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Modifiable Risk Factors for the Spread of *Klebsiella pneumoniae* Carbapenemase-Producing Enterobacteriaceae Among Long-Term Acute-Care Hospital Patients

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Abstract

Objective.—To identify modifiable risk factors for acquisition of *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriaceae (KPC) colonization among long-term acute-care hospital (LTACH) patients.

Design.—Multicenter, matched case-control study.

Setting.—Four LTACHs in Chicago, Illinois.

Participants.—Each case patient included in this study had a KPC-negative rectal surveillance culture on admission followed by a KPC-positive surveillance culture later in the hospital stay. Each matched control patient had a KPC-negative rectal surveillance culture on admission and no KPC isolated during the hospital stay.

Results.—From June 2012 to June 2013, 2,575 patients were admitted to 4 LTACHs; 217 of 2,144 KPC-negative patients (10.1%) acquired KPC. In total, 100 of these patients were selected at random and matched to 100 controls by LTACH facility, admission date, and censored length

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of stay. Acquisitions occurred a median of 16.5 days after admission. On multivariate analysis, we found that exposure to higher colonization pressure (OR, 1.02; 95% CI, 1.01–1.04; P = .002), exposure to a carbapenem (OR, 2.25; 95% CI, 1.06–4.77; P = .04), and higher Charlson comorbidity index (OR, 1.14; 95% CI, 1.01–1.29; P = .04) were independent risk factors for KPC acquisition; the odds of KPC acquisition increased by 2% for each 1% increase in colonization pressure.

Conclusions.—Higher colonization pressure, exposure to carbapenems, and a higher Charlson comorbidity index independently increased the odds of KPC acquisition among LTACH patients. Reducing colonization pressure (through separation of KPC-positive patients from KPC-negative patients using strict cohorts or private rooms) and reducing carbapenem exposure may prevent KPC cross transmission in this high-risk patient population.

Carbapenem-resistant Enterobacteriaceae (CRE) are a serious public health threat due to limited antibiotic treatment options and high mortality of CRE bacteremia.[1–5] *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriaceae (KPC) have been identified worldwide and are the most common CRE reported in the United States.[6] KPC are highly prevalent among patients in long-term acute-care hospitals (LTACHs); KPC colonization prevalence sometimes reaches 50%.[7,8]

LTACHs are specialized hospitals where patients with multiple comorbid medical conditions and acute-care needs are admitted for an average length of stay of ≥25 days.[9] Multiple medical comorbidities, recent exposures to acute care hospitals, high rates of antibiotic and medical device use, and long lengths of stay put LTACH patients at increased risk of colonization and infection with multidrug-resistant organisms such as KPC.[9,10]

We previously described the successful implementation of a KPC control bundle in 4 Chicago LTACHs.[11] The bundle comprised active surveillance for KPC rectal colonization at the time of admission and every other week thereafter; contact isolation and geographic separation of KPC-positive patients in ward cohorts or private rooms; daily bathing of all patients with 2% chlorhexidine gluconate-impregnated cloths; and healthcare worker education and adherence monitoring with an emphasis on hand hygiene.[11] During the KPC control intervention, the incidence rate of KPC colonization and infection decreased significantly, yet 10% of patients still acquired KPC during their stays. Therefore, in the present study we sought to identify modifiable risk factors for acquisition of KPC colonization in the LTACH population.

Methods

Study Design and Setting

We performed a matched case-control study to determine risk factors for acquisition of KPC colonization among patients at 4 Chicago LTACHs from June 2012 to June 2013 during implementation of a KPC control bundle.[11] The median number of beds at each LTACH was 109 (range, 94–165), with a total of 476 beds in the 4 LTACHs. The institutional review board at Rush University Medical Center reviewed and approved the study.

Definitions

Each case patient included in this study had a KPC-negative rectal surveillance culture on admission followed by a KPC-positive rectal surveillance culture later in the hospital stay. Control patients were patients with a KPC-negative rectal surveillance culture on admission, at least 1 subsequent KPC-negative rectal surveillance culture, and no KPC-positive rectal surveillance or clinical culture isolated during the hospital stay. Because surveillance cultures were performed every other week, the exact calendar date of KPC acquisition was not known for case patients; thus, we defined the date of KPC acquisition as the point midway between the last negative and the first positive surveillance culture. Cases and controls were matched 1:1 by LTACH, closest admission date (±14 days), and censored length of stay. Time to KPC acquisition was defined as the time from admission to KPC acquisition. Cases were analyzed from admission through the time to KPC acquisition and censored thereafter; controls were followed for the same length of time as their matched cases and censored thereafter.

To estimate the magnitude of potential exposure to KPC among patients at risk of acquiring KPC colonization, we calculated ward-level KPC colonization pressure for the period immediately before acquisition of KPC by case patients and their matched, KPC-negative controls. Colonization pressure was defined as the number of KPC-positive patients on the ward divided by the total number of patients on the ward at the date of the last negative surveillance culture before KPC acquisition for cases, or at the date of the matched negative surveillance culture for controls.[12]

Inclusion and Exclusion Criteria

Patients were eligible to participate in the study if they had a negative rectal surveillance culture for KPC upon admission and at least 1 subsequent rectal surveillance culture result reported during the hospital stay. Exclusion criteria were (1) length of stay <72 hours, (2) known clinical or surveillance culture positive for KPC before admission, and (3) clinical culture positive for KPC before surveillance culture was KPC-positive, which would have precluded imputation of acquisition date for cases.

Medical Record Review

Medical records were reviewed to collect patient demographics, comorbid medical conditions, Charlson comorbidity index,[13] history of infection or colonization with multidrug-resistant organisms (ie, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococci*, *Clostridium difficile*, extended-spectrum β-lactamase-producing gram-negative rods, multidrug-resistant *Acinetobacter baumannii*, or multidrug-resistant *Pseudomonas* spp.), clinical characteristics (ie, mental status, mobility, presence of wound or pressure ulcer, and fecal incontinence), presence of medical devices, and exposure to medications. Medications of interest were systemic antibiotics, gastric acid suppressing agents (H_2 blocker, proton pump inhibitor), and immunosuppressants. Systemic antibiotics were classified as follows (1 agent could be included in multiple categories): any β-lactam, extended-spectrum cephalosporin (third- or fourth-generation cephalosporin), carbapenem, β-lactam/β-lactamase inhibitor, parenteral vancomycin, enteral vancomycin, fluoroquinolone, tigecycline, and antibiotics with antianaerobic activity. To assess antibiotic

exposure immediately before KPC acquisition, we recorded antibiotic administration in the time interval from the date of last negative surveillance culture to the date of imputed KPC acquisition for cases and during the matched time interval for paired controls.

Microbiological Methods

Rectal swab specimens were obtained by inserting a sterile, polyester culture swab (BBL CultureSwab, Becton, Dickinson, Franklin Lakes, NJ) into the anal canal as previously described.[11] Specimens were screened for KPC by an ertapenem disk method; bla_{KPC} was confirmed by polymerase chain reaction.[14–16] Isolates that carried bla_{KPC} were identified to species and tested for antimicrobial susceptibility by the MicroScan Walkaway System (Siemens, Tarrytown, NY).

Statistical Analysis

Continuous variables were compared using the Student *t* test or the Mann-Whitney *U* test, and categorical variables were compared using the χ^2 test or the Fisher's exact test, where appropriate. All variables significant at $P \leq .10$ in univariate analyses were included in a multivariate logistic regression model. Stepwise backward elimination with the likelihood ratio test was used. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The calibration of the model was assessed using the Hosmer-Lemeshow goodness-of-fit test. Statistical significance was defined at $P < .05$ (2-tailed).

We used data from an earlier study to calculate an effect size of Cohen's h = .55 for the reduction in colonization prevalence attributable to the presence or absence of dementia.[17] The assumed effect size of h = .55, a sample size of 100 and a 1-tailed α of .05 provided a power of .84 to detect the difference in the proportion of patients with a risk factor for the study design. All analyses were performed using IBM SPSS Statistics version 22 software (IBM, Armonk, NY).

Results

Patient Demographics, Clinical Characteristics, and Antibiotic Exposure

During the study period, 217 (10.1%) of 2,144 eligible patients acquired KPC in the 4 LTACHs despite an ongoing bundled intervention. In total, 100 patients were randomly selected from these 217 patients and matched to 100 control patients. The mean age (± standard deviation) was 63.0 ±15.4 years for cases and 60.5 ± 14.1 years for controls. Overall, 44% of cases and 50% of controls were female. The largest LTACH (LTACH C) accounted for approximately half of the cases and controls (Table 1). The median censored length of stay (time to KPC acquisition for cases) was 16.5 days (interquartile range [IQR], 7.5–28.8 days). Overall, 96% of control admission dates were within 14 days of their matched case. Because most cases and controls were admitted on the same day and discharged at about the same time, they had the same number of surveillance cultures (median, 2; range 2–11).

On univariate analysis, case patients had significantly higher median Charlson comorbidity index values than control patients (4 vs 3; $P = .05$) (Table 1). Case patients were more

likely than control patients to be confused (73% vs 56%; $P = .01$), bed bound (93% vs 83%; $P = .03$), or incontinent of stool (82% vs 70%; $P = .05$); to have a percutaneous gastrostomy tube (64% vs 50%; $P = .05$); or to have received any β-lactam antibiotic (63% vs 49%; $P = .05$), carbapenem antibiotic (25% vs 14%; $P = .05$), or any antibiotic with antianaerobic activity (60% vs 44%; $P = .02$). There were no significant differences in exposures to other medications. The proportions of case and control patients with a history of MDRO colonization or infection were similar. Case patients were exposed to a higher median colonization pressure than control patients (26.8% vs 19.7%; $P = .005$) (Table 1). Notably, the observed range of colonization pressure exposure was wide for both cases and controls (0% to >85%).

On multivariate analysis (Table 2), colonization pressure (OR, 1.02; 95% CI, 1.01–1.04; for each 1% increase; $P = .002$), Charlson comorbidity index (OR, 1.14; 95% CI, 1.01–1.29; for each 1-point increase; $P = .04$), and exposure to carbapenem antibiotics (OR, 2.25; 95% CI, 1.06–4.77; $P = .04$) were independent risk factors for KPC acquisition. Notably, individual components of the Charlson comorbidity index were analyzed and were not found to be significant risk factors in the multivariate analysis. The Hosmer-Lemeshow test indicated a good model fit ($P = .63$).

Colonization Pressure and Odds of KPC Acquisition

Because KPC colonization pressure was identified as a strong, independent, and potentially modifiable risk factor for KPC acquisition, we further examined the odds of KPC acquisition for cases and controls across the entire range of observed colonization pressures. We divided colonization pressure into the following categories: 0% (n = 17 patients exposed), 0.1%–20% (n = 72 patients exposed), 20.1%–40% (n = 73 patients exposed), 40.1%–60% (n = 18 patients exposed), 60.1%–80% (n = 11 patients exposed), and 80.1%–100% (n = 9 patients exposed). Using a colonization pressure of 0% as the reference, the odds ratio for KPC acquisition increased significantly in a linear fashion as colonization pressure increased: For each 1% increase in colonization pressure, the odds of KPC acquisition increased by 2% ($P = .001$ for linear increase) (Figure 1).

Sensitivity Analysis

We performed a sensitivity analysis in which colonization pressure at the time of first positive surveillance culture (rather than at the time of the last negative surveillance culture) was included in the model. Colonization pressure (OR, 1.02; 95% CI, 1.00–1.03; for each 1% increase; $P = .03$), Charlson comorbidity index (OR, 1.15; (95% CI, 1.02–1.30; for each 1-point increase; $P = .03$), and exposure to carbapenem antibiotics (OR, 2.29; 95% CI, 1.09–4.82; $P = .03$) remained significant independent risk factors for KPC acquisition.

Discussion

In this multicenter, matched case-control study of LTACH patients, we found that KPC colonization pressure, exposure to carbapenem antibiotics, and Charlson comorbidity index were associated with acquisition of KPC colonization. Of the 3 risk factors identified in our study, 2 are potentially modifiable: carbapenem administration and colonization

pressure. Improving strategies to separate KPC-positive and KPC-negative patients and reducing carbapenem exposure through antibiotic stewardship represent approaches that should be emphasized in future interventions to control KPC in LTACHs. Strengths of our study include availability of longitudinal data on KPC colonization from admission and serial point prevalence surveys, which allowed us to estimate the date of acquisition of KPC colonization within a narrow time window. In turn, this ensured that predictive risk factors were measured before KPC acquisition and therefore were valid. Results of serial rectal colonization surveillance also allowed us to calculate accurate estimates of ward-level colonization pressure over time, a parameter that has been found to be critical in understanding the epidemiology of KPC and other multidrug-resistant organisms.[18–20]

Colonization pressure is usually defined as the proportion of patients colonized with a particular organism in a defined geographic area within a hospital during a specified time period.[12,21,22] In the current study, LTACH patients were exposed to a wide range of colonization pressures; the average colonization pressure of 29.3% was higher than colonization pressures typically observed in short-stay acute-care hospitals.[8,23] In some LTACHs in our study, KPC-positive patients were cared for on dedicated cohort wards. During occasional bed shortages, KPC-negative patients were admitted to KPC-positive cohort wards, leading to colonization pressures that exceeded 80%. Colonization pressure exerted a dose–response effect on the estimated odds of KPC acquisition and remained a significant risk factor for KPC acquisition at all levels of colonization pressure. These findings explain in part why control of KPC transmission in LTACHs with high baseline KPC prevalence is so difficult. Notably, KPC transmission occurred despite an ongoing bundled intervention.[11] High colonization pressure may compromise the barrier to cross transmission provided by chlorhexidine gluconate, contact precautions, and hand hygiene, which underscores the importance of developing more reliable approaches for geographical separation of KPC-colonized and at-risk patients.[12]

In addition to colonization pressure, we identified exposure to a carbapenem antibiotic to be a modifiable, independent risk factor for KPC acquisition. Carbapenem exposure has been identified as a risk factor for KPC or CRE colonization or infection in acute-care hospitals, ICUs, and LTACHs.[23–33] It is plausible that exposure to carbapenems provides pressure for selection or expansion of carbapenem-resistant bacteria in the microbial community of a patient's gut. Antimicrobial stewardship was not included in our previously published KPC control bundle.[11] Limiting carbapenem therapy in patients at-risk of KPC acquisition is an additional intervention that warrants expedited evaluation. Notably, a new Joint Commission Medication Management standard (MM.9.01.01) for accreditation that requires US hospitals, including LTACHs, to have an antimicrobial stewardship program in place became effective January 1, 2017.[34]

We also found that LTACH patients with higher Charlson comorbidity indices were at increased risk of KPC acquisition. Others have reported that comorbid conditions and the presence of medical devices were associated with KPC colonization or infection in LTACHs[23,35,36] and that MDRO acquisition likely is related to increased risk of exposure to invasive devices or antibiotics and to decreased host defenses.[37] Compared with control patients, case patients were more often confused, bedbound, and incontinent of stool and

were more likely to have a percutaneous gastrostomy tube in place. These factors are markers for greater need for hands-on care that might increase risk of cross-transmission via healthcare workers.

Our study has limitations. First, we could not determine the exact day of KPC acquisition because surveillance cultures were obtained every other week. Although we imputed the KPC acquisition date as the midpoint between the last negative and the first positive surveillance cultures of case patients, patients could have acquired KPC at any time between the last negative and the first positive culture survey. However, all variables were measured at a point that included the day of the last negative surveillance culture of case patients such that predictive risk factors were present before acquisition. Second, conversion from negative surveillance to positive surveillance cultures in our study could represent "unmasking" of KPC colonization rather than new acquisition of KPC due to cross-transmission, ie, KPC colonization may have been present but below the limit of detection of the rectal screening culture test at the time of LTACH admission. However, unmasking was probably uncommon given that the clinical sensitivity of our rectal swab culture assay exceeds 80%.[38] Nonetheless, risk factors identified in our study might be associated with either acquisition or unmasking. Detailed microbiologic analysis (eg, whole-genome sequencing) of isolates may help to more reliably differentiate these 2 processes. Third, this study was conducted during the implementation of a bundled intervention that included geographical separation of patients. However, because cases and controls were nondifferentially exposed to the same intervention and matched by facility, the effect estimate of colonization pressure risk is unlikely to be biased toward or away from the null. While most short-stay hospitals are not likely to have wards with median KPC prevalence as high as those seen among LTACH wards in this study, microenvironments of high colonization pressure are plausible even in facilities with low overall KPC prevalence, eg, if a KPC-negative patient is placed next door or in the same room as a KPC-colonized patient. Lastly, our case-control design was powered to identify predictors of moderate effect size; there may be residual predictors of small effect size that remain unidentified.

In conclusion, we found that LTACH patients who were exposed to higher colonization pressure or to a carbapenem antibiotic, or who had a higher Charlson comorbidity index were at increased risk of KPC acquisition as determined by serial rectal surveillance cultures. Of these risk factors, 2 are potentially modifiable, which underscores the importance for such high-risk populations of developing better approaches to reducing colonization pressure (through separation of KPC-positive patients from KPC-negative patients using strict cohorts or private rooms) and reducing carbapenem use through antimicrobial stewardship.

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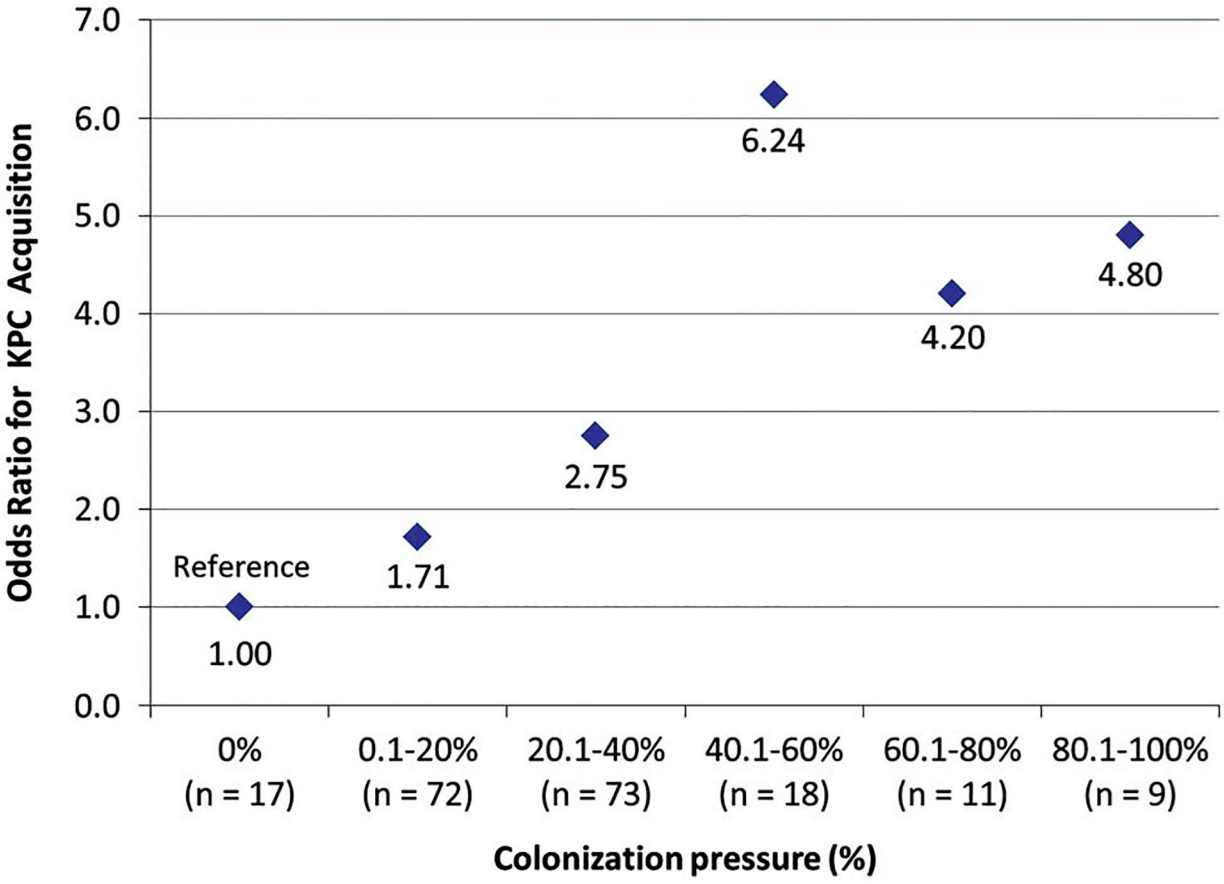

Figure 1.

Odds ratio for *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriaceae (KPC) acquisition by colonization pressure. The proportion of patients who acquired KPC increased as colonization pressure due to KPC increased ($P = .001$ for linear increase in odds ratio as colonization pressure due to KPC increased).

Table 1.

Univariate Analysis of Risk Factors for KPC Acquisition in Long-Term Acute-Care Hospitals (LTACHs)

Variable	Cases (n = 100), No. (%)[a]	Control (n = 100) No. (%)[a]	OR (95% CI)	*P* Value
Demographics				
Age, y mean (± SD)	63.0 (±15.4)	60.5 (±14.1)		.22
Female	44 (44)	50 (50)	.78 (.45–1.30)	.39
Race/ethnicity				.20
White	26 (26)	25 (25)		
Black	61 (61)	52 (52)		
Hispanic	6 (6)	15 (15)		
Other	7 (7)	8 (8)		
Matching variables				
LTACHs				
A	18 (18)	18 (18)		
B	18 (18)	18 (18)		
C	49 (49)	49 (49)		
D	15 (15)	15 (15)		
Censored length of stay, d, median (IQR)[b]	16.5 (7.5–30.5)	16.5 (7.0–28.0)		.72
Predictor variables				
Colonization pressure, %, median (range)	26.8 (0.0–96.2)	19.7 (0.0–86.6)		.005
Comorbid medical conditions				
Charlson comorbidity index, median (IQR)	4 (2–6)	3 (2–5)		.05
Cerebrovascular disease or dementia	41 (41)	31 (31)	1.55 (.87–2.77)	.14
Hemiplegia	17 (17)	17 (17)	1.00 (.48–2.09)	.99
Cardiovascular disease	44 (44)	38 (38)	1.28 (.73–2.26)	.39
Chronic pulmonary disease	68 (68)	68 (68)	1.00 (.55–1.81)	.99
Gastrointestinal disease including liver disease	9 (9)	8 (8)	1.14 (.42–3.08)	.80
Moderate to severe renal disease	31 (31)	23 (23)	1.50 (.80–2.82)	.20
Diabetes mellitus	50 (50)	46 (46)	1.17 (.67–2.05)	.57
Connective tissue disease	1 (1)	1 (1)	1.00 (.06–16.21)	.99
Solid tumor or hematological malignancy	16 (16)	10 (10)	1.71 (.74–3.99)	.20

Infect Control Hosp Epidemiol. Author manuscript; available in PMC 2021 August 23.

Variable	Cases (n = 100), No. (%)[a]	Control (n = 100) No. (%)[a]	OR (95% CI)	*P* Value
Human immune deficiency virus infection	2 (2)	2 (2)	1.00 (.14–7.24)	.99
Solid organ transplantation	1 (1)	0 (0)		
Gastrointestinal surgery	8 (8)	11 (11)	0.70 (.27–1.83)	.47
History MDRO colonization or infection				
Methicillin-resistant *Staphylococcus aureus*	32 (32)	34 (34)	0.91 (.51–1.65)	.76
Vancomycin-resistant *Enterococci*	17 (17)	13 (13)	1.37 (.63–3.00)	.43
Clostridium difficile	7 (7)	5 (5)	1.43 (.44–4.67)	.77
Extended-spectrum β-lactamase–producing gram-negative rod	6 (6)	8 (8)	0.73 (.25–2.20)	.58
Multidrug-resistant *Acinetobacter baumanii*	8 (8)	6 (6)	1.36 (.46–4.08)	.58
Multidrug-resistant *Pseudomonas* spp.	1 (1)	3 (3)	0.33 (.03–3.19)	.62
Clinical status				
Confused[c]	73 (73)	56 (56)	2.12 (1.18–3.84)	.01
Unresponsive[c]	20 (20)	20 (20)	1.00 (.50–2.00)	.99
Bedbound[c]	93 (93)	83 (83)	2.72 (1.08–6.89)	.03
Wheelchair bound[c]	3 (3)	5 (5)	0.59 (.14–2.53)	.72
Wound or pressure ulcer[c]	94 (94)	90 (90)	1.74 (.61–4.99)	.30
Incontinence of stool[d]	82 (82)	70 (70)	1.95 (1.00–3.80)	.05
Medical device [c]				
Tracheostomy	58 (58)	51 (51)	1.33 (.76–2.32)	.32
Central venous catheter	47 (47)	40 (40)	1.33 (.76–2.33)	.32
Percutaneous gastrostomy tube	64 (64)	50 (50)	1.78 (1.01–3.13)	.05
Nasogastric tube	4 (4)	10 (10)	0.38 (.11–1.24)	.10
Urinary catheter	71 (71)	69 (69)	1.10 (.60–2.02)	.76
Rectal tube	5 (5)	2 (2)	2.58 (.49–13.62)	.45
Exposure to medication [e]				
Any antibiotic	79 (79)	73 (73)	1.39 (.72–2.67)	.32
Any β lactam	63 (63)	49 (49)	1.77 (1.01–3.12)	.05
Extended-spectrum cephalosporin	18 (18)	10 (10)	1.98 (.86–4.53)	.10
Carbapenem	25 (25)	14 (14)	2.05 (.99–4.22)	.05

Variable	Cases (n = 100), No. (%)[a]	Control (n = 100) No. (%)[a]	OR (95% CI)	*P* Value
β-lactam/β-lactamase inhibitor	27 (27)	26 (26)	1.05 (.56–1.97)	.87
Parenteral vancomycin	36 (36)	33 (33)	1.14 (.64–2.05)	.66
Enteral vancomycin	15 (15)	8 (8)	2.03 (.82–5.03)	.12
Fluoroquinolone	15 (15)	19 (19)	0.75 (.36–1.58)	.45
Tigecycline	3 (3)	1 (1)	3.06 (.31–29.95)	.62
Antianaerobic agent	60 (60)	44 (44)	1.91 (1.09–3.35)	.02
Antifungal agent	17 (17)	13 (13)	1.37 (.63–3.00)	.43
H2 blocker or proton pump inhibitor	81 (81)	81 (81)	1.00 (.49–2.03)	.99
Immunosuppressant	13 (13)	21 (21)	0.56 (.26–1.20)	.13

Note. KPC, *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriaceae; MDRO, multidrug-resistant organism; OR, odds ratio; CI, confidence interval; SD, standard deviation.

[a] Unless noted otherwise.

[b] For case patients, length of stay was censored at the time of KPC acquisition; control patients were analyzed for the same length of time as their matched cases and were censored thereafter.

[c] On admission.

[d] After admission.

[e] After the last negative surveillance culture screening through the estimated date of acquisition.

Table 2.

Multivariate Analysis of Risk Factors for KPC Acquisition in Long-Term Acute-Care Hospitals (LTACHs)

Variable	OR (95% CI)	*P* Value
Colonization pressure, %	1.02 (1.01–1.04)	.002
Charlson comorbidity index	1.14 (1.01–1.29)	.04
Exposure to carbapenem antibiotics	2.25 (1.06–4.77)	.04

Note. KPC, *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriaceae; OR, odds ratio; CI, confidence interval.