12-6-2016

Evaluation of an empiric vancomycin dosing nomogram in achieving goal steady-state trough concentrations in obese adults weighing at least 100 kilograms

S. W. Johnson

R. D. Bowers

A. A. Cooper

C. L. Wente

D. Wilson

Bowers RD, Cooper AA, Wente CL, Wilson DT, Johnson SW, Drew RH. Evaluation of a vancomycin dosing nomogram in obese patients weighing at least 100 kilograms. Pharmacy Practice 2018 Jul-Sep;16(3):1204.
https://doi.org/10.18549/PharmPract.2018.03.1204

Original Research

Evaluation of a vancomycin dosing nomogram in obese patients weighing at least 100 kilograms

Riley D. BOWERS, April A. COOPER, Catherine L. WENTE, Dustin T. WILSON, Steven W. JOHNSON, Richard H. DREW.

Received (first version): 1-Feb-2018 Accepted: 4-Jul-2018 Published online: 13-Aug-2018

Abstract

Background: There remains variability in both practice and evidence related to optimal initial empiric dosing strategies for vancomycin.
Objective: Our primary objective was to describe the percentage of obese patients receiving vancomycin doses consistent with nomogram recommendations achieving targeted initial steady-state serum vancomycin concentrations. Secondary objectives were to describe the primary endpoint in subgroups based on patient weight and estimated creatinine clearance, to describe the rate of supratherapeutic vancomycin accumulation following an initial therapeutic trough concentration, and to describe the rate of vancomycin-related adverse events.
Methods: This single-center, IRB-approved, retrospective cohort included adult patients ≥ 100 kilograms total body weight with a body mass index (BMI) >30 kilograms/m2 who received a stable nomogram-based vancomycin regimen and had at least one steady-state vancomycin trough concentration. Data collected included vancomycin regimens and concentrations, vancomycin indication, serum creatinine, and vancomycin-related adverse events. Patients were divided into two cohorts by goal trough concentration: 10-15 mcg/mL and 15-20 mcg/mL.
Results: Of 325 patients screened, 85 were included. Goal steady-state concentrations were reached in 42/85 (49.4%) of total patients.
Conclusions: Achievement of initial steady-state vancomycin serum concentrations in the present study (approximately 50%) was consistent with the use of published vancomycin dosing nomograms.

Keywords

Drug Monitoring; Vancomycin; Nomograms; Drug Dosage Calculations; Obesity; Retrospective Studies

INTRODUCTION

More than one-third of adults in the United States are obese and consequently at a significantly increased risk for heart disease, stroke, and type 2 diabetes.[1] In addition to these health implications, the physiologic changes from obesity also impact pharmacokinetic and pharmacodynamic properties of drugs. These changes can impact both efficacy and toxicity, especially in antimicrobials such as vancomcyin.[2]

Vancomycin is a tricyclic glycopeptide antibiotic commonly used as therapy for infections caused by Gram-positive organisms, most notably methicillin-resistant Staphylococcus aureus (MRSA).[3] Published adult dosing recommendations for vancomycin in the general population are 15 to 20 mg/kg per dose every 8 to 24 hours (based upon total body weight [TBW] and estimated renal function).[4] However, such recommendations may be inadequate in obese patients due to increases in vancomycin clearance and volume of distribution.[5] In addition, when applied to obese patients, the large single doses resulting from such weight-based recommendations increase the risk of dose-related toxicities.[5]

Variability in both practice and lack of evidence related to optimal initial dosing strategies for vancomycin exist.[5] For example, dosing based on TBW achieves target steady-state trough concentrations more frequently then when based on ideal body weight (IBW).[2] In contrast, one study5 demonstrated that use of adjusted body weight (ABW) provided the best predictor to serum concentrations, and another[6] recommended using 45 to 65 mg/kg/day based on IBW.[5-6] In addition to weight-based dosing, published dosing nomograms have also been extensively evaluated.[7-9] Their efficacy in achieving initial goal trough concentrations (10-20 mcg/mL) has been shown to range from 40-60% on the initial regimen, but the majority excluded patients weighing more than 120 kg or limited the maximum single dose to 2 gms.[7-9] Studies analyzing appropriate vancomycin dosing and monitoring in obese patients have reported variable success rates. In one, approximately 60% of initial vancomycin steady-state concentrations were subtherapeutic (<10 mcg/mL), leading to increased risk of resistance and treatment failure.[8] Another concluded that obese patients most often reached target trough

Riley D. BOWERS. PharmD, BCPS. Department of Pharmacy Practice, College of Pharmacy & Health Sciences, Campbell University. Buies Creek, NC; & Cape Fear Valley Medical Center. Fayetteville, NC (United States). bowers@campbell.edu
April A. COOPER. PharmD. Department of Pharmacy Practice, College of Pharmacy & Health Sciences, Campbell University. Buies Creek, NC; & Duke Regional Hospital. Durham, NC (United States). april.cooper@duke.edu
Catherine Lewis WENTE. PharmD, CACP, BCPS. Department of Pharmacy Practice, College of Pharmacy & Health Sciences, Campbell University. Buies Creek, NC; & Duke Regional Hospital. Durham, NC (United States). Catherine.d.lewis@duke.edu
Dustin T. WILSON. PharmD, BCPS. Department of Pharmacy Practice, College of Pharmacy & Health Sciences, Campbell University. Buies Creek, NC; & Duke University Hospital. Durham, NC (United States). wilsond@campbell.edu
Steven W. JOHNSON. PharmD, BCPS, CCP, AAHIVP. Department of Pharmacy Practice, College of Pharmacy & Health Sciences, Campbell University. Buies Creek, NC; & Novant Health - Forsyth Medical Center. Winston-Salem, NC (United States). johnsonsw@campbell.edu
Richard H. DREW. PharmD, MS, FCCP. Department of Pharmacy Practice, College of Pharmacy & Health Sciences, Campbell University. Buies Creek, NC; & Duke University School of Medicine. Durham, NC (United States). Richard.drew@duke.edu

concentrations when given 20-30 mg/kg/day based on TBW.[9]

There has yet to be a consensus or guideline recommendations for dosing and monitoring in obese patients. At Duke University Hospital, a validated empiric dosing nomogram for patients weighing 50-100 kg has been in place since 2010. In order to fulfill an increasing and unmet need, an empiric vancomycin dosing nomogram was developed at Duke Regional Hospital (DRH) in 2016 targeting patients weighing 100 to 160 kg (see Appendix). While we hypothesized this nomogram would provide appropriate initial vancomycin dosing guidelines in this population, it had not been previously evaluated. The purpose of our study was to evaluate this newly-implemented vancomycin dosing nomogram in achieving goal steady-state trough concentrations for obese adult patients.

METHODS

The primary objective of this single-center, retrospective cohort study was to describe the percentage of obese patients receiving initial vancomycin doses consistent with nomogram recommendations achieving targeted initial steady-state serum vancomycin concentrations. The secondary objectives were to describe the primary endpoint in subgroups based on patient weight and estimated creatinine clearance (CrCl). We also sought to describe the percentage of patients maintaining a target steady-state trough concentration, on a consistent regimen, for one subsequent level following an initial target steady-state trough concentration to assess the rate of accumulation. Lastly, patients were evaluated for vancomycin-related adverse effects, including new-onset kidney injury and Red Man syndrome.

This single-center, retrospective cohort study was approved by the Duke University Health System Institutional Review Board and conducted at DRH, a 369-bed community hospital in Durham, NC. Patients >18 years-old, admitted to a general medicine or surgery unit from December 1, 2015 to February 1, 2017 were included. Subjects who weighed >100 kg and had a BMI of >30 kg/m2 who received at least 2 scheduled vancomycin doses following the appropriate loading dose (per nomogram recommendations) were included if at least one steady-state trough vancomycin concentration (defined as following at least the third dose of the regimen and drawn within 2 hours of the next sequential dose) was measured. Patients were excluded for any of the following: renal dysfunction (defined as an estimated CrCl <10 mL/min), unstable renal function (defined as a change in serum creatinine (SCr) of 0.5 mg/dL or 50% reduction in estimated CrCl between initial dose and time of subsequent trough measurement), moderate to severe liver dysfunction at baseline (defined as aspartate aminotransferase or alanine aminotransferase levels >two times the upper limit of normal (ULN), or a total bilirubin level >two times the ULN), ascites, burns (>20% total body surface area), within 30 days of solid organ or hematopoietic stem cell transplantation, had cystic fibrosis, were patients in the critical care unit, or were pregnant.

Patients were identified utilizing the Duke Enterprise Data Unified Content Explorer (DEDUCE). Separate admissions for the same patient were counted as individual cases. Data were collected using a Microsoft Access database and entry form. Patient demographics collected included gender, age, weight, height, BMI, and the presence of chronic kidney disease (CKD). Other data collected included vancomycin indication, vancomycin dosing regimens, and vancomycin serum trough concentrations, dates, and collection times. SCr and estimated CrCl at time of vancomycin initiation and trough concentration of maintenance regimen utilizing a modified Cockroft-Gault equation (removing weight and 72 from numerator and denominator, respectively).[10] Of note, in patients >70 years old, a SCr below 1 mg/dL was rounded to 1 mg/dL to calculate CrCl. For initial loading doses, patients received 25 mg/kg TBW unless they had impaired renal function indicated by new-onset kidney injury or CKD Stage IV or worse. In this case, patients were loaded with 20 mg/kg TBW. However, we incorporated our institution's policy of vancomycin dose capping at 2500 mg. For patients with therapeutic serum trough concentrations that were continued on the same regimen, SCr was collected again at the time of the next trough concentration. Lastly, presence of Red Man syndrome and new-onset kidney injury at the time of concentration collection (defined as an increase in SCr by 0.3 mg/dL or more within 48 hours, or an increase in SCr to 1.5 times baseline or more within the last 7 days, or urine output less than 0.5 mL/kg/h for 6 hours) was collected.[11] The institutional nomogram was developed with the above in mind, utilizing traditional vancomycin pharmacokinetic calculations including the Matzke equation for the elimination rate constant. For patients receiving multiple courses of vancomycin during a single admission, only the first course was included in the study.[12]

Data Analysis

The primary endpoint (initial steady-state serum vancomycin concentration within the indication-specific target range) and patient demographics were characterized using descriptive statistics. For the secondary objectives, the endpoints utilized were percentage of therapeutic trough concentrations in the pre-specified cohorts, percentage of patients experiencing vancomycin accumulation to a supratherapeutic level following an initial therapeutic concentration, and percentage of patients experiencing a vancomycin-related adverse event such as new-onset kidney injury. Patients were cohorted by CrCl (10-39 mL/min, 40-69 mL/min, 70-99 mL/min, and 100+ mL/min) and weight (100-119 kg, 120-139 kg, 140-159 kg, and 160+ kg).

RESULTS

Of 325 patients weighing over 100 kg and on vancomycin identified and screened, 85 (26.2%) met inclusion criteria. Patients were excluded for the following: doses were not consistent with nomogram recommendations (n=168), no trough concentration level (n=36), critical care unit status (n=28), BMI <30 kg/m2 (5), and weight <100 kg at time of vancomycin initiation (3). The study population was predominantly male with an average age of 60 years. Remaining subject demographics are summarized in Table 1. All subjects had an estimated CrCl > 30 mL/min and the

Table 1. Baseline demographic characteristics of included subjects (by cohort)			
Parameter	**Cohort**		
	10-15 mcg/mL (n=28)	**15-20 mcg/mL (n=57)**	**All patients (n=85)**
Age, yr	56.1 (11.8)	57.5 (15.2)	56.9 (13.0)
Gender, n (Male:Female)	15:13	37:20	52:33
Weight, kg	133.2 (35.6)	122.0 (17.6)	125.1 (25.3)
BMI, kg/m^{2} [a]	44.8 (12.7)	39.5 (7.3)	40.9 (9.5)
CrCl[b], mL/min	98.8 (22.1)	72.7 (24.6)	81.3 (26.7)
Indications, n(%)			
SSTI[c]	26 (92.9)	17 (29.8)	43 (50.1)
Osteomyelitis	0	16 (28.1)	16 (18.8)
Sepsis	0	11 (19.3)	11 (12.9)
Pneumonia	0	6 (10.5)	6 (7.1)
Bacteremia	1 (3.6)	4 (7.0)	5 (5.9)
Intra-abdominal	0	3 (5.3)	3 (3.5)
Other	1 (3.6)	0	1 (1.2)
Vancomcyin regimen			
1.5g Q12H	11	11	22 (25.9)
1.75g Q12H	5	10	15 (17.6)
2g Q12H	4	8	12 (14.1)
1.75g Q18H	0	8	8 (9.4)
1.25g Q8H	0	6	6 (7.1)
Other	8	14	22 (25.9)
Baseline renal disease			
CKD[d] Stage III-V	1 (3.6)	9 (15.8)	10 (11.8)
a. Body Mass Index b. Creatinine clearance in normalized Cockroft-Gault c. skin and soft tissue infections d. Chronic Kidney Disease			

mean CrCl was 81.3 mL/min. The majority of patients were in the 15-20 mcg/mL goal trough cohort and were receiving therapy for complicated skin and skin structure infections (SSTI).

Goal steady-state trough concentrations were reached in 42 patients (49.4%) with 27 (47.4%) in the 15-20 mcg/mL cohort and 15 (53.6%) in the 10-15 mcg/mL cohort. In the total population, 24.7% had subtherapeutic levels at steady state and 25.9% had supratherapeutic levels. There was also a similar distribution of subtherapeutic levels and supratherapeutic levels in each goal trough subgroup (Figure 1). Trough levels ranged from 6.1-30.9 mcg/mL. When this data was combined, 58 patients (68.2%) had levels that fell in the 10-20 mcg/mL range.

When divided into pre-specified subgroups based on goal trough concentrations, weight, and estimated CrCl (Table 2), the majority of patients fell into the 100-119 kg groups (n= 47, 55%). There were a limited number of patients >140 kg (n=13, 15%), and only 28 patients had an estimated CrCl <70 mL/min. 69% of the pre-specified subgroups containing at least one patient in the 15-20 mcg/mL goal cohort and 67% of the subgroups in the 10-15 mcg/mL cohort had mean trough concentrations at goal, respectively (Table 2). Notably, 16/21 (76%) of total patients with subtherapeutic trough concentrations had an estimated CrCl >70 mL/min. However, there were more patients in these subgroups and the majority still achieved goal trough concentrations (n=30, 52.6%). There was a noticeably higher rate of

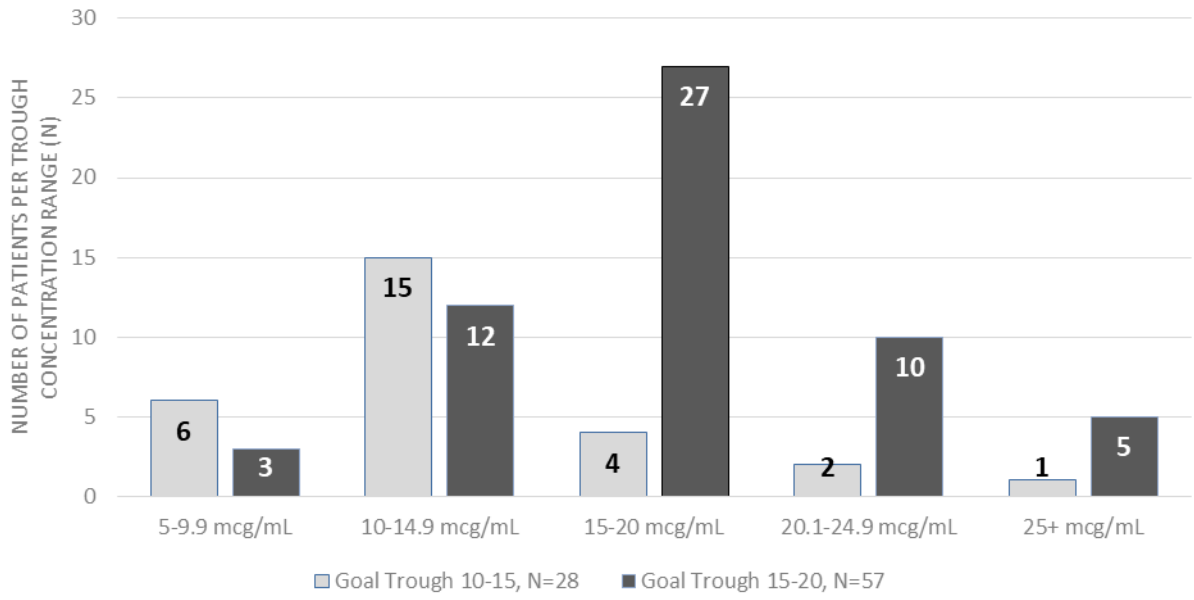

Figure 1. Number achieving trough concentrations based on target trough concentration goal.

Table 2. Subgroup analysis – average trough concentration (SD), mcg/mL

10-15 mcg/mL goal	**100-119 kg**	**120-139 kg**	**140-159 kg**	**> 160 kg**
10-39 mL/min	N/A	N/A	N/A	N/A
40-69 mL/min	17.0 (3.6)	22.8 (0)*	N/A	N/A
70-99 mL/min	14.4 (5.7)	11.5 (0)*	N/A	13.8 (1.6)
> 100 mL/min	10.7 (2.9)	9.8 (3.6)	14.5 (0)*	14.8 (3.8)
15-20 mcg/mL goal	**100-119 kg**	**120-139 kg**	**140-159 kg**	**> 160 kg**
10-39 mL/min	18.6 (2.4)	16.1 (0)*	N/A	N/A
40-69 mL/min	17.2 (4.8)	18.8 (4.3)	19.9 (0)*	14.2 + 6.1*
70-99 mL/min	16.9 (5.6)	18.7 (4.0)	11.5 (0)*	N/A
> 100 mL/min	12.6 (3.0)	23.2 (2.1)*	17.8 (0)*	15.4 (0)*

*<2 patients represented in the subgroup

patients reaching initial supratherapeutic trough concentrations in the CrCl <70 mL/min subgroups compared to those with a CrCl >70 mL/min (35.7% vs. 19.3%).

Very few patients were continued on the same vancomycin regimen following the achievement of a target trough concentration long enough to check a second concentration (n=11, 26.2%). Of these 11 patients, 5 experienced accumulation to a supratherapeutic trough concentration on the subsequent level, with a mean (SD) time to next level of 2.9 (SD=1.2) days. However, 3 (60%) of these patients developed new-onset kidney injury between the first and second concentration drawn.

No patients had to have vancomycin discontinued due to adverse events. Five patients experienced new-onset kidney injury during treatment and one patient was reported to have Red Man syndrome which was noted to improve when the infusion was administered at a slower rate. No other drug-related adverse effects were reported.

DISCUSSION

The results of our study found that our nomogram achieved target trough concentrations nearly 50% of the time. Prior attempts to utilize nomograms to provide initial dosing recommendations for vancomycin in obese patients have been met with variable success. One protocol employed a 20 mg/kg loading dose followed by 10 mg/kg/dose (based on TBW) every 12-24 hours in morbidly obese adults (BMI >40).[8] This dose was chosen based on previous findings that demonstrated a high rate of supratherapeutic concentrations with higher doses.[8] With this decreased dose, initial goal trough concentrations were achieved in 35.4% of patients, while subtherapeutic troughs occurred in 56.3% and supratherapeutic troughs in only 8.3% of patients.[8] Another recent retrospective study concluded that obese (BMI 30-40) and morbidly obese (BMI >40) patients most often reached target trough concentrations when given 20-30 mg/kg/day based on TBW.[9] However, this study had limitations which included a high rate of subtherapeutic trough concentrations (48%) and no loading doses were given.[9]

Compared to the aforementioned studies and another by Morrill et al, which utilized a similar dosing strategy and yielded 48% subtherapeutic initial trough levels, our study had a more even distribution of non-therapeutic trough concentrations.[7-9] Approximately 25% of patients had subtherapeutic trough levels with no level being lower than 6 mcg/mL, while another 25% of patients had supratherapeutic levels with only one level being greater than 30 mcg/mL (30.9). While we had a slightly higher rate of new-onset kidney injury during therapy compared to the previous trials, all patients experiencing kidney injury were on concomitant nephrotoxic medications including piperacillin-tazobactam, thiazide diuretics, and intravenous acyclovir.[8,9,13]

The results of this study fall within the range of results in previous studies evaluating vancomycin dosing nomograms, achieving goal steady-state trough concentrations nearly 50% of the time.[7,14-16] Unlike the majority of previous studies analyzing vancomycin nomograms, this study only included obese patients weighing at least 100 kg with no maximum weight.[4-7,14-16] When looking at the limited previous literature on vancomycin dosing in obese patients, our nomogram appears to be safe and similarly effective. Notable studies analyzing vancomycin dosing in obese patients have utilized protocols or nomograms that have based dosing on simplified mg/kg calculations paired with estimated renal function for determining frequency.[8,9,13] Our nomogram was developed utilizing traditional pharmacokinetic calculations for each subgroup using TBW for volume of distribution calculations and normalized CrCl which ultimately leads to a lower estimation of drug clearance in these patients. Utilizing this method of dosing, we predicted that our patients would receive large enough doses without experiencing toxic levels as a result of too frequent dosing.

This was also the first study to our knowledge to collect data on vancomycin accumulation in the real-world obese patient population. While our data is limited to 11 patients who were continued on their original therapeutic regimen long enough to receive a second trough level, it does reveal a concern for drug accumulation in this population. Nearly half (45%) of these patients experienced a subsequent supratherapeutic level following an initial therapeutic trough concentration and no change in dosing regimen. It is important to note that 3 of these patients had significant increases in SCr levels near the time of the follow-up level. Further studies are needed in this area to assess vancomycin adjustments in these patients to avoid potentially toxic accumulation.

Our study was not without limitations. Though our nomogram was designed using common calculations utilized in clinical practice, there are potential limitations with the pharmacokinetics of using the standard Vd, Matzke equation, and SCr rounding in the obese population.[12] However, there is no current consensus on the best method. AUC-based monitoring has also shown promising data, but until more implementable evidence

exists, many institutions will continue traditional vancomycin dosing.[17] With no active or historical comparator, we were only able to report descriptive statistics limiting ability to show any association with patient specific factors and vancomycin concentrations. We were also limited to a small sample size. Although over 300 patients were screened for inclusion, pharmacists were not required to utilize the nomogram during the evaluation period which led to many exclusions. We also excluded patients in the critical care unit per the institution's pharmacokinetic policy which limits extrapolation to these patients. This limited sample size and utilization also inhibited our ability to truly evaluate the effectiveness of our nomogram in patients with poor CrCl and those weighing over 140 kg. Lastly, we did not evaluate clinical outcomes of the patients.

CONCLUSIONS

Overall achievement of initial steady-state vancomycin serum concentrations in our study of obese patients (approximately 50%) was consistent with the use of published vancomycin dosing nomograms. Notably, our study had an even distribution of non-therapeutic trough concentrations (25% subtherapeutic and 25% supratherapeutic). Our study also added evidence for the risk vancomycin accumulation in continued dosing in this patient population. Future plans should include identifying patient-specific factors associated with non-therapeutic trough levels in the obese patient population and developing accurate pharmacokinetic models for this population.

ACKNOWLEDGEMENTS

This study was granted exempted status by the Duke University Health System Institutional Review Board

CONFLICT OF INTEREST

The authors of this manuscript have nothing to disclose concerning possible financial or personal relationships with commercial entities that may affect this presentation.

FUNDING

None.

References

1. Adult obesity facts. Centers for disease control and prevention. September 21, 2015. https://www.cdc.gov/obesity/data/adult.html (accessed July 17, 2016).
2. Polso AK, Lassiter JL, Nagel JL. Impact of hospital guideline for weight-based antimicrobial dosing in morbidly obese adults and comprehensive literature review. J Clin Pharm Ther. 2014 Dec;39(6):584-608. doi: 10.1111/jcpt.12200
3. Vancomycin [prescribing information]. Lake Forest, IL: Hospira; November 2014.
4. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, Dalovisio JR, Levine DP. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis. 2009;49(3):325-327. doi: 10.1086/600877
5. Leong JV, Boro MS, Winter M. Determining vancomycin clearance in an overweight and obese population. Am J Health Syst Pharm. 2011;68(7):599-603. doi: 10.2146/ajhp100410
6. Kubiak DW, Alquwaizani M, Sansonetti D, Barra ME, Calderwood MS. An Evaluation of systemic vancomycin dosing in obese patients. Open Forum Infect Dis. 2015;2(4):ofv176. doi: 10.1093/ofid/ofv176
7. Elyasi S, Khalili H. Vancomycin dosing nomograms targeting high serum trough levels in different populations: pros and cons. Eur J Clin Pharmacol. 2016;72(7):777-788. doi: 10.1007/s00228-016-2063-8
8. Kosmisky DE, Griffiths CL, Templin MA, Norton J, Martin KE. Evaluation of a new vancomycin dosing protocol in morbidly obese patients. Hosp Pharm. 2015 Oct;50(9):789-797. doi: 10.1310/hpj5009-789
9. Morrill HJ, Caffrey AR, Noh E, Laplante KL. Vancomycin dosing considerations in a real-world cohort of obese and extremely obese patients. Pharmacotherapy. 2015;35(9):869-875. doi: 10.1002/phar.1625
10. Wilhelm SM, Kale-Pradhan PB. Estimating creatinine clearance: a meta-analysis. Pharmacotherapy. 2011;31(7):658-664. doi: 10.1592/phco.31.7.658
11. Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Inter. 2012;2(1):1-138.
12. Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. Clin Pharmacokinet. 1986;11(4):257-282. doi: 10.2165/00003088-198611040-00001
13. Reynolds DC, Waite LH, Alexander DP, DeRyke CA. Performance of a vancomycin dosage regimen developed for obese patients. Am J Health Syst Pharm. 2012;69(11):944-950. doi: 10.2146/ajhp110324
14. Kullar R, Leonard SN, Davis SL, Delgado G Jr, Pogue JM, Wahby KA, Falcione B, Rybak MJ. Validation of the effectiveness of a vancomycin nomogram in achieving target trough concentrations of 15-20 mg/L suggested by the vancomycin consensus guidelines. Pharmacotherapy. 2011;31(5):441-448. doi: 10.1592/phco.31.5.441
15. O'brien KA, Mok S. Evaluation of the safety of a vancomycin nomogram used to achieve target trough concentrations. Hosp Pharm. 2015;50(10):900-910. doi: 10.1310/hpj5010-900
16. Leu WJ, Liu YC, Wang HW, Chien HY, Liu HP, Lin YM. Evaluation of a vancomycin dosing nomogram in achieving high target trough concentrations in Taiwanese patients. Int J Infect Dis. 2012;16(11):e804-e810. doi: 10.1016/j.ijid.2012.07.005
17. Finch NA, Zasowski EJ, Murray KP, Mynatt RP, Zhao JJ, Yost R, Pogue JM, Rybak MJ. The impact of vancomycin area under the concentration-time curve-guided dosing on vancomycin-associated nephrotoxicity: a quasi-experiment. Antimicrob Agents Chemother. 2017;61(12): e01293-e01217. doi: 10.1128/AAC.01293-17