and their frequencies of occurrence are summarized in Table 3. The mortality rate for blood culture-positive septic shock was 26 of 100 (26.0%) vs. 29/191 (15.2%) for blood culture-negative septic shock ($p = .03$). Of the 100 patients with positive blood cul-

Table 2. Source of infection

Source	No. of Patients (%)
Pneumonia	99 (34.0)
Urinary tract infection	71 (24.4)
Intra-abdominal	49 (16.8)
Skin and soft tissue	23 (7.9)
Indwelling intravascular catheter	11 (3.8)
Surgical wound	7 (2.4)
Endocarditis	4 (1.4)
Meningitis	3 (1.0)
Septic arthritis	2 (0.7)
Tuberculosis	1 (0.3)
Ear, nose, throat	1 (0.3)
Toxic shock syndrome	1 (0.3)
Unknown	40 (13.8)
Two or more sources	21 (7.2)

Table 3. Organisms isolated from the blood

	No. of Patients
Gram-positive organisms	
Staphylococcus aureus	21
Methicillin-sensitive	11
Methicillin-resistant	10
Coagulase-negative *staphylococcus*	1
Streptococcus pneumoniae	7
Other streptococcus species	9
Enterococcus species	8
Peptostreptococcus	1
Bacillus cereus	1
Clostridium perfringens	2
Diphtheroids	2
Micrococcus	1
Lactobacillus	1
Gram-negative organisms	
Escherichia coli	17
Klebsiella species	7
Proteus species	7
Serratia marcescens	4
Pseudomonas species	2
Enterobacter species	2
Vibrio vulnificus	1
Acinetobacter species	1
Morganella species	1
Citrobacter species	1
Yeast/fungi	
Candida species	3
Positive blood cultures	100

Table 4. Inhospital mortality: Triage to initial antibiotics

Time to Antibiotics	Number of Patients	Mortality (%)	Difference (%)	Odds Ratio[a]	95% Confidence Interval	Adjusted Odds Ratio[a]	95% Confidence Interval
≤1 hr	65	16.9	2.6	1.18	0.57–2.46	1.81	0.74–4.44
>1 hr	226	19.5					
≤2 hrs	155	21.3	−5.1	0.71	0.39–1.30	1.07	0.54–2.16
>2 hrs	136	16.2					
≤3 hrs	223	20.6	−7.4	0.59	0.27–1.27	0.66	0.27–1.63
>3 hrs	68	13.2					
≤4 hrs	255	20.4	−12.1	0.35	0.10–1.20	0.39	0.08–1.90
>4 hrs	36	8.3					
≤5 hrs	274	19.7	−13.8	0.25	0.03–1.96	0.69	0.07–6.86
>5 hrs	17	5.9					
≤6 hrs	281	19.6	−19.6	—	—	—	—
>6 hrs	10	0					

[a]Odds of death with increasing delays in antibiotic administration.

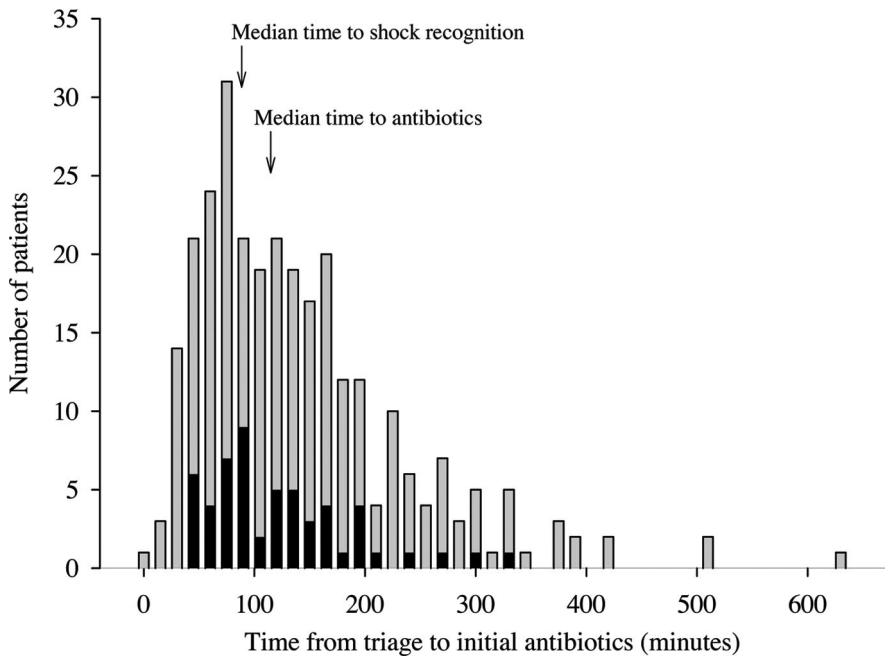

Figure 1. Graphic depiction of the time from triage to initial antibiotics in the entire cohort stratified by final hospital outcome. Gray bars represent patients who survived the hospitalization and black bars represent patients who died in the hospital.

tures, 91 received antibiotics in the ED to which the causative organism was susceptible. Of the nine patients who failed to receive appropriate antibiotics, seven of nine received broad-spectrum antibiotics to which the causative organism was resistant (multidrug-resistant Gram-negative rods in six of nine and multidrug-resistant enterococci in one of nine), and two of nine patients had fungemia that was untreated in the ED. The mortality for patients treated with appropriate antibiotics for blood culture-positive sepsis in the emergency department was 23 of 91 (25.3%) vs. three of nine (33.3%) for those treated with inappropriate antibiotics ($p = .69$).

The median time from triage to initial antibiotic administration was 115 mins (interquartile range, 65–175). Table 4 summarizes the relative mortality and odds ratios for death associated with hourly intervals from ED triage to antibiotic administration among all 291 subjects. Figure 1 depicts the time from triage to initial antibiotics in the entire cohort stratified by final hospital outcome (alive vs. dead). We found no association between inhospital mortality and the time from ED triage to administration of antibiotics during the first 6 hrs of resuscitation.

The median time to shock recognition among all subjects was 89 mins (interquartile range, 48–180). A total of 172 (59%) patients received antibiotics after shock recognition. When compared with patients who received antibiotics before shock recognition (n = 119), patients receiving antibiotics after shock recognition had a significant increase in the odds of death (odds ratio, 2.35; 95% CI, 1.12–4.53). Figure 2 depicts the time from shock recognition to initial antibiotics in the entire cohort stratified by final hospital outcome (alive vs. dead).

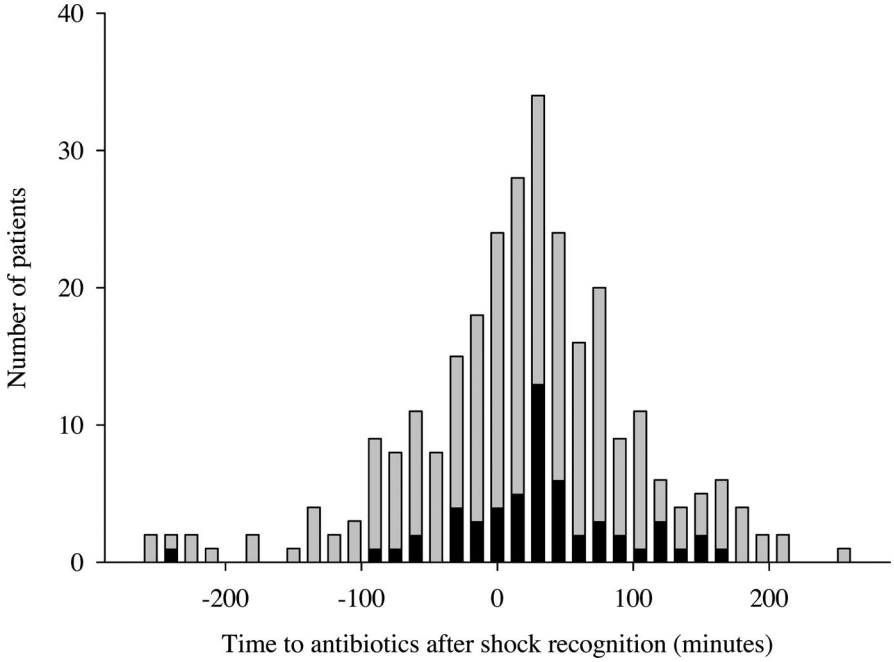

Figure 2. Graphic depiction of the time from shock recognition to initial antibiotics in the entire cohort stratified by final hospital outcome. Shock recognition is indicated by time 0. Subjects with negative times received antibiotics before shock recognition. Gray bars represent patients who survived the hospitalization and black bars represent patients who died in the hospital.

Table 5. Inhospital mortality: Shock recognition to initial antibiotics

Time to Antibiotics	Number of Patients	Mortality (%)	Difference (%)	Odds Ratio[a]	95% Confidence Interval	Adjusted Odds Ratio[a]	95% Confidence Interval
Before shock recognition	119	11.8	12	2.35	1.12–4.53	2.59	1.17–5.74
After shock recognition	172	23.8					
≤1 hr	101	25.8	−4.7	1.29	0.63–2.67	0.93	0.41–2.12
>1 hr	71	21.1					
≤2 hrs	145	24.1	−1.9	1.11	0.42–2.98	0.69	0.21–2.22
>2 hrs	27	22.2					
≤3 hrs	164	23.8	1.2	0.94	0.18–4.82	0.84	0.13–5.52
>3 hrs	8	25.0					

[a]Odds of death with increasing delays in antibiotic administration.

Table 5 summarizes the relative mortality and odds ratios for death associated with hourly intervals from shock recognition to antibiotic administration among the 172 subjects who received antibiotics after shock recognition. We found no increase in mortality associated with delay to administration of antibiotics during the first 3 hrs after shock recognition. Only eight patients received antibiotics after 3 hrs of shock recognition.

To attempt to control for potential confounders, we constructed a multivariate logistic regression model using inhospital death as the dependent variable. The final model included age, total Sequential Organ Failure Assessment score at enrollment, initial lactate, race, and achievement of lactate clearance goal. As the independent variables of most interest, time to antibiotics at each time point cutoff and appropriate antibiotics were forced into the final models. The final model demonstrated goodness of fit by Hosmer and Lemeshow's ($p = .27$). The adjusted odds ratios revealed no significant changes from the unadjusted odds ratios and are shown in Tables 4 and 5.

DISCUSSION

In this report, we document the association between timing of initial antibiotic treatment and mortality in ED patients undergoing a quantitative resuscitation protocol for septic shock. Our results indicate no association between time from triage to initial antibiotic administration and hospital mortality. However, our data suggest an increased risk of death if antibiotics are delayed until after the recognition of shock. Once a patient meets the consensus definition for shock, our data showed no association between subsequent hourly delays in antibiotic administration and mortality.

The Surviving Sepsis Campaign international consensus guidelines recommend always administering broad-spectrum antibiotics within the first hour of recognizing severe sepsis and septic shock (4). This recommendation is largely based on one large retrospective study published in 2006 (5). In that study, Kumar et al reported that administration of antimicrobials within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease in survival of 7.6%. These findings were not confirmed by our data presented in this report. There are several considerations that may explain these differences in findings. First, the Kumar et al study included all intensive care unit patients diagnosed with septic shock, and the overall reported mortality rate was 56%. Thus, it appears that this cohort of subjects had a higher severity of illness than the present study. Furthermore, we studied cohort of 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 19%, consistent with other studies of ED patients receiving early aggressive resuscitation (11–13). Although the study by Kumar et al attempted to control for the variability of resuscitation, it is likely that the initial resuscitative efforts across such a wide spectrum of patients in various care settings were considerably different. As such, the extrapolation of this retrospective data from an intensive care unit patient population to the earliest hours of resuscitation in ED patients receiving standardized resuscitation may be inappropriate. All of the patients in the current study underwent the same early recognition and aggressive treatment protocol, likely resulting in more uniform screening and initial resuscitative efforts, and may provide an additional explanation for the differences in findings. That is, when sepsis recognition and

resuscitation are early, aggressive, and prescribed, the administration of antibiotics measured in hourly increments of time is less important than is just administering the antibiotics during the initial resuscitative phase.

Our data are consistent with the findings of Gaieski et al, who published a retrospective analysis evaluating the timing of antibiotics and association with mortality in ED patients treated with an early goal-directed therapy protocol (14). However, similar to the study by Kumar et al, the Gaieski report emphasizes appropriateness of antibiotic administration in their conclusions. In our report, we made an *a priori* decision to evaluate only initial antibiotic administration and not put major emphasis on if the antibiotic coverage was considered appropriate, as has been proposed in studies by both Kumar and Gaieski (5, 14). We had two important rationales for our decision. First, although it makes intuitive sense to only measure the effect of an antibiotic with activity against the causative organism, the reality of accurately performing this measurement in a clinical setting, particularly the ED, is nearly impossible. Appropriateness of antibiotics is based on culture data not available for 24 to 96 hrs or longer after initial antibiotic administration and therefore it is impossible for a clinician to know if a prescribed antibiotic is appropriate. Thus, it seems inappropriate to require this standard when determining the effect of antibiotic timing on outcome. Our rationale is similar to that for determination of appropriateness of cardiac catheterization laboratory activation for ST-segment myocardial infarction being based on the initial evaluation and electrocardiogram, not the presence or absence of a culprit lesion (15). Second, despite the best attempt of authors to standardize the evaluation of appropriateness of antibiotics, the measure is performed retrospectively and is extremely complex and subject to interpretation. Interestingly, this issue is not just semantics, particularly given the high rate of culture-negative septic shock, 30% to 43% in the aforementioned studies, leading to a dual standard of appropriateness based on the presence or absence of a positive culture. Appropriateness in these cases of culture-negative sepsis is relegated to "broad spectrum," which can be argued to be less restrictive than the evaluation of culture-positive subjects. Furthermore, all studies of septic shock require a subjective analysis of the causative organism. Such a judgment is particularly difficult in cases in which more than one culture is positive with different organisms and subjective decisions as to the causative organism must be made, even if they are made with predefined decision rules. Factors such as presence of a indwelling urinary or venous catheter, presence of an immunocompromised state that allows "contaminants" to become virulent sources of infection, and nosocomial exposures all confound these analyses and are extraordinarily difficult to standardize and control.

With the aforementioned rational taken into consideration, appropriateness of antibiotics could have been an important confounder of our findings. Thus, we incorporated appropriateness of antibiotics in our multivariate model. These adjusted results were nearly identical to our unadjusted results. Namely, there appears to be no association between hourly delays in antibiotic administration after triage and mortality, even when controlling for appropriateness. We interpret these results to suggest that when all other parts of early resuscitation are sufficiently refined, the importance of timeliness of antibiotics appears to recede.

The strength of this study is that we prospectively studied the timing of antibiotic administration to ED patients with septic shock. All patients received a standardized, prescribed early recognition and resuscitation protocol, removing much of the variability in both patient population and early treatment present in other studies. In general, patients received antibiotics early in their hospital course with 75% of patients receiving initial antibiotics within 3 hrs and 97% within 6 hrs of triage.

This study has several weaknesses that deserve consideration. First, all three of the hospital systems have considerable experience with early quantitative resuscitation protocols, and our results may not be generalizable to hospitals without such protocols. Second, the vast majority of patients received antibiotics within 3 hrs of triage, and the relatively small numbers of patients in subsequent time points leads to wide CIs and makes it more difficult to draw definitive conclusions regarding associations as time points become progressively longer. Third, although we did not observe significant associations in our study, it is possible that a larger study would be able to detect a difference. Given our CIs, however, we would expect such an effect size to be small and significantly less than those previously reported (5, 14). Fourth, although our mortality rate is similar to previous reports (11–13), it is lower than reports in other septic shock populations (16, 17). Fifth, it is impossible in most cases to identify the exact time of onset of septic shock and thus the timing of antibiotics in relation to onset of shock can often not be ascertained. This is an inherent limitation to the nature of sepsis research. Finally, given the design of our study, we are only able to draw conclusions regarding associations and not causation.

CONCLUSION

In this large prospective study of ED patients with septic shock who received standardized early recognition and aggressive resuscitation at three experienced institutions, we failed to demonstrate an association between timing of antibiotic administration from ED triage and hospital mortality. A delay in antibiotics until after shock recognition, as compared with before, was associated with increased mortality; however, if antibiotics are administered after shock recognition, there is no increase in mortality with hourly delays.

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