REVIEW

Vancomycin dosing nomograms targeting high serum trough levels in different populations: pros and cons

Sepideh Elyasi[1] · Hossein Khalili[2]

Abstract

Purpose Utilization of higher doses of vancomycin to achieve the trough concentrations of 15–20 mg/L for complicated infections has been recommended by the Infectious Diseases Society of America clinical practice guideline in recent years. Concerning this recommendation, several nomograms have been constructed targeting this optimal trough level range in different populations of patients. In this review, we have collected available nomograms targeting high trough serum levels of vancomycin, particularly comparing their advantages and limitations.

Method The data were collected by searching Scopus, PubMed, Google scholar, Medline, and Cochrane database systematic reviews. The key words used as search terms were "vancomycin", "high trough level", "dosing nomogram", "dosing strategy", "neonates", "critically ill", "pediatrics", and "hemodialysis". We have included 17 related human studies published up to the date of this publication.

Results & conclusion Most of the available nomograms have determined the doses according to body weight and renal function. Their initial predicting success rate were 44–76 % for non-critically ill patients, 42–84 % for critically ill patients, 54 % for one nomogram specially designed for hemodialysis

patients, and 71 % for the only nomogram developed for neonates. Based on validation studies, in most of cases, using a vancomycin dosing nomogram significantly improved and accelerated achievement of target trough concentrations. However, it should be noted that there are limited data about patients' clinical and microbiological outcomes and they are only validated in narrow groups of patients. Thus, their widespread application could not be encouraged for all patients before performing adequately powered, prospective randomized studies.

Keywords Vancomycin · Dosing nomogram · High trough level

Background

For the last several decades, vancomycin has been the mainstay of therapy for methicillin-resistant *Staphylococcus aureus* (MRSA) infections in most of cases, and still remains the first-line choice [1–11].

Vancomycin has complicated pharmacokinetic characteristics that may be highly variable among different patients depending on their age, weight, concomitant diseases and especially renal function [1–3, 5, 8]. Thus, it is highly recommended to determine vancomycin doses individually and to monitor serum trough concentration as a surrogate marker instead of the area under the curve (AUC)/minimum inhibitory concentration (MIC), which is the best determinant of vancomycin efficacy. This is particularly important in conditions like prolonged vancomycin therapy (i.e., more than 48 to 72 h), renal impairment, pregnancy, burns, obesity, and also in critically ill patients to ensure that the therapeutic, nontoxic dose reaches the patients [5, 6, 9, 12, 13].

✉ Sepideh Elyasi
  elyasis@mums.ac.ir

1 Department of Clinical Pharmacy, Faculty of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

2 Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Previously, appropriate trough concentrations were considered to be between 5 and 15 mg/L, but due to the rising MIC values of MRSA for vancomycin, recommended trough concentrations have recently increased [9, 14].

A review published through a collaboration of the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP) recommended optimizing vancomycin dosing by use of actual body weight (15–20 mg/kg/dose IV administered every eight to 12 h) to achieve a trough concentration between 15 and 20 mg/L for complicated infections including endocarditis, osteomyelitis, meningitis, and hospital-acquired, health care-associated, or ventilator-associated pneumonia, and above 10 mg/L for other indications [15]. Targeting these higher trough concentrations increases the probability of achieving an AUC24/MIC ratio of 400 or higher, which is the best predictor of vancomycin efficacy [6, 9–11, 15, 16]. Moreover, it increases drug penetration to target sites, which may improve clinical outcomes [1, 2, 4]. However, inconsistent findings have been reported in some studies [4, 17–19].

Different nomograms have been developed to individualize pharmacokinetic monitoring of vancomycin. The use of a vancomycin dosing nomogram has been proven to be more cost-effective than conventional dosing. Moreover, it could increase the probability of achieving the target serum range, and requires minimal information about patients [5, 6, 18]. But several available vancomycin dosing nomograms, which are based on linear and non-linear regression, are complex models that need specialized pharmacokinetic information and costly computer programs with target trough serum concentrations of only 5–15 mg/L [20–24]. So, a necessity to develop novel nomograms targeting higher trough levels is thus identified [1–3, 5]. Now, some dosing nomograms have been designed to achieve these high trough levels.

In this review, we have collected available evidences about dosing nomograms for achieving vancomycin high trough levels in different populations, regarding their advantages and limitations.

Methods

The data were collected by searching the Scopus, PubMed, Google scholar, Medline, and Cochrane database systematic reviews. The key words used as search terms were "vancomycin", "high trough level", "dosing nomogram", "dosing strategy", "neonates", "critically ill", "pediatrics," and "hemodialysis".

Randomized clinical trials and prospective or retrospective observational human studies about vancomycin dosing nomogram development and validation for achieving high serum trough levels in different populations such as pediatrics, neonates, and critically and non-critically ill patients were included in this review. Twenty-one articles were retrieved in this field.

Irrelevant articles (basic experimental studies, non-English language reports, studies that did not include clinical endpoint assessments, and case reports) were excluded. A total of 17 relevant human studies published up to the date of this publication were included for review.

Results

This study is reported according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guideline [25].

A flowchart presenting the process of initiation and selection of the studies is shown in Figure 1. In the final step of selection, 17 eligible articles were included in this systematic review, which are summarized in Table 1.

Vancomycin dosing nomograms: non-critically ill patients

Most of the available vancomycin dosing nomograms were developed for use in non-critically ill patients.

Thalakada et al. [3] performed a retrospective study on patients who received vancomycin from January 2008 to June 2010, and had achieved a trough level of 14.5–20.5 mg/L, in two Canadian hospitals (St. Paul's & Vancouver General hospitals). They developed a vancomycin dosing nomogram for each hospital and finally an integrated nomogram by merging findings from both centers. Seventy-eight and 91 patients from St. Paul's and Vancouver General hospitals, respectively, were assigned to the development group. Multiple linear regression with age, initial serum creatinine and actual body weight were used as variables to predict dosing intervals. As actual body weight was not significantly associated with the predicted dosing interval, they omitted it from the regression equation. A loading dose of 25 mg/kg and a maintenance dose of 15 mg/kg (maximum: 2500 mg/dose) with dosing intervals mentioned in Table 1 (suppl.) was the final recommendation of Thalakada et al. Nomogram validation was performed using the second group of patients for whom the nomogram correctly predicted the appropriate dosing interval to attain a target trough level. The integrated nomogram had a prediction success rate of 56 %. As q18h dosing is rarely prescribed in the clinical setting, the validation results were reanalyzed after its exclusion, which improved the prediction rate to 71 %. Application of this nomogram is limited by the narrow range of patients' serum creatinine (0.5–1.6 mg/L) and by rounding the target trough level ranges [3].

A multicenter study was performed by Kullar et al. [5] prospectively in the United States to evaluate the effectiveness
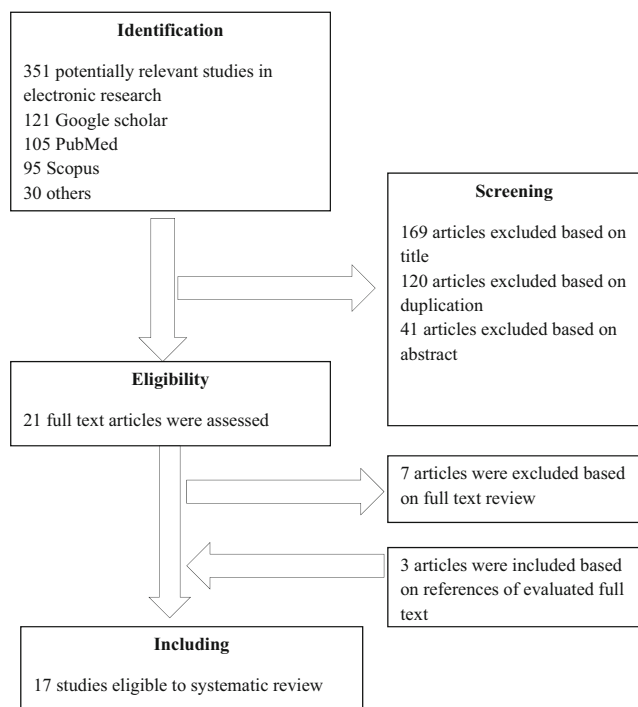
Identification

351 potentially relevant studies in electronic research
121 Google scholar
105 PubMed
95 Scopus
30 others

Screening

169 articles excluded based on title
120 articles excluded based on duplication
41 articles excluded based on abstract

Eligibility

21 full text articles were assessed

7 articles were excluded based on full text review

3 articles were included based on references of evaluated full text

Including

17 studies eligible to systematic review

Fig. 1 Flow diagram of study selection process

and safety of a newly designed vancomycin dosing nomogram, targeting trough levels of 15–20 mg/L (Table 2, suppl.). The nomogram was designed using standard vancomycin equations and population pharmacokinetic data derived from 704 patients from Detroit Medical Center using actual body weight and estimated creatinine clearance calculated by the Cockcroft-Gault equation. Two hundred patients received vancomycin based on this nomogram between June 2008 and November 2010, of which 58 % achieved the initial target trough of 15–20 mg/L and 83.8 % within a median of 2 days. They mentioned that the precision would improve if patients admitted to the intensive care unit (ICU) were excluded from analysis. Moreover, they proposed that administrating a loading dose could significantly reduce the time needed to achieve the targeted trough concentrations.

Nine patients (4.5 %) experienced nephrotoxicity, of which eight had trough serum concentrations ≥15 mg/L, but most of them (six patients) had received concomitant nephrotoxic drugs. It should be noted that the patient population was relatively young, weighed ≤110 kg, and had a stable renal function, which may have contributed to the low rate of nephrotoxicity occurrence [5].

Another protocol for vancomycin empiric dosing and monitoring was implemented at the University of Maryland Medical Center in May 2009. The protocol was incorporated into the computerized prescriber order entry (CPOE) system, which determined an initial vancomycin dose based on actual body weight (15 mg/kg/dose, maximum dose 2000 mg) and a dosing interval based on renal function (Table 3, suppl.).

Target trough level was proposed at 10–20 mg/L. A retrospective study comparing pre- and post-implementation time periods was performed by Devabhakthuni et al. [26] on patients admitted to the internal ward that had received at least one dose of vancomycin (225 patients in each group). The number of patients who received an appropriate initial dose increased significantly in the post-implementation group ($P < 0.001$) but dosing interval appropriateness remained unchanged ($P = 0.323$). This may have been due to normal renal function of the majority of the patients in both groups, making a dosing interval of 12 h suitable for them. But it should be noted that appropriate initial trough concentration (44 % vs 45 %; $P = 0.89$), mean number of levels checked (1.9 vs 2.1; $P = 0.56$), and duration of therapy (4.9 vs 5.0; $P = 0.77$) were almost similar between the two groups. It should be noted that more patients with renal dysfunction were included in the pre-implementation group, but the appropriateness of the selected dosing interval was also significantly higher in this subgroup of patients in the pre-implementation group (61 % vs. 28 %, $P < 0.001$) [26].

Two vancomycin dosing nomograms were also designed in Winchester Medical Center by Wesner and his colleagues [9] for target trough levels of 10–15 mg/L and 15–20 mg/L, separately. The loading and maintenance doses are mentioned in Table 4, suppl. and dosing intervals in Table 5, suppl. [based on clearance of creatinine (ClCr)]. Then, for validating these two nomograms, patients older than 18 years, weighing ≤120 kg, for whom vancomycin was ordered from January 10 to October 31, 2011, were randomly included in treatment (novel nomogram; 221 patients) or control (traditional pharmacokinetic methods; 252 patients) groups as part of a prospective trial. Twenty percent of the patients in each group were critically ill. The average age of patients in the control group was significantly higher. More patients in the treatment group achieved appropriate trough levels (44 % vs. 33 %, $P = 0.014$), and subtherapeutic levels (<10 mg/L) were significantly less common in this group ($P = 0.032$). But no significant difference in trough levels > 20 mg/L occurrence was reported ($P = 0.706$). Comparing obese and non-obese patients, the nomogram accuracy was not considerably different between them ($p = 0.19$). The pharmacist's impression about the nomogram significantly improved after this study, especially for its ease of use ($p = 0.033$) and time saving ($p = 0.008$), indicating that the reason for the nomogram's broad acceptance was not limited to its accuracy [9].

Lima et al. [7] designed a vancomycin dosing nomogram based on individualized pharmacokinetic parameters of 300 hospitalized patients by using a one-compartment model (Bauer method) in Brazil (Table 6, suppl.). The suggested loading dose was determined by multiplying total body weight by 25 mg, based on the IDSA guideline for MRSA therapy in seriously ill patients, and the maintenance dose was calculated based on total body weight and estimated creatinine

Table 1 Summary of the studies published to date about vancomycin dosing nomogram development and validation

	Method	Used parameters	Target trough level (mg/dL)	Validation type	No. of patients	Control group	Achieving target serum levels	Clinical & microbiological outcomes	Safety	Advantages	Limitations
Non-critically ill patients											
Thalakada et al. [3]	Population data (with multiple linear regression via Minitab software)	Initial serum creatinine, Age	14.5–20.5	Retrospective	105	No	- Fifty-six percent for integrated nomogram - Excluding q18h dosing, increased to 71 %	—	—	- Conducted in two hospitals - Including ICU patients	- Rounding target trough level - Excluded patients on hemodialysis & in emergency ward - Narrow range of patients' serum creatinine (0.5–1.6 mg/L)
Kullar et al. [5]	Population data	Total body weight, ClCr (Cockcroft-Gault)	15–20	Prospective	200	No	Initial: 58 % (83.8 % within two days)	—	4.5 % nephrotoxicity occurrence	- Included critically ill patients (26 % of patients) - Multicenter validation	- Excluded patients with ClCr <30 or >110 ml/min, weight >110 kg, recent transplant - Low average age of patients
Devabhakthuni et al. [26]	Population data	Actual body weight, ClCr	10–20	Retrospective	225	Yes (225 patients)	Forty-four percent vs 45 % for control group; P = 0.89	No sig. better outcome	—	- Computer-based program for dosing - Broad inclusion criteria - Included hemodialysis patients	- More patients with baseline renal dysfunction are included in preimplementation group - Limiting maximum dose to 2 g - Different timelines for pre- & post-implementation periods
Wesner et al. [9]	Population data	Actual body weight, ClCr	10–15 & 15–20	Prospective	221	Yes (252 patients)	- Forty-four percent vs. 33 %; P = 0.014 - Higher level of accuracy in non-obese patients	—	—	- Two separate nomograms for target trough level of 10–15 mg/L & 15–20 mg/L - Included critically ill patients - Separately evaluated obese patients - Pharmacists agreed that the nomogram was easy to use and saved time	- Excluded patients weighing >120 kg & with ESRD - Open-label study
Lima et al. [7]	Bauer model	Total body weight, ClCr (Cockcroft-Gault)	17.5	Not performed	—	—	—	—	—	-Dosing recommendation for hemodialysis patients - Computer-based program for dosing - Loading dose is defined	-Limited target trough level to 17.5 mg/L -Excluded patients weighting < 50 kg or >100 kg
Leu et al. [2]	Ambrose method	GFR, Body weight	5–15 & 15–20	Prospective	28 (48 control group)	Yes	- Forty-one percent vs. 12.1 %; P = 0.019	No sig. differences between the two groups.	No sig. differences between the two groups	-Two separate nomograms for target trough level of 5–15 mg/L & 15–20 mg/L	- Exclusion of pts. with ClCr <30 ml/min, weigh <30 kg, treatment course <3 days, or receiving

Table 1 (continued)

	Method	Used parameters	Target trough level (mg/dL)	Validation type	No. of patients	Control group	Achieving target serum levels	Clinical & microbiological outcomes	Safety	Advantages	Limitations
								- Lower mortality rate in nomogram group		- Control group	concurrent chemotherapy - Small sample size
Michalets et al. [27]	Population data	GFR (based on Cockcroft-Gault) Weight	≥15	Retrospective	67 (66 control group)	Yes	-Sixty-nine percent vs. 42 %; $P = 0.002$ -Seventy-six percent achieve an AUC24/MIC ≥400 (sig.better than control group; $P < 0.0001$)		-Sig. lower nephrotoxicity occurrence than control group ($P = 0.034$)	Evaluation of achievement to AUC24/MIC ≥400	–
Critically ill patients											
Golenia et al. [1]	Population data	GFR (based on MDRD formula Actual body weight)	15–20	Prospective	60	Yes (pre/post)	Forty-two percent vs. 19.3 %; $P = 0.0099$		No sig. difference in nephrotoxicity occurrence ($P = 1$)	- Loading dose is defined - Better estimation of GFR by using MDRD equation	- Small sample size - Excluded patients with eGFR < 30, recent transplant recipients, and obesity
Aubron et al. [28]	A 2-compartment model, uses a Bayesian estimation (with MM-USCPACK program)	Height Weight Age GFR (based on MDRD)	15–20	Prospective	48 (54 vancomycin course)	No	-Forty-two percent of patients		–		- Sig. reduction in predictability in patients with obesity, acute renal failure or severe illness - Heterogeneity in the timing & number of level measurements
Baptista et al. [8]	Population data	Body weight 8 h Clcr	20-30	Prospective cohort	25	Yes (pre/post)	Eighty-four percent vs. 51 %; $P < 0.005$		No clinical or laboratory side effects were reported	- Continuous infusion dosing regimen - Loading dose is defined	- Excluded patients with acute or chronic renal failure - Only performed on patients with severe sepsis or septic shock - Used 8 h CLCR, which is not accepted as a gold-standard method to assess kidney function
Ocampos-Martinez [39]	Population data	ClCr (calculated from 24 h urine collection and normalized to body surface area)	25-30	Prospective	261	No	Fifty-three, 33 and 14 % of patients had subtherapeutic levels on day 1, 2 and 3 of treatment		–	- Continuous infusion dosing regimen - Loading dose is defined	- Only included septic patients
Jeurissen [40]	Population data	Clcr (Cockcroft-Gault)	25	Not performed	–	–	–	–	–	- Continuous infusion dosing regimen - Loading dose is defined	
Saugel et al. [37]	Population data	Actual body weight ClCr	15–25	Retrospective	164 (75 control group)	Yes	Sig. higher subtherapeutic levels were reported on treatment day 1 (44 %), 2 (29 %), and	–	–	- Continuous infusion dosing regimen - Loading dose is defined	- Recommended for patients with normal renal function

Table 1 (continued)

	Method	Used parameters	Target trough level (mg/dL)	Validation type	No. of patients	Control group	Achieving target serum levels	Clinical & microbiological outcomes	Safety	Advantages	Limitations
Saugel et al. [41]	Population data	Actual body weight ClCr	15–25	Prospective	34		3 (23 %) in control group On treatment days 1 to 7, target serum levels achieved in 48, 39, 33, 26, 43, 57, and 69 % of patients			- Continuous infusion dosing regimen - Loading dose is defined	Small sample size
Maarseveen et al. [42]	Population data PK software package MW/Pharm	GFR (based on MDRD)	15–20	Prospective	80	No	Sixty-nine and 63 % achievement to target C24 and 80 and 72 % to target AUC, respectively in non-critically ill and critically ill patients	–	–	- Loading dose is defined - Critically ill patients are included in validation - Used AUC achievement as target	-Excluded patients on hemodialysis -Excluded patients weighing <50 kg or >100 kg
Hemodialysis patients											
Jeremiah et al. [43]	Population data	Body weight	15–20	Prospective	25 (28 vancomycin course)	Yes (pre/post)	- Fifty-four percent (better than conventional dosing) ($P = 0.053$)	–	–		-Small sample size
Neonates											
Zhao et al. [34]	One-compartment non-linear pharmacokinetic model with NONMEM software	Birth & current weight Postnatal age Serum creatinine	15–25	Prospective	58	Yes (pre/post)	Seventy-one percent vs. 41 %	–	–	- Dosing regimen for continuous infusion of vancomycin - Performed in three hospitals	
Pediatrics											
Gillon et al. [14]	Two available nomograms for adults	Actual body weight ClCr (modified Cockroft-Gault)	10–20	Retrospective	38 (48 trough level), achieved to target trough level	–	The mean daily dose prescribed to achieve a desired trough level (53 mg/kg/day) was significantly higher than the predicted dose by nomogram A ($P < 0.001$) and lower than predicted dose of nomogram B ($P < 0.001$)	–	–		Excluded patients with renal dysfunction, weight <40 kg, or admitted in ICU

GFR glomerular filtration rate, *MDRD* modification of diet in renal disease, *ICU* intensive care unit, *ClCr* clearance creatinine, *ESRD* end-stage renal disease, *ARC* augmented renal clearance, *sig.* significant

clearance. This nomogram was accessible via the facility's Medtrak e-prescribing system. Based on MRSA vancomycin MIC distribution at this hospital, target peak and trough concentrations of vancomycin were selected as 50 and 17.5 mg/L, respectively. For patients on hemodialysis the recommended dosing interval was four days. This nomogram has not yet been endorsed for use in patients weighing >100 kg or <50 kg. This nomogram has not yet been validated [7].

Leu et al. [2] developed the first vancomycin dosing nomogram targeting high trough concentration in an Asian population. They selected six pharmacokinetic models, including the Matzke, Birt, Ambrose, Burton, revised Burton, and Bauer methods, and predicted a vancomyicn trough level for 45 patients retrospectively, based on pharmacokinetic parameters obtained from these models (Table 7, suppl.). By comparing the predicted and reported trough levels, they found that the Ambrose method was the best predictor in this population. So, they created two nomograms for targeting trough concentrations of 5–15 mg/L and 15–20 mg/L.

For evaluating the efficacy and safety of these nomograms, a study was performed on patients with MRSA-positive cultures receiving vancomycin based on conventional regimen (group A; $n=48$) or nomogram (group B; $n=28$). Vancomycin dosing based on the nomogram significantly improved the achievement of high trough levels in comparison with conventional dosing (41.2 % vs. 12.1 %, $P=0.019$). The average duration of hospital stay was longer for group B, which may be due to factors like baseline conditions, co-morbidities, and concurrent drugs. However, the ICU stay rate was similar and the mortality rate was higher in group A. Moreover, there was no significant difference between the two groups [2].

As an AUC24/MIC ratio of 400 or higher is the best predictor of vancomycin efficacy, Michalets et al. [27] compared the outcome of patients that received vancomycin from 2005 to 2007 with a traditional dosing approach of 15–20 mg/kg/dose ($N=66$) and patients who received vancomycin from 2007 to 2009 based on the AUC24/MIC nomogram in a teaching hospital, targeting AUC24/MIC≥400 mg*h/L and trough level≥15 mg/L ($N=67$) (Table 8, suppl.). Seventy-six percent of patients in the nomogram group achieved the target AUC24/MIC, which was significantly higher than the traditional dosing group ($P<0.0001$). Furthermore, the prevalence of trough levels<15 mg/L was significantly lower in this group ($P=0.002$) and fewer patients experienced nephrotoxicity ($P=0.034$) [27].

So, it could be concluded that patient weight and creatinine clearance were the most significant parameters used in vancomycin dosing nomogram development in non-critically ill patients. Their initial predicting success rate was 44–76 %. This variation may be due to the different design of nomograms, specific inclusion and exclusion criteria for each study, and also the probable variations in quantification methods used in different centers for trough level measurement (which was not mentioned in most of the articles). Additionally, application of the majority of these nomograms is limited, as evidence for their clinical and microbiological outcome superiority in comparison with conventional dosing is whether not available or not significant. So, these nomograms should be validated in prospective, large, controlled studies before their widespread use is approved.

Based on available data, Michalets et al.'s nomogram is worthy of further evaluation, since in validation study it had a high achievement rate of AUC24/MIC>400, which is the best predictor of vancomycin efficacy.

Vancomycin dosing nomograms: critically ill patients

Several recently published vancomycin dosing nomograms targeting high serum levels have primarily focused on non-critically ill patients with stable pharmacokinetic parameters. But in critically ill patients, physiologic changes, various degrees of organ dysfunction, and some of the received treatments for life support may alter pharmacokinetic parameters, resulting in unsuccessful antibiotic dosing. Critically ill patients show up to a two-fold increase in the volume of distribution of vancomycin due to fluid shifts, which increases drug clearance. Moreover, vascular permeability and variations in intravascular volume could exacerbate this increment. So, it is necessary to monitor vancomycin serum levels more accurately in this population [1, 28].

A vancomycin dosing nomogram for ICU admitted patients was designed based on actual body weight and eGFR calculated by the Modification of Diet in Renal Disease (MDRD) equation in Boston to achieve trough levels of 15–20 mg/L (Table 9, suppl.). They claimed that the MDRD formula provides the most accurate estimation of eGFR [1].

To compare patients' outcomes before and after nomogram implementation, 57 and 60 patients were evaluated, respectively. In a three-month post-implementation evaluation, overall compliance with the nomogram was 49 %. The percentage of patients with trough level of 15–20 mg/L increased significantly from 19.3 to 41.67 % ($P=0.0099$). However, a nonsignificant increase in the number of patients with trough levels >20 mg/L was also reported (11 vs. 18 patients). It should be mentioned that 22 % of patients in the post-implementation group had not received a loading dose but they achieved a higher mean initial trough level in comparison with patients who had received a loading dose (20.6 ± 6.9 vs. 17.3 ± 7.3 mg/L, $P=0.15$). It may be due to the higher incidence of third-spacing occurrence in patients who received a loading dose or small sample size of the subgroup of patients who did not receive a loading dose. As they did not record the daily fluid status of patients, its impact on the results could not be evaluated.

There was no significant difference in nephrotoxicity occurrence between the two groups, but they still warranted close monitoring of patients for toxicity occurrence.

Applicability of this nomogram is limited in patients with eGFR < 30 ml/min/1.73^2 or those weighing more than 150 kg or less than 40 kg [1].

In a critically ill population in the ICU ward of Alfred Hospital in Melbourne, Australia, Aubron et al. [28] prospectively evaluated a computer program for the prediction of vancomycin serum levels that is available for non-critically ill patients. Prediction of serum vancomycin concentration was carried out by MM-USCPACK program, based on a two-compartment model using a Bayesian estimation algorithm, individualized by taking into account height, weight, age, and GFR (evaluated by MDRD formula). Forty-eight patients admitted between February and May 2010 in the ICU requiring intravenous treatment with vancomycin were enrolled in the study (54 vancomycin treatments). The trough levels were higher than 15 mg/L in only 42 % of patients. The precision of prediction was acceptable (interquartile range 3.5–18.9 %) and the relative bias for all predictions was equal to −1.3 %. Obesity, unstable renal function, and severe illness, expressed by a systemic organ failure assessment (SOFA) score >11, were factors influencing the prediction [28].

It seems that Golenia et al.'s nomogram—after confirmation in a larger population of critically ill patients, especially by focusing on clinical outcome—could be applicable at least in non-obese patients with normal kidney function. However, given the high prevalence of acute kidney injury (AKI) in this population, it is necessary to design a nomogram for vancomycin dosing in critically ill patients with renal dysfunction.

Nomograms for continuous infusion of vancomycin in critically ill patients

Based on the time-dependent bactericidal activity of vancomycin, continuous infusion (CI) has been suggested frequently as an alternative for intermittent infusion especially in critically ill patients. Fast achievement of the target steady-state, lower inconsistency in drug exposure, simpler therapeutic drug monitoring, ease of administration, and lower rates of nephrotoxicity, costs, and mortality are the main advantages of CI [6, 29–38]. However, based on consensus review of ASHP, IDSA, and SIDP, the priority of CI versus intermittent infusion regarding treatment outcome is questioned except in patients with ventilator-associated pneumonia caused by MRSA [15]. Moreover, different factors, especially augmented renal clearance (ARC; defined as a creatinine clearance exceeding 130 ml/min for at least 8 h), which is common in critically ill patients, could still lead to a high clearance of hydrophilic antibiotics and subtherapeutic serum levels.

There are some dosing regimens for CI of vancomycin in ICU patients targeting high serum concentrations that should be evaluated accurately before their widespread use.

A 13-month single-center retrospective study was conducted by Baptista et al. [8] in Portugal on all ventilated, adult patients with severe sepsis or septic shock who received vancomycin (79 patients). They developed a formula for optimizing vancomycin dosing by evaluating the correlation of vancomycin clearance and 8 h clearance of creatinine. The target steady-state concentration (Css) was 20–30 mg/L. The nomogram was tested prospectively in a cohort study on 25 patients. The number of patients who achieved an adequate vancomycin serum level in the first 24 h was significantly higher in the post-implementation group (51 % vs. 84 %, $P < 0.005$). Thirty-six percent of patients the in pre-implementation group were cases of ARC, most of which (72 %) had not achieved target Css, but all of the ARC patients in the post-implementation group (10 patients) met it. Nephrotoxicity occurred in 6.3 % of the pre-implementation group patients and in none of the post-implementation group. Actually, this dosing nomogram significantly increased the achievement of therapeutic concentrations in the first 24 h of treatment, particularly in patients exhibiting ARC [8].

In a retrospective study performed by Ocapmos-Martinez et al. [39] 261 septic ICU patients received vancomycin as a loading dose of 15 mg/kg over 60–90 min, independent of kidney function, and then 30 mg/kg infused over 24 h for patients with normal kidney function, 20–30 mg/kg for patients with 50 < ClCr < 80 ml/min, and 10–20 mg/kg for patients with ClCr <50 ml/min, with a target serum level of 20–30 mg/L. The ClCr was calculated from 24-h urine collection and normalized to body surface area. Subtherapeutic levels had been reported in 53, 33, and 14 % of patients on days 1, 2, and 3, respectively. High ClCr and male sex were proposed as the variables most strongly associated with insufficient serum levels [39].

Jeurissen and colleagues [40] also proposed that a loading dose of 1000 mg followed by a daily continuous infusion of up to 3000 mg is necessary for achieving a serum level of 25 mg/L in septic ICU patients with normal renal function. They included 20 patients who received vancomycin by continuous infusion between April 2009 and April 2010. Vancomycin clearance calculated by measured vancomycin serum concentration was used for creation of the nomogram [40].

In another retrospective study, Saugel et al. [37] compared patients treated with continuous infusion (a loading dose of 1000–1250 mg, followed by a 60 mg/h continuous infusion with target serum level of 15–25 mg/L) with patients treated with intermittent infusion. This CI regimen was sufficient for achievement to target trough concentration, but it usually resulted in subtherapeutic levels on the first days of treatment [37].

So, based on these findings, they designed a CI regimen with a higher loading dose. Then, an observational study was conducted by Saugel et al. between June 2012 to February 2013 on 34 ICU admitted patients who needed vancomycin and received it as a loading dose of 20 mg/kg (during 180 min) followed by a continuous infusion (20–30 mg/kg, based on renal function, over 24 h). The targeted serum level was 20–

30 mg/L (Figure 1, suppl.). The overall adherence to the guideline was 82 %. Forty-eight and 69 % of patients achieved a target level on the first and 7th days of treatment, respectively. However, they found supra-therapeutic serum levels especially on the second to fourth days of treatment [41]. It seems that the defined loading dose in the new regimen was too high.

In another study, Maarseveen et al. [42] designed a dosing nomogram for CI of vancomycin by simulation of CI using the PK software package MW/Pharm and a pharmacokinetic population model based on the historical population data of patients on intermittently dosed with vancomycin. This nomogram was developed based on eGFR calculated by MDRD formula (Table 10, suppl.). Vancomycin serum concentration of 15–20 mg/L at 24 h (C24) was set as the target level as well as an $AUC \geq 350$ mg.h.L^{-1}. Prospective validation performed on 35 general ward and 45 ICU patients showed 69 and 63 % achievement to target C24 and 80 and 72 % to target AUC, respectively. In this study patients weighing <50 kg or >100 kg and hemodialysis patients were excluded [42].

Therefore, considering all available findings on vancomycin dosing as CI, it seems that similar to with intermittent dosing it is difficult to suggest a dosing regimen that will reliably result in the therapeutic serum level in all patients and it is noteworthy that most studies evaluating this dosing regimen lack control groups. But based on available data, it can be hypothesized that these nomograms may be effective alternatives in comparison with current intermittent dosing procedure. Regarding the high achievement of target serum concentrations, it seems valuable to validate Baptista et al.'s nomogram in a larger population.

Vancomycin dosing nomograms: hemodialysis patients

One of the main causes of mortality in hemodialysis patients is infection, especially with Gram-positive bacteria penetrating from the dialysis site. Vancomycin is used in most of these cases but few data are available about its dosing in this population. Furthermore, regarding the drug's removal by hemodialysis, achieving the currently recommended high trough levels is more difficult in these patients.

One vancomycin dosing nomogram was introduced by Jeremiah et al. [43] in Darwin University, Australia, for hemodialysis patients in 2012. The initial dose of vancomycin is a loading dose of 25 mg/kg (maximum 2 g). Levels should be checked immediately at the beginning of the next dialysis session to guide further dosing according to the Table 11 (suppl.) (maximum administration rate 1 g/h). For evaluation of this nomogram, 25 hemodialysis patients that received 28 vancomycin courses were assessed retrospectively. A 25-mg/kg loading dose was administered in six patients but the others received a fixed dose of 1 g, and the mean trough level was significantly higher in the first group prior to the next dialysis session (16.9 vs 9.8 mg/L, $P = 0.01$). The maintenance dose was compatible with the nomogram in 97 % of cases. Trough levels of 15–20 mg/L were achieved in 54.4 % of patients [43]. This nomogram should be validated in a larger population prospectively and in comparison with a control group before its recommendation for general use is approved.

Vancomycin dosing nomograms: neonates

Late-onset sepsis (LOS) is a major cause of morbidity and mortality in neonates. Gram-positive bacteria are the most common pathogens (70 %) causing LOS, which usually have been treated with vancomycin for many years [24, 34]. An optimal dosing regimen for vancomycin in the neonate does not exist. Moreover, although no strong correlation between trough level and vancomycin efficacy is mentioned in neonates, adult target levels are usually used in this population. Due to various differences between neonates and adults in drug pharmacokinetic and pharmacodynamics, several different vancomycin dosing regimens are accessible in main pediatric handbooks and about 70 % of neonates only achieve subtherapeutic levels [44–48].

Continuous infusion of vancomycin could be an alternative for the usual intermittent infusion in neonates in order to accelerate achievement of target levels. Different regimens with or without a loading dose, adjusted based on weight, age, and/or renal function, have been proposed.

In a study conducted in three hospitals in France, the probability of reaching the target concentration in neonates with three different dosing regimens was assessed and vancomycin dosing was optimized using NONMEM software [34]. Patient-tailored optimized dosing regimens were evaluated in a prospective study. One hundred sixteen neonates receiving vancomycin as CI between November 2010 and June 2011 were included. They administered a loading dose of 10–15 mg/kg in two hospitals and no loading dose in the third one, and the recommended maintenance doses are summarized in Table 12 suppl. The target trough range was proposed as 15–25 mg/L. From 116 enrolled neonates, only 41.4 % of these patients achieved therapeutic trough levels and in 4.3 % of cases the trough level was <10 mg/L. Most of the subtherapeutic levels were observed in the hospital not using a loading dose, supporting its necessity given the long half-life of vancomycin in neonates.

Pharmacokinetic analysis was performed using the nonlinear modeling program NONMEM VI, taking into account birth and current weight, postnatal age (PNA), and serum creatinine to fit a one-compartment model. Then, 100 simulated trials were carried out to optimize the dosing, which demonstrated good predictive performance for the developed models. Clinical validation of this optimized regimen was tested in a prospective study on 58 neonates. Most of the patients (70.7 %) achieved the goal trough level and just 15.5 % had subtherapeutic concentration [34].

Eur J Clin Pharmacol (2016) 72:777–788

Based on Zhao et al.'s findings, it seems that this nomogram could be applicable in a NICU setting. However, it should first be validated in a large prospective clinical trial in comparison with conventional dosing before its widespread use is approved.

Vancomycin dosing nomograms: pediatrics

Based on recent guidelines, the recommended dosing of vancomycin for achieving trough levels of 15–25 mg/L in children with normal kidney function is 15 mg/kg every 6 h [10]. Unlike infancy and early childhood, little is known about the pharmacokinetic differences of teenagers and adults. This uncertainty makes it difficult to choose an appropriate vancomycin dosing regimen in teens. Vancomycin nomograms for adults may be applicable for older teens, as after puberty body mass and ClCr become similar to adults, but they should be evaluated in this population. Gillon et al. [14] assessed two nomograms designed for adult patients (Table 13 and 14, suppl.) in children older than 10 years, weighing ≥40 kg with normal renal function in a pediatric hospital in the USA. The targeted trough level range was proposed as 10–20 mg/L. Evaluating 165 trough level from 120 patients, 53 trough levels were in the desired range. Thirty-eight patients were enrolled in the final analysis. The mean daily dose prescribed to achieve a desired trough level (53 mg/kg/day) was significantly higher than the predicted dose by nomogram A (36 mg/kg/day) ($P < 0.001$) and lower than the predicted dose of nomogram B (73 mg/kg/day) ($P < 0.001$). Evaluating patient groups separately, the mean daily dose required for achieving the target trough level was 50 mg/kg/day in healthy children. Doses predicted by the nomogram were more appropriate for oncology patients [14]. So, application of nomograms developed in adult patients in pediatrics may cause some errors in vancomycin dosing and thus they are not usable before accurate evaluation and validation in this population.

Conclusion

Available data show that using a vancomycin dosing nomogram can be a useful tool for achieving high target trough concentrations in a greater percentage of patients earlier in the course of treatment. However, there are limited data about clinical and microbiological outcomes related to dosing based on these nomograms. So far, they are only validated in specific groups of patients, so they should be used with caution in the general population and clinical judgment should not be completely replaced with nomograms. In addition, some of these nomograms have not been validated or are only validated based on retrospective studies with small sample sizes that are not adequate for concluding their efficacy and safety.

Adequately powered, prospective randomized studies are needed to confirm the superiority of each nomogram. Finally, it should be noted that although most of these nomograms significantly improved achievement of target trough levels, the percentage of target level achievement has been between 40 and 70 % in most of cases, which is not ideal, and thus it seems necessary to continue development of more accurate nomograms for vancomycin dosing.

Compliance with ethical standards

Competing interests The authors of the manuscript have no competing interests to report with respect to this work.

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