JPPT | Editorial

Vancomycin Therapeutic Drug Monitoring in Children: New Recommendations, Similar Challenges

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The American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists have recently published revised guidelines for the therapeutic monitoring of vancomycin. Previous iterations of the guideline largely focused on targeting vancomycin trough concentrations (VTCs) in the range of 15 to 20 mg/L for therapeutic efficacy. The revised guidelines shift the focus of therapeutic monitoring directly to AUC/MIC-based therapeutic monitoring for children, with a suggestion of a goal AUC/MIC 400 to 800. The primary hesitation in applying these recommendations to children stems from the absence of pediatric clinical data demonstrating correlations with clinical outcomes and either VTC or AUC and no benefit in other secondary outcomes (e.g., recurrence, duration of bacteremia). One can glean indirectly from this that such aggressive dosing and monitoring strategies are unnecessary to achieve therapeutic success in the majority of children with serious methicillin-resistant *Staphylococcus aureus* infections. Providers should carefully weigh the potential unknown benefits of targeting vancomycin AUC 400 to 800 mg*hr/L in children with the known risks of acute kidney injury associated with increasing the dose of vancomycin as well as the substantial time, effort, and costs of this process.

ABBREVIATIONS AKI, acute kidney injury; AUC, area under the curve; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; VTC, vancomycin trough concentration

KEYWORDS AKI; AUC; editorial; guidelines; pediatrics; therapeutic drug monitoring; vancomycin, vancomycin trough

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Since emerging as a major community-acquired pathogen in the early 2000s, methicillin-resistant *Staphylococcus aureus* (MRSA) has continued to cause substantial morbidity in the pediatric population. Vancomycin is generally regarded as the drug of choice for the empiric management of known/suspected serious *S aureus* infection in children. The American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists have recently published revised guidelines for the therapeutic monitoring of vancomycin.[1] Previous iterations of this guideline largely focused on targeting vancomycin trough concentrations (VTCs) in the range of 15 to 20 mg/L for therapeutic efficacy based primarily on limited observational studies in adults.[2] This VTC range was believed to approximate an AUC to MIC ratio > 400. Although the original guidelines acknowledged the limitations in the available data, at many institutions it became routine practice for providers to perform dose adjustments to achieve this therapeutic window. The revised guidelines shift the focus of therapeutic monitoring directly to AUC/MIC. AUC can be mathematically derived through a variety of means, each with their own drawbacks. The current guidelines advocate for Bayesian-derived AUC monitoring to provide a more accurate picture of drug exposure. The authors have presented a very exhaustive review of the literature and should be congratulated for this body of work on such a challenging topic. Although the guidelines "suggest" vancomycin AUC-based therapeutic monitoring for children rather than making firm recommendations, significant challenges and questions exist in applying these pharmacokinetic goals derived from primarily studies of adults to the general pediatric population.

The primary hesitation in applying these recommendations to children stems from the absence of pediatric clinical data demonstrating improved overall outcomes for any specific vancomycin pharmacokinetic goal. Numerous investigators have previously studied vancomycin pharmacokinetics in children with regards to dosing, VTC, and AUC.[3–7] Although these are important data, the absence of correlations with clinical outcomes and either VTC or AUC is a significant limitation of these prior studies. In general, achieving a specific pharmacokinetic goal should not be equated with therapeutic success; most prior pediatric studies fail to address the simple utility of VTC or AUC/MIC in therapeutic outcomes. The authors suggest vancomycin be administered to achieve a target AUC of at least 400 mg*hr/L,

but < 800 mg*hr/L. In a series of MRSA bacteremia at Cincinnati Children's, Hahn et al[8] reported no difference in treatment failure rates among children achieving vancomycin AUC/MIC > 400 compared with those with AUC/MIC < 400; additionally, there was no benefit in terms of other secondary outcomes (recurrence, duration of bacteremia, etc).[8] There was a suggestion, in this study, that higher AUC/MIC was associated with acute kidney injury (AKI). More recently, Regen et al[9] did not find a significant association with treatment success and vancomycin AUC/MIC ≥ 400 in children with MRSA bacteremia; adverse effects such as AKI were not addressed in this study. Admittedly, a Bayesian approach to AUC calculation was not performed by these investigators and thus may have produced inaccurate estimations of vancomycin exposure. However, in a recent well-designed multicenter study in adults that used Bayesian AUC estimation, higher AUC/MIC did not reduce the risk of treatment failure but did substantially increase the risk of AKI.[10] Interestingly, these authors found that the highest rates of morbidity-free treatment success were among subjects in the lowest 2 quintiles of vancomycin exposure (AUC ≤ 515 mg*hr/L), although they were unable to define a lower boundary for treatment success.

Moreover, in studies examining vancomycin dosing and pharmacokinetics in children, 50% to 80% of children fail to achieve pharmacokinetic goals by either VTC or AUC.[8,11] Despite this high rate of "suboptimal therapy," widespread therapeutic failures have not been reported in children. One can glean indirectly from this that such aggressive dosing and monitoring strategies are unnecessary to achieve therapeutic success in the majority of children. One may ask, "Why would an AUC/MIC > 400 be beneficial in adults but not children?" This discrepancy in correlating outcomes of serious MRSA infections with vancomycin pharmacokinetic targets is likely a consequence of the lower rate of comorbidities in children compared with adults, as well as differences in disease presentation (as acknowledged by the guideline authors). The most common form of invasive staphylococcal infection in children is osteoarticular infections; for such infections that are frequently associated with purulent foci, source control likely plays a large role in achieving good outcomes.[12] In the adult studies of MRSA bacteremia, less than 10% to 15% of patients have bone or joint infections. In contrast, infective endocarditis is noted in a high proportion of adults (14% to 20% of patients)[13] with MRSA bacteremia, but this is not the case in children (1.4% in 1 recent study).[14] Furthermore, the duration of bacteremia in *S aureus* infection is much shorter in children (median duration of 2 days in some studies[15]) than in adults (6 days[16]) and mortality much lower (1% to 4.8% vs 10% to 20%[15–18]). Thus, although there may be theoretical benefit to achieving the pharmacokinetic parameters as outlined in the guidelines, it is unlikely to have a substantial effect in the pediatric population. The guidelines as written suggest that AUC targets of 400 to 800 mg*hr/L should be sought for all children receiving vancomycin. We believe (based on the evidence presented [or lack thereof]) that seeking to achieve such pharmacokinetic targets is unnecessary to achieve therapeutic success in the majority of children with serious MRSA infections. This is particularly true in the situation in which a child is improving on therapy without achieving the VTC or AUC values suggested as beneficial (in which case, we would not recommend performing dose adjustments).

As with any medication, aggressive dosing of vancomycin raises concerns about the potential for increasing drug toxicity. In 1 single center retrospective study, 19.4% of children receiving vancomycin developed AKI.[11] AKI associated with vancomycin is typically multifactorial and may be influenced by the specific subpopulation, exposure to concomitant nephrotoxic medications, and severity of illness.[19–21] Beyond the short-term implications of diminished renal function, stage 2 or 3 AKI was associated with increased mortality in children in a large multinational study.[22] Although numerous factors can contribute to AKI, previous single-center pediatric studies have shown that vancomycin troughs in excess of 10 to 15 mg/L, dosing ≥ 80 mg/kg/day and longer durations of vancomycin therapy are associated with AKI.[23] Other investigators examining children receiving vancomycin for any indication reported that VTC > 15 mg/mL and/or AUC/MIC ≥ 800 were independently associated with a > 2.5-fold increased risk of nephrotoxicity.[24] Although we agree with the authors of the guideline that "vancomycin exposure should be optimally maintained below the thresholds for AUC of 800 mg*hr/L and trough concentrations of 15 mg/L to minimize AKI," it is likely that providers aggressively seeking to achieve AUC 400 to 800 mg*hr/L will inadvertently "over-shoot the mark" contributing to unnecessary nephrotoxicity. Drug adverse events can likely be minimized by not performing dose escalations in patients who are otherwise doing well on therapy. Moreover, careful monitoring of renal function should occur in all patients receiving vancomycin.

As written, the guidelines state that "therapeutic monitoring may begin within 24–48 hours of initiation of vancomycin therapy for serious MRSA infections." One challenge with this is that very early in the course of therapy, the provider is unaware if the patient has MRSA or not (though they might suspect a gram-positive etiology). For example, in the patient with osteomyelitis whose blood cultures are negative, a culture positive for MRSA from material obtained at surgery or through a percutaneous aspiration may not be known for several days after admission. In fact, the vast majority of children started empirically on vancomycin will ultimately not be found to have a serious MRSA infection. Although vancomycin has activity against methicillin-susceptible *S aureus* (MSSA), β-lactams are

clearly the agents of choice.[25] A number of investigators have reported recent declines in pediatric MRSA across the country, particularly among invasive infections;[26–28] some centers have reported a rise in MSSA invasive infections concomitant with the decline in MRSA.[29] Thus, even in situations in which the microbiologic etiology is almost certainly *S aureus* (such as osteomyelitis), the likelihood of the infection being caused by MSSA is higher than that of MRSA. Therefore, if therapeutic drug monitoring and dose adjustments are being performed in the first 24 to 48 hours of therapy for all children receiving vancomycin, then it is likely that the vast majority of these interventions will be occurring in children without MRSA infections. Such procedures will produce additional unnecessary laboratory costs and opportunity costs of personnel (e.g., laboratory technicians, nursing, pharmacy). Some investigators have suggested not performing therapeutic drug monitoring of vancomycin in children in the first 72 hours of therapy except in a subset of cases such as those with critical illness or pre-existing renal dysfunction;[30] such an approach could conceivably reduce costs and unnecessary laboratory testing. These same investigators also noted that 75% of children receiving a vancomycin dose of 55 to 65 mg/kg/day achieved an $AUC_{24} \geq 400$ mg*hr/L using Bayesian analyses with a median of 0 dose adjustments. Thus, even assuming that achieving such pharmacokinetic goals is helpful in children, these data suggest the majority of children will not need dosage adjustment and that obtaining such information will not alter management.

This is not to say that achieving AUC/MIC goals would not be beneficial in selected pediatric patients. There are situations for which aggressive dosing/therapeutic drug monitoring may be beneficial including MRSA necrotizing pneumonia, the rare case of a MRSA CNS infection, when source control cannot be achieved or when a patient fails to improve despite optimal source control (albeit there is no clinical data for these practices either). Additionally, therapeutic drug monitoring is very important in the setting of known renal injury/insufficiency.

In conclusion, based on the lack of clinical data, providers should carefully weigh the potential unknown (or even theoretical) benefits of targeting vancomycin AUC 400-800 mg*hr/L in children with the known risks of AKI associated with increasing the dose of vancomycin as well as the substantial time, effort, and costs of this process. Additional research is sorely needed on this important topic, which can hopefully provide the evidence upon which more firm guidance can be developed.

ARTICLE INFORMATION

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REFERENCES

1. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm.* 2020;77(11): 835–864.
2. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adults summary of consensus recommendations from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Pharmacotherapy.* 2009;29(11):1275–1279.
3. Chhim RF, Arnold SR, Lee KR. Vancomycin dosing practices, trough concentrations, and predicted area under the curve in children with suspected invasive staphylococcal infections. *J Pediatric Infect Dis Soc.* 2013;2(3):292. doi:10.1093/jpids/pit032
4. Frymoyer A, Guglielmo BJ, Hersh AL. Desired vancomycin trough serum concentration for treating invasive methicillin-resistant Staphylococcal infections. *Pediatr Infect Dis J.* 2013;32(10):1077–1079.
5. Frymoyer A, Hersh AL, Benet LZ, Guglielmo BJ. Current recommended dosing of vancomycin for children with invasive methicillin-resistant *Staphylococcus aureus* infections is inadequate. *Pediatr Infect Dis J.* 2009;28(5):398–402.
6. Le J, Bradley JS, Murray W, et al. Improved vancomycin dosing in children using area under the curve exposure. *Pediatr Infect Dis J.* 2013;32(4):e155–e163.
7. Tkachuk S, Collins K, Ensom MHH. The relationship between vancomycin trough concentrations and AUC/MIC ratios in pediatric patients: a qualitative systematic review. *Paediatr Drugs.* 2018;20(2):153–164.
8. Hahn A, Frenck RW Jr, Allen-Staat M, et al. Evaluation of target attainment of vancomycin area under the curve in children with methicillin-resistant *Staphylococcus aureus* bacteremia. *Ther Drug Monit.* 2015;37(5):619–625.

9. Regen RB, Schuman SS, Chhim RF, et al. Vancomycin treatment failure in children with methicillin-resistant *Staphylococcus aureus* bacteremia. *J Pediatr Pharmacol Ther.* 2019;24(4):312–319.
10. Lodise TP, Rosenkranz SL, Finnemeyer M, et al. The Emperor's new clothes: prospective observational evaluation of the association between initial vancomycin exposure and failure rates among adult hospitalized patients with methicillin-resistant *Staphylococcus aureus* bloodstream infections (PROVIDE). *Clin Infect Dis.* 2020;70(8):1536–1545.
11. Knoderer CA, Nichols KR, Lyon KC, Veverka MM, Wilson AC. Are elevated vancomycin serum trough concentrations achieved within the first 7 days of therapy associated with acute kidney injury in children? *J Pediatric Infect Dis Soc.* 2014;3(2):127–131.
12. McNeil JC, Vallejo JG, Kok EY, et al. Clinical and microbiologic variables predictive of orthopedic complications following *S. aureus* acute hematogenous osteoarticular infections in children. *Clin Infect Dis.* 2019;69(11):1955–1961.
13. Holland TL, Arnold C, Fowler VG Jr. Clinical management of *Staphylococcus aureus* bacteremia: a review. *JAMA.* 2014;312(13):1330–1341.
14. Hsu AJ, Hamdy RF, Huang Y, et al. Association between vancomycin trough concentrations and duration of methicillin-resistant *Staphylococcus aureus* bacteremia in children. *J Pediatric Infect Dis Soc.* 2018;7(4):338–341.
15. McNeil JC, Kok EY, Forbes AR, et al. Healthcare-associated *Staphylococcus aureus* bacteremia in children: evidence for reverse vancomycin creep and impact of vancomycin trough values on outcome. *Pediatr Infect Dis J.* 2016 35(3):263–268.
16. Charles PG, Ward PB, Johnson PD, et al. Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate *Staphylococcus aureus*. *Clin Infect Dis.* 2004;38(3):448–451.
17. Moore CL, Osaki-Kiyan P, Haque NZ, et al. Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant *Staphylococcus aureus* with a high vancomycin minimum inhibitory concentration: a case-control study. *Clin Infect Dis.* 2012;54(1):51–58.
18. Hamdy RF, Hsu AJ, Stockmann C, et al. Epidemiology of methicillin-resistant *Staphylococcus aureus* bacteremia in children. *Pediatrics.* 2017;139(6):e20170183. doi:10.1542/peds.2017-0183
19. Slater MB, Gruneir A, Rochon PA, et al. Identifying high-risk medications associated with acute kidney injury in critically ill patients: a pharmacoepidemiologic evaluation. *Paediatr Drugs.* 2017;19(1):59–67.
20. Totapally BR, Machado J, Lee H, et al. Acute kidney injury during vancomycin therapy in critically ill children. *Pharmacotherapy.* 2013;33(6):598–602.
21. Constance JE, Balch AH, Stockmann C, et al. A propensity-matched cohort study of vancomycin-associated nephrotoxicity in neonates. *Arch Dis Child Fetal Neonatal Ed.* 2016;101(3):F236–F243.
22. Kaddourah A, Basu RK, Bagshaw SM, et al. Epidemiology of acute kidney injury in critically ill children and young adults. *N Engl J Med.* 2017;376(1):11–20.
23. Sinclair EA, Yenokyan G, McMunn A, et al. Factors associated with acute kidney injury in children receiving vancomycin. *Ann Pharmacother.* 2014;48(12):1555–1562.
24. Le J, Ny P, Capparelli E, et al. Pharmacodynamic characteristics of nephrotoxicity associated with vancomycin use in children. *J Pediatric Infect Dis Soc.* 2015;4(4):e109–e116.
25. McMullan BJ, Bowen AC, Blyth CC, et al. The epidemiology and mortality of *Staphylococcus aureus* bacteremia in a prospective cohort of Australian and New Zealand children. *JAMA Pediatrics.* 2016;170(10):979–986.
26. Sutter DE, Milburn E, Chukwuma U, et al. Changing susceptibility of *Staphylococcus aureus* in a US pediatric population. *Pediatrics.* 2016;137(4):e20153099. doi:10.1542/peds.2015-3099
27. Acree ME, Morgan E, David MZ. *S. aureus* infections in Chicago, 2006–2014: increase in CA MSSA and decrease in MRSA incidence. *Infect Control Hosp Epidemiol.* 2017;38(10):1226–1234.
28. Hulten KG, Mason EO, Lamberth LB, et al. Analysis of invasive community-acquired methicillin-susceptible *Staphylococcus aureus* infections during a period of declining CA-MRSA infections at a large children's hospital. *Pediatr Infect Dis J.* 2018;37(3):235–241.
29. Kok EY, Vallejo JG, Sommer LM, et al. Association of vancomycin MIC and molecular characteristics with clinical outcomes in methicillin-susceptible *Staphylococcus aureus* acute hematogenous osteoarticular infections in children. *Antimicrob Agents Chemother.* 2018;62(5):e00084–00018.
30. Olson J, Hersh AL, Sorensen J, et al. Intravenous vancomycin therapeutic drug monitoring in children: evaluation of a pharmacy-driven protocol and collaborative practice agreement [published online ahead of print July 25, 2019]. *J Pediatric Infect Dis Soc.* doi:10.1093/jpids/piz036