Appropriate Antibiotic Treatment in Severe Sepsis and Septic Shock: Timing Is Everything*

Marya D. Zilberberg, MD, MPH
Department of Health Services Research
EviMed Research Group, LLC
Goshen, MA; and
School of Public Health and Health Sciences
University of Massachusetts
Amherst, MA

Andrew F. Shorr, MD, MPH
Division of Pulmonary and Critical Care Medicine
Washington Hospital Center
Washington, DC

Timely administration of empiric antibiotics that cover the potential pathogen(s) in patients with severe infections remains the mainstay of successful treatment. Over a decade of research indicates that when such treatment is not timely, the patient's outcomes, including hospital mortality and length of stay (LOS), worsen significantly (1–9). In the setting of sepsis specifically, the Surviving Sepsis Campaign guideline recommends starting broad-spectrum coverage within the first hour of recognition of severe sepsis or septic shock (10). Despite this aggressive evidence-driven threshold of 1 hour, the sepsis bundle liberalizes this timeframe to 3 hours. A review of actual prescribing practices in this area suggests that fully one third of patients requiring aggressive initial therapy are left without appropriate coverage beyond even this 3-hour limit (11). This is a missed opportunity, given the well-characterized relationship indicating that for every hour's delay in administration of appropriate antimicrobials, there is a substantial penalty in patient mortality (12, 13). The relationship between antibiotic treatment delay and hospital resource use, however, has been less reliably characterized. In the current issue of *Critical Care Medicine*, Dr. Zhang et al (14) attempt to do just that.

In this single-center retrospective cohort study, the investigators hypothesized that time to appropriate antimicrobial treatment in the setting of culture-positive severe sepsis and/or septic shock would prolong both ICU and hospital LOS. Despite the shortcomings of this retrospective single-center project, such as limited generalizability, the authors used appropriate enrollment and analytic techniques to address bias, misclassification, and confounding, all issues that can plague observational, and particularly retrospective, studies. In the end, the authors reported a small increase in LOS of about 0.1 days per each 1-hour delay in the administration of appropriate therapy. In other words, waiting 6 hours to institute appropriate antibiotic treatment following identification of severe sepsis or septic shock increased LOS on average by more than half of a day. Notably, this estimate remained durable across several sensitivity analyses.

It is true that this does not appear to be a particularly large attributable increase in the LOS for each individual patient. However, given that 30% of the patients in the study by Zhang et al (14) received appropriate therapy 18 hours or longer after the recognition of their sepsis, in aggregate this small individual hourly delay can quickly add up to a gargantuan total. In this cohort alone, one would estimate that the additional days in the hospital associated with a delay in therapy totaled over 600 days. Applying this estimate in turn to the national burden of sepsis, estimated at 1 million annually in the United States, with one third of cases subject to an over 3-hour delay in therapy, would yield well over 99,000 extra days in the ICU and the hospital each year. When looked at in aggregate, the seemingly small individual impact of a delay in treatment is astounding.

What are the barriers to eliminating or at least contracting this delay in treatment? Because the pathway to inappropriate selection of empiric coverage is at least partly through antimicrobial resistance of organisms, a clinician who is unaware of current local patterns of resistance lacks a crucial tool for stratifying his/her patient's risk of harboring a resistant organism (15). Complicating the situation further is the fact that clinicians encounter both rare examples of resistance among common organisms, such as carbapenem-resistant Enterobacteriaceae, and relatively uncommon organisms with very high rates of resistant, such as *Acinetobacter* spp., where carbapenem resistance is seen in over 60% of all isolates. Because both cases represent a rare event, a clinician is less likely to cover these organisms empirically. The fact that Zhang et al (14) identified *Candida albicans* infection, a relatively infrequent cause of sepsis, to have the longest delay in treatment is consistent with this observation.

Despite these significant barriers to reducing the harm due to delays in appropriate antibiotic coverage, there are potential strategies that can be applied. Sepsis bundles represent one way to assure that no important and timely therapies are forgotten. Knowing local organisms and their resistance patterns can go a long way to tailoring empiric sepsis therapies. Beyond that, several instruments have been developed to aid in clinical identification of patients at high risk for resistant pathogens (16, 17). Although none is perfect, each may be of help in

*See also p. 2133.

Key Words: empiric therapy; length of stay; outcomes; sepsis

Dr. Zilberberg's institution received financial support from Cubist, Tetraphase, and Theravance. Dr. Shorr has served as a consultant to, speaker for, or received research support from: Actavis, Astellas, AstraZeneca, Bayser, Cubist, Medicines company, Merck, Nabriva, Pfizer, Roche, Tetraphase, and Theravance.

DOI: 10.1097/CCM.0000000000001219

reducing the burden of treatment delay. Although molecular diagnostics have held promise in this area of prompt pathogen identification, several hurdles remain to their adoption, one of which is their considerable costs. However, given that a delay in treatment may also carry considerable costs, additional studies need to examine the balance between these two cost centers. Finally, in some cases, it may be sensible to start coverage with the broadest possible agents with a rigid protocol for de-escalation upon receiving culture results. Although such a radical strategy raises questions regarding accelerating rates of antimicrobial resistance, there is little evidence that a brief exposure to a broad-spectrum antibiotic regimen would result in any rise in the risk for antimicrobial resistance. Regardless of which approach or combination of approaches are adopted, the study by Zhang et al (14) establishes a potential benchmark for measuring the cost-effectiveness of such approaches.

REFERENCES

1. Micek ST, Kollef KE, Reichley RM, et al: Health care-associated pneumonia and community-acquired pneumonia: A single-center experience. *Antimicrob Agents Chemother* 2007; 51:3568–3573
2. Iregui M, Ward S, Sherman G, et al: Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. *Chest* 2002; 122:262–268
3. Alvarez-Lerma F: Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-Acquired Pneumonia Study Group. *Intensive Care Med* 1996; 22:387–394
4. Zilberberg MD, Shorr AF, Micek ST, et al: Antimicrobial therapy escalation and hospital mortality among patients with health-care-associated pneumonia: A single-center experience. *Chest* 2008; 134:963–968
5. Shorr AF, Micek ST, Welch EC, et al: Inappropriate antibiotic therapy in Gram-negative sepsis increases hospital length of stay. *Crit Care Med* 2011; 39:46–51
6. Kollef MH, Sherman G, Ward S, et al: Inadequate antimicrobial treatment of infections: A risk factor for hospital mortality among critically ill patients. *Chest* 1999; 115:462–474
7. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, et al: Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. *Crit Care Med* 2003; 31:2742–2751
8. Harbarth S, Garbino J, Pugin J, et al: Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. *Am J Med* 2003; 115:529–535
9. Ferrer R, Artigas A, Suarez D, et al; Edusepsis Study Group: Effectiveness of treatments for severe sepsis: A prospective, multicenter, observational study. *Am J Respir Crit Care Med* 2009; 180:861–866
10. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41:580–637
11. Levy MM, Dellinger RP, Townsend SR, et al: The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis. *Intensive Care Med* 2010; 36:222–231
12. Kumar A, Roberts D, Wood KE, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34:1589–1596
13. Ferrer R, Martin-Loeches I, Phillips G, et al: Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: Results from a guideline-based performance improvement program. *Crit Care Med* 2014; 42:1749–1755
14. Zhang D, Micek ST, Kollef MH: Time to Appropriate Antibiotic Therapy Is an Independent Determinant of Postinfection ICU and Hospital Lengths of Stay in Patients With Sepsis. *Crit Care Med* 2015; 43:2133–2140
15. Zilberberg MD, Shorr AF, Micek ST, et al: Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: A retrospective cohort study. *Crit Care* 2014; 18:596
16. Shorr AF, Myers DE, Huang DB, et al: A risk score for identifying methicillin-resistant *Staphylococcus aureus* in patients presenting to the hospital with pneumonia. *BMC Infect Dis* 2013; 13:268
17. Shorr AF, Zilberberg MD, Reichley R, et al: Validation of a clinical score for assessing the risk of resistant pathogens in patients with pneumonia presenting to the emergency department. *Clin Infect Dis* 2012; 54:193–198

Evidence to Practice Gap: The Case of Dopamine*

Djillali Annane, MD, PhD

General Intensive Care Unit, Raymond Poincaré Hospital (AP-HP)

Laboratory of Cell death, Inflammation and Infection, UMR1173

University of Versailles SQY and INSERM

Versailles, France

The Surviving Sepsis Campaign is an international collaboration initiated in 2002 on the leadership of the Society of Critical Care Medicine and the European Society of Intensive Care medicine to provide physicians, patients and their family, and health policy makers with evidence-based recommendations for the care of patients with sepsis. There is a continuing effort to maintain the guidelines updated. One major modification between the second (2008) and third (2012) revisions is the recommendation for the use of vasopressor therapy. The 2008 recommendations left at the discretion of physicians the choice between dopamine and norepinephrine as the first-line vasopressor for the management of patients with septic shock (1). The 2012 revisions strongly recommended (grade 1B) only norepinephrine as the first option for vasopressor therapy and restricted the use of dopamine to a very specific group of patients at low risk of arrhythmias and presenting with abnormal low heart rate (2). Indeed, a meta-analysis of six studies (2,043 patients) showed a relative risk of short-term mortality of 0.91 (95% CI, 0.83–0.99) in favor of norepinephrine when compared with dopamine (2). In this issue

***See also p. 2141.**

Key Words: clinical practice; guidelines; sepsis; vasopressor

The author has disclosed that he does not have any potential conflicts of interest.

DOI: 10.1097/CCM.0000000000001214

Time to Appropriate Antibiotic Therapy Is an Independent Determinant of Postinfection ICU and Hospital Lengths of Stay in Patients With Sepsis*

David Zhang, MD[1]; Scott T. Micek, PharmD[2]; Marin H. Kollef, MD[3]

Objective: To assess the timing of appropriate antibiotic therapy as a determinant of postinfection hospital and ICU lengths of stay in patients with sepsis.

Design: Single-center retrospective cohort study (January 2008–December 2012).

Setting: One thousand two hundred fifty–bed academic hospital.

Patients: One thousand fifty-eight consecutive blood culture positive patients.

Interventions: We retrospectively identified adult patients with severe sepsis or septic shock. Timing of appropriate antibiotic therapy was determined from blood culture collection time to the administration of the first dose of antibiotic therapy with documented in vitro susceptibility against the identified pathogen. We constructed generalized linear models to examine the determinants of attributable lengths of stay.

Measurements and Main Results: The median (interquartile range) time from blood culture collection to the administration of appropriate antibiotic therapy was 6.7 hours (0.0–23.3 hr). Linear regression analysis adjusting for severity of illness and comorbid conditions identified time to appropriate antibiotic therapy to be an independent determinant of postinfection ICU length of stay (0.095-d increase per hr of time to deliver appropriate antibiotic therapy; 95% CI, 0.057–0.132 d; $p < 0.001$) and postinfection hospital length of stay (0.134-d increase per hr of time to deliver appropriate antibiotic therapy; 95% CI, 0.074–0.194 d; $p < 0.001$). Other independent determinants associated with increasing ICU length of stay and hospital length of stay were mechanical ventilation (both ICU and hospital lengths of stay) and incremental peak WBC counts (hospital length of stay only). Incremental changes in severity of illness assessed by Acute Physiology and Chronic Health Evaluation II scores and comorbidity burden assessed by the Charlson comorbidity score were independently associated with decreases in ICU length of stay and hospital length of stay.

Conclusions: We identified time to appropriate antibiotic therapy in patients with sepsis to be an independent determinant of postinfection ICU and hospital lengths of stay. Clinicians should implement local strategies aimed at timely delivery of appropriate antibiotic therapy to improve outcomes and reduce length of stay. (*Crit Care Med* 2015; 43:2133–2140)

Key Words: antibiotics; length of stay; septic shock; severe sepsis

Severe sepsis and septic shock are common causes of morbidity and mortality in hospitalized patients accounting for significant hospital expenditures (1, 2). The cornerstones of sepsis management revolve around timely administration of antimicrobial therapy, adequate infection site source control, and appropriate hemodynamic support focused on preserving organ function (3). It is well established that delayed administration of appropriate antibiotic therapy (AAT) targeting the causative pathogen(s) of sepsis results in excess mortality (4–6). Escalating antibiotic resistance has resulted in the administration of empiric antibiotic regimens that are often not effective against the bacterial pathogens responsible for severe infections (7–9). The clinical impact of delayed AAT, especially in patients with severe sepsis and septic shock, has been an important impetus for the development of new antibiotics directed against antibiotic-resistant bacterial strains and rapid diagnostic methods for pathogen and susceptibility identification (10). However, the development of novel therapeutics and diagnostics for sepsis is associated with increased upfront costs and must be balanced with

*See also p. 2258.

[1]Division of Medical Education, Washington University School of Medicine, St. Louis, MO.

[2]Division of Specialty Pharmacy Practice, St. Louis College of Pharmacy, St. Louis, MO.

[3]Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, MO.

This work was performed at Washington University School of Medicine and Barnes-Jewish Hospital in St. Louis, MO.

Dr. Kollef's institution received grant support from Accelerate Diagnostics. (The concept of the study, statistical analysis, writing, and approval of the article was solely performed by the authors.) Dr. Kollef's efforts were supported by the Barnes-Jewish Hospital Foundation. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: mkollef@dom.wustl.edu

DOI: 10.1097/CCM.0000000000001140

clinical and long-term economic benefits in order to promote their continued advancement (11). Given the lack of data relating the timeliness of AAT to economic markers of sepsis, we conducted a study with the aim of assessing the relationship between the time to AAT administration and ICU and hospital lengths of stay (LOS). Multivariate analyses were used to account for severity of illness and comorbidities, which have previously been shown to be important outcome determinants in the critically ill needing to be controlled for in attributable outcomes analyses (12).

MATERIALS AND METHODS

Study Location and Patient Population

This study was conducted at a university-affiliated, urban teaching hospital: Barnes-Jewish Hospital (1,250 beds). Over a 5-year period (January 2008–December 2012), all hospitalized patients with severe sepsis or septic shock and a positive blood culture obtained while admitted to an ICU were eligible for inclusion. Patients with polymicrobial infections were excluded. This study was approved by the Washington University School of Medicine Human Studies Committee and the St. Louis College of Pharmacy Investigational Review Board, both granting a waiver of patient consent.

Study Design and Data Collection

Using a retrospective cohort study design, patients with culture positive severe sepsis or septic shock were identified by the presence of a blood culture positive for Gram-negative bacteria, Gram-positive bacteria, or fungi combined with primary or secondary *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM) codes indicative of acute organ dysfunction and/or the need for vasopressors. The primary endpoint for the analysis was attributable ICU and hospital LOS. Patient-specific baseline characteristics and process of care variables were collected from the automated hospital medical record, microbiology database, and pharmacy database of Barnes-Jewish Hospital. Data collection for all patients was uniform regardless of the initial location of their hospitalization (ICU or general hospital ward). Only the first episode of severe sepsis or septic shock was evaluated. Baseline characteristics collected included: age, gender, location prior to admission, and the Charlson comorbidity score. The Acute Physiology and Chronic Health Evaluation (APACHE) II (13) score was calculated based on clinical data present during the 24 hours after the blood cultures were obtained. This was done to accommodate patients with community-acquired and healthcare-associated community-onset infections who only had clinical data available after blood cultures were drawn.

Definitions

All definitions were prospectively selected prior to initiation of the study. To be included in the analysis, patients had to meet the criteria for severe sepsis or septic shock based on discharge ICD-9-CM codes for acute organ dysfunction as previously described (14). Patients were classified as having septic shock if vasopressors (norepinephrine, dopamine, epinephrine, phenylephrine, or vasopressin) were initiated within 24 hours of the blood culture collection date and time. Attributable LOS was defined as the time from blood culture collection to discharge from the ICU or the hospital. For the purposes of this investigation, the time of death was equal to the time of discharge in nonsurvivors. Antimicrobial treatment was classified as appropriate if the antibiotic regimen administered was active against the identified pathogen based on in vitro antimicrobial susceptibility testing results. For extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria, initial use of a carbapenem was required to be classified as appropriate treatment. Multidrug resistance (MDR) was defined as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and Gram-negative bacteria that were nonsusceptible to at least one antimicrobial agent from at least three different antimicrobial classes (15).

Antimicrobial Monitoring

During the study, cefepime, gentamicin, vancomycin, and fluconazole use was unrestricted. Use of ciprofloxacin, imipenem, meropenem, piperacillin/tazobactam, linezolid, daptomycin, or micafungin was restricted and required preauthorization. Each ICU had at least one clinical pharmacist who reviewed antibiotic orders for approval to insure that dosing and interval of administration was adequate for patients based on body size, renal function, and resuscitation status. After daytime hours, the on-call clinical pharmacist reviewed and approved the antibiotic orders. The initial antibiotic dosages used for the treatment were as follows: cefepime, 1–2 g every 8 hours; piperacillin-tazobactam, 4.5 g every 6 hours; imipenem 0.5–1 g every 6 hours; meropenem, 1–2 g every 8 hours; ciprofloxacin, 400 mg every 8 hours; gentamicin, 5 mg/kg once daily; vancomycin, 15 mg/kg every 12 hours; linezolid, 600 mg every 12 hours; daptomycin, 6–8 mg/kg every 24 hours; fluconazole, 800 mg on the first day followed by 400 mg daily; and micafungin, 100 mg daily.

Starting in June 2005, with regular updates, a sepsis order set was implemented in the emergency department, general wards, and the ICUs with the intent of standardizing empiric antibiotic selection for patients with sepsis based on the infection type (i.e., community-acquired pneumonia, healthcare-associated pneumonia, and intra-abdominal infection) and the hospital's antibiogram (16, 17). However, antimicrobial selection, dosing, and de-escalation of therapy were still optimized by the treatment team including clinical pharmacists in these clinical areas. Given the relatively high rates of infection attributed to MRSA and antibiotic-resistant Gram-negative bacteria within the ICUs of Barnes-Jewish Hospital, primarily due to the high prevalence of healthcare exposure in this local population, empiric coverage for these pathogens was typically provided (4, 16, 17).

Antimicrobial Susceptibility Testing

The microbiology laboratory performed antimicrobial susceptibility of the bacterial and fungal isolates according to

guidelines and breakpoints established by the Clinical Laboratory and Standards Institute and published during the inclusive years of the study (18, 19). All classifications of antibiotic resistance were based on in vitro susceptibility testing using these established breakpoints.

Data Analysis

Continuous variables were reported as means with SDs or medians with 25th and 75th percentiles according to their distribution. The Student *t* test was used when comparing normally distributed data, and the Mann-Whitney *U* test was used to analyze nonnormally distributed data. Categorical data were expressed as frequency distributions and the chi-square test or Fisher exact test for small samples was used to determine if differences existed between groups. Spearman rank correlation was used to assess the statistical dependence of time to AAT and LOS. We constructed generalized linear models to examine the determinants of attributable LOS. The Akaike Information Criterion was used to assess the functional shapes of the covariates, and residual diagnostics were conducted to verify model assumptions (20). All tests were two-tailed, and a *p* value of less than 0.05 was determined to represent statistical significance. The analysis was repeated for hospital survivors and patients with septic shock. The former was done in order to remove the influence of hospital death on LOS and the latter to assess a cohort of patients where the clinical assessment of infection was more objectively accessible.

RESULTS

One thousand fifty-eight patients with severe sepsis or septic shock and positive blood cultures met the inclusion criteria. Three hundred ninety-nine patients (37.7%) died during their hospitalization and 319 (30.2%) died while in the ICU. Baseline characteristics of the patients are listed in **Table 1**. Most patients were admitted to the hospital from home. More than half of the study cohort received prior antibiotics in the 30-day period before the index infection. Infection-related characteristics are shown in **Table 2**. The most common sites of infection included the lung, intra-abdominal, and urinary tract. Community-acquired infection was present in 129 patients (12.2%), healthcare-associated community-onset infection in 235 patients (22.2%), and healthcare-associated hospital-onset infection in 694 patients (65.6%). Infection attributed to *Staphylococcus aureus* was most common followed by *Candida* species, *Escherichia coli*, *Klebsiella* species, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*. MDR bacterial infection was significantly more likely to be associated with prior antibiotic exposure compared with non-MDR bacterial infection (80.0% vs 56.5%; $p = 0.001$).

The most common antibiotic resistance phenotype identified was resistance to ciprofloxacin in Gram-negative bacteria followed by methicillin resistance in *S. aureus*, cefepime resistance, and piperacillin-tazobactam resistance in Gram-negative bacteria, carbapenem resistance and presence of ESBL production in Gram-negative bacteria, and vancomycin resistance in enterococci (Table 2). Seven hundred thirty-eight patients (69.8%)

TABLE 1. Baseline Characteristics of Study Cohort

Variable	*n* = 1,058
Age (mean ± SD, yr)	61.7 ± 16.6
Male gender, *n* (%)	617 (58.3)
Race,[a] *n* (%)	
White	667 (63.0)
African-American	317 (30.0)
Hospital admission source,[b] *n* (%)	
Home	574 (54.3)
Skilled nursing facility	81 (7.7)
Transfer from outside hospital	373 (35.3)
Charlson comorbidity score, median (IQR)	4.0 (2.0–7.0)
Acute Physiology and Chronic Health Evaluation II score, median (IQR)	18.0 (14.0–23.0)
Hemodialysis, *n* (%)	148 (14.0)
Immunosuppression, *n* (%)	274 (25.9)
Total parenteral nutrition, *n* (%)	61 (5.8)
Surgery, *n* (%)	
Abdominal	158 (14.9)
Nonabdominal	154 (14.6)
Central vein catheter, *n* (%)	604 (57.1)
Prior hospitalization,[c] *n* (%)	587 (55.5)
Prior bacteremia,[d] *n* (%)	147 (13.9)
Prior antibiotics,[d] *n* (%)	611 (57.8)
Duration of hospitalization prior to bacteremia, d, median (IQR)	1.4 (0.0–9.3)
Septic shock, *n* (%)	747 (70.6)
Mechanical ventilation, *n* (%)	433 (40.9)
Comorbidities, *n* (%)	
Congestive heart failure	257 (24.3)
Chronic obstructive pulmonary disease	280 (26.5)
Cirrhosis	159 (15.0)
Diabetes	277 (26.2)
Chronic kidney disease without dialysis	144 (13.6)
Underlying malignancy	265 (25.0)
HIV	13 (1.2)
Peak WBC count, median (IQR)	19.0 (11.0–34.0)

IQR = interquartile range.
[a]Race: unknown or other; 7.00%.
[b]Admission source: unknown or other; 2.80%.
[c]Within 90 d.
[d]Within 30 d including antibiotics administered during the index hospitalization and prior to the index hospitalization.

TABLE 2. Infection-Related Characteristics of Study Cohort

Variables	*n* = 1,058 (%)	Time to Appropriate Antibiotic Therapy (Hr)
Infection source		
CNS	11 (1.0)	5.0 (1.0–12.0)
Intra-abdominal	150 (14.2)	6.0 (0.0–26.3)
Vascular catheter related	99 (9.4)	9.0 (1.0–26.0)
Lung	224 (21.2)	3.5 (0.0–17.0)
Skin structure	66 (6.2)	9.0 (1.8–22.8)
Urinary tract	226 (21.4)	9.0 (1.0–24.0)
Unknown	350 (33.1)	8.0 (0.3–25.3)
Pathogens		
Acinetobacter species	33 (3.1)	15.5 (4.0–58.0)
Bacteroides species	41 (3.9)	12.0 (3.0–42.0)
Burkholderia cepacia	7 (0.7)	3.0 (0.0–10.0)
Candida albicans	65 (6.1)	32.0 (10.0–40.0)
Other *Candida* species	79 (7.5)	30.0 (4.5–41.5)
Enterobacter species	44 (4.2)	4.5 (0.0–16.0)
Enterococcus faecalis	70 (6.6)	13.0 (0.0–26.0)
Enterococcus faecium	59 (5.6)	30.0 (20.0–46.0)
Escherichia coli	105 (9.9)	3.0 (0.0–9.0)
Klebsiella species	74 (7.0)	3.0 (0.0–13.0)
Proteus species	15 (1.4)	6.0 (0.0–17.0)
Pseudomonas aeruginosa	60 (5.7)	5.4 (0.0–19.3)
Serratia marcescens	20 (1.9)	12.0 (0.0–29.0)
Staphylococcus aureus	248 (23.4)	4.0 (0.0–12.5)
Stenotrophomonas maltophilia	10 (0.9)	28.0 (4.0–65.0)
Streptococcus pneumonia	22 (2.1)	6.5 (0.8–9.3)
Other streptococcal species	41 (3.9)	4.0 (0.0–15.0)
Resistance phenotypes		
Methicillin-resistant *S. aureus*	122 (11.5)	5.0 (0.0–16.3)
Vancomycin-intermediate *S. aureus*	19 (1.8)	0.0 (0.0–14.0)
Vancomycin-resistant enterococci	61 (5.8)	30.0 (20.5–49.5)
Aminoglycoside resistant[a]	49 (4.6)	13.0 (4.0–58.0)
Cefepime resistant[a]	119 (11.2)	16.0 (3.0–58.0)
Carbapenem resistant[a]	63 (6.0)	16.0 (3.0–58.0)
Piperacillin-tazobactam resistant[a]	119 (11.2)	12.0 (1.0–29.0)
Ciprofloxacin resistant[a]	220 (20.8)	7.1 (0.0–20.0)
Extended-spectrum beta-lactamase resistant[a]	64 (6.0)	8.5 (1.0–16.0)
Multidrug resistant[a]	55 (5.2)	20 (5.8–60.0)
Appropriate initial empiric antibiotic regimen	738 (69.8)	
Time to appropriate therapy, median (IQR, hr)	6.7 (0.0–23.3)	

[a]Applies to infection with Gram-negative bacteria.

TABLE 3. Generalized Linear Model of Determinants of Attributable ICU Length of Stay (Days)

Variable	Point Estimate	95% CI	*p*
Time to appropriate antibiotic therapy (1-hr increments)	0.095	0.057–0.132	< 0.001
Charlson comorbidity score (1-point increments)	−0.493	−0.769 to −0.218	< 0.001
Acute Physiology and Chronic Health Evaluation II score (1-point increments)	−0.276	−0.434 to −0.118	0.001
Mechanical ventilation	6.228	4.263–8.193	< 0.001

Akaike Information Criterion = 8766.7.

TABLE 4. Generalized Linear Model of Determinants of Attributable Hospital Length of Stay (Days)

Variable	Point Estimate	95% CI	*p*
Time to appropriate antibiotic therapy (1-hr increments)	0.134	0.074–0.194	< 0.001
Charlson comorbidity score (1-point increments)	−0.674	−1.117 to −0.232	0.003
Acute Physiology and Chronic Health Evaluation II score (1-point increments)	−0.501	−0.755 to −0.248	< 0.001
Peak WBC count (1-unit increments)	0.122	0.034–0.210	0.007
Mechanical ventilation	8.482	5.319–11.646	< 0.001

Akaike Information Criterion = 9811.1.

received an initial empiric antibiotic regimen that was active against the causative pathogen, whereas 320 patients (30.2%) received an initial empiric antibiotic regimen that did not cover the causative pathogen. Patients receiving an initial empiric antibiotic regimen had significantly lower mortality compared with those who did not (35.1% vs 43.8%; $p = 0.008$). Time to AAT was longest for infection attributed to *Candida albicans* followed by other *Candida* species, *Enterococcus faecium*, *Stenotrophomonas maltophilia*, *Acinetobacter* species, and *E. faecalis*. Vancomycin resistance in enterococci was the phenotype with the longest time to AAT followed by MDR in Gram-negative bacteria, carbapenem or cefepime resistance in Gram-negative bacteria, and aminoglycoside resistance in Gram-negative bacteria.

The median (interquartile range) time from blood culture collection to the administration of AAT was 6.7 hours (0.0–23.3 hr). The durations of postinfection ICU and hospital LOS were directly related to the timing of AAT (**Figs. 1** and **2**). Time to AAT was an independent determinant of attributable ICU LOS (**Table 3**). For each hour delay in the administration of AAT, there was a 0.095-day increase in the attributable postinfection ICU LOS. Similarly, time to AAT was an independent determinant of attributable hospital LOS (**Table 4**). For each hour delay in the administration of AAT, there was a 0.134-day increase in the attributable postinfection hospital LOS. Tables 3 and 4 show that severity of illness markers (APACHE II score, peak WBC count, mechanical ventilation) and comorbid conditions indicated by the Charlson comorbidity score were also independent determinants of LOS, with increasing Charlson comorbidity scores and APACHE II scores being associated with shorter LOS. Repeating this analysis in the cohort of hospital survivors ($n = 659$) produced similar results. For each hour delay in the administration of AAT, there was a 0.049-day increase in the attributable postinfection ICU LOS. Similarly, for each hour delay in the administration of AAT, there was a 0.085-day increase in the attributable postinfection hospital LOS. A sensitivity analysis was performed in the subgroup of patients with septic shock ($n = 747$), demonstrating that for each hour delay in the administration of AAT, there was a 0.107-day increase in the attributable postinfection ICU LOS. Similarly, for each hour delay in the administration of AAT, there was a 0.130-day increase in the attributable postinfection hospital LOS.

DISCUSSION

Our study demonstrated that timing of AAT is an independent determinant of ICU and hospital LOS in blood culture positive patients with severe sepsis and septic shock. We also identified established severity of illness markers (mechanical ventilation, APACHE II score, and WBC count) and the Charlson comorbidity score as independent predictors of LOS. Not unexpectedly, we found that greater severity of illness and comorbidity burden were associated with reduced LOS. This appeared to be due to the greater mortality associated with increased illness severity and comorbidity burden. Although small, the quantitative increases in ICU and hospital LOS were most significant for patients with more prolonged delays in the administration of AAT. Individuals with a 24-hour delay in the administration of AAT would be expected to have ICU and hospital LOS increased by 2.3 days and 3.2 days, respectively. The longest delays in AAT observed in our study were attributed to infection with pathogens not covered by the typically prescribed

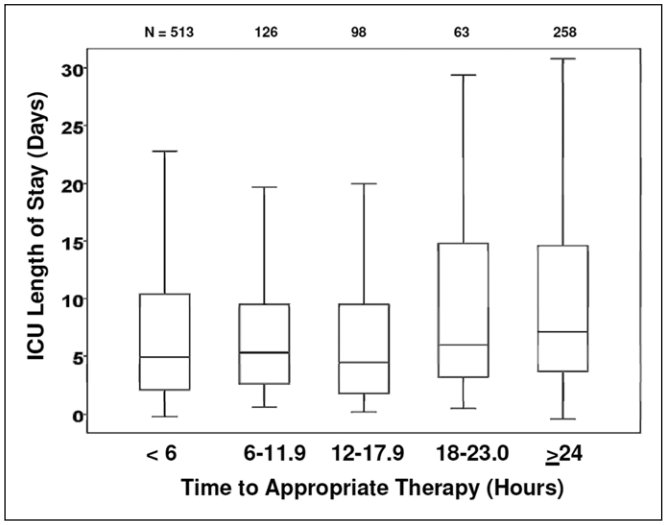

Figure 1. Box plots for attributable ICU stay (d) according to the delivery of appropriate antibiotics (hr). The *lines within the boxes* represent the median values, the *boxes* represent the 25th and 75th percentiles, and the *whisker lines* represent the 5th and 95th percentiles. Attributable ICU stay was determined from the blood culture collection time to ICU discharge or death. $p < 0.001$ for trend.

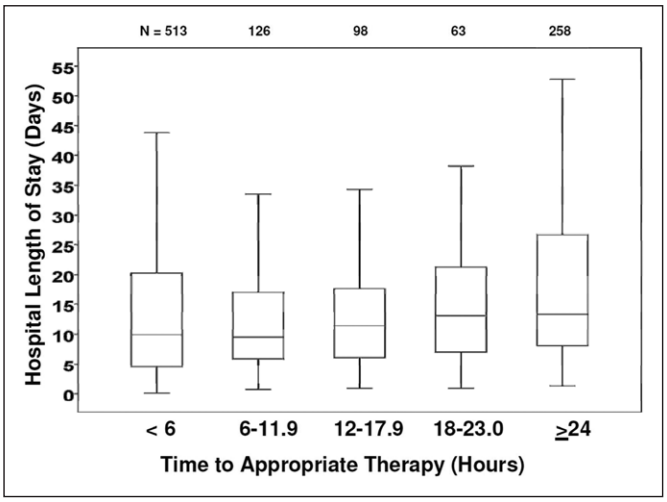

Figure 2. Box plots for attributable hospital stay (d) according to the delivery of appropriate antibiotics (hr). The *lines within the boxes* represent the median values, the *boxes* represent the 25th and 75th percentiles, and the *whisker lines* represent the 5th and 95th percentiles. Attributable hospital stay was determined from the blood culture collection time to hospital discharge or death. $p < 0.001$ for trend.

empiric antimicrobial regimens for critically ill patients at Barnes-Jewish Hospital, encompassing predominantly antibiotic-resistant Gram-negative nonfermenters, VRE, and *Candida* species. This explains the distributions observed in Figures 1 and 2, indicating that the greatest increases in LOS were driven by this important group of antibiotic-resistant pathogens that accounted for about 25% of the population.

Delayed administration of AAT has been linked to excess mortality in a variety of serious infections, including severe sepsis or septic shock, pneumonia, intra-abdominal infection, meningitis, and bacteremia (3–6). Several studies in patients with severe sepsis or septic shock have found that delays of 1–2 hours in the delivery of antibiotics can significantly increase the risk of mortality (5, 21, 22). This increased risk of death with delayed AAT has been the impetus for the development of various treatment strategies that have included the use of combination antibiotic therapy, empiric treatment based on surveillance cultures, and consultation by experts in infectious diseases in order to improve antibiotic utilization and patient outcomes (23–26). Within the ICUs of our own hospital, the use of combination antibiotic therapy, with the addition of an aminoglycoside to a carbapenem or antipseudomonal beta-lactam, for the empiric treatment of septic shock has become the norm in order to provide better coverage in patients with hospital-acquired and healthcare-associated infections (26).

We previously showed that prior antibiotic exposure was associated with prolonged hospital LOS for patients with Gram-negative sepsis (27). This was presumably related to the greater likelihood of infection with antibiotic-resistant pathogens and thus greater risk for delayed AAT in patients receiving prior antibiotics. Our current study supports this hypothesis by identifying prior antibiotic exposure to be more common in infections attributed to MDR bacteria. Our results are consistent with those of Muszynski et al (28) who found that pediatric patients with severe community-acquired pneumonia had longer hospital LOS and duration of mechanical ventilation when AAT was not initially prescribed. Similarly, Geerlings et al (29) demonstrated that the initial use of AAT was associated with shorter hospital LOS in a multicenter study from the Netherlands. These data, along with our current findings, suggest that ICU and hospital LOS could potentially be reduced if improvements in the delivery of AAT could be achieved. The development of novel antibiotics (10) in parallel with rapid diagnostics (30) offers future hope for achieving improved administration of AAT while minimizing the unnecessary use of broad-spectrum antibiotics. Furthermore, reductions in ICU and hospital LOS, along with clinical improvements, can be used as economic justifications for the development of new therapeutics and diagnostics for the management of sepsis.

Our study has a number of significant limitations. First, its retrospective design opens it up to various forms of bias. However, we focused on ICU and hospital LOS as the primary endpoint, which are not prone to ascertainment or recall bias. Second, the data derive from a single center and this necessarily limits the generalizability of our findings. As such, our results may not reflect what one might see at other institutions. For example, our use of empiric combination therapy using aminoglycosides may be an uncommon practice in other centers. Furthermore, Barnes-Jewish Hospital has a referral pattern that includes community hospitals, regional long-term acute care hospitals, nursing homes, and chronic wound, dialysis, and infusion clinics. Patients transferred from these settings are more likely to be infected with potentially antibiotic-resistant bacteria. Third, despite being a rather large cohort, we nevertheless may have lacked power to adjust for certain confounders that could affect our LOS endpoints. Fourth, we did not capture antibiotics administered at the referring skilled nursing facilities and

outside hospitals for transferred patients. Therefore, we may have missed the earlier administration of AAT at these sites. However, this is unlikely given that all transferred patients in this cohort were bacteremic either at presentation to our hospital or at a later point in their hospitalization when the infection occurred. Fifth, we assessed severity of illness after the blood cultures were obtained. This may have introduced a bias as some patients may have started to improve at this time resulting in lower severity of illness. Sixth, we excluded patients with polymicrobial infections. Another limitation of our study is that we used blood culture collection time as the point from which to assess timing of AAT as opposed to using a clinician driven time point of when infection was first considered to be present. This may have biased our determination of the timing of AAT, especially if delays occurred in obtaining blood cultures after suspicion for infection occurred. However, the analysis in the subgroup of patients with septic shock, presumably an infection that can be clinically assessed more objectively, produced similar results. Additionally, it is important to note that mechanical ventilation was a more important determinant of attributable LOS compared with timing of AAT. Finally, we cannot draw causality from our study. Prospective studies are required to determine the actual relationship between timing of AAT and LOS. Ideally, this would be done as part of clinical trials evaluating novel antibiotics or diagnostics in patients with severe sepsis and septic shock.

In summary, time to AAT appears to be an independent determinant of postinfection ICU and hospital LOS in blood culture positive patients with severe sepsis and septic shock. Unfortunately, severe sepsis and septic shock are increasingly caused by antibiotic-resistant pathogens, including Gram-negative nonfermenters, VRE, and *Candida* species, which promote delays in the delivery of AAT. Moving forward, ICU clinicians need to develop novel approaches for the treatment of patients with severe sepsis and septic shock that achieve timely application of AAT while avoiding the unnecessary use of antibiotics, especially broad-spectrum agents. Advances in new antibiotic development along with rapid diagnostics offer approaches for achieving this important balance.

ACKNOWLEDGMENTS

We thank Rebecca Light for her assistance in preparation of this article.

REFERENCES

1. Kahn JM, Le T, Angus DC, et al; ProVent Study Group Investigators: The epidemiology of chronic critical illness in the United States. *Crit Care Med* 2015; 43:282–287
2. Mitka M: Hospitalizations for extreme conditions mean extreme expenses, study verifies. *JAMA* 2010; 304:2579–2580
3. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41:580–637
4. Kollef MH, Sherman G, Ward S, et al: Inadequate antimicrobial treatment of infections: A risk factor for hospital mortality among critically ill patients. *Chest* 1999; 115:462–474
5. Kumar A, Roberts D, Wood KE, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34:1589–1596
6. Weiss SL, Fitzgerald JC, Balamuth F, et al: Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. *Crit Care Med* 2014; 42:2409–2417
7. Chung DR, Song JH, Kim SH, et al; Asian Network for Surveillance of Resistant Pathogens Study Group: High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. *Am J Respir Crit Care Med* 2011; 184:1409–1417
8. Cantón R, Akóva M, Carmeli Y, et al; European Network on Carbapenemases: Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. *Clin Microbiol Infect* 2012; 18:413–431
9. Brennan BM, Coyle JR, Marchaim D, et al: Statewide surveillance of carbapenem-resistant enterobacteriaceae in Michigan. *Infect Control Hosp Epidemiol* 2014; 35:342–349
10. Kollef MH, Micek ST: Rational use of antibiotics in the ICU: Balancing stewardship and clinical outcomes. *JAMA* 2014; 312:1403–1404
11. Darbà J, Kaskens L, Hark M, et al: Costs of surviving meningococcal disease in Spain: Evaluation for two cases of severe meningitis and septicaemia. *Vaccine* 2014; 32:5006–5012
12. de Smet AM, Kluytmans JA, Cooper BS, et al: Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med* 2009; 360:20–31
13. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–829
14. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
15. Magiorakos AP, Srinivasan A, Carey RB, et al: Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; 18:268–281
16. Micek ST, Roubinian N, Heuring T, et al: Before-after study of a standardized hospital order set for the management of septic shock. *Crit Care Med* 2006; 34:2707–2713
17. Thiel SW, Asghar MF, Micek ST, et al: Hospital-wide impact of a standardized order set for the management of bacteremic severe sepsis. *Crit Care Med* 2009; 37:819–824
18. Clinical Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing: Seventeenth Informational Supplement. M100–S17. Wayne, PA, Clinical Laboratory Standards Institute, 2007
19. Clinical Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing: Seventeenth Informational Supplement. M100–S22. Wayne, PA, Clinical Laboratory Standards Institute, 2012
20. Akaike H: A new look at the statistical model identification. *IEEE Trans Automat Contr* 1974; 19:716–723
21. Ferrer R, Martin-Loeches I, Phillips G, et al: Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: Results from a guideline-based performance improvement program. *Crit Care Med* 2014; 42:1749–1755
22. Ferrer R, Artigas A, Suarez D, et al; Edusepsis Study Group: Effectiveness of treatments for severe sepsis: A prospective, multicenter, observational study. *Am J Respir Crit Care Med* 2009; 180:861–866
23. Kerremans JJ, Verbrugh HA, Vos MC: Frequency of microbiologically correct antibiotic therapy increased by infectious disease consultations and microbiological results. *J Clin Microbiol* 2012; 50:2066–2068
24. De Bus L, Saerens L, Gadeyne B, et al: Development of antibiotic treatment algorithms based on local ecology and respiratory surveillance cultures to restrict the use of broad-spectrum antimicrobial drugs in the treatment of hospital-acquired pneumonia in the intensive care unit: A retrospective analysis. *Crit Care* 2014; 18:R152
25. Kumar A, Zarychanski R, Light B, et al; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group: Early combination antibiotic therapy yields improved survival compared

with monotherapy in septic shock: A propensity-matched analysis. *Crit Care Med* 2010; 38:1773–1785

26. Micek ST, Welch EC, Khan J, et al: Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to Gram-negative bacteria: A retrospective analysis. *Antimicrob Agents Chemother* 2010; 54:1742–1748
27. Johnson MT, Reichley R, Hoppe-Bauer J, et al: Impact of previous antibiotic therapy on outcome of Gram-negative severe sepsis. *Crit Care Med* 2011; 39:1859–1865
28. Muszynski JA, Knatz NL, Sargel CL, et al: Timing of correct parenteral antibiotic initiation and outcomes from severe bacterial community-acquired pneumonia in children. *Pediatr Infect Dis J* 2011; 30:295–301
29. Geerlings SE, Hulscher M, Prins JM: [Appropriate use of antibiotics shortens length of hospital stay]. *Ned Tijdschr Geneeskd* 2014; 158:A7288
30. Douglas IS, Price CS, Overdier KH, et al: Rapid automated microscopy for microbiological surveillance of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2015; 191:566–573