Does Appropriate Antibiotic Therapy Mean Only Adequate Spectrum and Timing?*

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A different way of looking at the response of a patient to a septic insult is conceptualizing a three-component model—the bug, the drug, and the mug (patient). Isolating and identifying the infective organism via microbiological techniques is standard. Depending on the susceptibility of the organism, one can use the appropriate active antibiotic. The third component of the triad, and the interaction of the three components, is not as straightforward nor simple as it seems. This editorial places in context some of the different pharmacokinetic (PK) responses of critically ill patients.

In this issue of *Critical Care Medicine*, Burnham et al (1) investigate a hospital-wide database (June 2009 to December 2013) for all positive blood isolates of Enterobacteriaceae—these organisms becoming increasingly resistant. Their primary endpoint was all-cause 30-day mortality, and secondary endpoints included ICU and hospital length of stay. From 510 patients with Enterobacteriaceae bacteremias (single organism growths), they provide supportive data that sepsis severity is an important predictor of death (2). More importantly, they also show that using the correct antibiotic, that is, that appropriate for organism susceptibility, plus correct timing of administration, is not enough to ensure a good outcome.

These findings are important, and make clinical sense. In essence, Burnham et al (1) look at the "bug and drug" part of the triad above.

*See also p. 1580.

Key Words: appropriate antibiotics; augmented renal clearance; dosing; pharmacokinetics

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It is likely that factors beyond the correct choice of antibiotic should be considered when treating patients with sepsis, particularly those requiring intensive care support. One such additional consideration is the optimal antibiotic PK exposure that should be delivered, given the susceptibility of the pathogen. Ensuring a PK exposure of antibiotic is very likely to be important to further maximize antibiotic effectiveness (3).

Recent observations regarding antimicrobial PKs in critically ill patients suggest a persistent knowledge gap with respect to the best use of antimicrobials in this patient population. From discovery to launch of drugs, seldom are these compounds specifically studied in critically ill patients. On top of this, comparative antibiotic studies are mostly performed to test noninferiority of a new agent (4). As a result, licensed antibiotic dosing is often simplified to a "one size fits all" concept in adult ICUs (4). In the critically ill, with changes in pathophysiology, and associated clinical interventions, such dosing has now been shown to be too simplistic (5).

It is well established that changes in drug PKs associated with common pathologies in the critically ill result in lower circulating (and tissue) antibiotic concentrations. In the article by Burnham et al (1), some of the predictors of mortality are known to be associated with PK and pharmacodynamic changes, which tend to lower many antibiotic concentrations. These include but are not limited to 1) increased volume of distribution (Vd) of hydrophilic drugs (increased sepsis severity and Acute Physiology and Chronic Health Evaluation score and cirrhosis), 2) hyperdynamic circulatory system associated with increased renal blood flow and elevated drug clearance (transplant; noting that African Americans seem also to have higher glomerular filtration rate than Caucasians), and 3) decreased pathogen susceptibility associated with previous healthcare exposure.

These changes can lead to a decreased achievement of therapeutic exposures of the prescribed antibiotic.

It is clear that target endpoints of antibiotic therapy may be more subtle than antihypertensive therapy guided by an easily measureable blood pressure. Appropriate antibiotic dosing implies adequate antibiotic concentrations. Although overdosing can occur, underdosing is often overlooked because of a lack of accurate dosing guidelines, which account for changes in Vd and clearance (6, 7).

Patients with severe infections tend to need, and be given, fluid in the initial resuscitative phase of sepsis. Leaky capillaries often compounded by hypoproteinemia predispose these patients to swelling with extravascular fluid extravasation. This will have little effect on lipophilic drugs as their typical Vd ("space" into which drug diffuses) is very large, and the relative increase in Vd in ICU is too small to produce an overall Vd change (8). Hydrophilic antibiotics, which primarily occupying the intravascular space, will also distribute into this increased extravascular water, and due their relatively small

initial Vd, this increase will produce a markedly large change (increase) in the Vd of such antibiotics. Due to this increased Vd, administering the same dose of an hydrophilic antibiotic to a patient with leaky capillaries will result in a lower concentration of the antibiotic in the serum, particularly a lower maximal concentration (C_{max}) (8).

Di Giantomasso et al (9) have demonstrated an increased organ blood flow early in sepsis. Clinically this means in the presence of normal renal function, an increased organ, namely renal blood flow, will translate into an increased glomerular filtration rate and hence an increased creatinine clearance. This clinical phenomenon has now been termed augmented renal clearance (ARC) (10). ARC will result in increased clearances of all renally eliminated drugs. In four multidisciplinary ICUs across the world, ARC has now been documented in more than 60% of patients admitted with a "normal" serum creatinine concentration (11). The practical implications of ARC with standard dosing of antibiotics with renal clearances (β-lactams, aminoglycosides, and glycopeptides) will be that the resultant serum antibiotic concentration will be low, often subtherapeutic (6, 7). This, plus the alterations of Vd within critically ill patients, often requires higher doses than standard to be administered to ensure that antibiotic exposures are achieved that are the same as those present in clinical validation studies.

Pharmacodynamics is another issue that needs to be accounted for in dosing. Although in a microbiology susceptibility report, "S" is associated with success, if the susceptibility of the pathogen is actually a minimum inhibitory concentration close to the break point, then the above PK changes may result in ineffective antibiotic exposures and treatment failure.

Although understanding the above principles can help attain better target antibiotic concentrations (loading doses for increased Vd, increased dosing particularly increased frequency to compensate for ARC), therapeutic drug (antibiotic) monitoring (TDM) is associated with more consistent attainment of target exposures (3, 12). TDM is commonly used to prevent toxicity (aminoglycosides and glycopeptides) or improve efficacy. However, recently more units are using TDM for β-lactams to improve efficacy (12).

Burnham et al (1) are to be congratulated for providing more evidence that "appropriate antibiotic therapy" is not enough to produce optimal outcomes. However, perhaps what was assessed in this study was not the complete story and that "appropriate antibiotic" should also be judged on the administration of an appropriate dose.

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Impact of Sepsis Classification and Multidrug-Resistance Status on Outcome Among Patients Treated With Appropriate Therapy*

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Objective: To assess the impact of sepsis classification and multidrug-resistance status on outcome in patients receiving appropriate initial antibiotic therapy.

Design: A retrospective cohort study.

Setting: Barnes-Jewish Hospital, a 1,250-bed teaching hospital.

Patients: Individuals with *Enterobacteriaceae* sepsis, severe sepsis, and septic shock who received appropriate initial antimicrobial therapy between June 2009 and December 2013.

Interventions: Clinical outcomes were compared according to multidrug-resistance status, sepsis classification, demographics, severity of illness, comorbidities, and antimicrobial treatment.

Measurements and Main Results: We identified 510 patients with *Enterobacteriaceae* bacteremia and sepsis, severe sepsis, or septic shock. Sixty-seven patients (13.1%) were nonsurvivors. Mortality increased significantly with increasing severity of sepsis (3.5%, 9.9%, and 28.6%, for sepsis, severe sepsis, and septic shock, respectively; $p < 0.05$). Time to antimicrobial therapy was not significantly associated with outcome. Acute Physiology and Chronic Health Evaluation II was more predictive of mortality than age-adjusted Charlson comorbidity index. Multidrug-resistance status did not result in excess mortality. Length of ICU and hospital stay increased with more severe sepsis. In multivariate logistic regression analysis, African-American race, sepsis severity, Acute Physiology and Chronic Health Evaluation II score, solid-organ cancer, cirrhosis, and transfer from an outside hospital were all predictors of mortality.

Conclusions: Our results support sepsis severity, but not multidrug-resistance status as being an important predictor of death when all patients receive appropriate initial antibiotic therapy. Future sepsis trials should attempt to provide appropriate antimicrobial therapy and take sepsis severity into careful account when determining outcomes. (*Crit Care Med* 2015; 43:1580–1586)

Key Words: multidrug resistance; sepsis mortality

Inappropriate initial antimicrobial therapy leads to higher mortality in patients with severe sepsis or septic shock (1–5). Multidrug-resistant (MDR) pathogens are prone to treatment with initial inappropriate antimicrobial therapy, but whether drug resistance alone increases mortality in the setting of appropriate therapy is unclear (6–10). The presence of severe sepsis with organ failure and shock requiring vasopressor support are predictors of greater mortality in populations with variable rates of appropriate antimicrobial therapy (1, 11–16). Neither the presence of severe sepsis or shock nor MDR as predictors of mortality has been studied in a cohort of patients with sepsis who all received appropriate initial antimicrobial therapy. Our primary goal was to compare 30-day all-cause mortality among patients with sepsis, severe sepsis, and septic shock treated with appropriate initial antimicrobial therapy to more directly assess the impact of sepsis severity on outcome. Our secondary objective was to examine the impact of MDR on mortality in the same cohort. We selected only patients with *Enterobacteriaceae* bacteremia for two reasons: 1) the prevalence of MDR *Enterobacteriaceae* infections is increasing worldwide (17–21) and 2) for a homogeneous population in order to minimize pathogen-related confounders.

***See also p. 1773.**

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MATERIALS AND METHODS

Study Location and Patient Population

This study was conducted at Barnes-Jewish Hospital, a 1,250-bed academic medical center located in St. Louis, MO. The study period was June 1, 2009, through December 31, 2013, corresponding to the length of time for which an electronic medical record was available that could verify time of antibiotic administration. All consecutive hospitalized patients with sepsis, severe sepsis, or septic shock and a positive blood culture for an organism in the *Enterobacteriaceae* family during the study period were analyzed for eligibility. This study was approved by the Washington University School of Medicine Human Studies Committee.

Study Design and Data Collection

Utilizing a retrospective cohort study design, all patients who are 18 years old or older with sepsis, severe sepsis, or septic shock were identified by the presence of a positive blood culture for an organism in the *Enterobacteriaceae* family. Patients were included only if they had positive blood cultures with a single organism from the *Enterobacteriaceae* family; patients with polymicrobial blood cultures were excluded from the study. *International Classification of Diseases,* 9th Edition (ICD-9) codes indicative of acute organ dysfunction or the need for vasopressors were used to classify patients as having severe sepsis or septic shock, respectively. The primary endpoint was all-cause 30-day mortality, calculated from the time that a positive blood culture was drawn. Secondary endpoints included length of hospital stay (LOS), length of ICU stay (ICU LOS), and the number of procedures performed. Only the first episode of sepsis, severe sepsis, or septic shock was evaluated. Baseline characteristics including age, gender, race, place of origin, healthcare exposure, receipt of antibiotics within 30 days of positive culture, presence of immunosuppression, Acute Physiology and Chronic Health Evaluation (APACHE) II (22) scores (calculated based on clinical data present during the 24 hr after positive blood cultures were drawn), Charlson Comorbidity Index, and medical comorbidities were obtained.

Definitions

Patients were considered to have a bloodstream infection due to *Enterobacteriaceae* if any blood culture obtained within 48 hours of developing sepsis, severe sepsis, or septic shock were positive for *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Klebsiella granulomatis, Proteus mirabilis, Proteus vulgaris, Enterobacter aerogenes, Enterobacter cloacae, Enterobacter sakasakii, Serratia marcescens, Citrobacter freundii, Citrobacter koseri, Citrobacter amalonaticus, Edwardsiella tarda, Hafnia alvei, Morganella morganii, Pantoea agglomerans, Plesiomonoas shigelloides, Providencia stuartii, Providencia rettgeri, Salmonella enterica, Shigella dysenterii, Shigella flexneri, Shigella sonnei, Shigella boydii, Yersinia enterocolitica, Yersinia pestis, Yersinia pseudotuberculosis, Ewingella americana, or Kluyvera* spp.

Patients were required to have at least one of the following ICD-9 codes: 995.91 (sepsis), 995.92 (severe sepsis), 038 (septicemia), 790.7 (bacteremia nosocomial), or 785.52 (septic shock). For patients to be included in the septic shock group, they had to receive blood pressure support with any of the following medications within 24 hours of positive blood culture: norepinephrine, phenylephrine, epinephrine, dopamine, dobutamine, or vasopressin. All patients had to receive appropriate initial antibiotic therapy, defined as antibiotics that had in vitro activity against the cultured organism (and were not single-agent aminoglycosides), that was administered within 12 hours of when a positive blood culture was drawn and continued for at least 24 hours. For extended-spectrum β-lactamase–producing organisms, initial use of a carbapenem was required to be classified as appropriate treatment. Antimicrobial susceptibilities were determined using disc diffusion methodology. MDR was defined as nonsusceptibility to at least one antimicrobial agent from at least three different antimicrobial classes (23). Appropriate antibiotics administered up to 12 hours before positive blood cultures were drawn were considered to have a time of administration of 0 minute. Patients with pathogens resistant to ampicillin were not considered to have received appropriate therapy if they received ampicillin/sulbactam.

Only the first episode of bacteremia during a hospitalization was considered. Patients who had an episode of bacteremia during their hospitalization prior to *Enterobacteriaceae* bacteremia were excluded (only two cases, one with *Staphylococcus epidermidis* and another with *Enterococcus*). The following organisms were considered contaminants if not recultured within 72 hours: coagulase-negative *Staphylococci*, *Corynebacterium*, *Propionibacterium acnes*, or Viridans group *Streptococcus*. Patients were excluded if they were under 18 years or if they had a blood culture positive for more than one organism. All patients who did not receive antibiotics within 12 hours of when positive blood cultures were drawn were excluded. Discharge on hospice was considered a mortality equivalent. All patients discharged on hospice were considered to expire at the time of hospital discharge. In the number of procedures analysis, codes for vasopressors and mechanical ventilation were not included in the final tally. Blood product administration was considered a procedure, but only one instance was counted. Otherwise, all ICD-9 procedure codes were considered in the number of procedures analysis. LOS was calculated from time a positive blood culture was drawn. Patients who never required ICU admission were considered to have an ICU stay length of 0 day. Healthcare exposure was defined as chemotherapy within the prior 30 days, residence in a nursing home or other long-term care facility, hospitalization in an acute care hospital for two or more days within the prior 90 days, or attendance at a hospital or hemodialysis clinic within the prior 30 days.

Thirty-day mortality was assessed using the BJC Healthcare informatics database. Barnes-Jewish Hospital serves as the main teaching institution for BJC Healthcare, a large integrated healthcare system of both inpatient and outpatient care. The system includes a total of 13 hospitals in a compact geographic region surrounding and including St. Louis, MO. Persons treated within this healthcare system are, in nearly all cases, readmitted to one of the system's participating hospitals or evaluated in a BJC Healthcare outpatient practice. If a patient who receives healthcare in the system presents to a nonsystem hospital, he/

she is often transferred back into the integrated system because of issues of insurance coverage. Death certificate records and autopsy reports are included in the informatics database. All data were derived from the informatics database provided by the Center for Clinical Excellence, BJC HealthCare.

Statistical Analysis

Thirty-day all-cause mortality was compared between the sepsis, severe sepsis, and septic shock groups. Univariate analysis was performed by chi-square or Fischer exact test where appropriate for categorical values. Student *t* test or Mann-Whitney *U* test was used where appropriate for continuous variables. Continuous variables were reported as means with SDs. Categorical data were expressed as frequencies. A *p* value of less than 0.05 was considered significant. Multivariate analysis comparing survivors and nonsurvivors was used to determine risk factors for mortality. Factors associated with mortality in univariate analysis ($p < 0.20$) were entered into a multivariate logistic regression analysis to determine odds ratios for mortality. All variables entered into the model were assessed for collinearity, and interaction terms were tested. Goodness-of-fit was assessed via the Hosmer-Lemeshow *c*-statistic. All tests were two-tailed. All analysis was done using SPSS v22 (IBM Corp., Armonk, NY).

RESULTS

Five hundred ten patients with sepsis, severe sepsis, or septic shock due to *Enterobacteriaceae* met the inclusion criteria. There were no cases with multiple episodes of *Enterobacteriaceae* bacteremia identified. Baseline characteristics of the patients are listed in **Table 1**. Patients with septic shock had the greatest

TABLE 1. Patient Characteristics According to Sepsis Severity and Survival Status

Characteristics	Sepsis (*n* = 172)	Severe Sepsis (*n* = 191)	Septic Shock (*n* = 147)	Survivors (*n* = 443)	Nonsurvivors (*n* = 67)	*p* Value (Survivors vs Nonsurvivors)
Age, yr	58.4 ± 15.9	61.9 ± 16.4[a]	59.6 ± 14.4	59.2 ± 16.0	65.2 ± 12.3	0.003
Male, % (*n*)	49.4 (85)	52.9 (101)	55.1 (81)	51.8 (229)	56.7 (38)	0.382
African-American, % (*n*)	25.6 (44)	37.2 (71)[a]	30.6 (45)	29.6 (131)	43.3 (29)	0.024
Mechanical ventilation, % (*n*)	0 (0)	16.2 (31)[a]	48.3 (71)[a,b]	16.0 (71)	46.3 (31)	< 0.001
Bone marrow transplant, % (*n*)	2.9 (5)	6.3 (12)	4.1 (6)	4.5 (20)	4.5 (3)	1
Solid-organ transplant, % (*n*)	3.5 (6)	5.2 (10)	3.4 (5)	4.5 (20)	1.5 (1)	0.338
Congestive heart failure, % (*n*)	9.9 (17)	14.1 (27)	21.8 (32)[a]	13.5 (60)	23.9 (16)	0.027
Chronic obstructive pulmonary disease, % (*n*)	10.5 (18)	15.2 (29)	20.4 (30)[a]	15.8 (70)	10.4 (7)	0.254
Diabetes mellitus, type 2, % (*n*)	25.0 (43)	30.4 (58)	32.0 (47)	28.9 (128)	29.9 (20)	0.872
Chronic kidney disease, % (*n*)	5.2 (9)	22.0 (42)[a]	12.2 (18)[a,b]	12.4 (55)	20.9 (14)	0.059
Renal replacement therapy, % (*n*)	1.2 (2)	2.6 (5)	6.1 (9)[a]	2.9 (13)	4.5 (3)	0.454
Solid-organ malignancy, % (*n*)	26.7 (46)	27.7 (53)	30.6 (45)	25.3 (112)	47.8 (32)	< 0.001
Leukemia, % (*n*)	19.2 (33)	20.4 (39)	15.6 (23)	20.1 (89)	9.0 (6)	0.029
Lymphoma, % (*n*)	5.8 (10)	6.3 (12)	5.4 (8)	5.6 (25)	7.5 (5)	0.555
Cirrhosis, % (*n*)	1.7 (3)	4.2 (8)	12.2 (18)[a,b]	3.6 (16)	19.4 (13)	< 0.001
Antibiotics within 30 d, % (*n*)	39.5 (68)	38.7 (74)	36.1 (53)	37.9 (168)	40.3 (27)	0.709
Healthcare exposure, % (*n*)	70.3 (121)	66.5 (127)	72.1 (106)	67.9 (301)	79.1 (53)	0.065
Multidrug resistance, % (*n*)	18.0 (31)	17.8 (34)	23.1 (34)	19.2 (85)	20.9 (14)	0.742
Time to appropriate antibiotics (hr)	3.6 ± 2.9	3.6 ± 3.2	3.0 ± 2.8[a]	3.4 ± 3.0	3.8 ± 3.2	0.314
Immunosuppressed, % (*n*)	37.2 (64)	38.7 (74)	33.3 (49)	36.8 (163)	35.8 (24)	0.877
Charlson Comorbidity Score	1.5 ± 1.2	1.8 ± 1.3[a]	1.5 ± 1.2	1.6 ± 1.3	2.0 ± 1.2	0.003
Acute Physiology and Chronic Health Evaluation II score	10.7 ± 3.6	12.5 ± 4.7[a]	17.6 ± 5.4[a,b]	12.8 ± 5.0	17.5 ± 6.2	< 0.001
Presence of multiple other pathogens, % (*n*)	5.2 (9)	11.0 (21)[a]	13.6 (20)[a]	9.5 (42)	11.9 (8)	0.528

(*Continued*)

TABLE 1. (*Continued*). Patient Characteristics According to Sepsis Severity and Survival Status

Characteristics	Sepsis (*n* = 172)	Severe Sepsis (*n* = 191)	Septic Shock (*n* = 147)	Survivors (*n* = 443)	Nonsurvivors (*n* = 67)	*p* Value (Survivors vs Nonsurvivors)
Patient origin, % (*n*)						
Nursing home, skilled nursing facility, or long-term acute care hospital	3.5 (6)	11.0 (21)[a]	11.6 (17)[a]	9.0 (40)	6.0 (4)	0.492
Community	67.4 (116)	49.7 (95)[a]	45.6 (67)[a]	55.5 (246)	47.8 (32)	0.233
Outside hospital	9.9 (17)	9.4 (18)	11.6 (17)	8.6 (38)	20.9 (14)	0.019
In hospital	19.2 (33)	29.8 (57)[a]	31.3 (46)[a]	26.9 (119)	25.4 (17)	0.797
Infection source, % (*n*)						
Central venous catheter	9.3 (16)	9.4 (18)	8.8 (13)	10.2 (45)	3.0 (2)	0.068
Genitourinary	40.7 (70)	43.4 (83)	42.2 (62)	42.4 (188)	40.3 (27)	0.741
Pulmonary	3.5 (6)	5.2 (10)	8.8 (13)[a]	4.7 (21)	11.9 (8)	0.177
Gastrointestinal	18.6 (32)	13.6 (26)	17.0 (25)	15.6 (69)	20.9 (14)	0.271
CNS	0 (0)	0.5 (1)	0.7 (1)	0.2 (1)	1.5 (1)	0.245
Skin/soft tissue	0.6 (1)	1.0 (2)	0.7 (1)	0.7 (3)	1.5 (1)	0.431
Unknown	25.6 (44)	25.6 (49)	21.1 (31)	24.8 (110)	20.9 (14)	0.484
Infected surgical vascular graft	0 (0)	1.0 (2)	0 (0)	0.5 (2)	0	1
Muscle	0.6 (1)	0 (0)	0 (0)	0.2 (1)	0	1
Joint	0 (0)	0 (0)	0.7 (1)	0.2 (1)	0	1
Osteomyelitis	0.6 (1)	0 (0)	0 (0)	0.2 (1)	0	1
Gynecologic	0.6 (1)	0 (0)	0 (0)	0.2 (1)	0	1

[a]$p < 0.05$ compared with sepsis group.
[b]$p < 0.05$ compared with severe sepsis group.
Values are reported as percentages (number) or mean value ± SD.

TABLE 2. Microbiology of *Enterobacteriaceae* Sepsis, Severe Sepsis, and Septic Shock

Pathogen	Sepsis, % (*n*)	Severe Sepsis, % (*n*)	Septic Shock, % (*n*)
Escherichia coli	57.5 (99)	55.5 (106)	52.4 (77)
Klebsiella pneumoniae	31.9 (55)	27.2 (52)	35.4 (52)
Klebsiella oxytoca	3.5 (6)	5.2 (10)	4.1 (6)
Enterobacter aerogenes	0 (0)	1.0 (2)	0.7 (1)
Enterobacter cloacae	2.9 (5)	4.2 (8)	2.0 (3)
Citrobacter freundii	0 (0)	0.5 (1)	0 (0)
Citrobacter koseri	0 (0)	0.5 (1)	0.7 (1)
Morganella morganii	0.6 (1)	0.5 (1)	0 (0)
Pantoea agglomerans	0.6 (1)	0 (0)	0 (0)
Hafnia alvei	0.6 (1)	0 (0)	0 (0)
Proteus mirabilis	2.3 (4)	0.5 (1)	3.4 (5)
Providencia stuartii	0 (0)	0 (0)	0.7 (1)
Serratia marcescens	0 (0)	0.5 (1)	0.7 (1)

APACHE II scores and need for mechanical ventilation. Time to appropriate initial antibiotic therapy was shortest for patients with septic shock. The distribution of pathogens is shown in **Table 2**. There was no significant difference in pathogen distribution according to sepsis classification. The most common organism was *E. coli*. There were no significant differences in the proportion of individual pathogens between survivors and nonsurvivors (data not shown). Among the 510 cases, 99 (19.4%) met MDR criteria. As the severity of sepsis increased, so did the LOS, ICU LOS, number of procedures, and mortality (**Table 3**). Kaplan-Meier curves confirmed that increasing sepsis severity was associated with greater 30-day mortality (**Fig. 1**). Total LOS, prevalence of MDR pathogens, and number of procedures performed were not significantly different between the survivors and nonsurvivors. Nonsurvivors had significantly longer ICU LOS (Table 3).

Age, Charlson Comorbidity Index, APACHE II, leukemia, cirrhosis, solid-organ malignancy, origin from an outside hospital, pulmonary source of infection, and congestive heart failure were significantly different between survivors and nonsurvivors in univariate analysis (Table 1). Time to antibiotic therapy after a positive blood culture was drawn did not differ between survivors and nonsurvivors. In multivariate analysis, patients who died were more likely to be African-American,

TABLE 3. Clinical Outcomes According to Sepsis Severity and Survival Status

Outcome	Sepsis	Severe Sepsis	Septic Shock	Survivors	Nonsurvivors
30-d mortality, % (*n*)	3.5 (6)	9.9 (19)[a]	28.6 (42)[a,b]		
Length of stay, d	9.2 ± 9.4	15.3 ± 14.7[a]	20.8 ± 22.6[a,b]	15.1 ± 17.2	13.1 ± 12.5
Length of ICU stay, d	2.5 ± 7.6	4.8 ± 10.9[a]	9.8 ± 13.2[a,b]	5.4 ± 11.4	6.1 ± 8.5[c]
Number of procedures	2.2 ± 2.1	3.2 ± 3.3[a]	5.5 ± 3.9[a,b]	3.4 ± 3.5	3.9 ± 3.3
Multidrug resistance, % (*n*)	18.0 (31)	17.8 (34)	23.1 (34)	19.2 (85)	20.9 (14)

[a]$p < 0.05$ compared with sepsis group.
[b]$p < 0.05$ compared with severe sepsis group.
[c]$p < 0.05$ compared with survivors.
Values are reported as percentages (number) or mean value ± SD.

have greater sepsis severity, have higher APACHE II scores, have solid-organ cancer, cirrhosis, and be transferred from an outside hospital (**Table 4**).

DISCUSSION

We found that sepsis severity predicted mortality among patients receiving appropriate initial antimicrobial therapy. The presence of MDR did not appear to influence outcome when the initial therapy was appropriate for the causative pathogen. Interestingly, patients with septic shock had a significantly shorter time to appropriate antibiotic administration than patients with sepsis alone, but still had significantly higher mortality. These results suggest that appropriate antimicrobials are insufficient to completely overcome the systemic calamity associated with septic shock. However, appropriate therapy is still crucial, as suggested by the low overall mortality in our cohort (13.1%) compared to studies with varying levels of appropriate empiric antimicrobial therapy (24). In the future, clinical trials should strive to provide appropriate antimicrobial therapy and take sepsis severity into careful account when determining outcomes. Unsurprisingly, as sepsis severity increased, LOS, ICU LOS, and number of procedures significantly increased. Length of stay was not statistically different between survivors and nonsurvivors, but this is likely a result of hospital stays truncated by death.

MDR was not statistically different when comparing sepsis severity groups nor between survivors and nonsurvivors. Past studies have posited that the presence of MDR leads to worse outcomes and possibly even conveys increased virulence (10, 25). Prior studies have shown that MDR is a risk factor for mortality in the setting of inappropriate initial antimicrobial therapy (26). Our study population included only patients who received appropriate antimicrobial therapy; we found no evidence of increased mortality due to MDR. Our data demonstrate that this increased mortality is negated with appropriate and timely antimicrobial therapy. The current paucity of agents to treat MDR pathogens limits our ability to administer appropriate initial therapy for many drug-resistant bacteria. Fortunately, there are quality improvement measures, improving molecular technologies, and new antimicrobials in the pipeline that provide hope to stay in step with increasing drug resistance (27–31).

African-American race as a risk factor for mortality is likely an unfortunate marker

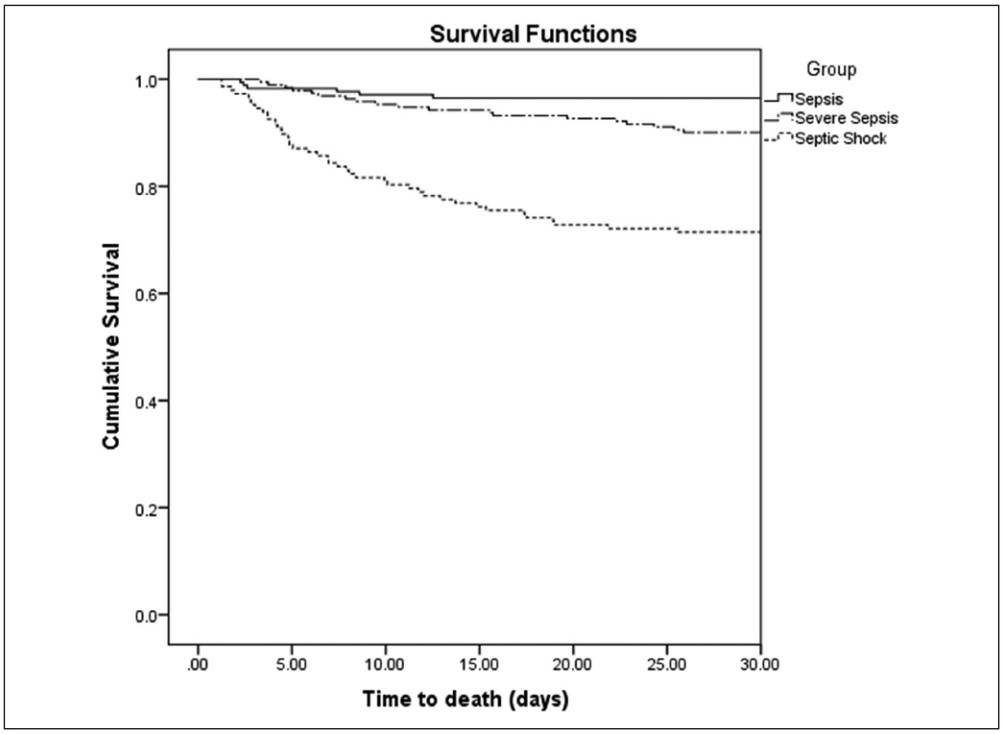

Figure 1. Kaplan-Meier curve for 30-d survival according to sepsis classification. Thirty-day survival was significantly lower for patients with septic shock ($p < 0.001$; log-rank test).

TABLE 4. Factors Associated With Mortality in Multivariate Logistic Regression Analysis

Factor	Odds Ratio (95% CIs)
Sepsis severity	2.07[a] (1.62–2.65)
African-American race	2.65 (1.93–3.66)
Acute Physiology and Chronic Health Evaluation II (1-point increments)	1.12 (1.09–1.15)
Solid-organ cancer	2.92 (2.14–3.97)
Cirrhosis	6.17 (3.82–9.97)
Patient origin from outside hospital	3.37 (2.21–5.12)

[a]Odds ratio for death between two groups (sepsis and severe sepsis, severe sepsis, and septic shock). When comparing sepsis and septic shock, the odds ratio is multiplied by two for each degree of separation.
Hosmer-Lemeshow *c*-statistic = 0.457.

for racial disparities in healthcare rather than a genetic predisposition. Transfer from an outside hospital may increase mortality because of the high level of acuity of patients transferred from institutions with limited resources. Increasing APACHE II scores, underlying malignancy, and cirrhosis have previously been shown to be independent risk factors for mortality in sepsis and reflect acute and chronic illness severity (1, 8, 26, 32).

Our study is limited in several ways. The retrospective nature of the study makes it difficult to elucidate possible confounders that could have biased the outcome measures. This was a single-center study, and results may not be generalizable to other centers. However, the lack of increased mortality with MDR pathogens should be applicable to other cohorts that have received appropriate therapy. We did not study outcomes in patients with Gram-positive infections or non-*Enterobacteriaceae* Gram-negative infections. It is possible that there would be different results in these populations and this is an area ripe for future studies. Another limitation is the method of determining 30-day mortality. It is possible that some patients died outside of the BJC Healthcare network and that we were unable to capture their mortality status. However, it is unlikely that this would have influenced our results given the clear signal observed between sepsis severity and outcome. We are also limited by a lack of antimicrobial minimum inhibitory concentration (MIC) data to determine if the administered antibiotics were therapeutic at a given MIC. However, our microbiology laboratory uses well-validated disc diffusion methodology to determine antimicrobial susceptibilities. Utilizing susceptibility data, our pharmacy uses an antimicrobial control program and reviews all antimicrobial orders as previously described (8), which minimizes inadequate therapy.

For ease of data collection and interpretation, we focused on culture-positive patients with sepsis. We recognize that historically, culture-negative patients fare better than their culture-positive counterparts. However, assessing antimicrobial appropriateness according to our definition was impractical without culture data. With improving molecular technologies, the number of culture-negative patients will likely decrease, thereby increasing the spectrum of patients who can be assessed for antimicrobial appropriateness. We are also limited in the assessment of differential outcomes based on specific pathogens due to the low frequency of infection with pathogens other than *E. coli* and *K. pneumoniae*.

In conclusion, severity of sepsis is an important predictor of mortality, even in patients who all receive appropriate initial antimicrobial therapy. In patients who receive appropriate initial therapy, we found no difference in outcome based on time to appropriate therapy, as long as it was administered within 12 hours after a positive culture was drawn. Our results will assist in the interpretation of outcomes in sepsis clinical trials. Additionally, physicians will now be better able to prognosticate for patient families with evidence to support the claim that the presence of shock quadruples the risk of death as compared with its absence, even in the setting of appropriate antimicrobials. Our findings suggest that appropriate initial antimicrobial therapy eliminates the impact of MDR on mortality, providing another impetus for improved diagnostics and antimicrobials for drug-resistant pathogens. Future studies can assess similar outcomes in patients with Gram-positive or Gram-negative non-*Enterobacteriaceae* sepsis.

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