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Public Health Efforts Can Impact Adoption of Current Susceptibility Breakpoints, but Closer Attention from Regulatory Bodies Is Needed

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ABSTRACT Microbiological testing, including interpretation of antimicrobial susceptibility testing results using current breakpoints, is crucial for clinical care and infection control. Continued use of obsolete *Enterobacteriaceae* carbapenem breakpoints is common in clinical laboratories. The purposes of this study were (i) to determine why laboratories failed to update breakpoints and (ii) to provide support for breakpoint updates. The Los Angeles County Department of Public Health conducted a 1-year outreach program for 41 hospitals in Los Angeles County that had reported, in a prior survey of California laboratories, using obsolete *Enterobacteriaceae* carbapenem breakpoints. In-person interviews with hospital stakeholders and customized expert guidance and resources were provided to aid laboratories in updating breakpoints, including support from technical representatives from antimicrobial susceptibility testing device manufacturers. Forty-one hospitals were targeted, 7 of which had updated breakpoints since the prior survey. Of the 34 remaining hospitals, 27 (79%) assumed that their instruments applied current breakpoints, 17 (50%) were uncertain how to change breakpoints, and 10 (29%) lacked resources to perform a validation study for off-label use of the breakpoints on their systems. Only 7 hospitals (21%) were familiar with the FDA/CDC Antibiotic Resistance Isolate Bank. All hospitals launched a breakpoint update process; 16 (47%) successfully updated breakpoints, 12 (35%) received isolates from the CDC in order to validate breakpoints on their systems, and 6 (18%) were planning to update within 1 year. The public health intervention was moderately successful in identifying and overcoming barriers to updating *Enterobacteriaceae* carbapenem breakpoints in Los Angeles hospitals. However, the majority of targeted hospitals continued to use obsolete breakpoints despite 1 year of effort. These findings have important implications for the quality of patient care and patient safety. Other public health jurisdictions may want to utilize similar resources to bridge the patient safety gap, while manufacturers, the FDA, and others determine how best to address this growing public health issue.

KEYWORDS breakpoints, CRE, carbapenem resistance, epidemiology, KPC, microbiology, public health, superbug

Antibiotic resistance (AR) and specifically multidrug-resistant organisms (MDROs) are global and increasing public health threats. Infections due to carbapenem-resistant *Enterobacteriaceae* (CRE) are particularly challenging, due to limited treatment options and attributable mortality rates of approximately 30% to 40% in serious infections (1–4). CRE are now considered an urgent threat in the United States (5, 6). Of particular

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concern, the Centers for Disease Control and Prevention (CDC) has reported a steady increase in the burden of disease from CRE (7, 8), and CRE are now endemic in many parts of the United States (9).

Early administration of active antimicrobial therapy can reduce morbidity and mortality rates for CRE infections (4, 10–12). The Clinical and Laboratory Standards Institute (CLSI) lowered the carbapenem MIC breakpoints for *Enterobacteriaceae* in 2010 (Table 1), based largely on pharmacokinetic/pharmacodynamic estimates of carbapenem efficacy. Multiple clinical studies support the change in the carbapenem breakpoints, demonstrating that ongoing use of obsolete (pre-2009) carbapenem breakpoints leads to treatment of patients with ineffective agents and higher patient mortality rates (2, 3). The U.S. Food and Drug Administration (FDA) recognized the CLSI *Enterobacteriaceae* carbapenem breakpoints in 2012, as now listed in the antibacterial susceptibility testing interpretive criteria of the FDA (13).

Failure to update breakpoints also prevents hospitals from identifying CRE-positive patients. Due to the missed opportunity to implement appropriate infection control measures, ongoing use of obsolete breakpoints is estimated to contribute to the spread of CRE by 3% to 5% annually (14). Ongoing use of obsolete carbapenem breakpoints may result in the failure to recognize and to respond to clinically relevant MDROs.

The California Antimicrobial Resistance Laboratory Network Assessment (CARLA) survey was conducted in 2015, as a joint project between the California Department of Public Health (CDPH), the Los Angeles County Department of Public Health (LAC-DPH), and academic investigators (15). The CARLA survey determined that 28% of hospital laboratories in California were using obsolete *Enterobacteriaceae* carbapenem breakpoints (15). Furthermore, many laboratories did not perform ancillary carbapenemase testing, as recommended by the CLSI if obsolete breakpoints were used (15). A limitation of the CARLA survey was that the factors that contributed to laboratories' continued use of obsolete breakpoints were not evaluated. We theorized that lack of awareness regarding which breakpoints were in use and/or lack of technical knowledge regarding how to update breakpoints were the primary drivers for the slow uptake of revised breakpoints. The purposes of the current study were (i) to determine why laboratories failed to update *Enterobacteriaceae* carbapenem breakpoints and (ii) to evaluate the impact of a public health intervention to provide logistical support to update the *Enterobacteriaceae* carbapenem breakpoints.

MATERIALS AND METHODS

The LAC-DPH has established a countywide AR/antimicrobial stewardship (AS) team composed of LAC-DPH liaison public health nurses and an AS physician. The AR/AS team is responsible for encouraging AS and infection control activities among the 97 acute care hospitals (ACHs) in the county. Based on the results of the CARLA survey (15) and the fact that Los Angeles County is known to be a focal point for CRE (16), the AR/AS team prioritized ensuring that the breakpoints applied by laboratories to carbapenem susceptibility results for *Enterobacteriaceae* strains met current FDA/CLSI standards. The LAC-DPH reached out to the 41 ACHs in Los Angeles County that had self-identified in the CARLA survey as using obsolete *Enterobacteriaceae* carbapenem breakpoints (15). These hospitals were targeted for a 1-year outreach program, from July 2017 to July 2018.

The AR/AS team held in-person meetings with each ACH laboratory director, microbiology supervisor, AS chair, and infection preventionist, as well as other invested hospital administrative and nursing staff members selected by the ACH. The AR/AS visits (i) determined which *Enterobacteriaceae* carbapenem breakpoints were in use by the laboratory, (ii) determined why the laboratory had not updated the breakpoints, if it had not yet done so, and (iii) promoted the implementation of current carbapenem breakpoints.

Following the visit, the AR/AS team provided each hospital with a guidance document for updating breakpoints, along with a sample verification protocol and template to document the results of the verification studies (17–19) (see the supplemental material). The AR/AS team provided further support by ordering the *Enterobacteriaceae* carbapenem breakpoint panel from the FDA/CDC AR Isolate Bank (https://www.cdc.gov/drugresistance/resistance-bank/index.html) for each laboratory. The laboratories were instructed to work with the local service technicians from their automated antimicrobial susceptibility testing (AST) instrument manufacturers to conduct the verification study, including updating the instrument software if necessary. The AR/AS team made periodic telephone calls to encourage progress and to troubleshoot as needed.

Data collected to monitor the success of this program included the ACHs targeted, the dates of site visits, the types of guidance and resources provided, and the date of full implementation of current *Enterobacteriaceae* carbapenem breakpoints. The outcome of the intervention was measured as the

TABLE 1 Current and historical carbapenem MIC breakpoints and CLSI recommendations for the use of carbapenemase tests for *Enterobacteriaceae*

Test and antimicrobial agent or recommendation	MIC breakpoint (μg/ml)[a]						CLSI recommendation	
	Historical (before 2010)			Current (2010 to present)				
	S	I	R	S	I	R	Historical (before 2010)	Current (2010 to present)
MIC test								
Doripenem	None			≤1	2	≥4		
Ertapenem	≤2	4	≥8	≤0.5[b]	1	≥2		
Imipenem	≤4	8	≥16	≤1	2	≥4		
Meropenem	≤4	8	≥16	≤1	2	≥4		
Carbapenemase test								
Indication for test performance							Imipenem or meropenem MIC of 2–4 μg/ml or ertapenem MIC of 2 μg/ml	Requested by infection control or for epidemiological studies
Routine reporting recommendation if carbapenemase is detected							Edit carbapenem S or I interpretations to R, regardless of MIC	Report MICs as tested, regardless of carbapenemase test result

[a]S, susceptible; I, intermediate; R, resistant.

[b]The *Enterobacteriaceae* ertapenem breakpoints were updated twice, to ≤0.25 in 2010 and then to ≤0.5 in 2012.

number of hospitals that updated *Enterobacteriaceae* carbapenem breakpoints. Data are presented following the SQUIRE reporting guidelines (20).

RESULTS

From July 2017 to September 2017, the AR/AS team conducted outreach to 41 hospitals that had indicated in the CARLA survey that they used obsolete carbapenem breakpoints. All 41 laboratories received in-person AR/AS team visits. By the time of the AR/AS visit, 7 laboratories (17%) had already updated to the current FDA/CLSI breakpoints after responding to the CARLA survey; these laboratories were not targeted for further follow-up efforts.

Among the remaining 34 laboratories, 27 (79%) assumed that their AST instruments were already applying current breakpoints. Seventeen laboratories (50%) were uncertain how to approach changing the breakpoints on their AST instruments, and 10 (29%) indicated that they lacked the resources to perform a verification study, as required by Clinical Laboratory Improvement Amendments (CLIA), to update the breakpoints on their systems. Only 7 facilities (21%) were familiar with the FDA/CDC AR Isolate Bank as a resource for verification studies. All 34 laboratories using obsolete breakpoints were accredited, 29 (85%) by the College of American Pathologists and 5 (15%) by the Joint Commission (Oakbrook Terrace, IL). Staffing in the laboratories included 28 laboratories (82%) with dedicated microbiology staff members, 5 (15%) with a microbiology laboratory director (with an MD or PhD degree dedicated to microbiology), and 29 (85%) with a clinical laboratory scientist who operated under a general pathology laboratory director.

All 34 hospitals agreed to work toward updating carbapenem breakpoints following the AR/AS team visit. After 1 year of follow-up monitoring, 16 laboratories (47%) had successfully updated breakpoints, 12 (35%) had received FDA/CDC AR Isolate Bank isolates but had not updated the breakpoints, and 6 (18%) were planning to update in the next year. Among the 18 hospitals that had not successfully implemented current breakpoints, barriers to implementation included too much clinical work/not enough staffing ($n = 12$), inability to update the laboratory information systems or electronic medical record to accommodate the breakpoint changes ($n = 5$), waiting until a new AST platform was installed ($n = 2$), and laboratory staff changes ($n = 3$).

DISCUSSION

Ongoing use of obsolete carbapenem breakpoints by clinical laboratories has serious clinical and public health implications. Application of obsolete carbapenem breakpoints to AST results can direct treating physicians to use inappropriate antimicrobial therapy, which in turn contributes to patient morbidity and death (2, 3). Failure to update breakpoints hinders the ability to identify CRE, impairing infection control initiatives and fueling the spread of CRE (14). The burden of CRE is known to be high in Los Angeles County (16), and we further estimate that approximately 20% of carbapenemase-producing *Enterobacteriaceae* strains in Los Angeles would be classified as carbapenem susceptible with the use of obsolete breakpoints (14, 15). Despite the potential implications for hospitals in Los Angeles County, we found that the use of obsolete breakpoints was common (35%) in local laboratories. We found that the greatest barriers to the adoption of updated breakpoints were a lack of technical expertise and a lack of awareness of the problem.

Nearly 80% of laboratories using obsolete breakpoints assumed that the regularly scheduled vendor maintenance of AST devices included breakpoint updates. However, AST devices are regulated by the U.S. FDA as class II devices, and AST device manufacturers are not required to update their platforms to current breakpoints if the original FDA clearance was obtained prior to the breakpoint change (in this case, 2009). AST device manufacturers may volunteer to resubmit data to the FDA to systematically update breakpoints during routine maintenance; however, not all manufacturers have submitted data to the FDA. Laboratories, physicians, and public health officials are encouraged to lobby AST device manufacturers directly to ensure that breakpoints are routinely updated on commercial AST systems.

The AR/AS team visits allowed the LAC-DPH to improve awareness of the problem and to encourage breakpoint updates. Prior to the AR/AS visit, most microbiology laboratory personnel did not feel empowered to initiate change, even when they were aware of the problem. The AR/AS team visits secured the cooperation of the AS and infection control leaders, who provided important administrative support for the breakpoint initiative. The availability and low cost of the FDA/CDC AR Isolate Bank isolates were commonly seen as important for gaining administrative support for breakpoint updates.

Modification of AST systems to current breakpoints requires a relatively straightforward verification study, usually including 30 to 40 isolates to confirm the performance of the AST system (17–19). As we demonstrated in the present study, however, breakpoint revisions are outside the scope of many local laboratories without the support of outside expertise. Materials we provide in the supplemental material were helpful. Technical support from the local representatives of AST device manufacturers proved to be crucial, because customized programming of the AST instruments was complex. The technical representatives for the AST device manufacturers, not the sales representatives, were best suited to supervise breakpoint changes for the AST software platforms.

Ongoing follow-up efforts after the AR/AS team visit proved to be valuable. The process of verification of new breakpoints is outside the typical laboratory workflow, and many facilities needed encouragement to complete the process. The AR/AS team helped with completing paperwork to request isolates from the FDA/CDC AR Isolate Bank and provided verification and reporting templates. Through collaboration with the AR/AS team visits and additional technical support, 100% of the hospitals began the process of updating breakpoints, and nearly one-half of the hospital laboratories were able to complete the updates within 1 year. The common reasons why laboratories did not complete the updates reflected low prioritization from the hospital administration, as demonstrated by inadequate laboratory staffing and support from information technology services to revise the electronic medical record or laboratory information systems.

One potential avenue for prioritizing breakpoint updates with hospital administrations would be through the Joint Commission or College of American Pathologists accreditation and inspection process. Laboratory accreditation is a priority for hospital administrations. While accreditation agencies such as the College of American Pathologists encourage the use of updated standards through proficiency testing surveys, they do not currently penalize laboratories for using obsolete breakpoints. Given the clear patient safety implications of failing to use appropriate breakpoints, accreditation bodies should consider options to require that microbiology laboratories use FDA/CLSI breakpoints (13).

There are a number of limitations to our study. While we were successful in improving the usage of current carbapenem breakpoints in Los Angeles County, we recognize that our experience may not be generalizable to other public health jurisdictions. Our AR/AS team includes academic investigators in infectious diseases (J.A.M.) and microbiology (J.H. and R.M.H.). However, we hope that sharing our experience and resources with other jurisdictions will encourage similar initiatives to be more widely adopted. We also recognize that there are multiple other recently updated breakpoints, such as the *Pseudomonas aeruginosa* carbapenem and piperacillin-tazobactam breakpoints, the *Enterobacteriaceae* aztreonam and cephalosporin breakpoints, and the *Acinetobacter baumannii* complex carbapenem breakpoints, as well as pending updates such as the *Enterobacteriaceae* and *Pseudomonas aeruginosa* fluoroquinolone breakpoints. At the present time, the FDA has recognized many but not all of these CLSI breakpoints, which complicates the matter of updating AST systems. Additionally, we did not collect information on how the breakpoint initiative affected patient outcomes, infection prevention practices, antimicrobial prescribing, or the CRE incidence rate in Los Angeles County.

Results from our initiative highlight the potential for public health services to

support local microbiologists in detecting and reporting CRE in a timely and effective manner. The interventions described in our study represent a promising approach that should be considered by other public health jurisdictions and health systems. However, our project raises questions regarding which authority is best suited to ensure that laboratories are following best practices. Reducing morbidity and mortality rates is clearly under the public health purview, but the role of public health departments in most jurisdictions is not to enforce current laboratory standards. The Joint Commission and the College of American Pathologists could play a role in addressing the ongoing problem of obsolete breakpoints. Regulatory oversight at either the state or federal level would be another means to definitively address the ongoing public health and patient safety problems created by the persistent use of outdated microbiological testing methods.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/JCM.01488-18.

SUPPLEMENTAL FILE 1, XLSX file, 0.03 MB.
SUPPLEMENTAL FILE 2, XLSX file, 0.02 MB.
SUPPLEMENTAL FILE 3, PDF file, 0.03 MB.
SUPPLEMENTAL FILE 4, PDF file, 0.1 MB.
SUPPLEMENTAL FILE 5, PDF file, 0.1 MB.

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