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ORIGINAL RESEARCH

Necessity of vancomycin trough concentrations to manage uncomplicated acute bacterial skin and skin structure infections: a laboratory stewardship analysis

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Abstract

Background: Recent recommendations by the American Society of Health System Pharmacists and Infectious Disease Society of America have provided guidance regarding vancomycin dosing and monitoring in serious infections (including methicillin-resistant *Staphylococcus aureus*); however, trough monitoring for uncomplicated acute bacterial skin and skin structure infections (ABSSSI) were not addressed. Vancomycin use appears to lead to a low incidence of acute kidney injury with short durations and a low trough goal (10–15 mg/L). Nevertheless, clinical studies have found no difference in clinical outcomes for ABSSSI regardless of vancomycin level. Therefore, it can be posed whether trough monitoring is necessary in this patient population.

Methods: This is a retrospective cohort study comparing vancomycin therapy duration for ABSSSI in adult, general medicine patients who received scheduled vancomycin with an initial creatinine clearance rate of ≥50 mL/minute and had at least one vancomycin trough. The objective of this study was to determine if vancomycin treatment duration differs for patients with ABSSSI with a subtherapeutic vancomycin trough (ST; <10 mg/L) compared with therapeutic trough (TT; ≥10 mg/L).

Results: There were 39 (67.2%) patients with ST compared with 19 (32.8%) with TT. A similar median vancomycin treatment duration for ST (48.25 hours) and TT (59.5 hours; p=0.65) was found. There was no statistical difference for hospital duration, time from last trough to vancomycin discontinuation, or incidence of acute kidney injury (p>0.05 for all).

Conclusion: Patients with ST and TT had similar vancomycin durations and clinical outcomes. It may be prudent for institutions to address vancomycin trough laboratory stewardship and associated costs.

Keywords: abscess, antimicrobial stewardship, cellulitis, drug monitoring, skin and connective tissue diseases, vancomycin.

Citation

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Introduction

Vancomycin is a glycopeptide antibiotic frequently used for the treatment of acute bacterial skin and skin structure infections (ABSSSI). In 2009, the American Society of Health System Pharmacists and Infectious Disease Society of America (IDSA) provided guidelines for vancomycin dosing and monitoring. However, these guidelines did not provide specific trough goals for uncomplicated ABSSSI but stated that, for uncomplicated bacterial infections, providers should aim for a trough goal of at least 10 mg/L (expert opinion, level of evidence and grade: IIIB) to decrease the risk of vancomycin-intermediate *Staphylococcus aureus*.[1] The 2009 guidelines stated that monitoring of vancomycin troughs is not necessary for treatment durations of less than 3–5 days (level of evidence and grade: IIb).[1] In 2020, the American Society of Health System Pharmacists/IDSA updated their guidelines recommending a ratio of 24-hour area

under the curve to minimum inhibitory concentration of between 400 and 600 mg×h/L for serious methicillin-resistant *S. aureus* (MRSA) infections.[2] Similar to the 2009 guidelines, uncomplicated ABSSSI management was not specifically discussed.[2]

Several clinical studies reported no difference in clinical outcome for vancomycin concentrations below and above 10 mg/L, as the mean vancomycin treatment duration was longer (7.0–7.8 days) than the 3–5 day recommendation for monitoring trough concentrations.[3–6] Furthermore, vancomycin-induced acute kidney injury (AKI) has been a potential concern. However, incidence has appeared to be low in patients with trough goals <20 mg/L, those with no baseline renal impairment, those receiving short courses of vancomycin therapy (<7 days), or in those not receiving concomitant nephrotoxic agents.[7–12] Finally, the guidelines recommend trough goals >10 mg/L to prevent potential vancomycin resistance; however, the literature supporting this recommendation is based on administering vancomycin for severe infections and managing MRSA and for extended therapy durations (over 14 days).[1]

As healthcare institutions continually look for measures to reduce costs, laboratory stewardship should be a consideration. The Society of Hospital Medicine includes the avoidance of repetitive complete blood counts and chemistry testing in stable patients as part of its 'Choose Wisely' campaign.[13] Overutilization of inpatient laboratory tests is well documented, and the overutilization of tests can lead to costly downstream spending.[14]

With minimal clinical data available to support vancomycin trough monitoring for short durations of therapy, there may be decreased vancomycin trough concentration utility in certain clinical conditions. The objective of this study was to determine if vancomycin treatment duration differs for patients with ABSSSI with a sub-therapeutic vancomycin trough (ST; <10 mg/L) compared with therapeutic trough (TT; ≥10 mg/L).

Methods

This was a retrospective cohort study of adult patients admitted to a general medicine unit at Mount Sinai Hospital, an urban, 319-bed, teaching hospital (Chicago, IL) and who received vancomycin for the management of an uncomplicated ABSSSI from January 1, 2016, through December 31, 2018. During this period, recommended monitoring for vancomycin for ABSSSI at our institution included dosing towards a low trough goal (10–15 mg/L). A vancomycin trough was defined as a level having been obtained approximately 60 minutes before the fourth dose to be administered. Dosing recommendations and adjustments were led by clinical pharmacists at the study hospital. Eligible patients had to have an admission creatinine clearance rate (CrCl, Cockcroft–Gault) ≥50 mL/minute, received scheduled vancomycin, and had a recorded trough (defined as a concentration obtained within 90 minutes before the third or fourth dose). Exclusion criteria were vancomycin administration duration of more than 5 days, documented trough goal of 15–20 mg/L, or AKI (serum creatinine >120% baseline) that did not resolve within 24 hours of initial vancomycin administration. A complete description of inclusion and exclusion criteria is presented in Table 1. The institutional review board at Mount Sinai Hospital (Study 19-02) approved this study. At this institution, the vancomycin policy recommends trough levels before the fourth or fifth dose regardless of underlying indication.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Adult general medicine patients • Initial creatinine clearance (Cockroft–Gault) ≥50 mL/minute • Received scheduled vancomycin • At least one obtained vancomycin trough (obtained within 90 minutes before the third or fourth dose)	• Acute kidney injury (serum creatinine >1.2× baseline) without 24-hour resolution • Received vancomycin for >5 days • Confirmed methicillin-resistant *Staphylococcus aureus* infection • Patient required intensive care unit admission or transfer • Patient required emergent surgery for source control or limb amputation • Vancomycin trough goal 15–20 mg/L • Peripheral arterial or vascular disease • Infections due surgical or post-traumatic site, burns, diabetic foot ulcers, wounds, or chronic skin ulcers • Pregnancy • Vancomycin required for other infectious causes • Vancomycin discontinued for growth of only gram-negative organisms • Vancomycin discontinued for infusion reactions

Patients were classified into one of two groups based on the initial vancomycin trough: ST (<10 mg/L) or TT (≥10 mg/L). The primary outcome was vancomycin treatment duration (defined as time from first to last administered dose) for patients with ST compared with TT. Secondary outcomes included the duration of hospital admission, time from last vancomycin concentration to discontinuation of vancomycin, baseline and final white blood cell (WBC) counts, baseline and final temperature values and incidence of AKI whilst receiving vancomycin.

Median values with interquartile ranges (IQR) were reported for non-parametric, interval data. The Mann–Whitney *U* test was used to compare the results for non-parametric, independent data. Statistical analyses were performed with Stata (College Station, TX, USA). A *p* value of less than 0.05 was considered statistically significant.

Results

Fifty-eight patients met the inclusion and exclusion criteria. There were 39 (67.2%) patients who had sub-therapeutic levels (median trough 6.7 mg/L, IQR 5.85–8.2 mg/L). The remaining 19 patients (32.8%) had therapeutic trough levels (median trough 12.6 mg/L, IQR 11.25–13.5 mg/L). Additional information on baseline characteristics can be found in Table 2. Baseline characteristics were similar except for those in the TT group having a higher median weight, which likely resulted in the higher vancomycin dosing seen.

For the primary outcome, there was no statistical difference in the median hours of vancomycin duration for ST (48.25, IQR 39–65.6) and TT (59.5, IQR 47.5–67.3; p=0.65) patients. When assessing the secondary outcomes, there was no statistically significant difference in the median days of hospital admission (p=0.96), time from last vancomycin level until agent discontinuation (p=0.59) and incidence of AKI (p=1). Additional information regarding secondary outcomes can be found in Table 3.

For patients with ST, 32 (82.1%) patients received a dose (n=16) or frequency (n=19) adjustment. Eight (21%) patients with ST had a second trough level drawn (median 13.7 mg/L, IQR 10.4–15.6 mg/L). In the TT group, 3 (15.8%) patients had a dose change due to levels above the stated 10–15 mg/L goal and 1 patient had a repeat trough (10.5 mg/dL). The median duration from last trough level until vancomycin discontinuation was shorter for ST (2.5 hours, IQR 1.6–17.4) compared with TT (13.5 hours, IQR 1.3–24.9).

There was no significant difference for initial and final values for serum creatinine, WBC and maximum temperature over 24 hours (Table 4). Most patients were documented as receiving vancomycin for cellulitis for both ST (n=26, 67%) and TT (n=16, 84.2%). There were more cultures obtained in the ST group (n=18, 47.4%) compared with the TT group (n=2, 10.5%). Additional culture information is provided in Table 5. Vancomycin discontinuation was most commonly due to patients being discharged (ST: n=31, 79.5% and TT: n=16, 84.2%).

Table 2. Baseline characteristics.

	Trough <10 mg/L	Trough ≥10 mg/L
Patients	39	19
Age (years), median (IQR)	40 (25–55.5)	56 (44–59.5)
Weight (kg), median (IQR)	72.7 (63.8–87.9)	94.5 (82.5–107)
Initial creatinine clearance (Cockcroft–Gault) (mL/min), median (IQR)	107.2 (87.6–125.1)	93.6 (70.8–128.6)
Initial dose (mg), median (IQR)	1250 (1000–1500)	1500 (1250–1625)
Loading dose administered (%)	21 (55.3)	9 (47.4)
Loading dose (mg), median (IQR)	1500 (1500–2000)	2000 (2000–2250)
Maintenance dose (mg), median (IQR)	1250 (1000–1500)	1500 (1250–1625)
Initial frequency, patients (%)		
Every 8 hours	2 (5.3)	0
Every 12 hours	32 (84.2)	19 (100)
Every 24 hours	4 (10.5)	0

IQR, interquartile range.

Table 3. Primary and secondary outcomes.

	Sub-therapeutic trough	Therapeutic trough	Difference (absolute)	*p* value
Primary outcome				
Vancomycin duration, median hours (IQR)	48.25 (39–65.6)	59.5 (47.5–67.3)	+11.25	0.65
Secondary outcomes				
Hospital admission duration, median days (IQR)	3 (3–4.5)	4 (3–4)	+1	0.96
Time from last trough until vancomycin discontinuation, median hours (IQR)	2.5 (1.7–17.4)	13.5 (1.3–24.9)	+11	0.59
Incidence of acute kidney injury (serum creatinine >1.2× baseline, %)	1 (2.5)	0	+1	1

IQR, interquartile range.

Table 4. Median baseline and final WBC, maximum 24-hour temperature and serum creatinine values.

	Trough <10 mg/L (IQR)	Trough ≥10 mg/L (IQR)	*p* value
WBC (cells/mm³)			
Baseline	10.2 (8.5–14.2)	8.4 (6.75–11.25)	0.07
Final	7.2 (5.8–10.4)	6.3 (5.7–7.6)	0.05
Difference (%)	−29.4	−25	–
Maximum 24-hour temperature (Fahrenheit)			
Initial 24 hours	98.8 (98.2–99.8)	98.6 (98.3–99.6)	0.88
Final 24 hours	98.7 (98.2–99.1)	98.7 (98.3–98.8)	0.81
Serum creatinine (mg/dL)			
Baseline	0.82 (0.68–0.93)	0.83 (0.68–0.89)	0.98
Final	0.69 (0.6–0.83)	0.65 (0.58–0.83)	0.81
Difference (%)	−15.9	−21.7	–

IQR, interquartile range; WBC, white blood cell.

Discussion

For adult, general medicine patients receiving vancomycin for ABSSSI with ST or TT, there were no statistical differences in the duration of vancomycin administration, hospital duration, time from last trough until vancomycin discontinuation, or incidence of AKI. We found that, frequently after concentrations were obtained, patients were nearing discontinuation of vancomycin and there was likely no clinical benefit of adjusting vancomycin based on trough concentrations in this select population.

To the best of our knowledge, only one study has directly assessed low and high trough concentrations in non-severe infections requiring short durations of treatment. Wan et al.[4] compared patients who received vancomycin for up to 14 days for non-deep-seated infections (defined as skin and soft tissue infections, urinary tract infections, bacteraemia without evidence of seeding and coagulase-negative *S. aureus* line infections) with low (≤10 mg/L) and high (>10 mg/L) trough concentrations. The authors found no significant difference in clinical cure rates for low (88%) and high trough concentrations (87%; OR 1.02, 95% CI 0.32–3.28; $p>0.99$). The median duration of vancomycin was 7 days in both groups.[4] This study included an assessment of vancomycin troughs in non-ABSSSI (bacteraemia, urinary tract infections), although the majority were classified as ABSSSI. Although

Table 5. Uncomplicated acute bacterial skin and skin structure infection wound cultures – organisms identified.

	Trough <10 mg/L (*n*=39)	Trough ≥10 mg/L (*n*=19)
Cultures obtained (%)	18 (47.4)	2 (10.5)
Gram-positive organisms		
Streptococcus anginosus	1	
Methicillin-sensitive *Staphylococcus aureus*	12	1
Staphylococcus lugdunensisis	1	1
Streptococcus milleri	1	
Streptococcus pyogenes	2	
Streptococcus viridans	1	
Group A streptococcus	1	
Gram-negative organisms		
Bacteroides spp.	1	
Morganella morganii	1	
Enterobacter spp.	1	
Klebsiella pneumoniae	1	
Proteus mirabilis	1	
Proteus vulgaris		1

different primary outcomes were reviewed, both studies found no significant impact on ST troughs and vancomycin duration.

Several departments (phlebotomy, chemistry, nursing and pharmacy) are utilized to obtain, process and analyse vancomycin concentrations. As there are several moving parts, error may be introduced. Potential errors include incorrectly drawing the trough concentration, delay in vancomycin administration, incorrect concentration assessment and inappropriate dose adjustment. A 3-month observational study illustrated the challenge of correctly monitoring vancomycin trough concentrations. The researchers found that only 31% had appropriate trough concentration monitoring in relation to frequency. Less than half (48.4%) of the patients were dosed correctly based on weight, indication and renal function, which resulted in only 15.7% of patients achieving targeted trough concentrations.[15]

Vancomycin concentrations result in direct and indirect costs and it could be argued that pharmacist time could be better used in other antimicrobial stewardship-related interventions. For instance, pharmacist-led antimicrobial stewardship interventions, such as intravenous to oral conversions, proper empiric selection of antibiotics and de-escalation based on culture results, have been well documented to reduce healthcare costs whilst not detrimentally impacting patient outcomes when performed appropriately.[16] A combination of reduced costs through decreased vancomycin monitoring along with reallocated pharmacist time to cost-saving antimicrobial stewardship interventions could significantly impact expenditures. The mean pharmacist time dedicated to dosing and adjusting vancomycin was previously found to be 43 minutes and was only cost effective if conducted in the context of the intensive care unit, oncology unit or for those receiving concomitant nephrotoxic medications.[12]

During the study period, 1143 vancomycin concentrations (random and trough) were collected, resulting in a total cost of approximately US$218,313 or US$72,771 annually. The vancomycin troughs obtained in this study comprised a small portion (5.8%) of the overall concentrations and cost (US$12,797). However, there are still gaps in vancomycin monitoring that could be reviewed and may result in a further reduction of vancomycin concentration ordering, including monitoring patients receiving vancomycin for urinary tract infections, pre-haemodialysis concentrations for all haemodialysis sessions, sepsis lacking a defined source or MRSA risk factors, or implementing a vancomycin dosing algorithm to ensure a higher proportion of appropriate trough concentrations. The potential direct cost savings from laboratory stewardship could be used for procurement of assays or equipment that can aid in optimizing patient care such as rapid diagnostic testing.

Reviewing the results from our study, it appears several potential stewardship interventions could have been performed, including utilizing more beta-lactam antibiotics in the setting of non-purulent cellulitis where empirical MRSA coverage was unlikely necessary. Additionally, only 11.8% of patients overall were changed to an oral regimen before discharge. After the completion of this study, the vancomycin monitoring policy was updated to include the most recent IDSA recommendations for the monitoring of the ratio of 24-hour area under the curve to minimum inhibitory concentration. In addition, another institution vancomycin policy update included a recommendation to delay obtaining troughs for patients with ABSSSI and CrCl >50 mL/min until after 5 days of vancomycin therapy assuming no change in renal function occurred during this period.

There are some limitations of this retrospective study. Although our study did not assess cure rates, our results used vancomycin administration and hospital admission duration as endpoints. These endpoints were used as surrogate markers for infection resolution. Due to the

retrospective nature of this study, it was difficult to accurately assess ABSSSI improvement via provider notes consistently and accurately. However, clinical markers of infectious resolution (WBC, temperature values) were assessed and no difference from baseline and final readings between the cohorts was found. The number of eligible patients for this study was small compared with the number who received vancomycin during the same period at our institution thus limiting potential external impact and potentially being underpowered, making it difficult to distinguish a true difference between the cohorts.

Conclusion

Patients with ST and TT had similar vancomycin durations and clinical outcomes, indicating that routine vancomycin trough monitoring for patients with ABSSSI without renal impairment is likely not necessary. It may be prudent for institutions to address vancomycin trough laboratory stewardship and associated costs. The ability to reallocate pharmacist time towards antimicrobial stewardship opportunities can assist with potential additional cost-saving measures.

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References

1. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health-Syst Pharm*. 2009;66:82–98. https://doi.org/10.2146/ajhp080434
2. 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. https://doi.org/10.1093/ajhp/zxaa036
3. Itani KMF, Dryden MS, Bhattacharyya H, Kunkel MJ, Baruch AM, Weigelt JA. Efficacy and safety of linezolid versus vancomycin for the treatment of complicated skin and soft tissue infections proven to be caused by methicillin-resistant Staphylococcus aureus. *Am J Surg*. 2010;199:804–816. https://doi.org/10.1016/j.amjsurg.2009.08.045
4. Wan M, Walker SAN, Martin E, Elligsen M, Palmay L, Leis JA. The impact of vancomycin trough concentrations on outcomes in non-deep seated infections: a retrospective cohort study. *BMC Pharmacol Toxicol*. 2018;19(47):1–9. https://doi.org/10.1186/s40360-018-0236-z
5. Kingsley J, Mehra P, Lawrence LE, et al. A randomized, double-blind, Phase 2 study to evaluate subjective and objective outcomes in patients with acute bacterial skin and skin structure infections treated with delafloxacin, linezolid or vancomycin. *J Antimicrob Chemother*. 2016;71:821–829. https://doi.org/10.1093/jac/dkv411
6. Lodise TP, Redell M, Armstrong SO, Sulham KA, Corey GR. Efficacy and safety of oritavancin relative to vancomycin for patients with acute bacterial skin and skin structure infections (ABSSSI) in the outpatient setting: results from the SOLO Clinical Trials. *Open Forum Infect Dis*. 2017;4(1):1–9. https://doi.org/10.1093/ofid/ofw274
7. Davies SW, Guidry CA, Petroze RT, Hranjec T, Sawyer RG. Vancomycin and nephrotoxicity: just another myth? *J Trauma Acute Care Surg*. 2013;75(5):830–835. https://doi.org/10.1097/TA.0b013e3182a74b70
8. Cunha BA, Mohan SS, Hamid N, McDermott BP, Daniels P. Cost-ineffectiveness of serum vancomycin levels. *Eur J Clin Microbiol Infect Dis*. 2007;26(7):509–511. https://doi.org/10.1007/s10096-007-0314-4
9. Van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. *Antimicrob Agents Chemother*. 2013;57(2):734–744. https://doi.org/10.1128/AAC.01568-12
10. Bosso JA, Nappi J, Rudisill C, et al. Relationship between vancomycin trough concentrations and nephrotoxicity: a prospective multicenter trial. *Antimicrob Agents Chemother*. 2011;55(12):5475–5479. https://doi.org/10.1128/AAC.00168-11
11. Tongsai S, Koomanachai P. The safety and efficacy of high versus low vancomycin trough levels in the treatment of patients with infections caused by methicillin-resistant Staphylococcus aureus: a meta-analysis. *BMC Res Notes*. 2016;9(1):455. https://doi.org/10.1186/s13104-016-2252-7
12. Darko W, Medicis JJ, Smith A, Guharoy R, Lehmann DF. Mississippi mud no more: cost-effectiveness of pharmacokinetic dosage adjustment of vancomycin to prevent nephrotoxicity. *Pharmacotherapy*. 2003;23(5):643–650. https://doi.org/10.1592/phco.23.5.643.32199
13. Bulger J, Nickel W, Messler J, et al. Choosing wisely in hospital medicine. *J Hosp Med*. 2013;9:486–492. https://doi.org/10.1002/jhm.2063
14. Zhi M, Ding EL, Theisen-Toupal J, Whelan J, Arnaout R. The landscape of inappropriate laboratory testing: a 15-year meta-analysis. *PLoS One*. 2013;8(11):e78962. https://doi.org/10.1371/journal.pone.0078962
15. Kabbara WK, El-Khoury G, Chamas NR. Prospective evaluation of vancomycin therapeutic usage and trough levels monitoring. *J Infect Dev Ctries*. 2018;12(11):978–984. https://doi.org/10.3855/jidc.9800
16. Magedanz L, Silliprandi EM, dos Santos RP. Impact of the pharmacist on a multidisciplinary team in an antimicrobial stewardship program: a quasi-experimental study. *Int J Clin Pharm*. 2012;34:290–294. https://doi.org/10.1007/s11096-012-9621-7