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MAJOR ARTICLE

# Increased Mortality Among Carbapenemase-Producing Carbapenem-Resistant *Enterobacteriaceae* Carriers Who Developed Clinical Isolates of Another Genotype

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***Background.*** Carbapenemase production by carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* (CP-CRE) is encoded by a variety of genes on mobile genetic elements. Patients colonized by 1 genotype of CP-CRE may be subsequently infected by another genotype of CP-CRE. We sought to determine whether CP-CRE carriers who developed infection with another genotype had a higher mortality risk.

***Methods.*** A retrospective cohort study was conducted using collected data from January 2012 to December 2016. Clinical isolates of CP-CRE were analyzed among the CP-CRE carriers who had developed an infection during their stay in the hospital. Comparison was made between CP-CRE carriers who developed clinical isolates of another genotype and those whose clinical isolates were of the same CP-CRE genotype that they were originally colonized with. The primary outcome analyzed was the 14-day mortality rate.

***Results.*** A total of 73 CP-CRE carriers who had developed infection were analyzed. Ten (15.4%) of the carriers who developed an infection with clinical isolates of the same CP-CRE genotype died within 14 days, whereas 5 (62.5%) of those who developed an infection with clinical isolates of a different genotype died. This represented a 6-fold increase (adjusted relative risk, 6.36; 95% confidence interval, 1.75–23.06; $P = .005$) in the 14-day mortality rate.

***Conclusions.*** CP-CRE carriers who developed clinical isolates of another genotype are at risk of increased mortality. This is a novel finding that is of interest to health care organizations worldwide, with profound implications for infection control measures, such as patient and staff cohorting.

**Keywords.** carbapenemases; CP-CRE; carbapenem-resistant *Enterobactericeae*; mortality; genotypes.

Carbapenem-resistant *Enterobacteriaceae* (CRE) are an emerging threat to health care communities globally because of the associated increase in health care burden and costs [1]. Resistance to carbapenems is a result of 2 main mechanisms—first through the production of extended-spectrum β-lactamases (ESBLs) and/or Amp C cephalosporinase (AmpC), combined with altered membrane permeability, and second through the production of carbapenemase. The latter is commonly referred to as carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* (CP-CRE) [2–4].

Carbapenemases are encoded by various genes found on mobile genetic elements such as plasmids and transposons [3–7]. Worldwide, the genotype $bla_{KPC}$ is most commonly reported, but other genotypes such as $bla_{OXA}$, $bla_{VIM}$, $bla_{NDM}$, and $bla_{IMP}$ are increasingly more common. These carbapenemases often do not arise from de novo mutation in bacterial cells and are not anticipated to endogenously arise during antibiotic therapy. Instead, carbapenemase-mediated resistance may be acquired through the spread of resistant bacteria (CP-CRE) or through the spread of carbapenemase-encoding mobile genetic elements that can be transferred between bacteria, including between different species and even among different genera [8, 9].

Patients colonized or infected with CP-CRE may introduce the bacteria into the hospital environment, leading to health care worker or environmental contamination. This can lead to subsequent dissemination to other unsuspecting patients [8]. After colonization, the organism can invade the bloodstream or other sterile sites, resulting in infections. This transmission model suggests that it is possible for CP-CRE-colonized patients to be subsequently infected with CP-CRE carrying another type of carbapenemase gene; for example, a patient colonized with a CP-CRE of the genotype $bla_{KPC}$ can be subsequently infected by another CP-CRE with the genotype $bla_{NDM}$. To date, there is

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no study on the mortality implications of CP-CRE carriers who subsequently develop CP-CRE infections of another genotype.

Many health care institutions have limited isolation rooms; hence, in order to cohort CP-CRE carriers, there are designated "CP-CRE" rooms or wards for patients with CP-CRE carriage. The close proximity of patients in these wards and the presence of a shared pool of health care staff increases the CP-CRE patient's risk of acquiring another CP-CRE. Our findings therefore hold serious implications for infection control measures, such as patient and staff cohorting, which is currently recommended to reduce nosocomial transmission of CP-CRE [10].

## METHODS

### Study Design

A retrospective, observational cohort study was conducted among known CP-CRE carriers admitted to our tertiary hospital, Singapore General Hospital (SGH; 1700 beds), from January 2012 to December 2016. All inpatients on admission were screened for CP-CRE carriage via stool specimens or rectal swabs if they fulfilled any of the following criteria: patients who (1) had a history of hospitalization in overseas or local private or local public hospitals in the past year, (2) were transferred from overseas or local hospitals, (3) were admitted to high-dependency, intermediate care areas and intensive care units (ICUs), and (4) were admitted to the hematology, oncology, and renal units. Clinical isolates were ordered by their attending physician based on clinical needs, as part of their treatment.

For our study, all clinical isolates of CP-CRE cultured by the laboratory at SGH from January 2012 to December 2016 were identified. All pregnant patients and specimens belonging to patients age <21 years were excluded. Urinary CP-CRE carriers who were defined as patients with positive urinary CP-CRE cultures but were not treated with antibiotics and had no documentation of CP-CRE urinary infection in their clinical notes, likely urinary colonization, were also excluded.

Patients' medical records were reviewed, and the following data were collected: demographics, preexisting medical conditions, microbiological data, antibiotic therapy, and outcomes.

Known CP-CRE carriers who developed clinical isolates that were different from their colonized genotypes were compared against CP-CRE carriers with clinical isolates of the same genotype. The primary outcome was the 14-day mortality rate (day 1 taken as the day the clinical isolate was collected). The secondary outcome was 30-day mortality.

The Singapore Health Services Institutional Review Board approved this study with a waiver of informed consent.

### Definitions

CP-CRE carriers were defined as those patients who had tested positive for CP-CRE in the screening test. Colonization genotypes were those identified from screening specimens, taken at least 1 day before their first positive CP-CRE clinical isolates. CP-CRE clinical isolates were defined as the patients' first positive CP-CRE culture that did not come from a screening specimen. For patients who had more than 1 positive clinical isolate, only the first positive clinical isolate obtained after the screening was included. The subsequent samples of positive clinical isolates were not included in this study.

In our laboratories, carbapenem nonsusceptibility was suspected on detection of reduced zone diameter on disc diffusion testing for carbapenems. The CarbaNP test was then performed on these suspected isolates to determine if any bacteria produced carbapenemases by phenotypic methods. Isolates with positive results were sent to the National Public Health Laboratory (NPHL) for polymerase chain reaction (PCR). Isolates that tested negative with the CarbaNP test would be further subjected to the modified Hodge test and the ROSCO disc test—with those samples that were tested positive for both sent to the NPHL for PCR [11]. At the NPHL, characterization of genes was performed by PCR assays targeting class A carbapenemases ($bla_{KPC}$, $bla_{GES}$, $bla_{IMI-1}$, and $bla_{NMC-A}$), class B metallo-β-lactamases ($bla_{NDM}$, $bla_{VIM}$, and $bla_{IMP}$), and class D carbapenemases ($bla_{OXA-48-like}$ and $bla_{OXA-23}$). All positive CP-CRE specimens and genotypes included in this study were based on the above genotypic confirmation by the NPHL.

Active empiric antibiotic therapy was defined, based on antimicrobial susceptibility testing, as at least 1 antibiotic to which the isolate was susceptible and was started within 24 hours from the time the clinical isolate was obtained. Active directed antibiotic therapy was defined, based on antimicrobial susceptibility testing, as at least 1 antibiotic that the clinical isolate was susceptible to, started within 5 days after the clinical isolate was obtained.

### Statistical Methods

Descriptive statistics for patients' variables were calculated using frequency count (percentage) or median (interquartile range), as appropriate. Comparisons between the same and different genotypic groups were made using the Mann-Whitney *U* test for continuous variables and the Fisher exact test for categorical variables with 2 groups and the Pearson $\chi^2$ test for categorical variables consisting of 3 or more groups. The relationship between genotype congruency status and mortality is summarized by relative risks (RRs) and their corresponding 95% confidence intervals (CIs).

Multivariate modeling was performed via Breslow-Cox regression. All tests were 2-tailed, and *P* values <.05 were statistically significant. Analyses were performed using the IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY), statistical package.

For our multivariate model, we first identified several potential confounders a priori. These were age, gender, presence of severe infection on day 1 (using the Evaluation for Severe Sepsis Screening Tool from the Surviving Sepsis Campaign)

[12], receipt of active empirical antibiotic therapy, and receipt of active definitive antibiotic therapy. In addition, covariates found to have a *P* value <.10 on univariate analysis and that resulted in a 10% or greater change in the adjusted relative risk were also identified as potential confounders. Next, we used a stepwise selection approach in our multivariate modeling, selecting only the covariates that resulted in a ≥10% change in regression coefficient or a reduction in standard error. Covariates that suggested collinearity when added were removed from the model. The covariates in our final model are age (>65 years), presence of severe infection on day 1, and clinical isolate genotype including $bla_{KPC}$.

## RESULTS

### Baseline and Microbiological Characteristics

A total of 357 individual patients with CP-CRE clinical isolates were identified during the study period. From these, 274 patients were excluded as they were not known CP-CRE carriers (either they had not been screened before their clinical isolate collection date or they had screened negative for CP-CRE). A further 10 patients who had positive urinary clinical isolates that most likely represented colonization were also excluded. The remaining 73 patients formed our study population (Figure 1).

The large portion of patients excluded may be a reflection of the low prevalence of CP-CRE carriage in our general community. It could also be a result of a lack of a universal screening scheme for all patients admitted to the hospital.

Among these 73 patients, 65 had CP-CRE clinical isolates of the same genotype that they were colonized with, whereas 8 had clinical isolates of a different genotype. Of significance in the baseline characteristics of the 2 groups, all 8 of the CP-CRE carriers who developed clinical isolates of a different genotype were male. All other baseline characteristics were not significantly different between the 2 groups (Table 1).

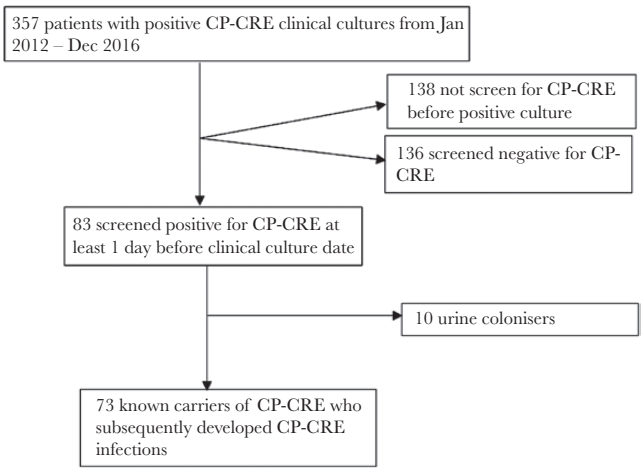


**Figure 1.** Flow diagram of study population section.

*Klebsiella* spp. accounted for more than half of the bacteria detected in clinical isolates of the group with the same CP-CRE genotype (39, 60%), followed by *Escherichia coli* (16, 24.6%) and *Enterobacter* spp. (9, 13.8%). In the group with a different CP-CRE genotype, *Klebsiella* spp. similarly accounted for most of the bacteria detected (6, 75%), followed by *Enterobacter cloacae* (1, 12.5%) and *Citrobacter* spp. (1, 12.5%).

Patients with CP-CRE clinical isolates of the same genotype had been predominantly colonized with $bla_{KPC}$ (49, 75.4%). In contrast, among patients with CP-CRE clinical isolates of a different genotype, their colonization genus distribution was more diverse, with equal numbers colonized with $bla_{KPC}$ and $bla_{NDM}$ (3, 37.5%) (Table 2).

Among patients with CP-CRE clinical isolates of the same genotype, a majority of these clinical isolate genotypes included $bla_{KPC}$ (48, 73.8%). In contrast, only 1 (12.5%) patient with CP-CRE clinical isolates of a different genotype had $bla_{KPC}$ (Table 2).

### 14-Day and 30-Day Mortality

A total of 15 (20.5%) patients died within 14 days; 5 (62.5%) were from the group of patients with CP-CRE clinical isolates of a different genotype, and 10 (15.4%) were from the group of patients with CP-CRE clinical isolates of the same genotype. In univariate analysis, the risk of dying within 14 days was 4 times greater for the group with clinical isolates of a different genotype compared with the group with the same genotype (RR, 4.06; 95% CI, 1.86–8.89; *P* = .008). In our multivariate model, the risk of dying increased to more than 6 times (aRR, 6.36; 95% CI, 1.75–23.06; *P* = .005) after adjustment for age (>65 years), presence of severe infection on day 1, and clinical isolate genotype including $bla_{KPC}$. All of the other covariates were not associated with an increase in 14-day mortality (Table 3).

The 30-day mortality rate corroborates with the finding on increased 14-day mortality; that is, there was a 3-fold increased mortality rate (aRR, 3.29; 95% CI, 1.22–8.90; *P* = .019) for the group with clinical isolates of a different genotype compared with the group with clinical isolates of the same genotype (Table 4).

## DISCUSSION

CP-CRE is a rapidly emerging problem in our global health care system. Our study represented the first effort to quantify the significance of CP-CRE infection of a different genotype on mortality among CP-CRE carriers. Our data demonstrate that CP-CRE-colonized patients who were later found with a CP-CRE clinical isolate of a different genotype were 6 times more likely to die within 14 days and 3 times more likely to die within 30 days, when compared with CP-CRE-colonized patients who were found with clinical isolates of the same genotype. Our findings suggest that acquisition and subsequent clinical infection of another genotype of CP-CRE by CP-CRE carriers represents a significant mortality risk.

**Table 1. Baseline and Treatment Characteristics of CP-CRE Carriers With CP-CRE Clinical Isolates of a Different Genotype and CP-CRE Carriers With Clinical Isolates of the Same Genotype**

| Variable | CP-CRE Carriers With Clinical Isolates of a Different Genotype | | *P* Value |
|---|---|---|---|
| | Yes (n = 8, 11%) | No (n = 65, 89%) | |
| Male | 8 (100) | 37 (56.9) | .02 |
| Age[a] | 59.9 (57.3–67.1) | 67.6 (59.2–77.9) | .28 |
| Ethnic group | | | |
| Chinese | 4 (50) | 44 (67.7) | |
| Malay | 0 (0) | 9 (13.8) | |
| Indian | 3 (37.5) | 6 (9.2) | |
| Others | 1 (12.5) | 6 (9.2) | .11 |
| Clinical isolate source | | | |
| Urinary/gential tract | 2 (25) | 12 (18.5) | .65 |
| Respiratory tract | 3 (37.5) | 20 (30.8) | .70 |
| Biliary system | 0 (0) | 2 (3.1) | 1.00 |
| Gastrointestinal tract | 0 (0) | 11 (16.9) | .60 |
| Skin and soft tissues | 2 (25) | 9 (13.8) | .60 |
| Bone/joint | 0 (0) | 1 (1.5) | 1.00 |
| Blood | 1 (12.5) | 10 (15.4) | 1.00 |
| Admission to intensive care unit | 4 (50.0) | 24 (36.9) | .48 |
| Length of ICU stay[a] | 4.5 (1.25–10.75) | 4.5 (2–16.5) | .68 |
| Days in hospital before CP-CRE clinical isolate collection[a] | 20.5 (4.25–48.5) | 26.0 (8.5–50.5) | .61 |
| Days from CP-CRE colonization to clinical isolate collection[a] | 29.5 (3.25–275.5) | 14 (5–38.5) | .45 |
| Comorbids | | | |
| Diabetes | 2 (25.0) | 26 (40.0) | .70 |
| Renal disease | 1 (12.5) | 18 (27.7) | .67 |
| Congestive cardiac failure | 0 (0) | 3 (4.6) | 1.00 |
| Chronic pulmonary disease | 2 (25.0) | 6 (9.2) | .21 |
| Moderate or severe liver disease | 2 (25.0) | 3 (4.6) | .09 |
| AIDS | 1 (12.5) | 0 (0) | .11 |
| Charlson score[a] | 3.5 (2.25–5.75) | 3 (2–4) | .42 |
| Hemodialysis | 1 (12.5) | 21 (32.3) | .42 |
| Solid organ transplant | 0 (0) | 2 (3.1) | 1.00 |
| Chemotherapy within the previous 6 mo | 0 (0) | 2 (3.1) | 1.00 |
| Chronic corticosteroid therapy | 0 (0) | 3 (4.6) | 1.00 |
| Absolute neutrophil count <200 cells/mL on day of clinical isolate collection | 0 (0) | 1 (1.5) | 1.00 |
| History of colonization with other MDROs[b] | | | |
| Methicillin-resistant *Staphylococcus aureus* | 3 (37.5) | 13 (20.3) | .36 |
| Vancomycin-resistant *Enterococci* | 2 (28.6) | 16 (26.7) | 1.00 |
| *Clostridium difficile* | 1 (16.7) | 3 (7.0) | .42 |
| Active empirical[c] antibiotic therapy | 0 (0) | 7 (10.8) | 1.00 |
| Active definitive[d] treatment antibiotic therapy | 0 (0) | 19 (29.2) | .10 |
| Severe sepsis present[e] | 5 (62.5) | 33 (50.8) | .71 |

Abbreviations: CP-CRE, carbapenemase-producing carbapenem-resistant *Enterobacteriaceae*; ICU, intensive care unit; MDROs, multidrug-resistant organisms.

[a]Variables reported as median (interquartile range); the other variables are all reported as frequency counts (%).

[b]Patients who screened positive for multidrug-resistant organisms in the 6 months before positive CP-CRE clinical culture.

[c]Based on antimicrobial susceptibility testing, represented as at least 1 antibiotic that the clinical isolate is susceptible to, started within 24 hours from the time the first positive clinical isolate was obtained.

[d]Based on antimicrobial susceptibility testing, represented as at least 1 antibiotic that the clinical isolate is susceptible to, started within to 5 days after the first positive clinical isolate was obtained.

[e]Based on the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2016. Evaluation for Severe Sepsis Screening Tool.

We postulate that the transfer of plasmids between the bacterium may have increased its virulence, thereby resulting in the increased in mortality rate. However, further work is required to characterize the associated plasmids to explore this hypothesis.

As colonization and infection rates of CP-CRE have been increasing in both pediatric and adult settings across the world, health care facilities have been active in implementing infection control measures to contain its transmission [6, 13–17]. From our understanding, CP-CRE transmission is postulated

**Table 2. CP-CRE Colonization and Clinical Isolate Genotypes of Carriers With Clinical Isolates of a Different Genotype and Carriers With Clinical Isolates of the Same Genotype**

| | CP-CRE Carriers With Clinical Isolates of a Different Genotype | | |
|---|---|---|---|
| Variables | Yes (n = 8, 11%) | No (n = 65, 89%) | *P* Value |
| Colonized genotype[a] | | | |
| *bla*$_{IMP}$ | 1 (12.5) | 0 (0) | |
| *bla*$_{KPC}$ | 3 (37.5) | 47 (72.3) | |
| *bla*$_{NDM}$ | 2 (25) | 7 (10.8) | |
| *bla*$_{OXA-181}$ | 0 (0) | 2 (3.1) | |
| *bla*$_{OXA-23}$ | 1 (12.5) | 0 (0) | |
| *bla*$_{OXA-232}$ | 0 (0) | 4 (6.2) | |
| *bla*$_{KPC}$ and *bla*$_{NDM}$ | 0 (0) | 1 (1.5) | |
| *bla*$_{NDM}$ and *bla*$_{OXA-232}$ | 0 (0) | 2 (3.1) | |
| *bla*$_{NDM}$ and *bla*$_{OXA-181}$ | 1 (12.5) | 1 (1.5) | |
| *bla*$_{OXA-232}$ and *bla*$_{NDM}$ and *bla*$_{KPC}$ | 0 (0) | 1 (1.5) | |
| Includes *bla*$_{KPC}$ | 3 (37.5) | 49 (75.4) | .039 |
| Includes *bla*$_{NDM}$ | 3 (37.5) | 12 (18.5) | .348 |
| Clinical isolate genotype[b] | | | |
| *bla*$_{IMP}$ | 1 (12.5) | 0 (0) | |
| *bla*$_{KPC}$ | 1 (12.5) | 48 (73.8) | |
| *bla*$_{NDM}$ | 2 (25.0) | 8 (12.3) | |
| *bla*$_{OXA-181}$ | 1 (12.5) | 2 (3.1) | |
| *bla*$_{OXA-232}$ | 2 (25.0) | 5 (7.7) | |
| *bla*$_{NDM}$ and *bla*$_{OXA-232}$ | 0 (0) | 2 (3.1) | |
| *bla*$_{NDM}$ and *bla*$_{OXA-48}$ | 1 (12.5) | 0 (0) | |
| Includes *bla*$_{KPC}$ | 1 (12.5) | 48 (73.8) | .001 |
| Includes *bla*$_{NDM}$ | 3 (37.5) | 10 (15.4) | .146 |

Abbreviation: CP-CRE, carbapenemase-producing carbapenem-resistant *Enterobacteriaceae*.

[a]Latest genotype of the CP-CRE screening specimen collected at least 1 day before the clinical isolate specimen.

[b]CP-CRE genotype of patient's first positive CP-CRE culture that is not a stool or rectal screening specimen.

to occur primarily through health care workers or environmental contamination [8, 18–21]. Current recommendations to curtail the spread of CP-CRE in health care facilities, such as the Centers for Disease Control and Prevention's (CDC's) CRE Toolkit, involve infection control measures such as cohorting of patients who are colonized or infected with CP-CRE and cohorting of staff responsible for their care [10]. The Oregon Health Authority likewise recommends geographical cohorting and staff cohorting for patients positive for CP-CRE [22]. Such cohorting strategies have been successful in Israel, where geographical cohorting of CP-CRE colonizers and staff cohorting were implemented. They managed to reduce the national nosocomial CRE acquisition rate from 55.5 incident cases per 100 000 patient-days per month during the peak of an outbreak in 2007 to 11.7 cases per 100 000 patient-days per month [23–25].

However, CP-CRE is not a single entity. Carbapenemases are classified by their molecular structure according to the Ambler classification system, with multiple genes coding for each class [4, 26]. Therefore, it is possible for a patient to acquire more than 1 genotype of CP-CRE. The discovery and global spread of other carbapenemase genes like NDM and OXA means that it is increasingly likely for colonized patients to acquire another

**Table 3. Fourteen-Day Mortality of CP-CRE Carriers With CP-CRE Clinical Isolates of a Different Genotype and CP-CRE Carriers With Clinical Isolates of the Same Genotype**

| Covariate | Relative Risk (95% CI) | *P* Value | Adjusted[a] Relative Risk (95% CI) | *P* Value |
|---|---|---|---|---|
| Different colonization and clinical isolate genotype[b] | 4.06 (1.86–8.89) | .008 | 6.36 (1.75–23.06) | .005 |
| Age >65 y | 1.71 (0.60–4.85) | .379 | 2.14 (0.57–7.93) | .257 |
| Clinical isolate genotype includes KPC | 0.98 (0.38–2.55) | 1 | 1.62 (0.40–6.64) | .501 |
| Severe infection present[c] | 1.38 (0.55–3.49) | .570 | 1.39 (0.47–4.08) | .547 |

Abbreviations: CI, confidence interval; CP-CRE, carbapenemase-producing carbapenem-resistant *Enterobacteriaceae*.

[a]Potential confounders included in the final model were age >65 years, clinical isolate genotype including *bla*$_{KPC}$, presence of severe infection on day 1.

[b]CP-CRE carriers with clinical isolate of a different genotype compared with CP-CRE carriers with clinical isolate of the same genotype.

[c]Based on the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2016. Evaluation for Severe Sepsis Screening Tool.

**Table 4. Thirty-Day Mortality of CP-CRE Carriers With CP-CRE Clinical Isolates of a Different Genotype and CP-CRE Carriers With Clinical Isolates of the Same Genotype**

| Covariate | Relative Risk (95% CI) | *P* Value | Adjusted[a] Relative Risk (95% CI) | *P* Value |
|---|---|---|---|---|
| Different colonization and clinical isolate genotype[b] | 2.22 (1.31–3.75) | .048 | 3.29 (1.22–8.90) | .019 |
| Age >65 y | 2.86 (1.23–6.66) | .006 | 3.80 (1.30–11.10) | .015 |
| Clinical isolate genotype includes KPC | 1.22 (0.63–2.37) | .614 | 1.17 (0.45–3.04) | .749 |
| Severe infection present[c] | 1.94 (1.02–3.71) | .053 | 2.22 (0.99–4.98) | .052 |

Abbreviations: CI, confidence interval; CP-CRE, carbapenemase-producing carbapenem-resistant *Enterobacteriaceae*.

[a]Potential confounders included in the final model were age >65 years, clinical isolate genotype including $bla_{KPC}$, presence of severe infection on day 1.

[b]CP-CRE carriers with clinical isolate of a different genotype compared with CP-CRE carriers with clinical isolate of the same genotype.

[c]Based on the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2016. Evaluation for Severe Sepsis Screening Tool.

CP-CRE genotype [6]. Although patient and staff cohorting have achieved much public good in reducing the spread of CP-CRE within health care facilities, it also presents a potential risk of transmitting different genotypes of CP-CRE among these cohorted patients [27].

Our novel finding indicates that there was a significant increase in mortality among CP-CRE carriers who subsequently developed CP-CRE clinical isolates of another genotype. This presents to health care organizations a potential dilemma between the good of public health achieved with patient and staff cohorting and the risk to the individual patient who is being cohorted. This is of particular relevance to countries such as ours, where hospitals tend to have multibedded cubicles or pods. In view of the significant implications of our findings, we earnestly encourage others to perform similar analyses with a larger cohort to both explore outstanding issues and determine the reproducibility of our results.

We are the first to demonstrate that infection of CP-CRE carriers by another genotype of CP-CRE is associated with increased mortality. Other strengths of our study include the utilization of a comprehensive and unbiased database of patients from the largest tertiary hospital in Singapore for the process of data extraction. The waiver of the need for informed consent also ensured that maximum numbers of patients were recruited to our study, over the span of 4 years.

Admittedly, there are several limitations. First, the number of CP-CRE carriers with subsequent clinical isolates of another genotype was small (n = 8), and these carriers were all male. Second, the limited sample size precluded analyses of certain subgroups, such as the differences that may exist due to different bacterial genera and differences in the various colonized–clinical isolate gene pairings. Third, although best efforts were made to include all variables associated with poor outcomes for patients with CP-CRE clinical isolates, it remains possible that there exists residual confounding that was not accounted for in our analysis. Lastly, our data were derived from a single center, where the carbapenemase gene distribution may differ from that in other regions of the world, limiting their generalizability.

In conclusion, we present the first finding of an increased mortality risk to CP-CRE carriers, when infected by another genotype of CP-CRE. We hope that our study spurs more research into this premise. We are also mindful that greater debate is needed, revolving around the ethics involved in balancing the public health importance of reducing CP-CRE transmission vs the increased individual mortality risk of the cohorted patient.

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## References

1. Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing *Enterobacteriaceae*. Emerg Infect Dis **2011**; 17:1791–8.
2. Livingstone D, Gill MJ, Wise R. Mechanisms of resistance to the carbapenems. J Antimicrob Chemother **1995**; 35:1–5.
3. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrob Agents Chemother **2010**; 54:969–76.
4. Ambler RP. The structure of beta-lactamases. Philos Trans R Soc Lond B Biol Sci **1980**; 289:321–31.
5. Rasmussen BA, Bush K, Keeney D, et al. Characterization of IMI-1 beta-lactamase, a class A carbapenem-hydrolyzing enzyme from *Enterobacter cloacae*. Antimicrob Agents Chemother **1996**; 40:2080–6.
6. Logan LK, Weinstein RA. The epidemiology of carbapenem-resistant *Enterobacteriaceae*: the impact and evolution of a global menace. J Infect Dis **2017**; 215:28–36.
7. Espedido B, Iredell J, Thomas L, Zelynski A. Wide dissemination of a carbapenemase plasmid among gram-negative bacteria: implications of the variable phenotype. J Clin Microbiol **2005**; 43:4918–9.
8. 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.
9. Queenan AM, Bush K. Carbapenemases: the versatile beta-lactamases. Clin Microbiol Rev **2007**; 20:440–58, Table of Contents.
10. Centers for Disease Control and Prevention. Facility guidance for control of carbapenem-resistant *Enterobacteriaceae* (CRE) – November 2015 Update CRE Toolkit. https://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html. Accessed 31 October 2017.
11. Lutgring JD, Limbago BM. The problem of carbapenemase-producing-carbapenem-resistant-*Enterobacteriaceae* detection. J Clin Microbiol **2016**; 54:529–34.
12. Surviving Sepsis Campaign. Evaluation for severe sepsis screening tool. http://www.survivingsepsis.org/SiteCollectionDocuments/ScreeningTool.pdf. Accessed 10 March 2017.
13. Logan LK. Carbapenem-resistant *Enterobacteriaceae*: an emerging problem in children. Clin Infect Dis **2012**; 55:852–9.

14. Suwantarat N, Logan LK, Carroll KC, et al. The prevalence and molecular epidemiology of multidrug-resistant *Enterobacteriaceae* colonization in a pediatric intensive care unit. Infect Control Hosp Epidemiol **2016**; 37:535–43.
15. Stillwell T, Green M, Barbadora K, et al. Outbreak of KPC-3 producing carbapenem-resistant *Klebsiella pneumoniae* in a US pediatric hospital. J Pediatric Infect Dis Soc **2015**; 4:330–8.
16. Pannaraj PS, Bard JD, Cerini C, Weissman SJ. Pediatric carbapenem-resistant *Enterobacteriaceae* in Los Angeles, California, a high-prevalence region in the United States. Pediatr Infect Dis J **2015**; 34:11–6.
17. Viau RA, Hujer AM, Marshall SH, et al. "Silent" dissemination of *Klebsiella pneumoniae* isolates bearing *K. pneumoniae* carbapenemase in a long-term care facility for children and young adults in northeast Ohio. Clin Infect Dis **2012**; 54:1314–21.
18. Bratu S, Landman D, Haag R, et al. Rapid spread of carbapenem-resistant *Klebsiella pneumoniae* in New York City: a new threat to our antibiotic armamentarium. Arch Intern Med **2005**; 165:1430–5.
19. Guet-Revillet H, Le Monnier A, Breton N, et al. Environmental contamination with extended-spectrum β-lactamases: is there any difference between *Escherichia coli* and *Klebsiella* spp? Am J Infect Control **2012**; 40:845–8.
20. Lerner A, Adler A, Abu-Hanna J, et al. Environmental contamination by carbapenem-resistant *Enterobacteriaceae*. J Clin Microbiol **2013**; 51:177–81.
21. Otter JA, French GL. Survival of nosocomial bacteria and spores on surfaces and inactivation by hydrogen peroxide vapor. J Clin Microbiol **2009**; 47:205–7.
22. Oregon Health Authority. Guidance for control of carbapenem-resistant *Enterobacteriaceae* (CRE) 2016 Oregon Toolkit. http://www.oregon.gov/oha/PH/DISEASESCONDITIONS/DISEASESAZ/CRE1/cre_toolkit.pdf. Accessed 1 November 2017.
23. Leavitt A, Navon-Venezia S, Chmelnitsky I, et al. Emergence of KPC-2 and KPC-3 in carbapenem-resistant *Klebsiella pneumoniae* strains in an Israeli hospital. Antimicrob Agents Chemother **2007**; 51:3026–9.
24. 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.
25. Schwaber MJ, Carmeli Y. An ongoing national intervention to contain the spread of carbapenem-resistant *Enterobacteriaceae*. Clin Infect Dis **2014**; 58:697–703.
26. Bush K, Fisher JF. Epidemiological expansion, structural studies, and clinical challenges of new β-lactamases from gram-negative bacteria. Annu Rev Microbiol **2011**; 65:455–78.
27. Rock C, Thom KA, Masnick M, et al. Frequency of *Klebsiella pneumoniae* carbapenemase (KPC)-producing and non-KPC-producing *Klebsiella* species contamination of healthcare workers and the environment. Infect Control Hosp Epidemiol **2014**; 35:426–9.