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Risk factors and Outcomes of Infections Caused by Extremely Drug-Resistant Gram-Negative Bacilli in Patients Hospitalized in Intensive Care Units

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Abstract

Background—Extremely drug-resistant gram-negative bacilli (XDR-GNB) increasingly cause healthcare-associated infections (HAIs) in intensive care units (ICUs).

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Methods—A matched case-control (1:2) study was conducted from February 2007 to January 2010 in 16 ICUs. Case and control subjects had HAIs caused by GNB susceptible to ≤1 antibiotic versus ≥2 antibiotics, respectively. Logistic and Cox proportional hazards regression assessed risk factors for HAIs and predictors of mortality, respectively.

Results—Overall, 103 case and 195 control subjects were enrolled. An immunocompromised state (OR=1.55, p=0.047) and exposure to amikacin (OR=13.81, p<0.001), levofloxacin (OR=2.05, p=0.005), or trimethoprim-sulfamethoxazole (OR=3.42, p=0.009) were factors associated with XDR-GNB HAIs. Multiple factors in both case and control subjects significantly predicted increased mortality at different time intervals after HAI diagnosis. At 7 days, liver disease (Hazard Ratio [HZ]=5.52), immunocompromised state (HR=3.41), and bloodstream infection (HR=2.55) predicted mortality; at 15 days, age (HR=1.02 per year increase), liver disease (HR=3.34), and immunocompromised state (HR 2.03) predicted mortality; and at 30 days, age (HR=1.02 per one year increase), liver disease (HR=3.34), immunocompromised state (HR=2.03), and hospitalization in a medical ICU (HR=1.85) predicted mortality.

Conclusions—HAIs caused by XDR-GNB were associated with potentially modifiable factors. Age, liver disease, and immunocompromised state, but not XDR-GNB HAIs, were associated with mortality.

Introduction

Antibiotic-resistant gram-negative bacilli (GNB) are increasingly common causes of healthcare-associated infections (HAIs) in intensive care units (ICUs) [1] and are associated with higher mortality rates, longer hospitalizations, and increased healthcare expenditures [2, 3]. Effective treatment for extremely drug-resistant (XDR) GNB infections is challenging due to limited therapeutic options [4].

In this study, we examined the epidemiology and outcomes of HAIs caused by XDR-GNB in the 16 ICUs affiliated with our medical center. We performed a case-control study to identify risk factors associated with XDR-GNB infections compared with non-XDR-GNB infections. We hypothesized that exposure to carbapenem agents would be associated with HAIs caused by XDR-GNB. In addition, we performed a survival analysis to explore if predictors for death changed 7, 15, and 30 days after diagnosis of an HAI. We hypothesized that HAIs caused by XDR-GNB would be associated with an increased hazard for mortality and that the effect would be most pronounced at 7 days, rather than at 15 or 30 days.

Materials and Methods

Study Design and Study Setting

This study was a prospective cohort study with a nested, matched case-control study. It was conducted from February 2007 to January 2010 in the 16 ICUs affiliated with NewYork-Presbyterian (NYP) Hospital located in New York City. NYP is a 2,278-bed (383 ICU-bed) tertiary-care facility affiliated with two medical schools, Columbia University College of Physicians and Surgeons and Weill Cornell Medical College. Study ICUs included medical (n=5), surgical (n=6), burn (n=1), and pediatric/neonatal (n=4) ICUs and had approximately 14,800 annual patient admissions. Institutional Review Board approval was obtained from

Columbia University Medical Center and Weill Cornell Medical College with a waiver of informed consent.

Study Subjects and Case Definitions

The cohort was defined as all patients admitted to the study ICUs during the study period. Case subjects were defined as patients hospitalized in the ICU with healthcare-associated bloodstream infections (BSIs), pneumonia (PNA), or urinary tract infections (UTIs) caused by XDR-*Acinetobacte*r spp., *Klebsiella pneumoniae*, or *Pseudomonas aeruginosa* (defined below). Control subjects were defined as patients hospitalized in the ICU with HAIs caused by non-XDR *Acinetobacte*r spp., *K. pneumoniae*, or *P. aeruginosa*. HAIs were diagnosed using the Centers for Disease Control & Prevention's National Hospital Safety Network (NHSN) definitions [5], but modified to include antimicrobial treatment. When feasible, case and control subjects were matched (1:2) by the following matching hierarchy: campus (Columbia or Cornell), type of ICU (medical or surgical), type of infection (BSI, PNA, or UTI), date of culture, and pathogen (*Acinetobacte*r spp., *K. pneumoniae*, or *P. aeruginosa*). Patients were excluded if their infections developed < 48 hours after hospital admission, were a non-study type of infection, e.g., skin and soft tissue infection, or were caused by a non-study pathogen.

XDR-GNB were the species described above, susceptible to ≤1 antimicrobial agent or only susceptible to imipenem and meropenem as determined by commercial broth microdilution susceptibility panels (described below). Non-XDR-GNB were susceptible to ≥2 antimicrobial agents. Susceptibility to tigecycline and polymyxin B were not included in the definitions of XDR- and non-XDR-GNB, as these agents were not consistently tested at the study sites. MICs were interpreted according to the Clinical and Laboratory Standards Institute breakpoints in effect during the study period [6-8].

Potential subjects were identified prospectively using EpiPortal, a web-based surveillance system developed by the NYP Department of Infection Prevention & Control and Department of Information Technology and Columbia University Department of Biomedical Informatics [9]. EpiPortal integrates data from different electronic systems (e.g., microbiology laboratories, pharmacy, medical records) to identify patients with epidemiologically significant organisms including multidrug-resistant pathogens. The electronic medical record of each potential subject was reviewed by a study physician to confirm case or control status and to determine the presence of comorbid conditions, antibiotic exposures, and medical device use (central venous catheter, mechanical ventilation, and/or urinary catheter). Demographic and microbiological data were also obtained from the electronic medical record.

At the Columbia campus, blood culture samples from adults were inoculated into BD Bactec Plus Aerobic/F and Bactec Lytic/10 Anaerobic/F bottles, while pediatric samples were inoculated into Bactec Peds Plus/F bottles (Becton Dickinson, Franklin Lakes, NJ). At the Cornell campus blood culture samples obtained from adults and children were inoculated into BactT Alert bottles (bioMérieux, Durham, NC). Respiratory and urine samples were plated onto MacConkey agar at both study sites. During the study period, the clinical microbiology laboratories used the Vitek 2 system (bioMérieux, Durham, NC) as the

primary method of antibiotic susceptibility testing (AST). The laboratory on the Columbia campus used the Vitek 2 AST GN09 prior to May 2009 and afterwards used GN35. The laboratory on the Cornell campus used Vitek 2 AST GN13 prior to January 2009 and afterwards used GN28 for *Klebsiella* and *Acinetobacter* spp. and GN31 for *Pseudomonas aeruginosa*. Both laboratories performed Etests (bioMérieux, Durham, NC) to determine susceptibility to polymyxin B and tigecycline for XDR strains if requested, and at Cornell, Etests for tigecycline were regularly performed after January 2009.

Risk Factors for HAIs and Predictors of Mortality

Risk factors evaluated for HAIs caused by XDR-GNB vs. non-XDR-GNB included age, sex, race and ethnicity; days of ICU and hospital stay prior to infection; comorbid conditions (defined below); exposure to antibiotics administered during hospitalization in the 30 days prior to infection; and use of medical devices in the 7 days prior to infection. Comorbid conditions were defined using APACHE II/III classification [10]. Briefly, liver disease was defined as biopsy-proven cirrhosis or portal hypertension; respiratory disease was defined as a chronic process resulting in severe exercise restriction; cardiovascular disease was defined as symptoms of cardiac insufficiency at rest; renal impairment was defined as the use of chronic dialysis; and immunocompromised state was defined as conditions that increased susceptibility to infection (e.g., leukemia/lymphoma, metastatic cancer) or receipt of immunosuppressant medications (e.g., chemotherapy, high dose steroids).

Potential predictors of mortality were infection with an XDR-GNB, age, sex, comorbid conditions, type of ICU, duration of ICU stay prior to infection, pathogen, type of infection, and time to effective therapy (defined below).

Outcomes

The onset of HAIs was defined as the first day of positive culture(s). Several outcomes related to antibiotic treatment were compared among case vs. control subjects. These included: (1) duration of therapy (calendar days) with ≥1 antibiotic(s) with GNB activity administered following HAI diagnosis; (2) the number of antibiotics with GNB activity; (3) time to effective therapy with ≥1 antibiotic(s) to which the infecting organism was susceptible *in vitro*, including tigecycline and polymyxin B; and (4) duration of effective therapy. Effective therapy was considered “not received” if the time to effective therapy was >7 days. In addition, the proportion of case vs. control subjects with persistently positive blood cultures (i.e., positive cultures for >1 calendar day) within 7 days of the first blood culture was determined. During the hospital admission in which the HAI was diagnosed, mortality was determined 7, 15, and 30 days after the HAI was diagnosed.

Statistical Analysis

To assess risk factors for HAIs, conditional logistic regression was used for bivariate analyses. Using a backward elimination approach, multivariable conditional logistic regression was used to examine potential risk factors associated with HAIs caused by XDR-GNB. The final model included age, sex, and length of stay prior to infection, and all risk factors significant at $p<0.05$.

To assess predictors of mortality, Cox proportional hazards regression was used for bivariate analyses. Using a backward elimination approach, multivariable Cox proportional hazards regression was used to examine potential predictors of risk of mortality at a specific time point (i.e., hazard). Three survival analyses were conducted to explore if predictors changed when the observation time for subjects was censored at 7, 15, and 30 days following HAI diagnosis. The final models included age and case status, and all predictors significant at $p<0.05$. Statistical analyses were completed in SAS 9.2 for Windows (SAS Institute Inc., Cary, NC).

Results

Subjects

During the study period, 103 case subjects and 195 control subjects were identified; 92 case subjects were matched to 2 control subjects and 11 were matched to 1 control subject. The demographic and clinical characteristics of subjects are shown in Table 1. Six case and 8 control subjects were <18 years old, including one case from the neonatal ICU. Consistent with the matching strategy, comparable proportions of subjects were hospitalized at each campus and type of ICU. Pneumonia was the most common HAI, followed by BSI. While the proportion of case and control subjects with HAIs caused by *K. pneumoniae* was similar, the proportions of infections caused by *Acinetobacter* spp. and *P. aeruginosa* were significantly different among case and control subjects ($p<0.001$); few HAIs were caused by XDR-*P. aeruginosa* or by non-XDR-*Acinetobacter* spp.

Antibiotic Susceptibilities of GNB Isolates

The antimicrobial susceptibilities of the GNB isolates from case and control subjects are shown in Table 2. Consistent with the case definitions, a greater proportion of non-XDR-GNB isolates were susceptible to aminoglycoside, fluoroquinolone, and β-lactam agents than XDR-GNB. Susceptibility to these antimicrobial classes varied from 0% to 16% among XDR isolates and from 86% to 99% among non-XDR isolates. Most XDR isolates had tigecycline MICs ≤2 μg/mL (68%, 58/85 tested) and polymyxin B MICs ≤2 μg/mL (90%, 75/83 tested).

Risk factors for XDR-GNB HAIs

The proportion of case and control subjects with comorbid conditions and device use is shown in Table 3. Compared to control subjects, case subjects were more likely to have chronic respiratory conditions and to require mechanical ventilation, but did not have a longer hospital or ICU length of stay prior to infection.

Inpatient antibiotic use during the 30 days prior to infection differed among case and control subjects as shown in Table 4. In the bivariate analyses, case subjects were more likely to have been exposed to several antimicrobial agents including amikacin, a carbapenem agent, linezolid, piperacillin-tazobactam, polymyxin B, tigecycline, trimethoprim-sulfamethoxazole, and vancomycin.

In the final multivariable analyses, four variables were identified as significant risk factors for HAIs caused by XDR-GNB as shown in Table 5. These included immunocompromised state and exposure to the antimicrobial agents amikacin, levofloxacin, or trimethoprim-sulfamethoxazole. Comorbid conditions and device use were not identified as risk factors.

Antibiotic Treatment and Persistently Positive Blood Cultures

The mean duration of antibiotic therapy was similar among case (15.7 days) and control (13.4 days) subjects (p=0.41). However, more antimicrobial agents with GNB activity were administered to case (mean 3.8 antibiotics) than to control (mean 3.1 antibiotics) subjects (p=0.001). Although the mean duration of effective therapy did not differ between case (11.1 days) and control (9.8 days) subjects (p=0.21), the mean time to effective therapy was longer for case (3.0 days) than control (1.3 days) subjects (p<.001). Furthermore, fewer case (83%) than control (96%) subjects received effective therapy within 7 days of their first positive blood culture (p<0.001). Among those who survived at least one week following their first positive blood culture, 12% (3/25) of case and 16% (7/44) of control subjects had persistently positive blood cultures (p=0.66).

Mortality

More case (59%) than control (31%) subjects died during their hospital stay (p<0.001). Among those who died, the mean survival after HAI was similar among case (22.6 days) and control (27.1 days) subjects (p=0.44). Among cases, 11 deaths occurred within 7 days of infection and 21 deaths occurred >30 days after infection. For those with BSIs, mortality was higher for case (77%, 26/34) than control (31%, 21/68) subjects (p<0.001). Similarly, for those with PNA, mortality was higher for case (58%, 29/50) than control (36%, 33/92) subjects (p=0.010). However, mortality was similar among case (32%, 6/19) and control (20%, 7/35) subjects with UTIs (p=0.53).

The multivariable Cox proportional hazards regression for 7-, 15-, and 30-day mortality is presented in Table 6. Case status was not an independent predictor of mortality at any of these time intervals, but an immunocompromised state or liver disease was an independent predictor. BSI was a significant predictor for 7-day mortality only, while older age was a significant predictor for 15- and 30-day mortality. Type of pathogen and time to effective therapy were not independent predictors of mortality.

Discussion

This is one of the largest recent studies to describe the epidemiology of HAIs caused by XDR-GNB among patients hospitalized in ICUs and to assess relevant outcomes including predictors of mortality. To further delineate the impact of HAIs caused by XDR-GNB, we performed a matched case-control study adjusting for previously identified predictors of HAIs caused by resistant pathogens including several comorbid conditions, use of medical devices, and length of stay [11]. We demonstrated that an immunocompromised state or previous treatment with amikacin, levofloxacin, or trimethoprim-sulfamethoxazole within 30 days of infection were risk factors for HAIs caused by XDR-GNB. While in-hospital mortality was higher among case subjects, XDR-GNB HAIs did not predict mortality at 7,

15, or 30 days after HAI diagnosis. However, BSIs caused by either XDR- or non-XDR-GNBs did predict mortality at 7 days.

Contrary to our hypothesis, we did not find that treatment with carbapenem agents was a risk factor for XDR infection. Several previous studies have also assessed antimicrobial exposures as risk factors for infection and/or colonization with XDR GNB, but have not had consistent findings. Henceforth in this discussion, we will use the term multi-drug resistant (MDR) GNB, as it is the term most commonly used by the authors cited, though definitions of XDR and MDR GNB may vary. Use of fluoroquinolone agents has been associated with HAIs caused by *K. pneumoniae* carbapenemase (KPC)-producing strains or carbapenem-resistant *A. baumannii* [12, 13]. Exposure to imipenem [14, 15], piperacillin-tazobactam [14], vancomycin [14, 15], or aminoglycoside agents [14, 15] has also been associated with detection of imipenem-resistant *P. aeruginosa* from clinical cultures. Furthermore, exposure to trimethoprim-sulfamethoxazole has been associated with MDR- *Stenotrophomonas maltophilia* [16], colonization with trimethoprim-sulfamethoxazole-resistant Enterobacteriaceae [17] and UTIs caused by trimethoprim-sulfamethoxazole-resistant *Escherichia coli* [18].

While an immunocompromised state has been described as a risk factor for HAIs [19], the association with MDR-GNB infection is less clear. Steroid use during the previous 30 days has been associated with infections caused by extended spectrum β-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae* [20]. Similarly receipt of antineoplastic, immunosuppressive, and immunomodulating agents has been associated with acquisition of MDR-GNB [21]. Conversely, others did not find that immune suppression (defined as solid or hematological malignancy, leukopenia, or chronic use of immunosuppressive agents) was associated with MDR-GNB infections [22].

However, studies of risk factors for MDR-GNB infections and/or colonization are difficult to compare. Study designs, study populations, local epidemiology, and definitions of resistance vary widely [23, 24]. Furthermore, risk factors may be affected by the route of acquisition of MDR-organisms (MDROs); MDROs may arise from *de novo* selection via antibiotic exposure or be transmitted from other patients, healthcare personnel, or the healthcare environment [25]. Additional factors may increase the risk of progression from colonization to infection such as medical devices, breakdown in mucosal barriers, or impaired immune function [11].

While others have reported that HAIs caused by MDR-GNBs were associated with increased mortality [26, 27], XDR case status was not a predictor of mortality in the current study, despite more deaths in case subjects. Notably, many deaths among case subjects occurred >30 days after infection and few deaths occurred within 7 days of infection, as would be expected for HAI-attributable mortality. Our survival analysis implicated two comorbid conditions, liver disease and an immunocompromised state, as independent predictors of mortality at 7, 15 and 30 days after HAIs. We speculate that the severity of illness associated with these comorbid conditions accounted for the increased risk of mortality. Others have also found that higher APACHE II scores and Charlson comorbidity indices have also been associated with an increased mortality risk [28].

We explored several predictors of mortality related to antibiotic treatment. We did not find that a delay in effective therapy impacted mortality—again likely confounded by the effect of comorbidities. Similarly, two previous studies have shown that timely administration of antibiotics was not associated with survival among patients with BSIs caused by carbapenem-resistant *K. pneumoniae* [2, 29]. In contrast, delays in appropriate therapy have been associated with mortality in patients with MDR *E. coli* and *P. aeruginosa* bacteremia [30, 31]. In the current study, while the mean duration of therapy was similar among case and control subjects, case subjects received more unique antibiotics. Thus, treatment of XDR-GNB most likely results in more antibiotic exposures and further antibiotic resistance.

This study had limitations. It was performed at a large, tertiary care hospital system in New York City and findings may not be generalizable to other settings; NYC is known to be an epicenter for XDR-GNB infections in ICUs [32]. Our definition of XDR-GNB was crafted prior to the recent international consensus definition which could further limit the generalizability of our findings [33]. We did not determine clonality and therefore could not distinguish if the infections were endemic or epidemic. The diagnosis of pneumonia, even using NHSN diagnostic criteria, lacks both sensitivity and specificity [34]. We did not assess the potential impact of removal of central venous catheters which may have impacted outcomes. Our matching hierarchy may have led to overmatching and selection bias [35]. The use of control subjects infected with susceptible GNBs may have inflated the odds ratios for antibiotic exposures since patients previously treated with antibiotic agents may be less likely to be infected with a susceptible organism [36]. Lastly, while comorbid conditions were associated with mortality, attributable mortality was no assessed.

Conclusion

XDR-GNB infections have emerged as a clinical threat to hospitalized patients, particularly to those in the ICU. We have demonstrated that XDR-GNB infections were associated with exposures to several antibiotics, some of which may be amenable to antibiotic stewardship [37]. Predictors for mortality after HAIs with XDR-GNB were not modifiable, as mortality was more likely to be associated with age and underlying diseases.

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Table 1

Characteristics of Case vs. Control Subjects with Healthcare-associated Infections Caused by Gram-Negative Bacilli

Characteristic	Case Subjects (n=103)	Control Subjects (n=195)	p-value[a]
	n (%)		
Age group			0.701
< 50 yrs	22 (21.4)	44 (22.6)	
50–75 yrs	57 (55.3)	94 (48.2)	
> 75 yrs	24 (23.3)	57 (29.2)	
Sex			1.00
Male	59 (57.3)	111 (56.9)	
Female	44 (42.7)	84 (43.1)	
Race			0.43
White	34 (33.0)	47 (24.1)	
Black	8 (7.8)	21 (10.8)	
Asian/Pacific Islander	2 (1.9)	4 (2.1)	
Other	15 (14.6)	30 (15.4)	
Unknown	44 (42.7)	93 (47.7)	
Ethnicity			0.63
Hispanic	12 (11.7)	18 (9.2)	
Non-Hispanic	30 (29.1)	51 (26.2)	
Unknown	61 (59.2)	126 (64.6)	
Campus[b]			1.00
Columbia University Medical Center	49 (47.6)	96 (49.2)	
Weill Cornell Medical Center	54 (52.4)	99 (50.8)	
ICU type[b]			0.82
Medical ICU	53 (51.5)	103 (52.8)	
Surgical and Burn ICU	50 (48.5)	92 (47.2)	
Type of infection[b]			1.00
Bloodstream	34 (33.0)	68 (34.9)	
Pneumonia	50 (47.6)	92 (47.2)	
Urinary tract	19 (19.4)	35 (17.9)	
Pathogen[b]			**<0.001**
Klebsiella pneumoniae	48 (46.6)	100 (51.3)	
Acinetobacter spp.	49 (47.6)	21 (10.8)	
Pseudomonas aeruginosa	6 (5.8)	74 (37.9)	

[a] Bivariate conditional logistic regression

[b] Variable included in matching hierarchy

ICU= Intensive care unit

Table 2

Comparison of Selected Susceptibility Profiles of Gram-Negative Bacilli Causing Healthcare-associated Infections among Case and Control Subjects

Antimicrobial Agent	Case Subjects (n=103)	Control Subjects (n=195)
	Susceptible n/N[a] (%)	Susceptible n/N[a] (%)
Amikacin	15/96 (15)	193/195 (99)
Cefepime	7/98 (7)	166/193 (86)
Ciprofloxacin	0/50 (0)	86/96 (90)
Gentamicin	16/102 (16)	178/196 (91)
Imipenem	1/67 (1)	129/142 (91)
Levofloxacin	0/102 (0)	167/195 (86)
Meropenem	6/82 (7)	127/140 (91)
Piperacillin-tazobactam	1/51 (2)	76/87 (87)
Polymyxin B[b]	75/83 (90)	14/14 (100)
Tigecycline[c]	58/85 (68)	5/9 (56)
Trimethoprim-sulfamethoxazole	1/101 (1)	100/121 (83)
Tobramycin	3/82 (4)	162/170 (95)

[a] n= number susceptible isolates and N= number of isolates with available results

[b] Interpretive criteria do not exist for the Enterobacteriacae when testing polymyxin B; therefore, the susceptible breakpoint of ≤2 μg/mL approved for *P. aeruginosa* and *Acinetobacter* spp. was employed for these organisms.

[c] Interpretive criteria do not exist for the *Acinetobacter* spp. when testing tigecycline; therefore, the susceptible breakpoint of ≤2 μg/mL approved for Enterobacteriacae was employed for these organisms.

Table 3

Risk Factors for Healthcare-associated Infections (HAIs) with Gram-Negative Bacilli: Comorbid Conditions and Medical Device Use[a]

Risk factors	Case Subjects N=103	Control Subjects N=195	p-value
Comorbid Conditions	n (%)		
None	47 (45.6)	113 (57.9)	0.12
Liver disease	5 (4.9)	9 (4.6)	0.90
Immunocompromised state	33 (32.0)	41 (21.0)	0.11
Cardiovascular disease	9 (8.7)	14 (7.2)	0.70
Chronic respiratory disease	12 (11.7)	7 (3.6)	**0.028**
Chronic renal impairment	15 (14.6)	15 (7.7)	0.22
Length of stay prior to HAI			
Hospital, mean ± SD (days)	28.8 ± 31.2	20.3 ± 23.9	0.13
ICU, mean ± SD (days)	11.5 ± 9.5	11.2 ± 17.3	1.00
Device use within 7 days of HAI			
Mechanical ventilation	85 (82.5)	124 (63.6)	**0.011**
Urinary catheter	93 (90.3)	156 (80.0)	0.17
Central venous catheter	81 (78.6)	143 (73.3)	0.48

[a] Bivariate Analyses

ICU= Intensive care unit

Table 4
Antimicrobial Use Within 30 days Prior to Healthcare-associated Infections

Antimicrobial Agent	Case Subjects N=103	Control Subjects N=195	OR (95%CI)	p-value[a]
	n (%)			
Amikacin	13 (12.6)	1 (0.5)	13.07 (2.96, 57.66)	**0.001**
Ampicillin	9 (8.7)	6 (3.1)	1.91 (0.84, 4.32)	0.12
Ampicillin-sulbactam	9 (8.7)	12 (6.1)	1.22 (0.64, 2.34)	0.54
Aztreonam	7 (6.8)	6 (3.1)	1.59 (0.70, 3.60)	0.27
Carbapenems	33 (32.0)	20 (10.3)	2.32 (1.44, 3.74)	**0.001**
Cefazolin	9 (8.7)	24 (12.3)	0.84 (0.47, 1.47)	0.54
Cefepime	20 (19.4)	19 (9.7)	1.53 (0.94, 2.48)	0.09
3rd generation cephalosporin[b]	13 (12.6)	15 (7.7)	1.36 (0.76, 2.41)	0.30
Clindamycin	3 (2.9)	6 (3.1)	1.00 (0.42, 2.40)	1.00
Daptomycin	6 (5.8)	5 (2.6)	1.63 (0.66, 4.00)	0.29
Gentamicin	14 (13.6)	15 (7.7)	1.28 (0.75, 2.18)	0.36
Levofloxacin	21 (20.4)	21 (10.8)	1.51 (0.94, 2.42)	0.09
Linezolid	22 (21.4)	12 (6.2)	2.37 (1.33, 4.20)	**0.003**
Macrolide[c]	19 (18.5)	19 (9.7)	1.53 (0.87, 2.68)	0.14
Metronidazole	25 (24.3)	38 (19.5)	1.13 (0.77, 1.64)	0.54
Oxacillin	6 (5.8)	12 (6.2)	0.85 (0.42, 1.70)	0.64
Piperacillin-tazobactam	73 (70.9)	101 (51.8)	1.46 (1.04, 2.06)	**0.029**
Polymyxin B	11 (10.7)	0 (0)	1.13 (1.28, 3.54)	**<0.001**
Tigecycline	10 (9.7)	2 (1.0)	5.16 (1.65, 16.13)	**0.005**
Tobramycin	31 (30.1)	34 (17.4)	1.57 (0.99, 2.47)	0.05
Trimethoprim-sulfamethoxazole	14 (13.6)	4 (2.1)	3.62 (1.56, 8.39)	**0.003**
Vancomycin	78 (75.3)	104 (53.3)	1.57 (1.12, 2.22)	**0.001**

[a] Bivariate Analyses

[b] Cefotaxime, ceftriaxone, ceftazidime

[c] Erythromycin or azithromycin

Table 5

Risk Factors Associated with Healthcare-associated Infections Caused by Extremely Drug-resistant Gram-Negative Bacilli, Multivariable analysis

Risk Factor[a]	OR (95% CI)	p-value
Immunocompromised state	1.55 (1.01, 2.39)	**0.047**
Amikacin	13.81 (2.96, 64.47)	**0.001**
Levofloxacin	2.05 (1.24, 3.40)	**0.005**
Trimethoprim-sulfamethoxazole	3.42 (1.36, 8.60)	**0.009**

[a] Age, sex, and hospital stay were forced into the final model and were not significant

Table 6

Predictors of Mortality after Healthcare-associated Infection (HAI) Diagnosis with Censoring at 7-, 15-, and 30-days

Predictors of Mortality	Multivariable Cox Proportional Hazards Analysis	
	Hazard Ratio (95% CI)	p-value
Death within 7 days		
Case status[a]	0.94 (0.42, 1.95)	0.87
Age (per one year increase)[a]	1.01 (0.99, 1.04)	0.22
Liver disease	5.52 (1.79, 16.99)	**0.003**
Immunocompromised state	3.41 (1.67, 6.96)	**0.001**
Bloodstream infection[b]	2.55 (1.32, 4.86)	**0.005**
Death within 15 days		
Case status[a]	1.39 (0.84, 2.31)	0.20
Age (per one-year increase)[a]	1.02 (1.00, 1.04)	**0.014**
Liver disease	3.24 (1.30, 8.07)	**0.012**
Immunocompromised state	2.66 (1.57, 4.50)	**<.001**
Death within 30 days		
Case status[a]	1.39 (0.90, 2.15)	0.14
Age (per one-year increase)[a]	1.02 (1.01, 1.03)	**0.002**
Liver disease	3.34 (1.56, 7.12)	**0.001**
Immunocompromised state	2.03 (1.33, 3.11)	**0.001**
Medical intensive care unit[c]	1.85 (1.22, 2.86)	**0.005**

[a] Case status and age were included *a priori* in the model

[b] Compared to urinary tract infection

[c] Compared to surgical intensive care unit