ACTIVATING VITAL ADVANCES IN ANTIMICROBIAL RESISTANCE TESTING AMONG LOS ANGELES COUNTY HEALTHCARE FACILITIES

BACKGROUND

Antibiotic resistance (AR) and multi-drug resistant organisms (MDRO) are an intensifying public health threat. Carbapenem-resistant Enterobacteriaceae (CRE) are especially concerning. CRE mortality rates are often as high as 30-40% [1-5] due to limited treatment options. In addition, many CRE can spread AR to other bacteria via plasmid-encoded genetic resistance mechanisms, called carbapenemases [6]. Given this, it is not surprising that CRE has been classified as a critically important and urgent global threat by the Centers for Disease Control and Prevention (CDC) and the World Health Organization [7-8]. While CRE has been steadily increasing in the United States [9-10], Los Angeles County (LAC) has been identified as a hotspot for CRE infections because of its large number of healthcare facilities and its international patient population [11], which create a complex system within which CRE and other MDROs can readily spread.

Early administration of microbiologically active antimicrobial therapy can reduce morbidity and mortality from CRE infections [5, 12-14]. This depends on accurate determination of the minimum inhibitory concentration (MIC) of the infecting organism to antibiotics. Interpretation of the MIC results is conducted using breakpoints, which categorize whether an antibiotic is resistant or susceptible to any given antibiotic and determine the probability of treatment success. The Clinical Laboratory Standards Institute (CLSI) provides guidance on what methodologies clinical laboratories should use to detect CRE and other nosocomial pathogens.

The CLSI updated the carbapenem MIC breakpoints for Enterobacteriaceae in 2010 based on data from multiple clinical studies demonstrating that ongoing use of the previous breakpoints resulted in higher patient mortality [3, 4]. Failure to update breakpoints also impacted infection control measures, which is estimated to contribute to a 3-5% annual spread of CRE [15]. Ongoing use of outdated CLSI breakpoints will result in the failure to recognize clinically and epidemiologically concerning MDROs such as CRE.

It is thus imperative that clinical laboratories are up-to-date on their CRE detection methods. To assess CRE detection practices amongst clinical laboratories, the Acute Communicable Disease Control Healthcare Outreach Unit (HOU) partnered with California Department of Public Health and academic investigators to conduct the California Antimicrobial Resistance Laboratory Network Assessment (CARLA) survey in 2015. The CARLA survey identified that 42% of hospital laboratories in LAC used outdated carbapenem breakpoints for Enterobacteriaceae [16]. Furthermore, many laboratories did not perform carbapenemase testing, as recommended by CLSI to ensure detection of carbapenemase-producing Enterobacteriaceae with use of outdated breakpoints [16].

Clinical laboratories must take manual steps to ensure their antimicrobial susceptibility testing (AST) instruments are up-to-date. However, the HOU theorized that lack of awareness of the problems

surrounding use of outdated breakpoints and/or technical knowledge of how to update breakpoints caused the delayed uptake of revised breakpoints. This prompted our initiative to better understand why laboratories failed to update breakpoints and, in turn, assist them in implementing up-to-date CRE detection methods.

OBJECTIVE

This report describes the HOU's efforts to update carbapenem breakpoints amongst targeted clinical laboratories in LAC to improve detection of CRE.

METHODS

HOU established the antimicrobial resistance/antimicrobial stewardship (AR/AS) team, composed of five HOU liaison public health nurses (LPHNs), an epidemiologist, and an infectious disease physician serving as the HOU's AR expert. Targeted hospitals were chosen based upon their responses to the question of using outdated CRE breakpoints in the CARLA survey. To be included in our target list, the labs had to respond with i or ii to the following question: What breakpoints does your laboratory use for carbapenems when testing Enterobacteriaceae?

i. Pre-2010 breakpoints only ←
ii. Pre-2010 breakpoints combined with tests for carbapenemase production ←
iii. Current CLSI M100 S25 breakpoints
iv. Other

The AR/AS team collaborated with CDC and local microbiology experts to develop a protocol that guides clinical laboratories through the process of updating CRE detection methods, which includes:

1. ordering verification panels from the Food and Drug Administration (FDA)/CDC AR Isolate Bank;
2. updating breakpoints in the AST instrument, which may involve scheduling a visit with the local service technician of their AST device manufacturer; and
3. conducting a verification study to ensure accurate results.

The team first conducted in-person visits with each hospital's laboratory director, microbiology supervisor, antimicrobial stewardship chair, and infection preventionist to discuss unique issues that were impacting their CRE detection methods and provide initial recommendations. Following the initial visit, the AR/AS team provided each hospital with the CRE breakpoint update protocol, sample verification study protocol, and template to document the results of the verification studies.

During follow-up consultations, the AR expert provided additional support, which included facilitating communication with the CDC, FDA, and local laboratory equipment representatives. The AR/AS team also checked in with each hospital regularly to encourage progress, and that their methods were thoroughly implemented.

RESULTS

Between July to August 2017, the AR/AS team conducted outreach to 41 hospitals who responded with i or ii to the question above. The survey was sent out to all hospitals in California in 2015, including 97 in Los Angeles (at the time of the survey). All 41 laboratories had in person AR/AS team visits. At the time of

the initial AR/AS visit, 7 (17%) had updated to the current CLSI breakpoint following the CARLA survey, and were not targeted for further follow-up.

Of the remaining 34 laboratories, 27 (79.4%) assumed their AST instruments were using current breakpoints. Half of laboratories (17, 50%) were uncertain of how to approach changing breakpoints on their AST instrument, and 10 (29.4%) indicated they lacked the resources to perform a verification study. Only 7 (20.5%) facilities were familiar with the FDA/CDC AR Isolate Bank as a resource for verification studies. All 34 laboratories using historical breakpoints were accredited, most were accredited by the College of American Pathologists (29, 85%), the others by the Joint Commission (5, 15%). Laboratory staffing included dedicated microbiology staff in 28 (82%) laboratories, a laboratory director with a specialization in microbiology (MD or PhD) in 5 (15%), and a clinical laboratory scientist in 29 (85%).

All 34 hospital laboratories agreed to work toward updating carbapenem breakpoints following the AR/AS team visit. After one year of follow-up, 15 laboratories (47%) successfully updated breakpoints; 12 (35%) received isolates but did not update; and 6 (18%) are planning to complete the update in 2018. Common barriers for the 19 laboratories failing to update the breakpoint included: too much clinical work and/or not enough staffing (12, 63%) and inability to update the laboratory information systems or electronic medical record (5, 26%). Other less common reasons included waiting on new testing platforms (n=2) and changes in laboratory staff (n=3).

DISCUSSION

Ongoing use of outdated carbapenem breakpoints by clinical laboratories is a public health problem. Failure to update breakpoints hampers infection control initiatives, hinders CRE treatment success, and helps fuel spread of CRE [2-5, 15]. Prior to the AR/AS visit, most microbiology laboratory personnel did not feel empowered to make changes, even when they were aware of the problem. However, with the cooperation of antimicrobial stewardship and infection control leadership—in conjunction with ongoing follow-up by the AR/AS team—the laboratories gained vital support for the breakpoint update initiative.

The AR/AS team visits allowed HOU to use existing resources for targeted outreach to engage hospital laboratories in updating carbapenem breakpoints. The key to success of the project was developing a strong system of collaborations with our CDC partners, local experts, representatives of AST device manufacturers, and individual hospital staff—especially the clinical laboratory scientist who typically leads the laboratory methodology validation efforts. The process of verifying new MIC breakpoints is outside the scope of typical laboratory work-flow, so many facilities needed encouragement and administrative support to complete the process. Thanks to the AR/AS team visits, all (100%) of targeted hospitals began the process of updating breakpoints and nearly half of the hospital laboratories completed the update within one year.

Physicians and other healthcare staff depend on the assurance that the results provided by their laboratory are accurate, significant, and clinically relevant. By improving laboratory detection methods, CRE will now be correctly classified in LAC hospital laboratories. This will decrease inappropriate antibiotic therapy and in turn decrease the risk of death from CRE infection. Now that CRE can be accurately

detected and reported, HOU can also improve our efforts to contain the spread of CRE within LAC. In addition, because LAC has a large international patient population, this project likely will also decrease the spread of CRE globally.

There are several limitations to this intervention. While the AR/AS team was successful with improving updated carbapenem MIC breakpoint usage in LAC, the HOU experience may not be generalizable to other public health jurisdictions. The AR/AS team includes academic investigators in infectious disease and microbiology. However, we hope that making our resources available to other jurisdictions will make our initiative more widely adoptable. To date, the FDA—which dictates which breakpoints AST instruments must use—has officially recognized many but not all CLSI breakpoints, which complicates the process of updating AST systems in a timely manner. Additionally, HOU did not collect information on how the breakpoint initiative impacted patient outcomes, infection prevention practices, antimicrobial prescribing, or the incidence rate of CRE in LAC.

Despite the large number of hospital laboratories in LAC using outdated CRE detection methods and limited staff resources, this project was a success. The AR/AS team's findings informed a need to do further broad education to improve AR detection practices across LAC. This project also greatly improved HOU's rapport with hospital laboratories, which is critical to detect and contain CRE and other AR bacteria of epidemiological concern. Now that these partnerships have been established, HOU will be able to continue to improve laboratory capabilities in our jurisdiction in the global fight against AR.

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