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Micek, Scott T.; Hampton, Nicholas; and Kollef, Marin, ,"Risk factors and outcomes for ineffective empiric treatment of sepsis caused by gram-negative pathogens: Stratification by onset of infection." Antimicrobial agents and chemotherapy.62,1. e01577-17. (2017).
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CLINICAL THERAPEUTICS

Risk Factors and Outcomes for Ineffective Empiric Treatment of Sepsis Caused by Gram-Negative Pathogens: Stratification by Onset of Infection

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ABSTRACT Sepsis and septic shock remain serious consequences of infections, with reported mortality rates in excess of 40 percent. Timely antibiotic therapy in cases of sepsis and septic shock is recognized as an important determinant of outcome. However, the administration of ineffective empirical treatment (IET) (an initial antibiotic regimen that is not active against the identified pathogen[s] based on *in vitro* susceptibility testing results) is associated with excess mortality compared to effective empirical treatment (EET). We examined all hospitalized patients at Barnes-Jewish Hospital with a sterile site (blood or pleural, abdominal, cerebrospinal, synovial, and pericardial fluid) culture positive for Gram-negative (GN) bacteria combined with a primary or secondary ICD-9-CM code for severe sepsis (995.92) or septic shock (785.52) between January 2010 and October 2015. Variables significantly associated with early-onset (<48 h of hospitalization) IET of GN sterile site sepsis and septic shock included age, recent hospitalization, and prior intravenous antibiotics. Late-onset IET was associated with increasing numbers of hospitalization days before infection onset and prior intravenous antibiotic administration. For patients with early-onset infection, we found no difference in rates of survival between patients receiving IET and EET. However, patients in the late-onset infection group receiving IET had a statistically lower rate of survival than those receiving EET. These data suggest that risk factors and outcomes for IET can vary based on the time of onset of infection. Our results also highlight the importance of prior intravenous antibiotic exposure as a risk factor for IET in infections by GN bacteria regardless of the time of onset of infection.

KEYWORDS Gram-negative, sepsis

Sepsis and septic shock remain deadly clinical entities despite treatment with antimicrobials due in large part to the resistance of the underlying pathogens and associated ineffective empirical treatment (IET) (1–4). The challenge to clinicians treating patients with sepsis is to determine which microorganisms should be covered with the initial antibiotic regimen. Traditionally, this has been accomplished with knowledge of the pathogens causing infections at the local hospital level, along with their antimicrobial susceptibilities, and the assessment of specific patient types likely to benefit from empirical broad-spectrum antibiotics (5–7). Unfortunately, the use of specific risk factors for analysis has been shown to result in limited overall accuracy in determining the need for broad-spectrum antibiotic therapy and can result in unnecessary use of such agents (8). To further address this important issue, we performed a cohort study to identify risk factors for IET of sepsis and septic shock caused by Gram-negative (GN) bacteria on the basis of the time of onset of infection. The rationale

Received 1 August 2017 **Returned for modification** 15 September 2017 **Accepted** 30 October 2017

Accepted manuscript posted online 6 November 2017

Citation Micek ST, Hampton N, Kollef M. 2018. Risk factors and outcomes for ineffective empiric treatment of sepsis caused by gram-negative pathogens: stratification by onset of infection. Antimicrob Agents Chemother 62:e01577-17. https://doi.org/10.1128/AAC.01577-17.

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TABLE 1 Baseline characteristics of study population[a]

Characteristic	Value(s) for indicated time of onset							
	Early (n = 520)				Late (n = 335)			
	Missing data, %	Ineffective therapy (n = 61)	Effective therapy (n = 459)	P value	Missing data, %	Ineffective therapy (n = 79)	Effective therapy (n = 256)	P value
Age (yrs) (mean ± SD)	0	64.7 ± 15.1	61.9 ± 14.1	0.154	0	59.0 ± 14.5	57.5 ± 14.9	0.409
Males	0	31 (50.8)	246 (53.6)	0.685	0	43 (54.4)	159 (62.1)	0.238
Race	6.7				6.6			
African-American	0	20 (32.8)	143 (31.2)	0.771	0	18 (22.8)	47 (18.4)	0.417
Caucasian	0	34 (55.7)	282 (61.4)	0.405	0	56 (70.9)	180 (70.3)	1.000
Medical condition								
Congestive heart failure	0	18 (29.5)	132 (28.8)	0.881	0	28 (35.4)	89 (34.8)	1.000
Chronic obstructive pulmonary disease	0	16 (26.2)	143 (31.2)	0.464	0	25 (31.6)	78 (30.5)	0.889
Dementia	0	0 (0)	13 (2.8)	0.381	0	1 (1.3)	2 (0.8)	0.555
Cirrhosis	0	18 (29.5)	133 (29.0)	1.000	0	29 (36.7)	82 (32.0)	0.494
Chronic kidney disease	0	27 (44.3)	152 (33.1)	0.088	0	27 (34.2)	77 (30.1)	0.490
Diabetes mellitus	0	22 (36.1)	179 (39.0)	0.780	0	30 (38.0)	79 (30.9)	0.272
Underlying malignancy	0	21 (34.4)	165 (35.9)	0.887	0	42 (53.2)	140 (54.7)	0.897
Human immune deficiency virus infection	0	0 (0)	7 (1.5)	1.000	0	2 (2.5)	2 (0.8)	0.237
Charlson comorbidity index, median (IQR)	3.5	7 (4–9)	6 (4–8)	0.046	0.9	6 (4–8.75)	5 (4–8)	0.083
Prior[b] hospitalization	0	46 (75.4)	228 (49.7)	<0.001	0	27 (34.2)	114 (44.5)	0.118
Receipt of antipseudomonal antibiotics prior to hospitalization	3.5	26 (51.0)	109 (24.2)	<0.001	0.9	22 (28.9)	56 (21.9)	0.219
Prior isolation of a Gram-negative organism	0	2 (3.3)	11 (2.4)	0.657	0	26 (32.9)	49 (19.1)	0.013
Direct ICU admission	0	26 (44.8)	199 (43.4)	0.889	0	27 (34.2)	58 (22.7)	0.054
Direct oncology admission	0	7 (11.5)	54 (11.8)	1.000	0	23 (29.1)	104 (40.6)	0.084
Median (IQR) no. of hospital days prior to infection	0	0 (0–0)	0 (0–0)	0.749	0	18 (8–30)	13 (8–24)	0.075
ICU prior to infection	0	6 (9.8)	21 (4.6)	0.114	0	48 (60.8)	113 (44.1)	0.010
Ventilator prior to infection	0	1 (1.6)	7 (1.5)	1.000	0	38 (48.1)	96 (37.5)	0.115
CVC prior to infection	0	6 (9.8)	37 (8.1)	0.621	0	71 (89.9)	234 (91.4)	0.656
Urinary catheter prior to infection	0	5 (8.2)	27 (5.9)	0.407	0	56 (70.9)	138 (53.9)	0.009
Prior antipseudomonal cephalosporin during admission	0	0	9 (2.0)	0.608	0	45 (57.0)	120 (46.9)	0.124
Prior carbapenem during admission	0	2 (3.3)	6 (1.3)	0.239	0	43 (54.4)	60 (23.4)	<0.001
Prior beta-lactam/beta-lactamase inhibitor during admission	0	0	6 (1.3)	1.000	0	26 (32.9)	45 (17.6)	0.007
Prior fluoroquinolone during admission	0	0	2 (0.4)	1.000	0	18 (22.8)	40 (15.6)	0.173
Prior aminoglycoside during admission	0	0	5 (1.1)	1.000	0	17 (21.5)	20 (7.8)	0.002
Prior nonantipseudomonal cephalosporin during admission	0	0	4 (0.9)		0	21 (26.6)	58 (22.7)	0.544
Organ dysfunction during admission	0				0			
Cardiovascular/shock		40 (65.6)	317 (69.1)	0.561		64 (81.0)	188 (73.4)	0.173
Respiratory		20 (32.8)	168 (36.6)	0.671		62 (78.5)	163 (63.7)	0.014
Hematologic		20 (32.8)	167 (36.4)	0.671		41 (51.9)	125 (48.8)	0.700
Renal		40 (65.6)	328 (71.5)	0.369		52 (65.8)	184 (71.9)	0.303
Hepatic		4 (6.6)	33 (7.2)	1.000		14 (17.7)	36 (14.1)	0.470

[a]Data represent number (percent) of patients unless otherwise indicated. CVC, central vein catheter; ICU, intensive care unit; IQR, interquartile range.
[b]Prior, within the previous 90 days.

for this study was to determine if the risk factors for IET among patients who were more likely to have community-acquired infections differed from the risk factors for those developing hospital-acquired infections.

RESULTS

We identified 855 consecutive patients with severe sepsis (n = 246; 28.8%) or septic shock (n = 609; 71.2%) due to infection of a sterile site (blood or pleural, abdominal, cerebrospinal, synovial, and pericardial fluid) by GN bacteria. Early infection occurred in 520 patients (60.8%) and late infection in 225 patients (39.2%). The median (interquartile range) time to infection in patients with late infection was 14 days (8 to 25). The baseline characteristics obtained are shown in Tables 1 and 2.

IET occurred in 61 (11.7%) patients with early-onset infection and was associated with a significantly higher Charlson comorbidity index, more prior hospitalization, and a higher incidence of intravenous antipseudomonal antibiotic therapy prior to admission (Table 1). Patients in the early-onset infection category that received IET were significantly more likely to be infected with *Enterobacter* sp. or *Stenotrophomonas*

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TABLE 2 Infection-related characteristics[a]

Characteristic	Value(s) for indicated time of onset							
	Early (n = 520)				Late (n = 335)			
	Missing data, %	Ineffective therapy (n = 61)	Effective therapy (n = 459)	P	Missing data, %	Ineffective therapy (n = 79)	Effective therapy (n = 256)	P
Culture site								
Abdominal fluid	0	8 (13.1)	43 (9.4)	0.359	0	21 (28.6)	24 (9.4)	<0.001
Blood	0	53 (86.9)	419 (91.3)	0.245	0	56 (70.9)	231 (90.2)	<0.001
Pleural fluid	0	3 (4.9)	7 (1.5)	0.101	0	3 (3.8)	6 (2.3)	0.445
Other sterile site	0	0	2 (0.4)	1.000	0	0	1 (0.4)	1.000
Pathogens								
Achromobacter sp.	0	2 (3.3)	2 (0.4)	0.070	0	2 (2.5)	1 (0.4)	0.140
Acinetobacter sp.	0	4 (6.6)	12 (2.6)	0.106	0	9 (11.4)	4 (1.6)	<0.001
Burkholderia sp.	0	1 (1.6)	0	0.117	0	5 (6.3)	2 (0.8)	0.009
Citrobacter sp.	0	0	6 (1.3)	1.000	0	2 (2.5)	7 (2.7)	1.000
Enterobacter sp.	0	12 (19.7)	34 (7.4)	0.006	0	11 (13.9)	35 (13.7)	1.000
E. coli	0	20 (32.8)	200 (43.6)	0.129	0	8 (10.1)	75 (29.3)	<0.001
Klebsiella sp.	0	11 (18.0)	111 (24.2)	0.337	0	10 (12.7)	72 (28.1)	0.004
Proteus sp.	0	2 (3.3)	34 (7.4)	0.294	0	1 (1.3)	6 (2.3)	1.000
Pseudomonas aeruginosa	0	12 (19.7)	71 (15.5)	0.456	0	13 (16.5)	65 (25.4)	0.127
Serratia sp.	0	0	10 (2.2)	0.615	0	2 (2.5)	14 (5.5)	0.377
Stenotrophomonas maltophilia	0	3 (4.9)	3 (0.7)	0.024	0	22 (27.8)	0	<0.001
Antibiotic resistance								
Cefepime	0	26 (42.6)	9 (2.0)	<0.001	0	47 (59.5)	18 (7.0)	<0.001
Meropenem	0	17 (27.9)	8 (1.7)	<0.001	0	41 (51.9)	11 (4.3)	<0.001
Piperacillin-tazobactam	5.7	26 (44.8)	68 (14.8)	<0.001	0.8	41 (68.3)	69 (27.0)	<0.001
Gentamicin	0	19 (31.1)	31 (6.8)	<0.001	0	46 (58.2)	17 (6.6)	<0.001
Ciprofloxacin	0	34 (55.7)	87 (19.0)	<0.001	0	47 (59.5)	44 (17.2)	<0.001
Ceftriaxone	0	54 (88.5)	132 (28.8)	<0.001	0	72 (91.1)	124 (48.8)	<0.001
Multidrug resistant	0	22 (36.1)	10 (2.2)	<0.001	0	47 (59.5)	14 (5.5)	<0.001

[a]Ineffective therapy data and effective therapy data represent number (percent) of patients.

maltophilia (Table 2). IET occurred in 79 (23.6%) patients with late-onset GN sterile site infection. Patients receiving IET in the late-onset infection category were significantly more likely to have had a prior isolation of a GN organism. In addition, intensive care unit (ICU) admission prior to GN sterile site infection; insertion of a urinary catheter prior to infection; receipt of intravenous carbapenem, a beta-lactam/beta-lactamase inhibitor, or aminoglycoside antibiotics; and respiratory failure occurred in significantly more IET patients in the late-onset infection category (Table 1). Patients with late-onset infection receiving IET were significantly less likely to have a bloodstream infection and to be infected with *Escherichia coli* and/or *Klebsiella* sp. In contrast, these patients were significantly more likely to have a positive abdominal fluid culture, and to be infected by *Acinetobacter* sp., *Burkholderia* sp., and/or *Stenotrophomonas maltophilia* (Table 2).

Multivarite logistic regression analysis (MVLRA) revealed that the factors that were independently associated with IET in patients with early-onset infection were different from those independently associated with IET in patients with late-onset infection. In patients with early-onset GN sterile site infection, the odds of receiving IET increased 2.5% with each increase in year of age and increased over 2-fold if the patient had previously been hospitalized or had received intravenous antipseudomonal beta-lactam antibiotics in the 90 days prior to admission. Factors independently associated with IET in the late-onset infection group were days of hospitalization prior to infection and receipt of intravenous carbapenem or beta-lactam/beta-lactamase inhibitor antibiotics in the 90 days prior to infection (Table 3). Both models demonstrated good fit based on the Hosmer-Lemeshow c-statistic P values (early, $P = 0.295$; late, $P = 0.463$). Kaplan-Meier curves comparing rates of survival between patients receiving IET and EET showed no difference in mortality in the early-onset infection group (Fig. 1A). Kaplan-Meier curves for patients with late-onset infection demonstrated that patients receiving IET had a statistically lower survival rate than patients receiving EET (Fig. 1B).

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TABLE 3 Risk factors for ineffective therapy, as determined by multivariate logistic regression[a]

Factor	Adjusted odds ratio (95% confidence interval)
Early infection	
Age	1.025 (1.002–1.048)
Hospital admission in the previous 90 days	2.257 (1.010–5.043)
Receipt of intravenous antipseudomonal beta-lactam antibiotics[b]	2.365 (1.159–4.826)
Late infection	
No. of days to isolation of a GN pathogen	1.018 (1.001–1.037)
Receipt of intravenous carbapenem antibiotics prior to isolation of a GN pathogen	5.726 (2.854–11.486)
Receipt of intravenous beta-lactam/beta-lactamase inhibitor antibiotics prior to isolation of a GN pathogen[b]	2.171 (1.119–4.212)

[a]Hosmer-Lemeshow c-statistic: early infection, $P = 0.295$; late infection, $P = 0.463$. GN, Gram-negative.
[b]In the 90 days prior to the onset of infection.

DISCUSSION

Our findings confirm the importance of prior intravenous antibiotic exposure as a risk factor for infection with antibiotic-resistant bacteria promoting IET (6, 9). We also demonstrated that the risk factors and outcomes for IET differ according to the onset of infection. The occurrence of a prior hospitalization for early-onset infections and days of hospitalization prior to infection for late-onset infections both represent greater exposure to the health care system. By increasing patient exposure to the health care system, the likelihood of patient colonization and subsequent infection with antibiotic-resistant bacteria is increased (6). Interestingly, hospital survival was impacted by IET only in patients in the late-onset infection group. This may be related to these infections occurring in individuals who are already hospitalized for other acute medical and surgical conditions and are thus at greater risk for mortality from IET due to the immune suppression resulting from their underlying disease process (10). Our results also highlight the complexity of identifying septic patients who are at risk for receiving IET due to the differences in risk factors for those with community-acquired infections compared to those with hospital-acquired infections.

Empirical antibiotic treatment of severe GN infections, especially in hospitals, where the presence of antibiotic-resistant infections is commonplace, can be problematic. On the one hand, clinicians desire to provide effective initial treatment to patients with serious infections in order to maximize clinical outcomes while trying to avoid the unnecessary use of broad-spectrum antibiotics in order to minimize the further emergence of resistance (11). Although we identified prior intravenous antibiotic exposure as a risk factor for IET regardless of the time of infection onset, its identification may be problematic, particularly for patients who received antibiotic therapy at a different hospital or in an outpatient setting. Most of the patients in our study had community-acquired infections necessitating knowledge of the history of prior intravenous antibiotic administration at the time of hospital admission. Unfortunately, many patients and their families may not know whether they received intravenous antibiotics in the previous 90 days or may not have the capacity to remember such treatment. Medical records from outside hospitals or outpatient treatment facilities are also frequently not available when antibiotic decision-making occurs for patients newly admitted to the hospital setting. For these reasons, surrogate markers for prior antibiotic exposure such as prior hospitalization and residence in a nursing facility have been advocated for as markers for high-risk infection with antibiotic-resistant bacteria and for the need for broad-spectrum antibiotic therapy (12). However, the use of these risk factors to guide the prescription of broad-spectrum antibiotics has been criticized for promoting unnecessary use of these agents and potentially encouraging the emergence of further antimicrobial resistance (13–15). Nevertheless, health care-associated infections are common in the United States, with the Centers for Disease Control and Prevention

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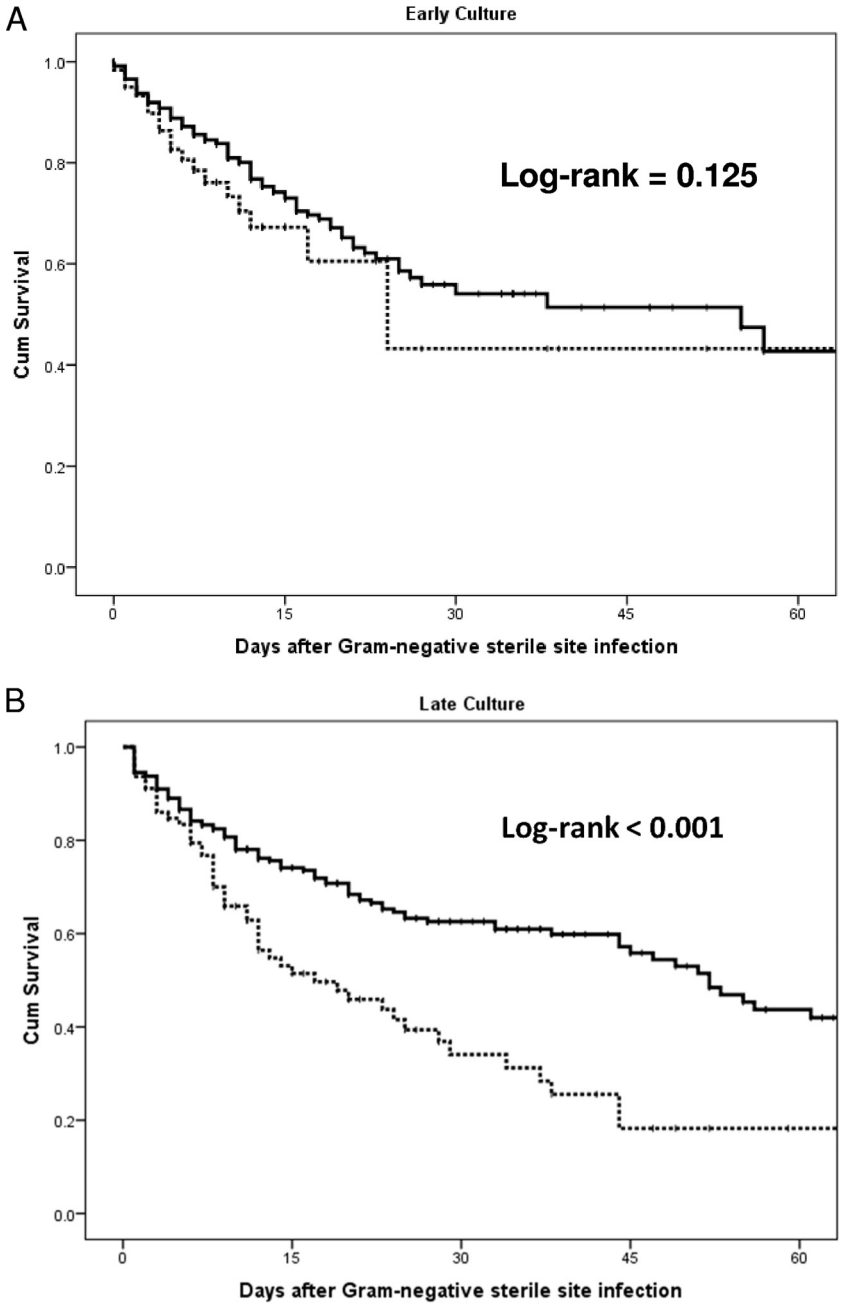

FIG 1 Kaplan-Meier curves for cumulative survival (Cum Survival), with the solid line representing patients who received effective therapy and the hatched line representing patients who received ineffective therapy. (A) Early culture group. (B) Late infection group.

estimating that more than 720,000 health care-associated infections occur in the United States per year, with many of these being attributed to antibiotic-resistant pathogens (16). This figure highlights the potential number of individuals for whom empirical antibiotic prescription is problematic.

We and others have utilized various statistical methods in an attempt to develop tools for guidance of administration of broad-spectrum antibiotics (5–7, 17–19). These algorithms were developed with the primary goal of improving upon the identification of patients with serious infections, primarily pneumonia and bacteremia, attributed to antibiotic-resistant bacteria. Given the limitations of methods for accurately identifying patients with serious infections attributed to antibiotic-resistant bacteria, the use of

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rapid molecular diagnostics has been advocated as a means of more precisely selecting empirical antibiotic treatment for such patients (20). Emerging data suggest that patient outcomes, as well as enhancement of antimicrobial stewardship practices, can be achieved with the use of these new technologies (21–23). Our study may provide guidance for identifying which patients might benefit the most from the application of these diagnostics. Patients identified to be at risk for IET, due to the prior administration of intravenous antibiotics, would be a reasonable group for the application of rapid diagnostics in order to confirm the need for broad-spectrum antibiotics and to avoid their unnecessary use when the presence of resistant bacteria has not been not identified (24).

Several limitations of our study should be recognized. First, the retrospective design did not allow determination of the exact cause of mortality. Furthermore, it is possible that we did not identify all cases of severe infections attributed to GN bacteria given the constraints of our definition. Second, the data were derived from a single center, and this necessarily limited the generalizability of our findings. As such, our results may not reflect what one might see at other institutions. For example, Barnes-Jewish Hospital has a regional 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, the selection of the 48-h threshold for early-onset infection was based on our desire to compare individuals with community-acquired infection to those having hospital-acquired infections and on the availability of pathogen identification and antimicrobial susceptibility testing (AST) at our institution. It is possible that our results would have differed had we selected a different threshold for separating early-onset infection from late-onset infection.

Another limitation of our study was that we performed multiple statistical analyses whereby some associations may have occurred by chance. Therefore, these findings should be interpreted with caution. For example, we found that early-onset IET was associated with prior intravenous administration of antipseudomonal beta-lactam antibiotics whereas late-onset IET was associated with prior administration of intravenous carbapenems and beta-lactam/beta-lactamase inhibitor antibiotics. These findings were likely a function of the differences in the predominant classes of intravenous antibiotics that patients received in the time period prior to their hospital admission and during the course of their index hospital stay, respectively. The more important results and conclusions from these data relate to the common link of prior intravenous antibiotic exposure to the development of IET regardless of the timing of the infection.

In conclusion, we confirmed the importance of prior intravenous antibiotic exposure as a risk factor for the administration of IET. Clinicians prescribing antibiotics to patients with serious infections likely caused by GN bacteria should attempt to identify the presence of this risk factor, especially among patients with late-onset or hospital-acquired infections. More importantly, there is an urgent need to identify better methods to guide the use of empirical therapy in patients with potentially life-threatening bacterial infections in this era of increasing antimicrobial resistance. Further investigation of rapid microbiologic diagnostics techniques should include studies aimed at improving the prescription of empirical antibiotic therapy in patients with suspected GN bacterial sepsis and septic shock.

MATERIALS AND METHODS

Study population and data source. This study was conducted at Barnes-Jewish Hospital, an academic referral center with 1,300 beds. The investigation was approved by the Institutional Review Boards of Washington University and the St. Louis College of Pharmacy, and the need for informed consent was waived. All patients hospitalized between January 2010 and October 2015 who showed the presence of a sterile site (blood or pleural, abdominal, cerebrospinal, synovial, and pericardial fluid) culture positive for GN bacteria combined with primary or secondary ICD-9-CM codes for severe sepsis (995.92) or septic shock (785.52) were eligible for inclusion. Data were collected from the hospital's electronic health record system provided by the Center for Clinical Excellence, BJC Healthcare.

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Study outcomes. The primary objective of this study was to identify the occurrence of early-onset and late-onset IET. The secondary objective of this study was to identify variables predicting IET among patients with early-onset and late-onset GN bacterial infection.

Definitions and study design. All definitions were prospectively selected prior to study initiation. Patients were categorized as early-onset infection if the GN pathogen was isolated within 48 h of hospital admission and late-onset infection if the GN pathogen was isolated after 48 h. IET was defined as an initial antibiotic regimen that was not active against the identified pathogen(s) based on *in vitro* susceptibility testing. Patients that were infected with an extended-spectrum-β-lactamase (ESBL)-producing organism(s) had to have received a carbapenem to be categorized as EET patients. Similarly, patients infected with organisms likely to produce AmpC β-lactamase (*Enterobacter* species, *Serratia* species, *Citrobacter freundii*) who initially received piperacillin-tazobactam were categorized as IET patients given that exposure to this antibiotic can lead to high-level expression of this enzyme, which can in turn lead to resistance or enhanced selection of resistant mutants during therapy. Only the first episode of sterile site infection was evaluated, but, in cases in which a GN pathogen(s) was isolated simultaneously from multiple sites (i.e., abdominal fluid and blood), all of the sites were accounted for in the results. Patients were excluded if an organism other than a GN species was isolated. For polymicrobial GN infections, the initial antimicrobial regimen had to be active against all pathogens to be classified as EET.

Prior intravenous antibiotic exposure was assessed using the BJC Healthcare Informatics database. Barnes-Jewish Hospital is the main teaching institution for BJC Healthcare, a large integrated health care system of both inpatient and outpatient care facilities. The system includes 13 hospitals in a compact geographic region surrounding and including St. Louis, MO. Barnes-Jewish Hospital has >50,000 admissions annually and the BJC system >140,000.

Antimicrobial monitoring. From January 2002 through the present, Barnes-Jewish Hospital utilized an antibiotic control program to help guide antimicrobial therapy for bacterial infections. During that time period, the use of cefepime, gentamicin, or vancomycin was unrestricted. However, initiation of intravenous ciprofloxacin, imipenem, meropenem, piperacillin-tazobactam, linezolid, ceftolazone-tazobactam, ceftazidime-avibactam, or daptomycin administration was restricted and required preauthorization from either a clinical pharmacist or an infectious diseases physician. Each intensive care unit (ICU) and the emergency department had a clinical pharmacist who reviewed all antibiotic orders to ensure that the dosing and interval of antibiotic administration were adequate for individual patients based on body size, renal function, and the resuscitation status of the patient. After daytime hours, the on-call clinical pharmacist or infectious diseases physician reviewed and approved the antibiotic orders.

The initial antibiotic dosages employed for the treatment of bacterial infections at the Barnes-Jewish Hospital were as follows: cefepime, 1 to 2 g every 8 h; piperacillin-tazobactam, 4.5 g every 6 h; imipenem, 0.5 g every 6 h; meropenem, 1 to 2 g every 8 h; ciprofloxacin, 400 mg every 8 h; gentamicin, 5 mg/kg of body weight once daily; vancomycin, 15 mg/kg every 12 h; linezolid, 600 mg every 12 h; ceftolazone-tazobactam, 1.5 g every 8 h; ceftazidime-avibactam, 2.5 g every 8 h; daptomycin, 6 mg/kg every 24 h (daptomycin was not prescribed for pneumonia).

Empirical therapy for patients with identified risk factors for infection with antibiotic-resistant GN bacteria in the ICUs and emergency department of Barnes-Jewish Hospital usually consists administration of an antipseudomonal penicillin (pipercillin-tazobactam) or a fourth-generation cephalosporin (cefepime) or a carbapenem (meropenem). An aminoglycoside is often also administered as a single dose in patients with septic shock and can be continued beyond the first 24 to 48 h depending on the patient's clinical response and availability of antimicrobial susceptibility data (25, 26).

Antimicrobial susceptibility testing and local antibiogram. The microbiology laboratory of Barnes-Jewish Hospital uses a VersaTREK automated microbial detection system (ThermoFisher Scientific, Waltham, MA) for blood and sterile site cultures and a Bruker BioTyper matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) system (Bruker, Billerica, MA) for pathogen identification. Antimicrobial susceptibility testing (AST) of the bacterial isolates was performed using the disk diffusion method according to guidelines and breakpoints established by the Clinical Laboratory and Standards Institute and published during the inclusive years of the study (27). All classifications of antibiotic resistance were based on *in vitro* susceptibility testing using these established breakpoints. Although the time to AST is highly variable, AST is available for most cases of infections by GN bacteria within 48 h of the culture signaling positive.

We recently published our data on the susceptibility patterns for GN bacterial infection causing sepsis and septic shock in bacteremic patients (19). Resistance to pipercillin-tazobactam was found in 462 (28.6%) of the isolates, while 352 (21.8%) were resistant to cefepime and 138 (8.5%) were resistant to carbapenems. A total of 153 isolates were resistant to both pipercillin-tazobactam and cefepime, and 106 (6.6%) were resistant to all 3 drugs of interest. The rate of extended-spectrum-β-lactamase identification was 3.3% (54 of 1,618 isolates), and the rate of carbapenase producers was 0.5% (8 of 1,618 isolates).

Data collection and statistical analysis. We collected data on demographic characteristics (age, race, and sex), comorbidities of interest (hemodialysis, immunosuppression, Charlson score, previous hospitalizations, and prior antibiotic therapy), clinical features (need for vasopressors or mechanical ventilation, central vein catheter, duration of hospitalization before bacteremia), microbiology (culture results and antibiotic susceptibility), treatment variables, and outcomes (hospital mortality).

Continuous variables were reported as means with standard deviations or medians with 25th and 75th percentiles according to the distribution. The Student *t* test was used for comparing normally distributed data, and the Mann-Whitney U test was employed to analyze non-normally distributed data. Categorical data were expressed as frequency distributions, and the chi-square or Fisher's exact test was

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used to determine if differences existed between groups. The relationship between IET and hospital mortality was evaluated by the use of the Kaplan-Meier method and the log rank test. We performed univariate analysis and MVLRA to identify risk factors associated with IET. All risk factors that were significant at 0.20 in the univariate analyses were included in the corresponding multivariable analyses. All variables entered into the models were examined for colinearity using the variance inflation factor (VIF) as a colinearity statistic. The model's goodness of fit was assessed via determination of the Hosmer-Lemeshow c-statistic. All tests were two-tailed, and a P value of <0.05 represented statistical significance (IBM SPSS Statistics, version 22.0 [SPSS]).

ACKNOWLEDGMENTS

The work performed by M.K. was supported by the Barnes-Jewish Hospital Foundation. This work was supported by an unrestricted grant from Merck. The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

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