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COMMENTARY

The Immaculate Carbapenemase Study

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ABSTRACT Carbapenemase-producing organisms, or CPOs, are Gram-negative pathogens that produce a transmissible carbapenemase and are typically resistant to most (sometimes all) antibiotics. We now face a global CPO pandemic of high mortality. In this issue of the *Journal of Clinical Microbiology*, Karlowsky et al. (J Clin Microbiol 55:1638–1649, 2017, https://doi.org/10.1128/JCM.02316-16) report the results of an extensive global surveillance study that provide much-needed information that enhances our understanding of carbapenemase-producing *Enterobacteriaceae* (CPE) and which will be valuable for the development of improved strategies for CPE control and therapy of infections.

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The Ebola-like mortality sometimes reported for the Gram-negative superbug pandemic stems from ineffective infection control and failures to provide timely, effective therapy (1). The initial warning of this threat appeared in 1991 with the report of a plasmid-mediated carbapenemase (2). Almost 2 decades later, transmissible carbapenemases had become a global problem (3) and clinical laboratories were urged to perform carbapenemase tests to detect them (4). The carbapenemase-producing organism (CPO) problem now extends beyond the treatment of bacterial infections and also threatens medical procedures that rely on antibiotics to protect vulnerable patients. In addition, CPOs are no longer just a problem of medical institutions but are everywhere, as was indicated by TV coverage of the Olympic Games, where they were detected even in seawater and on the beaches in Rio de Janeiro (5). The outlook has become so bleak that in September 2016, all 193 members of the United Nations pledged to rid the world of superbug infections (https://www.un.org/pga/71/wp-content/uploads/sites/40/2016/09/DGACM_GAEAD_ESCAB-AMR-Draft-Political-Declaration-1616108E.pdf). While not all superbugs are CPOs, they are the most dangerous because they have the greatest propensity to become totally antibiotic resistant and they cause the highest mortality.

Today, consensus exists about the need to control the CPO threat but there is disagreement about how best to do it. In the absence of definitive data, controversies have arisen about many issues, including the role of laboratory testing and optimal therapy (1, 6–9). Scientific argumentation and controversies can help to define the correct direction for obtaining new knowledge, but they may also delay appropriate action. In the case of the globally spreading, high-mortality CPO pandemic, it is vital that the most appropriate actions are taken quickly. Having good evidence on which to base decisions is integral to doing this. There is an urgent need for evidence of a more convincing nature to resolve the controversies and help bring about a reduction in CPO-associated mortality.

The laboratory controversies concern whether it is necessary to perform carbapenemase detection tests or, if such tests are done, whether they have relevance only for epidemiology and infection control and no relevance to therapy. The CLSI and EUCAST position is that carbapenemase testing is not required for therapeutic purposes but can be important for epidemiology and infection control and that *in vitro* susceptibility testing provides a reliable guide to therapeutic choices (10, 11). This view is opposed by claims that susceptibility testing of carbapenemase producers can be inaccurate and

unreliable and that there is poor correlation between *in vitro* susceptibility and therapeutic outcomes.

The inaccuracy issue arises because carbapenem susceptibility testing of KPC producers can give poor agreement between MICs determined by different methods and also because results can be irreproducible (7, 12–17). This has been attributed to the heteroresistance represented by the presence of colonies within carbapenem inhibition zones in Etest and disk tests (16). Carbapenem MICs of KPC producers can differ dramatically, with the KPC producers sometimes being susceptible in one test and resistant in another. For example, two KPC-producing *Klebsiella pneumoniae* isolates in one study had meropenem MICs of $\leq$1 μg/ml by one method and 16 μg/ml by another (17). Discordance between results raises the issue of determining which of the discordant results represents the accurate guide to therapy. In addition, clinical experience indicates that CPO infections are different from other infections and that monotherapy with a single active drug is essentially the same as no active therapy. In contrast, combination therapy with at least two active agents provides a clear survival benefit, especially if one of the active agents is a carbapenem (9). Therefore, an *in vitro* susceptibility result on its own may mislead a clinician by failing to indicate the need for combination therapy. Combination therapy may also reduce the risk of total antibiotic resistance emerging. This is an important consideration because the clinician may have only one opportunity to deliver effective therapy and the wrong choice may doom the patient to die from an untreatable infection.

The assertion that combination therapy is optimal is open to question. Definitive clinical trial data are lacking. The most convincing outcome data in support of combination therapy are from infections by producers of KPCs and metallo-β-lactamases. There are less data for infections by producers of other carbapenemases. Analyses of previous studies indicate that β-lactam monotherapy is as effective as but less nephrotoxic than combination therapy with a β-lactam and an aminoglycoside (18, 19). Unfortunately, the value of such analyses is uncertain as they do not include CPO infections. Given the high mortality rate of CPO infections and that the best information currently available is clinical experience, the case for combination therapy should warrant serious consideration.

In addition to these issues for which there are only limited data, there is an overall need for standardized, comprehensive global data about the genetic and phenotypic attributes of CPOs and their geographic occurrence. Previously published surveillance studies have provided many insights, but, collectively, their value is limited by their different methodologies and sampling approaches. In this issue, Karlowsky et al. report extensive global surveillance data for carbapenemase-producing *Enterobacteriaceae* (CPE) obtained from testing 103,960 isolates over the period 2008 to 2014 (20). The standardized sampling and reporting of the geographical distribution of CPE strains and their types of carbapenemase production extend and refine previous knowledge, providing an important resource for analysis and strategic planning. The data also provide insights into the controversy about whether carbapenemase detection tests are warranted.

The study isolates included 3,428 ertapenem-nonsusceptible *Enterobacteriaceae* isolates (MIC, $\geq$1 μg/ml) and 9,371 extended-spectrum-β-lactamase (ESBL)-positive ertapenem-susceptible isolates. These were screened for carbapenemase-encoding genes by microarray. Carbapenemase genes were detected in 1,485 ertapenem-nonsusceptible isolates and eight ertapenem-susceptible ESBL-positive isolates. On the basis of the assumption that the genes were functional, these isolates are referred to in the following as CPE isolates. These accounted for 1.4% of all *Enterobacteriaceae* isolates, with *Klebsiella pneumoniae* being the most common CPE. Not surprisingly, genes encoding KPC were the most common, followed by OXA-48-like and NDM genes. Less-common genes encoded GES, IMP, and VIM carbapenemases. The phenotypic CPE screening results provide important insights into the laboratory testing controversy. Consistent with what is widely known, ertapenem nonsusceptibility was a more sensitive screen than imipenem nonsusceptibility (MIC, $\geq$2 μg/ml) but had poor specificity.

The important finding was that almost 10% of the CPE isolates were imipenem susceptible, showing imipenem nonsusceptibility to be a poor screen for carbapenemases. While the majority (78.7%) of imipenem-susceptible CPE isolates harbored an OXA-48-like gene, imipenem susceptibility also occurred with isolates harboring GES, IMP, VIM, and KPC genes. It is clear from the study by Karlowsky et al. that carbapenem nonsusceptibility is a suboptimal carbapenemase screen with problematic sensitivity and specificity.

A issue which arises is whether, in the absence of ertapenem screening, laboratories should perform carbapenemase tests on *Enterobacteriaceae* isolates that are susceptible to imipenem. This issue is probably equally relevant to isolates that are susceptible to meropenem and/or doripenem. That is, does failure to detect carbapenemases in these isolates place patients at risk? Karlowsky et al. cite publications indicating potential risks of therapeutic failures and the loss of opportunities to obtain important information concerning infection control, epidemiology, and the emergence of novel carbapenemases. They also make the point that over 50% of imipenem-susceptible CPE isolates in the study were multidrug resistant, leaving few treatment options. This finding has implications for empirical therapy, antibiotic stewardship, and infection control. Since rapid carbapenemase test results can now be made available hours before susceptibility results, an early positive carbapenemase test result could provide an otherwise unavailable indicator that an isolate might be multidrug resistant. Perhaps the strongest justifications for carbapenemase testing are that *in vitro* susceptibility tests can be inaccurate and that reliance on susceptibility alone without knowing the carbapenemase status of the pathogen involves an element of risk.

Balanced against the arguments for performing carbapenemase tests on carbapenem-susceptible isolates is the unknown cost-benefit ratio. The imposition of additional testing on laboratories that are often hard-pressed due to minimal staffing and restricted budgets must be balanced against the potential benefit. Most carbapenemase tests are currently performed manually, and additional carbapenemase testing of susceptible isolates would be a significant extra burden of effort and cost. This would seem punitive to busy laboratories that do not encounter carbapenemase producers. Ideally, given that there can be important patient management value in carbapenemase testing, what is now needed is for laboratories to have access to such testing with no or minimal additional effort or cost. This can be achieved by using an approach in which automated analyzers provide ESBL testing in routine susceptibility panels. It would be beneficial if carbapenemase tests could be similarly added to the routine susceptibility panels of both automated and manual tests. This would mean that all isolates would be tested for carbapenemases and would eliminate the problem of creating an increased workload. It would also remove the need to use suboptimal screening with carbapenems to determine which isolates require a carbapenemase test, which would also remove the sometimes considerable confusion about whether or not particular isolates need to be tested for carbapenemases.

Until carbapenemase testing becomes available as part of the routine susceptibility test, the problem remains of how or whether to accommodate an increased workload of manually performed carbapenemase tests. Also, if additional testing is undertaken, is it possible to limit it to a manageable amount by prioritizing and testing only isolates from certain patients?

Overall, the study by Karlowsky et al. was a study of high clinical relevance. It provided important high-quality data that address some of the controversies that hamper effectiveness in reducing mortality and controlling the CPO pandemic. The study shed light on the high value of carbapenemase testing, the low value of carbapenem insusceptibility to screen for carbapenemases, and whether sole reliance on possibly unreliable susceptibility tests is justified to guide therapy for treatment of carbapenemase-associated infections. The paper is well written and exemplary in its tone and in the balanced manner in which the authors address the controversies and how they acknowledge issues where knowledge remains scant and incomplete. It is important that studies of this type continue to monitor and provide insights into this

serious global problem. Ideally, the scope of the work should now be expanded to include the non-*Enterobacteriaceae* that also contribute to the transmissible carbapenemase pandemic.

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