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**Delay in Antibiotic Administration is Associated with Mortality Among
Septic Shock Patients with *Staphylococcus aureus* Bacteremia**

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Abstract

Objectives: The relationship between the timing of antibiotics and mortality among sepsis shock patients has not been examined among patients specifically with *Staphylococcus aureus* (*S. aureus*) bacteremia.

Design: Retrospective analysis of a Veterans Affairs *S. aureus* bacteremia database.

Setting: One hundred twenty-two hospitals in the VA Health System.

Patients: Patients with septic shock and *S. aureus* bacteremia admitted directly from the emergency department to the intensive care unit from January 1, 2003 to October 1, 2015 were evaluated.

Intervention: Time to appropriate antibiotic administration and 30-day mortality.

Measurements and Main Results: A total of 506 patients with *S. aureus* bacteremia and septic shock were included in the analysis. Thirty-day mortality was 78.1% for the entire cohort and was similar for those participants with methicillin resistant (MRSA) and methicillin sensitive *S. aureus* (MSSA) bacteremia. Our multivariate analysis revealed that as compared to those who received appropriate antibiotics within one hour after ED presentation, each additional hour that passed before appropriate antibiotics were administered produced an odds ratio of 1.11 [95% CI: 1.02-1.21] of mortality within 30 days. This odds increase equates to an average adjusted mortality increase of 1.3% [95% CI: 0.4% - 2.2%] for every hour that passes before antibiotics are administered.

Conclusions: The results of this study further support the importance of prompt appropriate antibiotic administration for patients with septic shock. Physicians should consider acting quickly to administer antibiotics with *S. aureus* coverage to any patient suspected of having septic shock.

Key Words: *Staphylococcus aureus*; antibiotics; septic shock

Manuscript

Introduction

Sepsis is a significant global public health burden that afflicts over 31 million people and causes an estimated 5.3 million deaths annually [1]. International guidelines and federal quality measures call for timely administration of antibiotics to septic patients [2,3], and in the case of septic shock, now advise that they be given within the first hour [4].

Initial studies examining the relationship between time to antibiotics and sepsis mortality produced mixed results, but suggest a benefit from early antibiotic administration [5-19]. Two subsequent studies that examined large state-wide databases provide the most compelling evidence that early administration of antibiotics saves lives. A 2017 study of 35,000 septic patients in a California healthcare system showed that delays in antibiotic administration were associated with increased mortality [20]. The association was most pronounced among septic shock patients who suffered a 1.8% increase in the probability of mortality for each hour antibiotics were not provided. Additionally, an analysis of the New York State Sepsis Initiative revealed that timely completion of a sepsis bundle was associated with reduced mortality among septic patients [21]. Of the sepsis bundle components, early antibiotic administration was the component most strongly associated with the observed decrease in mortality.

Previous studies that evaluated the relationship between the timing of antibiotics and mortality among sepsis patients have, with one exception [19], studied a cohort of patients with sepsis from a variety of bacterial species. To date, the relationship between the timing of antibiotic administration and sepsis mortality has not been examined among septic shock patients with *Staphylococcus aureus* (*S. aureus*) bacteremia. Both methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA), are a leading cause of sepsis due to skin and soft tissue infections, endocarditis, osteoarticular infections, pneumonia, toxic shock syndrome, and line or medical device infections [22]. MRSA bacteremia is independently associated with sepsis mortality [23, 24]. Among critically-ill patients with MRSA

bacteremia mortality rates can exceed 60% [25]. Given the high rate of mortality among septic patients infected with *S. aureus*, it is important to determine if the relationships observed previously among patients with a heterogenous bacterial sepsis source also hold for those with *S. aureus* bacteremia.

We studied the relationship between the time of appropriate antibiotic administration following emergency department triage and mortality among patients with septic shock admitted to the intensive care unit (ICU) whose blood cultures revealed a *S. aureus* infection. We then examined the effects that MRSA and MSSA had on our findings.

Methods

Participants, data source, and data elements

We conducted a retrospective study of adult patients (age ≥ 18 years) with *S. aureus* (MRSA or MSSA) bacteremia admitted to 122 hospitals in the Veterans Affairs (VA) Health System from January 1, 2003 to October 1, 2015. We included patients who fulfilled the 2001 International Sepsis Definitions (Sepsis-2) for septic shock [26] using the International Classification of Disease Clinical Modification 9th edition diagnosis codes: 785.52 [27]. We included only those patients who presented to the emergency department (ED) with sepsis, were admitted directly to the intensive care unit (ICU), and received appropriate antibiotics. We excluded patients in whom establishing a “time zero” for antibiotic administration is difficult. This included patients who developed septic shock on a medical or surgical ward, were transferred from an outside hospital, or were directly admitted from an outpatient setting to the hospital. Patients who first received antibiotics more than 12 hours after ED triage were excluded since it is possible that these patients developed sepsis following admission to the ICU (Figure #1). Limiting the sample to ED patients admitted to the ICU enabled us to focus on those patients for whom a clear and reproducible “time zero” could be identified for tracking the time elapsed prior to antibiotic administration.

Clinical data for study participants were obtained from the national VA databases through a review of the electronic medical record (EMR) using automated electronic data extraction. Medical history and clinical characteristics extracted from each participant's EMR included: microbiologic and chemistry laboratory data, vital signs, the Acute Physiology and Chronic Health Evaluation (APACHE) III score, and pharmacy data including bar code medication administration records. Trained study personnel then manually extracted time of ED presentation, presence of shock and refractory shock, *S. aureus* appropriate antibiotic administration, and time from ED presentation to antibiotic presentation from the EMR using established chart review methodology [28]. We created a series of predetermined rules and a procedural manual for data extraction. Two data extractors, blinded to the study outcome, were trained by the lead investigator and required to show competence extracting 20 charts prior to independent data abstraction. Time of ED presentation was defined as the date/time the first ED vital signs were entered into the EMR. Shock was considered to be present if participants had as a systolic blood pressure <90 mmHg, a mean arterial pressure (MAP) <65 mmHg, or if vasopressor agents were initiated. Shock also had to have lasted for more than one hour and be refractory following 1000 ml of intravenous (IV) fluid. If, however vasopressor agents were initiated and were infused for more than one hour, a participant was considered to have refractory shock even if his/her vital signs became normal. In cases for which a participant did not receive either IV fluid or vasopressors, a participant was considered to have refractory shock if he/she had one hour of sustained hypotension (Supplementary Table 1). An *a priori* list of appropriate antibiotics was created for both MRSA and MSSA bacteremia (Supplementary Table 2). The date/time of the first use of one of these antibiotics was recorded as the antibiotic administration time. For cases in which multiple antibiotics were administered, the date/time of the first appropriate antibiotic recorded in the EMR was used in the analysis. Time to antibiotic administration was calculated as the difference between time from ED presentation to appropriate antibiotic administration. The outcome of interest, all-cause mortality within 30 days of the first positive *S. aureus* blood culture, was electronically extracted from the EMR.

The Institutional Review Board and Research and Development Committee of the Providence VA Health System approved this study with a waiver of informed consent for patients.

Statistical Analysis

Participant clinical and demographic characteristics were summarized using descriptive statistics. Chained multiple imputation (n = 20) was used to impute missing values for body mass index (BMI, n=13), APACHE III score (n=4), and systemic inflammatory response syndrome (SIRS) criteria present at the time of blood culture (n=38). Fisher's exact and Wilcoxon rank-sum tests were used to assess for differences between survivors and non-survivors for dichotomous and continuous characteristics, respectively.

Logistic regression modeling was used to evaluate the relationship between time of appropriate antibiotic administration and 30-day mortality using the dataset containing the original and the imputed missing variables. Separate models were created for the entire study sample and stratified by participants whose *S. aureus* was classified as MRSA or MSSA, if shock preceded or followed antibiotic administration, and if shock developed within 12 hours or after 12 hours from ED presentation. Time to antibiotics administration was entered into the model as a linear continuous variable, based on the method of fractional polynomials. We assessed 862 variables representing clinical characteristics including infections source, concomitant infections, APACHE score, medical history and current comorbidities as potential confounders of time to appropriate antibiotic therapy and mortality. Additional variables considered for the model were those believed to have clinical relevance in the relationship of time to antibiotic administration and mortality. Confounders were considered further if they changed the time to antibiotics administration variable coefficient more than $\pm 15\%$, regardless of statistical significance. Variables were considered to be effect-modifiers if they had a statistically significant interaction with the time to antibiotics administration. A stepwise forward selection process was used to create the final model. Variables were retained in the model if they changed at least one other model coefficient by $\pm 15\%$. This produced a multivariate model

adjusted for: index year, BMI, APACHE III score, infective arthritis, SIRS criteria present at the time of blood culture, and MRSA/MSSA. All analyses were performed using Stata/MP version 14.2.

Results

Participant Characteristics

We identified 506 study participants with *S. aureus* bacteremia and septic shock who met our inclusion and exclusion criteria (Figure 1), 268 (53%) with MRSA and 238 (47%) with MSSA. The median age of study participants was 65 years old (interquartile range [IQR] 58-75), 98.2% were male, and the median APACHE III score was 66 (IQR 52-81). We observed a significant amount of baseline organ dysfunction with a majority of participants having a concurrent diagnosis of a cardiovascular (91.3%), pulmonary (75.5%), rheumatologic (74.5%), hematologic (66.8%), central nervous system (64.2%), renal (60.9%), endocrine (60.1%), or psychiatric (59.3%) process (Table #1). Details of specific diagnoses that comprised each organ system are outlined in the appendix (Supplementary Table 3). Thirty-day mortality was 78.1% for the entire cohort, and was similar for those participants with MRSA or MSSA (80.3% vs. 76.1% $p < 0.28$). Univariate analysis showed that survivors were more likely than non-survivors to have a higher BMI, lower APACHE III score, a skin and soft tissue infection as the source of their bacteremia, and to have undergone surgery during hospitalization (Supplementary Table 4).

Antibiotic Administration and Blood Cultures

The median time to antibiotic administration from triage was 3 hours (IQR 1-5). All participants received an *a priori* defined appropriate antibiotic. For cases of MRSA, 96.3% of the participants received vancomycin as the first antibiotic administered with anti-MRSA activity. For cases of MSSA, 40.3% received vancomycin, 30.5% piperacillin/tazobactam, 13.9% ceftriaxone or cefepime, and 10.3% levofloxacin, moxifloxacin, or ciprofloxacin as the first antibiotic with anti-MSSA activity. Twenty-eight percent of participants received appropriate antibiotics upon arrival or within the first hour of care in the ED; 58.6% received antibiotics within the first 3 hours of care. The distribution of antibiotic administration

is displayed in Figure 2. Blood cultures were obtained in 95% of the participants within the first three days of hospitalization or in the two days preceding hospitalization.

Primary outcome: 30-day Mortality

Our multivariate analysis revealed that, as compared to those who received antibiotics within one hour following ED presentation, each additional hour that passed before antibiotics were administered produced an odds ratio of 1.11 ($p=0.01$) of 30-day mortality (Table 2 and Figure 3). This odds increase equates to an average adjusted mortality increase of 1.3% [95% CI: 0.4% - 2.2%] for every hour that passes before antibiotics are administered (Supplementary Table 5). The odds of mortality were not increased for time elapsed to antibiotic administration when participants were stratified by MRSA (OR 1.15; $p=0.06$) or MSSA (OR 1.08; $p=0.12$) status, and were similar for participants who developed shock either before (OR 1.14; $p=0.05$) or after antibiotic administration (1.09; $p=0.10$; Table 2). However, mortality was greater among the 298 participants who developed septic shock within 12 hours of ED presentation (OR 1.13; $p=0.03$).

Discussion

We examined the relationship between timing of appropriate antibiotic administration and mortality among patients with septic shock due to *S. aureus* bacteremia in the Veterans Affairs Healthcare System. We found that each elapsed hour between time of ED presentation and antibiotic administration was associated with a 11% increase in the odds of 30-day mortality. This effect was most notable among patients who developed shock within 12 hours after ED presentation.

Our findings enhance previous research on timing of antibiotic administration for patients with septic shock because we specifically focused on patients with *S. aureus* bacteremia. Our study differs from most previous research as we have identified a population where 100% of the participants have confirmed bacteremia. This dramatically reduces/eliminates the possibility that patients were included in our analyses

who were presumed to have septic shock but in fact in retrospect were never truly infected. This potential misclassification may have diminished the findings of previous studies who reported an association between the timing of antibiotics and mortality and were not able to document bacteremia among all participants.

The high 30-day mortality among our study population (78%) underscores the importance of antibiotic administration timing when *S. aureus* is the culprit organism. The elevated mortality rate reflects the severe acuity of these patients who had a significant amount of concomitant baseline organ dysfunction requiring ICU admission for septic shock. In comparison, in-hospital mortality among septic shock patients with non-bacteremic or bacteremic shock (from a variety of bacterial species) is approximately 51% [29].

We recognize that antimicrobial culture results and sensitivity data are rarely available when a septic patient first presents to the ED. Therefore, our study findings might only be practically applied for septic shock patients who are suspected to have *S. aureus* bacteremia. Nevertheless, *S. aureus* is the most common cause of septic shock [23]. When septic shock is believed to be secondary to skin/soft tissue, osteoarticular, endocarditis, and intravenous line or medical device infections, ED physicians will likely empirically administer antibiotics for *S. aureus*; whereas physicians may be less likely to consider a *S. aureus* infection in patients with pulmonary, abdominal or genitourinary infections. In our study, only 39% of patients had a sepsis source that would likely have been identified during the ED history and physical examination as attributable to *S. aureus* (skin, endocarditis, and osteomyelitis/osteoarthritis), while the majority had a less obvious source of *S. aureus* septic shock (pulmonary or genitourinary). The importance of appropriate antibiotics is well recognized in sepsis and in cases of *S. aureus* bacteremia. Inappropriate antibiotic administration is associated with increased mortality [30]. Sepsis mortality among patients with MRSA bacteremia is greater than mortality for MSSA bacteremia [23-25]. Additionally, inadequate initial dosing of vancomycin for MRSA septic shock is associated with mortality [31]. Our observation of similar mortality rates for MRSA (80.3%) and MSSA (76.1%) is likely due to the severity of illness among our study population. Our stratified analysis suggests that time to antibiotic administration might be more critical for

patients with MRSA (OR=1.15) compared to patients with MSSA (OR=1.08), although these results did not reach statistical significance. Rapid diagnostic techniques in the ED for *S. aureus* may have an important future role in identifying patients with *S. aureus*, and in differentiating MRSA from MSSA [32]. Until then, the results of this study suggest that physicians should empirically and rapidly administer broad spectrum antibiotics that include MRSA coverage for any case of suspected septic shock.

Recent work using large healthcare system and state-wide databases has demonstrated an association between antibiotic delay and mortality among patients with sepsis [20, 21], with the most robust associations being observed for patients with septic shock. The Surviving Sepsis Campaign (SSC) and the Centers for Medicare and Medicaid Services (CMS) sepsis core measure both call for the prompt administration of antibiotics for all patients with sepsis and septic shock [2, 3]. A recent analysis of septic patients, the majority of whom had received antibiotics within the CMS three-hour window, suggests that even shorter delays in antibiotic administration may be harmful. In their study, administration of antibiotics more than 125 minutes following sepsis identification (shock or SIRS criteria) was associated with increased mortality [33]. However, efforts to administer antibiotics quickly, especially in patients with lower illness severity, must be balanced with potential secondary harms. These harms include renal injury, hepatitis, drug associated rashes, myelosuppression, the emergence of antibiotic resistance [34], and expenditure of scarce ED resources [35]. While using robust methods, even well done analyses of large databases may suffer from unmeasured confounders and confounding by indication. This has led to calls to administer antibiotics as soon as septic shock is identified but adopt a more pragmatic approach towards septic patients where identification of organ dysfunction attributable to sepsis requires more time [36]. Our finding, that each hour delay in antibiotic administration is associated with a 1.3% increase in mortality among *S. aureus* septic shock patients is concordant with the septic shock subgroup described by Liu et al. (1.8%) [20], and suggests that physicians should quickly administer antibiotics in cases of septic shock.

Our study has limitations. First, the observational study design cannot establish a causal relationship between the timing of antibiotic administration and mortality. Second, the VA population is predominately male, which may limit the external validity of these findings to female patients with *S. aureus* bacteremia and septic shock. While some data suggest that male patients develop bacteremia at a higher rate than female patients [37], data on gender differences in sepsis mortality are mixed [38-40]. Therefore, we suspect we would observe similar results if this analysis was performed in a predominately female cohort. Third, our observed 30-day mortality rate of 78.1% is high. As noted previously, we suspect the high mortality is due to the patients selected for the study (*S. aureus* bacteremia, ICU admissions directly from the ED, multiple baseline organ dysfunction, and septic shock). We observed a statistically significant decline in 30-day mortality from 85.7% in 2004 to 69.5% in 2015 (Supplementary Table 6) in the VA hospitals that follows a similar decreasing international trend during a similar time period [41]. Previous estimates of *S. aureus* bacteremia are less than our observed mortality rates, but in few instances are patients with *S. aureus* bacteremia and septic shock examined. A 2002 cross sectional observational study of 190 ICUs across Europe found mortality rates of 37 and 42% for MSSA and MRSA sepsis, respectively, however less than half of these patient had septic shock [23]. Only small case control studies have examined patients with *S. aureus* bacteremia with concurrent septic shock and report mortality rates as high 72%, which is consistent with the results of our study [31, 42]. Our use of ICD-9 diagnosis codes to identify patients with septic shock is subject to misclassification bias. It is plausible that patients with septic shock who died were more likely to receive a formal diagnosis code of septic shock compared to septic shock patients who survived. A strength of our study is that we combine ICD-9 diagnosis with additional clinical variables: positive blood cultures, independent confirmation of shock by chart review, and direct admission from the ER to ICU. Combining ICD-9 diagnosis codes with clinical variables has been shown to increase the sensitivity and positive predicted value of the sepsis diagnosis code [43, 44], and the VA coding patterns for serious bacterial infection tend to be highly accurate [45]. Fourth, 41% of our study population

developed shock more than 12 hours after triage. In a stratified analysis among this group time to antibiotic administration was not associated with mortality. This suggests that prompt administration of antibiotics may only be beneficial for septic patients who present in, or rapidly develop, shock. Fifth, while stratified analyses suggested that a delay in antibiotic administration was associated with a higher odds ratio of mortality among patients with MRSA and for those patients who develop shock before antibiotic administration, these results did not reach statistical significance. This is likely due to the relatively small sample size for these subgroups, which limited our ability to characterize mortality trends. Further research that focuses on sepsis mortality and antibiotic administration in these populations is needed.

Conclusion

In summary, among septic shock patients with *S. aureus* bacteremia admitted directly from the ED to the ICU, we found that each hour delay in appropriate antibiotic administration is associated with an 11% increase in the odds of 30-day mortality. Physicians should consider acting quickly to administer antibiotics with *S. aureus* coverage to any patient suspected of having septic shock. Future work should investigate the relationship between the timing of antibiotics and mortality with other pathogens such as gram negative bacteria.

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Figure Legends:

Figure #1 Participant enrollment diagram.

Figure #2 Kernel density plot showing time to antibiotic administration from emergency department triage.

Figure #3 Odds ratios of 30-day mortality and the associated 95% confidence interval for time to first appropriate antibiotic administration. Multivariate model adjusted for: BMI, APACHE III score, infective arthritis, SIRS criteria present at the time of blood culture, and MRSA/MSSA , and continuous time.

