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BRIEF REPORT

Using Patient Risk Factors to Identify Whether Carbapenem-Resistant *Enterobacteriaceae* Infections Are Caused by Carbapenemase-Producing Organisms

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Evaluating all inpatient carbapenem-resistant *Enterobacteriaceae* (CRE) infections over a 1-year period, 47% were caused by carbapenemase-producing (CP) organisms. Compared with non-CP-CRE patients, patients with CP-CRE had an 18-fold greater odds of a recent stay in a foreign health care facility and a 3-fold greater odds of transfer from a post–acute care facility.

Keywords. carbapenemases; CRE; *Enterobacteriaceae*; KPC; MDRGN.

Carbapenem-resistant *Enterobacteriaceae* (CRE) remain a major cause of health care–associated infections and contribute to significant morbidity and mortality [1]. Of particular concern are carbapenemase-producing CRE (CP-CRE), for which resistance to carbapenems is generally conferred by plasmid-associated carbapenemase genes [1]. CP-CRE are believed to pose a greater threat of dissemination within health care facilities than non-CP-CRE [2, 3], and early identification of CP-CRE patients can facilitate appropriate isolation and/or patient cohorting. Timely identification may also be clinically informative, as evidence suggests that CP-CRE are associated with poorer patient outcomes [4].

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The Clinical Laboratory and Standards Institute (CLSI) has endorsed 2 assays to identify carbapenemase production [5], but both have limitations. The carba NP test requires fresh reagents be prepared regularly, and interpretations of results can be somewhat subjective [6]. Although the modified carbapenem inactivation method (mCIM) overcomes these challenges, the turnaround time for this culture-based technique is 18–24 hours [6]. Moreover, both assays are generally performed after susceptibility testing indicates that organisms are carbapenem-resistant, causing additional delays in appropriately isolating patients. Identifying patient-specific risk factors for infection with CP-CRE can circumvent this delay. Although existing studies have examined risk factors for CRE or CP-CRE, relative to susceptible *Enterobacteriaceae*, to our knowledge no analysis has identified risk factors to discriminate between CRE types; these risk factors may differ, and coupled with mounting evidence that carbapenemase status is both epidemiologically and clinically informative, are ripe for review. We evaluated all patients with CRE recovered from clinical isolates over a 1-year period to identify risk factors that distinguish CP-CRE from non-CP-CRE.

METHODS

Study Population

We conducted a retrospective, observational cohort study including all unique patients hospitalized at the Johns Hopkins Hospital between January and December 2016 with CRE recovered from clinical isolates from any source using CLSI criteria [5]. Patient data were manually extracted using available medical records from facilities within the Epic Care Everywhere Network, which includes a large number of inpatient and outpatient health care networks throughout the United States. Only the first CRE infection per patient was included. This study was approved by the Institutional Review Board, with a waiver of informed consent.

The following data were collected, with all information based on the period before the clinical culture date: (a) demographic data, (b) preexisting medical conditions, (c) culture source, (d) indwelling hardware, (e) transfer from a post–acute care facility; (f) foreign hospitalization in the previous 6 months, and within the previous 3 months before the current infection: (g) multidrug-resistant organism colonization or infection (multidrug-resistant *Pseudomonas aeruginosa*, multidrug-resistant *Acinetobacter baumannii*, extended-spectrum β-lactamase-producing *Enterobacteriaceae*, and carbapenem-resistant *Enterobacteriaceae*) [7], (h) days of inpatient and outpatient antibiotic therapy (extended-spectrum penicillins, third- and

fourth-generation cephalosporins, aztreonam, carbapenems, aminoglycosides, and fluoroquinolones), and (i) days of stay in any acute care facility.

Organism and Resistance Mechanism Identification

Bacterial genus and species were identified using matrix-assisted laser-desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics Inc., Billerica, MA). The BD Phoenix Automated System (BD Diagnostics, Sparks, MD) was used for antibiotic susceptibility testing.

Genomic DNA was extracted from isolates using the DNeasy Blood & Tissue Kit (QIAGEN, Inc., Valencia, CA). β-lactamase genes were identified with the Check-MDR CT103XL kit (CheckPoints, Wageningen, the Netherlands). The mCIM phenotypic assay was performed on all isolates. No discordance between genotypic and phenotypic results was identified. Positive and negative isolates were assigned as CP-CRE and non-CP-CRE, respectively.

Statistical Methods

Descriptive statistics for patient variables were calculated using median or frequency count, as appropriate. Comparisons between CP-CRE and non-CP-CRE groups were made using the Wilcoxon-Mann-Whitney test for continuous variables and the Pearson χ^2 test or Fisher exact test for categorical variables. All tests were 2-tailed, and P values ≤.05 were used for statistical significance testing. Analyses were performed using the STATA 13.0 (Stata Corp) statistical package.

RESULTS

In 2016, 96 unique patients at the Johns Hopkins Hospital had CRE clinical cultures. During this same period, cultures growing *Enterobacteriaceae* were collected from 2369 unique patients, yielding a CRE cumulative incidence of 4%. Of the 96 unique-patient CRE cultures, 45 (47%) were carbapenemase-producing and 51 (53%) were non-carbapenemase-producing. The carbapenemase genes identified in the 45 CP-CRE isolates included bla_{KPC} (83%), bla_{NDM} (11%), bla_{NDM} and $bla_{OXA48\text{-}like}$ (4%), and bla_{KPC} and bla_{NDM} (2%). The majority of CRE were *Klebsiella pneumoniae* (25 CP vs18 non-CP) or *Enterobacter cloacae* (3 CP vs 20 non-CP), with the distribution of the remaining isolates as follows: *Citrobacter freundii* (5 CP vs 2 non-CP), *Enterobacter aerogenes* (2 non-CP), *Escherichia coli* (8 CP vs 5 non-CP), *Klebsiella oxytoca* (2 CP), *Pantoea agglomerans* (1 CP), *Proteus mirabilis* (1 CP), and *Serratia marcescens* (4 non-CP).

Patient characteristics were generally similar between patients infected with CP-CRE and non-CP-CRE (Table 1); however, patients with CP-CRE were more likely to have had at least 1 overnight stay in a foreign health care facility within the previous 6 months (27% vs 2%; odds ratio [OR], 18.18; 95% confidence interval [CI], 2.26–46.53). Specific countries where patients with CP-CRE infections received medical care included India (bla_{KPC} [2], bla_{NDM} [3], bla_{NDM} and bla_{OXA} [1]), Italy (bla_{KPC} [1]), Kuwait (bla_{NDM} [1]), Pakistan (bla_{NDM} [1], bla_{NDM} and bla_{OXA} [1]), and Saudi Arabia (bla_{KPC} [1], bla_{NDM} [1]). Patients with CP-CRE were also more likely to have been transferred from post–acute care facilities compared with patients with non-CP-CRE (31% vs 12%; OR, 3.39; 95% CI, 1.17–9.78). All patients with post–acute care facility exposure in our cohort who developed CP-CRE infections were infected with organisms that were KPC producers.

DISCUSSION

Our findings suggest that patient-specific risk factors can identify which CRE causing clinical infections are carbapenemase-producing where resistance mechanism testing is currently unavailable. In particular, patients who recently received medical care in countries with a high burden of CP-CRE or who are presenting from post–acute care facilities are at an especially high risk of CP-CRE infection. Timely recognition of these patients can be critical to preventing CP-CRE from spreading, and the associated deleterious consequences. CP-CRE are highly transmissible in health care settings and have been nearly exclusively responsible for published CRE outbreaks [8–14]. This experience is consistent with data that suggest that non-CP-CRE may be less fit and potentially less virulent than CP-CRE [2], although conclusive data are lacking. Furthermore, CP-CRE have been associated with significant attributable mortality and poorer outcomes relative to non-CP-CRE [4].

In our cohort, recent hospitalization in a foreign country was associated with an 18-fold greater odds that a CRE infection would be carbapenemase-producing vs non-carbapenemase-producing. In the United States, available data suggest that CP-CRE comprise approximately half of all CRE isolates [15]. The proportion of *Enterobacteriaceae* that are carbapenem resistant is considerably higher in a number of other countries, as is the proportion of CP-CRE. In Greece and Italy, more than 50% of *K. pneumoniae* isolates are resistant to carbapenems [7], with the majority producing carbapenemases [1]. Similarly, the prevalence of CRE, again mostly as a consequence of carbapenemase production, is upwards of 50% in countries located in the Middle East and Indian subcontinent [16]. Increases in international travel resulting in unanticipated health care exposure in endemic settings, as well as "medical tourism," provide an opportunity for CP-CRE to spread across geographic regions [17], reminding us of the importance of obtaining thorough travel histories from hospitalized patients. In addition, although the majority of carbapenemases in the United States are KPC producers, 17% of our CP-CRE isolates produced non-KPC carbapenemases. Our findings suggest that we should remain vigilant for NDM, OXA-48-like, and other carbapenemase classes that are traditionally more common internationally.

Table 1. Description of Characteristics of a Cohort of Patients With Carbapenem-Resistant *Enterobacteriaceae* Recovered From Clinical Cultures, by Carbapenemase Status

Variables on Day 1 of Infection	Carbapenemase-Positive CRE (n = 45, 47%)	Carbapenemase-Negative CRE (n = 51, 53%)	*P* Value
Age, median (IQR), y	68 (55–70)	60 (52–70)	.21
Male sex, No. (%)	27 (60)	32 (63)	.84
Race/ethnicity, No. (%)			
White	20 (44)	31 (61)	
Black	14 (31)	10 (20)	.24
Latino	1 (2)	3 (6)	.62
Asian/Middle Eastern	9 (20)	4 (8)	.08
Preexisting medical conditions, No. (%)			
Diabetes	14 (31)	15 (29)	>.99
End-stage liver disease	2 (4)	4 (8)	.68
End-stage renal disease requiring dialysis	4 (9)	6 (12)	.75
Congestive heart failure (ejection fraction < 40)	9 (20)	8 (16)	.60
Structural lung disease[a]	12 (27)	9 (18)	.33
Immunosuppression,[b] No. (%)	15 (33)	26 (51)	.08
Indwelling hardware, No. (%)			
Biliary stent	1 (2)	4 (8)	.37
Gastrointestinal feeding tube	11 (24)	10 (20)	.63
Nephrostomy and/or Foley catheter	12 (27)	13 (25)	1.00
Chronic vascular hardware	18 (40)	11 (22)	.07
Multidrug-resistant gram-negative colonization or infection within the previous 3 mo, No. (%)			
Extended-spectrum β-lactamase	13 (29)	22 (43)	.20
Carbapenem-resistant *Enterobacteriaceae*	12 (27)	8 (16)	.22
Multidrug-resistant *Pseudomonas* species	4 (9)	1 (2)	
Multidrug-resistant *Acinetobacter* species	2 (4)	1 (2)	.60
Total duration of antibiotic therapy with gram-negative activity in previous 3 mo, median (IQR), d	6 (1–59)	16 (6–55)	.14
Total duration of hospitalization in the previous 3 mo before the current hospitalization, median (IQR), d	5 (0–28)	6 (0–31)	.92
Duration of time from hospital admission until positive culture, median (IQR), d	8 (1–21)	6 (1–26)	.23
At least 1 overnight stay in a foreign health care facility within the previous 6 mo, No. (%)	12 (27)	1 (2)	<.001
Admission from a post–acute care facility, No. (%)	14 (31)	6 (12)	.03
Specimen source, No. (%)			
Urine	21 (47)	21 (41)	
Respiratory[c]	14 (31)	14 (27)	.82
Blood	5 (11)	9 (18)	.40
Soft tissue/wound	2 (4)	6 (12)	.28
Intra-abdominal fluid	3 (7)	1 (2)	.34

Abbreviations: CRE, carbapenem-resistant *Enterobacteriaceae*; IQR, interquartile range.

[a]Chronic obstructive pulmonary disease, emphysema, chronic ventilator dependency.

[b]Human immunodeficiency virus (0 vs 4 patients), chemotherapy within the previous 6 months (8 vs 11 patients), recent immunosuppression use within the previous 30 days (5 vs 8 patients), solid organ transplantation (3 vs 7 patients), hematopoietic stem cell transplantation within the previous 12 months (3 vs 6 patients) in the carbapenemase-positive and carbapenemase-negative groups, respectively (not mutually exclusive).

[c]Sputum, endotracheal aspirate, pleural fluid, and bronchoalveloar lavage fluid.

Another increasingly recognized reservoir for CP-CRE is post–acute care facilities. In our study, patients admitted to the hospital from a post–acute care facility were 3 times more likely to have an infection with CP-CRE, compared with patients presenting from other settings. The medically complex patient population, prolonged lengths of stay, and significant rates of device and antibiotic utilization in post–acute care facilities establish an ideal setting for the emergence and dissemination of antibiotic resistance. These factors are also exacerbated by the convergence of high-risk patients from several acute care facilities. Our findings are consistent with available data indicating a high burden of CRE, and specifically CP-CRE, in post–acute care facilties. In an observational study of 64 long-term acute care hospitals (LTACHs) from across the United States, approximately 25% of *K. pneumoniae* isolates were carbapenem-resistant [18]. Data on the relative proportion of carbapenemase-producing isolates were not available; however, others have reported that CP-CRE accounts for a significant proportion

of carbapenem resistance in post–acute care facilities [19]. In a point-prevalence survey of 7 LTACHs in Chicago, Illinois, for example, 30% of patients were colonized with KPC-producing *Enterobacteriaceae* [19]. Our results reaffirm the importance of ascertaining whether patients admitted to acute care settings recently spent time in post–acute care facilities.

Importantly, because both foreign hospitalization and post–acute care facility transfer are exposures that predate hospital stay, many of the patients who developed CP-CRE infections in our cohort were likely colonized at hospital admission. Absence of exposure to foreign hospitalization and to a post–acute care facility for hospitalized patients who develop CP-CRE infection suggests a greater presumption of nosocomial acquisition in the acute care facility and warrants additional epidemiological investigations.

Our study has a number of limitations. It is a single-center study and should be repeated in larger and more diverse settings. Moreover, selective questioning of patients perceived as higher risk based on their ethnic background could have artificially inflated the importance of receiving medical care in certain countries. Additionally, although we completed a thorough chart review of inpatient and outpatient records, there likely were still missing data.

In summary, our study suggests that receiving medical care in high-risk countries and transfer from post–acute care facilities are significant risk factors that increase the likelihood that CRE infections are due to carbapenemase-producing organisms. We hope that others explore the possibility of preemptive isolation and other infection control strategies for these subpopulations.

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References

1. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing *Enterobacteriaceae*. Virulence **2017**; 8:460–9.
2. Goodman KE, Simner PJ, Tamma PD, Milstone AM. Infection control implications of heterogeneous resistance mechanisms in carbapenem-resistant *Enterobacteriaceae* (CRE). Expert Rev Anti Infect Ther **2016**; 14:95–108.
3. Facility guidance for control of carbapenem-resistant *Enterobacteriacea* (CRE). Available at: https://www.cdc.gov/hai/pdfs/cre/cre-guidance-508.pdf. Accessed 5 January 2018.
4. Tamma PD, Goodman KE, Harris AD, et al. Comparing the outcomes of patients with carbapenemase-producing and non-carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* bacteremia. Clin Infect Dis **2017**; 64:257–64.
5. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing*. 27th ed. CLSI supplement M100S. Wayne, PA: CLSI; **2017**.
6. Tamma PD, Opene BN, Gluck A, et al. Comparison of 11 phenotypic assays for accurate detection of carbapenemase-producing Enterobacteriaceae. J Clin Microbiol **2017**; 55:1046–55.
7. *Point Prevalence Survey of Healthcare Associated Infections and Antimicrobial Use in European Hospitals 2011–2012*. Stockholm: European Centre for Disease Prevention and Control; **2013**. Available at: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf. Accessed 15 January 2018.
8. Borgia S, Lastovetska O, Richardson D, et al. Outbreak of carbapenem-resistant *Enterobacteriaceae* containing blaNDM-1, Ontario, Canada. Clin Infect Dis **2012**; 55:e109–17.
9. Jin Y, Shao C, Li J, et al. Outbreak of multidrug resistant NDM-1-producing *Klebsiella pneumoniae* from a neonatal unit in Shandong Province, China. PLoS One **2015**; 10:e0119571.
10. Jamal WY, Albert MJ, Rotimi VO. High prevalence of New Delhi Metallo-β-Lactamase-1 (NDM-1) producers among carbapenem-resistant *Enterobacteriaceae* in Kuwait. PLoS One **2016**; 11:e0152638.
11. Silva KE, Cayô R, Carvalhaes CG, et al. Coproduction of KPC-2 and IMP-10 in carbapenem-resistant *Serratia marcescens* isolates from an outbreak in a Brazilian teaching hospital. J Clin Microbiol **2015**; 53:2324–8.
12. Chitnis AS, Caruthers PS, Rao AK, et al. Outbreak of carbapenem-resistant *Enterobacteriaceae* at a long-term acute care hospital: sustained reductions in transmission through active surveillance and targeted interventions. Infect Control Hosp Epidemiol **2012**; 33:984–92.
13. Schwaber MJ, Lev B, Israeli A, et al; Israel Carbapenem-Resistant Enterobacteriaceae Working Group. Containment of a country-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* in Israeli hospitals via a nationally implemented intervention. Clin Infect Dis **2011**; 52:848–55.
14. Kanamori H, Parobek CM, Juliano JJ, et al. A Prolonged outbreak of KPC-3-producing *Enterobacter cloacae* and *Klebsiella pneumoniae* driven by multiple mechanisms of resistance transmission at a large academic burn center. Antimicrob Agents Chemother. In press.
15. Guh AY, Bulens SN, Mu Y, et al. Epidemiology of carbapenem-resistant *Enterobacteriaceae* in 7 US communities, 2012-2013. JAMA **2015**; 314:1479–87.
16. *Antimicrobial Resistance: Global Report on Surveillance 2014*. Geneva: World Health Organization; **2014**. Available at: http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1. Accessed 15 January 2018.
17. van der Bij AK, Pitout JD. The role of international travel in the worldwide spread of multiresistant *Enterobacteriaceae*. J Antimicrob Chemother **2012**; 67:2090–100.
18. Han JH, Goldstein EJ, Wise J, et al. Epidemiology of carbapenem-resistant *Klebsiella pneumoniae* in a network of long-term acute care hospitals. Clin Infect Dis **2017**; 64:839–44.
19. Lin MY, Lyles-Banks RD, Lolans K, et al; Centers for Disease Control and Prevention Epicenters Program. The importance of long-term acute care hospitals in the regional epidemiology of *Klebsiella pneumoniae* carbapenemase-producing *Enterobacteriaceae*. Clin Infect Dis **2013**; 57:1246–52.