The Golden Hour of Antibiotic Administration in Severe Sepsis: Avoid a False Start Striving for Gold*

Arthur R. H. van Zanten, MD, PhD
Department of Intensive Care
Gelderse Vallei Hospital
Ede, The Netherlands

Sepsis is defined as a systemic inflammatory response to infection, and the annual prevalence is estimated at 19 million cases worldwide. Over the last 30 years, reported mortality rates in severe sepsis, defined as sepsis plus organ dysfunction, have dropped from over 80% to 20–30% due to advances in training, better surveillance and monitoring, prompt initiation of therapy, and organ support (1).

Antibiotics are essential for effective treatment of infections in critically ill patients. Therapy is founded on principles of appropriate drug selection based on (suspected) susceptibility patterns of the causative pathogen. The goal of antimicrobial administration is to achieve drug concentrations sufficiently effective to exert maximum killing at the infection site and to prevent the emergence of antimicrobial resistance (2). Selection of empirical antibiotics should be based on the suspected site of infection, setting such as community-acquired infection or nosocomial infection, medical and culture history, and local microbial susceptibility results.

The latest guidelines for the management of severe sepsis and septic shock provided by the Surviving Sepsis Campaign consortium recommend to timely commence appropriate IV broad-spectrum antibiotics after forming a probable diagnosis and obtaining cultures (1B/1C grade recommendations to administer antibiotics within 1 hr after diagnosis of either sepsis or septic shock) (3).

In general, "appropriate" treatment is defined as treatment matching the in vitro susceptibility of the pathogen. By performing a systematic review and meta-analysis of available studies, Paul et al (4) have demonstrated that the pooled odds ratio of appropriate antibiotic treatment during the first 48 hours for all-cause mortality was 1.60 (95% CI, 1.37–1.86), corresponding to a number needed to treat of 10 (95% CI, 8–15).

In addition, Kumar et al (5) in a retrospective study among 2,154 patients who received effective antibiotic therapy have observed that the survival rate was 80% in patients given antibiotics within the first hour of persistent or recurrent hypotension. However, for each hour of delay during the subsequent 6 hours, the chances of survival decreased by 7.6%. In multivariate analysis, the strongest predictor of outcome was time to effective antibiotic administration. Only half the patients received effective antibiotics within 6 hours of hypotension onset, and 30% had delays of more than 12 hours.

In this issue of *Critical Care Medicine*, Ferrer et al (6) report a retrospective analysis of a large dataset of 28,150 patients with severe sepsis and septic shock collected prospectively for the Surviving Sepsis Campaign in Europe, the United States, and South America. They showed that delay in first antibiotic administration was associated with increased in-hospital mortality. There was a linear increase in mortality risk for each hour delay in antibiotic administration. Reducing time to first antibiotic from more than 6 hours to less than 1 hour may induce a mortality reduction of 9.5% (33.1% to 24.6%). Strengths of this study are timing effects that were also observed in patients with severe sepsis and without septic shock, extending external validity to severe sepsis. In addition, beneficial effects of early antibiotic administration reported here are based on time from sepsis diagnosis and not related to onset of hypotension. Limitations of the study are lack of information on antibiotic appropriateness and focus control.

These combined observations underline the importance of timely and appropriate initiation of antibiotics in septic patients. Antibiotic therapy shows to be lifesaving within the "golden hour" after diagnosing severe sepsis or septic shock. However, there is possibly no other instance in medicine where therapy provided to a patient affects other patients and the society by potentially reducing the armamentarium of effective antibiotics in future patients. Therefore, it is of paramount importance to administer antibiotics to only patients who need antibiotics.

We have to be aware of a false start in patients with severe sepsis. This may be caused by underrecognition of sepsis patients, causing undertreatment and consequently late initiation of antibiotics. Furthermore, inappropriate antibiotic selection may result in failing empirical treatment. Providing practical guidelines to emergency department physicians to select patients at risk for highly resistant bacteria in microbiologically proven severe sepsis and septic shock has been shown

*See also p. 1749.

Key Words: antibiotics; appropriateness; mortality; sepsis; timing

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to reduce risk of initial inappropriate therapy (7). Finally, inappropriate antibiotic dosing, an often neglected but probably important factor, may cause therapy failure (8).

By contrast, a false start may also be relevant when antibiotics are given to patients without sepsis. Tachycardia or an elevated WBC count may reflect an inflammatory response due to bacterial infection; however, this can also be seen in many nonbacterial infections and more important many noninfectious conditions (9). Trying hard to avoid late initiation of antibiotics may lead to antibiotic administration to patients without infections. Risks for individual patients from side effects and allergies related to unnecessary antibiotic exposure are limited. However, unnecessary antibiotic use may increase the number of antibiotic exposure days, increasing the risk of resistance emergence in individuals as well as on a population scale. More importantly, when inflammatory signals are not due to an infection, the process to proper diagnosis is hampered, delaying initiation of the optimal therapy for noninfectious conditions, potentially reducing chances for a beneficial outcome.

When time to antibiotics in community-acquired pneumonia (not pulmonary sepsis), as is common in some countries, is used as a quality indicator, use of such indicators and the desire to meet required targets may have unintended consequences (10). At least five studies have shown that overuse of antibiotics in the emergency department may be the consequence (11). Therefore, clinicians should ensure that the infection diagnosis is robust to prevent unnecessary treatment with broad-spectrum antibiotics. All antibiotic treatments should be subject to review after 2–3 days and when culture results become available. After initial broad-spectrum antibiotic therapy, de-escalation based on culture results has been shown to reduce mortality in septic patients (12).

The "golden hour" for antibiotics in sepsis and septic shock has been clearly demonstrated; however, when striving for gold, we have to avoid making a false start concerning antibiotic misuse. Critical care antibiotic stewardship is essential to preserve effective antibiotic therapy for future patients.

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Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program*

Ricard Ferrer, MD, PhD[1]; Ignacio Martin-Loeches, MD, PhD[2]; Gary Phillips, MAS[3]; Tiffany M. Osborn, MD, MPH[4]; Sean Townsend, MD[5]; R. Phillip Dellinger, MD, FCCP, FCCM[6]; Antonio Artigas, MD, PhD[2]; Christa Schorr, RN, MSN[6]; Mitchell M. Levy, MD, FCCP, FCCM[7]

*See also p. 1931.

[1]Department of Intensive Care, Mútua Terrassa University Hospital, CIBER Enfermedades Respiratorias, Barcelona, Spain.

[2]Critical Care Center, Sabadell Hospital, CIBER Enfermedades Respiratorias, Corporacion Sanitaria Universitaria Parc Tauli, Autonomous University of Barcelona, Sabadell, Spain.

[3]The Ohio State University Center for Biostatistics, Columbus, OH.

[4]Department of Surgery and Emergency Medicine, Division of Acute Care Surgery, Surgical/Trauma Critical Care, Barnes Jewish Hospital, Washington University, St. Louis, MO.

[5]California Pacific Medical Center, San Francisco, CA.

[6]Brown University/Rhode Island Hospital, Providence, RI.

[7]Cooper University Hospital, Camden, NJ.

Dr. Levy had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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For information regarding this article, E-mail: mitchell_levy@brown.edu

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Objectives: Compelling evidence has shown that aggressive resuscitation bundles, adequate source control, appropriate antibiotic therapy, and organ support are cornerstone for the success in the treatment of patients with sepsis. Delay in the initiation of appropriate antibiotic therapy has been recognized as a risk factor for mortality. To perform a retrospective analysis on the Surviving Sepsis Campaign database to evaluate the relationship between timing of antibiotic administration and mortality.

Design: Retrospective analysis of a large dataset collected prospectively for the Surviving Sepsis Campaign.

Setting: One hundred sixty-five ICUs in Europe, the United States, and South America.

Patients: A total of 28,150 patients with severe sepsis and septic shock, from January 2005 through February 2010, were evaluated.

Interventions: Antibiotic administration and hospital mortality.

Measurements and Main Results: A total of 17,990 patients received antibiotics after sepsis identification and were included in the analysis. In-hospital mortality was 29.7% for the cohort as a whole. There was a statically significant increase in the probability of death associated with the number of hours of delay for first antibiotic administration. Hospital mortality adjusted for severity (sepsis severity score), ICU admission source (emergency department, ward, vs ICU), and geographic region increased steadily after 1 hour of time to antibiotic administration. Results were similar in patients with severe sepsis and septic shock, regardless of the number of organ failure.

Conclusions: The results of the analysis of this large population of patients with severe sepsis and septic shock demonstrate that delay in first antibiotic administration was associated with increased in-hospital mortality. In addition, there was a linear

increase in the risk of mortality for each hour delay in antibiotic administration. These results underscore the importance of early identification and treatment of septic patients in the hospital setting. (*Crit Care Med* 2014; 42:1749–1755)

Key Words: antibiotics; knowledge translation; performance improvement; performance metrics; sepsis; septic shock; severe sepsis

Sepsis is a worldwide syndrome that affects over 700,000 patients per year in the United States (1), with a high fatality rate, significant morbidity, and socioeconomic cost (2). Compelling evidence has shown that aggressive resuscitation bundles, adequate source control, appropriate antibiotic therapy, and organ support are cornerstones for the success in the treatment of patients with sepsis (3). Delay in the initiation of appropriate antibiotic therapy has been recognized as a risk factor for mortality. This assumption is not a new paradigm since Ehrlich's concept of "hit hard and fast" was first described in the early 1900 (4). More recently, Kumar et al (5) conducted in the United States and Canada a retrospective cohort study in 2,731 septic shock patients and found that effective antimicrobial administration within the first hour of documented hypotension was associated with 79.9% survival to hospital discharge. Treatment protocols targeting the rapid administration of appropriate antibiotics are now recognized as a key measure in the initial care of patients presenting with severe sepsis and septic shock (6).

Based on this evidence, the Surviving Sepsis Campaign (SSC) Guidelines recommended that after the recognition of severe sepsis or septic shock, IV broad-spectrum antibiotics should be administered as early as possible and always within 1 hour (for patients identified on the general medical wards) or 3 hours (for patients identified in the emergency department [ED]) (7). Nevertheless, these results need to be confirmed and the optimal timing of antibiotic administration remains uncertain in patients with sepsis. Therefore, the aim of this study was to analyze the association between timing of antibiotic administration and mortality to evaluate whether an optimal time window for empiric antibiotic administration could be found in these patients with severe sepsis and septic shock. Because of the global nature of the SSC, we also aimed to describe cultural differences in empiric antibiotic treatment for severe sepsis and septic shock.

MATERIAL AND METHODS

Sites and Patient Selection

The process of participation in the SSC is described in detail elsewhere (8). Eligible subjects were those admitted to an ICU having a suspected site of infection, two or more systemic inflammatory response syndrome criteria, and one or more organ dysfunction criteria (9). Clinical and demographic characteristics and time of presentation with severe sepsis or septic shock criteria were collected for analysis of time-based measures. Time of presentation was determined through chart review and defined in instructions to site data collectors on the Campaign website and educational materials. For patients enrolled from the ED, the time of presentation was defined as the time of triage. For patients admitted to the ICU from the medical and surgical wards and for patients in the ICU at the time of diagnosis, the time of presentation was determined by chart review for the diagnosis of severe sepsis. The patient was considered to have a nosocomial infection if severe sepsis or septic shock was discovered in the ICU more than 72 hours after admission or if severe sepsis or septic shock was discovered in the ward and the patient had been in the ward more than 72 hours prior to sepsis identification. Otherwise, the patient was considered to have a community infection.

Data Collection

Data were entered into the SSC database locally at individual hospitals into preestablished, unmodifiable fields documenting performance data and the time of specific actions and findings. Data stripped of private health information were submitted every 30 days to the secure master SSC server at the Society of Critical Care Medicine (Mount Prospect, IL) via file transfer protocol or as comma-delimited text files attached to e-mail submitted to the Campaign's server.

Institutional Review Board Approval

The global SSC improvement initiative was approved by the Cooper University Hospital Institutional Review Board (Camden, NJ) as meeting criteria for exempt status.

Analysis Set Construction

The analysis set was constructed from the subjects entered into the SSC database from January 2005 through February 2010. Inclusion was limited to sites with at least 20 subjects and at least 3 months of subject enrollment.

Antibiotics and Time to Administration

Once severe sepsis or septic shock was identified using the screening criteria established in the SSC initiative, patients were eligible for antibiotics. All dates and times in the SSC database are based on the time of presentation. Time to first antibiotic administration is reported as the difference between time of presentation (as recorded in the database and described above) and first antibiotic administration (also entered into the database through chart review by institutional data collector). For each antibiotic given to a particular patient, the name of the antibiotic and time of administration were recorded in the database. Patients could receive none, one, or multiple antibiotics. Throughout the rest of this manuscript, antibiotic administration implies the patient's first antibiotic. Subjects who did not receive any antibiotics in the first 6 hours, those with missing time of antibiotic administration, or subjects who were receiving antibiotics prior to presentation of severe sepsis were excluded from the data analysis.

Statistical Analysis

Since the study's goal was not to predict hospital mortality but rather to identify the role of timing of antibiotic

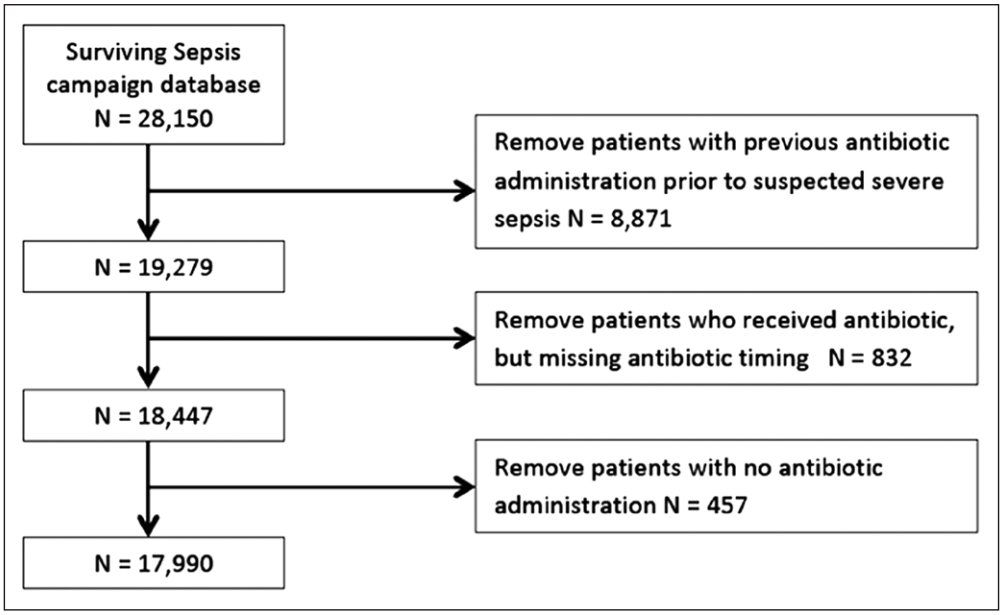

Figure 1. Patient enrollment diagram.

administration on survival, we used a risk factor modeling approach to determine which covariates to add to the model—a generalized estimating equation (GEE) population averaged logistic regression. Logistic regression was used to analyze hospital mortality since the database has complete information on the time to antibiotic administration on all subjects and their mortality status (no censoring). Time to only the patient's first antibiotics was entered into the model as a categorical variable, and only covariates that acted as either a confounder or an effect modifier were included. A confounder was identified when its addition to the model changed the odds ratio associated with the time to antibiotic administration by more than 10% in either direction, without considering statistical significance. A covariate that had a statistically significant interaction ($p < 0.05$) with antibiotic administration was considered to be an effect modifier. **Table S1** (Supplemental Digital Content 1, http://links.lww.com/CCM/A900) in the online appendix lists the 51 covariates that were considered possible confounders and effect modifiers. GEE population averaged logistic regression was used since patients are nested within a particular ICU. This method takes into account the variability within and between ICUs and uses this inherent correlation when estimating the SEs that are used to test model coefficients. The hierarchical nature of the SSC data lends itself to this type of analysis. All analyses were run using Stata 12.1 (Stata Corporation, College Station, TX).

RESULTS

A total of 28,150 patients with severe sepsis and septic shock from 165 ICUs were evaluated. Four hundred fifty-seven patients (457) received no antibiotics, 832 received antibiotics but were missing the timing of the antibiotics, and 8,871 patients received antibiotics prior to suspected sepsis. These patients were removed from the analysis set; thus, a total of 17,990 patients received antibiotics and were included in the analysis of time-to-antibiotic administration and mortality (**Fig. 1**).

Table 1 summarizes patient characteristics by antibiotic timing in 1-hour time periods up to 6 hours. All patients that received antibiotics after 6 hours were grouped together in this table since they only represented 12% of the observations. Hospital mortality is 32.0% in the first hour of antibiotic administration, drops to 28.1% in the second hours, and then steadily increases after that. It peaks at 39.6% in those receiving antibiotics after 6 hours. The median sepsis severity score (SSS) is the highest in the first hour compared with all other time points. The SSS was developed and validated on the SSC database and includes the elements available in the database such as location where sepsis was suspected (ED, ward, or ICU), geographic location (Europe, United States, South America), infection source (pneumonia, urinary tract infection, abdominal, etc.), various organ failures, hypotension (resolved and unresolved), mechanical ventilation, and other clinical characteristics (T. Osborn et al, unpublished observation, 2013). In the first hour, patients tend to have a higher proportion of severe sepsis/septic shock identified in the ICU (10.6%), compared with the same patients in the other time periods, higher mortality (46.6%) when severe sepsis/septic shock is identified in the ICU, higher proportion of pulmonary organ failure (30.8%), higher proportion of nosocomial infection (21.9%), higher septic shock (69.6%), longer hospital and ICU length of stays (13 and 5.1 d, respectively), and the lowest proportion of a single organ failure (40.1%). After 1 hour, hospital mortality steadily increases with a delay in antibiotic timing. The prevalence of nosocomial infection decreases during the first 3 hours of antibiotics administration and then increases when administered after 4 hours. The proportion of patients with 1 baseline organ dysfunction is highest in the first hour and then decreases with a delay in antibiotics.

Figure 2 and the odds ratios in **Table 2** are based on the same adjusted GEE population averaged logistic regression model. The model is adjusted for SSS, ICU admission source (ED, ward, vs ICU), and geographic region (Europe, United States, and South America). The relationship between hospital mortality and time to first antibiotic administration was fairly robust once we controlled for these three covariates, thus no additional covariates (for a list, see **Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A900) either confounded nor were effect modifiers of the relationship between hospital mortality and time to first antibiotic. The

TABLE 1. Patient Characteristics by Timing in Hours to the First Antibiotic

Patient Characteristic, *n* (%)	Antibiotic Timing (Hr)							
	0.0–1.0	1.0–2.0	2.0–3.0	3.0–4.0	4.0–5.0	5.0–6.0	> 6.0	*p*[a]
n	4,728	4,595	3,020	1,734	1,037	640	2,239	
Hospital mortality	1,512 (32.0)	1,292 (28.1)	863 (28.6)	517 (29.8)	337 (32.5)	234 (36.6)	885 (39.6)	< 0.001
Severity sepsis score, median (IQR)	58 (42–73)	50 (36–66)	49 (35–64)	49 (35–66)	51 (37–68)	53 (38–69)	57 (40–71)	< 0.001
Nosocomial infection	812 (17.2)	357 (7.8)	229 (7.6)	173 (10.0)	128 (12.3)	89 (13.9)	403 (18.0)	< 0.001
Septic shock	3,289 (69.6)	2,880 (62.7)	1,847 (61.2)	1,047 (60.4)	684 (66.0)	441 (68.9)	1,370 (61.3)	< 0.001
Hospital LOS, median days (IQR)	13 (6.4–25)	10 (5.6–19)	10.0 (5.6–19)	11 (5.9–20)	12 (5.9–23)	12 (6.3–22)	14 (7.3–29)	< 0.001
ICU LOS, median days (IQR)	5.1 (2.4–11)	4.1 (2.1–8.9)	4.2 (2.1–8.8)	4.3 (2.0–9.5)	4.9 (2.4–11)	4.6 (2.1–10)	6.7 (2.8–15)	< 0.001
LOS prior to ICU, median days (IQR)	0.1 (0.0–0.8)	0.1 (0.0–0.3)	0.1 (0.0–0.3)	0.1 (0.0–0.4)	0.2 (0.0–0.5)	0.2 (0.0–0.7)	0.2 (0.0–1.4)	< 0.001
Location where sepsis identified								
ED	3,028 (64.0)	3,716 (80.9)	2,424 (80.3)	1,322 (76.2)	727 (70.1)	417 (65.2)	1,294 (57.9)	< 0.001
ED mortality	797 (26.3)	935 (25.2)	629 (26.0)	352 (26.6)	209 (28.8)	132 (31.7)	404 (31.2)	< 0.001
Ward	1,198 (25.3)	680 (14.8)	469 (15.5)	326 (18.8)	244 (23.5)	177 (27.7)	689 (30.8)	< 0.001
Ward mortality	481 (40.2)	274 (40.3)	195 (41.6)	131 (40.8)	94 (38.5)	83 (46.9)	332 (48.2)	< 0.001
ICU	502 (10.6)	199 (4.3)	127 (4.2)	86 (5.0)	66 (6.4)	46 (7.2)	253 (11.3)	< 0.001
ICU mortality	234 (46.6)	83 (41.7)	39 (30.7)	34 (39.5)	34 (51.5)	19 (41.3)	149 (58.9)	< 0.001
Site of infection								
Pneumonia	2,388 (50.5)	2,308 (50.2)	1,398 (46.3)	729 (42.0)	430 (41.5)	252 (39.4)	982 (43.9)	< 0.001
Urinary tract infection	1,076 (22.8)	1,332 (29.0)	950 (31.5)	518 (29.9)	273 (26.3)	164 (25.6)	444 (19.9)	< 0.001
Abdominal	914 (19.3)	738 (16.1)	545 (18.1)	387 (22.3)	225 (21.7)	146 (22.8)	550 (24.6)	< 0.001
Meningitis	101 (2.1)	57 (1.2)	39 (1.3)	23 (1.3)	16 (1.5)	5 (0.8)	36 (1.6)	0.002
Skin	294 (6.2)	294 (6.4)	212 (7.0)	119 (6.9)	66 (6.4)	35 (5.5)	113 (5.1)	0.040
Bone	46 (1.0)	57 (1.2)	48 (1.6)	28 (1.6)	7 (0.7)	9 (1.4)	37 (1.7)	0.075
Wound	206 (4.4)	242 (5.3)	124 (4.1)	78 (4.5)	50 (4.8)	20 (3.1)	95 (4.3)	0.080
Catheter	169 (3.6)	157 (3.4)	106 (3.5)	75 (4.3)	37 (3.6)	29 (4.5)	88 (3.9)	0.596
Endocarditis	46 (1.0)	42 (0.9)	33 (1.1)	15 (0.9)	14 (1.4)	11 (1.7)	26 (1.2)	0.548
Device	54 (1.1)	51 (1.1)	43 (1.4)	24 (1.4)	16 (1.5)	9 (1.4)	22 (1.0)	0.704
Other infection	260 (9.7)	528 (11.5)	399 (13.2)	216 (12.5)	145 (14.0)	95 (14.8)	337 (15.7)	< 0.001
Baseline acute organ dysfunction								
Cardiovascular	4,221 (89.3)	4,123 (89.7)	2,689 (89.0)	1,510 (87.1)	888 (85.6)	541 (84.5)	1,800 (80.5)	< 0.001
Pulmonary	1,456 (30.8)	1,120 (24.4)	610 (20.2)	383 (22.1)	240 (23.1)	145 (22.7)	681 (30.5)	< 0.001
Renal	1,824 (38.6)	1,717 (37.4)	1,139 (37.7)	644 (37.1)	415 (40.0)	238 (37.2)	890 (39.8)	0.002
Hepatic	393 (8.3)	415 (9.0)	285 (9.4)	170 (9.8)	107 (10.3)	74 (11.6)	280 (12.5)	< 0.001
Hematologic	1,171 (24.8)	904 (19.7)	706 (23.4)	405 (23.4)	251 (24.2)	175 (27.3)	595 (26.6)	< 0.001

(*Continued*)

TABLE 1. (*Continued*). Patient Characteristics by Timing in Hours to the First Antibiotic

Patient Characteristic, *n* (%)	Antibiotic Timing (Hr)							*p*[a]
	0.0–1.0	1.0–2.0	2.0–3.0	3.0–4.0	4.0–5.0	5.0–6.0	> 6.0	
Number of acute organ dysfunction								
1	1,898 (40.1)	2,078 (45.2)	1,363 (45.1)	777 (44.8)	458 (44.2)	275 (43.0)	942 (42.1)	
2	1,653 (35.0)	1,587 (34.5)	1,060 (35.1)	608 (35.1)	358 (34.5)	227 (35.5)	732 (32.7)	
3	847 (17.9)	681 (14.8)	436 (14.4)	268 (15.5)	154 (14.9)	99 (15.5)	387 (17.3)	< 0.001
4	265 (5.6)	207 (4.5)	131 (4.3)	68 (3.9)	51 (4.9)	31 (4.8)	134 (6.0)	
5	65 (1.4)	42 (0.9)	30 (1.0)	13 (0.8)	16 (1.5)	8 (1.3)	41 (1.8)	
Cardiovascular								
No cardiovascular dysfunction	376 (7.9)	379 (8.3)	265 (8.8)	168 (9.7)	115 (11.1)	57 (8.9)	349 (15.6)	
Cardiovascular dysfunctionno hypertension	803 (17.0)	1,004 (21.8)	659 (21.8)	402 (23.2)	174 (16.8)	116 (18.1)	403 (18.0)	
Total shock	3,549 (75.1)	3,212 (69.9)	2,096 (69.4)	1,164 (67.2)	748 (72.1)	467 (73.0)	1,484 (66.4)	< 0.001
Lactate > 4	260 (5.5)	332 (7.2)	249 (8.3)	117 (6.8)	64 (6.2)	26 (4.1)	114 (5.1)	
Vasopressors only	2,273 (48.1)	1,938 (42.2)	1,309 (43.3)	769 (44.4)	522 (50.3)	346 (54.1)	1,126 (50.4)	
Lactate > 4 and vasopressors	1,016 (21.5)	942 (20.5)	538 (17.8)	278 (16.0)	162 (15.6)	95 (14.8)	244 (10.9)	

IQR = interquartile range, LOS = length of stay, ED = emergency department.
[a]*p* value based on Pearson chi-square test for categorical variables and Wilcox rank-sum test for continuous variables.

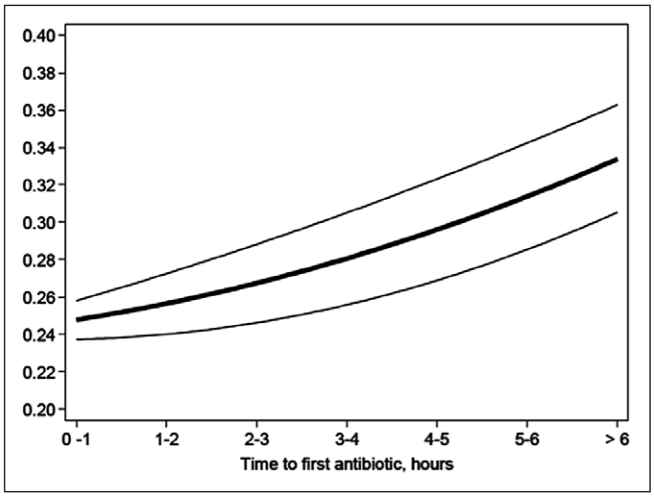

Figure 2. Predicted hospital mortality and the associated 95% CIs for time to first antibiotic administration. The results are adjusted by the sepsis severity score (SSS), ICU admission source (emergency department [ED], ward, vs ICU), and geographic region (Europe, United States, and South America). Probability of hospital mortality is based on the subject having the following specific characteristics: the patient is from the United States, admission source is the ED, and the SSS is 52 (median of all observations).

regression model uses the same seven time periods as shown in Table 1. Figure 2 illustrates the trend in hospital mortality over timing to first antibiotic, relative to suspicion of sepsis. Table 2 shows that the adjusted hospital mortality odds ratios steadily increase from 1.00 to 1.52 as time to antibiotic administration increases from 0 to greater than 6 hours where 0–1 hour is the referent group. The probability of mortality increases from 24.6% to 33.1% and is based on a subject having the following characteristics: from the United States, admission source is the ED, and the SSS is 52 (median of all observations).

DISCUSSION

The results of this study confirm, in the largest population of patients with severe sepsis and septic shock reported to date, that delay in antibiotic administration was associated with increased in-hospital mortality. In addition, we confirm the increasing risk associated with delay—there was a linear increase in the risk of mortality for each hour delay in antibiotic administration from the first through the sixth hour after patient identification This relationship between delay in antibiotic administration and mortality has been demonstrated before by Kumar et al (5). However, the population in that study was patients with septic shock, and the delay was from the onset of hypotension. Our study findings are distinct and unique in the population studied and the location of these patients in the hospital: similar results were found in patients with either severe sepsis or septic shock, and consistent results were also seen when patients were stratified by severity (number of organ failure) and whether sepsis was identified in the ED, on the wards, or in the ICU. This study demonstrates, for

TABLE 2. Adjusted Hospital Mortality Odds Ratio and Probability of Mortality for Time to Antibiotics Based on a Generalized Estimating Equation Population Averaged Logistic Regression Model

Time to Antibiotics (Hr)	OR[a]	95% CI	*p*	Probability of Mortality (%)[b]	95% CI
0–1[c]	1.00			24.6	23.2–26.0
1–2	1.07	0.97–1.18	0.165	25.9	24.5–27.2
2–3	1.14	1.02–1.26	0.021	27.0	25.3–28.7
3–4	1.19	1.04–1.35	0.009	27.9	25.6–30.1
4–5	1.24	1.06–1.45	0.006	28.8	25.9–31.7
5–6	1.47	1.22–1.76	< 0.001	32.3	28.5–36.2
> 6	1.52	1.36–1.70	< 0.001	33.1	30.9–35.3

OR = odds ratio.

[a]Hospital mortality odds ratio referent group is 0–1 hr for the time to antibiotics and is adjusted by the sepsis severity score (SSS), ICU admission source (ED, ward, vs ICU), and geographic region (Europe, United States, and South America).

[b]Probability of hospital mortality is estimated using the generalized estimating equation population averaged logistic regression model and is based on the subject having the following characteristics: from the United States, admission source is the ED, and the SSS is 52 (median of all observations).

[c]Antibiotics administered in the first hour are the referent group and thus the odds ratio by definition is 1.00 while the 95% CI and the p value are not generated by the regression model.

the first time, that delay in antibiotic administration has a significant negative impact on survival across all areas in the hospital and across levels of illness severity (organ dysfunction).

The most important finding from our study is the survival benefit associated with prompt antibiotic administration in severe sepsis and septic shock. The potential influence of delayed antibiotic therapy was first evaluated in patients with community-acquired pneumonia. In the early-1990, McGarvey and Harper (10) demonstrated that care processes that included antibiotic delivery within 4 hours were associated with lower pneumonia mortality at two community hospitals. More recently, Houck et al (11) described that among 13,771 patients who had not received outpatient antibiotic agents, antibiotic administration within 4 hours of arrival at the hospital was associated with reduced in-hospital mortality (6.8% vs 7.4%; adjusted odds ratio [AOR], 0.85; 95% CI, 0.74–0.98) and mortality within 30 days of admission (11.6% vs 12.7%; AOR, 0.85; 95% CI, 0.76–0.95). Kahn et al (12) observed a 4% point reduction in 30-day mortality among Medicare patients who received antibiotics within 4 hours of admission and appropriate oxygen therapy. Interestingly, this work highlights not only the early administration of antibiotics but also correlates the process of care with better outcomes. In a study of 261 patients in the ED, Gaieski et al (13) confirmed the association with timing of antibiotic therapy and mortality in patients with severe sepsis or septic shock. In our previous prospective observational study in 77 ICUs (14) based on propensity scores and adjusting for other treatments, we reported that among 2,796 severe sepsis/septic shock patients, empiric antibiotic treatment reduced mortality (treatment within 1 hr vs no treatment within first 6 hr of diagnosis; odds ratio, 0.67; 95% CI, 0.50–0.90; $p = 0.008$). Kumar et al (5) demonstrated that every additional hour without antibiotics increased the risk for death in septic shock patients by 7.6% during the first 6 hours. It is important to point out that this was a retrospective study over 15 years, and recruitment rates were relatively low, with 2,154 patients included from 10 sites (14 ICUs). Only 12% of patients had received antibiotics within the first hour. In addition, Kumar et al (5) focused on septic shock patients with appropriate antibiotic treatment. Our data demonstrate that the association between timing of antibiotic administration and mortality is not only true for patients with septic shock but also for patients with severe sepsis.

The relationship of prompt antibiotic and better outcomes might represent a surrogate marker for the quality of care in a broader sense. Other important sepsis treatments have shown time-dependency, like quantitative resuscitation (15) or source control (16). In fact, the meta-analysis of Barochia et al (3) showed that the implementation of SSC bundles was followed by an improvement in most of the sepsis process-of-care variables, including time-to-antibiotic treatment, followed by a mortality reduction.

Recent studies report low compliance with prompt administration of antimicrobial therapy. In these reports, although the SSC proposals were implemented, the mean delay to first infusion of antibiotics remained in excess of 3 hours (17), and as many as 68% of patients did not receive their first dose within this period (18). In addition, Kumar et al (5) reported that delays in administration of antibiotics are common: 79% of patients did not receive antibiotics until the onset of hypotension, and of those patients, only 14.5% received them within the first hour of hypotension. Only 32.5% received antibiotics by 3 hours and only 51.4% by 6 hours. It is important to note here that there is controversy about performance metrics for antibiotic timing in patients with pneumonia. In a retrospective review of patients with community-acquired pneumonia, Welker et al (19) demonstrated that while performance metrics decreased time to first antibiotic dose from 8 to 4 hours, there was also an associated reduction in the accuracy of diagnosis of pneumonia by ED physicians.

Our study has several limitations. As with any retrospective study, there is potential for residual confounding. Second, in our report, the main goal of the study was to evaluate only timing of initial antibiotic administration and not appropriateness since this variable is commonly based on culture data available only after 24–96 hours. Therefore, we could not assess the appropriateness of antibiotic therapy in this patient population. Inappropriate or inadequate antibiotic choices may confound our results. Current SSC guidelines recommend administration of broad-spectrum antibiotics, and our results demonstrate adherence to this recommendation, which might reduce, but not eliminate the likelihood of inadequate coverage. Additionally, this was a retrospective review that did not allow for analysis of the reasons for delay or the cause of the delay in antibiotic administration. We are unable, in the SSC database, to ascertain whether the delay in antibiotic administration was because of order writing, pharmacy delay, or other system factors.

In conclusion, this study demonstrates a significant association between delay in antibiotic administration over the first 6 hours after identification of patients with severe sepsis and septic shock and increasing mortality. These results underscore the importance of early identification and treatment of septic patients in the hospital setting. As mentioned often in the literature, sepsis is a time-dependent condition (like acute myocardial infarction or stroke) and should be recognized as an urgent situation that requires immediate response.

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