Journal of Pharmacoeconomics & Pharmaceutical Management

Journal Homepage: jppm.tums.ac.ir

Common Errors Related to Vancomycin Pharmacokinetics, Prescribed by Physicians in Iran: Suggesting Practical Approaches for Adjusting the Right Dose

Saghar Barati[1], **Zahra Sahraei**[1]

1. Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Use your device to scan and read the article online

Citation Barati S, Sahraei Z. Common Errors Related to Vancomycin Pharmacokinetics, Prescribed by Physicians in Iran: Suggesting Practical Approaches for Adjusting the Right Dose. Journal of Pharmacoeconomics and Pharmaceutical Management. 2018; 4(1-2):1-9.

Running Title Common Errors Related to Vancomycin Pharmacokinetics in Iran

Article Type Original Article

Article info:

Received: 25.04.2017

Revised: 12.06.2017

Accepted: 10.08.2017

Keywords:

Inappropriate prescribing, Iran, Pharmacokinetics, Vancomycin

ABSTRACT

Background: Vancomycin is a glycopeptide antibiotic that is widely used for the treatment of gram-positive microorganisms, including methicillin-resistant Staphylococcus aureus. It is a valuable antibiotic in practice; unfortunately, its excessive use and mistakes in prescription have increased bacterial resistance. Hence, this study seeks to investigate the common errors related to the pharmacokinetics of vancomycin prescription in teaching hospitals in Iran.

Methods: This study is an observational study that research orders with errors related to pharmacokinetics parameters of vancomycin. A total of 150 patients were enrolled in the study from May 2016 to September 2018 in teaching hospitals. Errors in drug prescription were identified based on literature resources.

Results: About 22.7% of patients did not receive the loading dose. Also, 85.3% of patients were prescribed a fixed dose, instead of weight-based dosing. About 46% of patients had kidney problems (chronic kidney disease or acute kidney injury) and all of them had received a much lower dose than they needed according to guidelines. Another 46% of patients did not undergo therapeutic dose monitoring correctly. Finally, 69.3% of patients had not received consequent doses after encountering a nontherapeutic trough level correctly. Also, none of 22 obese patients with a body mass index of greater than 40 kg/m^2, had received the proper dose.

Conclusion: Since the incorrect use of vancomycin significantly increases the prevalence of resistant organisms and, consequently, the mortality rate of patients, it is necessary to define guidelines for its use in the hospital.

*** Corresponding Author:**

Zahra Sahraei, PhD.

Address: *Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

E-mail: *zahra.sahraei@yahoo.com*

1. Introduction

Vancomycin is a glycopeptide antibiotic that has been in clinical use for a long time to treat the strains of Staphylococcus aureus [1, 2]. It is one of the most widely used antibiotics for the treatment of serious gram-positive infections, including Methicillin-Resistant S. Aureus (MRSA) [2], which is the most prevalent multi-drug resistant gram-positive pathogen in the world [2]. Unfortunately, excessive use of vancomycin during recent years has resulted in the development of vancomycin resistance strains, including vancomycin-resistant enterococci worldwide [3].

Errors related to medication prescription and administration are the most common type of medical errors in primary and secondary healthcare centers [4]. Kuo et al. reported that prescription errors account for 70% of medication errors, which increase morbidity and mortality for the patients [4]. In a study in Iran, more than half of the patients (56.2%) received vancomycin inappropriately, and the correct indication of prescribing was from 32% at the beginning of the prescribed period to 30.5% after 24 hours and 9% after 72 hours, and only 5.5% of the patients received the medication reasonably [5].

All types of vancomycin medical errors may happen during the prescription and administration phase, like administering the wrong drug for a specific indication, neglecting drug interactions or intravenous incompatibilities, prescribing the wrong dose. These mistreatments concerning the pharmacokinetic profile of vancomycin may lead to a nontherapeutic serum trough level despite choosing the proper antibiotic, which consequently results in vancomycin resistance or toxicity.

Regarding the concerns in this issue, and the lack of appropriate alternatives to vancomycin, the rational use of this drug is an important consideration. It seems necessary to prevent prescribing errors of vancomycin, which may lead to vancomycin resistance due to a nontherapeutic trough level and an increase in mortality rates of the patients. We tried to investigate common pharmacokinetics mistakes in the administration of vancomycin in Iran and provide rational guidelines for the appropriate dosing based on pharmacokinetic parameters.

2. Methods

This research was conducted at five teaching referral hospitals in different fields such as “Infectious diseases”, “Nephrology Diseases”, “Cardiac surgery”, “pulmonary diseases”, and “Gastrointestinal diseases” in Tehran. An observational study was done from May 2016 to September 2018. We reviewed all orders of vancomycin in the wards of the hospitals, including the intensive care units. Indications for ordering vancomycin were considered in each ward, and the prescribed dose, along with other aspects of vancomycin, were evaluated based on pharmacokinetic parameters. Any inpatient older than 12 years was included in the study.

A total of 150 patients and their vancomycin orders were evaluated during our rotations in 5 hospitals. These patients were admitted to the hospital at the time we spend there, and all of them were evaluated. The six mostly done mistakes related to pharmacokinetic parameters were sought: neglecting the loading dose, prescribing a fixed dose regardless of patient weight, extreme dose adjustment in renal failure, lack of therapeutic dose monitoring or not doing it properly, wrong approach to a nontherapeutic trough level, and inappropriate dose of vancomycin in obese patients or patients with volume status changes. The study data were gathered and entered into SPSS V. 23, and the frequency and percentages of each error were calculated.

3. Results

Results are shown in Table 1. Note that some patients had more than one prescribing error. Among 150 patients, the loading dose was neglected in 34 patients (22.7%). A fixed dose (instead of weight-based dosing) was prescribed for 128 patients (85.3%). The area under the serum concentration time curve (AUC) / Minimum Inhibitory Concentration (MIC) ratio was calculated for the patients based on the formula presented in “Clinical Pharmacokinetics” (explained thoroughly in the discussion section) [6]. Among 128 patients who had received a fixed dose regardless of their weight, 79 patients (61.7%) achieved the AUC/MIC ≥400, and the others did not meet the goal. Among the other 22 patients who had received weight-based dosing, 19 patients (86.4%) achieved the AUC/MIC ≥ 400 (P=0.02).

Out of the study patients, 69 (46%) had kidney problems (chronic kidney disease or acute kidney injury), and all of them had received a much lower dose than they needed according to guidelines [7]. Also, 69 patients (46%) did not undergo therapeutic dose monitoring cor-

Table 1. Percentage of each pharmacokinetic prescribing error

Error Type	No. (%)
Neglecting the loading dose	34 (22.7)
Prescribing a fixed dose instead of weight-based dosing	128 (85.3)
Extreme dose adjustment in renal failure or intermittent hemodialysis state	69 (46)
Lack of therapeutic dose monitoring or doing it not properly	69 (46)
Wrong approach to a nontherapeutic trough level	104 (69.3)
Inappropriate dosing of vancomycin in obese patients and patients with volume status changes	22 (14.7)

JPPM

rectly. Another 104 patients (69.3%) had not received consequent doses after encountering a nontherapeutic trough level correctly. Finally, none of 22 patients with a Body Mass Index (BMI) of greater than 40 kg/m^2 had received the proper dose.

4. Discussion

Neglecting the loading dose

Out of 150 patients, 34 patients (22.7%) had not received the loading dose of vancomycin. For the treatment of severe MRSA infections, such as endocarditis, pneumonia, meningitis, and sepsis, a loading dose of 25-30 mg/kg is recommended (based on actual body weight) to reach the desired trough concentration during the first 24-48 hours [8-10]. Given the risk of red man syndrome and possible anaphylaxis associated with large doses of vancomycin, the infusion time must be prolonged [11]. Each 1 g of vancomycin must be administered at least in 1 hour [8, 12]. A maximum single dose should not exceed 2000 mg [8] or 2500 mg [9]. Stanford university medical center suggests dose adjustments of 15-20 mg/kg^2 to be considered in patients with pre-existing renal failure [8].

Loading dose was neglected in 22.7% of hospitalized patients with serious infections. Because of the importance of achieving the therapeutic level soon for eradicating dangerous, life-threatening pathogens, it is necessary to consider a loading dose [9].

Prescribing a fixed dose instead of weight-based dosing

A fixed dose (instead of weight-based dosing) was prescribed for 128 patients (85.3%). The administration of vancomycin should be based on the weight of each patient. The parameter that best predicts the efficacy of vancomycin is the ratio of AUC to MIC [13]. The susceptibility breakpoint of vancomycin is 2 mg/L for S. aureus, and 4 mg/L for coagulase-negative Staphylococcus and Enterococcus spp, set by the Clinical and Laboratory Standards Institute (CLSI) [14], meaning that all S. aureus isolates with MICs of 2 mg/L or less and all coagulase-negative Staphylococcus and Enterococcus spp with MICs of 4 mg/L or less are susceptible to vancomycin, and the higher MICs are intermediate or resistant [14].

Despite these breakpoints, some reports have suggested that patients infected with S. aureus isolates who have MICs of 1-2 mg/L are less likely to have treatment success with vancomycin compared with those with lower MICs [13]. The AUC/MIC ratio of ≥400 is reasonable for pathogens with a MIC of 1 mg/L [13]. With higher MIC, the AUC must be higher to achieve treatment success [13]. In general practice, the MIC is considered to be 1 mg/L while using vancomycin as an efficient option [15-17]. A study involving patients with lower respiratory tract infections caused by S. aureus reported that an AUC/MIC ≥400 compared with an AUC/MIC< 400 was associated with improved clinical response and microbiologic eradication [18]. Here are some practical formulas derived from the book "Clinical Pharmacokinetics" for calculating vancomycin dosing based on the AUC/MIC ratio to understand its importance [6].

Estimating initial dose of vancomycin:

Step 1: Consider the loading dose of 25-30 mg/kg^2

Step 2: Maintenance dose should be based on 15-20 mg/kg every 8-12 hours

Step 3: Calculate vancomycin clearance (Clvanc). Clearance of vancomycin is achievable through various

formulas, according to previous studies, the Matzke et al. [19] formula is closer to actual results (Formula 1) [6]. For example, for an individual with Glomerular Filtration Rate (GFR) = 120 mL/min:

Formula 1.

Clvanc (mL/min)=(0.689× creatinine clearance [CrCl])+ 3.66 (Matzke method)

Clvanc (mL/min)=(0.689×120)+3.66

Clvanc (mL/min)=86.34 mil/min

Clvanc (L/h)=55.34 mil/min ×0.06=5.180 L/h

Step 5: Calculate $AUC_{0\text{-}24h}$ Using Formula 2:

Formula 2.

$$AUC_{0\text{-}24h}=\left(\frac{Daily\ dose}{Vancomycin\ clearance}\right)$$

In a person with a dose of 500 mg BD (twice a day): $AUC_{0\text{-}24h}=\frac{1000}{5.180}=193$

In a person with a dose of 750 mg BD: $AUC_{0\text{-}24h}=\frac{1500}{5.180}=289$

In a person with a dose of 1 mg BD: $AUC_{0\text{-}24h}=\frac{2000}{5.180}=386$

In a person with a dose of 1250 mg BD: $AUC_{0\text{-}24h}=\frac{2500}{5.180}=482$

Assuming the 1250 mg BD dosing:

If MIC was 0.5 mg/L: AUC24/MIC = 482 mg•h/L/0.5 mg/L=964

If MIC was 1.0 mg/L: AUC24/MIC =482 mg•h/L/1.0 mg/L =482

If MIC was 2.0 mg/L: AUC24/MIC =482 mg•h/L/2.0 mg/L =241

In general practice, MIC is considered to be 1 mg/L. Regarding the difficulties in calculating AUC in clinical practice, measuring serum trough levels of vancomycin (minimum concentration of vancomycin can be measured just before the next dose in the steady-state level) is a practical alternative that correlates with AUC. For the treatment of the infection related to the endocardium and bacteremia, the trough concentrations of 15-20 mg/L is ideal [13].

Trough concentrations less than 10 mg/L are associated with an increase in the development of vancomycin resistance [20, 21]. In these patients, 1250 mg twice a day is expected to produce a 15-20 mg/L trough level as it produces an AUC/MIC ratio of 486, which is higher than 400 and correlates with trough level of greater than 15 mg/L [22, 23]. In an individual with a bodyweight of 85 kg and normal kidney function, the dose of 1 g BD (twice a day) will not achieve the AUC/MIC ≥ 400. In cases with MIC >1 mg/L, the AUC/MIC ratio above 600-700 will be the goal of treatment that will increase the risk of renal toxicity [24].

The probability of achieving target AUC/MIC >400 is 100% for vancomycin MIC of 0.5 mg/L and 0% of the MIC value of 2 mg/L even if aggressive dosing strategies are used [25]. In patients with normal renal function, up to 3-4 g/d of vancomycin may be required to attain the target AUC/MIC ratio.

Vancomycin is injected at a dose of 15-20 mg/kg every 8 to 12 hours. If the MIC is 1 mg/L or less, the dose of 1 g BD could produce an AUC/MIC ratio of >400 in a proportion of subjects, not all of them. The data from animal models, in vitro and human studies, suggest that microbiologic success is optimized when the vancomycin AUC/MIC ratio exceeds 400. Also, to improve the clinical outcomes of complicated infections such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by S. aureus, total trough serum vancomycin concentrations of 15–20 mg/L are recommended to achieve target AUC/MIC [11, 13, 18, 26, 27].

Our recommendations are in line with a study done by Shahrami et al. that the necessity of early individualization and weight-based dosing of vancomycin was required for achieving goal trough levels, and the fact was concluded based on the results [28].

Extreme dose adjustment in renal failure or intermittent hemodialysis state

All of the patients with kidney problems had been received much lower doses than they should. Most physicians reduce vancomycin dosing, more than it is needed, in renal failure or patients on intermittent hemodialysis with concerns about nephrotoxicity. This action results in subtherapeutic concentrations of vancomycin and increasing the risk of treatment failure. Dose adjustment in renal failure should be made as follows in Table 2 [7].

Table 2. Vancomycin dosing guide in renal failure

Creatinine Clearance (mL/min)	Weight (kg)		
	40-55	55-75	75-100
	500 mg	750 mg	1000 mg
81-100	Q8H	Q12H	Q18H
54-80	Q12H	Q18H	Q24H
40-53	Q18H	Q24H	Q36H
27-39	Q24H	Q36H	Q48H
21-26	Q36H	Q48H	Q72H
16-20	Q48H	Q60H	Q84H
13-15	Q60H	Q84H	Q108H
10-12	Q72H	Q108H	Q144H

Intermittent hemodialysis

Loading dose must be considered (15-20 mg/kg), regardless of the dialysis schedule and patient renal function; this ensures rapid target concentration attainment. A random level should be drawn before the next hemodialysis session, and the trough level measured should guide the post hemodialysis dosing, as 30%-40% of vancomycin is removed after each high-flux hemodialysis session [29]. Patients should receive the drug again (usually 15 mg/kg) when the random vancomycin concentrations are less than 10-20 mg/L depending on the severity of the infection.

Random vancomycin concentrations of 15-20 mg/L are recommended for severe infections [29]. In a study, a loading dose of 1000 mg was considered during dialysis and subsequent 1-g doses were administered at the last hour of each dialysis session and almost the whole patients achieved serum trough level of more than 10 mg/L before the fourth dose and only 5% had a serum trough level of greater than 25 mg/L [30]. Physicians mostly neglect the two consecutive days and administer every 48-72 hours from the first day of therapy.

Continuous renal replacement therapy

Proper dosing of vancomycin in continuous renal replacement therapy requires close monitoring of therapeutic response, signs of adverse reactions due to drug accumulation, and target trough concentrations. The dosing recommendations are as follows [31]:

Continuous venovenous hemofiltration: A loading dose of 15–25 mg/kg, followed by 15 mg/kg every 24–48 hours or 500 mg q 24 h to 1500 mg q 48 h.

Continuous venovenous hemodialysis: A loading dose of 15-25 mg/kg, 15 mg/kg every 24 hor 1-1.5 g q 24 h

Continuous venovenous hemodiafiltration: A loading dose of 15-25 mg/kg, 15 mg/kg every 12 h or 1-1.5 g q 24 h

Dose adjustment in acute kidney injury

Adjusting Vancomycin dosing is not always necessary in AKI secondary to sepsis, as a rise in serum creatinine is a predictor of achieving a trough level of more than 15 mg/L [32]. Regarding the action of therapeutic dose monitoring, dose adjustment can be done whether supra/sup therapeutic concentrations of vancomycin are detected. Table 3 shows the diagnostic criteria of AKI based on AKIN and RIFLE criteria [33].

Lack of therapeutic dose monitoring or doing it improperly

A total of 69 patients (46%) did not undergo therapeutic dose monitoring correctly in our study. Measuring the vancomycin trough level is not always required. In patients with stable renal function, which the duration of treatment with vancomycin is expected to be ≤3-5 days, no therapeutic dose monitoring is needed [13]. Otherwise, trough concentrations of vancomycin are required as a marker to predict the AUC/MIC ratio. Vancomycin trough concentrations of 10-15 mg/L may be

Table 3. Diagnostic criteria of acute kidney injury based on AKIN and RIFLE criteria

Stage (Severity)	Serum Creatinine Concentration	Urine Output
Stage 1 (risk)	1.5–2× increase from baseline; or ≥0.3 mg/dL; or decrease in GFR >25%	< 0.5 mL/kg/h for >6 h
Stage 2 (injury)	2–3× increase from baseline; or decrease in GFR >50%	< 0.5 mL/kg/h for >12 h
Stage 3 (failure)	3× increase from baseline; or >4 mg/dL with an acute rise >0.5 mg/dL ; or on RRT; or decrease in GFR >75%	< 0.3 mL/kg/h for 24 h, or anuria for >12 h

GFR: Glomerular Filtration Rate; RRT: Renal Replacement Therapy

JPPM

acceptable in the skin and soft tissue infections. A minimum trough concentration of 10 mg/L is required to avoid resistance development [20]. However, a trough concentration of at least 15 mg/L is required for more severe infections [34].

For patients with an estimated creatinine clearance (CrCl) of ≥20 mL/min, vancomycin trough levels should be drawn before the fourth dose (steady state). Measuring trough concentrations before steady-state concentration may overestimate or underestimate the exact concentration. For patients with an estimated CrCl <20 mL/min, a random level can be drawn on day 3 (24 hours after the second dose) [13].

Follow-up trough concentrations can be performed weekly in hemodynamically stable patients. More frequent vancomycin trough concentrations may be required in critically-ill patients, individuals with unstable renal function or on concomitant nephrotoxic drug therapy, older patients with every 8 hours dosing administration, and patients who do not respond or deteriorate on current dosing. Note that the vancomycin trough level should not be drawn from the same infusion site [35].

The wrong approach to a nontherapeutic trough level

About 69.3% of patients did not receive the proper dose or interval after developing a nontherapeutic trough level. Based on our observations, clinicians generally increase the dosage in the case of nontherapeutic trough level or hold and reduce the dose if the trough is above the therapeutic limit, which is not necessarily correct. A practical approach when encountering a nontherapeutic trough level is as follows [36]:

$$\left(\frac{dose}{interval}\right)_{new}=\left(\frac{dose}{interval}\right)_{current}\times\left(\frac{c\ desired}{c\ measured}\right)$$

If the ratio of C desired/C measured is 1.5 or higher, the interval should be reduced (from 12 hours to 8 hours or from 24 hours to 12 hours), and if the ratio is less than 0.67, the interval should be increased (from 8 hours to 12 hours, from 12 hours to 24 hours or from 24 hours to 36 hours). If the ratio is between 0.67 and 1.5, then the dose will be altered without changing the interval.

For example, in a person with pneumonia who is on vancomycin 750 mg BD with a trough level of 10 mg/L, the desired trough is 15-20 mg/L. The ratio of the desired trough (17 mg/L) to the measured (10 mg/L) one is 1.7 which is higher than 1.5. So intervals should be reduced to every 8 hours without changing the dose.

If the trough level measured was 13 mg/L, the ratio (1.30) is between 1.5 and 0.67. So the dose should be altered without changing the interval:

Calculating the new dose: $\left(\frac{dose}{12}\right)_{new}=\left(\frac{750}{12}\right)_{current}\times\frac{17}{13}$

The new dose is approximately 980 mg BD, which can be rounded to 1000 mg BD.

Another simple equation for calculating the new dose in situations which the ratio of $\frac{C\ desired}{C\ measured}$ is between 1.5 and 0.67 is as follows: $Dose_{new}=Dose_{current}\left(\frac{C\ desired}{C\ measured}\right)$.

Note that "c" refers to the concentration of vancomycin in human serum.

For example, in a person with pneumonia who is on vancomycin 750 mg BD and trough level of 13 mg/L, the desired trough is 15-20 mg/L.

$Dose_{new}=750\left(\frac{17}{13}\right)=980$ mg, which should be administered twice a day and can be rounded to 1000 mg twice daily. It is also possible to estimate the concentration from dose [6] :

$$C_{new}=C_{current}\left(\frac{D\ new}{D\ current}\right)$$

$$C_{new}=13\left(\frac{1000}{750}\right)=17.3\ mg/ml$$

Generally, in low trough concentration, the dose of 750 mg BD will be increased to 1000 mg BD by physicians, which is not necessarily a correct approach, because it may still cause treatment failure.

Estimating the new AUC from the new dose is also possible from this simple equation:

$$AUC_{new} = AUC_{current} \left(\frac{D\ new}{D\ current}\right)$$

Trough concentration of vancomycin must be re-evaluated after determining the new dose and interval by the fourth dose or earlier if the patient is hemodynamically unstable with alterations in renal function or if the dosing interval is >24 hours. Note that whenever the trough level is above the goal (20-25 mcg/mL for a target of 15-20 mcg/mL), it is better to continue treatment with the new dose rather than holding vancomycin administration. Trough levels can be measured before the fourth dose after adjusting the new dose.

Inappropriate dosing of vancomycin in obese patients and patients with volume status changes

All of the obese patients in our study (14.7%) received a lower dose than they should. Physicians mostly prescribe the lower doses of vancomycin (<10 mg/L) in obese patients, concerning its nephrotoxicity, whereas it leads to a nontherapeutic trough level. Vancomycin dosing should be based on actual body weight in obese patients (>30% above ideal body weight), following the loading doses [8, 37]. There is a possibility to increase the dose up to 60 mg/kg/d. Single doses should not exceed 2 g. Each 1 g should not be administered in less than an hour [8, 12]. In the case of a nontherapeutic trough level, shortening the interval or continuous infusion is a reasonable approach [35, 37].

5. Conclusion

Despite extensive clinical use of vancomycin in recent years, the optimal dosing strategy for rapid achievement of therapeutic concentrations has remained a challenge for physicians. Intervention strategies should be primarily focused on the education and creation of a safe and cooperative working environment to minimize harm to the patient. Clinical pharmacists have an essential role in setting the appropriate dose which produces desired trough levels, and it is best to consult them for achieving treatment success.

Ethical Considerations

Compliance with ethical guidelines

Data were gathered in coordination with Deputy of Treatment of Shahid Beheshti University of Medical Sciences in each educational hospital.

Funding

This research did not receive any special grants from anywhere.

Authors contributions

All authors contributed in preparing this paper.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgements

The authors are thankful to the staff of Loghman Hakim, Labbafinezhad, Taleghani, Imam Hossein, and Masih Daneshvari hospitals.

References

[1] Tunkel AR, Hasbun R, Bhimraj A, Byers K, Kaplan SL, Scheld WM, et al. 2017 infectious diseases society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. Clin Infect Dis. 2017; 64(6)701-6. [DOI:10.1093/cid/cix152] [PMID] [PMCID]

[2] Moellering RC Jr. Vancomycin: A 50-year reassessment. Clin Infect Dis. 2006; (42 Suppl 1):S3-4. [DOI:10.1086/491708] [PMID]

[3] Bonten MJ, Willems R, Weinstein RA. Vancomycin-resistant enterococci: why are they here, and where do they come from? Lancet Infect Dis. 2001; 1(5):314-25. [DOI:10.1016/S1473-3099(01)00145-1] [PMID]

[4] Kuo GM, Touchette DR, Marinac JS. Drug errors and related interventions reported by United States clinical pharmacists: The American college of clinical pharmacy practice-based research network medication error detection, amelioration and prevention study. Pharmacotherapy. 2013; 33(3):253-65. [DOI:10.1002/phar.1195] [PMID]

[5] Ayubi MS, Elyasi S, Jannati M, Vahdati-Mashhadian N, Saberi MR, Naderi HR, et al. Vancomycin utilization evaluation in a tertiary teaching hospital in Mashhad, Iran. J Pharm Care. 2018; 5(3-4):44-48.

[6] Murphy JE. Basic & Applied Pharmacokinetics Self Assessment. 2014: ASHP. Maryland: Bethesda; 2014.

[7] Brown DL, Mauro LS. Vancomycin dosing chart for use in patients with renal impairment. Am J Kidney Dis. 1988; 11(1):15-9. [DOI:10.1016/S0272-6386(88)80168-9] [PMID]

[8] Stanford Hospital & Clinics, Stanford University Medical center. Adult Vancomycin Loading Dose Guidelines for the ED [Internet]. 2013 [Updated 2013 May] Available from: http://med.stanford.edu/content/dam/sm/bugsanddrugs/documents/dosing/2013VancEDloadingdose_000.pdf

[9] Šíma M, Hartinger J, Cikánková T, Slanař O. Importance of vancomycin loading doses in intermittent infusion regimens. J Infect Chemother. 2018; 24(4):247-50. [DOI:10.1016/j.jiac.2017.11.002] [PMID]

[10] Álvarez O, Plaza-Plaza JC, Ramirez M, Peralta A, Amador CA, Amador R. Pharmacokinetic assessment of vancomycin loading dose in critically ill patients. Antimicrob Agents Chemother. 2017; 61(8)e00280-17. [DOI:10.1128/AAC.00280-17] [PMID] [PMCID]

[11] Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al., Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011; 52(3): e18-55. [DOI:10.1093/cid/ciq146] [PMID]

[12] Sivagnanam S, Deleu D. Red man syndrome. Crit Care. 2003; 7(2):119-20. [DOI:10.1186/cc1871] [PMID] [PMCID]

[13] Rybak M, Lomaestro B, Rotschafer JC, Moellering R Jr, Craig W, Billeter M, 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(1):82-98. [DOI:10.2146/ajhp080434] [PMID]

[14] Weinstein MP, Patel JB, Bobenchik AM, Campeau S, Cullen SK, Galas MF, et al. Performance standards for antimicrobial susceptibility testing. Pennsylvania: Clinical and Laboratory Standards Institute; 2016.

[15] Kishk OA, Lardieri AB, Heil EL, Morgan JA. Vancomycin AUC/MIC and corresponding troughs in a pediatric population. J Pediatr Pharmacol Ther. 2017; 22(1):41-7. [DOI:10.5863/1551-6776-22.1.41] [PMID] [PMCID]

[16] Moise PA, Forrest A, Bhavnani SM, Birmingham MC, Schentag JJ. Area under the inhibitory curve and a pneumonia scoring system for predicting outcomes of vancomycin therapy for respiratory infections by Staphylococcus aureus. Am J Health Syst Pharm. 2000; 57(Suppl. 2):S4-9. [DOI:10.1093/ajhp/57.suppl_2.S4] [PMID]

[17] Rodriguez CA, Agudelo M, Zuluaga AF, Vesga O. Generic vancomycin enriches resistant subpopulations of Staphylococcus aureus after exposure in a neutropenic mouse thigh infection model. Antimicrob Agents Chemother. 2012; 56(1):243-7. [DOI:10.1128/AAC.05129-11] [PMID] [PMCID]

[18] Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clinical pharmacokinet. 2004: 43(13):925-42. [DOI:10.2165/00003088-200443130-00005] [PMID]

[19] Matzke GR, McGory RW, Halstenson CE, Keane WF. Pharmacokinetics of vancomycin in patients with various degrees of renal function. Antimicrobial Agents and Chemother. 1984; 25(4):433-7. [DOI:10.1128/AAC.25.4.433] [PMID] [PMCID]

[20] Howden BP, Ward PB, Charles PG, Korman TM, Fuller A, du Cros P, et al. Treatment outcomes for serious infections caused by methicillin-resistant staphylococcus aureus with reduced vancomycin susceptibility. Clin Infect Dis. 2004; 38(4):521-8. [DOI:10.1086/381202] [PMID]

[21] Charles PG, Ward PB, Johnson PD, Howden BP, Grayson ML. Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate Staphylococcus aureus. Clin Infect Dis. 2004; 38(3):448-51. [DOI:10.1086/381093] [PMID]

[22] Bel Kamel A, Bourguignon L, Marcos M, Ducher M, Goutelle S. Is Trough concentration of vancomycin predictive of the area under the curve? a clinical study in elderly patients. Ther Drug Monit. 2017; 39(1):83-7. [DOI:10.1097/FTD.0000000000000359] [PMID]

[23] Neely MN, Youn G, Jones B, Jelliffe RW, Drusano GL, Rodvold KA, et al. Are vancomycin trough concentrations adequate for optimal dosing? Antimicrob Agents Chemother. 2014; 58(1):309-16. [DOI:10.1128/AAC.01653-13] [PMID] [PMCID]

[24] Ibrahim N, Manan MM. AUC/MIC ratio as a tool in determining effectiveness of garasent® for the prevention of early onset sepsis in hospitalized neonates. Int J Pharm Pharm Sci. 2014; 6(Suppl 3):24-8.

[25] Mohr JF, Murray BE. Point: Vancomycin is not obsolete for the treatment of infection caused by methicillin-resistant Staphylococcus aureus. Clin Infect Dis. 2007; 44(12):1536-42. [DOI:10.1086/518451] [PMID]

[26] Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis. 2006; 42(Supplement_1):S35-9. [DOI:10.1086/491712] [PMID]

[27] Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of β-lactams, glycopeptides, and linezolid. Infect Dis Clin North Am. 2003; 17(3):479-501. [DOI:10.1016/S0891-5520(03)00065-5] [PMID]

[28] Shahrami B, Najmeddin F, Mousavi S, Ahmadi A, Rouini MR, Sadeghi K. Achievement of vancomycin therapeutic goals in critically ill patients: Early individualization may be beneficial. Crit Care Res Pract. 2016; 2016:1245815. [DOI:10.1155/2016/1245815] [PMID] [PMCID]

[29] Crew P, Heintz SJ, Heintz BH. Heintz, vancomycin dosing and monitoring for patients with end-stage renal disease receiving intermittent hemodialysis. Am J Health Syst Pharm. 2015; 72(21):1856-64. [DOI:10.2146/ajhp150051] [PMID]

[30] Taylor ME, Allon M. Practical vancomycin dosing in hemodialysis patients in the era of emerging vancomycin resistance: A single-center experience. Am J Kidney Dis. 2010; 55(6):1163-5. [DOI:10.1053/j.ajkd.2010.03.016] [PMID] [PMCID]

[31] Trotman RL, Williamson JC, Shoemaker DM, Salzer WL. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. Clin Infect Dis. 2005; 41(8):1159-66. [DOI:10.1086/444500] [PMID]

[32] Blot S, Lipman J, Roberts DM, Roberts JA. The influence of acute kidney injury on antimicrobial dosing in critically ill patients: Are dose reductions always necessary? Diagn Microbiol Infect Dis. 2014; 79(1):77-84. [DOI:10.1016/j.diagmicrobio.2014.01.015] [PMID]

[33] Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney International Supplements. 2012. 2(1):1-138.

[34] Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant Staphylococcus aureus bacteremia: Support for consensus guidelines suggested targets. Clin Infect Dis. 2011; 52(8):975-81. [DOI:10.1093/cid/cir124] [PMID]

[35] Reseau De Sante Horizon Health Network, Reseau De Sante Vitalite Health Network. Vancomycin dosing & monitoring guideline [Internet] 2018 [Updated 2018 Sep]. Available from: https://en.horizonnb.ca/media/927891/vancomycin_dosing_and_monitoring_guidelines.pdf

[36] Herman RA. Cases: Gentamicin &vancomycin pharmacokinetics [Internet]. 2016 [Updated 2016 Feb 29]. Available from: https://rherman.pharmacy.uiowa.edu/CPK/AbxCasesHandout.pdf

[37] Ziadi STR, Roberts JA. Drug dosing in obesity. Sydney: Springer; 2016.