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BRIEF REPORT

Risk Factors for Colistin-Resistant Carbapenem-Resistant *Klebsiella pneumoniae* in the Postacute Care Setting

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We assessed risk factors for colistin resistance among carbapenem-resistant *Klebsiella pneumoniae* (CRKP) from 375 patients in long-term acute care hospitals. Recent colistin or polymyxin B exposure was associated with increased odds of colistin resistance (adjusted odds ratio = 1.11 per day of exposure, 95% confidence interval = 1.03–1.19, $P = .007$).

Keywords. carbapenem-resistant *Klebsiella pneumoniae*; colistin; long-term acute care hospitals.

Patients with chronic critical illness (CCI), comprising those who survive acute critical illness but require prolonged intensive care therapies, experience a substantial risk of infections caused by multidrug-resistant organisms (MDROs) due to their extensive healthcare and antibiotic exposures. Among these organisms, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is of particularly high clinical and epidemiologic importance due to its limited armamentarium of treatment options and high incidence among CCI patients. For example, an 8- to 9-fold higher prevalence of CRKP colonization has been reported among patients of long-term acute care hospitals (LTACHs) than those of short-stay hospitals [1, 2]. Colistin, a polymyxin antibiotic, is considered an important last-line antibiotic for the treatment of CRKP infections due to its in vitro activity against carbapenem-resistant Enterobacterales and the amount of clinical experience for its use in treating these infections [3, 4]. However, colistin resistance among CRKP has been increasingly reported, and infection with colistin-resistant CRKP is associated with increased mortality compared to infection with colistin-susceptible isolates [5, 6]. Despite this, risk factors for colistin-resistant CRKP infection remain poorly defined among CCI patients, with no published studies to date that specifically address patients admitted to LTACHs. Given the multiple comorbidities that are especially prevalent among CCI patients, including prolonged weaning from mechanical ventilation, complex wound care, prolonged presence of urinary and vascular catheters, malnutrition, acute care hospitalizations, and frequent or prolonged antibiotic exposures, unique risk factors for colistin-resistant CRKP are likely to exist in this population. In this study, we aimed to evaluate risk factors for colistin resistance among CRKP clinical isolates from patients in LTACHs.

METHODS

Study Design and Population

The study was performed as a secondary analysis of data from a multicenter prospective observational study conducted at 21 LTACHs in the United States (12 California, 6 Texas, 2 Florida, 1 Kentucky) that are part of a national LTACH network [7]. All patients with a CRKP clinical culture, defined as *K pneumoniae* with a meropenem and/or imipenem minimum inhibitory concentration (MIC) ≥4 µg/mL or ertapenem MIC ≥2 µg/mL, from August 1, 2014 through July 24, 2015 were included [8]. Species confirmation using standard biochemical methods and polymerase chain reaction (PCR) targeting the *mdh* gene, PCR detection of the bla_{KPC-1} gene, and carbapenemase activity testing (Rapid CARB kit; Rosca Diagnostica, Taastrup, Denmark) were performed, as described elsewhere [9]. Among patients with recurrent isolates during the study period, only the first isolate per patient was included in primary analyses. In a secondary analysis, patients with recurrent CRKP cultures were included more than once if ≥30 days had elapsed from their previous CRKP episode.

Data Collection

Colistin susceptibility testing was performed using a Sensititre lyophilized broth microdilution panel (Thermo Fisher, Waltham, MA) [10]. A breakpoint of >2 mg/L was used to define colistin resistance, per current Clinical and Laboratory Standards Institute (CLSI) and European Committee on

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Antimicrobial Susceptibility Testing (EUCAST) interpretative criteria [11, 12]. Nonresistant isolates were designated as "susceptible", in concordance with EUCAST terminology, for clarity. Clinical data on patients were collected from the integrated and shared electronic health record of participating LTACHs.

Statistical Analysis

Data were analyzed using Stata/IC 16.1 (College Station, TX). Mixed-effects binomial regression with a random effect of facility was performed to evaluate risk factors for colistin resistance. Variables with $P < .20$ in unadjusted analyses were included in adjusted models. Two-tailed P values are reported.

RESULTS

Patient Characteristics

A total of 375 CRKP episodes were included in the primary analysis, including 247 (65.9%) episodes with colistin-susceptible CRKP and 128 (34.1%) with colistin-resistant CRKP. Cohort characteristics are summarized in Table 1.

Risk Factors for Colistin Resistance

In unadjusted analyses, number of days of colistin or polymyxin B exposure in the preceding 30 days was positively associated with odds of colistin-resistant CRKP (odds ratio [OR] = 1.08 per day, 95% confidence interval [CI] = 1.01–1.16, $P = .021$). In contrast,

Table 1. Characteristics of Patients With Carbapenem-Resistant *Klebsiella pneumoniae* in 21 Long-Term Acute Care Facilities, August 1, 2014 Through July 24, 2015[a]

Characteristics	Entire Cohort (*N* = 375)	Colistin-Susceptible CRKP (*N* = 247)	Colistin-Resistant CRKP (*N* = 128)
Age (years)	72.9 (63.8–81.8)	72.1 (63.9–80.5)	74.0 (63.6–83.3)
Male sex	195 (52.0%)	129 (52.2%)	66 (51.6%)
Cirrhosis	15 (4.0%)	12 (4.9%)	3 (2.3%)
Stage IV–V chronic kidney disease	119 (31.7%)	74 (30.0%)	45 (35.2%)
Congestive heart failure	75 (20.0%)	51 (20.6%)	24 (18.8%)
Acute kidney injury	166 (44.3%)	109 (44.1%)	57 (44.5%)
Malignancy	46 (12.3%)	35 (14.2%)	11 (8.6%)
Anoxic brain injury or CVA causing paresis	72 (19.2%)	46 (18.6%)	26 (20.3%)
Gastrostomy tube	139 (37.1%)	88 (35.6%)	51 (39.8%)
Obesity	20 (5.3%)	12 (4.9%)	8 (6.3%)
Underweight or malnutrition	97 (25.9%)	70 (28.3%)	27 (21.1%)
Organ transplant	8 (2.1%)	5 (2.0%)	3 (2.3%)
COPD or chronic bronchitis	66 (17.6%)	45 (18.2%)	21 (16.4%)
Ventilator-dependent respiratory failure	114 (30.4%)	81 (32.8%)	33 (25.8%)
Stage IV or V decubitus ulcer	75 (20.0%)	47 (19.0%)	28 (21.9%)
Culture Source			
Blood	33 (8.8%)	25 (10.1%)	8 (6.3%)
Respiratory	199 (53.1%)	120 (48.6%)	79 (61.7%)
Urine	133 (35.5%)	95 (38.5%)	38 (29.7%)
Wound	10 (2.7%)	7 (2.8%)	3 (2.3%)
LTACH length of stay (days)	20 (6–42)	20 (5–43)	20 (6.5–41.5)
Prior LTACH admission within past 1 year	19 (5.1%)	10 (4.0%)	9 (7.0%)
Central line	208 (55.5%)	137 (55.5%)	71 (55.5%)
Tracheostomy	248 (66.1%)	157 (63.6%)	91 (71.1%)
Urinary catheter	207 (55.2%)	144 (58.3%)	63 (49.2%)
Antibiotic Use for ≥48 Hours in the prior 30 Days			
Colistin or Polymyxin B	41 (10.9%)	16 (6.5%)	25 (19.5%)
Fluoroquinolone (ciprofloxacin, levofloxacin)	60 (16.0%)	45 (18.2%)	15 (11.7%)
Broad-spectrum cephalosporin (ceftriaxone, cefepime, ceftaroline, ceftazidime)	91 (24.3%)	64 (25.9%)	27 (21.1%)
Carbapenem (meropenem, imipenem, ertapenem)	138 (36.8%)	86 (34.8%)	52 (40.6%)
Piperacillin-tazobactam	54 (14.4%)	39 (15.8%)	15 (11.7%)
Aminoglycoside (amikacin, gentamicin, tobramycin)	67 (17.9%)	40 (16.2%)	27 (21.1%)
Tigecycline	47 (12.5%)	27 (10.9%)	20 (15.6%)
Trimethoprim-sulfamethoxazole	11 (2.93%)	5 (2.0%)	6 (4.7%)
Aztreonam	11 (2.93%)	6 (2.4%)	5 (3.9%)

Abbreviations: COPD, chronic obstructive pulmonary disease; CI, confidence interval; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CVA, cerebrovascular accident; LTACH, long-term acute care hospital.

[a]Counts and percentages are reported for categorical variables. Medians and interquartile ranges are reported for continuous variables.

presence of a urinary catheter (OR = 0.68, 95% CI = .50–.92, P = .014), prior fluoroquinolone exposure (OR = 0.92 per day, 95% CI = .85–.99, P = .021), and prior broad-spectrum cephalosporin exposure (OR = 0.95 per day, 95% CI = .92–.99, P = .019) were associated with decreased odds of colistin-resistant CRKP. In adjusted analyses, prior colistin or polymyxin B exposure was associated with increased odds of colistin-resistant CRKP (aOR = 1.11 per day, 95% CI = 1.03–1.19, P = .007), whereas ventilator-dependent respiratory failure (aOR = 0.66, 95% CI = .45–.95, P = .028) and prior broad-spectrum cephalosporin exposure (aOR = 0.95, 95% CI = .91–.99, P = .011) were associated with decreased odds of colistin-resistant CRKP (Table 2).

Secondary Analyses

In a secondary analysis that included both first and recurrent CRKP episodes during the study period (N = 430), 144 (33.5%) were colistin resistant. In unadjusted analyses, prior colistin or polymyxin B exposure was associated with increased odds of colistin-resistant CRKP (OR = 1.08 per day of exposure, 95% CI = 1.01–1.15, P = .017), whereas prior fluoroquinolone or broad-spectrum cephalosporin exposure were associated with decreased odds of colistin-resistant CRKP (fluoroquinolones: OR = 0.91 per day, 95% CI = .85–.98, P = .011; broad-spectrum cephalosporins: OR = 0.95 per day, 95% CI = .92–.99, P = .010) (Supplementary Table 1). Findings were

Table 2. Unadjusted and Adjusted Analysis of Risk Factors for Colistin Resistance in Carbapenem-Resistant *Klebsiella pneumoniae* Among Patients in Long-Term Acute Care Facilities (N = 375)

	Unadjusted Models		Adjusted Model	
Characteristics	OR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
Age (per year)	1.01 (0.99–1.03)	.24	…	
Male sex	0.97 (0.69–1.35)	.85	…	
Cirrhosis	0.46 (0.10–2.24)	.34	…	
Stage IV–V chronic kidney disease	1.29 (0.66–2.51)	.46	…	
Congestive heart failure	0.90 (0.53–1.53)	.69	…	
Acute kidney injury	1.01 (0.68–1.51)	.96	…	
Malignancy	0.56 (0.21–1.49)	.25	…	
Anoxic brain injury or CVA causing paresis	1.10 (0.63–1.91)	.74	…	
Gastrostomy tube	1.17 (0.79–1.74)	.43	…	
Obesity	1.32 (0.51–3.45)	.57	…	
Underweight or malnutrition	0.67 (0.39–1.16)	.15	0.66 (0.40–1.08)	.097
Organ transplant	1.06 (0.26–4.37)	.93	…	
COPD or chronic bronchitis	0.85 (0.50–1.44)	.54	…	
Ventilator-dependent respiratory failure	0.70 (0.45–1.09)	.12	0.66 (0.45–0.95)	**.028**
Stage IV or V decubitus ulcer	1.17 (0.58–2.37)	.67	…	
Culture source	…	.078	…	.11
Blood (reference)	…		…	
Respiratory	2.15 (0.85–5.44)	.11	2.40 (0.78–7.43)	.13
Urine	1.31 (0.46–3.75)	.62	1.51 (0.49–4.64)	.47
Wound	1.41 (0.73–2.74)	.31	1.64 (0.75–3.58)	.21
Length of stay (per day)	1.00 (1.00–1.00)	.26	…	
Prior LTACH admission within past 1 year	1.70 (0.60–4.86)	.32	…	
Central line	1.00 (0.66–1.52)	>.99	…	
Tracheostomy	1.41 (0.93–2.16)	.10	1.21 (0.79–1.84)	.38
Urinary catheter	0.68 (0.50–0.92)	**.014**	0.85 (0.63–1.14)	.28
Days of antibiotics in prior 30 days	…		…	
Colistin or polymyxin B	1.08 (1.01–1.16)	**.021**	1.11 (1.03–1.19)	**.007**
Fluoroquinolone (ciprofloxacin, levofloxacin)	0.92 (0.85–0.99)	**.021**	0.92 (0.85–1.00)	.053
Broad-spectrum cephalosporin (ceftriaxone, cefepime, ceftaroline, ceftazidime)	0.95 (0.92–0.99)	**.019**	0.95 (0.91–0.99)	**.011**
Carbapenem (meropenem, imipenem, ertapenem)	1.01 (0.98–1.03)	.66	…	
Piperacillin-tazobactam	0.99 (0.93–1.04)	.59	…	
Aminoglycoside (amikacin, gentamicin, tobramycin)	1.02 (0.97–1.08)	.45	…	
Tigecycline	1.02 (0.97–1.07)	.47	…	
Trimethoprim-sulfamethoxazole	1.03 (0.90–1.17)	.71	…	
Aztreonam	1.03 (0.95–1.12)	.47	…	

Bold text denotes *P* value <.05.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRKP, carbapenem-resistant *Klebsiella* pneumoniae; CVA, cerebrovascular accident; LTACH, long-term acute care hospital; OR, odds ratio.

[a]Variables with P < .20 in unadjusted models were included in the adjusted model.

similar in adjusted analysis, with colistin or polymyxin B exposure associated with increased odds (adjusted odds ratio [aOR] = 1.10 per day, 95% CI 1.04–1.17, $P = .002$), fluoroquinolone exposure associated with decreased odds (aOR = 0.91 per day, 95% CI = .85–.98, $P = .018$), and broad-spectrum cephalosporin exposure associated with decreased odds (aOR = 0.95 per day, 95% CI = .91–.98, $P = .004$) of colistin-resistant CRKP.

In a secondary analysis in which antibiotic exposures were considered as dichotomous variables, colistin or polymyxin B use for ≥48 hours in the preceding 30 days was associated with increased odds of colistin-resistant CRKP in unadjusted analysis (OR = 3.47, 95% CI = 1.61–7.50, $P = .002$). In adjusted models, colistin or polymyxin use for ≥48 hours (aOR = 4.55, 95% CI = 2.40–8.60, $P < .001$) and culture source (test for joint significance, $P = .042$) were associated with colistin-resistant CRKP, and ventilator-dependent respiratory failure was associated with decreased odds of colistin resistance (aOR = 0.65, 95% CI = .46–.92, $P = .015$) (Supplementary Table 2).

DISCUSSION

To our knowledge, this is the first study to explore risk factors for colistin-resistant CRKP among patients in a postacute care setting. Our finding of prior colistin or polymyxin B exposure as a risk factor for colistin-resistant CRKP aligns with the results of studies performed in other patient populations. For example, prior colistin administration was associated with an approximately 6-fold increase in odds of colistin-resistant infection in an analysis of hospitalized patients in Italy with CRKP bloodstream infection, whereas colistin administration was associated with twice the odds of colistin-resistant CRKP bloodstream infection among a cohort of intensive care unit patients in Greece [13, 14]. Although there was an apparent protective association between prior cephalosporin exposure and colistin resistance in our analysis, there is not a clear mechanistic explanation for this finding, which may potentially be due to the presence of unmeasured confounding. One possibility is that patients without a prior history of infections caused by MDROs may have preferentially received cephalosporins rather than broader spectrum alternative antibiotics. In addition, cephalosporin exposure in the preceding 30 days could have been a negative surrogate marker for exposure to broader spectrum antibiotics in the more remote past. Likewise, the lower odds of colistin-resistant CRKP among patients with ventilator-dependent respiratory failure in our primary analysis might reflect the possibility that patients with ventilator dependence have had less overall healthcare exposure compared to those who have already been liberated from mechanical ventilation.

This study has several limitations. First, bias may have been introduced by unmeasured confounders such as preceding acute- and postacute healthcare exposures outside of the LTACH network, history of colistin-resistant CRKP infection before the study period, and unmeasured comorbidities. Second, some of the variables in our analysis lack granularity; for example, we do not have data on the duration of instrumentation or mechanical ventilation among patients receiving these interventions. Third, although we aimed to increase generalizability through a multicenter study design, results still may not be generalizable to other LTACHs or to non-LTACH health settings. Finally, because antibiotic use patterns may have changed in recent years with the introduction of several new antibiotics with activity against multidrug-resistant Gram-negative organisms, including the novel β-lactam/β-lactamase inhibitor combinations ceftazidime-avibactam, imipenem-cilastatin-relebactam, and meropenem-vaborbactam as well as the siderophore cephalosporin cefiderocol, our findings should be validated in more recent cohorts. Due to the availability of and preference towards these newer antibiotics, colistin resistance in CRKP may also have decreased relevance in current clinical practice [15].

CONCLUSIONS

In conclusion, prior colistin or polymyxin B exposure was a strong risk factor for colistin resistance in this sample of CRKP from LTACH patients. Considering that colistin-resistant CRKP has been associated with excess mortality, this finding emphasizes the importance of effective antimicrobial stewardship programs to ensure rational use of colistin and other last-line antibiotics [5].

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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