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Analysis of the activities of the clinical pharmacy service in the use of vancomycin in a public hospital in Belo Horizonte

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Abstract

Objective: To characterize the population in vancomycin use, and analyze the parameters of indication, effectiveness and safety used by clinical pharmacists in the drug utilization review. **Method:** This is a cross-sectional study with retrospective collection of medical records of patients who used intravenous vancomycin from March 2022 to March 2023. The results of therapeutic monitoring of vancomycin and pharmaceutical interventions related to this antibacterial were evaluated. **Results:** The study included 919 patients with 1026 hospital admissions. The mean age of the population was 56.8±17.9 years and 50.9% were older than 60 years. In the period evaluated, 9379 vancomycin prescriptions were identified. The most prevalent reason for vancomycin prescription was "others: cite in observation" (15.1%), followed by "respiratory infection - nosocomial pneumonia" (14.8%). The care line responsible for most of the vancomycin prescriptions (42.9%) were the intensive care. Only 23.5% of the serum vancomycin trough concentrations results were in the range considered ideal, i.e. 15-20mg/L. Among the results that were outside the reference range, 38.2% were supratherapeutic (≥20.1mg/L) and 18.7% were subtherapeutic (≤9.9mg/L). In the drug utilization review led by pharmacists, 190 interventions were performed with the medical team. The therapeutic monitoring of vancomycin was the most prevalent intervention (44.7%) of which 87.1% were accepted. **Conclusion:** The study showed a high rate of serum vancomycin trough concentrations results outside the therapeutic range (76.5%) indicating the need to strengthen the institutional protocol and clinical staff training. The clinical pharmacist had an important role in identifying this risk by performing drug utilization review and therapeutic monitoring of vancomycin.

Key words: antimicrobial stewardship; drug utilization review; drug monitoring; vancomycin; pharmaceutical services

Análise das ações do serviço de farmácia clínica no uso de vancomicina em um hospital público de Belo Horizonte

Resumo

Objetivo: Caracterizar a população em uso de vancomicina, além de analisar os parâmetros de indicação, efetividade e segurança empregados por farmacêuticos clínicos na revisão do uso desse medicamento. **Método:** Trata-se de um estudo transversal com coleta retrospectiva de dados de prontuário de pacientes que utilizaram vancomicina por via intravenosa no período de março de 2022 a março de 2023. Foram investigados os resultados da vancocinemia (nível do vale plasmático) e as intervenções farmacêuticas realizadas relacionadas a este antibacteriano. **Resultados:** O estudo incluiu 919 pacientes com 1026 atendimentos distintos. A média de idade da população foi de 56,8±17,9 anos, sendo 50,9% com idade superior ou igual a 60 anos. No período avaliado, foram identificadas 9379 prescrições de vancomicina. Verificou-se que a justificativa mais prevalente para prescrição de vancomicina foi categorizada como "outros: citar em observação" (15,1%), seguida da "infecção respiratória – pneumonia nosocomial" (14,8%). A linha de cuidado intensivo foi responsável pela maior parte das prescrições de vancomicina (42,9%). Apenas 23,5% dos resultados de vancocinemia se apresentavam na faixa de 15-20mg/L, considerada ideal. Dentre os resultados de vancocinemia fora da faixa de referência, 38,2% encontravam-se supraterapêuticos (≥20,1mg/L) e 18,7% subterapêuticos (≤9,9mg/L). Com a revisão de uso de medicamentos realizada por farmacêuticos, 190 intervenções foram realizadas junto à equipe médica, sendo a monitorização terapêutica a mais prevalente (44,7%) e, destas, 87,1% foram aceitas. **Conclusão:** O estudo evidenciou um elevado número de resultados de vancocinemia fora da faixa terapêutica preconizada como ideal (76,5%) indicando a necessidade do fortalecimento do protocolo institucional, com treinamento do corpo clínico. O farmacêutico clínico mostrou-se atuante na identificação desse risco, ao realizar a criteriosa revisão de uso de medicamentos, e a solicitação da monitorização terapêutica de vancomicina.

Palavras-chaves: gestão de antimicrobianos; revisão de uso de medicamentos; monitoramento de medicamentos; vancomicina; assistência farmacêutica**.**

Introduction

Antimicrobial drug resistance has become a global concern and has a significant impact on healthcare due to unfavorable outcomes, such as therapeutic failure, increased morbidity and mortality, and higher healthcare[1] costs. The indiscriminate use of antimicrobials (ATM) and inadequate or non-existent infection prevention and control programs are contributing factors to the emergence of resistant[2] microorganisms. In this context, a more judicious use of the available therapeutic arsenal is necessary, as the pace of development of new therapeutic agents is lagging behind the emergence of microbial[3] resistance mechanisms.

One of the strategies adopted in hospitals to optimize ATM use is the implementation of an antimicrobial stewardship program (ASP). ASP is an organizational approach that involves a set of actions aimed at preventing adverse events, reducing selection and dissemination of resistant microorganisms, and improving ATM use. ASP mandates the involvement of a clinical pharmacist, preferably specialized in infectious diseases and ATM stewardship. This professional should work alongside a multidisciplinary team, including infectious disease physicians, a nurse from the Hospital Infection Control Committee (HICC), and a clinical[4] microbiologist.

The role of the pharmacist in ASP focuses on optimizing pharmacotherapy, which includes therapeutic monitoring of ATM through dose individualization to avoid subtherapeutic or supratherapeutic[4] concentrations. Serum level measurement is relevant for various ATMs, especially vancomycin, a drug used in hospitals to treat infections caused by Gram-positive[5] aerobic and anaerobic bacteria. Vancomycin pharmacokinetics can vary significantly among patients, particularly the elderly, due to variations in physiological[6] parameters. Additionally, patients in intensive care units are at higher risk of developing nephrotoxicity, requiring more frequent[7] monitoring. Thus, guidelines recommend therapeutic monitoring of vancomycin in patients at risk of nephrotoxicity, those with renal dysfunction, and those undergoing therapy for more than five days[8].

The analysis of the area under the curve to minimum inhibitory concentration ratio (AUC/MIC) of vancomycin has been defined as the best strategy for achieving clinical[9] efficacy. However, the full implementation of this method in clinical practice faces challenges related to cost, infrastructure, and professional training, as well as technical[10] execution. An international survey revealed that individualization of vancomycin pharmacotherapy using the gold standard AUC/MIC method was performed in only 11% of the hospitals surveyed, predominantly located in North America (21%) and high-income countries (17%), indicating the difficulty in adopting this method[10]. Therefore, although AUC/MIC calculation is recommended, measuring the trough serum[9] concentration is still adopted as an alternative measure.

Given the need for therapeutic monitoring of vancomycin, pharmacists can provide recommendations for dose or frequency adjustments[11] according to vancomycin serum concentration. Studies investigating the services and clinical pharmaceutical conduct regarding dosing adjustment to promote microbiological effectiveness and reduce adverse events are relevant in the current scenario. Thus, this research aimed to characterize the population using vancomycin, in addition to analyzing the indication, effectiveness, and safety parameters employed by clinical pharmacists in the review of this medication's use.

Methods

Study Design

A cross-sectional study with retrospective data collection was conducted in April 2023, covering the period from March 2022 to March 2023.

Study Location

The study was conducted in a philanthropic hospital of the Unified Health System linked to the Federal University of Minas Gerais (UFMG), located in the northern region of Belo Horizonte. The institution is open for emergency care 24 hours a day, provides care to medium and high complexity patients, has 420 beds, and serves as a reference for more than 1.5 million people. The hospital has a closed clinical staff, covering areas such as trauma, clinical, surgical, neurological, and vascular diseases, as well as high-risk pregnancy and adult and neonatal intensive care units. The care provided is multidisciplinary and based on the Care Line model.

Pharmaceutical care is involved in all activities related to medication, from selection to usage monitoring. The team consists of pharmacists, academics, pharmacy assistants, stock clerks, and administrative assistants to carry out clinical and assistive activities. In the clinical pharmacy, there are five preceptor pharmacists, four resident pharmacists, and four students. Among the activities carried out, drug utilization review for patients in medical, surgical, maternity, neurology, palliative care, frail older adults, emergency, and intensive care units stands out.

Drug Utilization Review

Conducted with the assistance of NoHarm.ai, an artificial intelligence tool that connects with the hospital's operating system (MVSOUL®) and laboratory management software (Matrix®). This interface identifies potential prescription errors such as medication and therapeutic duplicity, maximum dose, drug interactions, dose adjustment in renal or hepatic disease, treatment duration, among others[12].

During the drug utilization review, if non-conformities are identified, the pharmacist intervenes with the prescribing physician or, if unavailable, with the on-call physician to suggest potential adjustments. The pharmacist's interventions are recorded in both the electronic medical record and NoHarm.ai, ensuring traceability of actions taken, and the monitoring of process and results through indicators.

Regarding the process of ATM use, clinical cases are evaluated and discussed with HICC to define the most appropriate treatment. When prescribing an ATM, the physician must select a justification from pre-determined options in the electronic medical record system. For cases not fitting the available options, the physician should select "other: note in observation" and describe the corresponding infection site in the observation field. The overall process of ATM use in the institution was described by Medeiros et al[13].

Therapeutic Monitoring of Vancomycin

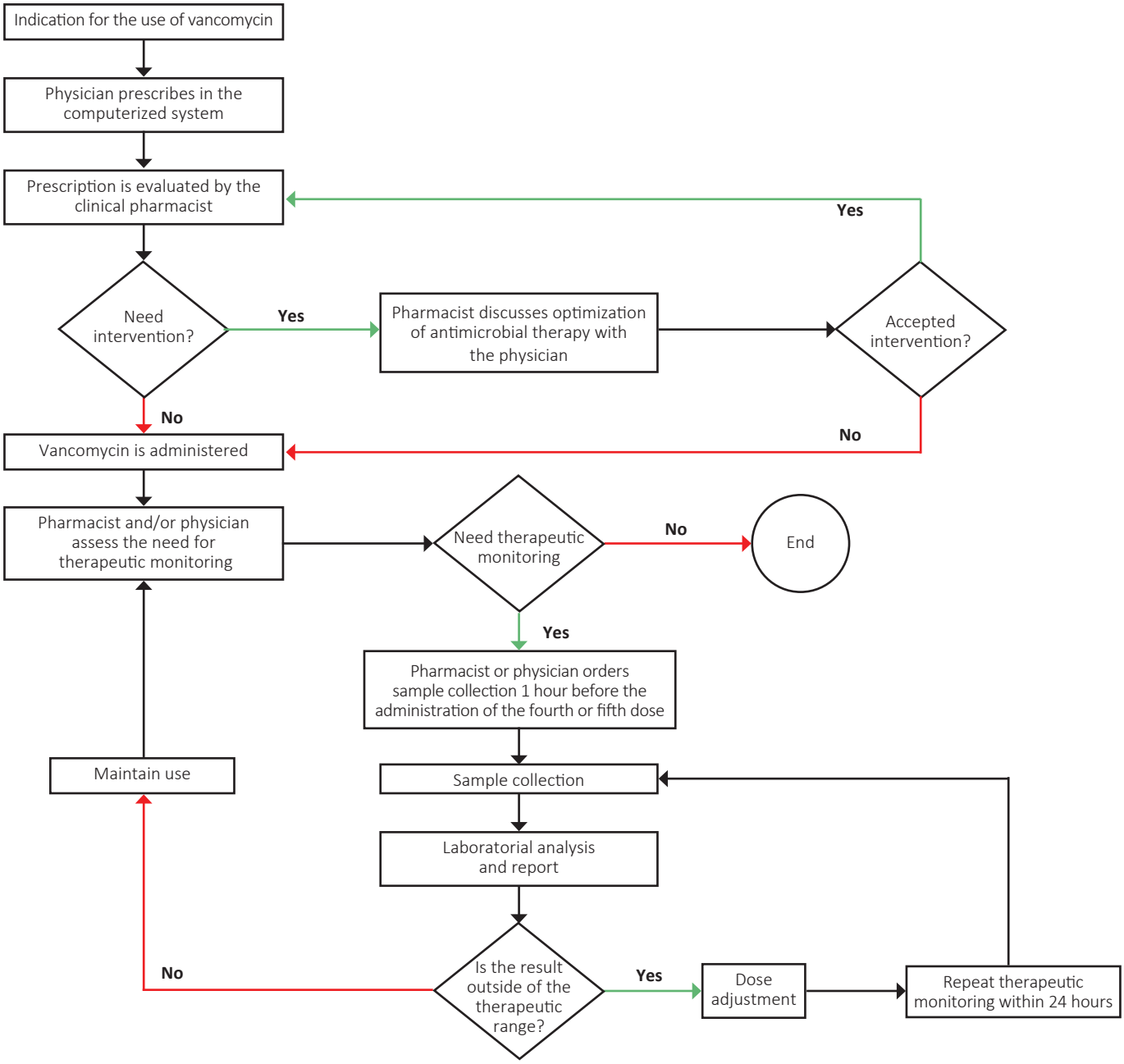
The serum vancomycin trough concentration data considered sample collection one hour before the administration of the fourth or fifth dose. The measurement of the serum trough concentration

is conducted using an immunoassay with VANC VITROS® Reagent (VITROS Chemistry Products). The therapeutic range is considered to be 10-20 mg/L, with the ideal range being 15-20 mg/L[14]. The hospital did not have an institutional protocol for therapeutic monitoring of vancomycin. For dose adjustment, healthcare professionals rely on various databases such as Micromedex®, UpToDate®, and Sanford®. Both physicians and pharmacists are authorized to request laboratory tests to monitor therapeutic[15] outcomes. **Figure 1** presents the specific process of vancomycin use and therapeutic monitoring.

Data Collection and Study Variables

All patients who received intravenous vancomycin between March 2022 and March 2023 were included. No exclusion criteria were applied. The variables of interest analyzed were: (i) total number of patients who used vancomycin; (ii) number of vancomycin prescriptions; (iii) sex; (iv) age; (v) justification for vancomycin use (predetermined in the electronic medical record system); (vi) care line responsible for the prescription; (vii) total number of patients who had vancomycin level tests requested; (viii) results of serum vancomycin trough concentration (therapeutic range: 10-20 mg/L; ideal range:

Figure 1: Process of vancomycin use.



15-20 mg/L[3]); (ix) types of interventions made by pharmacists regarding vancomycin (predetermined in the NoHarm.ai system at the investigated institution); (x) status of the interventions (accepted; not accepted; not accepted with justification). There was no follow-up of patients and outcomes of vancomycin pharmacotherapy.

Data were collected by a single trained researcher from reports generated by the MVSOUL®, Matrix®, and NoHarm.ai software used at the institution and exported to a Microsoft Excel® spreadsheet.

Data Analysis

The results for each variable were compiled and described in charts. Statistical analysis was performed descriptively by determining absolute numbers, mean, and standard deviation.

Ethical Aspects

This study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and approved by the Research Ethics Committee - Certificate of Presentation for Ethical Consideration (CAAE) 54060321.8.0000.5149, which waived the need for the Informed Consent Form (ICF).

A Data Use Consent Form (DUCF) was completed by the involved researchers.

Results

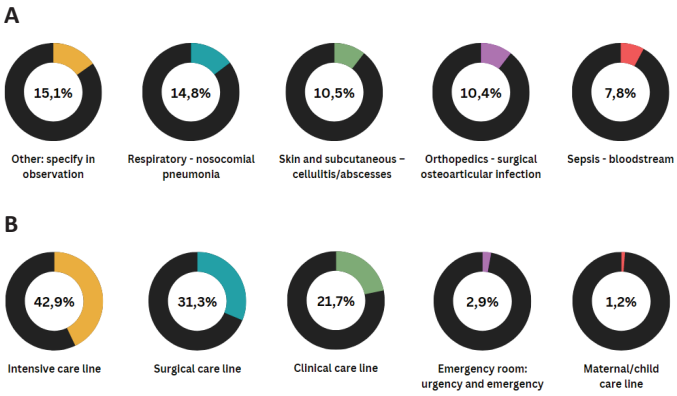
During the evaluated period, 919 patients received vancomycin prescriptions, totaling 9379 prescriptions. The majority were male (n=602; 65.5%), with an average age of 56.8±17.9 years, with 50.9% aged 60 years or older and 46% aged between 20 and 59 years **(Table 1)**. The average duration of vancomycin use was 8.6±8.8 days. Some patients were readmitted, resulting in 1026 distinct treatments.

Table 1. Demographic characteristics of the patients (n=919). Belo Horizonte, 2023.

	n	%
Sex		
Female	317	34.5
Male	602	65.5
Age		
0-19	28	3.1
20-59	423	46
≥ 60	468	50.9

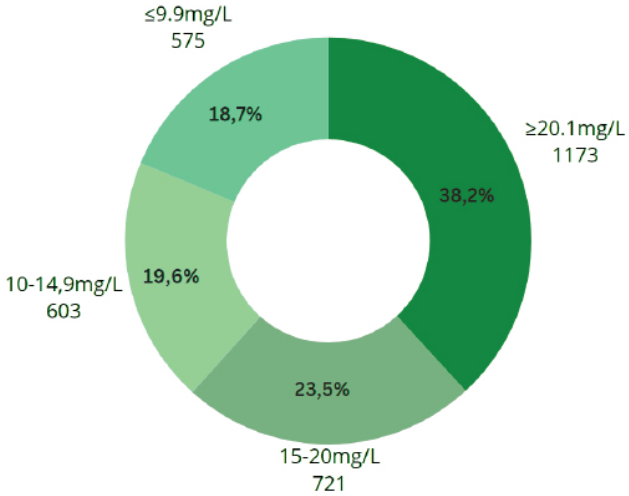
The most frequent justification for vancomycin prescription was categorized as "other: specify in observation," representing 15.1% (n=1418), followed by respiratory infection – nosocomial pneumonia (n=1389; 14.8%) and skin and subcutaneous infection – cellulitis/abscesses (n=982; 10.5%) **(Figure 2A)**. On average, each patient had 1.5±0.8 justifications for the prescription. The highest number of vancomycin prescriptions was made by the intensive care line (n=4024; 42.9%), surgical care line (n=2937; 31.3%), and clinical care line (n=2036; 21.7%) **(Figure 2B)**.

Figure 2. Characterization of vancomycin prescriptions according to (A) prescription justification and (B) care line (n=9379). Belo Horizonte, 2023.



Serum vancomycin concentration tests were requested by physicians or pharmacists in 59.9% of treatments (n=615) and 3072 tests were performed. It was observed that 38.2% (n=1173) of the serum vancomycin trough concentration were supratherapeutic (≥20.1 mg/L) and 18.7% (n=575) subtherapeutic (≤9.9 mg/L). Only 23.5% (n=721) of the results were within the 15-20 mg/L range, and 19.6% (n=603) were between 10-14.9 mg/L **(Figure 3)**.

Figure 3. Results of serum vancomycin trough concentration according to therapeutic range. Subtherapeutic: ≤9.9 mg/L; Lower therapeutic range: 10-14.9 mg/L; Ideal therapeutic range: 15-20 mg/L; Supratherapeutic: ≥20.1 mg/L. Belo Horizonte, 2023.

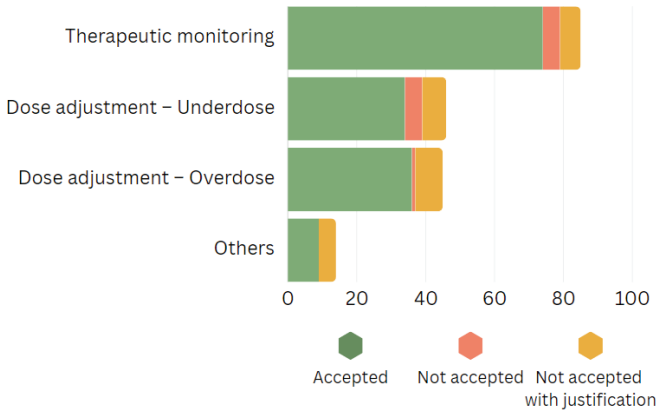


Therapeutic monitoring was the most prevalent pharmaceutical intervention (n=85; 44.7%). The number of interventions related to vancomycin underdose (n=46; 24.2%) and overdose (n=45; 23.7%) was similar **(Table 2)**. Of the interventions performed, 80.5% (n=153) were accepted, 13.7% (n=26) were not accepted with justification, and 5.8% (n=11) were not accepted without justification **(Figure 4)**. The acceptance rate of interventions related to therapeutic monitoring, underdose, and overdose were 87.1% (n=74), 73.9% (n=34), and 80% (n=36), respectively.

Table 2. Pharmaceutical interventions related to vancomycin treatment (n=190). Belo Horizonte, 2023.

Type of pharmaceutical intervention	n	%
Therapeutic monitoring	85	44,7
Dose adjustment – Underdose	46	24,2
Dose adjustment – Overdose	45	23,7
Medication suspension	7	3,7
Proposed therapeutic alternative (substitution)	3	1,6
Rescheduling	2	1,1
Change in administration frequency	1	0,5
Inappropriate dilution/diluent	1	0,5
Total	190	100

Figure 4. Types of pharmaceutical interventions related to vancomycin and acceptance rate by type of intervention (n=190). Belo Horizonte, 2023.



Discussion

The most frequent intervention during drug utilization review was the request for therapeutic monitoring of vancomycin. A high number of supra- and subtherapeutic serum vancomycin trough concentration were observed, emphasizing the need for active clinical pharmacist involvement in optimizing ATM[11,16] use.

Most of the study's patients are elderly, a population more susceptible to adverse effects from vancomycin use due to differences in pharmacokinetic profiles associated with aging[8,17]. Pediatric prescriptions were also evaluated, another population with different vancomycin pharmacokinetic profiles and more prone to adverse[9] events. These findings reinforce the importance of developing an institutional protocol for therapeutic monitoring of vancomycin, which should be strictly followed.

However, even with a clinical protocol guiding ATM use, the average duration of vancomycin prescription may vary depending on infection extent and the unit's[5,18] microbiological profile. Due to its broad spectrum for Gram-positive bacteria, vancomycin is often used empirically, leading to variable therapy duration as it may be discontinued after bacterial[5,18] sensitivity test results. Additionally, its applicability in different infection types also contributes to the heterogeneity in treatment duration observed in this study. Prolonged administration of this drug is associated with the risk of toxic levels and may promote bacterial[19] resistance development. Literature data suggest that patients monitored by pharmacists had a shorter duration of vancomycin therapy and reduced incidence of nephrotoxicity[20]. This study did not evaluate this aspect, which is a perspective for future studies.

Another strategy to improve the use of ATM is the requirement to record the clinical indication in the prescription[4]. In the present study, the justification "others - cite in observation" accounted for a significant portion of prescriptions (15.1%), suggesting low accuracy in the completion of justifications by the clinical staff. Multiple justifications per patient were also observed, which can be attributed to hospital readmissions for different types of infections or the transfer of the patient to another inpatient unit with subsequent reclassification of the infection. The lack of specificity in categorizing infections is a critical issue and requires an approach to improve ATM[4] use. It is necessary to investigate the underlying reasons for choosing this justification ("others- cite in observation") and assess the need to standardize other indications. Moreover, to improve the quality of clinical justifications, it is imperative to maintain periodic multidisciplinary training focused on ATM prescription and providing personalized feedback after pharmacist-led[4,13] drug utilization review.

The second most frequent indication for vancomycin use observed in the study was nosocomial pneumonia (14.8%). The Infectious Diseases Society of America (IDSA) guidelines endorse vancomycin treatment for pneumonia caused by methicillin-resistant Staphylococcus aureus (MRSA)[18]. Additionally, this guideline recommends the same therapy for empirical treatment in patients with risk factors for MRSA, such as previous intravenous ATM use within 90 days, hospitalization in a unit where MRSA prevalence is above 20% or unknown, or those at high risk of mortality[21]. In the institution where the study was conducted, ATM prescription reviews are performed by the HICC. Empirical treatment follows institutional protocols, and after obtaining sensitivity test results, antimicrobial therapy can be escalated or de-escalated[13]. Therefore, it is considered that the prescription justifications identified in the study are in accordance with recommendations for prudent ATM use.

The intensive care unit (ICU) accounted for the highest number of vancomycin prescriptions (42.9%), a trend justified by the high prevalence of MRSA infections usually found in these units[22]. ATMs are commonly used by patients in intensive care due to the severity of diseases, immunosuppression related to critical illnesses, and exposure to invasive procedures, making these patients more susceptible to infections and related[23] complications. Critically ill patients are also more likely to develop vancomycin-induced nephrotoxicity compared to ward patients, which underscores the importance of therapeutic[24] monitoring.

Together, these results suggest the potential of therapeutic monitoring to optimize vancomycin use in these patients. Therapeutic monitoring is established as a strategic action in the context of the ASP to ensure effectiveness and avoid toxicity during ATM[4] treatment. However, in the present study, it was observed that the number of requests for therapeutic monitoring of vancomycin was significantly lower than the number of days vancomycin was prescribed, suggesting that many patients may not have had therapeutic monitoring prescribed or that the monitoring frequency was inappropriate.

The frequency of therapeutic monitoring of vancomycin should be based on each patient's clinical criteria. Frequent or daily monitoring is recommended for hemodynamically unstable patients, such as those with end-stage renal disease, and once-weekly monitoring

for stable[9] patients. However, an international survey revealed that vancomycin dose adjustments were more frequently determined by the attending[10] physician's clinical judgment. In this study, the most frequent pharmaceutical intervention was the request for vancomycin therapeutic monitoring, which had a high acceptance rate. When included in the team, the pharmacist can contribute to increasing the frequency of vancomycin therapeutic monitoring until the therapeutic target is reached, in addition to ensuring the test is collected when vancomycin reaches its steady[5,11,25] state.

A high prevalence of results of serum vancomycin concentration above 20 mg/L (38.2%) was observed in this study, which is a concern due to the potential risk of adverse effects such as nephrotoxicity, especially in patients with other associated[26] risk factors. Conversely, results below 10 mg/L can lead to therapeutic failure and induce bacterial resistance, besides being associated with higher mortality[9]. A portion of results between 10-14.9 mg/L (19.6%) was observed. However, according to the literature, it is suggested that vancomycin serum concentration should be maintained above 10 mg/L, ideally between 15-20 mg/L, for treating severe[8,27] infections. In a similar study, 42.9% of results were observed with levels <10 mg/L and 15.3% ≥20 mg/L[14].

The high rate of results outside the ideal therapeutic range can be explained by the absence of an established protocol in the hospital containing recommendations on criteria for requesting the therapeutic monitoring of vancomycin, dose adjustments based on serum vancomycin concentration, and frequency of sample collection. These results reaffirm the demand for multiprofessional involvement in ATM therapeutic monitoring. The pharmacist's role in collaboration with other members of the multiprofessional team, including laboratory professionals, doctors, and HICC, should occur from the initial patient evaluation and correct indication for therapeutic monitoring to the release of results and dose[28] recommendation.

This study had limitations due to information bias related to the completion of justifications for vancomycin use, where inaccurate records compromise the characterization of indications. Additionally, the sample collection time for the test and the vancomycin administration time were not evaluated. Although these times are predetermined by the institution's system, some serum vancomycin concentrations may have been underestimated or overestimated.

As a strong point, the study highlights the description of vancomycin use and its therapeutic monitoring in a public teaching hospital, where the pharmacist is responsible for requesting the serum vancomycin trough concentration. Despite the local reality not yet having accurate pharmacokinetic and pharmacodynamic software to allow therapeutic monitoring through the AUC/MIC parameter, the pharmacist-led drug utilization review has the potential to optimize the pharmacotherapy of patients using vancomycin at the institution.

Conclusion

The study evidenced a high number of serum vancomycin trough concentration outside the recommended therapeutic range (76.5%), indicating the need to strengthen the institutional protocol, with clinical staff training. The clinical pharmacist played an active role in identifying this risk by conducting a thorough drug utilization review and requesting therapeutic monitoring of vancomycin.

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Contributors

ACA, AFM, and CMB participated in the project conception, data analysis and interpretation, and manuscript writing. CLL, EFD, MAM and MCB participated in the critical review of the text. All authors approved the final version of the work to be published.

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Conflict of Interest

The authors declare no conflict of interest.

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