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Analysis of Vancomycin monitoring in an intensive care unit of a hospital in the Southern Zone of São Paulo

Johnny Dias dos Santos[1], Débora Driemeyer Wilbert[2], Felipe Campos Vale[3]

[1]Pharmacist, Resident in the Multiprofessional Residency Program in Clinical Emergencies and Trauma at Santo Amaro University (UNISA), São Paulo – SP, Brazil
[2]Co-advisor, Physiotherapist, Ph.D. in Psychology, Professor, and Coordinator of the Multiprofessional Residency Program at Santo Amaro University (UNISA), São Paulo – SP, Brazil
[3]Advisor, Pharmacist, Master in Sciences from the Preventive Medicine Program, FMUSP, and Professor at Santo Amaro University (UNISA), São Paulo – SP, Brazil

ABSTRACT

OBJECTIVE

To analyze the monitoring of serum vancomycin concentrations, aiming to establish a correlation between the timing of vancomycin therapeutic drug monitoring (TDM) initiation and the occurrence of adverse events in critically ill patients.

METHOD

This observational and retrospective study was conducted in a general hospital in the southern region of São Paulo from July 2023 to July 2024, with data collected through the review of electronic medical records. Patients admitted to the ICU and treated with vancomycin, either empirically or in a targeted manner, were stratified into three groups based on the timing of serum concentration monitoring. Statistical analysis was descriptive, highlighting relevant clinical and laboratory variables. The analyzed variables included demographic data (age and sex), laboratory parameters (serum vancomycin concentrations in µg/mL and serum creatinine levels), the need for dosage adjustments, concomitant use of antimicrobials, and the occurrence of adverse events, with an emphasis on nephrotoxicity.

RESULTS

The study analyzed 102 patients, with emphasis on Group 1, where 25% of the 40 patients reached the therapeutic target, presenting lower rates of adverse events. In Group 2, 90.9% of the 11 patients with concentrations <15 µg/mL showed an increase in leukocytes and C-reactive protein, indicating a higher prevalence of underdosing. In Group 3, 72.2% of the 18 patients exhibited increased serum creatinine levels, demonstrating a greater renal impact.

CONCLUSION

Early monitoring of serum vancomycin concentrations, after the third or fourth dose, was associated with better clinical outcomes, including lower rates of adverse events and a higher proportion of patients within the ideal therapeutic range.

KEYWORDS

First collection of TDM Vancomycin; Adverse events of Vancomycin; Monitoring of serum concentrations.

Corresponding author:
Johnny Dias dos Santos
Santo Amaro University (UNISA), São Paulo – SP
Rua Isabel Schmidt, 349 - Santo Amaro, São Paulo - SP Cep: 04743-030
E-mail: bjohnny@estudante.unisa.br
ORCID ID: https://orcid.org/0009-0004-7158-4004

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INTRODUCTION

Patients admitted to intensive care units (ICUs) are at high risk of acquiring infections caused by multidrug-resistant microorganisms (MDROs).[1] One of the main therapeutic options for treating these infections is vancomycin, a glycopeptide antibiotic that acts by binding to the D-alanyl-D-alanine precursor of the bacterial cell wall, inhibiting peptidoglycan synthesis. Discovered in the 1960s from the Actinobacteria *Amycolatopsis orientalis*, vancomycin is widely indicated for the treatment of infections caused by resistant gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus pneumoniae, Clostridium difficile*, and *Enterococcus faecium*.[2-4]

Vancomycin is a bactericidal antibiotic whose efficacy depends on its time- dependent pharmacodynamics, based on the ratio between the area under the serum concentration curve (AUC) and the minimum inhibitory concentration (MIC) of the pathogen.[2,5] The target pharmacokinetic-pharmacodynamic (PK/PD) index for therapeutic efficacy is AUC24h/MIC ≥400, which reflects antimicrobial exposure in relation to its minimum effective activity. This characteristic differentiates vancomycin from dose-dependent drugs, eliminating the need for peak concentration measurements.[6-11]

Despite its widespread use, vancomycin has a narrow therapeutic range and is associated with nephrotoxicity. Studies report that acute kidney injury (AKI) occurs in 5% to 43% of treated patients, with up to 59% of these cases attributed to the use of the drug.[12,13] In the clinical setting, adverse events may be indicated by laboratory abnormalities such as increased serum creatinine levels, leukocytosis, and elevated C- reactive protein (CRP), suggesting a risk of nephrotoxicity or therapeutic failure. Therapeutic drug monitoring (TDM) is therefore essential to optimize the safety and efficacy of treatment, particularly in critically ill patients who require individualized dosage adjustments due to conditions such as renal or hepatic insufficiency.[8]

In 2009, guidelines published by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP) established parameters for the use of vancomycin, including therapeutic targets, monitoring methods, and dosage adjustments. These protocols marked a milestone in standardizing vancomycin clinical management and emphasized the importance of monitoring its serum concentrations.[9-11]

Vancomycin monitoring (vancomycinemia) involves blood sample collection at the trough concentration point (30 to 60 minutes before the next dose, after reaching a steady state), typically before the fourth or fifth dose. The data obtained guide necessary therapeutic adjustments to achieve PK/PD targets and minimize adverse events.[7,9,10]

Regulation RDC (Collegiate Board Resolution) 585/2013 assigns pharmacists a key role in pharmacotherapeutic follow-up, including planning, ordering laboratory tests, and individualizing dosing regimens to ensure treatment safety and efficacy. This role is particularly relevant in monitoring antimicrobials in ICU patients.[14]

This study aims to analyze the monitoring of vancomycin serum concentrations, seeking to establish a correlation between the timing of TDM initiation and the occurrence of adverse events in critically ill patients.

METHODS

This observational, retrospective study was conducted in an intensive care unit of a general hospital located in the southern zone of São Paulo, covering the period from July 2023 to July 2024. Data were obtained through a review of electronic medical records using the institutional platforms MV SOUL, PEP MV, and CEACSUL. MV SOUL is an integrated hospital management system developed by MV Sistemas, encompassing all hospital processes, including the Electronic Patient Record (PEP), which enables structured documentation of clinical history, laboratory tests, prescriptions, and patient progress. CEACSUL is an institutional platform designed for the control and management of healthcare services, optimizing the analysis of clinical and administrative data.

Patients included in the study were those aged 18 years or older, admitted to intensive care units, who received intravenous vancomycin therapy for at least four consecutive days. Both patients who underwent vancomycin dose adjustments and those who did not were included, as well as patients who underwent hemodialysis during the treatment period, regardless of whether the therapy was empirical or targeted. Cases of monotherapy and combination therapy with other antimicrobials were also considered. Patients with incomplete clinical records or insufficient information regarding vancomycin use and monitoring were excluded from the analysis.

Patients were stratified into three groups based on the timing of therapeutic drug monitoring:

- Group 1: Monitoring performed after the third or fourth dose of vancomycin.
- Group 2: Monitoring performed after the fifth dose.
- Group 3: Patients without serum concentration monitoring during treatment.

Data collection followed a meticulous and structured approach. Initially, patients treated with vancomycin were screened using the MV SOUL system. Then, the analysis of medical progress notes and prescriptions in PEP MV allowed the identification of those admitted to the intensive care unit. Subsequently, laboratory tests available in CEACSUL were reviewed to obtain data on vancomycin serum concentrations, serum creatinine levels, and other relevant variables. Patient classification into groups was based on the start of treatment and the date of vancomycinemia request, also determining the need for dose adjustments after obtaining laboratory results.

The collected variables included demographic data (age and sex), vancomycin serum concentrations (µg/mL), serum creatinine levels during treatment, the need for dose adjustments, concomitant use of antimicrobials, and the occurrence of adverse effects associated with vancomycin use, such as nephrotoxicity.

Continuous data were presented as mean ± standard deviation (SD), while categorical data were presented as absolute numbers and percentages. Statistical analyses were exclusively descriptive and conducted using Microsoft Excel to systematically organize and summarize the collected data.

This study followed the ethical principles established by Resolution No. 466/2012 of the National Health Council. The research protocol was approved by the Research Ethics Committee (CEP) of the University of Santo Amaro (Approval Number 6.895.660, CAAE 80552924.8.0000.0081) and by the Participating Institution (CAAE 80552924.8.3001.5447) through the Plataforma Brasil system. Strict measures were adopted to ensure the confidentiality and privacy of patient information, guaranteeing that no identifiable data were recorded or shared.

RESULTS

A total of 102 patient samples from intensive care units receiving vancomycin were included in the study. Among these patients, 64 were male (63%) and 38 were female (37%), with an average age of 57.2 years (± 19.7). During the VCM treatment period, 35 patients (34.31%) required renal replacement therapy (hemodialysis) due to acute or chronic renal failure (Table 1).

In addition to vancomycin, about 90% of the participants received other antimicrobials in combination, including more than one in some cases. In the sample, the antimicrobial meropenem was the most frequently chosen, being used in more than 60% of the cases (Table 1).

Table 1 - Characteristics of participants who receiv vancomycin (n=102)

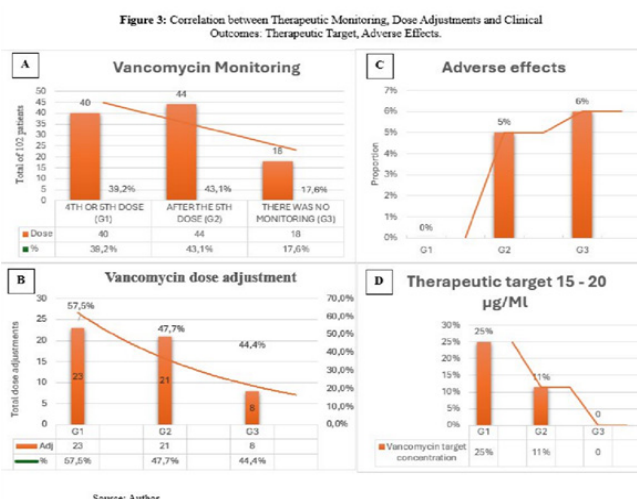
Characteristic	n	%
Sex		
Male	64	63
Female	38	37
Renal replacement therapy (RRT)		
Underwent RRT	35	34.1
Did not undergo RRT	67	65.6
Vancomycin combined with[1]:		
Meropenem	65	63.7
Piperacillin + Tazobactam	16	15.6
Polymyxin B	15	14.7
Other Antimicrobials	17	16.6
No combination	11	9.8
Group distribution		
Group 1 – monitoring after 3rd or 4th dose	40	39.2
Group 2 – monitoring after 5th dose	44	43.1
Group 3 – no monitoring of serum concentrations	18	17.6

[1] Some participants received more than one combination.

Source: Authors (2025)

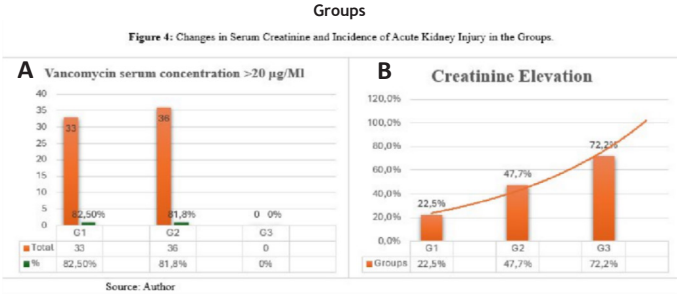
Participants were divided into three groups (Table 1): group 1 – therapeutic drug monitoring performed after the third or fourth dose of vancomycin; group 2 – therapeutic monitoring performed after the fifth dose of vancomycin; and group 3 – patients without serum concentration monitoring during treatment (Figs. 1A, 1B, 1C, 1D, 2A, 2B, and 3).

Figure 1 - Correlation between Therapeutic Drug Monitoring, Dose Adjustments, Adverse Effects, and Therapeutic Target.



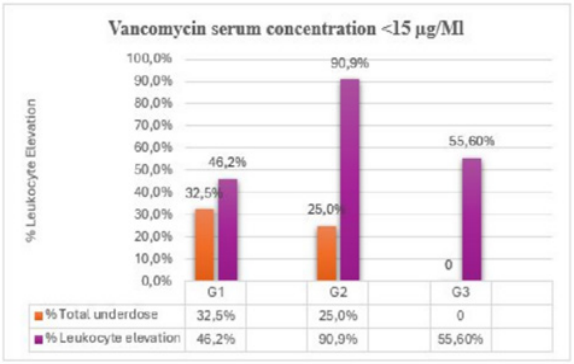
Source: Authors (2025)

Figure 2 - Changes in Serum Creatinine and Incidence of Acute Kidney Injury in the Groups



Source: Authors (2025)

Figure 3 - Subtherapeutic Vancomycin Concentrations and Adverse Events Associated with Therapeutic Failure



Source: Authors (2025)

In group 1, 40 patient samples that met the established criteria for analysis were included (Fig. 1A). Of these, 23 (57.5%) had dose adjustments during the treatment period and serum vancomycin concentration monitoring (Fig. 1B). Data analysis revealed that 33 patients (82.5%) had vancomycin serum concentrations above 20 µg/mL, characterizing an overdose (Fig. 2A). In this context, elevations in serum creatinine were observed in nine patients (22.5%), suggesting potential associated nephrotoxicity (Fig. 2B).

Additionally, 13 patients (32.5%) showed vancomycin serum concentrations below 15 µg/mL, indicating underdosing. Among these, six patients (46.15%) exhibited elevated leukocyte counts and C-reactive protein (CRP) during or after the subtherapeutic vancomycin results, which may indicate a risk of therapeutic failure (Fig. 3). Nevertheless, 10 patients (25%) reached the ideal therapeutic range (15–20 µg/mL), and no adverse effects related to vancomycin use were recorded in the medical records analysis (Fig. 1D).

In group 2, 44 samples were included according to the established criteria (Fig. 1A). Among them, 21 patients (47.73%) had dose adjustments during the treatment period and vancomycin serum level monitoring (Fig. 1B). Data analysis showed that 36 patients (81.8%) presented vancomycin serum concentrations above 20 µg/mL, characterizing an overdose (Fig. 2A). Elevations in serum creatinine were observed in 21 patients (47.7%), possibly related to supratherapeutic vancomycin levels (Fig. 2B).

On the other hand, 11 patients (25%) had serum concentrations below 15 µg/mL, indicating underdosing. Of these, 10 patients (90.9%) showed increased leukocyte counts and CRP during or after the laboratory identification of subdosing, suggesting a risk of therapeutic failure (Fig. 3). Only five patients (11.4%) reached the ideal therapeutic range (15–20 µg/mL), as shown in Figure 1D, while two patients (5%) presented adverse effects attributed to vancomycin use (bacterial resistance to vancomycin and suspected drug reactions), as recorded in the medical records (Fig. 1C).

In group 3, 18 patient samples that met the established criteria for analysis were included (Fig. 1A). During the vancomycin treatment period, eight patients (44.4%) had their doses adjusted (Fig. 1B), based on clinical follow-up (since they did not undergo serum vancomycin concentration monitoring). An increase in serum creatinine was observed in 13 patients (72.2%), indicating a potential renal impact associated with the antimicrobial use (Fig. 2B).

Furthermore, 10 patients (55.6%) presented elevated leukocyte counts and CRP during treatment, possibly indicating an inflammatory response or risk of failure in infection control (Fig. 3). Although most patients showed significant laboratory changes, one adverse event (6%) related to vancomycin use was also identified, as documented in the medical records (Fig. 1C).

DISCUSSION

Vancomycin (VCM), widely used as empirical and targeted therapy in the management of severe infections caused by Staphylococcus aureus, presents significant challenges in the

context of critically ill patients in Intensive Care Units (ICU). In this population, complex pathophysiological alterations often lead to substantial modifications in pharmacokinetic parameters, including renal clearance, volume of distribution, and half- life of the drug. Factors such as acute kidney injury (AKI), chronic kidney disease (CKD), renal replacement therapy (RRT), sepsis, and liver failure introduce variations that may compromise the achievement of therapeutic serum concentrations within the target range, as per IDSA guidelines. Moreover, these conditions, frequently associated with hemodynamic and metabolic changes, exacerbate the difficulty in predicting VCM pharmacokinetics, increasing the risk of underdosing or toxicity.[15-17]

ICU patients with sepsis often develop acute kidney injury (AKI), which is present in approximately 50% of cases and frequently requires the implementation of renal replacement therapy (RRT), either continuous or intermittent.[19] In the present study, 34.3% of patients with acute or chronic renal failure underwent intermittent hemodialysis. These patients showed minimum vancomycin concentrations with high variability, attributed to the complex renal clearance that can lead to supratherapeutic serum levels (>20 µg/mL), exacerbating the risk of nephrotoxicity and worsening renal dysfunction. Additionally, the literature suggests that intermittent hemodialysis presents greater difficulty in achieving and maintaining the target serum concentrations of VCM (15-20 µg/mL) when compared to continuous infusion.[20,21] Our findings support this observation, with 67.6% of the 102 patients exhibiting at least one vancomycin concentration greater than 20 µg/mL.

In contrast, a multicenter retrospective cohort study by Ramirez-Osorio et al. concluded that there were no statistically significant differences in clinical outcomes between monitored and non-monitored patients, suggesting that monitoring vancomycin serum levels may not substantially impact clinical outcomes in populations undergoing RRT.[18]

Serum creatinine is widely recognized as a standard biomarker of kidney function, routinely used to estimate glomerular filtration rate (GFR). It is also frequently employed in the classification of acute kidney injury (AKI) based on established criteria in the literature.[22]

In this study, an elevation in serum creatinine was identified as one of the main variables associated with adverse events related to vancomycin use. However, the coadministration of other antimicrobials, such as ß- lactams and carbapenems, may have contributed to the outcomes observed in the groups that underwent serum concentration monitoring of VCM. Notably, 90.2% of the patients included in the study received vancomycin in combination with meropenem, piperacillin-tazobactam, or polymyxin B. Several pieces of evidence in the literature suggest that the combination of vancomycin with ß-lactams, amphotericin B, aminoglycosides, or carbapenems is associated with an increased risk of AKI compared to monotherapy with vancomycin.[23-27]

In contrast, Miano et al., in a prospective cohort with 739 patients, observed that the combined use of vancomycin with a ß-lactam elevated serum creatinine levels but did not result in changes in alternative renal function biomarkers, such as cystatin C and blood urea nitrogen. This finding suggests that the increase in creatinine may reflect pseudotoxicity, as there was no impact on relevant clinical outcomes such as the need for dialysis or increased mortality.[28]

Additionally, Whitenack et al. concluded that the combination of VCM with piperacillin-tazobactam did not result in significant renal function deterioration when compared to the combination with cefepime, reinforcing the complexity of the underlying mechanisms of renal toxicity in this population.[29]

In a retrospective study conducted in China, Liu et al. investigated the therapeutic drug monitoring (TDM) of vancomycin in 119 ICU patients. The results demonstrated that only 69 patients (<50%) underwent TDM, with fewer than 15% achieving the ideal therapeutic range (15-20 mg/L). Moreover, more than half of the dose adjustments were made late, outside the recommended timeframe. The authors attributed these limitations to the fact that sample collections, serum concentration monitoring, and dose adjustments were restricted to weekdays during business hours in Chinese hospitals.[21]

Ye et al., in their systematic review and meta-analysis, concluded that patients undergoing vancomycin TDM have significantly higher clinical efficacy rates and a lower risk of toxicity compared to those who are not monitored.[30] Our findings support this conclusion, particularly in group 1, which showed lower rates of adverse events, no records of therapeutic failure in medical charts, and a higher percentage of patients with serum concentrations within the ideal therapeutic range (25%) when compared to groups 2 and 3. Additionally, Peng et al., in a cohort study with 18,056 patients, demonstrated that vancomycin TDM in clinical practice allows for timely therapeutic adjustments, contributing to reduced toxicity, successful pharmacotherapeutic management, and a lower mortality rate in critically ill patients. These findings emphasize the importance of early and individualized vancomycin monitoring, preferably after the third or fourth dose, to optimize pharmacotherapy and achieve desired pharmacokinetic targets.[16]

Based on the results, it is evident that the collection of vancomycin concentrations within the recommended period, followed by appropriate dose adjustments, is directly associated with a higher percentage of patients achieving the therapeutic range (15-20 mg/L).[31] In group 2, where monitoring was performed late, after the fifth dose, there was a lower proportion of dose adjustments (47.7%), and only 11.4% of the 44 patients reached the therapeutic target. Bakke et al., in an observational study conducted in an intensive care unit, reported that approximately 50% of the 83 patients did not receive adequate dose adjustments after vancomycin concentration results, leading to subtherapeutic concentrations and unsatisfactory outcomes.[32] Similarly, Liu et al. reported that only 14.5% of patients in their study achieved the therapeutic level of vancomycin, which is consistent with the results observed in our group 2.[21]

The World Health Organization (WHO) defines adverse drug reactions as harmful and unintended responses arising from the therapeutic use of drugs. In the context of antimicrobial use, laboratory changes such as elevated serum creatinine, leukocytosis, and increased C-reactive protein (CRP) may indicate adverse events associated with vancomycin use, suggesting a risk of nephrotoxicity or therapeutic failure. According to the vancomycin monitoring guidelines established by Rybak et al. in 2009, nephrotoxicity is characterized by an increase in serum creatinine of at least 0.5 mg/dL or greater than 50% above baseline value, for a minimum of two consecutive days.[9,11,33]

In our analysis, the comparison between the three groups revealed that group 3 had the highest proportion of patients with elevated serum creatinine (72.2%), followed by group 2 (47.7%), and finally group 1 (22.5%). These findings are consistent with the results of a retrospective cohort study conducted by Davies SW et al., which demonstrated that vancomycin trough levels greater than 20 µg/mL were associated with a significant increase in serum creatinine.[34]

The relationship between vancomycin (VCM) and nephrotoxicity is well recognized, with studies highlighting that minimum concentrations ≥20 µg/mL are significantly associated with a higher risk of acute kidney injury (AKI). However, the incidence of vancomycin-induced AKI is also influenced by confounding variables such as age, comorbidities, and the concomitant use of other nephrotoxic drugs.[11,35-39] An experimental study conducted by Takigawa M et al. using mice showed that older individuals were highly susceptible to acute kidney injury (AKI) during vancomycin administration.[40] This finding aligns with the results of the present study, where the average age of the patients was 57.2 years, emphasizing the impact of aging on susceptibility to vancomycin-induced nephrotoxicity.

Increased renal clearance (ARC), defined as a creatinine clearance greater than 130 mL/min/1.73 m^2, age, and vancomycin loading dose are factors widely reported in the literature as significantly associated with subtherapeutic vancomycin serum concentrations.[41] Huang Y et al. demonstrated in their study that administering a vancomycin loading dose was effective in achieving the target minimum concentration early, reducing the risk of subtherapeutic concentrations and therapeutic failure, especially in patients with ARC and other predisposing factors.[42]

Yang T et al., when investigating factors related to antimicrobial treatment and bacterial resistance, concluded that

an increase in leukocyte count and C-reactive protein (CRP) is associated with a longer duration of antimicrobial therapy, thus increasing the patient's risk.[43] These findings corroborate with the results obtained in our study. Among the patients analyzed, 13 had vancomycin serum concentrations below 15 µg/mL in group 1, of which 46.15% exhibited an increase in leukocytes and CRP. In group 2, consisting of late-monitored patients, 11 had serum concentrations below 15 µg/mL, and 90.9% of them demonstrated increased leukocytes and CRP, reinforcing the influence of late monitoring on inflammatory and therapeutic outcomes. Additionally, Tsutsuura M et al., in their systematic review and meta-analysis, observed that vancomycin minimum concentrations ≥15 µg/mL were associated with significantly lower rates of therapeutic failure.[36] These results emphasize the importance of achieving and maintaining adequate serum concentrations to optimize clinical outcomes and minimize the risk of therapeutic failure.

Our study has some limitations. It is a retrospective analysis conducted at a single center, and although the total number of patients was significant, the division into subgroups resulted in smaller sample sizes, which may introduce selection bias. Additionally, some important variables, such as patients' body weight, fever spikes, and other clinical manifestations, were not collected, limiting the interpretation of factors associated with vancomycin serum concentrations and clinical outcomes. Finally, the statistical analysis was exclusively descriptive, which restricts the identification of inferential associations between the variables. Despite these limitations, the findings highlight relevant points for clinical practice, reinforcing the need for prospective and multicenter studies to validate the observed results.

CONCLUSION

The results of this retrospective study demonstrated that early monitoring of vancomycin serum concentrations, conducted after the third or fourth dose, was associated with better clinical outcomes, including lower rates of adverse events and a higher proportion of patients within the target therapeutic range. In contrast, late monitoring or its absence showed a higher prevalence of both supra- and subtherapeutic levels, reflecting the challenges in managing critically ill patients in settings with complex pathophysiology and operational limitations.

These findings reinforce the importance of adequate therapeutic monitoring and dose adjustments based on vancomycin therapeutic drug monitoring (TDM) as an essential tool to optimize pharmacotherapy. Prospective and multicenter studies with robust inferential statistical analysis are needed to confirm these results and guide interventions that minimize adverse events and improve outcomes.

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