Continuing Challenges for the Clinical Laboratory for Detection of Carbapenem-Resistant Enterobacteriaceae

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Over the last decade, carbapenem-resistant Enterobacteriaceae (CRE) have become an urgent threat to health in the United States and elsewhere in the world (1, 2). The Centers for Disease Control and Prevention (CDC) have reported a steady increase in the burden of disease from CRE, particularly, carbapenem-resistant Klebsiella pneumoniae, in the United States (3, 4). Surveillance data from Chicago showed that 30% of residents of long-term-care hospitals (LTACHs) and 3.3% of patients in hospital intensive care units (ICUs) were CRE carriers, suggesting that CRE infections are now endemic in parts of the United States (5).

The spread of CRE in the U.S. health care system comes at a great cost because there are limited available treatment options and high attributable mortality from CRE (6, 7).

Spread of CRE in the United States appears to be driven by movement of patients though the health care system (8, 9). For instance, the CDC epicenters program demonstrated that patient transfers led to regional spread of CRE across 26 health care facilities in four counties (8). The transfer of CRE-colonized patients not only moves these organisms between institutions but also accelerates the epidemic through subsequent patient transmission events at each institution as the incidence of CRE increases (10) (11). To this point, a study of New York hospitals found that the odds of a patient acquiring CRE increased by 15% for each 1% increase in overall patient colonization at the facility (12).

Recent research has shown some promising findings for curbing the spread of CRE. Hayden and colleagues demonstrated that the use of an infection prevention bundle that included chlorhexidine bathing and strict isolation practices in a high-CRE-burden LTACH was able to significantly reduce the rates of both new CRE acquisitions and bacteremia cases (13). Computer model estimates suggest that a coordinated regional response, compared to individual hospital actions, has the potential to reduce or even eliminate CRE transmission (10, 11).

Such interventions require an understanding of the prevalence of CRE at the institutional level. However, the true burden of CRE at the local, regional, or national level remains poorly understood. Our limited understanding of CRE burden is due in part to challenges faced by the clinical laboratory at identifying CRE—in both clinical and surveillance cultures. In 2010, the Clinical and Laboratory Standards Institute (CLSI) revised the carbapenem breakpoints for the Enterobacteriaceae, and the U.S. Food and Drug Administration (FDA) followed suit by revising the drug product labeling to include these revised breakpoints. However, no manufacturer of commercial automated antimicrobial susceptibility test (AST) systems has obtained FDA clearance for these new standards, despite over 5 years having passed since their approval. Almost all laboratories in the United States rely on these systems for routine AST, and few have the resources to conduct the studies required to establish the performance of these systems with the revised breakpoints. The few reports in the literature that evaluated the performance of the automated systems used off label with the revised breakpoints have documented performance ranging from suboptimal to acceptable (14, 15).

Nonetheless, the use of the revised breakpoints is the best way to detect carbapenem resistance, as is evidenced by the fact that laboratories that have implemented the revised breakpoints detect significantly more CRE than laboratories that have not (16). Unfortunately, there is no indication these companies will have the breakpoints cleared for use in the near future, and at present the FDA does not have a mechanism by which to compel revision of breakpoints on AST systems.

Detection of CRE in rectal surveillance cultures is also a challenge for laboratories but may be an important measure by which to reduce or prevent nosocomial spread of CRE. There are no FDA-cleared tests for the detection of CRE in rectal, perirectal, or stool specimens, necessitating that laboratories develop their own methods. Various institutions have done so, using either culture or molecular means whose methods (and, presumably, levels of...
performance) differ from institution to institution. The most standardized method for CRE surveillance is that described by the CDC for detection of carbapenemase-producing *Klebsiella* spp. and *Escherichia coli* in rectal swabs (http://www.cdc.gov/hai/pdfs/labSettings/Klebsiella_or_Ecoli.pdf). The CDC method is not, however, well suited to routine clinical laboratory use. Primarily, it is exceedingly laborious, requiring confirmatory testing on a substantial number of colonies that give positive screening results for potential carbapenem resistance. Mathers and colleagues performed testing on 588 rectal swabs by the CDC method—138 isolates from 91 specimens were screen positive. Confirmatory testing for carbapenem resistance (which took 186 h of technologist time) found only 7 (5%) of these to represent true CRE results. Similarly, during an outbreak of NDM-producing CRE in a Colorado hospital, a total of 90 h of technologist time was dedicated to working up growth of 135 *Enterobacteriaceae* isolates that were ultimately found to be carbapenem susceptible among 560 CRE surveillance cultures performed (17). Despite the additional effort, the CDC method has been found to be less sensitive than other methods, including those that employ chromogenic media (18, 19). However, the chromogenic media available for CRE, including ChromID Carba (bioMérieux, Durham NC), Hardy-Chrom CRE (Hardy Diagnostics, Santa Maria, CA), and Brilliance CRE agar (Remel, Lenexa KS), are marked as research use only (RUO) at this time, limiting their utility for clinical practice. Performance results differ for these media, and preenrichment with carbapenem broth may enhance sensitivity (20). All culture methods can take up to 4 days, particularly if broth enrichment procedures are used.

Molecular tests are thus an attractive alternative to cultures if a laboratory has the resources for such testing. Molecular tests deliver a shorter turnaround time than cultures, thereby allowing nearly real-time implementation or removal of infection control precautions, and are generally thought to be more sensitive than cultures. Three commercial, RUO tests have been used to detect CRE in rectal surveillance specimens, as components of laboratory-developed tests: NucliSENS EasyQ KPC (bioMérieux), the Xpert MDRO (Cepheid) assay, and the Check-Direct CPE (Checkpoints; Wageningen, The Netherlands). The Check-Direct CPE targets the largest number of carbapenemase genes, detecting the majority of those identified to date in the United States (i.e., \( \text{bla}_{KPC}, \text{bla}_{NDM}, \text{bla}_{OXA-48}, \text{and} \text{bla}_{VIM} \)), with the exceptions of \( \text{bla}_{IMP} \) and \( \text{bla}_{SME} \). While these tests cannot detect phenotypic carbapenem resistance (i.e., that caused by a mechanism other than carbapenemase, such as an outer membrane porin mutation combined with other beta-lactamases), their advantage is that they provide a means to detect the specific mechanism of carbapenem resistance. Few clinical laboratories have the capability of identifying the mechanism of carbapenem resistance, and yet this information can be exceedingly useful to outbreak investigations by identifying patients colonized with CRE that harbor the same resistance mechanism and are thus potentially part of an outbreak. Furthermore, carbapenemase genes are harbored on highly mobile genetic elements, and the ability to detect the spread of a particular gene may aid in identifying plasmid-mediated outbreaks that occur across patients and genera of the *Enterobacteriaceae* (21).

The article by Lau and colleagues in this issue of the *Journal of Clinical Microbiology* (JCM) (22) evaluates the performance of the CheckPoint CPE for detection of CRE in rectal surveillance cultures. The article brings up several interesting and important points with regard to CRE surveillance testing. Most importantly, however, the authors demonstrated an unacceptable number of false-positive results by this test—an overall 88% specificity and a 22% positive predictive value were reported. All false-positive results were due to targets, such as \( \text{bla}_{NDM} \) and/or \( \text{bla}_{VIM} \) \( \text{bla}_{NDM, VIM} \) and \( \text{bla}_{OXA-48} \)-like, with a low incidence in the United States. Specificity is critical for surveillance tests for CRE, as colonization status drives implementation of contact precautions for a patient, and their CRE-positive status may be carried forward to subsequent admissions to the health care facility. More important is the potential negative impact for patients who are registered in electronic “XDRO” databases on the basis of false-positive results (23). These databases may be shared between institutions, allowing rapid identification of CRE-colonized patients and implementation of infection control precautions. As such, incorrect identification of patients as CRE colonized, by a positive PCR result for carbapenemase genes, has the potential to negatively impact the patient’s medical care going forward. At the facility level, identification of a CRE-colonized patient by PCR may pull the trigger for implementation of costly and time-consuming contact precautions or of even broader point prevalence studies to identify the source and potential spread of CRE.

It is clear that multi-institutional control of CRE is required to reduce the spread of these difficult-to-treat organisms. However, better tools are required to identify CRE by laboratories. The efforts by Lau and colleagues to advance the field of CRE detection are laudable, but we still need testing methodologies that are more sensitive and specific. The clinical microbiology community must pressure diagnostics manufacturers to revise carbapenem breakpoints for the *Enterobacteriaceae* which will allow laboratories to detect CRE. In addition, we urge the further development of accurate tools, such as molecular assays, for the detection of CRE-colonized patients.

**REFERENCES**


Correction for Humphries and McKinnell, Continuing Challenges for the Clinical Laboratory for Detection of Carbapenem-Resistant Enterobacteriaceae

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Volume 53, no. 12, p. 3712–3714, 2015. Page 3712, column 2, lines 3–6: The sentence beginning “However” should be replaced with the following two sentences. “However, no manufacturer of commercial automated antimicrobial susceptibility test (AST) systems has obtained FDA clearance for all these new standards, despite over 5 years having passed since their approval. Some have received clearance for select carbapenems on their systems.”