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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 read with interest "Evaluation of Empiric β-Lactam Susceptibility Prediction among *Enterobacteriaceae* by Molecular β-Lactamase Gene Testing" by Spafford and colleagues (1). We commend the authors for their analysis of nationwide susceptibility/resistance gene data to provide an examination beyond that of an individual institution. In their analysis of 5,739 *Enterobacteriaceae* from 72 hospitals in the United States, including 683 (11.9%) ceftriaxone-resistant isolates, the authors demonstrated that using the absence of a resistance marker detected by Verigene (CTX-M, KPC, or NDM) to predict ceftriaxone susceptibility would result in a very major error (VME) rate of 18.6%. That is, 127/683 isolates that were resistant to ceftriaxone would not be detected by the molecular test. The authors then assess the impact that this VME rate would have at different resistance rates and alarmingly demonstrate that if the rate of ceftriaxone resistance at one's institution was 50%, molecular testing would fail to capture resistance in 1 out of 10 isolates tested! This leads the authors to caution against using genotypic results for de-escalation efforts and stress the benefit of rapid phenotypic tests.

While we agree that rapid phenotypic results are welcome, we feel that this current analysis understates the confidence that clinicians can have that an isolate will be ceftriaxone susceptible in the absence of these resistance markers. While it is true, per the author's analyses, that a VME rate (i.e., predicted susceptibility when resistance is actually present) approaching 20% would occur, this type of approach is inconsistent with how clinicians use these tests. What a clinician wants to know is, "If the molecular test is negative for a resistance gene, how confident can I be that the isolate is susceptible to the target drug?" In order to make that assessment, one needs to assess the negative predictive value of the test by considering all isolates for which the test is negative (both those resulting in a VME and those susceptible to the target drug). In the data presented, there were 5,056 isolates that were ceftriaxone susceptible. Let us assume that those are test negative (in the absence of CTX-M, KPC, or NDM). Additionally, there were 127 test-negative, ceftriaxone-resistant isolates. That means that 5,056/5,183 (97.5%) test-negative isolates were ceftriaxone susceptible. That is powerful information for clinicians, as it changed the pretest probability from 11.9% to 2.5% resistance. All clinicians would feel more comfortable with an antibiogram that predicted 98% susceptibility versus 88%. While it is true that the "miss rate" goes up as the rate of resistance does, the impact of the negative test actually increases. If the resistance rate is 40% pretest, a negative test would decrease this to 8.4%. This information can then be combined by clinicians with the severity of illness and an assessment of response (or lack thereof) to current therapy to make an informed

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decision about the patient. While we agree with the authors that understanding the limitations of a test and assessing local epidemiology are critically important, we feel that if local data matched this national data set, it would strongly support de-escalation (or lack of escalation) for most patients with a negative molecular test.

REFERENCE

1. Spafford K, MacVane S, Humphries R. 2019. Evaluation of empiric β-lactam susceptibility prediction among *Enterobacteriaceae* by molecular β-lactamase gene testing. J Clin Microbiol 57:e00674-19. https://doi.org/10.1128/JCM.00674-19.