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Article

Vancomycin dosing nomograms as a tool to improve antibiotic use: a scoping review

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This scoping review aimed to summarize studies that developed vancomycin dosing nomograms. A search was performed in MEDLINE, Embase, Scopus, LILACS, and Google Scholar for studies published from January 2009 until January 2014. Two authors performed the study selection and data extraction. Disagreements were resolved by the third author. Forty-three studies were included. Most of them were conducted in the U.S. (48.8%), developed for the adult population (81.4%), specifically for critically ill patients (39.7%), used population data as a method to create the nomogram (67.5%), considered the serum trough concentration as the pharmacodynamic target for developing the dosing nomogram (83.7%), chose intermittent infusion (76.8%) and recommended loading doses administration in their dosing nomogram (65.1%). Twenty-eight studies evaluated the dosing nomogram; 19 (67.8%) achieved optimal vancomycin serum levels. However, most studies were observational designs, with small sample sizes and few nomograms developed based on AUC-guided dosing. Moreover, data on the clinical and microbiological outcomes of the patients enrolled in the studies are lacking. Vancomycin dosing nomograms were shown to be a valuable tool to guide the achievement of the PK/PD target, mainly in Middle-Income Countries. More robust methods for the development and evaluation of vancomycin dosing nomograms should be applied and associated with vancomycin TDM.

Keywords: Vancomycin. Methicillin-resistant *Staphylococcus aureus*. Drug Utilization. Dosing nomogram. Antibiotic stewardship.

INTRODUCTION

Vancomycin has conventionally been used as a first-line antibiotic for treating methicillin-resistant *Staphylococcus aureus* (MRSA) and other gram-positive beta-lactam–resistant bacterial infections. The efficacy of vancomycin in treating MRSA infections is supported by over five decades of use and is similar compared to other antibiotics (Zhang *et al.*, 2023).

The rising incidence of infections caused by beta-lactam–resistant gram-positive bacteria requires the need to optimize the dosage regimen of vancomycin (Álvarez *et al.*, 2016). Therefore, it is strongly advised to use vancomycin based on patient-specific parameters, rather than use standard dosage regimens (i.e. 1000 mg twice daily for all patients), to improve the effectiveness of vancomycin therapy (Lake, Peterson, 1985).

A recent consensus guideline emphasizes that appropriate dose regimens, administration, and therapeutic drug monitoring (TDM) strategies of vancomycin optimize clinical efficacy and ensure safety for patients (Rybak *et al.*, 2020). For TDM, the trough concentrations between 15-20 mg/L were recommended as a surrogate marker of the pharmacokinetic and pharmacodynamic (PK/PD) index of vancomycin activity, although a systematic review suggests that his parameter is associated with higher nephrotoxicity (Lim *et al.*, 2023) Thus, an individualized PK/PD target of the 24 h area under the curve to minimum inhibitory concentration (AUC_{24h}/MIC) ratio of 400-

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600 mg*h/L is the preferred monitoring parameter since it is associated with better clinical efficacy and safety of vancomycin (Rybak *et al.*, 2020). However, the implementation of this complex process can face barriers, including the need for specialized and expensive computer software, lack of familiarity of the pharmacist or provider, clinician support, protocols to TDM guidance, and logistic challenges (Bradley, Lee, Sadeia, 2022), influencing the choice of appropriate vancomycin dosing by health professionals.

Moreover, it is known that the initial appropriate dosage regimen of vancomycin assists in achieving positive clinical outcomes and preventing bacterial resistance (Carland *et al.*, 2021). In this context, a dosing nomogram is an alternative tool to provide initial dosage regimens of vancomycin, promoting rapid and easy calculation, increasing the probability of reaching the PK/PD target, and having a low cost of implementation (Elyasi *et al.*, 2016). A review reported that different vancomycin dosing nomograms have been created to customize dose regimens for specific patient groups, highlighting the significant improvement in PK/PD target achievement in most cases (Elyasi *et al.*, 2016). However, the lack of detail on how they conducted the review, such as the date range of the literature search, a well-established search strategy using controlled vocabulary terms, the use of two independent reviewers for the selection and data extraction of the studies as well as the fact that it was done before publication of the recent consensus guidelines limits its usefulness. There remains a need to comprehensively identify the vancomycin dosing nomograms published in the literature to date to assist health professionals in the best clinical decision-making**.** Therefore, this scoping review aimed to map and summarize the initial vancomycin dosing nomograms developed for inpatients.

METHODS

A scoping review was conducted to explore the literature and summarize evidence regarding vancomycin dosing nomograms for inpatients. In contrast to the systematic reviews that often focus on a specific and well-defined question, scoping reviews serve a broader purpose, identifying the types of evidence available within a specific field, analyzing knowledge gaps, and investigating the research methods employed in a specific topic. This review was conducted following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement for Scoping Reviews (PRISMA-ScR) (Tricco *et al.*, 2018). The review protocol was registered on the Open Science Framework (OSF) (https://doi.org/10.17605/OSF.IO/UNRMD).

Search strategy

A comprehensive literature search published from January 1st, 2009 until January 17th, 2024 was performed in MEDLINE (via PubMed), Embase (via Elsevier), Scopus, and LILACS (Latin American and Caribbean Health Sciences Literature) to identify relevant studies. In addition, a grey literature search was conducted in Google Scholar up to the third page of results (60 registries), excluding patents and citations, to identify studies not indexed in the databases listed above. This timeframe was chosen as 2009 was the year the first consensus review for therapeutic monitoring of vancomycin by the American Society of Health-System Pharmacists, Infectious Disease Society of America, and Society of Infectious Disease Pharmacists was published. The search strategy included keywords and medical subject headings related to vancomycin, nomograms, drug dosage calculations, clinical protocols, and practice guidelines. Duplicate studies were eliminated. Moreover, all the references cited in the included articles were reviewed to identify any studies that might have been missed. The full strategy search for all databases can be found in the Supplemental Material.

Study selection

Studies that developed vancomycin dosing nomograms for inpatients of any age were included.

Studies not published in scientific journals, qualitative studies, literature reviews, and other types of documents such as books/book chapters, letters to the editor, editorials, comments, patient education brochures, and recommendations were excluded. In addition, studies published in non-Roman characters were also excluded.

The studies retrieved from the databases were allocated to the Software Mendeley to exclude duplicate files. Then, a single file was transferred to the Rayyan QCRI program to analyze the titles and abstracts of the articles and analyze complete articles whose abstracts were previously selected. All titles and abstracts were independently screened and selected by two authors (G.F.T and M.B.V). Full-text articles were obtained and reviewed to determine whether the article met the eligibility criteria. If the full text of the article was not available in the databases, the corresponding authors were contacted by email or through ResearchGate (www.researchgate.net). Disagreements were resolved through a third author (T.M.L).

Data extraction and synthesis of results

For each included study, information such as author, country, year of publication, population study, the method used to create the dosing nomogram, PK/PD parameter, patient condition (e.g. critically ill, obese, hemodialysis, etc.), type of infusion, loading dose administration, sample size, evaluation of dosing nomogram (e.g., tested in a real population), desired therapeutic vancomycin targets (defined as the number of patients that achieved 50% or more the target according to the PK/PD target of each study) as well as subtherapeutic and supratherapeutic vancomycin targets 24-hours after the first dose were extracted. Two authors (G.F.T and M.B.F) independently completed the data extraction using a preformatted spreadsheet in Microsoft Excel. Disagreements were resolved with a third author (T.M.L). The results of this scoping review are presented as a narrative and tabular synthesis. The original ideas and concepts presented in the included studies were recognized and maintained.

Following the PRISMA-ScR guidelines, no quality assessment was performed because scoping reviews aim to identify all the available evidence and highlight their main characteristics, regardless of the quality of such evidence (Tricco *et al.*, 2018).

RESULTS

The electronic search found 3,272 potentially relevant studies. After removing duplicates and reviewing the titles and abstracts, 85 articles were selected for full-text reading. In addition, three relevant studies were identified through a manual search. Of these, 43 studies met the inclusion criteria and were included for review. A flowchart of the literature search is shown in Figure 1. The references for excluded articles, with the reasons for their exclusion, are available in the Supplemental Material S2.

Characteristics of the included studies

The characteristics of the 43 studies included in this scoping review are summarized in Table I. Most studies were conducted in the United States of America (n = 20, 48.8%), a few in Canada (n = 3, 7.0%) and the Czech Republic, Brazil, Italy, and Japan (n = 2, 4.6% each). Most of them were developed for use in the adult population, including the elderly (n = 35, 81.4%).The year of publication of the studies was varied, with most publications in 2018 (n = 7, 16.2%), followed by 2020 (n = 6, 13.9%), 2014 (n = 5, 11.6%), and 2012/2015 (n = 4, 9.3% each).

There was a predominance of vancomycin dosing nomograms developed specifically for critically ill patients (n = 17, 39.7%), followed by general patients (n = 13, 30.2%), obese patients (n = 7, 16.2%), non-critically ill patients (n = 3, 7.0%), patients undergoing hemodialysis (n = 3, 7.0%), and other conditions (n = 2, 4.6%). Regarding the method for dosing nomogram calculation, most studies used population data derived from the specific study site (n = 30, 69.8%), followed by the literature review (n = 8, 16.8%). Five studies (11.6%) did not report the method for

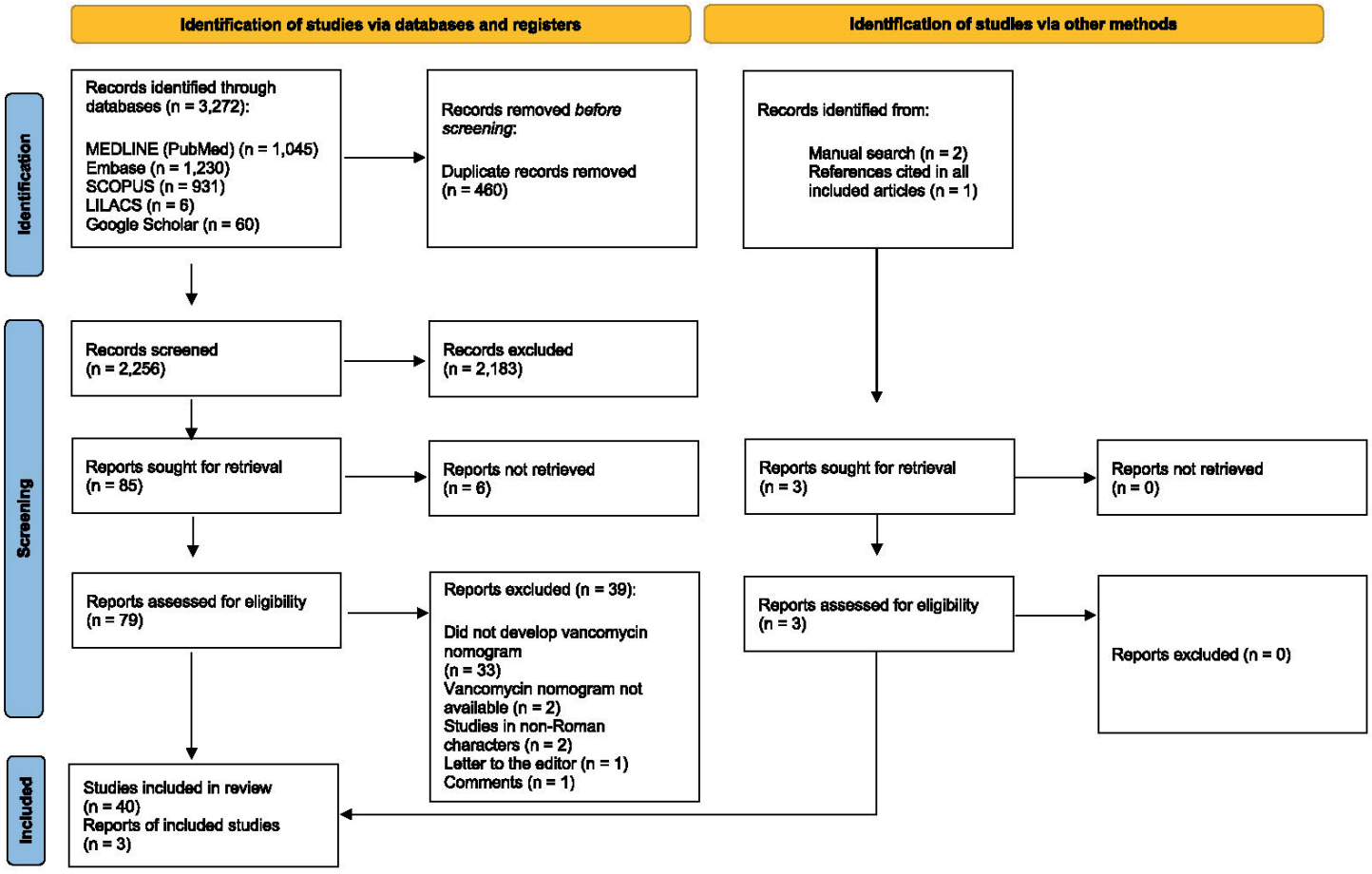

FIGURE 1 - Study selection flowchart through literature search.

dosing nomogram calculation. Moreover, the majority of studies considered the serum trough concentration as the PK/PD parameter for developing the dosing nomogram (n = 34, 79.1%), followed by the area under the concentration-time to MIC (n = 8, 18.6%). Only one study (n =1, 2.3%) considered both parameters. In addition, most studies chose the intermittent type of infusion) (n = 34, 79.0%) and recommended loading doses in their dosing nomogram (n = 31, 72,0%).

AUC_{24}h/MIC (24 h area under the curve to minimum inhibitory concentration), CrCl (creatinine clearance), N (no), NR (not reported), PK/PD (pharmacokinetic/pharmacodynamic), USA (United States of America), Y (yes).

Data of studies that evaluated the vancomycin dosing nomogram

All data extracted from each article can be found in Table II. Evaluation of vancomycin dosing nomograms was reported in 28 studies (65,11%).Of these, 25 studies (89.3%) were conducted in the adult population and 3 (10.7%) in the neonatal and pediatric populations. For specific patients, eleven studies (39.3%) assessed the vancomycin nomograms for critically ill patients, eight studies (28.6%) assessed for general patients, four studies (14.3%) assessed for obese patients, three studies (10.7%) assessed for non-critically ill, and two studies (7.1%) assessed for patients undergoing hemodialysis. Only two studies that used the area

TABLE I - Characteristics of the studies included in this review (n = 43) *(continues)*

Authors, year	Country	Method used to create the nomogram	PK/PD parameter	Patient condition	Type of infusion	Loading dose administration
Adults (including elderly)						
Ables *et al.*, 2023	USA	Literature review	AUC_{24h}/MIC	Hemodialysis	Intermittent	Y
Baptista *et al.*, 2014	Portugal	Population data	Trough concentration	Critically ill	Continuous	Y
Batchelder, Lutheran, Frens, 2020	USA	NR	Trough concentration	Obese	Intermittent	Y
Bowers *et al.*, 2018	USA	Population data	Trough concentration	Obese (except critically ill)	Intermittent	Y
Crass *et al.*, 2018	USA	Population data	AUC_{24h}/MIC	Obese	Intermittent	Y
Denetclaw *et al.*, 2015	USA	NR	Trough concentration	Obese	Intermittent	Y
Devabhakthuni *et al.*, 2012	USA	NR	Trough concentration	Non-critically ill	Intermittent	N
Frazee *et al.*, 2017	USA	Population data	Trough concentration	Critically ill	Intermittent	Y
Golenia *et al.*, 2013	USA	Population data	Trough concentration	Critically ill	Intermittent	Y
Goti *et al.*, 2018	USA	Population data	Trough concentration	General	Intermittent	Y
Ho *et al.*, 2023	New Zealand	Literature review	Trough concentration	Hemodialysis	Intermittent	Y
Kosmisky *et al.*, 2015	USA	Population data	Trough concentration	Obese	Intermittent	Y
Kullar *et al.*, 2011	USA	Population data	Trough concentration	Non-critically ill	Intermittent	N
Leu *et al.*, 2012	Taiwan	Population data	Trough concentration	General (except undergoing dialysis)	Intermittent	N
Levin, Glasheen, Kiser, 2016	USA	Literature review	Trough concentration	Critically ill	Intermittent	N
Lewis, Mueller, 2018	USA	Population data	AUC_{24h}/MIC	Critically ill	Continuous	Y
Lima *et al.*, 2014	Brazil	Population data	Trough concentration	General (except obese)	Intermittent	Y
Luo *et al.*, 2014	Canada	NR	Trough concentration	Non-critically ill with leukemia/bone marrow transplant	Intermittent	N (CrCl > 49 mL/min) Y (CrCl 24-48 mLmin)
Masich *et al.*, 2020	USA	Population data	AUC_{24h}/MIC	Critically ill and obese	Intermittent	N
McCluggage *et al.*, 2010	USA	Population data	Trough concentration	General	Intermittent	N
McGrady *et al.*, 2020	USA	NR	Trough concentration	Non-critically ill	Intermittent	Y
Medellín-Garibay *et al.*, 2017	Spain	Population data	Trough concentration	Critically ill	Continuous	Y
O'Brien and Mock, 2015	USA	Literature review	Trough concentration	General (except end-stage renal disease)	Intermittent	Y

TABLE I - Characteristics of the studies included in this review (n = 43) *(continues)*

Authors, year	Country	Method used to create the nomogram	PK/PD parameter	Patient condition	Type of infusion	Loading dose administration
Oda *et al.*, 2020	Japan	Population data	AUC_{24h}/MIC	General	Intermittent	Y
Okada *et al.*, 2018	Japan	Population data	Trough concentration	Allogeneic Hematopoietic Stem-Cell Transplantation	Intermittent	N
Pea *et al.*, 2009	Italy	Population data	Trough concentration	Critically ill	Continuous	Y
Saugel *et al.*, 2014	Germany	Literature review	Trough concentration	Critically ill	Continuous	Y
Sin *et al.*, 2018	USA	Population data	Trough concentration	Critically ill	Continuous	Y
Spadaro *et al.*, 2015	Italy	Literature review	Trough concentration	Critically ill	Continuous	Y
Thalakada *et al.*, 2012	Canada	Population data	Trough concentration	General (except end-stage renal disease)	Intermittent	Y
van Maarseveen *et al.*, 2014	Netherlands	Population data	Trough concentration and AUC_{24h}/MIC	General	Continuous	Y
Wesner *et al.*, 2013	USA	Population data	Trough concentration	General (except renal replacement therapy)	Intermittent	Y
Williams *et al.*, 2020	Australia	Literature review	Trough concentration	Critically ill	Both	Y
Yoon *et al.*, 2018	South Korea	Population data	Trough concentration	General	Intermittent	N
Zelenitsky *et al.*, 2012	Canada	Population data	Trough concentration	Hemodialysis	Intermittent	Y
Neonates and children						
Daylami, Sridharan, Qader, 2020	Bahrem	Population data	AUC_{24h}/MIC	Critically ill (except end-stage renal disease)	NR	N
Janssen *et al.*, 2015	Belgium	Population data	AUC_{24h}/MIC	General	Intermittent	Y
Pokorná *et al.*, 2019a	Czech Republic	Population data	Trough concentration	Critically ill (except renal replacement therapy)	Intermittent	N
Pokorná *et al.*, 2019b	Czech Republic	Population data	Trough concentration	Critically ill (except renal replacement therapy)	Intermittent	Y
Reilly *et al.*, 2019	USA	Population data	Trough concentration	Critically ill	Intermittent	N
Silva *et al.*, 2021	Brazil	Literature review	Trough concentration	General	Intermittent	Y
Smit *et al.*, 2021	USA	Population data	AUC_{24h}/MIC	General and obese	Intermittent	Y
Tang *et al.*, 2021	China	Population data	Trough concentration	Critically ill	Intermittent	N

under the concentration-time to MIC as the PK/PD target evaluated the vancomycin dosing nomogram. All studies evaluated the nomograms based on observation studies, except Wesner *et al.* (2013) which performed an interventional trial. The mean sample size in the adult and neonatal/pediatric patients was 292.7 (ranging from 29 to 2570) and 81.3 (ranging from 22 to 182), respectively. Nineteen studies (67.8%) reported that the patients achieved the desired therapeutic vancomycin targets. It is important to note that the two studies with a large sample size did not describe these achievements. Data of each nomogram developed for specific patients and achieved these desired targets are described below.

Critically ill patients

Nine studies (Baptista *et al.*, 2014; Frazee *et al.*, 2017; Levin, Glasheen, Kiser, 2016; Medellín-Garibay *et al.*, 2017; Sin *et al.*, 2018; Spadaro *et al.*, 2015; Pokorná *et al.*, 2019a; Pokorná *et al.*, 2019b; Reilly *et al.*, 2019) (81.8%) reported success in achieving the desired therapeutic vancomycin targets in the enrolled patients; six studies in adult patients (Baptista *et al.*, 2014; Frazee *et al.*, 2017; Levin, Glasheen, Kiser, 2016; Medellín-Garibay *et al.*, 2017; Sin *et al.*, 2018; Spadaro *et al.*, 2015) and three studies in neonatal and pediatric patients (Pokorná *et al.*, 2019a; Pokorná *et al.*, 2019b; Reilly *et al.*, 2019).

Regarding the adult population, the mean sample size evaluated in the studies was 149 (ranging from 52 to 348). Of the six studies analyzed, most of them (n = 4, 66.6%) used continuous infusion (Baptista *et al.*, 2014; Medellín-Garibay *et al.*, 2017; Sin *et al.*, 2018; Spadaro *et al.*, 2015), and all studies, except Levin, Glasheen, and Kiser (2016) proposed a loading dose for the nomogram. Moreover, all studies considered the serum trough concentration as a PK/PD parameter. The desired therapeutic targets were different for each nomogram. These targets varied from 15 to 30 mg/L (Baptista *et al.*, 2014; Medellín-Garibay *et al.*, 2017; Sin *et al.*, 2018; Spadaro *et al.*, 2015) and 10 to 20 mg/L (Frazee *et al.*, 2017; Levin, Glasheen, Kiser, 2016) for continuous and intermittent infusion, respectively. All studies achieved the desired therapeutic target 24 hours after the first vancomycin dosing. Spadaro *et al.* (2015) related that the therapeutic target was achieved only in patients with ClCr $\leq$ 50 mL/min using serum trough concentration target between 15-25 mg/L as PK/PD parameter. The average rate of the desired therapeutic target was achieved in 66.6% of patients, ranging from 50.0 to 84.0%. All studies, except Frazee *et al.* (2017), reported the sub-therapeutic (an average level of 17.8%, ranging from 3.8% to 35.0%) and supra-therapeutic vancomycin targets (an average level of 21.1%, ranging from 8.0% to 36.0%) achieved in the patients.

Regarding the neonate and pediatric population, the mean sample size evaluated in the studies was 81.3 (ranging from 22 to 182). Two studies (Pokorná *et al.*, 2019a; Pokorná *et al.*, 2019b) excluded patients with renal replacement therapy from the analysis. All studies used intermittent infusion and two studies (Pokorná *et al.*, 2019a; Reilly *et al.*, 2019) did not propose a loading dosing for the nomogram. In addition, all studies considered the serum trough concentration as a PK/PD parameter, varying the desired therapeutic target between 10-30 mg/L. The average rate of the desired therapeutic target 24 hours after the first vancomycin dosing was achieved in 65.8% of patients (ranging from 62.0% to 68.0%). Moreover, all studies described the sub-therapeutic and supra-therapeutic vancomycin targets achieved in the patients, with an average level of 12.3% (ranging from 9.0% to 18.0%) and 21.8% (ranging from 14.0% to 29.0%), respectively.

Non-critically ill patients

One Kullar *et al.* (2011) study (33.3%) described the success of the achievement of the desired therapeutic target 24 hours after the first vancomycin dosing in the patients. This study evaluated 200 patients, used intermittent infusion, did not propose a loading dose for the nomogram, and considered the serum trough concentration as a PK/PD parameter, with the desired therapeutic target between 15-20 mg/L. The rate of

the desired therapeutic target in 24 hours after the first vancomycin dosing was achieved in 58.0% of patients and sub- and supra-therapeutic levels of 19.5% and 22.5%, respectively.

General patients

Four studies (Leu *et al.*, 2012; Oda *et al.*, 2020; Thalakada *et al.*, 2012; van Maarseveen *et al.*, 2014) (50.0%) showed that the patients achieved the desired therapeutic target 24 hours after the first vancomycin dosing. The mean sample size evaluated in the studies was 69 (ranging from 43 to 106). Two studies (Leu *et al.*, 2012; Thalakada *et al.*, 2012) excluded patients with renal replacement therapy or end-stage renal disease from the analysis. All studies, except van Maarseveen *et al.* (2014) used intermittent infusion. All studies proposed a loading dose for the nomogram, except Leu *et al.* (2012). Regarding the PK/PD parameter, three studies (Leu *et al.*, 2012; Thalakada *et al.*, 2012; van Maarseveen *et al.*, 2014) considered the serum trough concentration (varying the desired therapeutic target between 5-20 mg/L) and one study considered the AUC_{24h}/MIC (varying the desired therapeutic target between 350-400 mg·h/L) (Oda *et al.*, 2020). The average rate of the desired therapeutic target was achieved in 73.2% of patients, ranging from 63.0 to 81.8%. van Maarseveen *et al.* (2014) showed that the average rate of the desired therapeutic target was lower among patients admitted to the ICU (67.5%) compared to other settings (74.5%). Two reported the sub-therapeutic (an average level of 17.4%, ranging from 11.5% to 23.4%) and supra-therapeutic vancomycin targets (an average level of 7.0%, ranging from 6.4% to 7.7%) achieved in the patients.

Obese patients

Three studies (Batchelder Lutheran, Frens., 2020; Bowers *et al.*, 2018; Denetclaw *et al.*, 2015) (75.0%) reported that the patients achieved the desired therapeutic target 24 hours after the first vancomycin dosing. The mean sample size evaluated in the studies was 181.3 (ranging from 54 to 320). All studies used intermittent infusion, proposed a loading dose for the nomogram, and considered the serum trough concentration as a PK/PD parameter, varying the desired therapeutic target between 10-20 mg/L. It is important to note that the Batchelder, Lutheran, and Frens (2020) study evaluated two nomograms. Moreover, Bowers *et al.* (2018) assessed three ranges of the desired therapeutic target: 10-15, 15-20, and 10-20 mg/L. The average rate of the desired therapeutic target was achieved in 74.5% of patients, ranging from 53.6 to 96.8%. In the Batchelder, Lutheran, and Frens study, only patients who received dosage regimens from one of the nomograms achieved the desired target. Bowers *et al.* (2018) reported that patients evaluated in the serum trough concentration range between 10-15 and 10-20 mg/L achieved the desired target. All studies described the sub-therapeutic and supra-therapeutic vancomycin targets achieved in the patients, with an average level of 10.3% (ranging from 0.0% to 21.4%) and 15.1% (ranging from 3.2% to 25.0%), respectively.

Patients undergoing hemodialysis

Two studies (Ho *et al.*, 2023; Zelenitsky *et al.*, 2012) (100.0%) reported success in the achievement of desired therapeutic vancomycin targets. The mean sample size evaluated in the studies was 30 (ranging from 29 to 31). All studies used intermittent infusion, proposed a loading dose for the nomogram, and considered the serum trough concentration as a PK/PD parameter, varying the desired therapeutic target between 10-20 mg/L. The average rate of the desired therapeutic target was achieved in 66.5% of patients, ranging from 56.0% to 76.9%. However, Zelenitsky *et al.* (2012) reported that the therapeutic target was not achieved in patients who considered the serum trough concentration target between 15-20 mg/L as the PK/PD parameter. The sub- and supra-therapeutic vancomycin targets were only described by Zelenitsky *et al.* (2012), with levels of 19.2% and 3.9%, respectively.

TABLE II - Data of studies that evaluated the vancomycin dosing nomogram (n = 28)*(continues)*

Authors, year	Study design	Patient condition	Sample size	Definition of desired therapeutic target	% patients that achieved the desired therapeutic in 24-hours after the first dose	% patients that achieved the subtherapeutic target in 24-hours after the first dose	% patients that achieved the supratherapeutic target in 24-hours after the first dose	Achievement of the therapeutic target by patient*
Adults (including elderly)								
Baptista *et al*., 2014	Prospective cohort	Critically ill	104	20 - 30 mg/L	84	8	8	Y
Batchelder, Lutheran, Frens, 2020	Retrospective cohort	Obese	320	A: 10 - 20 mg/L (Nomogram I) B: 10 - 20 mg/L (Nomogram II)	A: 49.7 B: 66	A: 24 B: 15	A: 26.3 B: 19	A: N B: Y
Bowers *et al*., 2018	Retrospective cohort	Obese (except critically ill)	170	A: 10-15 mg/L B: 15-20 mg/L C: 10-20 mg/L	A: 53.6 B: 47.4 C: 68.2	A: 21.4 B: 26.3 C: 10.6	A: 25 B: 26.3 C: 21.2	A: Y B: N C: Y
Denetclaw *et al*., 2015	Prospective cohort	Obese	54	10 - 20 mg/L	96.8	0.0	3.2	Y
Devabhakthuni *et al*., 2012	Retrospective cohort	Non-critically ill	450	10 - 20 mg/L	44	46	10	N
Frazee *et al*, 2017	Prospective cohort	Critically ill	135	10 - 20 mg/L	50	NR	NR	Y
Golenia *et al*, 2013	Prospective cohort	Critically ill	60	15 - 20 mg/L	42	28	30	N
Goti *et al*., 2018	Retrospective cohort	General	1812	10 - 20 mg/L	46.7	NR	NR	N
Ho *et al*., 2023	Retrospective cohort	Hemodialysis	31	15 - 20 mg/L	56	NR	NR	Y
Kosmisky *et al*., 2015	Retrospective cohort	Obese	48	A: 10-20 mg/L B: 10-15 mg/L C: 15 - 20 mg/L	A: 35.4 B: 18.2 C: 10.8	A: 56.3 B: 54.6 C: 81.1	A: 8.3 B: 27.3 C: 8.1	A: N B: N C: N

TABLE II - Data of studies that evaluated the vancomycin dosing nomogram (n = 28)*(continues)*

Authors, year	Study design	Patient condition	Sample size	Definition of desired therapeutic target	% patients that achieved the desired therapeutic in 24-hours after the first dose	% patients that achieved the subtherapeutic target in 24-hours after the first dose	% patients that achieved the supratherapeutic target in 24-hours after the first dose	Achievement of the therapeutic target by patient*
Kullar et al., 2011	Prospective cohort	Non-critically ill	200	15 - 20 mg/L	58	19.5	22.5	Y
Leu et al., 2012	Prospective cohort	General (except undergoing dialysis)	43	A: 5 - 15 mg/L B: 15 - 20 mg/L	A: 80.8 B: 41.2	A: 11.5 B: 35.3	A: 7.7 B: 23.5	A: Y B: N
Levin, Glasheen, Kiser, 2016	Prospective cohort	Critically ill	183	10 - 20 mg/L	69.4	13	17.6	Y
Luo et al., 2014	Prospective cohort	Non-critically ill with leukemia/ bone marrow transplant	48	> 10 mg/L	21	NR	NR	N
Medellín-Garibay et al., 2017	Retrospective cohort	Critically ill	72	20 - 30 mg/L	57	35	8	Y
O'Brien and Mock, 2015	Retrospective cohort	General (except end-stage renal disease)	100	10 - 20 mg/L	21.7	NR	NR	N
Oda et al., 2020	Retrospective cohort	General	47	AUC24h/ MIC ≥ 400mg·h/L	70.2	23.4	6.4	Y
Saugel et al., 2014	Prospective cohort	Critically ill	34	20 - 30 mg/L	48	16	36	N
Sin et al., 2018	Prospective cohort	Critically ill	52	15 - 25 mg/L	82.7	3.8	13.4	Y

TABLE II - Data of studies that evaluated the vancomycin dosing nomogram (n = 28)*(continues)*

Authors, year	Study design	Patient condition	Sample size	Definition of desired therapeutic target	% patients that achieved the desired therapeutic in 24-hours after the first dose	% patients that achieved the subtherapeutic target in 24-hours after the first dose	% patients that achieved the supratherapeutic target in 24-hours after the first dose	Achievement of the therapeutic target by patient*
Spadaro et al., 2015	Retrospective cohort	Critically ill	348	A: 15 - 25 mg/L (CrCl > 50 mL/min) B: 15 - 25 mg/L (CrCl ≤ 50 mL/min)	A: 44 B:57	A:20 B:21	A:35 B:22	A: N B: Y
Thalakada et al., 2012	Retrospective cohort	General (except end-stage renal disease)	106	15 - 20 mg/L	71	NR	NR	Y
van Maarseveen et al., 2014	Prospective cohort	General	80	A: 15 - 20 mg/L B: AUC24h/MIC ≥ 350mg·h/L	A: 63 (ICU) and 69 (non-ICU) B: 72 (ICU) and 80 (non-ICU)	A: NR B: NR	A: NR B: NR	A: Y B: Y
Wesner et al., 2013	Prospective, open-label trial	General (except renal replacement therapy)	221	10 - 20 mg/L	44 (39 for obese patients and 49 for non-obese patients)	20.8	8.1	N
Yoon et al., 2018	Retrospective cohort	General	2570	A: 10 - 15 mg/L B: 15 - 20 mg/L	A: 45 B: 36.2	A: NR B: NR	A: NR B: NR	N
Zelenitsky et al., 2012	Prospective cohort	Hemodialysis	29	A: 10 - 20 mg/L B: 15 - 20 mg/L	A: 76.9 B: 34.6	A: 19.2 B: 61.5	A: 3.9 B: 3.9	A: Y B: N
Neonates and children								
Pokorná et al., 2019a	Retrospective cohort	Critically ill (except renal replacement therapy)	22	10 - 20 mg/L	68	18	14	Y
Pokorná et al., 2019b	Retrospective cohort	Critically ill (except renal replacement therapy)	40	15 - 30 mg/L	67.5	10	22.5	Y

TABLE II - Data of studies that evaluated the vancomycin dosing nomogram (n = 28)*(continues)*

Authors, year	Study design	Patient condition	Sample size	Definition of desired therapeutic target	% patients that achieved the desired therapeutic in 24-hours after the first dose	% patients that achieved the subtherapeutic target in 24-hours after the first dose	% patients that achieved the supratherapeutic target in 24-hours after the first dose	Achievement of the therapeutic target by patient*
Reilly et al., 2019	Retrospective cohort	Critically ill	182	10 - 20 mg/L	62	9	29	Y

AUC_{24}h/MIC (24 h area under the curve to minimum inhibitory concentration), CrCl (estimated creatinine clearance), ICU (intensive care unit), N (no), NR (not reported), Y (yes).

*Considered the achievement of the therapeutic target in 50% or more of the patients.

DISCUSSION

To the best of our knowledge, this is the first scoping review regarding vancomycin dosing nomograms for inpatients. Forty-three studies were included; most of them performed in the United States of America, developed for the adult population (including the elderly), considered the serum trough concentration as the PK/PD parameter, population data for developing the dosing nomogram, with an intermittent infusion, and recommended loading doses. Twenty-eight studies evaluated the dosing nomogram for specific patient conditions. More than half of them achieved the desired therapeutic target, showing the potential for using these nomograms in clinical practice. Moreover, the nomograms identified in this review can assist institutions in developing vancomycin dosing protocols. However, most studies were observational designs, with small sample sizes and few nomograms were developed based on AUC-guided dosing. Futhermore, the nomograms assessed for neonate and pediatric populations were developed only for critically ill patients. Finally, data on the clinical and microbiological outcomes of the patients enrolled in the studies are lacking, highlighting that future research should focus on more robust methods of development, the use of recent better evidence, and the evaluation of vancomycin dosing nomograms.

Most of the studies included in this review involved adults, including the elderly. Studies involving pediatric and neonatal patients were first published in 2016 and increased from 2019 onwards. A reason for this may be that the consensus guidelines published in 2009 did not include these patients in the recommendations since adequate data were unavailable (Rybak *et al.*, 2009). With the increasing number of studies, the recommendations for the use of vancomycin and monitoring for infants were better described in the updated vancomycin TDM consensus guideline published in 2020 (Rybak *et al.*, 2020). However, few studies evaluated the nomograms for this population to date, calling attention to more studies to be assessed in these specific patients.

Critically ill patients, who require optimized dosing due to their variable pharmacokinetics, were most often included in the studies reviewed. In addition, most studies recommended loading doses and chose continuous infusion. Since the first vancomycin TDM guideline, loading doses have been recommended to rapidly achieve targeted ranges of serum vancomycin concentrations during the first few days of therapy, especially in critically ill patients (Lim *et al.*, 2023; Rybak *et al.*, 2020). Moreover, a systematic review showed that the administration of vancomycin by continuous infusion had similar efficacy and was associated with a lower risk of nephrotoxicity when compared with intermittent infusion, making this

type of infusion an alternative recommendation in the revised guideline (Flannery *et al.*, 2020). Our findings showed that most studies reported success in achieving the desired therapeutic vancomycin targets in this population, reinforcing the importance of the nomograms for adequate initial vancomycin dosing.

The revised consensus guideline recommended the use of the AUC/MIC ratio as the best PK/PD index, rather than the surrogate marker - serum trough concentration, to minimize vancomycin-associated acute kidney injury while achieving clinical efficacy (Rybak *et al.*, 2020). Our findings showed that the vancomycin serum trough concentration was predominantly used as the PK/PD parameter for developing the vancomycin dosing nomograms. However, a recent systematic review showed that AUC/MIC dosing strategies are associated with a significantly lower incidence of vancomycin-induced AKI compared to trough-based dosing strategies, although the quality of evidence was considered low (Lim *et al.*, 2023). The AUC-guided vancomycin dosing also demonstrates cost–benefits compared to trough-guided dosing (Lee *et al.*, 2021). In addition, pharmacokinetic equations can be used to estimate the AUC for the initial total daily dose of vancomycin (Mcgrady *et al.*, 2020). Thus, it is necessary to develop new nomograms or update the existing nomograms based on the most current scientific evidence.

Population data was the main method for dosing nomogram calculation in the majority of included studies. It is preferable to use population-level data rather than only a literature review in developing nomograms because it allows for the model to be more accurate (Rybak *et al.*, 2020), although most of these nomograms are often based on small sample sizes.

There are no vancomycin dosing nomograms specifically for the elderly. It is known that the clearance of vancomycin is diminished in these patients, leading to higher concentrations, and they are also more likely to suffer from comorbidities and take more concomitant medications, making them more vulnerable to vancomycin toxicity (Kim *et al.*, 2022). Moreover, few dosing nomograms were developed for obese patients and patients undergoing hemodialysis. Obesity may alter vancomycin's volume of distribution, resulting in lower serum concentrations initially, but leading to accumulation with continued use (Wong *et al.*, 2022), and patients undergoing hemodialysis may have a prolonged distribution phase, a residual renal function, and a nonrenal clearance, highlighting the need for the individualized vancomycin dosage regimens (Crew, Heintz, Heintz, 2015). Researchers should be encouraged to develop vancomycin dosing nomograms for these and other specific populations.

It is important to highlight that these dosing nomograms do not replace TDM. Moreover, there are some potential pitfalls associated with their use, such as variability in patient factors, assumptions about the pharmacokinetics of vancomycin, and failure to adapt to the changing conditions of the patients. However, they are a tool that can be used along with TDM to guide dosing decisions. Moreover, not every institution has sufficient equipment to perform adequate TDM and this scenario is worse in middle-income countries (Bradley, Lee, Sadeia, 2022). For example, The Brazilian Health Regulatory Agency (ANVISA) conducted a national evaluation of Antimicrobial Stewardship Programs (ASP) in Brazilian Hospitals, highlighting that only 47.65% (863 out of 1,209) had implemented the program (Anvisa, 2022). Moreover, a survey on vancomycin monitoring practices involving 79 healthcare professionals from Brazilian hospitals showed that only 59% of hospitals performed vancomycin TDM, particularly by trough concentrations (Morales-Junior *et al.*, 2022). These results demonstrate that vancomycin TDM is not a reality in many hospitals and vancomycin is frequently prescribed based on standard dosage regimens. Therefore, dosing nomograms can be a powerful tool to provide more appropriate initial vancomycin dosing.

Regarding evaluating vancomycin dosing nomograms, more than half of the studies achieved the desired vancomycin target levels while approximately one-quarter of the vancomycin target levels were sub- or supra-therapeutic. Although most of these dosing

nomograms significantly improved the achievement of target levels, their percentage is not ideal. In addition, it is known that subtherapeutic concentrations can contribute to antibiotic resistance and supratherapeutic concentrations can increase the risk of nephrotoxicity (Lim *et al.*, 2023).

This study has some limitations. Although a comprehensive literature search strategy was used, some studies may have been missed because they were not indexed in the searched databases or were not retrieved due to paid access restrictions. Moreover, this review does not include vancomycin dosing nomograms developed by organizations or institutions that have not been published in scientific journals. Finally, the results of the evaluated nomograms should be interpreted with caution, since the choice of the desired therapeutic vancomycin target, although entirely logical, was arbitrary.

CONCLUSION

Vancomycin dosing nomograms reviewed in these studies were shown to be a valuable tool to guide the achievement of the PK/PD target, and associated with vancomycin TDM, can increase clinical efficacy and patient safety. However, the majority of studies were observational with limited patient sample size and there are limited clinical and microbiological outcomes data of patients involved in the studies. Moreover, a few nomograms were developed using the updated recommendation of AUC-guided dosing. More robust methods for the development and evaluation of vancomycin dosing nomograms should be applied. Widespread vancomycin TDM, which is inappropriately still lacking in many medical centers, and, nonetheless, tools to calculate vancomycin dosing according to AUC_{24h}/MIC should be realistically available.

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Supplementary material
SI - Search strategy

Electronic Bibliographic Databases	Search Strategy
EMBASE	#1 'vancomycin'/exp OR 'vancomycin' OR 'adimicin' OR 'amplobac' OR 'balcorin' OR 'diatracin' OR 'edicin' OR 'firvanq' OR 'firvanq kit' OR 'icoplax' OR 'ifavac' OR 'levovanox' OR 'lyphocin' OR 'maxivanil' OR 'norimko' OR 'selamat' OR 'vamysin' OR 'vanauras' OR 'vancam' OR 'vancamycin' OR 'vanccostacin' OR 'vanco' OR 'vanco-teva' OR 'vancocid' OR 'vancocin' OR 'vancocin cp' OR 'vancocin hcl' OR 'vancocin hcl pulvules' OR 'vancocin hydrochloride' OR 'vancocina' OR 'vancocina cp' OR 'vancocine' OR 'vancoled' OR 'vancomax' OR 'vancomicina' OR 'vancomycin complex' OR 'vancomycin hcl' OR 'vancomycin hydrochloride' OR 'vancomycine' OR 'vancor' OR 'vancosan' OR 'vancox' OR 'vankomicin' OR 'vankomycin' OR 'vanmicina' OR 'vanococin' OR 'varedet' OR 'voncon' OR 'vondem' #2 'nomogram'/exp OR 'nomogram' OR 'nomograms' OR 'nomograph' OR 'dose calculation'/exp OR 'dose calculation' OR 'calculation, dosage' OR 'dosage calculation' OR 'dose finding' OR 'drug dosage calculation' OR 'drug dosage calculations' OR 'drug dose calculation' OR 'drug dose calculations' OR 'practice guideline'/exp OR 'practice guideline' OR ' clinical practice guidelines' OR 'guidelines' OR 'guidelines as topic' OR 'practice guidelines' OR 'practice guidelines as topic' OR 'clinical protocol'/exp OR 'clinical protocol' OR 'clinical protocols' OR 'clinical research protocol' #3 [2009-2022]/py #4 [embase]/lim NOT ([embase]/lim AND [medline]/lim) #5 ('article'/it OR 'article in press'/it) #6 #1 AND #2 AND #3 AND #4 AND #5
Medline (Pubmed)	#1 "Vancomycin"[Mesh] OR (Vancomycin) OR (Vancomycin Hydrochloride) OR (Hydrochloride, Vancomycin) OR (Vancomycin Sulfate) OR (Sulfate, Vancomycin) OR (Vancomycin-ratiopharm) OR (Vancomycin Hexal) OR (Vancomycine Dakota) OR (AB-Vancomycin) OR (Vanco Azupharma) OR (Diatracin) OR (VANCO-cell) OR (Vanco-saar) OR (Vancocin) OR (Vancocin HCl) OR (Vancomycin Lilly) OR (Vancocine) OR (Vancomicina Abbott) OR (Vancomicina Chiesi) OR (Vancomicina Combino Phar) OR (Vancomicina Norman) OR (Vancomycin Phosphate (1:2)) OR (Vancomycin Phosphate (1:2), Decahydrate) #2 "Nomograms"[Mesh] OR (Nomograms) OR (Nomogram) OR (Partin Tables) OR (Partin Table) OR (Table, Partin) OR (Tables, Partin) OR (Partin Nomograms) OR (Nomogram, Partin) OR (Nomograms, Partin) OR (Partin Nomogram) OR "Drug Dosage Calculations"[Mesh] OR (Drug Dosage Calculations) OR (Calculation, Drug Dosage) OR (Calculations, Drug Dosage) OR (Dosage Calculation, Drug) OR (Dosage Calculations, Drug) OR (Drug Dosage Calculation) OR (Pharmaceutical Calculations) OR (Calculation, Pharmaceutical) OR (Calculations, Pharmaceutical) OR (Pharmaceutical Calculation) OR (Pharmaceutical Arithmetic) OR (Arithmetic, Pharmaceutical) OR "Practice Guidelines as Topic"[Mesh] OR (Practice Guidelines) OR (Clinical Guidelines as Topic) OR (Best Practices) OR (Best Practice) OR "Clinical Protocols"[Mesh] OR (Protocol, Clinical) OR (Protocols, Clinical) OR (Clinical Protocol) OR (Treatment Protocols) OR (Protocols, Treatment) OR (Treatment Protocol) OR (Clinical Research Protocol) OR (Research Protocols, Clinical) OR (Protocols, Clinical Research) OR (Research Protocol, Clinical) OR (Clinical Research Protocols) OR (Protocol, Clinical Research) #3 ("2009/01/01"[Date - Publication] : "3000"[Date - Publication]) #4 #1 AND #2 AND #3

Electronic Bibliographic Databases	Search Strategy
Scopus	TITLE-ABS-KEY("Vancomycin" OR "Vancomycin Hydrochloride" OR "Hydrochloride, Vancomycin" OR "Vancomycin Sulfate" OR "Sulfate, Vancomycin" OR "Vancomycin-ratiopharm" OR "Vancomycin Hexal" OR "Vancomycine Dakota" OR "AB-Vancomycin" OR "Vanco Azupharma" OR "Diatracin" OR "VANCO-cell" OR "Vanco-saar" OR "Vancocin" OR "Vancocin HCl" OR "Vancomycin Lilly" OR "Vancocine" OR "Vancomicina Abbott" OR "Vancomicina Chiesi" OR "Vancomicina Combino Phar" OR "Vancomicina Norman" OR "Vancomycin Phosphate (1:2)" OR "Vancomycin Phosphate (1:2), Decahydrate") AND TITLE-ABS-KEY("Nomograms" OR "Nomogram" OR "Partin Tables" OR "Partin Table" OR "Table, Partin" OR "Tables, Partin" OR "Partin Nomograms" OR "Nomogram, Partin" OR "Nomograms, Partin" OR "Partin Nomogram" OR "Drug Dosage Calculations" OR "Calculation, Drug Dosage" OR "Calculations, Drug Dosage" OR "Dosage Calculation, Drug" OR "Dosage Calculations, Drug" OR "Drug Dosage Calculation" OR "Pharmaceutical Calculations" OR "Calculation, Pharmaceutical" OR "Calculations, Pharmaceutical" OR "Pharmaceutical Calculation" OR "Pharmaceutical Arithmetic" OR "Arithmetic, Pharmaceutical" OR "Practice Guidelines as Topic" OR "Clinical Guidelines as Topic" OR "Best Practices" OR "Best Practice" OR "Clinical Protocols" OR "Protocols, Clinical" OR "Clinical Protocol" OR "Treatment Protocols" OR "Protocols, Treatment" OR "Treatment Protocol" OR "Clinical Research Protocol" OR "Research Protocols, Clinical" OR "Protocols, Clinical Research" OR "Research Protocol, Clinical" OR "Clinical Research Protocols" OR "Protocol, Clinical Research") AND PUBYEAR AFT 2009 AND (LIMIT-TO (DOCTYPE, "ar"))
Lilacs	(MH:Vancomycin OR (Vancomycin) OR (AB-Vancomycin) OR (Diatracin) OR (Hydrochloride, Vancomycin) OR (Sulfate, Vancomycin) OR (VANCO-cell) OR (Vanco Azupharma) OR (Vanco-saar) OR (Vancocin) OR (Vancocin HCl) OR (Vancocine) OR (Vancomicina Abbott) OR (Vancomicina Chiesi) OR (Vancomicina Combino Phar) OR (Vancomicina Norman) OR (Vancomycin Hexal) OR (Vancomycin Hydrochloride) OR (Vancomycin Lilly) OR (Vancomycin Phosphate (1:2)) OR (Vancomycin Phosphate (1:2), Decahydrate) OR (Vancomycin Sulfate) OR (Vancomycin-ratiopharm) OR (Vancomycine Dakota) OR MH:D09.400.420.925$ OR MH:D12.644.233.925$) AND (MH:Nomograms OR (Nomograms) OR (Nomogram) OR (Nomogram, Partin) OR (Nomograms, Partin) OR (Partin Nomogram) OR (Partin Nomograms) OR (Partin Table) OR (Partin Tables) OR (Table, Partin) OR (Tables, Partin) OR MH:E01.789.650$ OR MH:E05.318.740.500.625$ OR MH:E05.599.835.895$ OR MH:G17.582$ OR MH:N05.715.360.750.530.530$ OR MH:N06.850.520.830.500.625$ OR MH:Drug Dosage Calculations OR (Drug Dosage Calculations) OR (Arithmetic, Pharmaceutical) OR (Calculation, Drug Dosage) OR (Calculation, Pharmaceutical) OR (Calculations, Drug Dosage) OR (Calculations, Pharmaceutical) OR (Dosage Calculation, Drug) OR (Dosage Calculations, Drug) OR (Drug Dosage Calculation) OR (Pharmaceutical Arithmetic) OR (Pharmaceutical Calculation) OR (Pharmaceutical Calculations) OR MH:E02.319.305$ OR MH:Practice Guidelines as Topic OR (Practice Guidelines) OR (Best Practice) OR (Best Practices) OR (Clinical Guidelines as Topic) OR MH:N04.761.700.350.650$ OR MH:N05.700.350.650$ OR MH:VS3.003.001.006.004$ OR MH:Clinical Protocols OR (Clinical Protocols) OR (Clinical Protocol) OR (Clinical Research Protocol) OR (Clinical Research Protocols) OR (Protocol, Clinical) OR (Protocol, Clinical Research) OR (Protocols, Clinical) OR (Protocols, Clinical Research) OR (Protocols, Treatment) OR (Research Protocol, Clinical) OR (Research Protocols, Clinical) OR (Treatment Protocol) OR (Treatment Protocols) OR MH:E02.183$ OR MH:N05.715.360.330.125$ OR MH:VS3.003.001.006.003$) AND (da:((year_cluster:[2009 TO 2021]))) AND (db:("LILACS"))
Google Scholar	("vancomycin") AND ("Nomogram*" OR "Drug Dosage Calculations" OR "Practice Guidelines" OR "Clinical Protocol*") Since 2009. Until 3th page Exclude: patents and citations

SII - List of excluded studies

Reason for exclusion	Authors	Title	Reference
Did not develop vancomycin nomogram	Bang *et al.*	Development of a new pharmacokinetic model for target-concentration controlled infusion of vancomycin in critically ill patients.	Clin Exp Pharmacol Physiol. 2022 Feb;49(2):202-211.
	Šíma *et al.*	Initial dosing of intermittent vancomycin in adults: estimation of dosing interval in relation to dose and renal function	Eur J Hosp Pharm. 2021 Sep;28(5):276-279.
	Lines *et al.*	Evaluation of a trough-only extrapolated area under the curve vancomycin dosing method on clinical outcomes	Clin Pharm. 2021 Feb;43(1):263-269.
	Wang *et al.*	Dose optimization of vancomycin for critically ill patients undergoing CVVH: A prospective population PK/PD analysis	Antibiotics (Basel). 2021 Nov 13;10(11):1392.
	Flannery *et al.*	First-Dose Vancomycin Pharmacokinetics Versus Empiric Dosing on Area-Under-the-Curve Target Attainment in Critically Ill Patients.	Pharmacotherapy. 2020 Dec;40(12):1210-1218.
	Lu JJ *et al.*	A Population Pharmacokinetics Model for Vancomycin Dosage Optimization Based on Serum Cystatin C	Eur J Drug Metab Pharmacokinet. 2020 Aug;45(4):535-546.
	Issaranggoon *et al.*	Correlation of the vancomycin 24-h area under the concentration-time curve (AUC24) and trough serum concentration in children with severe infection: A clinical pharmacokinetic study	Infect Dis. 2020 Mar;92:151-159.
	Bae *et al.*	Application of Pharmacometrics in Pharmacotherapy: Open-Source Software for Vancomycin Therapeutic Drug Management.	Pharmaceutics - Volume 11, Issue 5, 2019
	Colin *et al.*	Vancomycin Pharmacokinetics Throughout Life: Results from a Pooled Population Analysis and Evaluation of Current Dosing Recommendations	Pharmacokinet. 2019 Jun;58(6):767-780.
	Setiawan *et al.*	Optimization of Intermittent Vancomycin Dosage Regimens for Thai Critically Ill Population Infected by MRSA in the Era of the "MIC Creep" Phenomenon	Phenomenon. Acta Med Indones. 2019 Jan;51(1):10-18.
	Chung *et al.*	Evaluation of vancomycin target trough attainment with published dosing regimens in the neonatal intensive care unit population	J Neonatal Perinatal Med. 2019;12(1):21-27.
	Hoegy *et al.*	Continuous intravenous vancomycin in children with normal renal function hospitalized in hematology-oncology: prospective validation of a dosing regimen optimizing steady-state concentration.	Fundam Clin Pharmacol. 2018 Jun;32(3):323-329.
	Ishii *et al.*	Validation of a Nomogram for Achieving Target Trough Concentration of Vancomycin: Accuracy in Patients With Augmented Renal Function	Ther Drug Monit. 2018 Dec;40(6):693-698.
	Brown *et al.*	Allometric versus consensus guideline dosing in achieving target vancomycin trough concentrations	Am J Health Syst Pharm. 2017 Jul 15;74(14):1067-1075.
	Pitaksontayothin *et al.*	The use of Monte Carlo simulation to predict vancomycin dosage for methicillin-resistant staphylococcus aureus in Thai patients of various ages and with varying degrees of renal function	Asian Biomed. 2017 11(4):379-385

Reason for exclusion	Authors	Title	Reference
	Lin *et al.*	Population pharmacokinetics of vancomycin in adult Chinese patients with post-craniotomy meningitis and its application in individualised dosage regimens	Eur J Clin Pharmacol. 2016 Jan;72(1):29-37.
	Maxson, Pate, and Starr	Evaluation of weight-based vancomycin dosing for hospitalized hemodialysis patients	Ren Fail. 2016 Nov;38(10):1677-1682.
	El Nekidy *et al.*	Predicting Maintenance Doses of Vancomycin for Hospitalized Patients Undergoing Hemodialysis.	Can J Hosp Pharm. 2016 Sep--Oct;69(5):341-347.
	Guilhaumou *et al.*	Pediatric Patients With Solid or Hematological Tumor Disease: Vancomycin Population Pharmacokinetics and Dosage Optimization.	Ther Drug Monit. 2016 Oct;38(5):559-66.
	Blot *et al.*	Does contemporary vancomycin dosing achieve therapeutic targets in a heterogeneous clinical cohort of critically ill patients? Data from the multinational DALI study	Crit Care. 2014 May 15;18(3):R99.
	Gillon, Cassat, Di Pentima	Validation of two vancomycin nomograms in patients 10 years of age and older.	J Clin Pharmacol. 2014 Jan;54(1):35-8.
	Swartling *et al.*	Short term impact of guidelines on vancomycin dosing and therapeutic drug monitoring	Int J Clin Pharm. 2012 Apr;34(2):282-5.
	Maki *et al.*	Initial dose of vancomycin based on body weight and creatinine clearance to minimize inadequate trough levels in Japanese adults	Eur J Clin Microbiol Infect Dis. 2012 Oct;31(10):2537-43.
	Zegbeh *et al.*	Vancomycin: what dosages are needed to achieve efficacy in paediatric hematology/oncology?	Arch Pediatr. 2011 Aug;18(8):850-5.
	Yamamoto *et al.*	Proposal of a pharmacokinetically optimized dosage regimen of antibiotics in patients receiving continuous hemodiafiltration	Antimicrob Agents Chemother. 2011 Dec;55(12):5804-12.
	Fernández de Gatta *et al.*	Vancomycin dosage optimization in patients with malignant haematological disease by pharmacokinetic/pharmacodynamic analysis.	Clinical pharmacokinetics - Volume 48, Issue 4, pp. 273-80, 2009
	Crumby *et al.*	Pharmacokinetic comparison of nomogram-based and individualized vancomycin regimens in neonates	Am J Health Syst Pharm. 2009 Jan 15;66(2):149-53.
	Baiocco *et al.*	Impact of implementing a vancomycin protocol to reduce kidney toxicity: A comparative study.	Front Pharmacol. 2023 Sep 28;14:1154573.
	Gomez *et al.*	Implementation of a Vancomycin Dose-Optimization Protocol in Neonates: Impact on Vancomycin Exposure, Biological Parameters, and Clinical Outcomes.	Antimicrob Agents Chemother. 2022 May 17;66(5):e0219121
	Heus *et al.*	Model-informed precision dosing of vancomycin via continuous infusion: a clinical fit-for-purpose evaluation of published PK models	Int J Antimicrob Agents. 2022 May;59(5):106579.
	Liu *et al.*	Two Innovative Approaches to Optimize Vancomycin Dosing Using Estimated AUC after First Dose: Validation Using Data Generated from Population PK Model Coupled with Monte-Carlo Simulation and Comparison with the First-Order PK Equation Approach	Pharmaceutics. 2022 May 7;14(5):1004.
	Robinson *et al.*	Implementing AUC Monitoring in a Pharmacist-Managed Vancomycin Dosing Protocol: A Retrospective Cohort Study.	HCA Healthc J Med. 2023 Apr 28;4(2):157-165.

Reason for exclusion	Authors	Title	Reference
	Wolfe *et al.*	Assessing Nephrotoxicity Associated With Different Vancomycin Dosing Modalities in Obese Patients at a Community Hospital	Hosp Pharm. 2022 Aug;57(4):532-539.
Vancomycin nomogram not available	Hovey *et al.*	Implementation of a Pharmacist-Driven Vancomycin and Aminoglycoside Dosing Service in a Pediatric Hospital	J Pediatr Pharmacol Ther. 2022;27(4):340-346.
	Phillips *et al.*	Safety and Feasibility Assessment of a Pharmacy-Driven AUC/MIC Vancomycin Dosing Protocol in a Multicenter Hospital System	Microbiol Spectr. 2023 Feb 22;11(2):e0331322.
Study in non-Roman characters	Hurumi Y, Nakao Y, Ono M, *et al.*	Clinical utility of initial vancomycin dosing nomogram	J. Tokyo Med. Univ. 2018;76(1):57-63.
	Suchánková H, Lečbychová K, Strojil J, *et al.*	Individualized dosing of vancomycin in geriatric patients.	Epidemiol Mikrobiol Imunol. 2020 Winter;69(4):172-180.
Letter to the editor	Šíma M, Hartinger J, Štenglová N, *et al.*	Creatinine Clearance Estimations for Vancomycin Maintenance Dose Adjustments	Am J Ther. 2018 Sep/Oct;25(5):e602-e604.
Comments	Heil EL, Claeys KC, Mynatt RP, *et al.*	Making the change to the area under the curve-based vancomycin dosing.	Am J Health Syst Pharm. 2018 Dec 15;75(24):1986-1995.