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RESEARCH ARTICLE

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Risk factors for carbapenem-resistant Enterobacterales infection among hospitalized patients with previous colonization

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Abstract

Background: We aimed to identify the risk factors for subsequent carbapenem-resistant Enterobacterales (CRE) infections in patients with initial rectal colonization with CRE.

Methods: We conducted a retrospective case–control study on inpatients with rectal CRE colonization between January 2019 and December 2020. Clinical and microbiological data were extracted from hospital patients' medical records and the clinical microbiology laboratory. Risk factors were assessed and compared between patients with CRE colonization who had subsequent infections and those who did not have infections.

Results: Among 1064 patients screened for CRE, we enrolled 205 patients with rectal CRE colonization. Among the 205 colonized bacteria, 78.5% were *Klebsiella pneumoniae*, with 62.9% of them producing *Klebsiella pneumoniae* carbapenemase (KPC). Multivariate logistic regression analysis revealed that more than three times hospitalization ($p = 0.026$), being in a coma ($p = 0.019$), and exposure to carbapenems ($p = 0.015$) were independent risk factors for CRE clinical infection among CRE rectal carriers.

Conclusion: This is the first study to report that more than three times hospitalization is an independent risk factor for subsequent CRE clinical infection in CRE intestinal carriers. Carbapenem-resistant *Klebsiella pneumoniae* is the most important species isolated from hospitalized CRE rectal carriers and is the most common cause of subsequent infections.

KEYWORDS
carbapenem-resistant Enterobacterales, rectal colonization, risk factors, subsequent infection

Xia Chen and Mao Zhou contributed equally.

1 | INTRODUCTION

In the past decade, carbapenem-resistant Enterobacterales (CRE) has become a public health concern worldwide.[1] CRE is highly resistant to most available antimicrobial agents; moreover, they are associated with high morbidity and costs.[2] CRE infection is associated with a higher 30-day mortality rate than other infections (63.8% vs. 33.4%).[3] Rectal CRE carriers considerably contribute to the transmission of these microorganisms in hospital settings,[4] with the rate of CRE infections among asymptomatic CRE carriers ranging from 0.3% to 69.5%.[5–8] CRE colonization is an independent risk factor for CRE infections, with intensive care unit (ICU) patients with CRE colonization having at least a twofold increased risk of CRE infection.[9] CRE infections are more among patients with previous CRE colonization (65%) than in those without (27%, $p < 0.0001$).[10] Approximately 50% of ICU patients with intestinal CRE colonization from a hospital in Northern Manhattan developed CRE infection within 30 days, with the CRE infection rate being 10.8 times higher than that in non-colonized patients.[10] Other risk factors for CRE include exposure to certain antimicrobials (fluoroquinolones and cephalosporins) and invasive procedures involving a scope device.[11] We previously reported that 8.5% of hospitalized patients had rectal CRE colonization, with the dominant clone strain being *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae* ST11.[12] Among rectal carriers of the carbapenem-resistant *Klebsiella pneumoniae* (CRKP), 37.1% of the cases developed subsequent CRKP clinical infection.[13] Colonization is considered a prerequisite for infection; however, the extent to which colonized patients develop CRE infections remains unclear. Moreover, there is insufficient clinical evidence regarding the risk factors for subsequent CRE infections in patients with rectal CRE colonization.[5–8] Sufficient clinical evidence could inform decision-making regarding infection-control interventions, including screening and contact precautions, for colonized patients. Therefore, we aimed to establish risk factors for subsequent clinical CRE infections among CRE rectal carriers to identify high-risk inpatients and prevent CRE infections.

2 | MATERIALS AND METHODS

2.1 | Study design and definitions

This was a single-center, cross-sectional, retrospective study performed at Xiangya hospital of Central South University in China, which is a 3500-bed teaching hospital with an annual admission of >130,000 inpatients. Hospitalized patients who were admitted to intensive care units and hematologic department with stool samples submitted for routine analysis were screened for CRE. We enrolled cases with positive CRE screening results and without prior CRE infections from January 2019 to December 2020. Previous colonization defined as CRE rectal colonization prior to clinical infection. The CRE case group (patients with subsequent infection) was defined as CRE rectal carriers who developed subsequential CRE infections with identical species as colonized CRE after 48 h of positive screening test.[14,15] The isolation of CRE strains before or within 48 h after admission was excluded. Cases without complete medical records were also excluded. The control group comprised CRE rectal carriers without subsequent CRE infections.

Carbapenem-resistant Enterobacterales infections included bloodstream infection, pneumonia, peritonitis, wound infection, and urinary tract infection. Moreover, subsequent CRE infection was defined as CRE isolated in relevant infection sites and presenting signs and symptoms.[16]

2.2 | Data collection

We collected the following clinical data from electronic medical records of patients with CRE colonization: general information (sex, age, department, duration of hospital stay, previous hospitalization, alcohol drinking history, smoking history, hospital transfer and sickbed change, and ICU admission), underlying conditions (hypertension, heart disease, diabetes mellitus, hematopathy, lung disease, renal disease, liver disease, pancreatitis, enteritis, gastritis, craniocerebral trauma, and solid tumor), invasive procedures and devices (arterial catheter, central venous catheter, endotracheal intubation, tracheotomy, mechanical ventilation, urinary catheter and nasogastric tube, and previous surgery in 1 and 3 months), coma condition (the Glasgow Coma Scale score ≤8),[17] antibiotic exposure (penicillin, cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, β-lactam/β-lactamase inhibitors, vancomycin, tigecycline, metronidazole, and anti-fungal agents).

2.3 | Microbiological procedure and resistance gene detection

Stool samples of hospitalized patients were screened for CRE using MacConkey agar and 10 μg meropenem discs as aforementioned.[12] All isolated bacteria were identified using MALDI Biotype systems (Bruker). The sensitivity of imipenem and meropenem was detected using the Kirby-Bauer method. *Escherichia coli* strain ATCC 25922 was used for quality control. The results were interpreted using the Clinical and Laboratory Standards Institute M100 breakpoints.[18] Polymerase chain reaction (PCR) was performed as previously described,[12] targeting the genes encoding bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP}, and bla_{OXA-48} to confirm carbapenemase.

2.4 | Statistical analysis

Statistical analysis was performed using SPSS version 22.0 software (IBM Corporation). The normality of data distribution was analyzed using the Shapiro–Wilk test. Numerical values were expressed as mean ± SD (for normal distribution) or as the median and percentiles

(for non-normally distribution). Between-group comparisons of continuous variables were performed using Student's *t* test (for normal distribution) or the Wilcoxon rank-sum test (for non-normally distribution). Categorical variables were compared using the chi-square test or Fisher's exact test. We calculated the *p* value, odds ratio (OR) value, and 95% confidence intervals (CI) of the variables. Variables with a two-tailed *p* value ≤0.05 in the univariate analysis were included in the logistic regression model for the multivariate analysis. Statistical significance was set at $p \leq 0.05$. The independent risk factors were checked for multicollinearity.

3 | RESULTS

3.1 | Patient cohort and clinical characteristics

Among 1064 patients screened for CRE, we enrolled 205 patients with rectal CRE colonization. The cases of rectal CRE colonization were mainly distributed in the central ICU (66%, 32.2%), respiratory ICU (51%, 24.9%), and hematology department (26%, 12.7%). Overall, 100 (48.8%) carriers who developed subsequent CRE clinical infections were included in the case group. The main clinical infection was pneumonia (61.0%), followed by bloodstream (26.0%), urinary tract infection (10.0%), and wound infections (3.0%). The other 105 CRE carriers without subsequent CRE infections were included in the control group.

3.2 | Microbial characteristics

Table 1 shows microbial characteristics. Among 205 colonized bacteria, 161 (78.5%), 24 (11.7%), 8 (3.9%), 5 (2.4%), 3 (1.5%), 3 (1.5%), and 1 (0.5%) were *K. pneumoniae*, *E. coli*, *Enterobacter cloacae*, *Citrobacter freundii*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, and *Raoultella planticola*, respectively. *K. pneumoniae* was the most important species among hospitalized rectal CRE carriers and was the most common cause of subsequent infections. *Escherichia coli* was more common in the case group than in the control group (17.0% vs 6.7%; $p = 0.021$).

All rectal CRE isolates were carbapenemase-producing Enterobacterales, 129 (62.9%), 44 (21.5%), 24 (11.7%), and 5 (2.4%) produced KPC, New Delhi metallo-beta-lactamase, verona Integron-encoded MBL, and imipenemase. Moreover, three isolates carried two types of carbapenemase genes (bla_{NDM} and bla_{VIM} in two isolates as well as bla_{KPC} and bla_{NDM} in one isolate).

3.3 | Risk factors analysis

The length of hospital stay was significantly longer in the case group than in the control group (interquartile range, 27 vs. 21 days, $p = 0.020$). A total of 43 patients had been previously hospitalized more than three times, including 28 (28.0%) and 15 (14.3%) in the case and control groups, respectively, with a significant between-group difference ($p = 0.016$). Univariate analysis revealed that compared with patients in the control group, those in the case group were more likely to have undergone central venous catheter insertion (62.0% vs. 42.9%, $p = 0.006$), tracheotomy (34.0% vs. 18.1%, $p = 0.009$), nasogastric tube insertion (68.0% vs. 50.5%, $p = 0.011$); been in a coma condition (21.0% vs. 7.6%, $p = 0.006$); and received carbapenems (72.0% vs. 54.3%, $p = 0.009$) and amikacin (13.0% vs. 3.8%, $p = 0.017$). There was no statistically significant difference in sex, age, history of smoking or alcohol use, history of surgery, and ICU admission. Furthermore, there was no statistically significant difference in most comorbidities, including solid tumor, hypertension, diabetes mellitus, hematopathy, and organ transplantation (Table 2).

Multivariate logistic regression analysis revealed that more than three times previous hospitalization (OR 2.438, 95% CI 1.115–5.333, $p = 0.026$), being in a coma condition (OR 3.137, 95% CI 1.203–8.178, $p = 0.019$), and carbapenems exposure (OR 1.571, 95% CI 0.174–4.488, $p = 0.015$) were independent risk factors for CRE clinical infection among CRE rectal carriers (Table 3).

In the group of patients with more than three times previous hospitalization, there was no statistically significant difference regarding age, sex, and comorbidities between the patients with subsequent infections and those without ($p > 0.05$; Table S1).

TABLE 1 Species distribution of positive rectal carbapenem-resistant Enterobacteriaceae screening cases

Species	Case group ($n = 100$, %)	Control group ($n = 105$, %)	Total ($n = 205$, %)	*p*
Klebsiella pneumoniae	76 (76.0)	85 (81.0)	161 (78.5)	0.388
Escherichia coli	17 (17.0)	7 (6.7)	24 (11.7)	0.021*
Enterobacter cloacae	2 (2.0)	6 (5.7)	8 (3.9)	0.312
Citrobacter freundii	1 (1.0)	4 (3.8)	5 (2.4)	0.395
Klebsiella aerogenes	1 (1.0)	2 (1.9)	3 (1.5)	1.000
Raoultella planticola	0 (0.0)	1 (1.0)	1 (0.5)	1.000
Klebsiella oxytoca	3 (3.0)	0 (0.0)	3 (1.5)	0.228

*$p < 0.05$.

TABLE 2 Univariate analysis of risk factors associated with subsequent carbapenem-resistant Enterobacterales (CRE) clinical infection among CRE carriers

Variables	Case group ($n = 100$)	Control group ($n = 105$)	p
General information			
Male sex, *n* (%)	76 (76.0%)	80 (76.2%)	0.975
Median age (range), years	51 (31–66)	53.5 (41.5–67)	0.109
Age ≥65 years, *n* (%)	37 (37.0%)	30 (28.6%)	0.198
Length of stay (days), IQR (range)	21 (13–34)	27 (15.25–47)	0.020*
Previous hospitalization, *n* (%)	47 (47.0%)	41 (39.0%)	0.250
Previous hospitalizations >1, *n* (%)	41 (41.0%)	33 (31.4%)	0.154
Previous hospitalizations >2, *n* (%)	28 (28.0%)	20 (19.0%)	0.130
Previous hospitalizations >3, *n* (%)	28 (28.0%)	15 (14.3%)	0.016*
History of smoking, *n* (%)	30 (30.0%)	35 (33.3%)	0.608
History of alcohol, *n* (%)	16 (16.0%)	17 (16.2%)	0.970
Comorbid conditions, *n* (%)			
Solid organ tumor	10 (10.0%)	13 (12.4%)	0.589
Lung disease	30 (30.0%)	25 (24.0%)	0.337
Hypertension	28 (28.0%)	25 (23.8%)	0.493
Heart disease	12 (12.0%)	11 (10.5%)	0.730
Diabetes mellitus	15 (15.0%)	18 (17.1%)	0.676
Hematopathy	15 (15.0%)	27 (25.7%)	0.057
Renal disease	11 (11.0%)	6 (5.7%)	0.170
Liver disease	14 (14.0%)	12 (11.4%)	0.580
Biliary tract disease	3 (3.0%)	3 (2.9%)	1.000
Pancreatitis	5 (5.0%)	7 (6.7%)	0.611
Enteritis	6 (6.0%)	2 (1.9%)	0.249
Being in coma condition (Gcs score ≤8)	21 (21.0%)	8 (7.6%)	0.006*
Organ transplantation	2 (2.0%)	3 (2.9%)	0.548
Pyohemia	3 (3.0%)	3 (2.9%)	1.000
Invasive procedures, *n* (%)			
Central venous catheter	62 (62.0%)	45 (42.9%)	0.006*
Arterial catheter	60 (60.0%)	54 (51.4%)	0.217
Endotracheal intubation	44 (44.0%)	39 (37.1%)	0.317
Tracheotomy	34 (34.0%)	19 (18.1%)	0.009*
Mechanical ventilation	50 (50.0%)	46 (43.8%)	0.375
Nasogastric tube	68 (68.0%)	53 (50.5%)	0.011*
Urinary catheter	65 (65.0%)	56 (53.3%)	0.090
Other clinical parameters, *n* (%)			
Previous surgery (in a month)	20 (20.0%)	22 (21.0%)	0.866
Artificial prosthesis	0 (0.0%)	3 (2.9%)	0.262
Use proton pump inhibitors	55 (55.0%)	49 (46.7%)	0.233
Using chemotherapeutic drugs	15 (15.0%)	14 (13.3%)	0.732
Admission to ICU, *n* (%)	60 (60.0%)	55 (52.4%)	0.272
Transfer from another hospital, *n* (%)	16 (16.2%)	13 (12.4%)	0.440
Antimicrobial exposure, *n* (%)			
Penicillin	1 (1.0%)	5 (4.8%)	0.237
Cephalosporins	23 (23.0%)	18 (17.1%)	0.295

TABLE 2 (Continued)

Variables	Case group ($n = 100$)	Control group ($n = 105$)	p
Carbapenems	72 (72.0%)	57 (54.3%)	0.009*
Aztreonam	3 (3.0%)	1 (1.0%)	0.579
Latamoxef	2 (2.0%)	2 (1.9%)	1.000
β-lactam/β-lactamase inhibitors	71 (71.0%)	65 (61.9%)	0.168
Vancomycin	34 (34.0%)	31 (29.5%)	0.491
Teicoplanin	11 (11.0%)	11 (10.5%)	0.904
Amikacin	13 (13.0%)	4 (3.8%)	0.017*
Gentamicin	6 (6.0%)	4 (3.8%)	0.687
Tobramycin	0 (0.0%)	1 (1.0%)	1.000
Fluoroquinolones	37 (37.0%)	38 (36.2%)	0.904
Linezolid	23 (23.0%)	31 (29.5%)	0.289
Tigecycline	15 (15.2%)	10 (9.5%)	0.221
Colistin	15 (15.2%)	9 (8.6%)	0.145
Tetracycline	14 (14.0%)	9 (8.6%)	0.218
Metronidazole	7 (7.0%)	2 (1.9%)	0.150
Sulfamethoxazole	4 (4.0%)	2 (1.9%)	0.635
Azithromycin	2 (2.0%)	4 (3.8%)	0.723
Antifungal agents	50 (50.0%)	47 (44.8%)	0.453
The use of antibiotics ≥3, *n* (%)	69 (69.0%)	59 (56.2%)	0.058

*$p < 0.05$.

TABLE 3 Multivariable logistic regression for factors associated with subsequent carbapenem-resistant Enterobacteriaceae infections

Variables	OR (95% CI)	p
Length of stay (days)	1.007 (0.996–1.018)	0.225
Previous hospitalizations >3	2.438 (1.115–5.333)	0.026*
Being in coma condition	3.137 (1.203–8.178)	0.019*
Central venous catheter	1.579 (0.830–3.071)	0.161
Tracheotomy	1.488 (0.683–3.245)	0.317
Nasogastric tube	1.571 (0.799–3.091)	0.191
Carbapenems exposure	2.295 (1.174–4.488)	0.015*
Amikacin exposure	2.758 (0.785–9.686)	0.113

*$p < 0.05$.

4 | DISCUSSION

Carbapenem-resistant Enterobacterales colonization is an important risk factor for infection.[9,19] We found that CRKP was the most important strain among cases with rectal CRE colonization and clinical infections (78.6% and 76.0%, respectively), which is consistent with the results of other domestic studies.[4,5] A previous study showed that CRE isolates in Miami-Dade County were predominantly *K. pneumoniae*.[20] Consistent with previous studies, the main carbapenem-resistant bacteria in bloodstream infections among rectal carriers was *K. pneumoniae* (73.8% of the cases).[21] A recent study on 702 patients suggested that carriers of carbapenemase-producing *K. pneumoniae* may have an increased likelihood of prolonged carriage.[22]

A previous Chinese study found that 37.1% of intestinal CRKP carriers developed clinical CRKP infections; additionally, ICU admission was an independent risk factor for subsequent clinical infections among intestinal CRKP carriers.[13] We observed no statistically significant difference in terms of hospitalization in the ICU. This could be attributed to a large proportion of patients being from the ICUs. The proportion of clinical CRE infections in our study is consistent with that reported in a tertiary medical center in Israel (48.8% vs. 47%).[23]

Previous exposure to fluoroquinolones and carbapenems is independent risk factors for CRE infection.[5,24] We found that prior exposure to carbapenems was an independent risk factor for clinical CRE infection in rectal CRE carriers, which is consistent with previous study.[22] However, prior exposure to fluoroquinolones was not associated with CRE subsequent infection among rectal CRE carriers in this study. Notably, we found that more than three times hospitalization and being in a coma condition were independent risk factors. Being in coma might be associated with receiving more invasive procedures such as tracheal intubation, urinary catheter insertion, or venous catheter insertion, which may increase the risk of

subsequent infection when the patient colonized CRE. Patients with multiple admissions may increase the risk of exposure to colonized CRE. Additionally, repeated admissions indicate underlying disease, weakened immunity, long-term antibiotic use, and repeated invasive procedures, which may increase the risk of subsequent infection among CRE colonizer.

This study has several limitations. First, this was a single-center study, which limits the generalizability of our findings. Second, since this was a retrospective study, we could not implement a comorbidity index for measuring the severity of comorbid conditions, which increased the risk of selection bias. Third, the genetic relatedness between the colonization and subsequent infection strains was not analyzed, although we enrolled patients with subsequent CRE infections caused by the same species as the colonized CRE. Molecular analysis need be performed to confirm this in the future. Nonetheless, this study provides findings that could inform infection control in this population.

5 | CONCLUSION

In conclusion, we found that *K. pneumoniae* was the dominant strain responsible for rectal CRE colonization and subsequent clinical infections in hospitalized patients. Further, we found that more than three times hospitalization were an independent risk factor for clinical CRE infections in intestinal CRE carriers. Additionally, prior carbapenems use and being under coma conditions were independent risk factors for clinical CRE infections among rectal CRE carriers. Our findings may inform clinicians to take effective measures for preventing subsequent nosocomial infections in patients at a high risk of rectal CRE colonization.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. XC, JZJ, QY, and WEL collected and analyzed the patient data, MZ written the first draft of the article and HLL proofread the final draft. All authors read and approved the final article.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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