Overprediction of Carbapenemase-Containing Isolates by an Automated AST Instrument's Computer Algorithm

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Guest: Dr. Kathryn Rice is a co-chief resident of the Anatomic and Clinical Pathology Residency program at the University of Maryland Medical Center.

Randye Kaye: Hello, and welcome to this edition of *JALM* Talk from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

In clinical microbiology laboratories, rapidly advancing technologies are available to identify microbial pathogens and inform treatment of infections. Automated platforms that identify microorganisms and define phenotypic antimicrobial susceptibility profiles are commonly used in today's microbiology laboratories. These platforms often include advanced reporting capabilities that analyze minimum inhibitory concentration patterns to predict antibiotic resistance mechanisms.

One such platform, the VITEK 2, is generally accepted as a reliable method for identification and susceptibility testing. However, less is known about the performance of resistance mechanism prediction software. Carbapenemase-producing gram-negative bacteria are an urgent and expanding public health threat. Rapid and accurate identification of carbapenemase-producing organisms has important implications for both individual patient therapy decisions and for infection control efforts to prevent spread within healthcare facilities. When it comes to prediction of carbapenemase production by automated instruments, such as the VITEK 2, previous studies have yielded mixed findings.

In an original article published in the November 2022 issue of *JALM*, the authors compared predictions from the VITEK 2 with the results of a modified carbapenemase inactivation method in an academic medical center laboratory to evaluate the reliability of the VITEK 2 in routine workflow for the detection of carbapenemases.

Today, we're joined by the first author of the article, Dr. Kathryn Rice. Dr. Rice is currently a co-chief resident of the Anatomic and Clinical Pathology Residency program at the University of Maryland Medical Center. She plans to pursue

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a career in academic medicine and forensic pathology. Welcome, Dr. Rice. Let's start with this. What is the VITEK 2 and how is it used in the microbiology laboratory?

Kathryn Rice: So, as you mentioned in the intro, the VITEK 2 is an automated microbial identification and antibiotic susceptibility testing platform developed by bioMerieux. You can get a variety of different cards to use with the machine, and each one of those cards maintains different wells with either biochemical assays or different concentrations of antibiotics.

In our lab, we're using the AST-GN74 card to test for antibiotic susceptibility and gram-negative bacteria. We inoculate those cards with a known suspension of bacteria and then the machine will detect changes in the turbidity of each of the wells. The VITEK 2 then uses this data to assign what we call an MIC, or a minimum inhibitory concentration, to each antibiotic tested. The data is then sent to the advanced expert system, or the AES, which will match the data to its database of other isolates it's tested.

I believe the last time I saw an that advertisement for it, they said they had over 3,600 phenotypes and 55,000 MICs in their database. So, it uses all of that statistical information to predict the most likely phenotype or isolate, and sometimes it gives a definitive answer and sometimes it just says it might be one of these two or three options. But by providing the laboratory with the species identification and antibiotic susceptibilities, it saves us quite a bit of tech time and makes it, along with other products that are similar to it, very popular in microbiology labs.

Randye Kaye: All right, thank you. Now, can you just briefly summarize for our listeners the concept of predicting resistance mechanisms and what are carbapenemases?

Kathryn Rice: So, I guess before we get to what is a carbapenemase, I should probably touch on what is a carbapenem, and it is a kind of antibiotic. It's a subset of something we call the beta-lactam antibiotics, and you can think of it as like this big powerful antibiotic that we use on some of our most resistant and aggressive bacterial infections. So, then the carbapenemase is the enzyme that the bacteria produces in order to break down that antibiotic. There are a couple different mechanisms by which it can do that and many different varieties of carbapenemases.

But the really important thing to remember is that of all the ways a bacteria can be resistant to a carbapenem, the carbapenemase is the one that not only gives the bacterial resistance to carbapenem, but also to the rest of the beta-lactam family, making it an extremely resistant bacteria.

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The VITEK 2 and the AES like we talked about earlier can identify which isolates have that resistance mechanism through a bunch of statistical analysis. But you can also identify them more specifically with genetic testing, or like we do in our lab, phenotypic testing.

Randye Kaye: All right, thank you. So, if there's overprediction of resistance mechanisms, what is the impact on patient care?

Kathryn Rice: I think the root of that question comes down to antibiotic stewardship, which is how we decide as clinicians what antibiotics we want to treat a patient with. We can probably all agree that we want to give patients the antibiotics that are going to work the best against their infections. But what a lot of people don't think about is that we also have to consider what will do the least amount of harm to the patient, whether it is in terms of side effects or how long they're going to have to stay in the hospital.

Additionally, we also want to keep options open for future patients by protecting some of our more powerful antibiotics and not using them unless absolutely necessary. Because every time we use them, we give bacteria the chance to develop resistance to those antibiotics, or similarly, we select for bacteria that have already developed resistance for those antibiotics. So, if I tell a clinician, "Hey, your bacteria contain a carbapenemase. You can no longer use this humongous list of antibiotics, including the carbapenems and the beta-lactams," then I'm forcing that clinician to use one of the very few other strong antibiotic choices. And if I'm doing that consistently because the machines and the tests that I'm running are grossly overpredicting the resistance to the carbapenems, then I am essentially ensuring that we're building even more resistant bacteria in our patient population.

And antibiotic stewardship is important all around, but especially in carbapenemases and carbapenems because they are already one of our last resort kind of drugs.

Randye Kaye: I understand, that makes sense. So, your study compared the performance of the VITEK 2 with the results of a modified carbapenemase inactivation method. So, can you explain how this test works?

Kathryn Rice: Sure. So, you start with a little disc that has been impregnated with a bunch of antibiotics. In this case, we use a meropenem disc. Meropenem being one of the specific kinds of carbapenems. We then put that little disc inside a suspension or a liquid with our bacterial isolate in it and you incubate it for a while, so it gives the bacteria a chance to interact with that antibiotic. We then remove the disc and

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plate it on a plate filled with some sort of bacteria that we know to be susceptible to that antibiotic.

In our lab, we use a specific strain of *E. coli*. Then if my isolate of interest that was in the liquid preparation had created a carbapenemase, that carbapenemase would have digested all of the antibiotic in the disc. So, when I then put that antibiotic on the plate with *E. coli*, there's no antibiotic left in the disc because it's already been digested, and the *E. coli* can grow straight up to it.

However, if my islet in the suspension did not produce a carbapenemase, the antibiotic will still be active and the E. coli will leave a ring of empty space around the disc because it can't grow very close to it.

Randye Kaye: So, let's talk about the study. What were the major findings? How did the VITEK 2 perform?

Kathryn Rice: So, our study found that the VITEK 2 has only a 30.3% positive predictive value in the identification of carbapenemase-containing organisms, which if you want to think about it a different way, means that two-thirds of the time, it's saying that there is a carbapenemase when there isn't one, which as we talked about with antibiotic stewardship, is quite a big deal.

Randye Kaye: Yeah.

Kathryn Rice: Also, interesting to know, it's testing carbapenems in the various wells and then not only gives us the resistance mechanisms but it also tells you all the different MICs it's calculated. And about a sixth of the isolates that it ran and predicted to have a carbapenemase were not even resistant carbapenems in the data that it gave us, so they had susceptible MIC values. We did think a little bit about how that could be and we proposed a hypothesis in the paper but we'd probably don't need to get into the weeds of it right now.

Randye Kaye: Well, they can always read the article, of course. So, based on the results of your study, are you going to continue to use the VITEK 2 in your lab?

Kathryn Rice: Yeah. We are going to continue using the VITEK 2, which probably sounds absurd considering the data I just shared with you.

But the VITEK 2 is actually used for so much more than just carbapenemase testing. And there is really good research out there to show that other facets of microbial testing on the VITEK 2 are accurate, improve turnaround times and overall lab workflow. So, we're definitely going to continue to using it, but we will definitely also continue to do that additional

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layer of phenotypic testing to confirm any time it tells us there's a carbapenemase.

Randye Kaye: All right, thank you. So, one final question, what would you say, what's your hope? What do you hope that readers of *JALM* and listeners of *JALM* Talk will take away from your study?

Kathryn Rice: So, I would say for people that work in a microbiology lab that are using the VITEK 2, we want you to consider using it simply as a screening test and then, as we do in our lab, performing some sort of extra confirmatory testing, whether it be a phenotypic test like the modified carbapenemase inactivation method, or maybe you want to use a genetic test. But for people that don't use the VITEK 2 or maybe don't even work in microbiology, we really just want you to take our paper as a reminder to be vigilant with the instruments that you're using, especially if those are marketed to provide interpretation. We find that it's very important that you understand how it reaches that interpretation and how that may affect the results that you receive, the way you practice, and ultimately, your patients.

Randye Kaye: All right, very interesting. Thank you so much for joining us today.

Kathryn Rice: Thank you.

Randye Kaye: That was Dr. Kathryn Rice from the University of Maryland, describing the *JALM* article "Overprediction of Carbapenemase-Containing Isolates by an Automated AST Instrument's Computer Algorithm." Thanks for tuning into this episode of *JALM* Talk. See you next time, and don't forget to submit something for us to talk about.

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