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REVIEW

A Systematic Review of Vancomycin Dosing in Patients with Hematologic Malignancies or Neutropenia

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Objective: To provide a comprehensive review of vancomycin dosing in patients with hematologic malignancies or neutropenia.

Methods: PubMed, Embase and the Cochrane Library were searched through April 2, 2020. Original studies relevant to vancomycin dosing regimen in adults with hematologic malignancies or neutropenia were included. No restriction was applied in study design and language. A descriptive analysis was performed.

Results: Twenty-three studies were included eventually, of which eighteen were case series studies, four were cohort studies and another one was a randomized controlled trial. Five case series studies made a clinical audit of conventional vancomycin dosing in patients with malignancies or neutropenia, showing that the proportion of patients with sub-therapeutic trough levels remained high, ranging from 32% to 88%. Seven case series studies and four cohort studies demonstrated that vancomycin clearance (CLva) tended to be higher in patients with hematologic malignancies or neutropenia, whereas volume of distribution (V) seemed to be comparable to the control group. Five studies proposed individualized initial dosing regimen per the pharmacokinetic changes; however, no prospective validation has been conducted in clinical setting. Additionally, four case series studies suggested that the correlation between vancomycin clearance and estimated creatinine clearance was relatively poor, bringing a great challenge to proper dosing strategy. A randomized controlled trial stated that therapeutic drug monitoring (TDM) of vancomycin could decrease the incidence of nephrotoxicity in immunocompromised febrile patients with hematologic malignancies.

Conclusion: The available evidence indicates that conventional vancomycin dosing leads to suboptimal concentration in patients with hematologic malignancy or neutropenia. TDM accompanied by pharmacokinetic interpretation can decrease the risk of nephrotoxicity. The individualization of the initial dosing regimen and mechanisms of augmented clearance require further research.

Keywords: vancomycin, hematologic malignancy, neutropenia, pharmacokinetics, evidence-based practice

Introduction

A proper dosing regimen is the cornerstone of antimicrobial therapy, which has a great impact on treatment outcome, development of drug resistance as well as dose-dependent toxicity. Traditionally, the use of reduced doses in patients with renal impairment has been widely accepted. Dosage adjustments for patients with renal failure have been listed in labels of various medications and relevant clinical guidelines.[1,2] However, more and more studies have underlined the

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existence of augmented renal clearance (ARC), especially in critically ill patients,[3] patients with brain injury[4] and neurosurgery,[5] which could result in antibiotics' sub-therapeutic concentrations and poorer outcomes. In this case, an assumption could be made that dosing regimens should be optimized according to the degree of increase in renal function, similar to the downward dose adjustments in patients with renal dysfunction.

Risk of infections will increase in patients with neutropenia, which occurs frequently after chemotherapy for cancer, especially hematologic malignancies.[6] Therefore, the administration of optimal antibiotics was recommended in clinically or microbiologically documented infections.[7] Additionally, patients with hematologic malignancies or neutropenia have been reported to have enhanced renal clearance,[8,9] which would affect the systematic exposure of antibiotics predominately excreted through urine, including the commonly used anti-pseudomonas beta-lactams, aminoglycosides and vancomycin. Hence, the optimization of dosing regimens' might also be required under the circumstance.

To our knowledge, vancomycin is one of the most well-studied antibiotics with respect to therapeutic drug monitoring (TDM).[2,10,11] In spite of the potential changes in pharmacokinetic parameters and possible clinical failure proposed in patients with hematologic malignancies or neutropenia,[8,9] neither increased dosing regimen nor TDM of vancomycin has been recommended in these patients, implying that the evidence was insufficient or the integration of evidence into practice should be strengthened. Notably, no comprehensive review has been conducted on this issue.

The objective of this study was to gain an in-depth understanding of the current status of vancomycin dosing regimen, pharmacokinetics and optimization of vancomycin dosing in patients with hematologic malignancies or neutropenia, which could be of great value for clinical practice and identifying knowledge gaps for future research.

Methods

We conducted this systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12]

Data Sources and Searches

PubMed, Embase and the Cochrane Library were searched from their respective inception to July 26th., 2018. A complementary search was also performed to identify the most recent articles (published before April 2, 2020). The search terms included hematologic malignancy, neutropenia and vancomycin. Both mesh terms and text words were used. The search strategy is detailed in Tables S1–S3. Reference lists of the retrieved articles and related reviews were also examined manually for additional studies.

Eligibility Criteria

All records that comprised of adult patients with hematologic malignancies or neutropenia were included. When the proportion of hematologic malignancies or neutropenia was greater than 80% in one individual arm, the arm could be assumed to be patients with hematologic malignancies or neutropenia, respectively. Furthermore, all the patients were required to receive intravenous vancomycin. Outcomes should involve at least one of the followings: vancomycin serum concentration, pharmacokinetic (PK) parameters, vancomycin dosing, clinical response and nephrotoxicity. The exclusion criteria were as follows: (1) insufficient clinical data; (2) study types were cases, reviews or editorials; (3) the analysis was not relevant to vancomycin dosing regimen; (4) duplicate publication. No restriction was applied in language.

Study Selection

Two reviewers (N. H. and W. L.) screened titles and abstracts per the eligibility criteria to identify potential publications independently at first. Then, the full text was assessed for final inclusion. Any disagreement was resolved by discussion between the 2 reviewers or by consulting a third reviewer (S. Z.).

Data Extraction

A pre-specified data form was used to extract the following information: study characteristics (the first author's name, year of publication, study design, country, sample size), patients' baseline characteristics (characteristics of patients included, proportion of patients with neutropenia, gender, age, weight, renal function), vancomycin dosing, timing of vancomycin serum concentration sampling, outcomes of interest. The data

extraction was performed by one reviewer (N. H.) and checked by another reviewer (W. L.). Discrepancies were addressed by discussion between two reviewers or consultation with the third reviewer (S. Z.) if necessary.

Quality Assessment

The methodological quality of each included study was assessed by 2 reviewers (N. H. and X. L.) independently, and disagreements were resolved by discussion. The potential risk of bias in the randomized controlled trials was assessed using Cochrane risk of bias.[13] The quality of cohort studies was assessed per the Newcastle-Ottawa Scale (NOS) scale.[14] Concerning case series studies, we used National Institutes of Health (NIH) Quality Assessment Tool (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). As no validated tool for pharmacokinetic studies was available, we used the ClinPK Statement, a reporting guideline for clinical pharmacokinetic studies to assess their quality.[15]

Data Analysis

To summarize all the information concerning vancomycin dosing in patients with hematologic malignancies or neutropenia, a descriptive analysis was performed.

Results

Of the 6404 potentially relevant published reports identified, 46 reports proved potentially eligible after duplicates removed and abstracts screened. On full-text screening, 23 studies were ultimately included in the systematic review (Figure 1). The list of the excluded studies in the process of full-text screening is detailed in Table S4.

The basic characteristics of the included studies can be found in Table S5. All the 23 studies[16–38] were published in English, of which three[16,18,19] were conference abstracts. One study[33] was a simulation study without an actual clinical data. Two studies[20,32] adopted the same set of data with different analyses methods. Therefore, twenty-one sets of clinical data were finally included. In 18 studies,[17,18,20,22-31,34–38] vancomycin was infused intermittently, and 2 studies adopted continuous infusion,[19,21] whereas the remaining 1 conference abstract did not report the specific dosing regimen.[16] For single-arm studies, nine studies included neutropenic hematologic patients consecutively,[16,18,20,21,26,28,31,34,35] while 6 studies included patients with hematologic

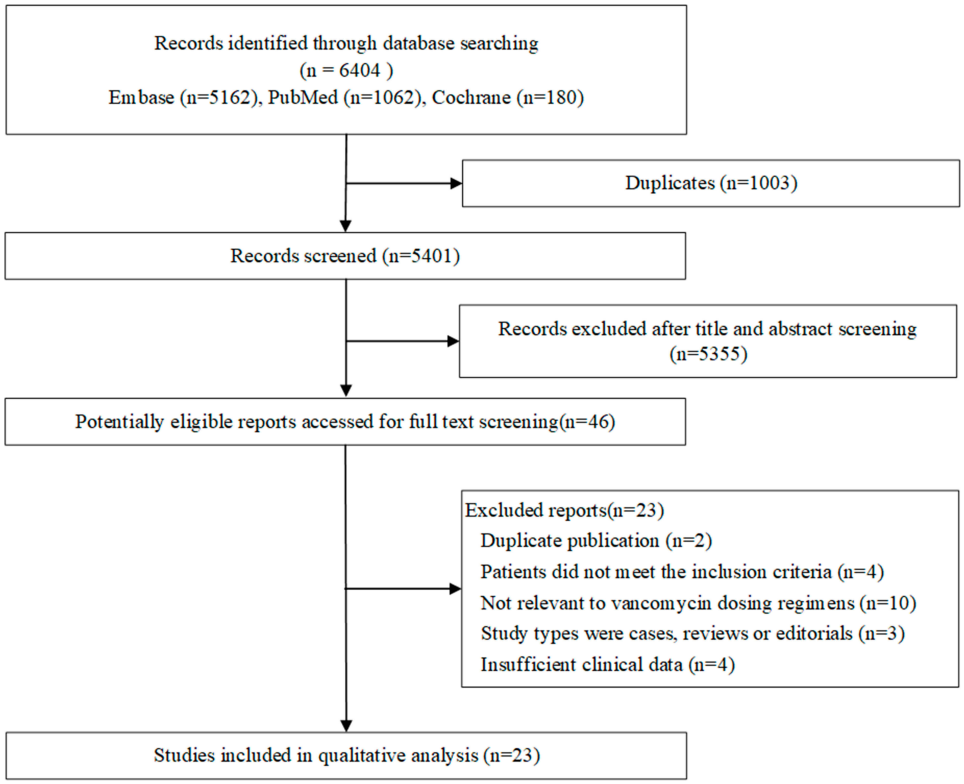

Figure 1 Flow chart of study selection.

malignancies without distinguishing neutropenia from non-neutropenia.[17,19,22,27,29,38] Additionally, another two studies included hospitalized patients and took neutropenia as a risk factor.[30,36] Concerning comparative cohort studies, there were two studies comparing neutropenic patients with non-neutropenic patients,[23,25] and another 2 studies focused on the difference between hematologic malignant patients and control groups.[24,37]

Concerning the quality assessment of these included studies, 4 studies were not assessed, of which 3[16,18,19] were conference abstracts and one[33] was a simulation pharmacokinetic study. The detailed results of quality assessment are shown in Tables S6–S9. Overall, included studies were of adequate quality.

All the included studies were classified according to their objectives as follows:

Clinical Audit of Vancomycin Dosing

Seven studies[16–22] aimed to make a clinical audit of conventional vancomycin dosing in patients with hematologic malignancies or neutropenia. The characteristics and summary of results in each study are listed in Table 1. Six studies reported the proportion of patients with sub-therapeutic concentrations in routine clinical care, and five of which reported value ranging from 32% to 88%. However, Vazin et al[22] did not report the specific vancomycin dosing, yielding result (3.6%) that differed significantly from other 5 studies. Furthermore, Vermis et al[19] stated that to attain therapeutic vancomycin levels, vancomycin maintenance dose (41.7 mg/kg/d vs. 32.7 mg/kg/d) was significantly higher when ARC (estimated CL_{CR} greater than 120 mL/min) was present in hematologic malignant patients. Overall, vancomycin concentrations following conventional dosage were insufficient in patients with hematologic malignancies or neutropenia.

The Potential Change in Pharmacokinetic Parameters

Comparative Studies Between Patients with Hematologic Malignancies or Neutropenia and Control Groups

Two studies[23,25] were comparative cohort studies between neutropenic patients and non-neutropenic patients, and another 2 studies[24,37] focused on the difference between patients with hematologic malignancies and the control group. The characteristics of the four studies are summarized in Table 2.

Although both neutropenic patients and the control group applied the standard dosage and consistent sampling time in Choi et al,[23] the median serum vancomycin concentration was lower in neutropenic patients than the control group (9.1 mg/L vs. 12.1 mg/L, $P < 0.0001$). Multiple logistic regression analysis still revealed a significant association between sub-therapeutic vancomycin concentration (trough serum concentration <10 mg/L) and neutropenia (odds ratio [OR]: 1.75; P=0.029).

Additionally, Haeseker et al[25] primarily investigated neutropenia and hematologic malignancy's effect on pharmacokinetic parameters, whereas Al-Kofide et al[24] and Izumisawa et al[37] focused on the effect of hematologic malignancy. Concerning specific pharmacokinetic parameters, vancomycin clearance (CLva) was higher in patients with hematologic malignancies or neutropenia (Table 3). However, the results for volume of distribution (V) were still conflicting (Table 3). Notably, five patients in Haeseker et al[25] received vancomycin in both neutropenic and nonneutropenic period and presented a reversible augmented CLva in the nonneutropenic period (91 ± 26 mL/min vs. 45 ± 10 mL/min, P=0.009).

Development and Validation of PK Models

Although seven studies[20,26-29,36,38] calculated vancomycin's pharmacokinetic parameters in patients with hematologic malignancies or neutropenia, only three studies[29,36,38] used non-linear mixed effects modelling. The characteristics and PK parameter of studies included are listed in Table 4, showing a marked difference in CLva from those reported for patients with non-hematologic malignancy and non-neutropenia.[39,40] Notably, one study[36] included neutropenia as one of the covariates affecting vancomycin clearance, of which vancomycin clearance is increased in patients with neutropenia by 27.7%. Nevertheless, V seemed to be comparable to normal controls without hematologic malignancy and neutropenia.[39,40] Additionally, all the PK parameters had great inter-individual variation among patients with hematologic malignancies or neutropenia.

The Potential Effect of Neutropenia on Creatinine Clearance (CL_{CR})

Four studies[25,28,30,31] reported the potential effect of neutropenia on CL_{CR}. Hirai et al[30] conducted a single-center retrospective study in 292 patients with normal serum

creatinine concentration, and demonstrated that febrile neutropenia was an independent risk factor of ARC (OR: 2.76; 95% CI: 1.11–6.67; $P = 0.0254$). However, Haeseker et al[25] showed that the estimated CL_{CR} was not significantly different between patients with neutropenia and non-neutropenia (Table 2).

Three studies evaluated the correlation between CLva and estimated CL_{CR} solely. Soto et al[31] included 45 neutropenic (<1000/mm^3) hematologic patients and demonstrated that the correlation coefficient between CLva (106 ± 37 mL/min) and estimated CL_{CR} (84.7 ± 32 mL/min) was 0.42. Le Normand et al[28] illustrated a poor correlation in neutropenic patients (100/mm^3) as well (n = 10, $r = 0.281$). According to Hirai et al,[30] the non-ARC patients showed a significant correlation between CL_{CR} ad CLva ($r = 0.8726$, $P < 0.0001$); however, no such relationship was observed in patients with ARC ($r = 0.1029$, $P = 0.4866$).

Above all, although CL_{CR} possibly has an increase in patients with neutropenia, estimated CL_{CR} itself could not identify the specific patients with ARC, which brought difficulty to the prediction of CLva.

Optimization of Initial Vancomycin Dosing Regimen

Six studies[24,25,32,33,36,38] were relevant to the optimization of initial vancomycin dosing regimen. Taghizadeh-Ghehi et al[32] evaluated the applicability of the most cited vancomycin one-compartment models developed in common patients using data from their recent study.[20] They demonstrated that none of the seven pharmacokinetic models performed well to calculate initial vancomycin dosage in Iranian patients underwent hematopoietic stem cell transplantation. Using a published population pharmacokinetic (PPK) model[29] in patients with hematologic malignancies, Fernandez et al[33] performed Monte Carlo simulation to calculate vancomycin dosages required in the specific subpopulation. When standard vancomycin dosing (2000 mg/d) was given, cumulative fraction of response (CFR) for *S. aureus* was 90.4%, 47.3% and 31.2% for CL_{CR} values of <60, 60–120 and >120 mL/min, respectively. If a CFR of 80% was considered to be clinically appropriate, vancomycin doses of 3000 and 4000 mg/d for a CL_{CR} 60–120 and >120 mL/min should be used. Okada et al[38] also proposed a vancomycin dosing nomogram in patients undergoing allogeneic hematopoietic stem-cell transplantation based on PPK model and Monte Carlo simulation. Suggested vancomycin dosing is 1g per 12 hours when CL_{CR} ranging from 75 to 90 mL/min, 0.75 g per 8 hours when CL_{CR} ranging from 90 to 120 mL/min, 1g per 8 hours when CL_{CR} ranging from 120 to 175 mL/min, and 1.25 g per 8 hours for CL_{CR} greater than 175 mL/min. Based on individualized pharmacokinetic parameters calculated by AI-Kofide et al,[24] the actual dosing regimen for cancer patients should be 60 mg/kg/day, which doubled the required dose for the general population (30 mg/kg/d). Haeseker et al[25] demonstrated that to achieve the same AUC_{24}, the mean dosage in patients with neutropenia was significantly higher than the control group (2017 ± 720 vs 1521 ± 727 mg, $P < 0.001$). In this case, they concluded that the daily dose should be increased with 33% in patients with neutropenia (from 15 mg/kg twice daily to 13 mg/kg three times daily). Similarly, another study[36] suggested a 25% increase for vancomycin dosing in neutropenic patients. However, the dosing algorithms aforementioned were inconsistent to some extent and have not been validated in the prospective clinical setting. Hence, no simple upward dose adjustment can be put up with great validity and the initial dosing recommendation still remains investigational.

Evaluation and Implementation of Vancomycin TDM

Two aspects of TDM have been explored before, including the target trough concentration and the evaluation of TDM-guided vancomycin therapy. Suzuki et al[35] retrospectively included 63 febrile neutropenic patients with hematologic malignancies and investigated the association of first trough concentration at steady state with clinical efficacy and nephrotoxicity. They proposed that the cut-off value of vancomycin trough concentration should be around 11.5 mg/L in these patients.

To assess the effectiveness and safety of vancomycin TDM and pharmacokinetic interpretation, Fernandez et al[34] performed a prospective randomized study in 70 immunocompromised febrile patients with hematologic malignancies. Although there was no significant difference in clinical response rate and duration of fever between TDM-guided group (n=37) and control group (n=33), the incidence of nephrotoxicity significantly decreased (13.5% vs. 42.4%, $P < 0.05$).

Table 1 Studies with Clinical Audit of Vancomycin Dosing

Author (Year)	Country	Study Design	Characteristics of Patients Included	Patients with Neutropenia (%)	Sample Size	Age (Years)	Gender (M/F)
Hochart 2011[21]	France	Single-center retrospective study	Acute myeloid leukemia patients with febrile neutropenia	100%	54 (67 vancomycin treatment courses, VTCs)	50 ± 13.6	27/27
O'Donnell 2011[16] (conference abstract)	UK	Single-center retrospective study	Bone marrow transplant patients who experienced an episode of febrile neutropenia	100%	12	NR	NR
Donovan 2012[18] (conference abstract)	United states	Retrospective study	Neutropenic adult patients	100%	198	NR	NR
Vazin 2012[22]	Iran	Prospective study	Patients in a hematology-oncology ward who received at least 3 successive doses of vancomycin and had serum vancomycin concentrations at steady state	88%	58	36.58 ± 14.33	44/14
Ghehi 2013[20]	Iran	Single-center prospective study	Adults receiving vancomycin for neutropenic fever after HSCT	100%	46	32.9 ± 12.45	30/16
Luo 2014[17]	Canada	Single-center prospective study	Leukemia/bone marrow transplant outpatients (at least two doses of vancomycin)	42%	48	54.5[b]	24/24
Vermis 2014[19] (conference abstract)	Belgium	Single-center retrospective study	Patients with hematologic malignancies	72%	96 (112 VTCs)	NR	NR

Notes: [a]Proportion of patients with normal renal function; [b]median; [c]ARC was defined as calculated creatinine clearance exceeding 120 mL/min (Cockcroft–Gault formula).
Abbreviations: NR, not reported; HSCT, hematopoietic stem cell transplantation; VTC, vancomycin treatment course; ARC, augmented renal clearance.

Discussion

Brief Summary of the Systematic Review

Several descriptive studies demonstrated that their routine vancomycin dosing was inadequate for effective antimicrobial therapy. Regarding the alterations in PK parameters, studies showed that CLva tended to be higher in patients with hematologic malignancies or during febrile neutropenia, whereas V seemed to be comparable to the control groups. Although several pharmacokinetic models have been developed and a few dosing regimens have been proposed, there is still no consensus on initial vancomycin dosing in patients with hematologic malignancies or neutropenia. The available evidence indicates that TDM and optimal

Weight (kg)	Renal Function	Vancomycin Dosing Regimen	Timing of Serum Vancomycin	Summary of Results
73 ± 18.1	107.5 ± 35.4 mL/min	Continuous infusion; loading dose: 15.5 ± 3.3 mg/kg; maintenance dose: 35.4 ± 6.9 mg/kg/d	At 24 hours for patients with a loading dose and 48 hours for patients without any loading dose.	▪ the target serum level for continuous infusion was greater than 20 mg/L, and only 6 (12%) cases achieved the target
NR	NR	NR	At 24 hours, then twice weekly.	▪ 32% of trough levels were subtherapeutic (< 5 mg/L).
NR	NR	Intermittent infusion; 15 – 20 mg/kg/dose and administration times are determined by renal function	NR	▪ 25.3% of patients achieved therapeutic trough concentrations (15 – 20 mg/L)
68.05 ± 12.61	57/58 (98.2%) [a]	Intermittent infusion; Correcting dosage based on creatinine clearance was given to 10 (17.23%) of the patients	Blood samples were taken from the patients who received vancomycin for 3 consecutive days, and just before the administration of the next dose.	▪ vancomycin trough serum concentration range was 15.59 ± 13.02 mg/L ▪ subtherapeutic trough level (< 10 mg/L) was detected in 3.6% of patients ▪ 53.3% had a level above the maximum therapeutic concentration
74.8 ± 16.6	102.5 ± 35.33 mL/min	Intermittent infusion; 31.9 (±10.5) mg/kg/d	Within 30 minutes prior to the fourth dose	▪ 25 (54.3%) patients had trough concentrations of <10 mg/L ▪ 6 patients (13%) had trough levels of < 5 mg/L
NR	77 μmol/L[b]	Intermittent infusion; once-daily (2073 ± 338 mg/d)	NR	▪ 10 (21%) patients had therapeutic vancomycin trough concentrations (i.e., greater than 10 mg/L)
NR	NR	Continuous infusion; loading dose: 15 mg/kg, maintenance dose: 30 mg/kg/d	NR	▪ ARC[c] was observed in 73 VTC with an average renal clearance of 147.0 mL/min versus 79.0 mL/min. ▪ Therapeutic vancomycin levels (20 mg/L) were obtained on day 5 (median) with an average vancomycin maintenance dose of 41.7 mg/kg/day when ARC was present versus 32.7 mg/kg/day on day 3.

pharmacokinetic interpretation can help in decreasing the risk of nephrotoxicity.

Implications for Clinical Practice

In view that standard dosing is inadequate for some patients with hematologic malignancies or neutropenia, improper dosing should be considered as a possible reason when clinical improvement was not achieved in these patients with suspected or documented Gram-positive infection. Therefore, optimization of dosing regimen must be considered in both initial dosing and dose adjustment. However, it still remains a question of how to identify the patients with ARC accurately, which makes the individualization of initial dosing difficultly. For

Table 2 The Characteristic of Comparative Studies

Author (Year)	Country	Study Design	Characteristics of Patients Included	Sample Size	Grouping		Gender (M/F)	Age (Years)	
					Study Group	Control Group		Study Group	Control Group
Neutropenic patients vs non-neutropenic patients									
Haeseker 2014[25]	Netherlands	Single-center prospective study	Adults received vancomycin intravenously and had at least two plasma samples	171	Neutropenia (< 500/mm^3): n=56	Non-neutropenia: n=115	104/67	55 ± 13	61 ± 14
				68 (a subset of patients with hematologic malignancies)	Neutropenia (< 500/mm^3): n=55	Non-neutropenia: n=13	NR	NR	NR
Choi 2017[23]	Korea	Single-center retrospective study	Adults receiving routine TDM of vancomycin (trough and peak).	1307	Neutropenia (< 500/mm^3) n=162	Non-neutropenia: n=1145	728/579	54 (37–65)[#]	56 (45–64)[#]
Patients with hematologic malignancies vs non-cancer patients									
Al-Kofide 2009[24]	Saudi Arabia	Single-center retrospective study	Adults receiving vancomycin therapy	31	Cancer patients (proportion of patients with hematologic malignancies was 88.9%): n=18	Patients without cancer: n=13	NR	48.5 ± 20.2	43.4 ± 22.1
Izumisawa 2019[37]	Japan	Retrospective cohort study	Adults receiving > 3 days of vancomycin therapy	522	Hematologic malignancy patients: n=261	Non-malignancy patients: n=261	321/201	65.6 ± 13.6	67.2 ± 16.9

Notes: [#]Median (interquartile range); [a]proportion of patients with hematologic malignancy; [b]proportion of patients with neutropenia; [c]the absolute count of neutrophils.
Abbreviations: NR, not reported; V, volume of distribution; Vss, volume of distribution at steady state; CLva, vancomycin clearance; $t_{1/2}$, half-life; TDM, therapeutic drug monitoring.

example, Soto et al[31] and Le Normand et al[28] demonstrated that the correlation between estimated CL_{CR} and CLva was poor. Haeseker et al[41] also showed that CLva algorithms based on estimated CL_{CR} were unsuitable in these patients. Additionally, Taghizadeh-Ghehi et al[32] demonstrated that none of the seven most cited vancomycin one-compartment models performed well to calculate initial dosage. In this case, TDM of vancomycin could be valuable in patients with hematologic malignancies or neutropenia. Without performing TDM, the extremely high dosing could not be administered. Furthermore, previous studies demonstrated that pharmacokinetic dosing programs using measured vancomycin serum levels could predict vancomycin levels with acceptable accuracy and precision.[42] Therefore, we recommend, when possible, TDM-guided therapy to optimize vancomycin therapy in patients with hematologic malignancy or neutropenia. Above all, the systematic review

Weight (kg)		Patients with Hematologic Malignancies/ Neutropenia n(%)		Renal Function		Vancomycin Dosing Regimen	Timing of Serum Vancomycin	Determination of Pharmacokinetic Parameters	Outcomes
Study Group	Control Group	Study Group	Control Group	Study Group	Control Group				
NR	NR	55/56 (98.2%)[a]	13/115 (11.3%)[a]	113 ± 57 mL/min	107 ± 78 mL/min	Intermittent infusion; an initial loading dose of 15 mg/kg + dose individualization based on TDM and renal function.	Two plasma samples (peak and trough concentration)	Maximum a posterior (MAP) Bayesian estimation (MW/Pharm 3.60, Mediware, the Netherlands)	CLva, V
NR	NR	55 (100%)[a]	13 (100%)[a]	114 ± 57 mL/min	111 ± 58 mL/min				
62.0 (56.0–70.0)[#]	60.0 (53.0–68.7)[#]	135 (83.3%)[a]	184 (16.1%)[a]	0.6 (0.5–0.8) [#] mg/dL	0.7 (0.5–0.9) [#] mg/dL	Intermittent infusion; 1000 mg vancomycin every 12 h	Steady-state serum vancomycin concentration (after at least the fourth dose)	Posterior Bayesian estimation (Abbott's PKS software)	Serum trough vancomycin concentration at steady state, $t_{1/2}$
66.7 ± 17.1	68.9 ± 14	NR[b]	NR[b]	105.4 ± 62.3 mL/min	87.2 ± 27.5 mL/min	Intermittent infusion; Initial vancomycin dosing regimens were chosen by attending physicians	Peak and trough vancomycin serum concentration (after the third dose or at steady state)	Pharmacokinetic equations	CLva, V, $t_{1/2}$
55.0 ± 10.3	56.2 ± 13.1	1.47 ± 2.46 × $10^3/\mu L$[c]	7.80 ± 4.66 × $10^3/\mu L$[c]	77.0 ± 29.2 mL/min	74.1 ± 35.6 mL/min	Intermittent infusion; Initial dosing was not pre-specified	After ≧ 3 days following the start of administration	Bayesian estimation using TDM software Ver 3.3	Trough concentration, CLva, Vss, $t_{1/2}$

underlines the necessity to perform vancomycin TDM in patients with hematologic malignancies or neutropenia, which might be overlooked previously.

Implications for Further Research

According to the comprehensive systematic review, several knowledge gaps have been identified, and are summarized as follows:

- The mechanism of the altered PK parameters warrants investigation, which could help us judge whether the phenomenon was deceptive or not.

Two scenarios should be considered to clarify the mechanism of the altered PK parameters. On the one hand is the further research in clinical settings. First, most of the studies did not distinguish whether the change in pharmacokinetic parameters was due to

Table 3 The Pharmacokinetic Parameters in Comparative Studies

Author (Year)	Sample Size	Vancomycin Clearance (mL/min)			$T_{1/2}$ of Vancomycin (h)			V (L)		
		Hematologic Malignancies or Neutropenia	Control Group	*P* value	Hematologic Malignancies or Neutropenia	Control Group	*P* value	Hematologic Malignancies or Neutropenia	Control Group	*P* value
Neutropenic patients vs. non-neutropenic patients										
Haeseker 2014[25]	171	67 ± 26	50 ± 22	<0.001	–	–	–	62 ± 32	56 ± 29	0.304
	68 (subset of patients with hematologic malignancies)	68 ± 26	53 ± 16	0.024	–	–	–	62 ± 32	59 ± 18	0.691
Choi 2017[23]	1307	–	–	–	7.4 h (5.9–10.7 h) #	8.9 h (6.9 −12.0 h)#	<0.0001	–	–	–
Patients with hematologic malignancies vs. non-cancer patients										
Al-Kofide 2009[24]	31	110.1 ± 42	71.2 ± 22.2	0.005	8.6 ± 7.1	5.4 ± 1.9	0.111	70 ± 45	31.1 ± 8.3	0.002
Izumisawa 2019[37]	522	0.055 ± 0.017 L/h/kg	0.051 ± 0.019 L/h/kg	<0.05	32.7 ± 13.0	37.1 ± 18.8	<0.05	1.81 ± 0.57 L/kg	1.84 ± 0.62 L/kg	>0.05

Notes: –, not reported; #, median (interquartile range).

hematologic malignancy or neutropenia. The effect of hematologic malignancy can be complicated by neutropenia and vice versa. Only Haeseker et al[25] demonstrated that the augmented clearance was associated with neutropenia rather than hematologic malignancies with a limited sample size. As previous studies showed vancomycin clearance was higher in patients with hematologic malignancies than solid tumors[43] and the difference between solid malignancies and control groups was attenuated,[44] we assume that the phenomenon might be explained by different proportions of patients with neutropenia. In other words, it is the neutropenia that affects pharmacokinetic changes per se. Conventional doses of vancomycin may not offer adequate systematic exposure in febrile neutropenic patients rather than hematologic malignancy without neutropenia. Further studies are needed to elucidate the exact effect between hematologic malignancies and neutropenia. Second, studies focused on non-neutropenic immunocompromised states are limited currently. Whether the pharmacokinetic changes exist in non-neutropenic immunocompromised states can help in interpreting the mechanism. Third, none of the studies evaluated the change in measured CL_{CR}, which might also be helpful for understanding the mechanism and identifying patients with ARC.

On the other hand, the physiological mechanism responsible for ARC has not been well-defined, which can be investigated using in vitro studies and animal models. Several assumptions have been put up, including: (1) possible changes in renal function and urine flow can be induced by cancer, systematic inflammation and increased intravenous fluid; (2) tubular secretion apart from glomerular filtration; (3) non-renal elimination of vancomycin, such as hepatic conjugation; (4) cancer and neutropenia could enhance vascular permeability, which would induce increased vancomycin extravasation and low serum concentrations.[20,23-25,28,29] The above assumptions require further exploration.

- No PPK model has been developed in patients with hematologic malignancies and concomitant neutropenia, which could help with determining individualized initial dose.
- The optimization of vancomycin dosing in patients with hematologic malignancies or neutropenia requires further research. For example, prospective validation of vancomycin initial dosing regimens, stages of enhanced CL_{CR} and a consensus of initial dosing strategies are urgently needed worldwide.
- Few studies on the PKs of vancomycin in patients with hematologic malignancies or neutropenia reported clinical outcomes. Taking safety endpoints as an example, some studies illustrated that patients with hematologic malignancies may be vulnerable to nephrotoxicity.[45,46] In this case, the target trough concentration for these patients might be different from other patients and require further research. Indeed, it should be noted that the establishment of the relationship between accelerated vancomycin elimination and outcomes of clinical effectiveness is difficult due to the complexity of these patients.

Strengths and Limitations

To our knowledge, this is the first comprehensive review concerning vancomycin dosing optimization in patients with hematologic malignancy or neutropenia. Additionally, the characteristics and the key results of each individual study are presented in Tables 1–4, which can provide specific details for physicians, pharmacists as well as researchers. However, as the available evidence to date was limited and diverse, no quantitative analysis was performed. Clinical heterogeneity existed across studies. For example, patients included had different types of hematologic malignancies and no consistent definition of neutropenia has been applied among studies. Nevertheless, we consider that this systematic review maps the relevant literature on this topic, allowing us to pay attention to the optimization of vancomycin dosing in patients with hematologic malignancy or neutropenia.

Conclusion

The available evidence indicates that conventional vancomycin dosing leads to suboptimal concentration in patients with hematologic malignancy or neutropenia. TDM accompanied by pharmacokinetic interpretation can decrease the risk of nephrotoxicity. The individualization of the initial dosing regimen and mechanisms of augmented clearance require further research.

Table 4 Characteristics and Results of Studies for Developing PK/PPK Models

Author (Year)	Country	Study Design	Characteristics of Patients Included	Patients with Neutropenia (%)	Sample Size	Number of serum Concentrations	Age	Gender (M/F)	Weight (kg)
Pharmacokinetic analysis									
Kureishi 1990[26]	Canada	Single-center prospective study	Patients with acute leukemia and had absolute granulocyte below 500/mm^3	100%	25	NR	NR	NR	NR
Le Normand 1994[28]	France	Single-center prospective study	Patients with hematologic malignancies who were neutropenic (100/mm^3)	100%	10	130	36.2 (range: 18–50)	4/6	64.6 ± 10.4
Jarkowski 2011[27]	United states	Single-center prospective study	Acute myeloid leukemia patients receiving vancomycin	NR	25	NR	59.12 ± 16.26	17/8	86.05 ± 19.42
Ghehi 2013[20]	Iran	Single-center prospective study	Patients with neutropenic fever after HSCT	100%	20	40	29.9 ± 9.5	NR	72.5 ± 15.2 (ABW)
Population pharmacokinetic model									
Buelga 2005[29]	Spain	Single-center retrospective study	Adult inpatients with an underlying hematologic malignancy	43.7%	215	1004	51.5 ± 15.9	119/96	64.7 ± 11.3
Okada 2018[38]	Japan	Single-center retrospective study	Patients undergoing allo-HSCT who received preventive treatment with vancomycin	NR	75	227	49 (range: 17–69)	49/26	59.4 (range: 39.4–104.5)
Bury 2019[36]	The Netherlands	Retrospective matched cohort study	Intravenous vancomycin therapy for ≥ 2 days and at least one available vancomycin concentration	26.7%	116	742	61.4 ± 13.4	67/49	NR

Abbreviations: V, volume of distribution; CL, clearance; Ke, elimination rate constant; $t_{1/2}$, half-life; NR, not reported; ABW, adjusted body weight; TBW, total body weight; CL_{CR}, creatinine clearance; Vc, volume of central compartment; Vss, steady-state volume of distribution; Vp, distribution volume of peripheral compartment.

Renal Function	Vancomycin Dosing	Timing of Vancomycin Sampling	Pharmacokinetic Modeling Method	Model	Pharmacokinetic Parameters			
					V	CL	Ke (h^{-1})	$t_{1/2}$ (h)
NR	Intermittent infusion; 15 mg/kg q12h	Prior to infusion and at 1 and 3 h post-infusion daily during the first 3 days and every 3 to 7 days thereafter	Equations with two steady-state samples	One-compartment model	0.61 ± 0.21 L/kg	NR	NR	5.6 ± 1.8
141.2 ± 36.2 mL/min	Intermittent infusion; 1000 mg every 12 h	The first dose: prior to injection, at the end of the infusion, and 11 samples collected until 11 h after the end of the infusion	G-Pharm computer program	Two-compartment model	Vc: 22.9 ± 11.4 L	158 ± 51 mL/min	NR	2.94 ± 0.84
85.72 ± 37.28 mL/min/1.73m^2	Intermittent infusion; 1970.00 ± 605.19 mg/d	Three samples: 1 h, 3–8 h, and 8–24 h post-infusion	Maximum a priori Bayesian estimation using Adapt 5	Two-compartment model	Vc: 0.23 L/kg Vss: 0.60 L/kg	0.14 L/h/kg	NR	NR
104.7 ± 37.0 mL/min	Intermittent infusion; 31.9 (±10.5) mg/kg/d (69.6%:1g q12h; 17.4%:1g q8h)	First steady-state trough (within 30 minutes prior to the fourth dose), peak concentration, random sample	Equations with two steady-state samples	One-compartment model	0.60 (0.44–0.76) L/kg	0.090 (0.071–0.109) L/h/kg 109.7 (82.7–136) mL/min	0.16 (0.13–0.19)	4.9 (3.8–6.0)
89.4 ± 39.2 mL/min	Intermittent infusion	Blood sampling was ordered as required clinically	Nonlinear mixed-effect modeling approach (NONMEM)	One-compartment model	CL (L/h): 1.08 × CL_{CR} (Cockcroft and Gault) (L/h); CV_{CL}: 28.16% V (L) =0.98 ×TBW; CV_V:37.15%.			
113 (range: 47–253) mL/min	Intermittent infusion initial dosage of 1 g/12 hours (if the CL_{CR} was >75 mL/min/1.73 m2).	Immediately before administering vancomycin,1 hour after drug administration and at some other points as necessary	Nonlinear mixed-effect modeling approach (NONMEM)	Two-compartment model	Vc (L)= 39.2 × (TBW/59.4)^0.78; CV_{Vc}=14.2% CL (L/h) =4.25 × (CL_{CR}/113)^0.70; CV_{CL}=25.2% Vp (L) =56.1; CV_{Vp}=66.9%			
Median 92.7 mL/min	Intermittent infusion The specific dosing was not pre-specified	NR	Nonlinear mixed-effect modeling (NONMEM)	Two-compartment model	CL(L/h) = 3.22+(1+0.00834 × (CL_{CR} −104)) × $1.277^{NEUTROPENIA}$; CV_{CL}=33.0%			

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Disclosure

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