

**Article:**

Mark J. Biagi, David A. Butler, and Eric Wenzler.

AUC-Based Monitoring of Vancomycin: Closing the Therapeutic Window.

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Guest: Dr. Mark Biagi is an infectious diseases pharmacotherapy fellow at the University of Illinois at Chicago.

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.

Measuring vancomycin levels has long been an important component of laboratory therapeutic drug monitoring. Such measurements are important for obtaining optimal targets serum concentrations for drug dosing, while avoiding vancomycin induced nephrotoxicity. "AUC-Based Monitoring of Vancomycin: Closing the Therapeutic Window" was published in the January 2019 issue of *The Journal of Applied Laboratory Medicine*. This review evaluates shifting the conventional therapeutic drug monitoring approach of vancomycin from trough monitoring, to an area under the curve approach for more appropriate drug dosing.

The first author is Dr. Mark Biagi. Dr. Biagi is currently an infectious diseases pharmacotherapy fellow at the University of Illinois at Chicago. His research interests include in vitro testing of novel agents and antibiotic combinations against multidrug resistant, gram-negative pathogens and optimizing the pharmacokinetics and pharmacodynamics of antimicrobials in special patient populations. Welcome to the podcast, Dr.Biagi.

Dr. Mark Biagi:

Thank you.

Randye Kaye:

To begin with, can you tell me, what is the current state of vancomycin monitoring in clinical practice?

Dr. Mark Biagi:

Well, many institutions and clinicians are still practicing based on the 2009 vancomycin guidelines, which recommend using trough monitoring prior to the fourth dose with targets of 10 to 20 depending on the indication.

However, in the past few years, some institutions have begun the shift towards AUC-based monitoring in place of the long held traditional trough-based monitoring methods.

One thing that I've seen a lot in practice during my time is the belief or maybe it's an assumption that serum trough concentrations of less than 15 are "subtherapeutic," but I can tell there's very few things in the clinical practice that make me cringe more than hearing this. Troughs have been shown time and time again to not be associated with the efficacy of vancomycin. It's entirely possible for a patient to have therapeutic exposure to vancomycin, but have troughs less than 15. I think it happens more commonly than most of us realize.

Unfortunately, what happens in practice far too often with trough monitoring is vancomycin doses are empirically increased if the trough is below 15, which may simply be raising the risk of toxicity but providing no additional benefit if that patient is already achieving acceptable exposure to vancomycin.

Randye Kaye: Is there anything else you want to say about the reasoning for this paradigm shift of moving from trough-based monitoring to AUC-based monitoring?

Dr. Mark Biagi: Yeah, it's been well-established for years that the driver of efficacy against MRSA for vancomycin is the AUC to MIC ratio, typically with a goal of 400. However, for many years, trough monitoring and AUC monitoring have each been plagued by one major limitation apiece. Troughs are particularly useful for safety monitoring as elevated troughs are well associated with nephrotoxicity. But the problem is that time and time again, troughs have not been shown to be associated with the efficacy of vancomycin, like I stated earlier.

On the other hand, AUC monitoring has historically been limited by the opposite problem, actually. We knew what AUC to MIC goal to target for efficacy, but the problem was that there is no well-established AUC cut off associated with toxicity. So, for many years, we were sort of stuck in the middle so to speak between trough monitoring and AUC monitoring. But in recent years, we've had studies come out that have begun to define AUC values that are predictive of nephrotoxicity, which means we can use AUC monitoring now to monitor for both the efficacy and safety of vancomycin.

Randye Kaye: Okay great. So, to perform AUC-based monitoring, what methods are available and what are the strengths and limitations of these methods?

Dr. Mark Biagi: That's a good question that a lot of clinicians are going to be asking in the coming years. It's expected that an update to the 2009 guidelines will be published in the near future and are going to recommend AUC-based monitoring in place of

trough-based monitoring. So it's important for us to understand, how do we do this? How do we calculate AUC? There are three general approaches to do that.

The first method is the Rodvoid method which relates the patient's calculated creatinine clearance to total body clearance of vancomycin. Now, there are more sophisticated approaches to the Rodvoid method, but the utility of the Rodvoid method lies in the fact that it does not require any serum concentrations to calculate it. Which means it's useful for optimizing the empiric dosing of patients with suspected staph aureus infections.

The second approach is the trapezoidal approach which uses two postinfusion serum concentrations to calculate the AUC. Now the trapezoidal approach will give you a more individualized AUC estimate than the Rodvoid method, but it has to be kept in mind that in order to do the trapezoidal approach, you have to have those two serum concentrations, which means it takes time before you are able to perform the trapezoidal approach. You can't use it upfront.

The third method to calculate AUC is the Bayesian approach which is the most complex of the three. In the simplest terms, the Bayesian approach uses both population pharmacokinetics as well as patient-specific pharmacokinetics and serum concentrations.

Similar to the trapezoidal approach, using two postinfusion serum concentrations from the same dosing interval will give you the most robust AUC calculation with the least amount of bias. But unlike the trapezoidal approach, a Bayesian approach allows for any number of concentrations to be obtained at any time postinfusion, and a benefit is that they don't need to be collected during steady state.

On top of that, the Bayesian approach can account for various variables to optimize dosing such as a loading dose and it can also account for disease states such as critical illness, neutropenia, and others when incorporating the population pharmacokinetics into that calculation. The Bayesian approach is accomplished using various software programs, there's many that are available. Some of them are free. Some of them are quite costly. Those ones that come with extra cost are those ones that kind of give you those fancy functions where can you incorporate more population pharmacokinetics like the disease state for example.

Randy Kaye:

So, you may have already covered these, but are there any other limitations you want to talk about when you have

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AUC-based monitoring compared to trough-based monitoring?

Dr. Mark Biagi:

I think the biggest limitation going forward with AUC-based monitoring is going to be implementation. I think almost everyone is comfortable with trough-based monitoring because it's been the standard for so long. So, this change in practice I think is going to be the limitation going forward.

Other limitations with AUC monitoring include increased time requirements in terms of medical staff, pharmacy staff, nursing staff, because of the requirement to draw multiple concentrations and to perform these complex calculations.

The other thing that I think everyone needs to keep in mind is our AUC-based monitoring is really specific to staph aureus. Our AUC to MIC targets are driven from studies looking at staph aureus bacteremia, staph aureus pneumonia, so that AUC to MIC target is specific to staph aureus.

There is some word coming out that starting to define the AUC to MIC goal of enterococcus but before we have more data, we really don't know what that goal is. So, if you're treating a patient without staph aureus, it's important to keep in mind that these numbers we keep talking about are specific to staph aureus.

Randye Kaye:

Okay, thank you. So, a lot of changes possibly ahead. Do you believe that trough-based monitoring will have any clinical utility in the future or do you think AUC-based monitoring will completely eliminate the need for trough-based monitoring?

Dr. Mark Biagi:

That's another really good question as we talk about AUC monitoring. I don't think it would be appropriate to completely abandon the trough-based monitoring that we're used to. Given the increased cost and time requirements that are likely to be associated with AUC monitoring, trough monitoring alone may still be appropriate for patients with mild to moderate infections, such as skin and soft tissue infections. And with the long-standing track record and clinical comfortability with trough monitoring, it may still have a role alongside AUC monitoring in patients with severe infections who are also at an increased risk of nephrotoxicity of baseline, such as patients with underlying kidney disease or severely ill patients who are receiving multiple nephrotoxic agents in addition to vancomycin.

Randye Kaye:

All right, thank you and last question. Any final thoughts for our listeners?

Dr. Mark Biagi:

I think the take home message here is that the shift to AUC monitoring is on the horizon. It's coming and preparing for it now is going to be the key to efficient implementation. So, each institution needs to think about how they can best make this change at their site and I think one of the very important things to take home from this is that providing staff education for this change and why we're doing this, how we're going to do this, is going to be of paramount importance get everyone on the same page with this anticipated change.

Randye Kaye:

That was Dr. Mark Biagi from the University of Illinois at Chicago talking about "AUC-Based Monitoring of Vancomycin: Closing the Therapeutic Window" from the January 2019 issue of JALM. Thanks for tuning in for "JALM Talk." See you next time and don't forget to submit something for us to talk about.