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Influx of Multidrug-Resistant, Gram-Negative Bacteria in the Hospital Setting and the Role of Elderly Patients With Bacterial Bloodstream Infection

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Abstract

BACKGROUND—Multidrug-resistant (MDR) gram-negative bacteria are reported increasingly frequently among isolates recovered from elderly patients. The clinical epidemiology of bloodstream infection (BSI) due to MDR gram-negative bacteria among elderly patients is unknown.

OBJECTIVE—To characterize the clinical epidemiology of BSI due to MDR gram-negative bacteria among elderly patients at hospital admission in an effort to provide a greater understanding of these serious infections and ultimately to improve patient outcomes.

DESIGN—Case-control study.

SETTING—Tertiary care hospital in Boston, Massachusetts.

PATIENTS—Patients 65 years of age and older.

METHODS—From 1999 to 2007, computerized medical records were reviewed for BSI due to MDR gram-negative bacteria within 48 hours of hospital admission. Risk factors for BSI due to these bacteria were identified.

RESULTS—MDR gram-negative bacteria were recovered from 61 (8%) of 724 elderly patients with BSI caused by gram-negative bacteria. Over the $8\frac{1}{2}$- year study period, the percentage of MDR gram-negative bacteria among bloodstream isolates increased from 2 (1%) of 199 to 34 (16%) of 216. Empiric therapy was ineffective for 38 (63%) of 60 patients with BSI caused by MDR gram-negative bacteria. The variables independently associated with BSI due to these bacteria were as follows: residency in a long-term care facility (odds ratio [OR], 4.9 [95% confidence interval {CI} 1.6–14.9]; P =.006), presence of an invasive device (OR, 6.0 [95% CI, 1.5–23.5]; P =.01), severe sepsis (OR, 7.9 [95% CI, 1.7–37.1]; P =.009), and delayed initiation of effective therapy (OR, 12.8 [95% CI, 3.9–41.1]; P < .001).

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CONCLUSION—The 16-fold increase in BSI due to MDR gram-negative bacteria at hospital admission among elderly patients, especially among those who resided in long-term care facilities prior to admission, contributes further to the expanding body of evidence that these patients are the main reservoirs of MDR gram-negative bacteria. Given their contribution to the influx of antimicrobial-resistant bacteria in the hospital setting, infection control interventions that target this high-risk group need to be considered.

Bacteremia due to gram-negative organisms ranks among the most serious infections encountered in clinical practice, with mortality rates that approach 45%.[1] The incidence of sepsis caused by gram-negative bacteria is highest among elderly patients, who are twice as likely as younger individuals to die of this infection.[2] The proportion of gram-negative bacteria resistant to multiple antimicrobials is rapidly increasing throughout the world and is posing an additional challenge in the treatment of sepsis.[3–7] Elderly patients are at particularly high risk of harboring multidrug-resistant (MDR), gram-negative bacteria.[8,9] In one long-term care facility, MDR gram-negative bacteria were recovered from 21.8% of clinical cultures and were more commonly recovered than other types of antimicrobial-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci.[8] Another study identified advanced age as a risk factor for MDR gram-negative blood stream infection (BSI) at hospital admission.[9] Despite increasing documentation of MDR gram-negative bacteria as emerging pathogens of great concern among those who treat elderly patients, the epidemiology of BSI due to these bacteria remains poorly understood. The goal of this study was to characterize the clinical epidemiology of BSI due to MDR gram-negative bacteria among elderly patients at hospital admission in an effort to provide a greater understanding of these serious infections and ultimately to improve patient outcomes.

METHODS

The study was conducted at the Beth Israel Deaconess Medical Center, a 530-bed, academic tertiary care hospital where an average of 27,000 patients are admitted each year. The institution's Clinical Committee of Investigation approved this study.

Definitions

MDR bacteria were defined as bacteria that were resistant or intermediately susceptible to 3 or more of the following antimicrobials or antimicrobial classes: (1) extended-spectrum penicillins (ampicillin-sulbactam or piperacillin-tazobactam); (2) carbapenems (imipenem or meropenem); (3) ceftazidime; (4) fluoroquinolones (ciprofloxacin or levofloxacin); and (5) aminoglycosides (gentamicin, tobramycin, or amikacin). BSI was defined according to Centers of Disease Control and Prevention criteria.[10] Severe sepsis was defined as BSI with a Pitt bacteremia score greater than 4.[11,12] This scoring system measures the severity of illness associated with BSI on admission by summing the points assigned to several clinical observations. These points are assigned as follows: (1) a temperature of 35.1°C–36.0°C or 39.0°C–39.9°C scores 1 point, and a temperature of either 35°C or less or 40°C or more scores 2 points; (2) systolic blood pressure less than 90 mm Hg for longer than 1 hour despite adequate fluid resuscitation, receipt of vasopressors, and/or receipt of mechanical

ventilation score 2 points each; (3) cardiac arrest scores 4 points; and (4) altered mental status scores 1 point for disorientation, 2 points for stupor, and 4 points for coma.[12]

Effective antimicrobial therapy was defined as receipt of at least 1 antimicrobial active against the MDR gram-negative bacteria recovered at the time blood culture results were obtained. If an aminoglycoside was the only antimicrobial administered that was active against the MDR gram-negative organism responsible for the patient's bacteremia, therapy was considered inappropriate.

Identification of MDR Gram-Negative Bacteria in Blood Cultures

To determine and describe the prevalence and antimicrobial coresistance patterns of MDR gram-negative bacteria recovered from blood cultures, we reviewed computerized microbiological records for patients admitted during the period from January 1, 1999, to April 13, 2007. Records from patients 65 years of age and older who had MDR gram-negative bacteria isolated from blood samples obtained within 48 hours after admission were identified and selected for analysis. Patients with polymicrobial culture results were excluded. Patients who transferred from another hospital to the study hospital were also excluded unless they had had less than 48 hours of exposure to a hospital setting before collection of the first blood sample with a positive culture result.

Case-Control Study

A case-control study was performed to determine the risk factors associated with BSI due to MDR gram-negative bacteria at hospital admission among elderly patients. Case patients were defined as patients 65 years of age and older who had MDR gram-negative bacteria recovered from culture of at least 1 blood sample obtained within 48 hours after admission. Control subjects were patients 65 years of age and older who had gram-negative bacteria susceptible to all antimicrobials tested recovered from culture of at least 1 blood sample obtained within 48 hours after admission. Two control subjects were chosen for each case patient, and all 3 individuals were matched with respect to the gram-negative bacterial species recovered. If multiple control subjects were available, we selected the control subjects whose time of admission was closest to that of the relevant case patient. Patients with BSI due to gram-negative bacteria susceptible to all antimicrobials tested were selected as control subjects specifically to address the risk factors associated with multidrug resistant gram-negative bloodstream isolates.

Data Collection

Record review included computerized medical, pharmacy, and microbiological data, including patient demographic characteristics, site of residence prior to admission, ambulatory status, and presence of an invasive device at admission, as well as any data about surgery, intensive care unit exposure, and duration of antibiotic treatment within 90 days before admission. Possible residence sites were long-term care facilities, other hospitals, or patients' homes. Invasive devices included indwelling urinary catheters, central venous catheters, and nephrostomy tubes, tracheostomy tubes, and percutaneous gastroenterostomy tubes. The Charlson score was used to provide a composite score for comorbid conditions.[13]

Long-term receipt of hemodialysis and any requirement for immunosuppressive medications were also documented.

The initial antimicrobial treatment received after admission and the number of hours that elapsed between collection of the first blood sample that yielded a positive culture result and the initiation of effective antimicrobial therapy were abstracted from pharmacy and microbiology computerized databases. The total length of hospital stay after admission and in-hospital mortality were also recorded.

Identification and Susceptibility Profile of Bacterial Isolates

Identification and susceptibility testing were performed in accordance with Clinical and Laboratory Standards Institute guidelines[14] by using the automated Vitek I system (bio-Mérieux). The susceptibility thresholds used to define resistance (ie, minimal inhibitory concentration) were as follows: ampicillin-sulbactam, 32/16 μg/mL or greater; piperacillin-tazobactam, 128 μg/mL or greater; imipenem or meropenem, 8 μg/mL or greater; ceftazidime, 16 μg/mL or greater; aminoglycosides, 8 μg/mL or greater; ciprofloxacin, 2 μg/mL or greater; and levofloxacin, 4 μg/mL or greater. Production of extended-spectrum β-lactamase was determined by use of the combination-disk method.[15]

Statistical Analysis

Statistical analysis was performed with Stata, version 7.0 (Stata). Temporal trends in antimicrobial resistance were analyzed by use of the χ^2 test for trend. Continuous variables were dichotomized at the mean, including age, Charlson score, duration of any antimicrobial exposure during the 90 days prior to study enrollment, and Pitt bacteremia score. Categorical variables were analyzed by use of the χ^2 test. Variables that were statistically significant on univariate analysis were entered into a conditional logistic regression model. A 2-sided P value of .05 or less was considered statistically significant.

RESULTS

Longitudinal Trends in BSI at Admission

During the study period, 724 patients 65 years of age and older had gram-negative bacteria recovered from at least 1 culture of a blood sample collected within 48 hours after hospital admission. Samples from 61 patients (8%) yielded 61 gram-negative isolates that met the criteria for multidrug resistance. The proportion of elderly subjects with BSI due to MDR gram-negative bacteria increased significantly throughout the $8\frac{1}{2}$-year study period ($P < .001$) (Figure 1).

Characterization of MDR Gram-Negative Isolates

The distribution of MDR gram-negative bacteria according to species was as follows: 29 (48%) of 61 isolates were *Escherichia coli,* 19 (31%) were *Klebsiella pneumoniae,* 11 (18%) were *Proteus mirabilis,* and 2 (3%) were *K. oxytoca*. MDR gram-negative isolates of the same species and antimicrobial susceptibility pattern as those recovered from the blood were recovered from urinary tract sites (35 [58%] of 61 patients), abdominal sites (9 patients

[15%]), or pulmonary sites (5 patients [8%]) sampled within 24 hours after collection of a blood sample that yielded a positive culture result.

Table 1 shows resistance to individual antimicrobial agents or drug classes for each MDR gram-negative species. Forty-four (72%) of 61 MDR gram-negative isolates were coresistant to 3 different antimicrobial groups, and 17 (28%) were coresistant to 4 antimicrobial groups. The 2 most common coresistance profiles were a 3-drug pattern that involved resistance to extended-spectrum penicillins, fluoroquinolones, and aminoglycosides, which was observed in 36 isolates (59%), and a 4-drug pattern that involved resistance to extended-spectrum penicillins, ceftazidime, fluoroquinolones, and aminoglycosides, which was observed in 17 isolates (28%). Table 2 shows the percentage of MDR gram-negative bacteria with each coresistance profile, according to species. A total of 24 (39%) MDR gram-negative isolates were found to produce extended-spectrum β-lactamase; this group included 7 (24%) of 29 *E. coli* isolates and 17 (89%) of 19 *K. pneumoniae* isolates.

Characteristics of Patients With BSI Due to These Bacteria

Complete records were available for 60 of 61 elderly patients who had BSI due to MDR gram-negative bacteria within 48 hours after hospital admission. Clinical and demographic characteristics for case patients and control subjects are presented in Table 3.

The stepwise conditional logistic regression model included all variables that were statistically significant on univariate analysis, with the exception of renal insufficiency and chronic pulmonary disease, which are represented in the Charlson score. Four variables were independently associated with BSI due to MDR gram-negative bacteria at admission: residency in a long-term care facility (odds ratio [OR], 4.9 [95% confidence interval {CI}, 1.6–14.9]; $P = .006$), presence of an invasive device on admission (OR, 6.0 [95% CI, 1.5–23.5]; $P = .01$), severe sepsis (ie, Pitt bacteremia score greater than 4) (OR, 7.9 [95% CI, 1.7–37.1]; $P = .009$), and delayed initiation of effective antibiotic therapy for 24 hours or more after the time a blood sample that yielded a positive culture result was collected (OR, 12.8 [95% CI, 3.9–41.1]; $P < .001$).

Case patients were more likely than control subjects to have a mean length of stay after admission of 7 days or longer (36 [60%] of 61 case patients vs 37 [31%] of 120 control subjects; unadjusted OR, 1.1 [95% CI, 1.1–1.2]; $P < .001$). The mortality rate was also greater among case patients than control subjects (11 case patients [18%] died vs 6 control subjects [5%]; unadjusted OR, 4.8 [95% CI, 1.5–15.3]; $P = .008$).

Empiric Antibiotic Therapy at Admission for Patients With BSI

The empiric therapy chosen at the time of admission was ineffective for 38 (63%) of 60 patients with BSI due to MDR gram-negative bacteria. The distribution of ineffective antimicrobial therapy, by drug or drug class, was as follows: ampicillin-sulbactam was chosen for 3 patients, for 3 (100%) of whom it was ineffective; ampicillin was chosen for 5 patients, for 5 (100%) of whom it was ineffective; fluoroquinolones were chosen for 21 patients, for 21 (100%) of whom they were ineffective; gentamicin was chosen for 1 patient, for whom it was ineffective (100%); ceftazidime was chosen for 2 patients, for 1 (50%) of whom it was ineffective; and ceftriaxone was chosen for 16 patients, for 7 (43%) of whom it

was ineffective. There were 6 patients who received piperacillin-tazobactam, 5 who received meropenem, and 1 who received cefepime; for these 3 groups of patients, these drugs were effective therapy.

DISCUSSION

Our study documented a 16-fold increase in the incidence of BSI due to MDR gram-negative bacteria in elderly patients at hospital admission over an $8\frac{1}{2}$-year study period. The percentage of bloodstream isolates that were MDR increased from 1% in 1999–2000 to 16% in 2005–2007. Twenty-four (39%) of 61 MDR gram-negative isolates were found to produce extended-spectrum β-lactamase. This dramatic rise in the incidence of MDR gram-negative bacteria is of great concern because the therapeutic options available to physicians for the treatment of infections caused by MDR bacteria are severely limited. The problem created by the paucity of effective antimicrobials is compounded by immunosenescence among elderly patients and their higher mortality rates from BSI due to gram-negative bacteria, compared with younger individuals.[2,16]

The MDR gram-negative isolates identified in this study were resistant to commonly prescribed antimicrobials. Sixty-one (100%) of 61 MDR gram-negative isolates were resistant to ampicillin-sulbactam, 60 (98%) were resistant to fluoroquinolones, and 25 (41%) were resistant to ceftazidime. Although a 3-drug pattern of resistance was the most common, 17 isolates (28%) were resistant to 4 antimicrobials. Ineffective empiric therapy was initiated for 38 (63%) of 60 elderly patients with BSI due to MDR gram-negative bacteria at admission. Ampicillin-sulbactam and fluoroquinolones were the antimicrobials most commonly prescribed for those who received ineffective empiric therapy, which reflects the high rate of resistance to these antimicrobials. Timely initiation of effective antibiotic therapy has been shown to be critical in reducing morbidity and mortality rates among those with severe infection.[17–20] In this study, the great majority of MDR gram-negative isolates remained susceptible to piperacillin-tazobactam and carbapenems. Clinicians who treat patients at high risk for infection with MDR gram-negative bacteria should become familiar with the antimicrobial susceptibility patterns of the organisms typically found in their institution and region and initiate empiric antimicrobial therapy accordingly.

The most common presumed origin of BSI was the urinary tract, because 35 (58%) of 61 patients had the same MDR gram-negative species recovered from urine and blood samples. The origin can only be presumed because phenotypic, as opposed to genotypic, analysis was performed. Given the frequency of urinary tract infections among elderly patients and the high resistance rates among the pathogens that cause such infections, initial empiric treatment with ampicillin or fluoroquinolones at the time of admission may no longer be as effective as it was in the past for this patient population.

The elderly patients at highest risk of BSI due to MDR gram-negative bacteria were residents of long-term care facilities and those who had invasive devices. These patient characteristics identify a subgroup of patients who may potentially benefit from treatment with broader-spectrum antimicrobials, given the high likelihood of infection with MDR gram-negative bacteria. Previous studies have delineated the long-term care facility

population as an increasingly important reservoir of MDR gram-negative bacteria with the potential for spreading antibiotic-resistant organisms into other settings.[21,22] These risk factors and others associated with harboring antimicrobial-resistant bacteria, including poor functional status, urinary or fecal incontinence, and the presence of multiple comorbidities,[23,24] are not easily modifiable. Substantial attention has focused on antimicrobial exposure because this is a potentially modifiable risk factor. It is estimated that 40%–80% of antimicrobial use for the general long-term care facility population is inappropriate.[25–29] Extensive use of antimicrobials for long-term care facility residents with advanced dementia, especially during the 2 weeks prior to death, has also been documented.[30] Since antimicrobial exposure promotes both the exogenous and endogenous acquisition of antimicrobial-resistant bacteria,[31] improving antimicrobial prescribing patterns has become a major focus of preventive strategies.[32] Rigorous attention to hand hygiene and other infection control practices that limit patient-to-patient transmission of antimicrobial-resistant pathogens are also important prevention strategies.

In this study, elderly patients with BSI due to MDR gram-negative bacteria were more likely to have severe sepsis at hospital admission than were control subjects, as evidenced by their significantly higher Pitt bacteremia scores. Mortality rates were higher among case patients; 11 (18%) of 61 case patients with BSI caused by MDR gram-negative bacteria died, compared with 6 (5%) of 120 control subjects with BSI due to gram-negative bacteria that were susceptible to all antimicrobials tested. The length of hospital stay was also longer for case patients than control subjects. These preliminary findings, unadjusted for potential confounders, warrant confirmation by a study designed to directly address the outcomes of elderly patients with BSI due to MDR gram-negative bacteria.

Our study has several limitations. First, a case-control study was necessary, given the infrequent occurrence of BSI due to MDR gram-negative bacteria. To minimize measurement and selection bias, computerized medical records were used; however, several important variables, such as functional status at admission, outpatient antibiotic exposure, and infection-attributable mortality, could not be assessed in this retrospective study.[33] Second, the definition for MDR gram-negative bacteria used in this study was based on the antimicrobials for which our microbiology laboratory commonly reports susceptibility profiles, and we have used this definition in previous studies.[34] Studies that use alternative definitions may produce different results. Third, although our study demonstrated a dramatic rise in the number of MDR gram-negative bacteria recovered, it likely underestimates the burden imposed by MDR gram-negative bacteria because we did not address infections other than BSI nor did we address colonization status. Fourth, the study reflects the experience of a tertiary care academic hospital, and its findings may not be generalizable to other healthcare settings. Lastly, the goal of this study was to determine the factors associated with BSI due to MDR gram-negative bacteria, and therefore control subjects were chosen from the population of patients with BSI caused by gram-negative bacteria susceptible to all antimicrobials tested. Choosing control subjects whose blood cultures were negative for gram-negative bacteria or for whom blood culture results were not obtained would have addressed a different question.[35]

This study characterizes the clinical epidemiology of BSI due to MDR gram-negative bacteria in elderly patients at hospital admission. The results indicate a dramatic rise in BSI caused by MDR gram-negative among elderly patients; in addition, 38 (63%) of 60 case patients were treated with ineffective therapy at admission. It is important for healthcare workers to be aware of this increasing trend in order to optimize antimicrobial prescribing patterns for this high-risk patient population. This study further emphasizes the role of long-term care facility residents as reservoirs of MDR gram-negative bacteria and their contribution to the influx of these antimicrobial-resistant bacteria into the hospital setting.[8,9,22] Infection control interventions targeted at this high-risk group may be warranted.

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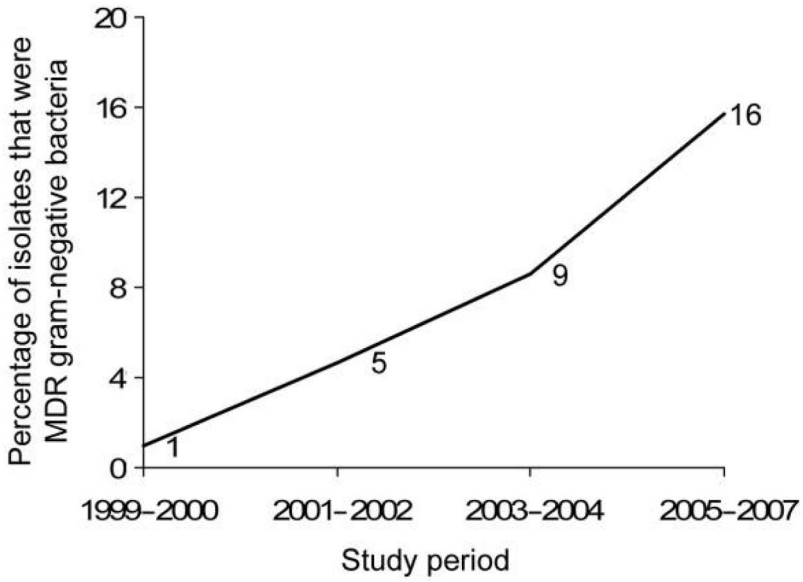

FIGURE 1.

Prevalence of multidrug-resistant (MDR), gram-negative bacteria among bloodstream isolates. Isolates were recovered from samples obtained within 48 hours after hospital admission from patients 65 years of age and older during an $8\frac{1}{2}$- year study period. ($P <$. 001)

TABLE 1

Resistance to Antimicrobials Among Multidrug-Resistant (MDR) Gram-Negative Isolates Recovered from Elderly Patients With Bacteremia, According to Species

Antimicrobial(s) or antimicrobial class	No. (%) of isolates			
	Total (*N* = 61)	MDR *Escherichia coli* (*n* = 29)	MDR *Klebsiella* species (*n* = 21)	MDR *Proteus mirabilis* (*n* = 11)
Ampicillin-sulbactam	61 (100)	29 (100)	21 (100)	11 (100)
Piperacillin-tazobactam	5 (8)	0 (0)	5 (8)	0 (0)
Ceftazidime	25 (41)	7 (24)	18 (86)	0 (0)
Carbapenems[a]	0 (0)	0 (0)	0 (0)	0 (0)
Fluoroquinolones[b]	60 (98)	29 (100)	20 (95)	11 (100)
Aminoglycosides[c]	54 (89)	27 (93)	16 (76)	11 (100)

[a] Imipenem or meropenem.

[b] Ciprofloxacin or levofloxacin.

[c] Gentamicin, tobramycin, or amikacin.

TABLE 2

Coresistance Profiles of Multidrug-Resistant (MDR) Gram-Negative Isolates Recovered from Elderly Patients With Bacteremia, According to Species

	No. (%) of isolates			
Coresistance profile	**Total (*N* = 61)**	**MDR *Escherichia coli* (*n* = 29)**	**MDR *Klebsiella* species (*n* = 21)**	**MDR *Proteus mirabilis* (*n* = 11)**
ESP- FQ-AMG	36 (59)	22 (76)	3 (15)	11 (100)
ESP-CTZ-FQ-AMG	17 (28)	5 (17)	12 (60)	0 (0)
ESP-CTZ-FQ	7 (11)	2 (7)	5 (25)	0 (0)
ESP-CTZ-AMG	1 (2)	0 (0)	1 (1)	0 (0)

NOTE. Three isolates in the extended-spectrum penicillins (ESP)–ceftazidime (CTZ)–fluoroquinolones (FQ)–aminoglycosides (AMG) group were resistant to piperacillin-tazobactam, and 2 isolates in the ESP-CTZ-FQ group were resistant to piperacillin-tazobactam.

TABLE 3

Demographic and Clinical Characteristics of Elderly Patients With And Without Bloodstream Infection Due to Multidrug-Resistant, Gram-Negative Bacteria at Hospital Admission

	No. (%) of participants			
Variable	**Case patients (*n* = 60)[a]**	**Control subjects (*n* = 120)**	**OR (95% CI)**	***P***
Age ≥79 years	24 (40)	61 (50)	0.6 (0.3–1.2)	.16
Female sex	24 (40)	63 (52)	0.6 (0.3–1.1)	.12
Chronic pulmonary disease	13 (22)	11 (9)	2.8 (1.1–6.8)	.03
Chronic renal insufficiency	18 (30)	20 (17)	2.2 (1.0–4.7)	.04
Diabetes mellitus	12 (20)	19 (16)	1.3 (0.6–2.9)	.5
Long-term receipt of hemodialysis	4 (7)	5 (4)	1.9 (0.4–8.9)	.4
Charlson index score ≥4	37 (62)	51 (42)	2.2 (1.2–4.3)	.02
Receipt of immunosuppressive treatment	7 (12)	19 (16)	0.8 (0.3–1.9)	.5
Invasive device present[b]	29 (48)	18 (15)	8.3 (3.1–21.8)	<.001
Nonambulatory	36 (60)	35 (29)	4.0 (2.0–8.5)	<.001
Long-term care facility resident	34 (57)	26 (22)	5.1 (2.4–11.0)	<.001
Events during the 90-day period before admission				
Antibiotic exposure for ≥7 days	26 (43)	18 (15)	5.5 (2.3–12.9)	<.001
≥1 hospitalization	41 (68)	46 (38)	3.0 (1.6–5.6)	.001
Admission to intensive care unit	17 (28.3)	10 (8)	4.3 (1.8–10.3)	.001
Surgery	19 (32)	15 (13)	2.8 (1.4–5.9)	.005
Severe sepsis[c]	14 (23)	8 (7)	4.2 (1.6–11.0)	.003
Admitted to the intensive care unit	29 (48)	23 (19)	3.9 (1.9–7.9)	<.001
≥24 h delay in receipt of effective therapy	25 (41)	10 (8)	6.2 (2.8–13.6)	<.001

NOTE. CI, confidence interval; OR, odds ratio.

[a] There were 60 complete medical records available for 61 patients.

[b] Includes tracheostomy, gastroenterostomy, and nephrostomy tubes; central venous catheters; or long-term indwelling Foley catheters.

[c] Pitt bacteremia score >4.