2019

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Open Forum Infectious Diseases

BRIEF REPORT

Pathogen-Negative Sepsis—An Opportunity for Antimicrobial Stewardship

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Sepsis is a common reason for empiric antibiotics among hospitalized patients. We found that the median duration of empiric antibiotics (interquartile range) was 6 (4–9) days among 1047 survivivors with pathogen-negative sepsis. These findings suggest that patients with pathogen-negative sepsis could represent an important opportunity for antimicrobial stewardship.

Keywords. pathogen-negative; sepsis; stewardship.

Sepsis is the most common indication for treatment with empiric antibiotics among hospitalized patients [1, 2]. At the same time that sepsis makes up a greater proportion of the conditions cared for within intensive care units (ICUs), the rates of antimicrobial resistance have increased [3]. Given the success of sepsis bundles to improve patient outcomes, the Surviving Sepsis Campaign Guidelines now recommend broad-spectrum antibiotics within 1 hour of presentation in all patients with suspected sepsis [4, 5]. Unfortunately, these recommendations fail to acknowledge the difficulties in establishing an accurate diagnosis of sepsis attributed to underlying infection, the adverse effects of routine antimicrobial administration, whether broad-spectrum antibiotic therapy is necessary in all patients with presumed sepsis, and whether the administered antibiotic regimen is active against the offending pathogens [6, 7].

A recent study found that 89% of patients meeting study inclusion criteria for sepsis were pathogen-negative [8]. These same investigators showed that patients with pathogen-negative sepsis had only slightly shorter durations of postsepsis hospitalization, compared with pathogen-positive patients, during which empiric antibiotic therapy would presumably have been admninistered [8]. The large percentage of pathogen-negative patients with sepsis and recent calls to treat such patients within 1 hour of presentation suggest that more patients with pathogen-negative sepsis will receive empiric antibiotic therapy. Therefore, we performed a retrospective cohort study to better understand the potential opportunity for antimicrobial stewardship among patients with pathogen-negative sepsis.

METHODS

This study was conducted at Barnes-Jewish Hospital, a 1250-bed academic medical center located in St. Louis, Missouri. The study period was January 1, 2010, through December 31, 2017. All consecutive hospitalized patients with sepsis during the study period were analyzed for eligibility. This study was approved by the Washington University School of Medicine Human Studies Committee.

Utilizing a retrospective cohort study design from a previously validated database, all patients age ≥18 with sepsis were identified. Patients were included only if they had international classification of diseases (ICD)-9 (995.92 and 785.52) and ICD-10 (R65.20 and R65.21) codes indicative of severe sepsis or septic shock. Only the first episode of sepsis was evaluated. Baseline characteristics included age, gender, race, Acute Physiology and Chronic Health Evaluation (APACHE) II scores (calculated based on clinical data present during the 24 hours after starting empiric antibiotics), Charlson Comorbidity Index, and medical comorbidities. The start time for empiric antibiotics relative to the diagnosis of sepsis was determined using the difference in calendar days from obtaining microbiologic cultures (blood, urine, respiratory, other sterile sites including viral cultures and/or viral polymerase chain reaction) to the start of empiric antibiotics for presumed sepsis. Total duration of empiric antibiotic therapy was assessed by counting calendar days of inpatient intravenous antibiotic therapy after clinical diagnosis of sepsis.

To be included in the study, patients had to receive empiric intravenous antibiotics targeting likely community-acquired or health care–acquired pathogens based on the treating physician's assessment. Identification of the site of infection as the source of sepsis was based on review of the medical record. When the site of infection was described as unknown or undocumented in the medical record, it was recorded as such. Discharge on hospice was considered a mortality equivalent. All data were derived from the informatics database provided by the Center for Clinical Excellence, BJC HealthCare.

We compared antibiotic treatment duration between pathogen-negative survivors receiving ≤3 days, 4–7 days, and >7 days of antibiotics for presumed sepsis. Univariate analysis

Received 8 July 2019; editorial decision 4 September 2019; accepted 5 September 2019.

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Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofz397

was performed by chi-square or Fisher exact test where appropriate for categorical values. The Student *t* test, Mann-Whitney *U* test, or Kruskal-Wallis test was used where appropriate for continuous variables. Continuous variables were reported as means with standard deviations or medians with interquartile ranges. Categorical data were expressed as frequencies. A *P* value of <.05 was considered significant. All tests were 2-tailed. All analyses were done using SPSS, version 24.

RESULTS

During the study period, 1486 consecutive pathogen-ngative patients with sepsis were identified, with 1047 survivors. Hospital mortality was 29.5% (439 nonsurvivors). Nonsurvivors had greater APACHE II scores (median [interquartile range {IQR}], 20 [16–24] vs 14 [11–18]; $P < .001$), Charlson Comorbidity Index scores (median [IQR], 5 [3–7] vs 4 [2–6]; $P < .001$), and significantly lower total antibiotic days (median [IQR], 4 [2–7] vs 6 [4–9] days; $P < .001$) and hospital duration (median [IQR], 6 [3–11] vs 8 [5–14] days; $P < .001$).

Among the 1047 pathogen-negative survivors, the duration of empiric antibiotic therapy had a wide range (median [IQR], 6 [4–9] days). Greater APACHE II scores and Charlson Comorbidity Index scores occurred with increasing duration of empiric therapy (Table 1). Patients receiving mechanical ventilation also received longer courses of empiric antibiotics. Ventilator days, ICU days, hospital length of stay, and discharge to a nursing facility were greater among patients receiving more prolonged empiric courses of antibiotics.

Specific sites of infection identified as the source of sepsis (pneumonia, urinary tract, enteric, joint space, and central nervous system) were associated with increasing duration of empiric antibiotics (Table 1). Conversely, unknown or undocumented sites of infection correlated with shorter durations of

Table 1. Characteristics for Hospital Survivors With Pathogen-Negative Sepsis

	Duration of Empiric Antibiotic Treatment			
Characteristic	≤3 d (n = 219)	4–7 d (n = 454)	>7 d (n = 374)	*P*
Age, y	60.2 ± 17.7	61.1 ± 16.3	60.5 ± 14.8	.758
Male	95 (43.4)	226 (49.8)	158 (42.2)	.070
Race				
White	133 (60.7)	299 (65.9)	252 (67.4)	.116
Black	76 (34.7)	128 (28.2)	94 (25.1)	
Other	10 (4.6)	27 (5.9)	28 (7.5)	
APACHE II	12 [8–16]	14 [11–17]	16 [12–20]	<.001
Charlson Comorbidity Index	3 [1–6]	4 [2–6]	4 [2–6]	.003
Days to empiric antibiotics[a]	2 [0–8]	0 [0–5]	0 [0–4.25]	<.001
Mechanical ventilation	23 (10.5)	115 (25.3)	174 (46.5)	<.001
Renal replacement therapy	7 (3.2)	9 (2.0)	17 (4.5)	.110
Ventilator days	4 [3–5]	7 [6–9]	11 [15–22]	<.001
ICU days	0 [0–2]	2 [0–4]	5 [2–10]	<.001
Hospital LOS, d	0 [0–0]	0 [0–1]	0 [0–4]	<.001
Discharge disposition				
Home	106 (48.4)	185 (40.7)	93 (24.9)	<.001
Home health	40 (18.3)	120 (26.4)	103 (27.5)	
SNF/LTAC	38 (17.4)	112 (24.7)	150 (40.1)	
Other	8 (3.7)	10 (2.2)	10 (2.7)	
30-d readmission	3 (1.4)	18 (4.0)	19 (5.1)	.074
Postantibiotic cultures[b]	54 (24.7)	149 (32.8)	130 (34.8)	.032
ID diagnosis				
Pneumonia	7 (3.2)	42 (9.3)	67 (17.9)	<.001
Urinary tract	76 (34.7)	175 (38.5)	194 (51.9)	<.001
Intraabdominal	6 (2.7)	21 (4.6)	25 (6.7)	.093
Enteric	5 (2.3)	47 (10.4)	101 (27.0)	<.001
Joint space	3 (1.4)	9 (2.0)	38 (10.2)	<.001
CNS	7 (3.2)	9 (2.0)	20 (5.3)	.030
Unknown[c]	130 (59.4)	212 (46.7)	98 (26.2)	<.001

Data are expressed as number (percentage), mean ± SD, or median [interquartile range].

Abbreviations: APACHE II, acute physiology and chronic health evaluation; CNS, central nervous system; ICU, intensive care unit; ID, infectious disease; LOS, length of stay; LTAC, long-term acute care facility; SNF, skilled nursing facility.

[a]Calendar days from the time when microbiologic cultures were obtained.

[b]Culture specimens obtained following the start of empiric antibiotic therapy for sepsis.

[c]The site of infection is described as such or undocumented in the medical record.

empiric antibiotic therapy (Table 1). Patients with a site of infection identified as the source of sepsis had similar rates of having appropriate blood cultures and/or other bodily fluid cultures obtained as part of their evaluation compared with patients with an unknown site of infection (94.2% vs 94.6%; $P = .807$). Figure 1 shows that the overall duration of antibiotic therapy was statistically greater among patients with a clinically suspected site of infection compared with those with an unknown or undocumented site of infection (median [IQR], 7 [5–11] vs 5 [3–7] days; $P < .001$). The urinary tract was the most commonly identified site of infection. The duration of antibiotic therapy was statistically greater among patients with a urinary tract site of infection compared with those with an unknown or undocumented site of infection (median [IQR], 7 [4–11] vs 5 [3–7] days; $P < .001$).

DISCUSSION

Our data suggest that the duration of empiric antimicrobial therapy in pathogen-negative sepsis is related to patient severity of illness and documented site of infection. The complexity of antibiotic decision-making in critically ill patients is illustrated by a study of ICU-acquired pneumonia (ICUAP) [9]. Three hundred forty-three patients with ICUAP were prospectively enrolled, of whom 140 (41%) had no microbiological confirmation, 121 (35%) patients developed ICUAP with multidrug-resistant organisms (MDROs), and 82 (24%) were non-MDROs. All 3 patient groups had similar baseline characteristics including previous antibiotic use and prior hospital admission. Initially appropriate antibiotic therapy (IAAT) was associated with better ICU survival, and an adjusted multivariate regression logistic analysis identified infection with MDROs as a risk factor for greater ICU mortality. However, antibiotic consumption was greater in patients without microbiologic confirmation compared with those who were culture-positive.

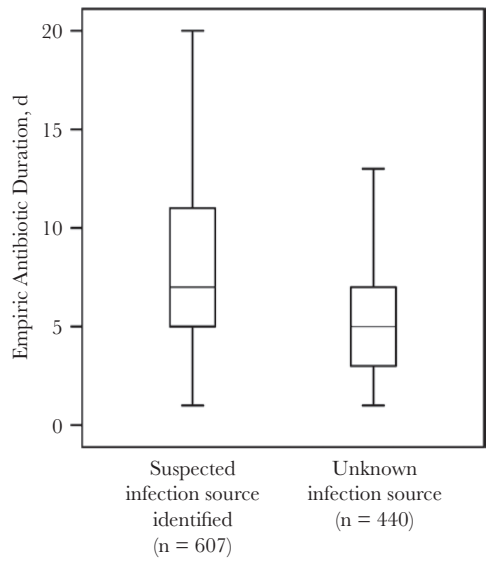

Figure 1. Box plot distributions for the duration of empiric antibiotic therapy for pathogen-negative surviving patients with sepsis according to whether they had an identified site of infection as the source of sepsis or whether the site of infection was unknown or undocumented in the medical record. 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 ($P < .001$ for the comparison of the distribution of values for the 2 box plots).

We previously demonstrated that patients with pathogen-negative health care–associated pneumonia (HCAP) had lower severity of illness, hospital mortality, and shorter durations of antibiotic therapy compared with pathogen-positive HCAP patients [10]. We also demonstrated that critically ill patients with pneumonia could safely have their antimicrobial therapy de-escalated based on microbiologic assessment [11]. However, a study employing a large administrative data set from the National Inpatient Sample (NIS) found that individuals with pathogen-negative sepsis had a greater mortality compared with those with pathogen-positive sepsis [12]. The authors of this study proposed several possible explanations for the greater mortality among pathogen-negative patients, including the observed greater disease severity and delays in empiric antibiotic administration and/or antibiotic durations that were inadequate [12]. The latter possibilities were merely hypotheses unsupported by their data. However, it is important to note that among pathogen-positive patients who received IAAT covering the offending pathogens, the severity of sepsis has been shown to be the most important determinant of outcome [13]. These observations emphasize the importance of discerning the impact of host factors and disease severity on patient outcomes, which may not be modifiable by antimicrobial therapy.

The deleterious effects of antibiotic use for pathogen-negative infections has been well described in a number of clinical settings [6, 12]. Moreover, the overuse of antibiotics paves the way for development of multidrug-resistant bacteria. This was nicely illustrated in a recent study of critically ill adult patients who received antipseudomonal β-lactam antibiotics, demonstrating that each additional day of exposure to cefepime, meropenem, and piperacillin-tazobactam was associated with an increased risk of new resistance development [14]. These studies illustrate the potential harm of unnecessary antibiotic administration.

There are several limitations of our study. First, the data come from a single center and may not be representative of other hospitals. Second, the retrospective nature of the study limits our ability to determine all potential indications for the prescribed empiric antibiotic therapy. Third, we did not determine whether antibiotic de-escalation occurred in our patients receiving empiric therapy. Lastly, we may have missed patients empirically treated for pathogen-negative sepsis who did not have clinical specimens obtained for microbiologic evaluation.

In summary, our data suggest that patients with pathogen-negative sepsis may represent an important opportunity for antimicrobial stewardship, assuming that many of these

patients received some form of unnecessary therapy. Given the outcome benefits observed with the combined use of molecular rapid diagnostic testing and antimicrobial stewardship programs, similar approaches in individuals with pathogen-negative sepsis should be considered regardless of their severity of illness [15]. Future studies of antimicrobial stewardship directed at patients with pathogen-negative sepsis and septic shock are needed to optimize the administration of antibiotic therapy.

Acknowledgments

Financial support. Dr. Kollef's efforts were supported by the Barnes-Jewish Hospital Foundation. There are no other funding sources to report.

Potential conflicts of interest. None of the authors has any conflicts of interest to report. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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