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Carbapenem-Resistant *Enterobacteriaceae* (CRE): A Statewide Survey of Detection in Massachusetts Hospitals

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Background

Antibiotic resistance is increasing worldwide. While much infection control focus has been on gram-positive organisms, concern is growing regarding more extensive antimicrobial resistance in gram-negative organisms. Carbapenems have been used increasingly over the past decade to treat infections due to *Enterobacteriaceae* producing extended spectrum β -lactamases (ESBLs). Emergence of carbapenem-resistant *Enterobacteriaceae* (CRE) severely limits antibiotic options to treat such infections.¹ Moreover, it has been shown that patients infected with CREs suffer a 3-fold increase in mortality compared to patients with infection due to susceptible strains.²

Given the threat CREs pose and the increased reliance on automated susceptibility testing, it is important to assess the prevalence of CREs and how reliably they are detected. It is particularly important to know the current variance in testing methods in light of recent changes in guidelines for antimicrobial susceptibility testing of *Enterobacteriaceae* released by the Clinical and Laboratory Standards Institute (CLSI) in June 2010 and updated in January 2011.³

Methods

Online surveys were sent to all 70 Massachusetts acute-care hospital microbiology laboratories and corresponding infection prevention teams in December 2010. Standardized questions were used to estimate the proportion of hospitals detecting CREs in 2010 and to analyze current microbiological methods for CRE detection. Hospitals were asked what

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platforms were routinely used to work-up *Enterobacteriaceae* and confirm carbapenemase production; whether laboratories were following the June 2010 CLSI guidelines; and what carbapenem MIC cutoffs were used to prompt CRE consideration. Data were analyzed using SPSS (SPSS Inc., Chicago IL) to calculate chi-square statistics and a Spearman Rank Correlation Coefficient.

Results

Of the 70 hospitals surveyed, 45 responses from microbiology laboratories and 49 responses from infection prevention teams were received; 63 hospitals responded to one or both surveys, representing 90% of Massachusetts hospitals. Non-responding hospitals were located in all regions of the state except for Boston and Metro-Boston regions. Hospitals reported detecting from 0 to >12 unique CRE isolates in 2010. Detection of CREs was observed state-wide, with 49% of respondents having detected CREs in 2010; 33% reported no CREs; 13% did not know; and 5% did not answer this question. (Figure 1) Teaching hospitals were more likely to report CREs (75%) than non-teaching hospitals (46%) ($p=0.036$). CREs were detected with a significantly greater frequency in larger hospitals (Fisher's exact, $p < 0.05$). Seven hospitals reported >12 CREs.

Of the 45 responding microbiology laboratories, 93% reported detecting CREs by automated systems. Forty-four percent of hospitals performed additional workup for resistant *Enterobacteriaceae*; two facilities performed the modified Hodge test, while others reported using single or multiple confirmatory tests (60% disk-diffusion, 20% E-tests, 40% automated systems, 10% broth dilution). Fifty-one percent of hospitals reported following the June 2010 CLSI guidelines; however, only one hospital reported correct use of the >0.5 mcg/ml ertapenem MIC currently recommended to prompt consideration of a CRE. Stratified analysis of ertapenem MIC cutoffs used for CRE detection showed that the lower the cutoff used, the more likely the institution was to recognize a CRE (Spearman rank order correlation coefficient: -0.489 , $p=0.013$). (Data not shown).

Discussion

In 2007, the Centers for Disease Control and Prevention (CDC), reported that 8.7% of *Klebsiella pneumoniae* isolates in the U.S. were resistant to carbapenems compared with less than 1% reported in 2000.^{5, 6} However, statewide prevalence has not been reported. We report the first statewide estimation of CRE prevalence in the United States. Our findings indicate that nearly half of all Massachusetts hospitals detected CREs in 2010. While CREs were detected in teaching hospitals more than non-teaching hospitals, they were still detected across all regions of the state and in all types of hospitals: teaching and non-teaching, small and large, and those in rural and urban settings.

Limitations of this study include voluntary participation in the survey, recall bias, and selection bias. Some recall bias was improved by contacting hospitals that responded to both the microbiology laboratory survey and the infection prevention survey with discordant reports of CRE detection. Since the specific number of CREs identified in 2010 was not requested, prevalence of CREs in Massachusetts could not be determined.

Detection of CRE bacteria through susceptibility testing is often difficult as these organisms may appear to be carbapenem susceptible.¹ Performance of automated systems is variable; between 7–87% of KPC-producing organisms may be falsely classified as susceptible to carbapenems.¹ Many microbiology laboratories use supplementary tests to confirm carbapenemase production, given the limitation of automated systems and the difficulty of identifying CREs.

June 2010 CLSI guidelines replaced an earlier recommendation to use the modified Hodge test to confirm carbapenem resistance with a decreased MIC breakpoint for carbapenems for all *Enterobacteriaceae*: for ertapenem the threshold for susceptibility was decreased from 2 mcg/ml to 0.25 mcg/ml.^{1,7} While the CLSI has revised its guidelines, required Food and Drug Administration approval and subsequent modification of automated systems are pending. Few hospitals have yet been able to implement these changes--just one site surveyed in Massachusetts routinely used the lower MIC breakpoint for ertapenem.

We demonstrate that hospitals that used lower ertapenem MIC breakpoints detected more CREs. Given the overwhelming reliance on automated systems and the inconsistency in use of confirmatory tests, we suspect many CREs have gone unrecognized. Awareness of both the widespread prevalence of CREs and the implications of new CLSI testing guidelines should help to address this problem.

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Figure 1.

49% (31/63) of Massachusetts Hospitals Surveyed Reported Detection of CREs
 CREs are detected in 49% of Massachusetts hospitals, in all 7 regions of the state. 13% of hospitals are unaware if CREs have been isolated and 5% of hospitals did not answer the question