Using Carbapenem Resistance Levels to Discriminate Between Carbapenemase Producing and Non-Carbapenemase Producing Carbapenem-Resistant *Enterobacteriaceae*

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Background

- Carbapenem-resistant *Enterobacteriaceae* (CRE) are a growing threat in the United States and globally
- CRE infections are associated with higher mortality rates than infections due to carbapenem-susceptible *Enterobacteriaceae*[1,2]
- CRE was made reportable to the Philadelphia Department of Public Health (PDPH) in April of 2018
- Some carbapenem resistance genes encode for carbapenemase enzymes located on highly transmissible plasmids
- Early detection of carbapenemase-producing CRE (CP-CRE) and aggressive infection prevention and control measures are important in preventing transmission
- Phenotypic laboratory tests to detect carbapenemase production or genotypic tests to identify CP genetic mechanisms, are needed to differentiate CP-CRE from non-CP-CRE

Our Project

- The goal of our analysis was to determine if there are patterns of CRE resistance in Philadelphia isolates that would allow the use of a predictive model to effectively differentiates CP and non-CP-CRE
- Another goal of the project was to better understand testing capabilities of Philadelphia laboratories
- An MIC cutoff value between non-CP-CRE and CP-CRE could be useful to clinicians in situation where tests for carbapenemase production are not available
- In this analysis sensitivity in detecting CP-CRE would be more important than specificity since it would be more important to capture all CP-CRE than it would be to correctly classify non-CP-CRE

Methods

- Resistance and carbapenemase profiles of CRE reported to PDPH between June 2018, when reporting and testing for carbapenemase became more complete, and February 2020 were analyzed
- Local clinical laboratory testing capability was assessed through reporting and phone interviews
- Overall association between increased resistance levels and carbapenemase genes was calculated
- Receiver Operating Characteristic (ROC) curves were plotted and the area under the curve (AUC) were calculated
- Sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) were calculated for each possible MIC cutoff value
- MIC cutoff values were evaluated for their level of use to differentiate non-CP-CRE and CP-CRE
- All data cleaning and analysis were performed in SAS 9.4 software

Results

- Of the 13 clinical microbiology laboratories in Philadelphia, only 5 (38%) conduct phenotypic tests and only 3 (23%) conduct genotypic testing

Table 1. Current CP testing capabilities of 14 clinical laboratories in Philadelphia

	n (%)
Detection Method	
mCIM or other phenotypic testing	5 (38%)
PCR or other genotypic testing	3 (23%)

- Once a CRE report is received, PDPH requests laboratories that do not conduct phenotypic or genotypic CP testing to submit isolates to the Pennsylvania Bureau of Laboratories (PA BOL) for mechanism testing

Results Continued

- 438 CRE were reported between June 2018-February 2020
- 351 (80.1%) had genetic mechanism testing performed and were included in our analysis.
- Doripenem resistance was not analyzed as few isolates were tested for it
- For other carbapenems with each increase in MIC dilution the odds of an organism being CP-CRE increased.
- ROC analysis revealed that meropenem and imipenem performed well in distinguishing non-CP-CRE and CP-CRE (AUC 0.82 and 0.79 respectively) and ertapenem performed poorly as a predictor (AUC 0.61)
- Table 4 shows characteristics of each cutoff value with MICs equal to below the cutoff being classified as non-CP-CRE, and those above the cutoff being classified as CP-CRE.

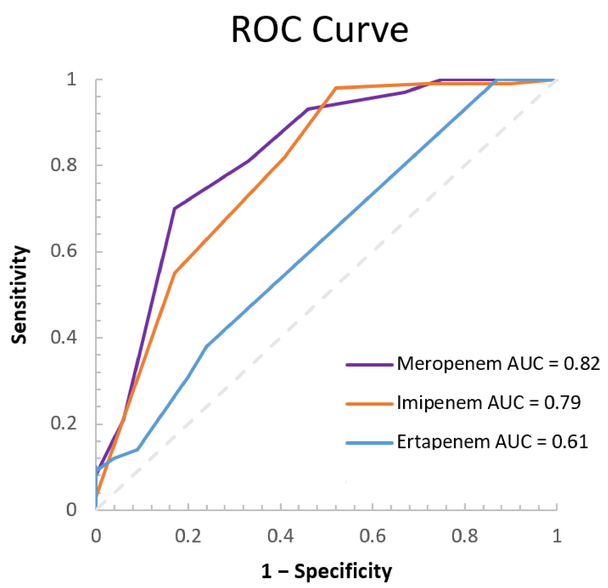
Table 2. Characteristics of the CRE cases reported to PDPH that had genetic mechanism testing performed (n=351).

	n (%)
Genus and Species	
Klebsiella pneumoniae	192 (54.7%)
Enterobacter cloacae	53 (15.1%)
E. coli	52 (14.8%)
other *Enterobacteriaceae*	54 (15.4%)
Carbapenemase Production	
CP-CRE	255 (72.6%)
Genetic Mechanism	
KPC	220 (62.7%)
NDM	22 (6.3%)
OXA 48	2 (0.6%)
Dual KPC and NDM	1 (0.3%)
Carbapenems Tested	
Ertapenem	186 (53.0%)
Meropenem	191 (54.4%)
Imipenem	116 (33%)
Doripenem	9 (2.6%)
Laboratory Where CP Testing was Performed	
PA BOL or other Public Health Lab	251 (71.5%)
Hospital Lab	100 (28.5%)

Table 3. Odds ratios for organism being CP-CRE per one standard dilution increase in MIC

Carbapenem	OR (95% CI)
Ertapenem	1.43 (1.11–1.83)
Meropenem	2.20 (1.72–2.81)
Imipenem	2.52 (1.70–3.793)

Figure 1. ROC Curve displaying the use of three carbapenem MIC levels to distinguish non-CP-CRE and CP-CRE



Results Continued

Table 4. Meropenem, imipenem, and ertapenem sensitivity, specificity, PPV, and NPV at each MIC cutoff value

Meropenem				
MIC (µg/mL)	**Sensitivity** (95% CI)	**Specificity** (95% CI)	**PPV** (95% CI)	**NPV** (95% CI)
0.5	97% (94-100)	33% (20-45)	79% (73-85)	81% (64-98)
1	**94% (89-99)**	**54% (40-67)**	**84% (79-90)**	**76% (62-90)**
2	81% (75-88)	67% (55-80)	87% (81-93)	57% (45-70)
4	70% (62-77)	83% (72-93)	92% (86-97)	51% (40-61)
8	21% (14-28)	94% (89-100)	91% (81-100)	31% (34-38)
Imipenem MIC cutoff to identify CP-CRE				
MIC (µg/mL)	**Sensitivity** (95% CI)	**Specificity** (95% CI)	**PPV** (95% CI)	**NPV** (95% CI)
0.5	99% (97-100)	28% (11-44)	80% (73-88)	89% (68-100)
1	**98% (95-100)**	**48% (30-66)**	**85% (78-92)**	**88% (71-100)**
2	82% (73-90)	59% (41-77)	86% (80-93)	52% (34-69)
4	55% (45-66)	83% (69-97)	91% (83-98)	38% (26-50)
8	3% (0-7)	100% (100-100)	100% (100-100)	26% (18-34)
Ertapenem MIC cutoff to identify CP-CRE				
MIC (µg/mL)	**Sensitivity** (95% CI)	**Specificity** (95% CI)	**PPV** (95% CI)	**NPV** (95% CI)
0.5	100% (100-100)	13% (4-22)	74% (67-80)	100% (100-100)
1	38% (30-46)	76% (65-87)	79% (69-89)	33% (25-42)
2	31% (24-40)	80% (69-90)	79% (68-90)	32% (24-40)
4	14% (8-20)	91% (83-98)	79% (63-95)	30% (23-37)
8	12% (7-18)	96% (91-100)	89% (74-100)	31% (24-38)

Discussion

- Barriers to mechanism testing indicate MIC cutoff values may be useful to clinicians in cases when mechanism testing cannot be done
- Imipenem had the best performing MIC cutoff value of 1 µg/mL where PPV is 85% (95% CI: 78-92) and NPV is 88% (95% CI: 71-100)
- Meropenem's best performing MIC cutoff value, also at 1 µg/mL, performed similarly with a PPV of 84% (95% CI: 79-90) and an NPV of 76% (95% CI: 62-90)
- Both cutoffs had high sensitivity, the 1 µg/mL imipenem MIC cutoff having a sensitivity of 98% (95% CI: 95-100) and the 1 µg/mL meropenem MIC cutoff having a slightly lower sensitivity of 94% (95% CI: 89-99)
- In contrast, all ertapenem cutoff points performed poorly, either having unacceptably low sensitivity or specificity
- MIC cutoff values of 1 µg/mL for imipenem and 1 µg/mL for meropenem could be useful in classifying CRE when additional testing is delayed or unavailable
- A similar analysis was conducted in 2016 using CRE detected at Johns Hopkins Hospital. They found good cutpoints for all carbapenems: 0.5 µg/mL for ertapenem and 2 µg/mL for both meropenem and imipenem. If they had valued sensitivity to a similar extent as we have, their findings for meropenem and imipenem may have been similar. Still, differences in their findings indicates heterogeneity by geographic location or over time[5]

Limitations and Next Steps

- Testing and reporting practices may have introduced selection bias: Even though reporting is mandatory, reporting of CRE was relatively incomplete near the beginning of PDPH's CRE surveillance and not all isolates are tested for carbapenemase
- CRE isolates are usually only tested for resistance to one or two carbapenems so the MIC values for the other carbapenems is unknown
- Findings may not be generalizable to other populations in different geographic areas
- Similar studies should be conducted in other jurisdictions that have made CRE reportable in order to inform their healthcare systems of whether antibiotic resistance levels can distinguish CP and non-CP-CRE.

Citations

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