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AUTHOR REPLY

Reply to Pogue and Heil, "The Clinical Impact of a Negative Molecular β-Lactamase Gene Test for *Enterobacteriaceae*: Let's Not Let Perfect Be the Enemy of Really Good"

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We thank Dr. Pogue and Dr. Heil for their commentary on our study of resistance mechanisms for Gram-negative bacteria in the United States and agree that these tests can provide tremendous value to antimicrobial stewardship. We further agree with the authors that the use of these tests for de-escalation purposes is optimal when the practitioner has a good understanding of their local resistance patterns. Not all hospitals are equipped with advanced stewardship programs with the expertise and resources to evaluate local epidemiology and interpret molecular resistance genotype tests. The limitation of this was demonstrated by Rivard and colleagues in their evaluation of a test that detected CTX-M from positive blood cultures at seven Cleveland Clinic Health System sites (1). The investigators found that when this test was combined with antimicrobial stewardship, the time to antimicrobial de-escalation was reduced a median of 15 h at the academic medical center site ($P < 0.001$) but was largely unchanged at the six regional hospitals evaluated. At these sites, the authors found that the test was being used primarily as a tool to identify resistant pathogens for therapy escalation purposes, rather than as a tool for de-escalation (1). A second study similarly demonstrated that clinicians are more confident initiating or escalating therapy based on the results of genotypic tests, as opposed to de-escalating therapy. Among 382 physicians surveyed, 86% indicated that they would escalate therapy based on a report of *Enterococcus* with *vanA* detected, but only 53% indicated that they would de-escalate therapy based on the results of *S. aureus* that was negative for *mecA* (2).

Routine evaluation of local epidemiology is typically limited to construction of an annual institutional antibiogram that summarizes data for all patients. However, select patient populations, for example, those with prior exposure to health care facilities or antimicrobial therapy within the past month, are well documented to have much higher prevalences of antimicrobial-resistant infections (3). As the prevalence of resistance increases, the negative predictive value (NPV) of a genetic resistance marker test decreases. The definition of what constitutes an acceptable NPV for major therapeutic decisions (like antimicrobial de-escalation) differs by clinician, but a recent survey of 238 internal medicine physicians found that they require a threshold of 90% (interquartile range, 80 to 95%) for patients with severe sepsis (4). Dependent on the local epidemiology and individual patient risk factors, the NPV for genotypic tests can be below this threshold.

To highlight this point, we compared data from the Johns Hopkins Medical Center (JHMC) to those reported by Drs. Pogue and Heil for the University of Maryland Medical Center (UMMC). Both hospitals are large academic medical centers in Baltimore, MD, and both studies evaluated bacterial isolates collected during roughly the same time period (2014 to 2015 at JHMC and 2015 to 2016 at UMMC). At JHMC, the prevalence of ceftriaxone nonsusceptibility was 25% (5). A test for CTX-M would have an NPV of 89.9%

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among the 482 ceftriaxone-nonsusceptible isolates evaluated in this study, right at the limit of what was defined as acceptable by internal medicine physicians by the aforementioned survey (4). In contrast, at UMMC, only 16.4% of isolates were ceftriaxone resistant, 87% of which harbored CTX-M, and the NPV for this test was 97% (6). These data highlight how knowledge of individual hospital epidemiology is crucial to maintaining the value of these tests. Slight changes to the epidemiology (prevalence or mechanisms of resistance) can easily result in a perceived unacceptable NPV and loss of physician confidence. We again stress that the use of genotypic tests to predict antimicrobial susceptibility requires routine correlation between genotypic and phenotypic results and action (further surveillance, trending, etc.) when these do not agree. Not all antimicrobial stewardship programs and not all clinical laboratories have resources for such activities, but for those that do, we agree that molecularly based rapid diagnostics can be of value to antimicrobial stewardship efforts.

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