Quantifying The Burden Of Contact Precautions Of Carbapenem-Resistant Enterobacteriaceae (cre) In Hospital Settings

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Quantifying the Burden of Contact Precautions of Carbapenem-resistant Enterobacteriaceae (CRE) in Hospital Settings

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Abstract

Carbapenem-resistant Enterobacteriaceae (CRE) are a group of multi-drug resistant organisms (MDROs) that is currently considered an important and urgent public health concern due to their high mortality rates, antibiotic resistance, and their potential for rapid transmission. These pathogens are more commonly seen in healthcare-associated infections with some also occurring in the community. This study focused on distinguishing CRE into two distinct groups based on resistance mechanism: carbapenemase-producing CRE (CP-CRE) and non-CP-CRE. In order to determine if testing for carbapenemase can be useful in infection prevention, we aimed to quantify the total hospitalization in days per patient within a 90-day follow-up period after carbapenemase test results were available for both of the CP-CRE and non-CP-CRE patient groups, using the statewide hospitalization and CRE surveillance data from the 2017 calendar year, provided by the Connecticut Hospital Association and the Connecticut Department of Public Health (CT DPH). The study sample consisted of a total of 126 patients (32 CP-CRE, 94 non-CP-CRE). Adjusting for age and sex, we found that CP-CRE patients had 31.6% fewer hospitalization days than non-CP-CRE patients (P<0.0001). We also found that the number of distinct hospitalizations per patient in each group while controlling for age and sex was not statistically significant (P=0.3250). Our results suggest that carbapenemase testing can be informative in possibly guiding treatment or cohorting patients, but further studies with a greater sample size and addressing the limitations of this study need to be conducted for improved interpretations.
Acknowledgements

I would like to sincerely thank Dr. Dembry and Dr. Banach as my advisors for their unwavering patience, support, and guidance throughout this entire process. I would also like to thank Meghan Maloney, my preceptor at the Connecticut Department of Public Health, for her endless encouragement and mentoring. I am extremely appreciative and grateful for my advisors and preceptor as my time at YSPH would not have been as fulfilling and enriching without their help. Finally, I would like to thank my family and friends for the support and positivity they have constantly given me throughout my time at YSPH.
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I. **Introduction**

Multi-drug resistant organisms (MDROs) have been a major public health issue ever since the first widespread use of antibiotics starting with penicillin in the 1940s. These microorganisms are resistant to one or more classes of antimicrobials, making it difficult to provide effective treatment. One method in which drug resistance develops is through antibiotic selective pressure, where previous drug exposure or incomplete or inadequate treatment regimens may select for a particular favorable mutation that allows for the microorganism to persist. Drug resistance can also be acquired through the exchange of genetic material, where genes that confer resistance to a particular antibiotic are transferred from one microorganism to another, most commonly mediated through plasmids. This mechanism is especially concerning since resistance can even be transferred between different types of bacteria through these plasmids, which may frequently carry resistance genes against more than one antibiotic class, such as fluoroquinolones or aminoglycosides.

One particular subset of MDROs known as carbapenem-resistant Enterobacteriaceae (CRE) are a group of Gram-negative bacteria of great public health concern due to their high levels of antibiotic resistance and potential for rapid transmission. Enterobacteriaceae, such as *Escherichia coli* and *Klebsiella pneumoniae*, are normally a component of the intestinal microbiota, but are also one of the most common causes of infection in both the community and healthcare settings, leading to various illnesses such as urinary tract infections (UTIs), septicemia, pneumonia, meningitis, etc. CRE infections are mostly prominent in healthcare settings where there are vulnerable individuals at risk due to being immunocompromised, experiencing various other comorbidities, receiving indwelling catheters, or undergoing invasive procedures. In a meta-analysis conducted by van Loon *et al.* (2018), several of the greatest risk
factors associated with acquiring CRE included the use of medical devices, previous antibiotic use, invasive procedures, and ICU admissions.

CRE infections are also a growing concern since carbapenems (which include doripenem, meropenem, imipenem, and ertapenem) are one of the broadest spectrum class of antibiotics available and are typically used as a last resort treatment in combatting antibiotic-resistant Gram-negative infections. Carbapenems are part of the beta-lactam class of antibiotics, which function by disrupting proper bacterial cell wall synthesis. They are a relatively new class of drugs developed in response to increasing resistance seen against other therapy options. Therefore, these drugs are highly important in treating a wide variety of healthcare-associated infections. However, due to carbapenem resistance and the lack of development of new effective drugs, possible treatment options become increasingly limited. Additionally, there is increasing concern of potential spread of carbapenem resistance into the community or into other organisms.

This concern is also exacerbated by the presence of carbapenemase-producing CRE (CP-CRE), which is distinct from non-CP-CRE due to their contrasting resistance mechanisms. Non-CP-CRE have resistance mechanisms comprised of beta-lactamase enzymes (AmpC or Extended-spectrum beta-lactamase) in addition to porin mutations that prevent proper drug penetration or the formation of efflux pumps that actively transport drugs out of the organism. On the other hand, as their name implies, CP-CRE are able to produce carbapenemases which directly break down carbapenems in addition to many other beta-lactam molecules. These enzymes are often encoded on mobile genetic elements (typically plasmids), and therefore can contribute to rapid spread of resistance among Enterobacteriaceae and even other types of Gram-negative bacteria, including naïve bacteria that may never have had any prior exposure to
carbapenems\textsuperscript{12}. Additionally, the majority of existing beta-lactamase inhibitors, including clavulanic acid, are not effective against carbapenemases\textsuperscript{13}, which makes it difficult to work around carbapenemase-mediated resistance. Recently, novel beta-lactam/beta-lactamase inhibitor combinations, such as ceftazidime/avibactam, have been shown to be effective against certain types of carbapenemases, including \textit{Klebsiella pneumoniae} carbapenemases (KPC)\textsuperscript{6,14}. However, occurrences of resistance against even these newer therapy options have already been observed\textsuperscript{15,16}, adding to the growing concerns of effectively treating carbapenemase-mediated resistance. In general, these enzymes are believed to contribute to the overall rapid spread of resistance, result in high mortality rates, and are responsible for the overall increase in CRE in the United States\textsuperscript{10}. In the US, the first CP-CRE isolate was identified in 1996 and in a relatively short period of time every state (with the exception of Idaho and Maine) has had at least one report of CP-CRE as of 2015\textsuperscript{9}. This highlights the swift spread of carbapenemase-mediated resistance and emphasizes the specific need to address CP-CRE transmission and prevention.

In order to target CP-CRE, it is important to be able to discern the two resistance mechanisms in an efficient and timely manner. However, it has been difficult developing criteria based on drug susceptibility patterns that are able to correctly distinguish the two groups due their overlapping antibiotic susceptibility profiles\textsuperscript{9}. The CDC’s CRE phenotypic surveillance definition (2015) has lower specificity for CP-CRE, particularly in areas with low burdens of infection\textsuperscript{9}. In Connecticut, surveillance for CRE has been implemented since 2014 based on a phenotypic case definition and was made a laboratory reportable condition (although carbapenemase testing was fairly limited in the clinical laboratories at this time). With a revised and less complicated case definition, mandatory submission of all CRE isolates, and the availability of advanced molecular testing at the CT State Public Health Laboratory (CT SPHL)
in 2017, every identified CRE case is able to be genetically characterized, elucidating the mechanism of resistance and allowing for earlier identification of outbreaks and more timely initiation of investigations, screening of potentially exposed individuals, and a greater understanding of the epidemiology of CRE in healthcare settings across the state\textsuperscript{17}. Carbapenemase testing becomes especially helpful to make a conclusive distinction in patients’ diagnoses and for surveillance; however, it is not widely used as it is not currently recommended for guiding treatment regimens as well as limited laboratory capabilities\textsuperscript{10}. This has further implications with regards to infection prevention procedures as individuals with CRE infections are generally placed on contact precautions for prolonged periods of time. Contact precautions refer to proper hand hygiene, gloves, gowns, single rooms, and environmental and equipment cleaning in order to avoid direct or indirect physical transmission of the pathogen\textsuperscript{9,18}. In conjunction with single patient rooms, contact precautions can greatly limit the spread of microorganisms to other susceptible individuals within the healthcare facility\textsuperscript{18}. However, the use of single patient rooms for every infected or colonized CRE patient can present logistical challenges for many healthcare facilities. As an alternative option, healthcare professionals may consider cohorting of CRE-positive patients in multi-occupancy rooms so that there is greater availability of hospital rooms for other patients (although it is important to emphasize that contact precautions should be implemented for each individual patient within the cohort). Furthermore, there are currently no set guidelines for discontinuing transmission-based precautions since there is a limited number of studies that address this issue\textsuperscript{19}. This is important to establish since prolonged contact precautions can be difficult for healthcare professionals, strains resources, and potentially leads to unfavorable outcomes regarding patients’ quality of care\textsuperscript{20}, although this remains an on-going debate as some studies show no significant difference
in adverse outcomes\textsuperscript{21}. There is additional difficulty in establishing these guidelines and determining procedures for discontinuing precautions since the length of CRE colonization or carriage can be long and varied, and generally has not been well-studied in patients who are hospitalized or readmitted\textsuperscript{22}. According to the Society for Healthcare Epidemiology of America (SHEA) Expert Guidance document (2018), it is recommended that discontinuation of contact precautions for non-CP-CRE infections be determined on a case-by-case basis depending on the last positive culture, presence of a clinical infection, current antibiotic use, and screening culture results\textsuperscript{19}. For CP-CRE, both the CDC CRE toolkit (2015) and the 2018 SHEA guidance document recommend contact precautions to be indefinitely maintained\textsuperscript{19,22}.

By utilizing these recommendations in conjunction with carbapenemase testing, there is potential to allow for improved decision-making and efficiency with regards to the use and prioritization of contact precautions and cohorting of affected individuals, especially in high CRE burden areas where there may be limited resources and availability of single patient rooms. Carbapenemase testing can help improve the control and spread of CRE by helping to distinguish patients based on their resistance mechanisms and may assist with the efficient use of hospital resources and available space. For instance, healthcare professionals may decide to distinguish CP-CRE and non-CP-CRE patients and group them separately rather than use single rooms for each individual or cohorting them together as one CRE group and unknowingly risking the transmission of carbapenemase-mediated resistance to non-CP-CRE infected patients. This study is designed to quantify the total length of hospitalization in days for patients with either CP-CRE infections or with non-CP-CRE infections in the state of Connecticut from the time of diagnosis using the CT SPHL results. Ultimately, this study can potentially provide some insight on the practicality of carbapenemase testing in elucidating how to prioritize patients and inform
decisions for contact precautions and cohorting. The study also aims to characterize the two patient groups in order to determine if there are fundamental differences that may contribute to the likelihood of having a certain type of infection. I hypothesize that patients with CP-CRE will have a greater number of total hospitalization days over a period of 90 days following CRE identification than patients with non-CP-CRE, as a result of extremely limited treatment options for CP-CRE infections which may contribute to a reduced rate of recovery and more serious outcomes that may prolong hospitalization stay.

II. Methods

This study was conducted using the Connecticut Department of Public Health’s (CT DPH) CRE surveillance data and the Connecticut Hospital Association’s CHIME hospitalization data (which was shared for use by CT DPH) for the 2017 calendar year. A case-control design was used where controls consisted of individuals with non-CP-CRE diagnoses and cases consisted of individuals with CP-CRE diagnoses. CP-CRE was determined based on carbapenemase production (phenotypic mCIM) and antibiotic susceptibility results provided by the CT SPHL. Additionally, CHIME hospitalization data for the 2016 calendar year and state death certificate data for the 2017 calendar year were utilized as a part of the analysis comparing the CP-CRE and non-CP-CRE groups.

Individuals were included in this study if they had a clinical isolate submitted to the CT SPHL and had a non-missing laboratory isolate receipt date for the calendar year 2017 (Figure 1). From this group, individuals with missing phenotypic mCIM results and inconclusive carbapenem susceptibility results were excluded. Individuals with positive phenotypic mCIM results were considered to have CP-CRE regardless of their carbapenem susceptibility profiles. On the other hand, individuals with negative phenotypic mCIM results that were non-susceptible
to one or more carbapenems were classified as non-CP-CRE. Individuals with isolates that were found to be susceptible to all four carbapenems at the CT SPHL were classified as non-CP-non-CRE organisms. However, this group of isolates were classified together with the non-CP-CRE for this analysis due to the assumption that the hospitals would have viewed the individuals as CRE-positive patients and were selected for CT SPHL isolate submission based on a carbapenem resistant result at the clinical laboratory. A data merge was performed by creating a Cartesian Product between the CRE and the CHIME inpatient hospitalization data using each of the patient’s first four letters of their first and last names, date of birth, and sex. A Cartesian Product was used so all possible combinations of the CRE cases and hospitalizations are matched (rather than arbitrary matching of a single hospitalization to a case). In order to maintain a consistent follow-up period, patients with isolates that were received by the CT SPHL between 1/1/2017 through 10/2/2017 were used in the analysis so that every individual had a 90-day follow-up period in calendar year 2017.

**Figure 1.** Flow chart of merging process of the 2017 CRE and CHIME datasets.
The total hospitalization in days per patient was calculated as the sum of all of the lengths of stay that each patient had after their first CRE was identified. Depending on if they had one index hospitalization or multiple subsequent hospitalizations due to readmissions, the length of stay for the first index hospitalization was calculated from the point of diagnosis (which was assumed for consistency purposes to be the date in which the isolate was received by the CT SPHL) to the discharge date. The length of stay for a subsequent hospitalization due to readmission (if the patient had any) was calculated from the admission date of that particular hospitalization to the discharge date. Additionally, the number of distinct hospitalizations post-diagnosis was determined for each patient. Comparisons between the CP-CRE and non-CP-CRE groups were made for age, sex, race/ethnicity, organism, specimen source, prior hospitalization, and death within 90 days. Prior hospitalizations were determined by using the CHIME hospitalization data for the 2016 calendar year and merging to those patients with isolates from 2017. Finally, death within the 90-day follow-up period was examined by utilizing the 2017 state death certificate data and determining if the date of death occurred within the follow-up period.

The Wilcoxon-Mann-Whitney test, chi-square test, and Fisher’s exact test were used to make comparisons between the CP-CRE and non-CP-CRE groups. A Poisson regression analysis was conducted to determine the association between carbapenemase diagnosis and (1) total hospitalization in days per patient; (2) number of hospitalizations per patient. The analysis was also adjusted for age and sex. Data management, cleaning, and analysis were conducted using Microsoft Access and SAS 9.4.
III. **Results**

   **i. Study population**

   In the 2017 calendar year, there was a total of 293 reported CRE cases and over 1.7 million hospitalizations in Connecticut. Out of these CRE cases, 220 had state lab diagnostic testing results regarding carbapenemase production and antibiotic susceptibility. By considering only inpatient settings, the number of hospitalizations during the study period was reduced to 361,075. After the data merging process was completed and patients were matched with their corresponding hospitalizations, there was a total of 166 patients (40 CP-CRE, 126 non-CP-CRE) with reported cases throughout the 2017 calendar year. There were no patients that experienced isolates with different carbapenemase statuses or patients that changed status (i.e., from non-CP-CRE to CP-CRE, or vice versa). After including only patients with cases between 1/1/2017 through 10/2/2017 in order to allow for complete 90-day follow-up periods for each patient, a total of 126 patients (32 CP-CRE, 94 non-CP-CRE) were included in the analysis.

   **ii. Comparison of CP-CRE and Non-CP-CRE patient characteristics**

   CP-CRE and non-CP-CRE patients were generally uniformly represented across age and sex (Table 1). The median age for CP-CRE patients was slightly greater at 71.5 years whereas the median age for non-CP-CRE patients was 68.0 years, but this was not statistically significant (P=0.4047). Both study groups had approximately equal representation of female and male patients (P=0.7601). A significant association exists between race/ethnicity and carbapenemase diagnosis, where non-CP-CRE patients were more likely to be non-Hispanic White and CP-CRE patients were more likely to be Hispanic (P=0.0295). There was also a significant association between organism type and carbapenemase diagnosis, where CP-CRE patients were more likely to be diagnosed with *K. pneumoniae* isolates while non-CP-CRE patients were more likely to
have *E. cloacae* isolates (P<0.0001). The specimen source was also examined for its association with carbapenemase status, but was not found to be statistically significant (P=0.9783). There were no significant associations found between carbapenemase status and death within 90 days (P=0.8578) or carbapenemase status and prior hospitalizations in the 2016 calendar year (P=0.8403).

**Table 1.** Comparison of the CP-CRE and Non-CP-CRE patient groups.

<table>
<thead>
<tr>
<th></th>
<th>CP-CRE (n=32)</th>
<th>Non-CP-CRE (n=94)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (median, IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under 65</td>
<td>71.5 (59.0-79.5)</td>
<td>68.0 (48.0-79.0)</td>
<td>0.4047&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>65 and over</td>
<td>10 (31.25%)</td>
<td>41 (43.62%)</td>
<td>0.2183&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td>0.7601&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Female</td>
<td>15 (46.90%)</td>
<td>47 (50.00%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (53.10%)</td>
<td>47 (50.00%)</td>
<td></td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td>0.0295&lt;sup&gt;3&lt;/sup&gt; *</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>16 (50.00%)</td>
<td>66 (72.53%)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>4 (12.50%)</td>
<td>12 (13.19%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>10 (31.25%)</td>
<td>9 (9.89%)</td>
<td></td>
</tr>
<tr>
<td>Other, Non-Hispanic</td>
<td>2 (6.25%)</td>
<td>4 (4.40%)</td>
<td></td>
</tr>
<tr>
<td><strong>Organism</strong></td>
<td></td>
<td></td>
<td>&lt;0.0001&lt;sup&gt;3&lt;/sup&gt; *</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>4 (12.50%)</td>
<td>53 (56.99%)</td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>24 (75.00%)</td>
<td>16 (17.20%)</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>3 (9.38%)</td>
<td>14 (15.05%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (3.13%)</td>
<td>10 (10.75%)</td>
<td></td>
</tr>
<tr>
<td><strong>Specimen Source</strong></td>
<td></td>
<td></td>
<td>0.9783&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Urine</td>
<td>17 (60.71%)</td>
<td>48 (53.93%)</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>3 (10.71%)</td>
<td>9 (10.11%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>3 (10.71%)</td>
<td>14 (15.73%)</td>
<td></td>
</tr>
<tr>
<td>Wound/Bone/Skin</td>
<td>1 (3.57%)</td>
<td>5 (5.62%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (14.29%)</td>
<td>13 (14.61%)</td>
<td></td>
</tr>
<tr>
<td><strong>Prior hospitalization</strong></td>
<td></td>
<td></td>
<td>0.8403&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Yes</td>
<td>17 (53.13%)</td>
<td>48 (51.06%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15 (46.88%)</td>
<td>46 (48.94%)</td>
<td></td>
</tr>
<tr>
<td><strong>Death within 90-day period</strong></td>
<td></td>
<td></td>
<td>0.8578&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (18.75%)</td>
<td>19 (20.21%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>26 (81.25%)</td>
<td>75 (79.79%)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Total number of patients and percentages in each group may not sum due to missing data and rounding.

<sup>1</sup>Wilcoxon-Mann-Whitney, <sup>2</sup> Chi-square, <sup>3</sup>Fisher’s exact

* P<0.05
Table 2. Poisson regression analysis of the association between carbapenemase diagnosis and (1) total hospitalization length; and (2) number of hospitalizations (post-diagnosis).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CP-CRE (n=32)</th>
<th>Non-CP-CRE (n=94)</th>
<th>Unadjusted RR (95% CI)</th>
<th>P value</th>
<th>Adjusted RR$^1$ (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hospitalization days per patient</td>
<td>3.5</td>
<td>7.0</td>
<td>0.622 (0.539, 0.717)</td>
<td>P&lt;0.0001</td>
<td>0.684 (0.592, 0.790)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>(median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of hospitalizations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>22 (68.75%)</td>
<td>56 (59.57%)</td>
<td>0.734 (0.424, 1.27)</td>
<td>0.2693</td>
<td>0.758 (0.436, 1.32)</td>
<td>0.3250</td>
</tr>
<tr>
<td>1</td>
<td>6 (18.75%)</td>
<td>19 (20.21%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 or more</td>
<td>4 (12.50%)</td>
<td>19 (20.21%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$Adjusted for age and sex

### iii. Total hospitalization days and number of hospitalizations per patient

The median number of total hospitalization days per patient among the CP-CRE and non-CP-CRE groups were 3.5 and 7.0 days, respectively (Table 2). In the unadjusted Poisson regression examining the role of carbapenemase diagnosis on total hospitalization days, CP-CRE patients had 37.8% fewer hospitalization days than non-CP-CRE patients (P<0.0001). Controlling for age and sex results in a slightly reduced but still significant difference, where CP-CRE patients had 31.6% fewer hospitalization days than non-CP-CRE patients (P<0.0001). When examining the number of distinct hospitalizations per patient in each group while controlling for age and sex, there was no significant difference between CP-CRE and non-CP-CRE patients (P=0.3250).

### IV. Discussion

#### i. Differences in Race/Ethnicity, Organism between CP-CRE and Non-CP-CRE patients

In our comparison of the two patient groups, CP-CRE patients were more likely to be Hispanic, making up 31.25% of the CP-CRE group in this study (Table 1). This is especially interesting since the Hispanic population in Connecticut is approximately 16.13%, according to the National Center for Health Statistics (NCHS) Annual State-level Age, Sex, Race, Hispanic
Ethnicity estimates (July 2017). The proportion of Hispanic individuals in the CP-CRE study group is almost twice the proportion of Hispanic individuals in Connecticut, which raises questions regarding specific risk factors or other characteristics for this particular group of patients. Although the small number of individuals in our study limit proper extrapolation of the results, it would be informative to further investigate race/ethnicity to determine if Hispanic individuals are truly disproportionately affected by CP-CRE and what may contribute to this difference.

Additionally, our comparison also indicated that CP-CRE patients were more likely to have *K. pneumoniae* isolates, which is a major cause of both community and hospital-associated infections, especially with the presence of carbapenemases. On the other hand, non-CP-CRE patients were more likely to have *E. cloacae* complex isolates, which have become problematic in healthcare settings, especially for individuals on mechanical ventilation. A study further investigating healthcare exposures would be informative to determine if there are specific procedures that contribute to a greater risk of acquiring a particular type of CRE (with regards to both organism and resistance mechanism).

**ii. Difference in total hospitalization days for CP-CRE and Non-CP-CRE patients**

Interestingly, there is a difference in total hospitalization days between the two study groups where CP-CRE patients appear to have fewer hospitalization days, even after adjusting for age and sex (Table 2). This result contrasts with our initial hypothesis that CP-CRE patients would have a greater number of hospitalization days due to limited treatment options that may impede recovery and potentially lead to other serious outcomes. Additionally, some studies even suggest that CP-CRE can be more virulent, which can imply a longer hospitalization stay if the
infected individuals are more ill. As for our particular study, there are a few possibilities to explain our results.

According to a study comparing mortality outcomes between CP-CRE and non-CP-CRE patients by Tamma et al. (2017), the investigators found that CP-CRE patients had approximately 4 times greater odds of mortality within a 14-day period and 3 times greater odds within a 30-day period than non-CP-CRE patients after adjusting for severity of illness, underlying comorbidities, and type of antibiotic treatment\textsuperscript{26}. Greater virulence and risk of mortality may contribute to a shorter length of hospitalization for CP-CRE patients if they expire at a higher rate than non-CP-CRE patients. Further investigation incorporating both length of hospitalization and mortality outcomes would be important to study and informative in supporting this particular idea. However, when death outcomes were examined for our particular study, there was no significant difference between the two groups, suggesting that the rate at which patients expire may not be the underlying cause of the difference in total hospitalization days. The exact occurrence of death can be explored in order to see if timing of deaths differ between the two groups. Additionally, an unpublished mortality analysis conducted by the CDC using the Multi-Site Gram-negative Surveillance Initiative (MuGSI) data found higher rates of mortality in non-CP-CRE patients (communication with M. Maloney, CT DPH), which contrasts with results from Tamma et al. The difference in results in these studies may further imply that death rates may not be related with the total length in hospitalization; however, it would be more practical to see if similar results are obtained in other states, especially those with greater burden of CRE, before making any conclusive statements.

Another possibility explaining our results that would need further investigation is the use of various types of antibiotic treatment regimens. The same study by Tamma et al. reported that
CP-CRE patients were less likely than non-CP-CRE patients to be given active empiric antibiotic treatments, although this was not statistically significant\(^2^6\). The authors define active empiric treatment as consisting of at least one antibiotic given within 24 hours from the time that the first positive blood culture was obtained\(^2^6\). On the other hand, active directed antibiotic treatment was defined as consisting of at least one antibiotic given after antibiotic susceptibility testing results are available and up to 7 days after the first positive blood culture was obtained\(^2^6\). Despite there being no significant difference in the use of empiric therapy between the two groups in the Tamma et al. study, it is an important factor to consider for the patients in Connecticut. Since empiric therapy is primarily based on clinician experience and non-CP-CRE patients were more likely to initially receive this type of therapy, this patient group may be experiencing greater exposure to various antimicrobial drugs that may potentially be ineffective and causing weakened immune states with disruptions to patients’ commensal bacteria. This can contribute to longer lengths of hospitalizations for non-CP-CRE patients which can increase the possibility in which these patients may acquire other infections and the chance of developing additional resistance during their stays.

The reasons for hospital admission may be interesting to explore as a possible explanation for the difference in total hospitalization days. The primary reason for hospital admission of CP-CRE patients may have been directly due to the CP-CRE infection. On the other hand, the non-CP-CRE patients may have been initially admitted due to another underlying condition and the CRE diagnosis was a secondary or subsequent event. Due to a potential difference in underlying conditions or primary reason of hospitalization, this may possibly result in a longer hospitalization for non-CP-CRE patients. One of the major limitations of this particular study is that we were unable to investigate comorbidities and primary causes of
admission; however, this would be another crucial aspect of further research that should be conducted to learn more about these two groups. It would also be important to study hospitalization exposure in both the previous calendar year and prior to carbapenemase diagnosis in order to give an indication of the extent of prior hospital exposure and learn of any differences that may exist between the two groups. It is suggested that carbapenem resistance mechanisms are acquired in different ways for the CP-CRE and non-CP-CRE organisms, and this may contribute to different risk factors for patient acquisition. Although more evidence is necessary, some of the data suggest that non-CP-CRE organisms are believed to primarily acquire their resistance through antibiotic exposure and clonal expansion, while CP-CRE organisms obtain their resistance through horizontal transfer (without necessarily having previous antibiotic exposure). In a future study, it would be interesting to examine both prior hospitalizations and antibiotic exposures to see if these factors may explain why the non-CP-CRE group have longer hospitalizations than CP-CRE patients. It may also be informative to scrutinize the period between hospital admission and CRE diagnosis in order to determine if the CRE was a cause of admission or attributed to hospital exposures. Only prior hospitalizations in the previous calendar year (2016) were able to be examined for this study, but no statistically significant association was found.

Lastly, an alternative theory in explaining the difference in hospitalization days between the two patient groups may be attributed to the type of culture (surveillance or clinical). Although the isolates in Connecticut’s CRE surveillance system should all represent clinical cultures (according to surveillance and submission guidelines), there are potentially some isolates that were collected from patients without clinical infection. It may be the case that some of the CP-CRE patients may have been identified through surveillance cultures rather than
clinical cultures, indicating that colonization of these patients was being picked up and they may not actually have been infected or sick. Asymptomatic colonization can contribute to a shorter hospitalization period compared to the non-CP-CRE patients. For a future study, differences in surveillance and clinical cultures should be an important aspect to explore between the two groups to determine if this is true.

iii. Potential implications in infection control and cost

Although this study has several limitations and has additional factors to investigate, the current results indicate that the difference in hospitalization days between CP-CRE and non-CP-CRE patients advocates for the importance in distinguishing carbapenemase status among CRE patients in order to possibly cohort individuals with similar infection types. The investigators of the previously mentioned study describing differences in mortality outcomes between the two patient groups also agree that distinguishing the carbapenem resistance mechanism is necessary to allow for improved treatment decisions\(^\text{26}\). Many hospitals and other healthcare facilities are limited in their resources and laboratory capabilities to distinguish the carbapenem resistance mechanisms\(^\text{26}\). There are also very few studies that that have provided strong evidence suggesting to do so\(^\text{26}\). As a result, healthcare facilities typically manage CRE patients as one general group using the same infection control procedures regardless of resistance mechanism. These procedures include contact precautions and the use of single patient rooms, which may not be realistic in many hospitals due to limited resources. Cohorting of patients and even cohorting of healthcare professionals may be additionally used as a way of conserving resources. However, in light of the results of this and Tamma \textit{et al.} studies, there is a great concern of mixing patients with CRE with different resistance mechanisms who have significantly different outcomes. This unnecessarily exposes some patients to greater risks for worse clinical outcomes if cohorting of
both CP-CRE and non-CP-CRE patients together unknowingly occur. Additionally, as observed in this study, there are instances where the clinical labs would diagnose some patients to be non-CP-CRE, but the state lab determines some individuals to actually have non-CP-non-CRE organisms due to differing antibiotic susceptibility profiles. However, from the hospital’s standpoint, a non-CP-non-CRE patient is treated under the assumption that they have a CRE organism since it takes time for state lab results to inform the clinical labs. Consequently, these patients would be at risk of receiving incorrect/inadequate treatment or at risk of acquiring a CRE organism if they are cohorted with other non-CP-CRE patients.

Ideally, it would be best if cohorting was utilized based on resistance mechanism and perhaps even organism type so that resistance profiles are less likely to be mixed. In particular, CP-CRE pose a greater need to separate out from non-CP CRE since their carbapenemase resistance genes are encoded on mobile genetic elements and are associated with a relatively low fitness cost to the organisms, making them readily transmissible and retained\textsuperscript{12}. Through this method, naïve non-CP-CRE have the potential to gain the ability to survive against drugs that they may never have previously been exposed to\textsuperscript{12}. This would further limit effective treatment options for these patients, putting them in a more difficult situation with potentially worse outcomes. It would also be helpful to use carbapenemase testing to distinguish patients with CP-CRE so that they can be appropriately prescribed new drug options when they become available\textsuperscript{26}. Although development of new drugs against CP-CRE have been slow\textsuperscript{5, 8}, it is suggested that these treatments be strictly reserved for patients with confirmed CP-CRE organisms\textsuperscript{26}. Prioritizing CP-CRE patients for these new treatments and cohorting based on carbapenemase activity can possibly allow for better control over any resistance that may develop with the use of these drugs and keep it from spreading to all CRE. Carbapenemase
testing can help to improve prescribing decisions and prevent non-CP-CRE patients from being unnecessarily exposed to these novel antibiotics that should have been reserved for those with true carbapenemase activity.

Due to differences in patient mortality outcomes and potentially total hospitalization days (from this study) between CP-CRE and non-CP-CRE patients, carbapenemase testing has the potential to be beneficial for cohorting and treatment decisions. Carbapenemase testing can be costly and resource-intensive for hospitals if conducted on-site in their clinical laboratories; however, the benefits of carbapenemase testing may outweigh the costs of managing CRE infections, especially in high burden areas. This cost would generally be associated with the components of contact precautions, which include gowns, gloves, time delegated to put on/off the protective wear, environmental/equipment cleaning, and the use of single patient rooms, which takes away from available space and time for addressing other patients. There are also clinical costs associated with patient isolation that should be considered, as adverse outcomes have been studied, such as decreased or delayed healthcare worker contact, lower patient satisfaction, and greater non-infectious events, depression, and anxiety. However, it is important to note that there is on-going debate on whether or not adverse outcomes are associated with patient isolation procedures as it is difficult to have definitive studies with comparable control groups without jeopardizing the safety and care of these patients.

Additionally, there may be publication bias toward studies associating contact precautions with unfavorable outcomes.

There are currently no studies investigating the costs of CP-CRE and non-CP-CRE infections, but there are a few that attempt to model the economic burden of certain multi-drug resistant infections. One particular model examined the cost of CRE infections, although the
investigators did not distinguish between CP-CRE and non-CP-CRE infections. The investigators found that the cost of a single CRE infection (regardless of the type of infection, which included bacteremia, intra-abdominal, pneumonia, complicated urinary tract infection) from the hospital perspective was about $29,157. Costs from the hospital perspective consisted of the opportunity cost of lost bed days due to the additional length of stay attributable to the CRE infection. Based on this model, CRE infections generally can be quite costly and as a result, it would be of the utmost importance to determine whether the benefit of carbapenemase testing would outweigh the cost of managing CRE infections as one general category. With carbapenemase testing, there would be opportunities to cohort patients based on their resistance mechanisms and free up single-occupancy rooms and bed space to other types of patients. Alternatively, CP-CRE patients can be prioritized for single-occupancy rooms. In especially high burden settings, carbapenemase testing can possibly aid with discontinuation of precautions if these facilities need to conserve resources and reduce costs by prioritizing CP-CRE patients and continuing them on contact precautions while deciding on a case-by-case basis if discontinuation of precautions should occur for non-CP-CRE patients (as the 2018 SHEA guidance document suggests). While it is typical to implement contact precautions for all CRE patients, there may be some facilities in high burden areas that would seriously need to consider prioritizing certain types of patients.

V. Conclusions

There are several limitations associated with this study. Due to the limited sample size, this study may not have had the necessary power to detect a significant difference, making it difficult to generate any conclusive remarks about the two patient groups. Furthermore, this study was conducted using Connecticut state data; therefore, the results may not be appropriately
interpretable for other states, especially those with contrasting CRE prevalence and incidence rates. Mortality outcomes for this study was conducted using the addition of the state death registry, which is separate from the CHIME hospitalization and CRE surveillance datasets used for the other analyses. Lastly, comorbidities and other MDROs were unable to be adjusted for in our analyses due to limitations in the available information. A future study investigating similar outcomes and addressing all of these limitations would be an ideal and potentially informative next step to take.

In conclusion, our study indicates that there is a significant association between carbapenemase diagnosis and total hospitalization days, where CP-CRE patients were associated with having fewer hospitalization days than non-CP-CRE patients. The direction of this association contrasts with a different study comparing mortality outcomes between the two patient groups, where CP-CRE patients were unfavorably at greater odds of dying than non-CP-CRE patients. Nevertheless, there appears to be a preliminary consensus that there are significant differences in clinical outcomes between CP-CRE and non-CP-CRE patients, which suggest that carbapenemase diagnostic testing has the potential to be useful in improving the care of these patients. Additional studies that specifically distinguish CP-CRE and non-CP-CRE infections need to be conducted in order to make definitive conclusions to ultimately improve the care of these patients while mitigating strains on hospital resources.
References


