Therapeutic Drug Monitoring of Vancomycin in Patients with Altered Pharmacokinetics: A Narrative Review on Pharmacokinetic Assessments

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Abstract

Introduction: Vancomycin is a glycopeptide antibiotic that is considered as the drug of choice against many Gram-positive bacterial infections, especially Methicillin-resistant Staphylococcus aureus (MRSA). Also, it is a hydrophilic drug with predominantly renal elimination. Given the vancomycin narrow therapeutic index, therapeutic drug monitoring (TDM) is essential to achieve an optimum clinical response and avoid vancomycin-induced adverse drug reactions including nephrotoxicity and ototoxicity. Although different studies are available on vancomycin pharmacokinetic assessment and vancomycin TDM, still there are controversies regarding the selection among different pharmacokinetic parameters including trough concentration (Cmin), the daily area under the curve to minimum inhibitory concentration (AUC24h/MIC) ratio, AUC of intervals (AUCτ), elimination constant (k), vancomycin clearance (ClV) and methods of their calculations for TDM purposes. Methods: In this review, different pharmacokinetic parameters for vancomycin TDM have been discussed in detail along with corresponding advantages and disadvantages, based on the literature review. Determination of vancomycin concentration at steady state (Css) during 24h continuous injection are mentioned. Also, vancomycin pharmacokinetic assessments are discussed in detail in patients with altered pharmacokinetic parameters including those with renal and/or hepatic failure, critically ill patients, patients with burn injuries, intravenous (IV) drug users, obese and morbidly obese patients, those with cancer, patients undergoing organ transplantation, and vancomycin administration during pregnancy and lactation. Results and Discussion: An individualized dosing regimen is required to guarantee the optimum therapeutic results and minimize severe adverse reactions such as acute kidney injury (AKI) in these special groups of patients with altered pharmacokinetic parameters. Also, according to the pharmacoeconomic data on vancomycin TDM, pharmacokinetic assessments would be cost-effective in the mentioned groups of patients with altered pharmacokinetics and associated with shorter hospitalization period, faster clinical stability status, and shorter courses of inpatient vancomycin administration.

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Abstract:

Introduction: Vancomycin is a glycopeptide antibiotic that is considered as the drug of choice against many Gram-positive bacterial infections, especially Methicillin-resistant *Staphylococcus aureus* (MRSA). Also, it is a hydrophilic drug with predominantly renal elimination. Given the vancomycin narrow therapeutic index, therapeutic drug monitoring (TDM) is essential to achieve an optimum clinical response and avoid vancomycin-induced adverse drug reactions including nephrotoxicity and ototoxicity. Although different studies are available on vancomycin pharmacokinetic assessment and vancomycin TDM, still there are controversies regarding the selection among different pharmacokinetic parameters including trough concentration (C_{min}), the daily area under the curve to minimum inhibitory concentration (AUC_{24h}/MIC) ratio, AUC of intervals (AUCτ), elimination constant (k), vancomycin clearance (Cl_V) and methods of their calculations for TDM purposes.

Methods: In this review, different pharmacokinetic parameters for vancomycin TDM have been discussed in detail along with corresponding advantages and disadvantages, based on the literature review. Determination of vancomycin concentration at steady state (C_{ss}) during 24h continuous injection are mentioned. Also, vancomycin pharmacokinetic assessments are discussed in detail in patients with altered pharmacokinetic parameters including those with renal and/or hepatic failure, critically ill patients, patients with burn injuries, intravenous (IV) drug users, obese and morbidly obese patients, those with cancer, patients undergoing organ transplantation, and vancomycin administration during pregnancy and lactation.

Results and Discussion: An individualized dosing regimen is required to guarantee the optimum therapeutic results and minimize severe adverse reaction such as acute kidney injury (AKI) in these special groups of patients with altered pharmacokinetic parameters. Also, according to the pharmacoeconomic data on vancomycin TDM, pharmacokinetic assessments would be cost-effective in the mentioned groups of patients with altered pharmacokinetics and associated with shorter hospitalization period, faster clinical stability status, and shorter courses of inpatient vancomycin administration.

Keywords: Vancomycin; therapeutic drug monitoring (TDM); altered pharmacokinetics; acute kidney injury (AKI); individualized pharmacotherapy.

What's known?

- Vancomycin TDM is essential to obtain optimum clinical efficacy and avoid vancomycin-associated nephrotoxicity.
- Vancomycin TDM using AUC-based monitoring would be prior to trough-only monitoring approach in terms of lower nephrotoxicity occurrence and higher clinical efficacy.
- According to the pharmacoeconomic assessments vancomycin TDM would be affordable.

What's new?

- In this focused review on vancomycin TDM, the altered pharmacokinetic parameters in special groups of patients including renal failure, hepatic failure, critically ill patients, burn injuries, IV drug users, obese and morbidly obese patients, and pregnant or breastfeeding women have been considered.
- Recommendations on individualized pharmacokinetic assessments have been provided in these special groups of patients with altered pharmacokinetic characteristics.
- Using different pharmacokinetic parameters for the purpose of vancomycin TDM has been discussed in detail with emphasis on their pros and cons.

1. Introduction

Vancomycin is a glycopeptide antibiotic that is effective against many gram positive microorganisms [1], especially Methicillin-resistant*Staphylococcus aureus* (MRSA) [2-4]. It is a hydrophilic drug with log P of -3.1, which is almost completely excreted from urine. In patients with normal kidney function, about 80 to 90% of the vancomycin single-dose administration would be excreted unchanged in urine within 24 hours [5, 6]. So, in cases with renal dysfunction, vancomycin clearance could be diminished and dose reduction or interval time enhancement is required [7]. Vancomycin has a minimal oral absorption, so, the preferred route of administration in systemic infections is intravenous (IV) route that results in 100% systemic availability or absolute bioavailability [8]. The approved indication of oral vancomycin is limited to *Clostridium difficle*infection where systemic absorption is not required and vancomycin administration, with a dosage range of 125-500 mg every 6 hours, can induce local effects [9]. Bearing in mind the narrow therapeutic index, therapeutic drug monitoring (TDM) is essential to avoid serious adverse reactions related to over-dose exposure or response failure associated with under-dose therapy [10]. Although vancomycin has been prescribed more than 60 years, still controversies are remaining about drug dosing, pharmacokinetics, and pharmacodynamic aspects of drug therapy [3]. The recommended dose of vancomycin in critically ill patients with severe infection would be a loading dose of 20-35 mg/kg (max: 3 g), followed by the maintenance dose of 15-20 mg/kg every 8 to 12 hours, based on target plasma trough concentration of 15-20 μg/ml or AUC_{24h}/MIC values of 400-600 μg.h/ml [9]. It seems that loading dose administration can enhance target trough concentration achievement in both patients with preserved and impaired renal function. However, the results of a reported retrospective observational study revealed that loading dose administration in patients with normal renal function was not associated with rapid target trough concentration achievement prior to administration of the vancomycin third dose in comparison to the control group who did not receive loading dose. The most important risk factors that could delay the target trough concentration achievement were higher serum albumin and higher GFR values [11]. So, further larger clinical trials are warranted to prove the efficacy and safety of loading dose administration in cases with normal and impaired renal functions. The most important adverse reaction related to vancomycin administration is vancomycin-associated nephrotoxicity correlated with higher trough concentrations and a higher area under the curve (AUC) values. As reported, AUC_{24h}[?]667 μg.h/ml and trough concentration [?]18.2 μg/ml could enhance the risk of vancomycin nephrotoxicity up to 3 to 4 folds [12]. Other risk factors of vancomycin associated nephrotoxicity include critically ill conditions, obesity and morbid obesity, and patients with underlying kidney disease. Also, simultaneous administration of vancomycin with other nephrotoxic agents including amphotericin B, IV contrast agents, aminoglycosides, loop diuretics such as furosemide, vasopressors, piperacillin-tazobactam, and flucloxacillin can enhance the risk of vancomycin associated acute kidney injury (AKI) [12]. Vancomycin associated nephrotoxicity may aggravate the mortality rate and prolong the hospital stay, especially in critically ill patients [2]. The other less common adverse reaction related to vancomycin overdose, ie., ototoxicity is significantly associated with high vancomycin plasma peak (C_{max}) concentrations [7]. In the present review, vancomycin TDM and pharmacokinetic data in population with altered pharmacokinetics including patients with renal and/or hepatic failure, critically ill ones, patients with burn injuries, intravenous (IV) drug users, obese and morbidly obese patients, those with cancer, patients undergoing organ transplantation, and vancomycin administration during pregnancy and lactation are summarized as schematically depicted in Fig. 1. The main goal of this study was to assess different pharmacokinetic parameters that can affect vancomycin TDM in special groups

of patients with altered pharmacokinetic characteristics. Also, pharmacoeconomic aspects of vancomycin TDM in these groups of patients have been discussed.

2. Methods

Respective literature was reviewed on Scopus, PubMed, Web of Science, and Google Scholar databases using the key search terms "vancomycin", "therapeutic drug monitoring (TDM)", "nephrotoxicity", "pharmacokinetics", "pharmacodynamics", "trough concentration", "peak concentration", "area under the curve (AUC)", "critically ill patients", "burn injuries", "obese patients", "cancer", "renal failure", "hepatic failure", "organ transplantation", "pregnancy", and "lactation" from 1950 through December 2020. In doing so, titles and abstracts of the related articles were considered for further assessment, with review and original articles included. First, different pharmacokinetic parameters used in vancomycin TDM were discussed and reviewed. Then advantages, disadvantages as well as the clinical efficacy of those parameters were summarized. The focus of this review has been on one-compartmental models already used extensively in the clinical settings. Vancomycin TDM in patients with altered pharmacokinetics were reviewed and summarized, too. Last but not least, pharmacoeconomics and cost-effectiveness of vancomycin TDM were discussed.

3. Pharmacokinetic parameters used in vancomycin efficacy and toxicity assessments

The most common recommended pharmacokinetic parameters for vancomycin TDM are trough concentration, area under the curve of total daily dose (AUC_{24h}) to minimum inhibitory concentration (MIC) ratio, and steady state plasma concentration (C_{ss}) for continuous infusion [13]. AUC refers to the total drug exposure to the administered dose in a defined time period. It has been suggested that AUC_{24h}/MIC[?]400, in microorganisms with minimum inhibitory concentration (MIC) of [?] 1 mg/L, can be an important indicator of successful drug response [9]. Trough concentration assessment is the simplest method of vancomycin pharmacokinetic evaluation. It has been recommended that trough concentration of 15-20 μg/ml would be a suitable target concentration with promising drug efficacy and safety [3]. But previous studies revealed that in many patients, AUC_{24h}/MIC values of [?]400 could be achieved with lower values of trough concentrations (<15 μg/ml) and these trough values could be associated with lower risk of vancomycin-induced nephrotoxicity [14, 15]. So, AUC calculation can be considered as the preferred method for vancomycin pharmacokinetic assessments. Another advantage of AUC calculation is the simplicity of vancomycin dosing based on AUC values according to the Eq. 1 [3].

$$Vancomycin\ dose = \frac{\mathrm{Cl}}{\mathrm{AUC}_{24h}} \quad \text{(Eq. 1)}$$

Where vancomycin dose is in mg/day, Cl is drug clearance in L/h, and AUC_{24h} is the area under the cure of total daily dose in mg.L/h.

Also, there are controversies regarding the intermittent or continuous infusion of vancomycin and previous studies failed to reach a superiority for either method. The most important advantages of continuous infusion over intermittent infusion are less variability in vancomycin plasma concentrations, less dependency on time and number of prepared blood samples, and lower incidence of AKI [12]. Results of a recent meta-analysis have demonstrated that although continuous infusion of vancomycin was accompanied by lower incidence of nephrotoxicity, there was no significant difference between continuous and intermittent infusion approaches in terms of clinical efficacy and mortality rate in the patients receiving vancomycin [16]. During intermittent infusion, trough concentration sampling should be done just before the next dose administration when steady state concentration (C_{ss}) is achieved, i.e., after 4 to 6 elimination half-lives (about 48 hours in normal kidney patients) [3] and can be used for the purpose of vancomycin TDM during continuous infusion approach. Upon intermittent vancomycin infusion, pharmacokinetic parameters such as k and V_d can be calculated

through Eq. 2 and Eq. 3, using two level plasma sampling. To do so, one sample should be the first peak concentration (one hour after the end of infusion) and the other one can be drawn at an optional time during the interval dosing and before the next dose infusion.

$C_t = (C_{\max})e^{-k(t-t')}$ (Eq. 2)

Where C_t is plasma concentration at time t in mg/L, C_{max} is the first peak concentration in mg/L, k is elimination constant in h^{-1}, t is the time of second blood sampling in h, and t´ is the infusion time in h.

$C_{\max} = \frac{K_0}{k \times V_d}(1 - e^{-kt'})$ (Eq. 3)

Where C_{max} is the first peak concentration in mg/L, K_0 is the drug infusion rate in mg/h, k is elimination constant in h^{-1}, V_d is volume of distribution in L, and t´ is the infusion time in h.

Then, steady state concentrations could be calculated using the aforementioned pharmacokinetic parameters according to Eq. 4 and Eq. 5 [3].

$C_{ss}^{\max} = \frac{K_0(1-e^{-kt'})}{k \times V_d(1-e^{-k\tau})}$(Eq. 4)

$C_{ss}^{\min} = C_{ss}^{\max}e^{-k(\tau-t')}$(Eq. 5)

Where C_{ss}^{max} and C_{ss}^{min} are peak and trough concentrations at steady state, respectively in mg/L, K_0 is drug infusion rate in mg/h, k is elimination constant in h^{-1}, V_d is the volume of distribution in L, t´ is the infusion time in h, and τ is drug interval in h.

During the continuous infusion of vancomycin, steady state concentration could be calculated through the Eq. 6, in which vancomycin clearance is estimated from creatinine clearance through the Eq. 7 [17].

$C_{ss} = \frac{K_0}{Cl}$ (Eq. 6)

$Cl = 0.04\,(Cl_{cr}) + 0.22$ (Eq. 7)

Where C_{ss}steady state plasma concentration is in mg/L, K_0 is infusion rate in mg/h, Cl is vancomycin clearance in L/h, and Cl_{cr} is creatinine clearance that is equal to the estimated glomerular filtration rate (eGFR) in L/h.

According to these formulas, target C_{ss} values of 20-30 µg/ml and AUC_{24h} values of 400-700 mg.h/L can be achieved. In continuous infusion regimen, loading dose of 20 mg/kg accelerates the steady state concentration achievement. Afterwards, continuous infusion should be immediately initiated upon loading dose administration. According to Eq. 8, it was suggested that in continuous infusion approach, AUC_{24h} could be calculated by one sample after steady state achievement [3].

$AUC_{24h} = C_{ss} \times 24$ (Eq. 8)

Where AUC_{24h} is the area under the curve of total daily dose and C_{ss} is the steady state vancomycin plasma concentration.

3.1. Trough concentration

Since many years ago, monitoring of the vancomycin trough concentration has been considered as an accurate, practical, and simple approach for vancomycin TDM purposes. Pros and cons of the trough-only vancomycin monitoring approach are summarized in Table 1. Sample preparation for trough concentration assessment should be done after steady-state concentration achievement. The suitable sampling time in patients with normal renal function can be scheduled after 48 hours of drug administration or before the forth dose. The exact time of sampling should be just before the next dose or up to 30 minutes prior to the next dose. Target trough concentration of 15-20 µg/ml was recommended in critically ill patients with severe Gram-positive infections [11]. Previous studies on vancomycin pharmacokinetics claimed that vancomycin trough concentration had a good correlation with AUC values, especially in adult patients with GFR[?]100

ml/min. Also, it was maintained that in such patients, trough concentration of 15-20 μg/ml may result in AUC/MIC values of [?]400 μg.h/ml in microorganisms with MIC[?]1 μg/ml [14]. Higher vancomycin trough concentrations (>20 μg/ml) are associated with vancomycin-induced nephrotoxicity. But not all patients with trough concentration of >20 μg/ml proceeded to nephrotoxicity. Nephrotoxicity occurred in about 25-40% of the patients with trough concentration of >20 μg/ml [14]. Although the target trough concentration of 15-20 μg/ml was suggested as an optimum concentration in vancomycin TDM assessments, it was reported that trough concentration of >12.1 μg/ml was significantly associated with an enhanced risk of nephrotoxicity occurrence [18]. Results of a population pharmacokinetic and vancomycin dose simulation study revealed that trough concentrations were highly varied among participating patients with different and/or same renal functions. So, it seems that in order to achieve a suitable clinical response and acceptable vancomycin efficacy with AUC values of 400 to 700 μg.h/ml, trough concentration of >15 μg/ml is not necessary in many patients and can induce nephrotoxicity with no further superior efficacy. Up to 60% of adult patients with trough concentration of <15 μg/ml could achieve target AUC_{24h}/MIC target values of [?]400 μg.h/ml [19]. We can conclude that the preferred approach to vancomycin TDM and pharmacokinetic assessments could be AUC of intervals (AUCτ) calculation rather than trough-only monitoring approach [14]. As per the recent 2020 vancomycin guideline, AUC_{24h}/MIC values of 400-600 μg.h/ml for severe MRSA infections would be a better alternative target to trough concentration of 15-20 μg/ml for vancomycin TDM purposes [19]. It was reported that AUC_{24h}/MIC values of [?]400 μg.h/ml was associated with better clinical outcomes in septic patients and AUC_{24h}/MIC values of [?]650 μg.h/ml was associated with lower risk of vancomycin induced AKI [19, 20]. Another drawback in trough-only monitoring approach could be the possible errors in sampling time. Results of a recent prospective study have revealed that fewer than half of the collected samples were within the normal range of trough concentration sampling times (10-12 hours post-dose) [21]. In general, trough-only monitoring approach with target concentration of 15-20 μg/ml has no longer been supported by recent infectious guidelines due to its lack of clinical efficacy and higher rate of vancomycin-induced nephrotoxicity [22]. According to a retrospective cohort study on vancomycin TDM, trough concentration-based dosing was accompanied by higher treatment failure rate and higher acute kidney injury occurrence in comparison to AUC-based dosing approach [22]. Trough-based vancomycin dose adjustment can be achieved through the Eq. 9 [23].

$D_2 = (\frac{C_{t2}}{C_{t1}}) \times D_1$ (Eq. 9)

While D_2 is the new dose in mg, C_{t2} is the target steady-state trough concentration in mg/L, C_{t1} is the current trough concentration in mg/L, and D_1 is the previous dose in mg resulting in plasma trough concentration of C_{t1}.

3.2. Peak concentration

Peak concentration is defined as the vancomycin plasma concentration drawn 1 hour after the end of the 1 hour-infusion period in order to pass the distribution phase [14]. There are controversies about the necessity of plasma peak concentration calculation for vancomycin TDM purposes [25]. Results of many population pharmacokinetic studies revealed that peak concentration was not associated with either vancomycin efficacy or vancomycin-induced nephrotoxicity [14]. However, peak concentration can be used as an essential point in AUC of interval calculation [14]. It was reported that using both trough and peak concentrations in AUC calculation could enhance the precision of assessments in comparison to trough-only consideration in AUC calculation [26]. Results of a recent Bayesian model-based population study have revealed that AUC estimation using peak and trough concentrations was worse than using trough-only approach. The same study claimed that using a peak concentration that drawn just after the end of the infusion period would be better in calculation of AUC values using peak and trough concentrations. So, it seems that peak concentration can be assessed just after the end of 1 hour-infusion in order to achieve better estimation in AUC calculation, especially in one-compartment models. Although the results of a recent pragmatic randomized controlled trial suggested that peak-trough-based TDM approach was significantly associated with higher therapeutic and clinical cure rate, compared to trough-only-based TDM approach, they failed

to show a significant difference in all-cause mortality and vancomycin-induced nephrotoxicity between these two TDM approaches [23]. Peak-trough-based vancomycin dose adjustment could be achieved through the Eq. 10 and Eq. 11 [23] as well as by individualized calculation of pharmacokinetic parameters, as mentioned in the Introduction.

$\tau = \frac{(\ln C_{\text{peak}} - \ln C_{\text{trough}})}{K_e} + t'$(Eq. 10)

$Dose = C_{\text{peak}} \times K_e \times V_d(\frac{1-e^{-K_e\tau}}{1-e^{-K_e t'}})$(Eq. 11)

Where τ is dosing interval in h, C_{peak} is steady-state peak concentration in mg/L, C_{trough} is steady-state trough concentration in mg/L, K_e is elimination constant in h^{-1}, t' is infusion time in h, V_d is volume of distribution in L andDose is the new vancomycin dose in mg.

3.3. AUC

Based on recent reports on vancomycin dosing, AUC_{24h}could be the preferred approach to TDM purposes [27]. Pros and cons of the AUC-based vancomycin monitoring approach are summarized in Table 2. AUC_{24h} calculation can be done, based on Bayesian software programs using a trough-only sampling approach or peak-trough sampling approach, while the latter results in higher accuracy in AUC estimation [12]. Vancomycin dose adjustment and AUC calculation, based on available Bayesian software programs including Adult and Pediatric Kinetics (APK), BestDose, DoseMe, InsightRx, and Precise PK can be considered as an alternative approach to practical uses of clinicians and pharmacists for the purpose of vancomycin TDM and dose-optimization. Such available soft wares are simple, flexible, and user friendly that can be used by pharmacists and clinicians in the field of vancomycin TDM [28]. Results of a recent review article on the evaluation of the accuracy and efficacy of such Bayesian tools have revealed that similar AUC estimation could be achieved through this approach in comparison to pharmacokinetic equations using two-point blood sampling assay for TDM purposes [29], but further larger meta-analysis and systematic review studies are required, especially for patients with altered pharmacokinetics to assess their accuracy and clinical efficacy in comparison to previous approaches such as AUC calculation using trapezoidal method and individualized pharmacokinetic parameters calculation using at least two vancomycin plasma concentration.

The recommended target value of [?]400 μg.h/ml with MIC value of <1 μg/ml as well as a cut-off point of [?]600 μg.h/ml should be considered to avoid vancomycin-induced AKI occurrence [30]. It was reported that although there was a significant correlation between trough concentration and $AUC_{24h,}$ it was moderate (R^2 of 0.51). Results of a recent population pharmacokinetic study has revealed that AUC values could vary about 30-folds in the patients with different renal functions, lending support to the importance of vancomycin TDM and individualized pharmacotherapy to avoid vancomycin-induced nephrotoxicity in over-dose patients and prevent clinical response failure in under-dose individuals. Also, the studies indicated that trough-only monitoring approach could not be an accurate and suitable surrogate of AUC calculation since the significant correlation was not obvious [14, 24]. It was suggested that an AUC_{24h} threshold value of 700 μg.h/ml should be considered to avoid vancomycin-induced nephrotoxicity. AUC_{24h} values of >700 μg.h/ml were significantly associated with higher incidence of vancomycin-induced nephrotoxicity [14]. Results of a retrospective pharmacokinetic study on American population revealed that patients with AUC_{24h}[?]297 μg.h/ml had more than 2.7-fold improvement in clinical response in comparison to those with lower AUC_{24h} values. Also, it was reported that patients with AUC_{24h}[?]710 μg.h/ml had more than 7-folds higher risk of nephrotoxicity occurrence due to vancomycin over-exposure [31]. In a recent prospective study, among the participants, 19% had therapeutic trough concentration while 70% of them had therapeutic AUC values. Also, the results of this study revealed that 31% of the patients with AUC[?]400 μg.h/ml had trough concentration of <10 μg/ml with 68% of whom were with trough concentration of <15 μg/ml, suggesting that AUC rather than the vancomycin trough concentration can be considered as a suitable pharmacokinetic parameter, in order to obtain enough clinical efficacy with lower incidence of nephrotoxicity. The acceptable AUC targets can be achieved with lower plasma trough concentrations [21]. Results of a retrospective pharmacokinetic study in Japanese population revealed that AUC-guided vancomycin TDM (target AUC>400 μg.h/ml),

compared to trough-guided TDM (target trough concentration of 15-20 µg/ml), could be associated with lower risk of nephrotoxicity occurrence [32, 33]. Overall, according to the reports, AUC-guided, Bayesian estimation dosing of vancomycin was accompanied by lower incidence of vancomycin-induced nephrotoxicity, shorter duration of antibiotic therapy, fewer blood samples, less vancomycin exposure, and less over-dose occurrence with cost-effectiveness. So, it seems reasonable to shift from trough-only-guided dosing approach to AUC-guided dosing approach for vancomycin TDM in referral hospitals in order to maintain the therapeutic window [21, 34]. Besides the many advantages mentioned about the use of AUC_{24h}/MIC target concentration of 400-600 µg.h/ml for MRSA infections, yet there are some drawbacks that should be taken into accounts. First, the target AUC_{24h}/MIC value of 400-600 µg.h/ml does not contribute to other Gram-positive microorganisms that are less virulent than MRSA, such as Methicillin-resistant coagulase negative *Staphylococcus aureus* . Also, it seems that the recommended concentration of 400-600 µg.h/ml is suitable for sepsis, pneumonia, and endocarditis while other severe infections such as meningitis and osteomyelitis may require different AUC target values. Meanwhile, a recent meta-analysis has revealed that AUC_{24h}/MIC target concentration of >400 µg.h/ml is not associated with reduced morbidity and mortality in severe cases of MRSA infection [19].

3.4. Vancomycin clearance (Cl_V)

Vancomycin clearance (Cl_V) is considered as a pharmacokinetic parameter in the prediction of vancomycin efficacy and toxicity. Results of a previous observational study on vancomycin administration revealed that Cl_V was correlated with creatinine clearance (calculated via Cockcroft-Gault equation), serum creatinine, gender, age, weight, and neutropenia. There was a correlation with R^2 of 0.5 between $Cl_V$and creatinine clearance, so it seems that Cl_V should not be considered as a suitable predictor in vancomycin clinical pharmacokinetic assessments. Results of this study revealed that creatinine clearance had a good correlation with 24h-urine creatinine (with R^2 of 0.8-0.9). It seems that creatinine clearance calculation using 24h-urine creatinine assessment can promote the correlation between Cl_V and creatinine clearance in vancomycin TDM. In general, it can be suggested that Cl_V, due to its high prediction errors, can not serve as a suitable and practical clinical pharmacokinetic parameter for TDM purposes [35].

3.5. Elimination constant (k)

Elimination constant (k) is an indicator of renal function during the administration of a hydrophilic drug such as vancomycin with almost complete renal excretion. So, the higher the k values, the better kidney function is predictable. While in patients who progress to AKI due to vancomycin exposure, lower k values and higher t $\frac{1}{2}$ amounts are expected. In cases with normal renal function with t $\frac{1}{2}$ of about 4-6 hours, k values of 0.115-0.173 h^{-1} are acceptable and the values lower than the mentioned values can be considered as an alternative pharmacokinetic parameter for early detection of vancomycin associated nephrotoxicity.

4. Vancomycin TDM Assessments in Patients with Altered Pharmacokinetics

4.1. Patients with renal failure

Patients with renal insufficiencies have difficulties in drug elimination and further drug accumulation, longer drug half-lives, with nephrotoxicity occurrence being predictable. So, in such patients the need for TDM and pharmacokinetic assessments is clear in order to prevent the occurrence of vancomycin overdose, especially vancomycin-associated nephrotoxicity. There is a positive correlation between vancomycin clearance and creatinine clearance. In patients with renal failure and reduced GFR, vancomycin clearance is diminished and drug accumulation is predictable [36]. It was reported that the normal half-life of vancomycin (t $\frac{1}{2}$ of 4-6 hours) might be enhanced up to 100-200 hours in patients with acute or chronic anuria [37]. Also,

non-renal clearance of vancomycin was reduced in patients with chronic renal failure which can precipitate this drug accumulation [38]. In cases with end stage renal disease (ESRD) who require dialysis, it was reported that vancomycin is poorly dialyzable during low-flux hemodialysis process, given its high molecular weight of 1450 Dalton. So, the recommended dosing schedule in these ESRD patients could be once-weekly administration. During high-flux hemodialysis, vancomycin clearance may reach 40-130 ml/min, leading to vancomycin removal of 89.6-93.4% after a high-flux dialysis session. The recommended dosage of vancomycin in patients undergoing hemodialysis mainly depends on the time of vancomycin administration (intra-dialysis *vs* . after the end of the dialysis session) and dialyzer permeability (high *vs*.low permeability), as presented in Table 3 [12]. Patient's weight and duration of each hemodialysis session can significantly affect the amount of vancomycin clearance post high-flux dialysis. In patients undergoing high-flux dialysis, vancomycin should be administered three times a week during the last hour of the hemodialysis session or after the end of hemodialysis [36].

It has been hypothesized that in patients with ESRD, vancomycin has lower protein binding concentrations which resulting in higher free drug and higher C_{max} (peak concentration) values. So, lower dose requirement in ESRD patients could also be attributed to the lower plasma protein binding of vancomycin [36]. Results of a recent population pharmacokinetic study indicate that vancomycin clearance and central volume of distribution (V_c) are significantly different between dialysis and non-dialysis patients. It was recommended that nomogram-based vancomycin dosing in dialysis patients would be helpful in order to achieve optimum pharmacokinetic parameters such as trough concentration and AUC [39]. There are limited data on vancomycin dosing in patients with chronic kidney disease (CKD), who do not require dialysis (CKD stages of II-IV). Based on the linear positive correlation between creatinine clearance (GFR) and vancomycin clearance in CKD patients, vancomycin intermittent dosing can be adjusted, as shown in Table 4 [5, 9].

In all CKD patients, the administration of a loading dose of 25-30 mg/kg could be helpful in facilitating the achievement of target trough concentration of >15 μg/ml. Reportedly, the recommended dose of vancomycin empirical therapy in critically ill patients with AKI undergoing continuous renal replacement therapy (CRRT), can be the loading dose of 1.5 gram, followed by maintenance dose of 500 mg every 8 hours. Generally, it is emphasized that higher vancomycin doses are required in CRRT patients than doses recommended in previous literature in order to achieve target trough and AUC values [40]. The most important concern about vancomycin administration in patients with renal failure is the risk of vancomycin-associated nephrotoxicity due to overdose exposure. Such an adverse reaction could be precipitated by co-administration of other nephrotoxic agents in poly-pharmacy patients [5]. . As reports suggest, vancomycin dosing based on GFR and TBW in patients with renal failure and variable kidney function can result in response failure or vancomycin-associated nephrotoxicity due to under-dose and over-dose occurrence, respectively. So, vancomycin TDM with precise monitoring of pharmacokinetic parameters seems essential to achieve optimum individualized pharmacotherapy and better clinical response [41]. Besides, other effective antimicrobials with MRSA coverage such as linezolid, tigecycline, and daptomycin can be considered due to their extra-renal elimination route. Therefore, no dose adjustment is required for these drugs in patients with renal failure [5].

4.2. Patients with liver diseases

Non-renal clearance (Cl_{nr}) of vancomycin is reduced in patients with hepatic failure [38]. Results of a retrospective pharmacokinetic study in patients with liver disease revealed no significant association between pharmacokinetic parameters and biochemical parameters of liver function such as bilirubin, transaminases (AST and ALT), Gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), serum albumin, and lactate dehydrogenase (LDH). It seems that vancomycin pharmacokinetics is not significantly influenced in patients with hepatic failure. This study revealed that in patients with hyperbilirubinemia, only V_d and $t_{\frac{1}{2}}$ values were enhanced but not significantly [42]. In a recent pharmacokinetic study, mean trough concentration and AUC/MIC values were higher in patients with moderate to severe liver disease in comparison to the patients with normal or mild liver disease due to the vancomycin prolonged half-lives [43, 44]. The higher

pharmacokinetic parameters values resulted in the higher rate of AKI in patients with moderate to severe liver disease, compared to normal or mild liver disease, but the difference was not statistically significant [44]. An important point in patients with hyperbilirubinemia could be laboratory error occurrence in serum creatinine assessments which can under-estimate the serum creatinine values. This point should be considered in conditions developing to acute kidney injury due to vancomycin exposure and pre-existing liver disease.

4.3. Critically ill patients

Critically ill patients admitted to intensive care units (ICU) may have different pharmacokinetic parameters in comparison to normal patients, leading to different dosing recommendations [45]. Results of a recent prospective study on vancomycin pharmacokinetics have revealed that trough concentration should not be considered as an adequate surrogate of AUC_{24h} in these patients [46]. Sepsis is a common cause of death among critically ill patients, which can induce physiologic changes in patients such as endothelial permeability enhancement that can result in capillary leakage syndrome (CLS), vasodilation due to nitric oxide, pro-coagulation effects due to cytokine release syndrome (CRS), and variations in the biosynthesis of proteins. The physiological changes in septic patients give rise to pharmacokinetic changes in critically ill patients [47]. Creatinine clearance could be changed in septic patients either due to AKI or augmented renal clearance (ARC) phenomenon. Also, serum albumin was significantly reduced in sepsis, possibly due to CLS and CRS. Serum albumin reduction might induce higher free dug amounts [47]. V_d and Cl_V enhancement are predictable in septic patients, suggesting the need for higher dose requirement in critically ill patients with sepsis [48]. In septic patients who develop to multi-organ failure (MOF), vancomycin administration is not appropriate because of low penetration to solid organs such as lung and other effective antimicrobials with better tissue penetration should be considered [48]. Results of a recent pharmacokinetic study reported that in critically ill patients receiving vancomycin, the respective clearance was significantly associated with age, creatinine clearance, and serum creatinine [46]. Data of a previous pharmacokinetic study in critically ill patients also emphasized that creatinine clearance alone could not be a sufficient predictor of renal function in critically ill patients. Higher trough and peak concentrations after nomogram-based vancomycin dosing in critically ill patients could be attributed to tubular damage in such septic patients, leading to the reduced vancomycin elimination and higher plasma concentrations [49]. Plasma trough concentration of 15 μg/ml during intermittent vancomycin administration and steady state concentration of 20-30 μg/ml during continuous vancomycin infusion could be optimal in critically ill obese patients [50]. In critically ill trauma ICU patients, vancomycin clearance was found to be higher than that in medical ICU patients. Since vancomycin-associated AKI in critically ill patients admitted to ICU is not completely reversible, close drug monitoring is essential in these patients with altered pharmacokinetics in order to avoid further morbidities and mortality associated with AKI occurrence [12].

4.4. Patients with burn injuries

Since MRSA is a common source of nosocomial infections among hospitalized patients with severe burn injuries, vancomycin can serve as an antibiotic of choice in the patients. Burn injuries can induce pathophysiological changes in patients that can result in changes in pharmacokinetic aspects of drugs. During the hyper metabolic phase, more than 48 hours after burn injuries, creatinine clearance is significantly enhanced that cause higher drug Cl values. Since vancomycin has renal excretion, individualized pharmacotherapy and pharmacokinetic assessments are necessary in patients with severe burn injuries in order to obtain target trough concentrations and AUC values. Results of a case control retrospective study on patients with burn injuries revealed that patients with burns had significantly higher vancomycin Cl in comparison to the controls. Yet, there are controversies about the mechanism of this enhanced vancomycin Cl values and it is suggested that changes in creatinine clearance, enhanced tubular secretion, and increased glomerular filtration rate in patients with burns may be the possible mechanisms. Results of this study revealed that the administration of the same dose of 1 gram vancomycin every 12 hours could significantly result in lower trough concentrations in patients with burns in comparison to the controls. Also, it was revealed that V_d

was not significantly different between case and control groups. So, it is emphasized that vancomycin administration in traumatic patients admitted to ICU should be individualized, based on actual body weight (ABW) and measured plasma concentrations [51]. Also, the results of a previous pharmacokinetic study on patients with burns, IV drug users and control group indicated that burns patients had significantly higher creatinine clearance, vancomycin clearance and renal clearance in comparison to the other groups, that might be attributed to the higher Cl_{nr}, higher GFR values, and altered protein binding amounts in burns patients [52]. In general, it seems that due to higher Cl_V and lower trough concentrations, individualized pharmacotherapy and precise vancomycin TDM are required in order to avoid antimicrobial resistance and response failure due to under-dose vancomycin therapy in patients with burn injuries [51]. As reported in an algorithmic study in patients with thermal injuries, the optimum trough and AUC values could be achieved through the empiric adjustment of the doses, as presented in Table 5 [53].

4.5. IV drug users

Vancomycin is a commonly administered drug in IV drug users due to Gram-positive infections including staphylococcal endocarditis [54]. The pharmacokinetics of vancomycin might be altered in these patients. Results of a pharmacokinetic study revealed that the mean Cl_V was about 31% higher in IV drug users in comparison to that in the control group. However, the difference was not statistically significant. Given the higher Cl_V values in IV drug users, individualized pharmacotherapy and higher doses of vancomycin are required in order to achieve target trough and AUC values and better clinical response [52].

4.6. Pregnancy and lactation

Vancomycin administration is recommended as an antimicrobial agent during pregnancy to prevent the group B *Streptococcal* (GBS) infection transmission from mother to fetus, as a prophylactic agent before cesarean section, and treatment of *Clostridium difficle*infection. Vancomycin can cross the placenta and reach amniotic fluid, fetal serum, and cord blood [55], and no respective adverse reactions such as ototoxicity and nephrotoxicity have been reported in fetus after maternal administration of vancomycin during second and third trimesters [56]. The pharmacokinetic parameters of vancomycin might be changed during pregnancy while t $\frac{1}{2}$ remains unchanged and V_d and total Cl may be enhanced indicating the need for higher dose administration, individualized pharmacotherapy, and precise plasma concentration monitoring in pregnant women. Nevertheless, it is also warned about the potential induction of fetal malformations due to the administration of injectable vancomycin formulations that have polyethylene glycol (PEG) 400 and/or N-acetyl D-alanine (NADA) as excipients. [57].

Vancomycin administration is suggested in lactating women with *Clostridium difficle* infections. Since vancomycin has poor oral absorption, the amount of vancomycin that can pass through the milk is limited and breast feeding could be acceptable during vancomycin oral administration. Upon IV administration, vancomycin can be detected in milk with relative infant dose (RID) of 4.8%. Since the RID value is less than 10%, vancomycin IV administration during lactation seems to be acceptable, but decision making on breast feeding during pharmacotherapy should be based on risk/benefit assessments [57]. Given the vancomycin high molecular weight (MW of 1450 Dalton) and hydrophilic nature (log P of -3.1), it has less tendency to pass into the breast milk compartment [58].

4.7. Patients with organ transplantation

Results of a retrospective cohort study on pre- and post-lung transplantation in cystic fibrosis patients receiving vancomycin revealed that pharmacokinetic parameters can be altered after solid organ transplantation such as lung transplantation. So, it seems that the population pharmacokinetic data used in vancomycin dosing in pre-transplantation could not be used for post-transplant counterparts. The most obvious post transplantation changes were significant reduction in k and increment of t $\frac{1}{2}$, that can be attributed to the

decreased renal clearance and administration of immunosuppressive drugs including cyclosporine and tacrolimus and antimicrobial agents such as trimethoprim/sulfamethoxazole and valganciclovir that are highly nephrotoxic [59].

4.8. Obese patients

Weight-based vancomycin dosing is dependent on the volume of distribution (V_d) values. The value based on patient's weight was reported between 0.26–1.25 L/kg. So, the estimated V_d values in obese patients are higher than that in non-obese ones. The higher estimated V_d values in obese patients could result in higher trough concentrations and further drug toxicity incidence [3]. Another method of $V_d$calculation regardless of weight is based on Eq. 12 [60].

$V_d = \frac{\text{Vancomycin dose}}{C_{\max} - C_{\min}}$ (Eq. 12)

Where V_d is the volume of distribution in L, vancomycin dose is in mg, C_{max} is peak concentration in mg/L, and C_{min} is trough concentration in mg/L.

According to Eq. 13 and Eq. 14, in obese patients with larger V_d values and the same Cl, the smaller elimination constants and longer half-life values are predictable. Therefore, obese patients require higher doses of vancomycin with larger intervals of administration, compared to non-obese patients [3].

$Cl = k \times V_d$ (Eq. 13)

Where Cl is vancomycin clearance in L/h, k is elimination constant in h^{-1}, and V_d is the volume of distribution in L.

$t_{1/2} = \frac{0.693}{k}$ (Eq. 14)

Where $t_{1/2}$ is the drug half-life in h and k is the elimination constant in h^{-1}.

It has been reported that total body weight (TBW)-based vancomycin dosing in obese and over-weight pediatric patients may give rise to higher vancomycin plasma trough concentrations and higher risk of nephrotoxicity occurrence, compared to normal body habitus pediatrics. So, the necessity of vancomycin TDM in these population would be obvious [57]. Results of a retrospective cohort study revealed that vancomycin trough concentration was negatively correlated with body mass index (BMI) and creatinine clearance values, that is, the patients with higher BMI (BMI[?]24 kg/m^2) and augmented creatinine clearance, had lower trough concentration after administration of the same doses of 1 gram vancomycin every 12 hours. Thus, personalized pharmacotherapy and individualized dose adjustment are required in such patients [61]. Administration of hydrophilic drugs such as vancomycin to obese patients can result in higher $V_d$values and lower plasma concentrations. Low plasma trough concentration in the patients may lead to clinical response failure. Accordingly, precise concentration monitoring in obese patients is essential to prevent both response failure and nephrotoxicity due to under-dose and over-dose vancomycin administration, respectively. As reports indicate, vancomycin administration with dosage of 1 gram every 8 hours may result in appropriate target trough concentrations in obese patients with BMI[?]24 kg/m^2, and further plasma sample assessments are required for each patient [61]. Continuous vancomycin infusion in obese patients can lead to lower vancomycin daily dose exposure and improve therapeutic plasma concentration with better clinical response, compared to non-obese patients [50]. Results of a pharmacokinetic study based on Bayesian model revealed that both actual body weight (ABW) and lean body weight (LBW) were independent predictors of V_d. According to the results of this study, in these obese patients, V_d and t 1/2 values were enhanced and total Cl was diminished. Also, it was reported that initial vancomycin dosing based on ABW could be superior to LBW, since ABW would be a better predictor of pharmacokinetic parameters [62]. Also, reports show that in morbidly obese patients with TBW of up to 200 kg, administration of vancomycin with daily dose of 35 mg/kg (max 5.5 g/day) in 2 divided doses, may result in target trough concentration of 5.7-14.6 µg/ml and AUC_{24h} values of >400 µg.h/ml. In such obese patients, TBW could be a suitable predictor of Cl_V. Enhanced V_d and Cl_Vwere reported in these groups of patients [63], the enhanced V_d amounts could be attributed to the

higher adipose tissue and muscle mass in obese patients. Considering the higher blood volume and cardiac output in obese patients, increased blood flow and increased Cl_V would be predictable. Obese patients may have elevated amount of circulatory plasma proteins that can alter the amounts of vancomycin protein binding and the percentage of free drug available in plasma and target sites [64, 65]. Taking into account the pharmacokinetic changes in obese and morbidly obese patients, individualized pharmacotherapy and close plasma concentration monitoring during vancomycin administration is strongly recommended.

4.9. Patients with cancer

Vancomycin is a common antibiotic administered in cancer patients complicated with pneumonia. Also, cancer can alter different pharmacokinetic parameters in patients receiving vancomycin. Although the results of previous studies reported no significant differences in pharmacokinetic parameters of cancer and non-cancer patients [66], results of a recent pharmacokinetic study have demonstrated that cancer patients were with significantly higher V_d and Cl, in comparison to the control group, leading to significantly lower initial trough concentrations in this group of patients. So, in cancer patients higher doses of vancomycin may be required to achieve target trough and AUC values and ensure optimum clinical response. Doses up to 60 mg/kg/day may be required in cancer patients in order to achieve optimum clinical response, given their higher V_d and Cl_V values [67]. It was reported that cystatin-C measurement before and during vancomycin therapy can serve as a good predictor of required dose in cancer patients [68]. Also, patients with solid malignancies had higher Cl_V values that resulted in lower vancomycin plasma concentration. Therefore, precise and early plasma concentration monitoring could be helpful to achieve effective target concentrations with minimal unwanted adverse reactions [69]. Results of a retrospective study in advanced cancer patients revealed that cachexia associated with cancer can give rise to changes in pharmacokinetic parameters during vancomycin administration. Glomerular filtration rate did not show a significant difference between cachectic and non-cachectic patients but systemic $Cl_V$was significantly lower in cachectic cancer patients which resulted in drug accumulation and higher vancomycin plasma concentrations. Also, the rate of AKI occurrence in cachectic cancer patients during vancomycin administration was significantly higher in comparison to that in the control group. So, cancer cachexia could be considered as an important independent risk factor of vancomycin-induced AKI [70].

5. Pharmacoeconomic aspects and cost-benefit evaluation of TDM center establishment

There are controversies regarding the cost-benefit of TDM center establishment for the patients receiving vancomycin in developing countries. Results of many pharmacoeconomic analysis studies revealed that by considering the total cost of TDM establishment including the costs of work time of involved nurses, costs of sample preparation and analysis, costs of laboratory analysis, and payment of pharmacists involved in this drug monitoring centers, were significantly lower than the costs of nephrotoxicity management and longer hospitalization in cases of vancomycin-associated nephrotoxicity [17]. Results of a pre- and post-intervention observational study revealed that TDM group patients had shorter hospitalization period, faster clinical stability status, and shorter courses of inpatient vancomycin administration, compared to historical control group patients but all-cause mortality rate was the same in these two groups of patients [71]. So, vancomycin TDM could be significantly associated with lower costs both for patients and health care systems. According to the reports, pharmacist-guide vancomycin TDM could be associated with faster initial target trough concentration achievement and improved safety and efficacy of pharmacotherapy during hospitalization. The most important advantages of pharmacists' intervention include the prevention of vancomycin associated nephrotoxicity and avoidance of further costs related to persistent renal failure due to vancomycin over-exposure [71]. In general, pharmacist-guided pharmacotherapy especially during the current COVID-19 pandemic would be essential to gain optimal and individualized pharmacotherapy based on pharmacokinetic and pharmacodynamics aspects of administered drugs and prevention of major drug-drug interactions [72-75].

6. Conclusion

In conclusion, vancomycin TDM is essential in order to achieve optimum clinical response with minimal unwanted adverse reactions associated with vancomycin over-dose exposure. Different pharmacokinetic parameters have been considered for the purposes of vancomycin TDM establishment. The most common approaches are AUC-guided TDM and trough concentration-guided TDM. According to the results of many studies noted in the present review, it seems that AUC-guided TDM could be associated with lower risk of vancomycin associated AKI. Also, due to the altered pharmacokinetic parameters in patients with special conditions including renal failure, hepatic failure, cancer, organ transplantation, obesity, pregnancy, lactation, burn injuries, critically ill patients, etc. individualized dosing regimen is required to guarantee the optimum therapeutic results and minimize severe adverse reactions such as AKI.

Competing interests:

The authors declare that they have no competing interests.

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Data Availability Statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions:

PG contributed in study design, data gathering, and writing-original draft, reviewing and editing. AA contributed in supervision, study design, data gathering, writing-reviewing and editing. SM contributed in conceptualization, supervision, study design, data gathering, and writing- reviewing and editing. All authors read and approved the final manuscript.

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Tables:

Table 1. Pros and cons of the trough-only vancomycin monitoring approach

Advantages
Requirement of only one sample preparation. Simplicity of analysis and assessment. Suitable pharmacokinetic parameter fo

Table 2. Pros and cons of AUC-based vancomycin monitoring approach in comparison to trough-only monitoring approach.

Advantages
Better predictor of vancomycin efficacy among other pharmacokinetic parameters [21]. Lower risk of vancomycin associated

Table 3. Recommended dosage of vancomycin in patients undergoing hemodialysis.

Time of vancomycin administration	Dialyzer permeability	Loading dose	Maintenance dose	Dosing interval
After the end of the dialysis	High	25 mg/kg	10 mg/kg	Three-times weekly[1]
	Low	25 mg/kg	7.5 mg/kg	Three-times weekly[1]
Intra-dialysis	High	30 mg/kg	10-15 mg/kg	Three-times weekly[1]
	Low	30 mg/kg	7.5-10 mg/kg	Three-times weekly[1]

[1]Dosing should be adjusted, based on at least weekly pre-dialysis plasma concentration monitoring.

Table 4. Vancomycin intermittent dosing based on patient's renal function.

CKD stage	CKD stage
I	I
II	II
III	**IIIA**
	IIIB
IV	IV
V	V
Patients on intermittent Hemodialysis (Three-times weekly)	Patients on intermittent Hemodialysis (Three-times weekly)
Patients on peritoneal Hemodialysis	Patients on peritoneal Hemodialysis
Patients on CRRT[4]	Patients on CRRT[4]

[1]Glomerular filtration rate

[2]More frequent vancomycin plasma concentration assessments should be done in order to achieve the optimum trough concentration.

[3]Based on dialyzer permeability

[4]Continuous renal replacement therapy

Table 5. Vancomycin dosing in patients with burn injuries, based on renal function

GFR[1] (ml/min/1.73m^2)	Recommended dose	Dosing interval
[?]80 and age [?]40 and serum creatinine [?]0.8 mg/dl	15 mg/kg	Q6h?¿?
80	15 mg/kg	Q8h
31-79	15 mg/kg	Q12h?¿?
30[2]	15 mg/kg	Q24h

[1]Glomerular filtration rate

[2]This algorithm has not been validated in the patients with very low GFR values, low BMI values, and those undergoing hemodialysis and should be used with caution in such patients.

Figures:

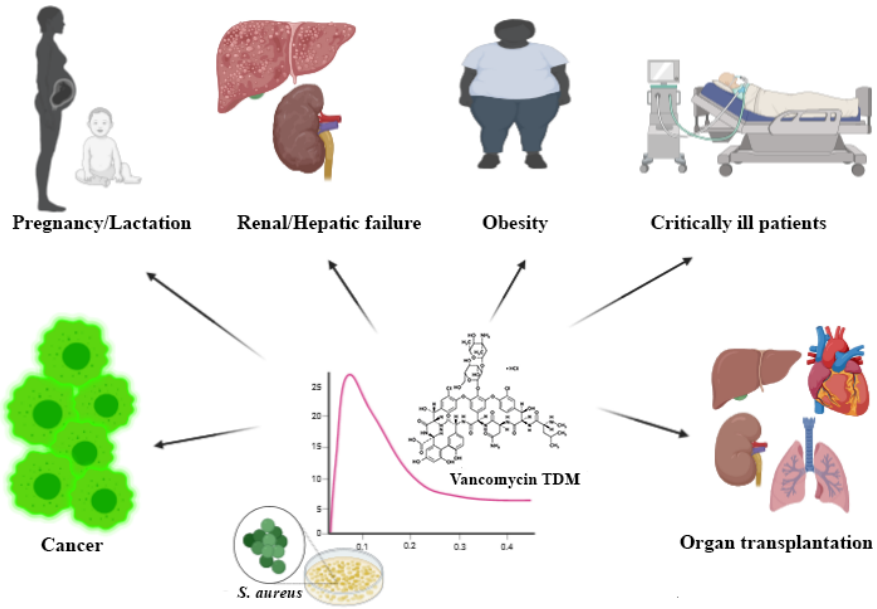

Fig. 1. Schematic view of therapeutic drug monitoring of vancomycin in patients with altered pharmacokinetics.

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