Study: elevated vancomycin MICs no cause for concern

Ann Griswold, PhD

December 2014—Elevated vancomycin minimum inhibitory concentrations do not increase the risk of death in patients with Staphylococcus aureus bacteremia, according to the findings of a comprehensive meta-analysis published in the Oct. 9 issue of JAMA.

Despite widespread speculation about rising vancomycin resistance, or "MIC creep," the authors find little evidence to challenge the current CLSI susceptibility breakpoint of ≤ 2 µg/mL for vancomycin.

Dr. Kalil

"After an extensive approach and analysis, we found that MICs of one and two have pretty much similar mortality," says coauthor Andre C. Kalil, MD, MPH, a professor of medicine in the Infectious Diseases Division of the University of Nebraska Medical Center. The results remained consistent across a variety of study designs, microbiological susceptibility assays, MIC cutoffs, clinical outcomes, durations of bacteremia, and histories of previous vancomycin exposure and treatment.

The findings may help boost clinicians' confidence in vancomycin therapy and stave off opportunities for S. aureus to develop multidrug resistance, the authors note.

"Based on an MIC of two, some physicians might change the patient's therapy to daptomycin because the literature essentially suggested there were vancomycin failures if the MIC was over one," says coauthor Paul D. Fey, PhD, D(ABMM), a professor of pathology and microbiology at the University of Nebraska Medical Center and medical director of the clinical microbiology laboratory. Dr. Fey interpreted the susceptibility test results and contributed microbiology expertise to the study.

Dr. Fey

That strategy may be unnecessary, the new findings suggest. "In terms of the bedside, an elevated MIC by itself should not lead clinicians to rush to switch therapies in patients with SAB [S. aureus bacteremia]," Dr. Kalil says. "If we can prevent unnecessary changes to new or alternative antibiotics, we're not only helping patients who are being treated now—we're also helping future patients with these infections."

The Nebraska Medical Center study refutes three previous meta-analyses linking elevated vancomycin MICs to poor patient outcomes. Those analyses have been noted for including heterogeneous patient populations, combining multiple sites of infection, and evaluating bias-laden endpoints such as treatment failure.

“This is certainly an important contribution to the existing evidence in this subject matter,” says Stefan Riedel, MD, PhD, D(ABMM), of the recently published study. He is an assistant professor of pathology at The Johns Hopkins University and director of the clinical pathology laboratories at Johns Hopkins Bayview Medical Center. He is also a member of the CAP’s Microbiology Resource Committee.

“What I liked about this article, contrary to some of the other meta-analyses, is that it really focused on bloodstream infections,” says Dr. Riedel, who was not involved with the study. “They have a very concise patient population in which to assess the question they’re asking, which is this: Does the MIC that the microbiology lab reports influence the outcome of treatment?”

According to the findings, the answer is no—but there’s more to the story.

“MRSA is a significant problem in clinical medicine, but the question is how significant is it?” asks Dr. Riedel. “Clinicians hear that some antimicrobial susceptibility testing methods may render either slightly higher or lower MICs and they say, well, maybe we’re overcalling or undercalling resistance. Maybe there’s a MIC creep; maybe there will be a treatment failure. So they turn to the laboratory and to the pathologists and ask, ‘What are the MIC distributions for MRSA in the laboratory? What are the susceptibility test methods used in your laboratory? Do we need to use alternative drugs for treatment?’”

Pathologists and laboratory professionals are faced with the difficult task of guiding clinicians through these uncertainties, Dr. Riedel says.

To provide definitive answers to these longstanding questions, Dr. Kalil and coauthor Trevor C. Van Schooneveld, MD, spent nearly two years searching reports of mortality and vancomycin MIC data in humans with S. aureus bacteremia. Aiming to find every article published on vancomycin-resistant S. aureus, the authors searched PubMed, Embase, the Cochrane Library, Evidence-Based Medicine BMJ, and the American College of Physicians Journal Club from inception through April 2014. They examined abstracts presented at annual meetings of the Infectious Diseases Society of America, the Interscience Conference on Antimicrobial Agents and Chemotherapy, and the Society for Healthcare Epidemiology of America. Occasionally, they contacted the authors of old studies for clarification.

“It was a very long process, going through literally thousands of abstracts and references,” Dr. Kalil recalls. In all, 38 studies, encompassing 8,291 patients with SAB, met their inclusion criteria. Then they began the painstaking process of extracting information from the reports.

“There were many, many variables. It was fascinating because other meta-analyses had not really examined these many variables,” Dr. Kalil says. The authors tracked patient age, MIC cutoffs, type of susceptibility assay, heteroresistance test results, methicillin resistance status, duration of bacteremia, intensive care unit exposure, APACHE II score, Charlson score, previous vancomycin exposure, presence of endocarditis, antistaphylococcal drugs used for treatment, vancomycin trough levels, and all-cause mortality.

“We looked at every facet of the problem. Literally, the variables that you see here represent everything you could ever collect from these studies. There’s nothing more that could be extracted,” Dr. Kalil says.

The database they created to house the entries grew until it became unwieldy. “You could scroll down the computer screen, and scroll and scroll, and it just kept going,” he says, laughing. “It’s funny because you think it shouldn’t be too hard. I mean, the studies are already published. All you have to do is a literature search. But this was an exhaustive effort.”

As they parsed the various studies, the authors defined high-vancomycin MIC as values greater than or equal to 1.5 mg/L as measured by the Epsilometer test, or E-test. Clinicians tend to be more likely to explore alternative antimicrobial treatment options when the MIC is 1.5 or higher, Dr. Fey notes.

Subgroup analyses were performed to assess mortality with regard to different MIC cutoffs, microbiology

susceptibility assays, methicillin-resistant status, and the presence of heteroresistance. The authors focused on all-cause mortality, however, as the primary outcome.
Their findings revealed an overall mortality rate of 26.1 percent for the 8,291 episodes of SAB. When all data were pooled together, mortality was 26.8 percent versus 25.8 percent in patients with high- versus low-vancomycin MICs, respectively.

When the authors looked exclusively at the highest-quality studies performed to date, as scored on the Newcastle-Ottawa scale, they calculated an estimated mortality rate of 26.2 percent versus 27.8 percent in patients with high- versus low-vancomycin MICs, respectively.

Of the 7,232 patients with methicillin-resistant S. aureus infections, mortality was 27.6 percent versus 27.4 percent in patients with high- versus low-vancomycin MICs, respectively.

Dr. Riedel and colleagues conducted a study in which they compared the performance of various commercially available susceptibility test methods against the gold standard method, the CLSI broth dilution method (Riedel S, et al. J Clin Microbiol. 2014;52[6]:2216–2222). They found evidence of variation in MICs—specifically, a difference of one doubling dilution—depending on the test method used. The JAMA study noted a similar variation between broth microdilution and E-test results. But within each method, mortality rates remained similar for high- and low-vancomycin MICs, the authors report.

“The interesting concept is that clinicians may look at a MIC of two and say, ‘Well that’s why the patient doesn’t respond.’ My impression from this study is that it may be simplistic to think that it’s the MIC breakpoint. Clinicians need to search for other possible causes of a perceived or real vancomycin treatment failure rather than turning straight to the MIC,” Dr. Riedel says.

The severity index of the disease may play a role, he postulates, or perhaps a treatment failure could result from the inability to achieve an appropriate serum concentration of vancomycin for a particular patient.

The role of microbial pathophysiology and virulence in regard to patient mortality is complex. Previous studies have observed declining growth rates and reduced virulence in bacteria that acquire vancomycin resistance gradually through the stepwise acquisition of compensatory mutations, as might occur in a patient on long-term vancomycin therapy. The JAMA findings point to the same conclusion, Dr. Kalil notes. “The suggestion here is that not every S. aureus with a high MIC is going to be more harmful. Some may even be less harmful. That’s why, when you look at our results, you see a range that goes from better survival to worse survival. When you put the numbers together, no survival difference was observed.”

Dr. Riedel

Though the study focused on patients with bacteremia, the data set included patients with infections at various sites, including the skin, soft tissue, urinary tract, and lungs. “That’s an important point for understanding the relation to mortality rates,” Dr. Riedel explains. “If someone has a soft tissue infection, a deep-seated abscess, or maybe an osteomyelitis and is now bacteremic with MRSA, then it is certainly conceivable that this type of bloodstream infection will be much more difficult to eliminate and could therefore be perceived as vancomycin failure using a standard approach. Some of the other meta-analyses did not make this point.”

Dr. Kalil notes that the authors’ meticulous endeavor almost didn’t pay off. During the scramble to gather data for the study, other meta-analyses were published on the same topic.

“We thought for sure we had been scooped,” Dr. Kalil recalls. “But the fun part is that even though it took us longer than usual, and other studies had been published, we stuck together and made a decision to go for a high-profile journal, because our message has very important implications for both practice and research.”
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