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Vancomycin Therapeutic Drug Monitoring – Less May be More

by Tom Dilworth, PharmD

Vancomycin has been the mainstay of empiric gram-positive therapy among hospitalized patients for decades.[1-3] Yet, as an antibiotic, vancomycin is severely limited by its slow bactericidal activity, poor treatment response, high rates of infection relapse and – most importantly for pharmacists – its narrow therapeutic index and highly variable inter-patient pharmacokinetics (e.g. protein binding, volume of distribution) that require therapeutic drug monitoring (TDM).[1,4-7] Most experienced inpatient pharmacists can recount innumerable cases of unpredictable vancomycin serum exposure, almost always among patients at the extremes of body weight and/or organ function. Pharmacists may spend an inordinate amount of time managing patients' vancomycin exposure for little appreciable gains in patient care. Herein I will advance three ideas for discussion: 1) micromanaging patients' serum vancomycin exposure to achieve a pharmacokinetic goal does not universally enhance vancomycin efficacy, 2) many patients on empiric vancomycin do not require the drug beyond 48-72 hours, and 3) we should shift our focus toward de-escalating patients off empiric vancomycin therapy – both those who no longer have an indication for vancomycin and those who may benefit from alternative antibiotic therapy. By making vancomycin stewardship a priority we can reduce the number of patients requiring vancomycin TDM and invest pharmacist time into other patient care activities.

Vancomycin is one of the most commonly prescribed antibiotics in the United States (U.S.).[8] Its upward trend in use started in the late 1980's and early 90's[9]; however, contemporary data indicate skyscraping vancomycin utilization continues despite declining rates of methicillin-resistant *Staphylococcus aureus* (MRSA).[8,10-12,†] In many hospitals, pharmacists are consulted to manage patients' vancomycin dosing and pharmacokinetics. Remarkably, despite years of clinical use and untold scientific publications, there is no high-quality consensus on how to dose and monitor vancomycin. What is unequivocal is that the 24-hour area under the concentration time curve (AUC) is the pharmacokinetic parameter predictive of vancomycin efficacy against *S. aureus in vitro*.[13] A vancomycin AUC of 400mg/L*hour is most often cited as the AUC necessary for efficacy, but the target AUC may be less than that *in vivo*.[14] Historically, a standard regimen of vancomycin 1 gram every 12 hours was prescribed for patients with normal renal function, with dose reductions for those with impaired renal function.[15] Serum TDM was not routine and when done it was a mix of peaks, troughs, and peaks with troughs. Historical goal trough levels were often 5-10mg/L, much lower than current trough targets. As TDM became more available and common, dosing nomograms were developed to allow for patient-specific dosing in an effort to optimize vancomycin exposure for all patients.

Following observance of high vancomycin clinical failure rates despite ostensibly "susceptible" organisms, and with few alternative antibiotic options, the 2009 vancomycin consensus guidelines advocated for a target trough of 15-20mg/L for patients with severe infections.[16] The guidelines suggested that 15-20mg/L was a surrogate for an AUC of 400mg/L*hr, claiming at the time that AUC calculations were too cumbersome for widespread use. Pharmacokinetic/pharmacodynamic data supporting the 2009 guideline recommendations were derived almost entirely from study of *Staphylococcus aureus*; a fact unacknowledged at the time but lucidly declared in the 2019 draft version of the impending 2020 guideline update. The 2009 recommendation for increased vancomycin exposure was based on scant human data and, seemingly, without extensive consideration of the toxicity widespread acceptance of this recommendation could beget – other than casually stating "…there are no data indicating that achieving these trough concentrations over time is well tolerated and safe." The idea that securing a goal trough of 15-20mg/L, or an AUC of ~400mg/L*hour, will optimize vancomycin efficacy and improve patient outcomes remains largely unchallenged. This despite at least 12 studies indicating there is no relationship between a trough of 15-20mg/L and treatment success.[17-28] Recent AUC data arrive at the same conclusion.[14,29-33] Yet the 2019 guidelines draft included a recommendation for determining AUC for all patients on vancomycin; either by inserting one serum level into a population pharmacokinetic model to estimate the AUC or by gathering two levels during the same dose interval to estimate the AUC using the trapezoidal rule.[34] The solitary argument supporting vancomycin AUC determinations is that it will result in less acute kidney injury (AKI) – by way of lower vancomycin exposure. However, the studies supporting this claim examined AKI in general, usually by

[†] While reducing the amount of empiric vancomycin use is prudent, requiring further study, it is not the subject of this column. Given contemporary rates of MRSA empiric MRSA coverage is still warranted.

elevations in serum creatinine rather than vancomycin attributable AKI or severe AKI requiring renal replacement therapy.[15,35-37] A brief elevation in serum creatinine that resolves may not be clinically meaningful and the specificity of serum creatinine for identifying reduced renal function is low.[38] A recent study found much lower rates of attributable AKI in intensive care unit (ICU) patients on vancomycin than previously reported.[39] Additionally, severe AKI in this population was attributable to vancomycin only if the trough was greater than 20mg/L.

Two issues with the argument that using AUC-based vancomycin monitoring reduces AKI are 1) whether patients need the drug beyond a brief empiric duration and 2) whether AUC calculations are necessary to reduce vancomycin exposure – or if this could be done from the start. The idea of obtaining drug levels within the first 24-48 hours to calculate an AUC for all patients on empiric vancomycin seems illogical and wasteful. Acutely ill patients often present in a dynamic physiological state rendering initial pharmacokinetic data unsuitable to inform subsequent dosing decisions once these physiologic alterations resolve. Despite claims that the relationship between trough and AUC is variable, it does hold for many patients.[40-44] By drawing on decades worth of trough data another strategy emerges: reducing the target trough (e.g. 10-15mg/L) and dosing intensity to minimize AKI risk. Indeed, this approach is supported by new data showing lower vancomycin MICs among MRSA in the U.S. with the community-acquired, USA300 MRSA strain becoming endemic in the population and overtaking certain, more resistant hospital strains.[45] The vancomycin MIC necessary to inhibit 90% of *S. aureus* (MIC_{90}) in the U.S. is believed be 1mg/L and MICs of 2mg/L may represent laboratory measurement error.[34]

The prosaic nature of vancomycin pharmacokinetic management can belie just how often this drug is prescribed as empiric therapy. It is worth reiterating that vancomycin is one of the most commonly prescribed antibiotics in U.S. hospitals.[8] A 2014 analysis found over 10% of hospitalized patients were prescribed vancomycin.[46] Moreover, 35.7% of these vancomycin prescriptions had potential for improvement – most commonly, diagnostic cultures revealed no gram-positive organism (21.6%) but patients still received vancomycin for more than 72 hours. A recent study of over 3,500 patients with hospital-acquired pneumonia found approximately 5% had MRSA pneumonia.[47] The authors reported that 94% of the cohort was over-treated with vancomycin. Additionally, in a 19-month study of over 12,000 ICU patients at a tertiary care facility only 3.7% of had a positive MRSA nasal swab (indicating nasal MRSA colonization).[48] However, of the over 11,000 patients with a negative nasal swab and no evidence of a MRSA infection, 36.3% received vancomycin. Among patients with a negative MRSA nasal swab started empirically on vancomycin, vancomycin continued for more than 3 days in 20.6% of patients; a median of 2 additional days of vancomycin therapy. A Brazilian study demonstrated, similarly, that almost 70% of patients initiated on vancomycin at a university hospital received the drug for more than 3 days without an indication for vancomycin use.[49] In a small sample of vancomycin-treated patients requiring TDM, only 5% had a confirmed MRSA infection.[50] The available evidence suggests empiric vancomycin use is common but many patients don't require therapy beyond 48-72 hours. Pharmacists and clinicians should examine the following questions every day for patients on vancomycin:

1. Why is the patient on vancomycin?
2. Does the patient still need vancomycin today?
3. If vancomycin is indicated, is the patient clinically responding to the current regimen without accompanying toxicity?

Utilizing a vancomycin pharmacokinetic consultation to perform a vancomycin "timeout" – a formal re-assessment of the need for vancomycin therapy – was shown in a recent, observational study to reduce vancomycin consumption.[51] Further study is needed to advance this idea within our profession, but it stands to reason that future studies would yield similar results. Using MRSA nares screening alongside additional diagnostic and culture data should allow for safe discontinuation of empiric vancomycin in many patients.[52-55] Vancomycin can be successfully discontinued in culture-negative pneumonia without affecting mortality while reducing length of stay and AKI incidence.[56,57] The negative predictive value (NPV) of an MRSA nares swab is remarkably high, especially in areas with low prevalence of MRSA pneumonia. However, there is an inverse relationship between its NPV and MRSA pneumonia prevalence. Many studies looking at the NPV of MRSA nares had MRSA pneumonia prevalence rates below 10%. To the contrary, a study of medical ICU patients at a large U.S. tertiary care facility found a NPV of only 84.4% with a 13.4% rate of MRSA pneumonia.[58] Save that study, the preponderance of evidence suggests the NPV of MRSA nares is high. A recent meta-analysis including over 5,000 patients and a pooled MRSA pneumonia prevalence of 10% demonstrated a NPV of 96.5%.[53] Given these data, pharmacists should collaborate with local providers to develop protocols that leverage MRSA nares screening and diagnostic cultures to reduce unnecessary vancomycin use. The impact of such protocols can be examined by measuring local vancomycin consumption data (e.g. days of antibiotic therapy per 1,000 days present).

Considering the previously noted limitations of vancomycin therapy, it's important to acknowledge that our anti-MRSA armamentarium has expanded greatly in the last few years. This includes a much better command of how to effectively dose daptomycin, the use of ceftaroline and an ever-growing understanding of combination antibiotic therapy.[59-61] With this knowledge and experience it is sensible to continually assess patients who require vancomycin therapy for appropriate clinical response and to recommend changing antibiotic therapy for any patient failing to respond to vancomycin in a timely manner. Some patients may benefit from alternative antibiotic therapy from the start.[60-61]

Ultimately, empiric vancomycin is prescribed often. We must be judicious in our application of forthcoming vancomycin monitoring guidance in favor of prudent vancomycin use and TDM with a primary focus on stewardship. Many patients don't need this drug more than 48-72 hours. For those patients, pharmacokinetic monitoring

offers little to no value and adds expense. Time spent on unnecessary vancomycin monitoring prevents pharmacists from focusing on other valuable patient care activities. Additionally, we must abandon the idea that vancomycin efficacy is predicated largely on a target serum exposure. We should minimize vancomycin exposure in order to minimize toxicity risk – this can be done from the outset by de-intensifying initial dosing. And finally, we must consider alternative therapy in lieu of increasing the vancomycin dose for those patients with suboptimal clinical response. For this beleaguered antibiotic less may be more.

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