Impact of previous antibiotic therapy on outcome of Gram-negative severe sepsis*

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Objective: **To determine whether exposure to antimicrobial agents in the previous 90 days resulted in decreased bacterial susceptibility and increased hospital mortality in patients with severe sepsis or septic shock attributed to Gram-negative bacteremia.**

Design: **A retrospective cohort study of hospitalized patients (January 2002 to December 2007).**

Setting: **Barnes-Jewish Hospital, a 1200-bed urban teaching hospital.**

Patients: **Seven hundred fifty-four consecutive patients with Gram-negative bacteremia complicated by severe sepsis or septic shock.**

Interventions: **Data abstraction from computerized medical records.**

Measurements and Main Results: ***Escherichia coli*** **(30.8%),** ***Klebsiella pneumoniae*** **(23.2%), and** ***Pseudomonas aeruginosa*** **(17.6%) were the most common isolates from blood cultures. Three hundred ten patients (41.1%) had recent antibiotic exposure. Cefepime was the most common agent with previous exposure (50.0%) followed by ciprofloxacin (32.6%) and imipenem or meropenem (28.7%). Patients with prior antibiotic exposure had significantly higher rates of resistance to cefepime (29.0% vs. 7.0%), piperacillin/tazobactam (31.9% vs. 11.5%), carbapenems (20.0% vs. 2.5%), ciprofloxacin (39.7% vs. 17.6%), and gentamicin (26.1% vs. 7.9%) ($p < .001$ for all comparisons). Patients with recent antibiotic exposure had greater inappropriate initial antimicrobial therapy (45.4% vs. 21.2%; $p < .001$) and hospital mortality (51.3% vs. 34.0%; $p < .001$) compared with patients without recent antibiotic exposure. Multivariate logistic regression analysis demonstrated that recent antibiotic exposure was independently associated with hospital mortality (adjusted odds ratio, 1.70; 95% confidence interval, 1.41–2.06; $p = .005$). Other variables independently associated with hospital mortality included use of vasopressors, infection resulting from** ***P. aeruginosa*****, inappropriate initial antimicrobial therapy, increasing Acute Physiology and Chronic Health Evaluation II scores, and the number of acquired organ failures.**

Conclusions: **Recent antibiotic exposure is associated with increased hospital mortality in Gram-negative bacteremia complicated by severe sepsis or septic shock. Clinicians caring for patients with severe sepsis or septic shock should consider recent antibiotic exposure when formulating empiric antimicrobial regimens for suspected Gram-negative bacterial infection. (Crit Care Med 2011; 39:1859–1865)**

KEY WORDS: sepsis; Gram-negative; antibiotics; outcome; resistance

Inappropriate initial antimicrobial therapy, defined as an antimicrobial regimen that lacks *in vitro* activity against the isolated organism(s) responsible for the infection, has been associated with excess mortality in patients with severe sepsis and septic shock (1–5). This is largely related to increasing bacterial resistance to antibiotics as a result of their greater use and limited availability of new agents (6, 7). Escalating rates of antimicrobial resistance lead many clinicians to empirically treat critically ill patients with presumed infection with a combination of broad-spectrum antibiotics, which can perpetuate the cycle of increasing resistance (7). Conversely, inappropriate initial antimicrobial therapy can lead to treatment failures and adverse patient outcomes (8). Individuals with severe sepsis appear to be at particularly high risk of excess mortality when inappropriate initial antimicrobial therapy is administered (5, 9).

The most recent Surviving Sepsis Guidelines recommend empiric combination therapy targeting Gram-negative bacteria, particularly for patients with known or suspected *Pseudomonas* infections, as a means to decrease the likelihood of administering inappropriate initial antimicrobial therapy (10). The choice of an antimicrobial regimen that is active against the causative pathogen(s) is problematic because the treating physician usually does not know the susceptibilities of the pathogen(s) for the selected empiric antibiotics at the time of antibiotic prescription. However, information regarding previous antibiotic exposure, especially during the same hospitalization or with hospital readmission, is usually available. Therefore, we performed a study with two main goals. The first goal was to determine whether recent antibiotic exposure resulted in decreased antimicrobial susceptibility among Gram-negative bacteria associated with bacteremic severe sepsis or septic shock. The second goal was to ascertain whether recent antibiotic exposure was

***See also p. 1995.**

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associated with increased hospital mortality.

MATERIALS AND METHODS

Study Location and Patient Population. This study was conducted at a university-affiliated, urban teaching hospital: Barnes-Jewish Hospital (1200 beds). Over a 6-yr period (January 2002 to December 2007); all hospitalized patients with Gram-negative bacteremia were eligible for inclusion. This study was approved by the Washington University School of Medicine Human Studies Committee.

Study Design and Data Collection. Using a retrospective cohort study design, patients with Gram-negative sepsis were identified by the presence of a blood culture positive only for Gram-negative bacteria combined with primary or secondary International Classification of Diseases, 9th Revision, Clinical Modification codes indicative of acute organ dysfunction. 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 (intensive care unit or general hospital ward). Only the first episode of severe sepsis or septic shock attributed to Gram-negative bacteremia was evaluated. Electronic inpatient and outpatient medical records available for all patients in the BJC Healthcare System (13 hospitals and multiple community health locations) were reviewed to determine prior antibiotic exposure.

The baseline characteristics collected included age, gender, race, history of congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, chronic liver disease, underlying malignancy, and end-stage renal disease requiring dialysis. The Acute Physiology and Chronic Health Evaluation II (11) and Charlson comorbidity scores were calculated based on clinical data present during the 24 hrs after the positive blood cultures were obtained. This was done to accommodate patients with community-acquired and health care-associated community-onset infections who only had clinical data available after blood cultures were drawn. The primary outcome variable was all-cause hospital mortality. Secondary outcomes evaluated included antimicrobial susceptibility and proportion of patients receiving inappropriate initial antimicrobial therapy.

Definitions. All definitions were prospectively selected before initiation of the study. To be included in the analysis, patients had to meet criteria for severe sepsis based on discharge International Classification of Diseases, 9th Revision, Clinical Modification codes for acute organ dysfunction as previously described (12). The organs of interest included the heart, lungs, kidneys, bone marrow (hematologic), brain, and liver. Patients were classified as having septic shock if vasopressors (norepinephrine, dopamine, epinephrine, phenylephrine, or vasopressin) were initiated within 24 hrs of the blood culture collection date and time.

Antimicrobial treatment was classified as appropriate if the initially prescribed antibiotic regimen was active against the identified pathogen based on *in vitro* susceptibility testing and administered within 24 hrs after blood culture collection. For patients with polymicrobial infection, the initial antimicrobial regimen had to be active against all identified pathogens to be classified as appropriate. Appropriate antimicrobial treatment also had to be prescribed for at least 24 hrs. However, the total duration of antimicrobial therapy was at the discretion of the treating physicians. Antimicrobial exposure was any exposure to an antibiotic within the preceding 90 days. Antimicrobial reuse was defined as retreatment with the same antibiotic or antibiotic class to which the patient was previously exposed in the preceding 90 days. Multidrug-resistant isolates were defined as a bacterial isolate with *in vitro* resistance to at least two antipseudomonal antibiotics, which included cefepime, piperacillin–tazobactam, imipenem or meropenem, gentamicin or tobramycin, or amikacin.

Antimicrobial Monitoring. From January 2002 through the present, Barnes-Jewish Hospital used an antibiotic control program to help guide antimicrobial therapy. During this time, the use of cefepime and gentamicin was unrestricted. However, initiation of intravenous ciprofloxacin, imipenem, meropenem, or piperacillin–tazobactam was restricted and required preauthorization from either a clinical pharmacist or infectious diseases physician. Each intensive care unit had a clinical pharmacist who reviewed all antibiotic orders to ensure that 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 reviewed and approved the antibiotic orders. The initial antibiotic dosages used for the treatment of Gram-negative infections at Barnes-Jewish Hospital were as follows: cefepime, 1–2 g every 8 hrs; piperacillin–tazobactam, 4.5 g every 6 hrs; imipenem 0.5 g every 6 hrs; meropenem, 1 g every 8 hrs; ciprofloxacin, 400 mg every 8 hrs; and gentamicin, 5 mg/kg once daily.

Starting in June 2005, a sepsis order set was implemented in the emergency department, general medical wards, and the intensive care units with the intent of standardizing empiric antibiotic selection for patients with sepsis based on the infection type (i.e., community-acquired pneumonia, health care-associated pneumonia, intra-abdominal infection, etc.) and the hospital's antibiogram (13, 14). However, antimicrobial selection, dosing, and de-escalation of therapy were still optimized by clinical pharmacists in these clinical areas.

Antimicrobial Susceptibility Testing. The microbiology laboratory performed antimicrobial susceptibility of the Gram-negative blood isolates 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 (15, 16).

Data Analysis. Continuous variables were reported as mean ± SD. The Student's *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-squared test was used to determine whether differences existed between groups. We performed multiple logistic regression analysis to identify clinical risk factors that were associated with hospital mortality (SPSS, Inc, Chicago, IL). All risk factors that were significant at 0.20 in the univariate analysis were included in the corresponding multivariable analysis. All variables entered into the model were examined to assess for collinearity. All tests were two-tailed, and a p value $<.05$ was determined to represent statistical significance.

RESULTS

Seven hundred fifty-four consecutive patients with bacteremic Gram-negative severe sepsis or septic shock were included in the study. The mean age was 59.3 ± 16.3 yrs (range, 18–99 yrs) with 394 (52.3%) males and 360 (47.7%) females (Table 1). There were 421 (55.8%) medical patients and 333 (44.2%) surgical patients. Five hundred ninety-six (79.0%) patients were in the intensive care unit and the mean duration of hospitalization was 10.2 ± 14.4 days (range, 1–96 days) at the time severe sepsis or septic shock occurred. The mean Acute Physiology and Chronic Health Evaluation II score was 23.7 ± 6.7 (range, 4–43) with the majority of patients requiring vasopressors (58.5%) and mechanical ventilation (55.3%). *Escherichia coli* (30.8%), *Klebsiella pneumoniae* (23.2%), and *Pseudomonas aeruginosa* (17.6%) were the most common organisms isolated from blood cultures. Fifty-six (7.4%) patients had polymicrobial bacteremia. Antipseudomonal agents were prescribed as empiric therapy in the majority of patients: cefepime (54.2%), ciprofloxacin (20.4%), aminoglycoside (18.2%), piperacillin–tazobactam (15.5%), and carbapenems (12.1%).

Three hundred ten (41.1%) patients had previous antimicrobial exposure dur-

Table 1. Baseline characteristics[a]

Variable	Prior Antibiotic Exposure (n = 310)	No Prior Antibiotic Exposure (n = 444)	p
Age, yrs	56.9 ± 16.6	60.9 ± 16.0	.001
Male	170 (54.8)	224 (50.5)	.235
Infection onset type			
Community-acquired	0 (0.0)	71 (16.0)	<.001
Health care-associated community-onset	30 (9.7)	236 (53.2)	
Health care-associated hospital-onset	280 (90.3)	137 (30.9)	
Duration of hospitalization before sepsis, days	20.4 ± 17.1	3.2 ± 5.3	<.001
Underlying comorbidities			
Congestive heart failure	53 (17.1)	91 (20.5)	.243
Chronic obstructive lung disease	62 (20.0)	74 (16.7)	.241
Chronic kidney disease	39 (12.6)	70 (15.8)	.221
Liver disease	37 (11.9)	57 (12.8)	.712
Active malignancy	95 (30.6)	146 (32.9)	.517
Diabetes	65 (21.0)	104 (23.4)	.426
Acute Physiology and Chronic Health Evaluation II score	23.5 ± 6.5	23.8 ± 6.9	.525
Charlson comorbidity score	4.3 ± 3.7	5.2 ± 3.6	.002
In intensive care unit when sepsis occurred	265 (85.5)	331 (74.5)	<.001
Vasopressors	207 (66.8)	234 (52.7)	<.001
Mechanical ventilation	221 (71.3)	196 (44.1)	<.001
Drotrecogin alfa (activated)	8 (2.6)	23 (5.2)	.077
Organ dysfunction			
Cardiovascular	214 (69.0)	253 (57.0)	.001
Respiratory	238 (76.8)	228 (51.4)	<.001
Renal	163 (52.6)	240 (54.1)	.690
Hepatic	24 (7.7)	31 (7.0)	.693
Hematologic	88 (28.3)	141 (31.8)	.322
Neurologic	17 (5.5)	31 (7.0)	.407
Number of organ failures	2.4 ± 1.0	2.1 ± 1.1	<.001
Source of bacteremia[b]			
Lungs	166 (53.5)	134 (30.2)	<.001
Urinary tract	67 (21.6)	163 (36.7)	<.001
Central venous catheter	16 (5.2)	40 (9.0)	.047
Intra-abdominal	64 (20.6)	73 (16.4)	.141
Unknown	8 (2.6)	41 (9.2)	<.001

[a]Data from hospital admission (demographics and underlying comorbidities) or within 24 hrs of obtaining a positive blood culture in patients with severe sepsis or septic shock; [b]defined using Centers for Disease Control criteria (http://www.cdc.gov/ncidod/dhqp/pdf/nnis/NosInfDefinitions.pdf). Values are expressed as number (%) and mean ± SD.

ing the preceding 90 days. Of these, cefepime was the most common agent with previous exposure (50.0%) followed by ciprofloxacin (32.6%), imipenem or meropenem (28.7%), piperacillin–tazobactam (19.0%), and aminoglycosides (14.5%). When compared with cases with no prior antimicrobial exposure, patients with prior exposure were significantly more likely to have health care-associated hospital-onset sepsis, sepsis occur in the intensive care unit setting, and a longer duration of stay before sepsis onset (Table 1). Patients with antimicrobial exposure were also significantly younger, had lower Charlson comorbidity scores, were more likely to have a pulmonary source of infection, and to require mechanical ventilation and vasopressor support. Patients with prior antibiotic exposure had higher rates of inappropriate initial antimicrobial therapy (45.5% vs. 21.2% $p < .001$) and hospital mortality (51.3% vs. 34.0%, $p < .001$) compared with patients without prior antibiotic exposure. Polymicrobial bacteremia was similar in patients with and without prior antibiotic exposure (6.5% vs. 8.1%; $p = .393$). Among patients with prior antibiotic exposure, all 310 (100%) had information available in the computerized medical record regarding their prior antibiotic exposure at the time antibiotic orders were entered.

Patients with prior antimicrobial exposure had significantly higher rates of infection with Gram-negative isolates that were resistant to cefepime (29.0% vs. 7.0%), piperacillin–tazobactam (31.9% vs. 11.5%), carbapenems (20.0% vs. 2.5%), ciprofloxacin (39.7% vs. 17.6%), and gentamicin (26.1% vs. 7.9%) ($p < .001$ for all susceptibility comparisons) (Table 2). Prior antibiotic exposure was also associated with infection caused by a multidrug-resistant isolate (37.4% vs. 11.3%; $p < .001$).

Among the 310 patients with prior antibiotic exposure, there were 165 (53.2%) who had antibiotic reuse. Patients with antibiotic reuse had longer hospital lengths of stay before the onset of sepsis and were more likely to have the lungs as the source of infection compared with patients with prior antibiotic exposure who did not have antibiotic reuse (Table 3). Patients with antibiotic reuse had similar rates of inappropriate initial antimicrobial therapy (46.7% vs. 44.1% $p = .656$) and hospital mortality (49.7% vs. 53.1%, $p = .549$) compared with patients with prior antibiotic exposure who did not have antibiotic reuse.

E. coli was statistically less likely to be associated with prior antibiotic exposure, whereas *P. aeruginosa* and *Acinetobacter* species were statistically more likely to be associated with prior antibiotic exposure (Table 4). *E. coli* and *K. pneumonia* were statistically less likely to be associated with the administration of inappropriate antimicrobial therapy and *Acinetobacter* species infection was statistically more likely to be associated with the administration of inappropriate therapy. Infection with *E. coli* and polymicrobial bacteremia were associated with a significantly greater survival, whereas infection with *P. aeruginosa* was associated with a significantly greater risk of hospital mortality (Table 4).

Hospital mortality was significantly greater for patients with recent antibiotic exposure compared with those without recent antibiotic exposure when stratified according to Acute Physiology and Chronic Health Evaluation II scores (Fig. 1). In the multivariate analysis of hospital mortality, prior antibiotic exposure was independently associated with hospital mortality (Table 5). Other characteristics that were independently associated with hospital mortality included use of vasopressors, infection resulting from *P. aeruginosa*, inappropriate initial antimicrobial therapy, increasing Acute Physiology and Chronic Health Evaluation II scores (1-point increments), and the number of acquired organ failures (one-organ increments).

DISCUSSION

Our study demonstrated that prior antibiotic exposure was associated with greater hospital mortality in patients with Gram-negative bacteremia compli-

Table 2. Patients infected with Gram-negative organism(s) susceptible to commonly prescribed antimicrobials for Gram-negative infections[a]

Antimicrobial Agent	Prior Antibiotic Exposure (n = 310)	No Prior Antibiotic Exposure (n = 444)	p
Cefepime	71.0%	93.0%	<.001
Piperacillin–tazobactam	68.1%	88.5%	<.001
Imipenem/meropenem	80.0%	97.5%	<.001
Ciprofloxacin	60.3%	82.4%	<.001
Gentamicin	73.9%	92.1%	<.001
Multidrug-resistant[b]	37.4%	11.3%	<.001

[a]Patients with polymicrobial bacteremia had to have all isolated bacteria susceptible to the antibiotic to be considered susceptible; [b]refers to the number of patients in each group having bacteremia with multidrug-resistant Gram-negative bacteria. Multidrug-resistant isolates were defined as a bacterial isolate with *in vitro* resistance to at least two antipseudomonal antibiotics, which included cefepime, piperacillin–tazobactam, imipenem or meropenem, gentamicin or tobramycin, or amikacin.

Table 3. Baseline characteristics[a]

Variable	Antibiotic Reuse (n = 165)	Prior Antibiotics Without Reuse (n = 145)	p
Age, yrs	56.3 ± 16.3	57.6 ± 16.8	.480
Male	88 (53.3)	82 (56.6)	.570
Infection onset type			
Community-acquired	0 (0.0)	0 (0.0)	.449
Health care-associated community-onset	14 (8.5)	16 (11.0)	
Health care-associated hospital-onset	151 (91.5)	129 (89.0)	
Duration of hospitalization before sepsis, days	22.9 ± 17.1	17.5 ± 16.6	.006
Underlying comorbidities			
Congestive heart failure	27 (16.4)	26 (17.9)	.715
Chronic obstructive lung disease	34 (20.6)	28 (19.3)	.776
Chronic kidney disease	22 (13.3)	17 (11.7)	.670
Liver disease	22 (13.3)	15 (10.3)	.418
Active malignancy	48 (29.1)	47 (32.4)	.527
Diabetes	35 (21.2)	30 (20.7)	.910
Acute Physiology and Chronic Health Evaluation II score	23.1 ± 6.3	23.9 ± 6.7	.273
Charlson comorbidity score	4.3 ± 3.7	4.3 ± 3.8	.965
In intensive care unit when sepsis occurred	139 (84.2)	126 (86.9)	.508
Vasopressors	108 (65.5)	99 (68.3)	.599
Mechanical ventilation	122 (73.9)	99 (68.3)	.271
Drotrecogin alfa (activated)	5 (3.0)	3 (2.1)	.728
Organ dysfunction			
Cardiovascular	112 (67.9)	102 (70.3)	.639
Respiratory	131 (79.4)	107 (73.8)	.244
Renal	88 (53.3)	75 (51.7)	.777
Hepatic	13 (7.9)	11 (7.6)	.923
Hematologic	46 (27.9)	42 (29.0)	.832
Neurologic	9 (5.5)	8 (5.5)	.981
Number of organ failures	2.4 ± 0.9	2.4 ± 1.0	.814
Source of bacteremia[b]			
Lungs	97 (58.8)	69 (47.6)	.048
Urinary tract	27 (16.4)	40 (27.6)	.017
Central venous catheter	9 (5.5)	7 (4.8)	.803
Intra-abdominal	33 (20.0)	31 (21.4)	.765
Unknown	4 (2.4)	4 (2.8)	1.000

[a]Data from hospital admission (demographics and underlying comorbidities) or within 24 hrs of obtaining a positive blood culture in patients with severe sepsis or septic shock; [b]defined using Centers for Disease Control criteria (http://www.cdc.gov/ncidod/dhqp/pdf/nnis/NosInfDefinitions.pdf). Values are expressed as number (%) and mean ± SD.

cated by severe sepsis or septic shock. This observation was confirmed in a stratified analysis of severity of illness and in a multivariate analysis controlling for potential confounding variables. Not surprisingly, other important determinants of outcome in the multivariate analysis included severity of illness makers such as the Acute Physiology and Chronic Health Evaluation II score, the need for vasopressors, and the number of acquired organ failures.

A likely explanation for the association we observed between hospital mortality and prior antibiotic exposure is the greater degree of antimicrobial resistance in the causative pathogen(s) of patients receiving prior antibiotics. This is supported by our finding of significantly greater antibiotic resistance among the Gram-negative bloodstream isolates obtained from patients with recent antibiotic exposure compared with bacterial isolates from patients without this exposure. Prior antibiotic exposure was also associated with significantly greater administration of inappropriate initial antimicrobial therapy, which has been associated with excess mortality in sepsis (1–5). Our study also confirmed the link between inappropriate initial antimicrobial therapy and hospital mortality.

A number of investigators have previously demonstrated an association between prior antibiotic exposure and subsequent infection with potentially antibiotic-resistant bacteria. The study by Seguin et al (17) showed that among patients with postoperative peritonitis, only antimicrobial treatment in the 3 mos preceding hospitalization and duration between first operation and reoperation were independent risk factors for infection with multidrug-resistant bacteria. A retrospective study examining the influence of previous antibiotic exposures on 267 episodes of *P. aeruginosa* bacteremia at a single center found that previous therapy with an antipseudomonal antibiotic increased the risk of subsequent resistance to that specific antibiotic by 2.5-fold (18). Similarly, the study by Trouillet et al (19) assessed risk factors for piperacillin-resistant *P. aeruginosa* infection in patients with ventilator-associated pneumonia. They found that previous exposure to a fluoroquinolone was associated with a 4.6-fold increase in risk of piperacillin resistance. Comparable studies have also identified exposure to previous antimicrobial therapy as a significant risk factor for infection with antibiotic-resistant Gram-negative bacteria (20–24).

Our study is unique in identifying prior antibiotic exposure as an independent risk factor for hospital mortality among patients with Gram-negative bacteremia complicated by severe sepsis or septic shock. This observation suggests that clinicians should search for and identify the presence of prior antibiotic

Table 4. Characteristics associated with specific Gram-negative species

	Prior Antibiotic Exposure (n = 310)	No Prior Antibiotic Exposure (n = 444)	Antibiotic Reuse (n = 165)	Prior Antibiotics Without Reuse (n = 145)	Inappropriate Treatment (n = 235)	Appropriate Treatment (n = 519)	Hospital Mortality (n = 310)	Hospital Survival (n = 444)
Escherichia coli	42 (13.5)	190 (42.8)[a]	19 (11.5)	23 (15.9)	41 (17.4)	191 (36.8)[a]	74 (23.9)	158 (35.6)[a]
Klebsiella pneumonia	73 (23.5)	102 (23.0)	35 (21.2)	38 (26.2)	42 (17.9)	133 (25.6)[a]	70 (22.6)	105 (23.6)
Pseudomonas aeruginosa	72 (23.2)	61 (13.7)[a]	38 (23.0)	34 (23.4)	42 (17.9)	91 (17.5)	71 (22.9)	62 (14.0)[a]
Acinetobacter species	41 (13.2)	22 (5.0)	24 (14.5)	17 (11.7)	44 (18.7)	19 (3.7)[a]	32 (10.3)	31 (7.0)
Polymicrobial bacteremia	20 (6.5)	36 (8.1)	7 (4.2)	13 (9.0)	11 (4.7)	45 (8.7)	16 (5.2)	40 (9.0)[a]

[a] $p < .05$. Values are expressed as number (%).

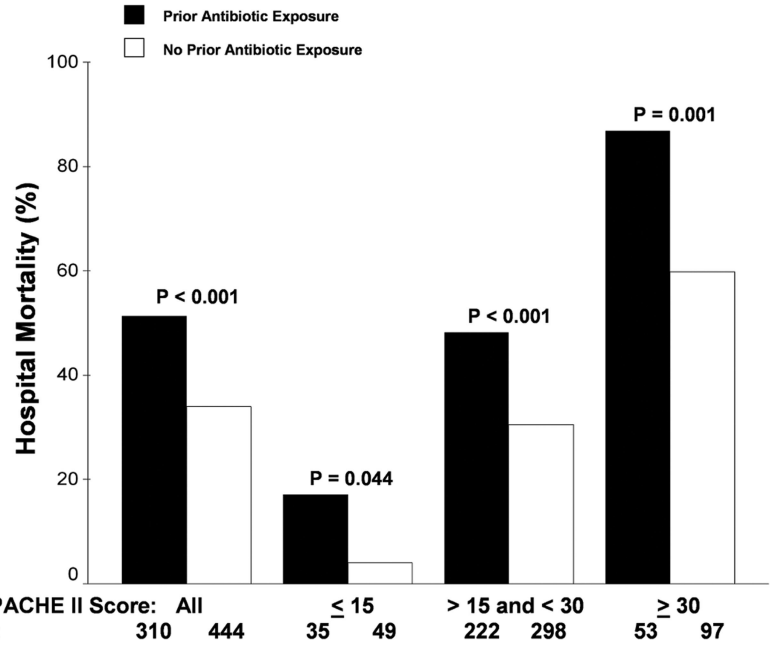

Figure 1. Hospital mortality stratified by Acute Physiology and Chronic Health Evaluation II (*APACHE II*) score.

Table 5. Multivariate analysis of independent risk factors for hospital mortality[a]

Variable	Adjusted Odds Ratio	95% Confidence Interval	*p*
Prior antibiotic exposure	1.70	1.41–2.06	.005
Use of vasopressors	1.83	1.47–2.29	.006
Pseudomonas infection	1.75	1.39–2.21	.016
Inappropriate initial therapy	2.03	1.66–2.49	<.001
Acute Physiology and Chronic Health Evaluation II score (1-point increments)	1.13	1.11–1.15	<.001
Number of organ failures (one–organ increments)	1.93	1.73–2.14	<.001

[a] Other covariates not in the table had a *p* value >.05, including age, health care-associated hospital-onset infection, *Acinetobacter* infection, mechanical ventilation, in the intensive care unit when sepsis occurred, and the lungs as the source of infection (Hosmer-Lemeshow goodness-of-fit test, $p = .464$).

exposure as an important consideration when prescribing empiric antibiotic therapy to patients with severe sepsis or septic shock. Interestingly, we found that all patients with prior antibiotic exposure, including those with antibiotic reuse, had retrievable information available in their bedside computerized medical record regarding prior antibiotic exposure at the time antibiotic orders were written. This suggests that the antibiotic exposure history of the patient was either ignored or not obtained in many cases. The identification of prior antibiotic exposure should result in specific therapeutic interventions, especially in critically ill patients.

Avoidance of prior drug classes in the empiric treatment regimens of patients with severe sepsis or septic shock would seem to be a logical approach for potentially minimizing the adverse consequences of recent antibiotic exposure. Unfortunately, a patient's antimicrobial exposure history may not be available when clinicians are making decisions regarding empiric treatment. Additionally, prior antibiotic exposure can select out bacteria that are resistant to multiple antibiotic classes (19, 23). Combination therapy targeting patients at risk for infection with antibiotic-resistant bacteria is another strategy for avoiding the potential outcome penalty associated with prior antibiotic exposure. We recently reported that combination empiric antimicrobial therapy directed against Gram-negative bacteria, using aminoglycosides as the preferred combination agent, was associated with greater initial appropriate therapy compared with monotherapy for Gram-negative bacteremia (25). Patients treated with combination therapy were significantly less likely to receive inappropriate initial antimicrobial therapy compared with monotherapy and had a lower risk of hospital mortality. Combination therapy has also been advocated by other investigators and several medical societies as a strategy to maximize appropriate initial therapy in patients at risk for infection with antibiotic-resistant bacteria (10, 26, 27).

We identified prior antibiotic exposure as a key factor associated with subsequent antibiotic resistance in Gram-negative bacteria and increased mortality when infection with resistant Gram-negative bacteria occurred. Antibiotic reuse is a type of prior antibiotic exposure in which the same antibiotic, or antibiotic class, is administered to patients. Antibiotic reuse was not found to be associated with increased mortality compared with prior

antibiotic exposure without reuse. This is likely explained by the observation that antibiotic exposure to Gram-negative bacteria can increase resistance to that specific class of drug as well as to other classes of antibiotics, presumably through shared mechanisms of resistance (6, 7). It is also important to note that patients with prior antibiotic exposure had significantly longer stays in the hospital before the onset of sepsis compared with those without prior antibiotic exposure. This suggests that patients with prior antibiotic exposure may have had more complicated medical conditions further predisposing them to colonization and infection with resistant bacteria.

There are several important limitations of our study that should be noted. First, the study was performed at a single center and the results may not be generalizable to other institutions. However, the findings from other investigators corroborate the potential role of prior antibiotic exposure as an important determinant of outcome for patients with serious Gram-negative infections (17, 18). Additionally, a similar association has been observed in patients with methicillin-resistant *Staphylococcus aureus* bacteremia and *Candida* bloodstream infection supporting the more general importance of prior antibiotic exposure as a potential outcome predictor (28–32). Second, the retrospective and observational nature of this study limits our ability to establish causality between prior antibiotic exposure and hospital mortality and limits our ability to assess the adequacy, indications, and use of de-escalation for the prior antibiotic therapy. However, the potential negative impact to the individual patient from prior antibiotic exposure can be profound and clinicians should consider this issue when prescribing empiric antibiotics to patients with severe sepsis or septic shock. Additionally, both prior antibiotic exposure and inappropriate therapy were independently associated with hospital mortality (Table 5). This suggests that factors other than inappropriate therapy may account for the excess mortality associated with prior antibiotic exposure. Such potential factors include prior hospitalization or intensive care unit stay, increased exposure to invasive procedures like dialysis, or a "double hit" to the host's immune system from repetitive infections.

Another important limitation of our investigation is that we could not determine the rationale physicians used in selecting the empiric antibiotic regimens for these patients. A better understanding of this phenomenon could provide institution-specific strategies for improved antibiotic use and the avoidance of inappropriate initial antimicrobial therapy, especially in septic patients. We also selected a time period of 90 days to assess the risk of prior antibiotic exposure. Other investigations have suggested that the risk of subsequent infection with antibiotic-resistant bacteria can be increased with prior antibiotic exposures occurring up to 12 mos earlier (33, 34). This is another area in which additional studies are required to better determine the relationship between the timing of prior antibiotic exposure and subsequent infection with antibiotic-resistant pathogens. Finally, our study focused on bacteremic patients with severe sepsis and septic shock. Therefore, our data cannot be applied to other types of infections or to bacteremic patients without severe sepsis or septic shock.

In conclusion, we observed that prior antibiotic exposure is relatively common and associated with increased mortality in patients with Gram-negative bacteremia complicated by severe sepsis or septic shock. This observation suggests that clinicians treating patients with suspected Gram-negative sepsis should attempt to identify whether prior antibiotic exposure occurred. In clinical situations in which recent antibiotic exposure is likely, but details concerning prior antibiotic exposure are unknown, combination empiric therapy directed against Gram-negative bacteria would be reasonable to increase the likelihood of appropriate therapy until susceptibility data become available (10, 25, 26). Given the importance of prior antibiotic exposure as a risk factor for antibiotic resistance, inappropriate therapy, and increased mortality, and the availability of electronic medical records at most hospitals, institutions should try to formalize an approach for identifying prior antibiotic exposure in infected patients. At the same time, antimicrobial agents should be used judiciously to avoid the emergence of resistance. Finally, the development of novel antimicrobials and rapid diagnostic techniques is needed given the rapidly rising rates of resistance to currently available antibiotics and the paucity of newly developed antimicrobials in the past two decades (6, 7).

REFERENCES

1. 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
2. Dhainaut JF, Laterre PF, LaRosa SP, et al: The clinical evaluation committee in a large multicenter phase 3 trial of drotrecogin alfa (activated) in patients with severe sepsis (PROWESS): Role, methodology, and results. *Crit Care Med* 2003; 31:2291–2301
3. 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
4. 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
5. Ferrer R, Artigas A, Suarez D, et al: Effectiveness of treatments for severe sepsis: A prospective, multicenter, observational study. *Am J Respir Crit Care Med* 2009; 180: 861–866
6. Arias CA, Murray BE: Antibiotic-resistant bugs in the 21st century—A clinical superchallenge. *N Engl J Med* 2009; 360:439–443
7. Boucher H, Talbot GH, Bradley JS, et al: Bad bugs, no drugs: No ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 48:1–12
8. Kollef MH: Broad-spectrum antimicrobials and the treatment of serious bacterial infections: Getting it right up front. *Clin Infect Dis* 2008; 47(Suppl 1):S3–S13
9. Barochia AV, Cui X, Vitberg D, et al: Bundled care for septic shock: An analysis of clinical trials. *Crit Care Med* 2010; 38:668–678
10. Dellinger RP, Levy MM, Carlet JM, et al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36:296–327
11. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13: 818–829
12. 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
13. 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* 2007; 34:2707–2713
14. 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
15. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing: Twelfth In-

formational Supplement. M100-S12. Wayne, PA, National Committee for Clinical Laboratory Standards, 2002
16. Clinical Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing: Seventeenth Informational Supplement. M100-S17. Clinical Wayne, PA, Laboratory Standards Institute, 2007
17. Seguin P, Fedun Y, Laviolle B, et al: Risk factors for multidrug-resistant bacteria in patients with post-operative peritonitis requiring intensive care. *J Antimicrob Chemother* 2010; 65:342–346
18. El Amari E, Chamot E, Auckenthaler R, et al: Influence of previous exposure to antibiotic therapy on the susceptibility pattern of *Pseudomonas aeruginosa* bacteremic isolates. *Clin Infect Dis* 2001; 33:1859–1864
19. Trouillet J, Vuagnat A, Combes A, et al: *Pseudomonas aeruginosa* ventilator-associated pneumonia: Comparison of episodes due to piperacillin-resistant versus piperacillin-susceptible organisms. *Clin Infect Dis* 2002; 34:1047–1054
20. Lodise TP Jr, Miller C, Patel N, et al: Identification of patients with *Pseudomonas aeruginosa* respiratory tract infections at greatest risk of infection with carbapenem-resistant isolates. *Infect Control Hosp Epidemiol* 2007; 28:959–965
21. Gasink LB, Fishman NO, Weiner MG, et al: Fluoroquinolone-resistant *Pseudomonas aeruginosa*: Assessment of risk factors and clinical impact. *Am J Med* 2006; 119: 526.e19–e25
22. D'Agata EM, Cataldo MA, Cauda R, et al: The importance of addressing multidrug resistance and not assuming single-drug resistance in case–control studies *Infect Control Hosp Epidemiol* 2006; 27:670–674.
23. Falagas ME, Kopterides P: Risk factors for the isolation of multi-drug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*: A systematic review of the literature. *J Hosp Infect* 2006; 64:7–15
24. Lodise TP, Miller CD, Graves J, et al: Clinical prediction tool to identify patients with *Pseudomonas aeruginosa* respiratory tract infections at greatest risk for multidrug resistance. *Antimicrob Agents Chemother* 2007; 51:417–422
25. Micek S, Welch E, Khan J, et al: Empiric combination antibiotic therapy is associated with improved outcome in Gram-negative sepsis: A retrospective analysis. *Antimicrob Agents Chemother* 2010; 54:1742–1748
26. Kumar A, Zarychanski R, Light B, et al: Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: A propensity-matched analysis. *Crit Care Med* 2010; 38: 1773–1785
27. American Thoracic Society and Infectious Diseases Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and health-care-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171:388–416
28. Fong RK, Low J, Koh TH, et al: Clinical features and treatment outcomes of vancomycin-intermediate *Staphylococcus aureus* (VISA) and heteroresistant vancomycin-intermediate *Staphylococcus aureus* (hVISA) in a tertiary care institution in Singapore. *Eur J Clin Microbiol Infect Dis* 2009; 28: 983–987
29. Lodise TP, Miller CD, Graves J, et al: Predictors of high vancomycin MIC values among patients with methicillin-resistant *Staphylococcus aureus* bacteraemia. *J Antimicrob Chemother* 2008; 62:1138–1141
30. Soriano A, Marco F, Martínez JA, et al: Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2008; 46:193–200
31. Leroy O, Gangneux JP, Montravers P, et al: Epidemiology, management, and risk factors for death of invasive *Candida* infections in critical care: A multicenter, prospective, observational study in France (2005–2006). *Crit Care Med* 2009; 37:1612–1618
32. Labelle AJ, Micek ST, Roubinian N, et al: Treatment-related risk factors for hospital mortality in *Candida* bloodstream infections. *Crit Care Med* 2008; 36:2967–2972
33. 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
34. Costelloe C, Metcalfe C, Lovering A, et al: Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: Systematic review and meta-analysis. *BMJ* 2010; 340:c2096