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Knowledge, Attitude and Practices (K.A.P.) of doctors prescribing Vancomycin in a Tertiary Care Hospital Towards Therapeutic Drug Monitoring (T.D.M.) of Vancomycin

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ABSTRACT

Objective: Vancomycin is frequently prescribed to treat infections caused by methicillin-resistant Staphylococcus aureus. Precise dosing through therapeutic drug monitoring is critical for optimising treatment outcomes, minimising toxicity, and reducing antimicrobial resistance. This study assessed the knowledge, attitudes, and practices of clinicians regarding therapeutic drug monitoring of vancomycin at our institution given the low utilisation rate of this service.

Methods: Clinicians from the internal medicine and paediatrics departments provided written informed consent for participation. Data on their knowledge, attitudes, and practices regarding vancomycin therapeutic drug monitoring were collected using a pre-validated questionnaire. Responses were analysed using Microsoft Excel version 2406.

Results: Of the 126 clinicians who were approached, 100 participated (50 from each department). Most respondents (79%) were postgraduate doctors with one to three years of experience. Although all participants were aware of therapeutic drug monitoring and 92% knew the service was available, the majority primarily recommended therapeutic drug monitoring for antiepileptic drugs. For vancomycin, only 42% regularly suggested therapeutic drug monitoring, 52% identified appropriate sampling timing, and 35% were aware of its therapeutic range. Although 93% acknowledged vancomycin's adverse effects, with 34% citing nephrotoxicity, only 46% recommended therapeutic drug monitoring in cases of toxicity. The cost of the service was noted as a barrier by 34%.

Conclusion: Clinicians were aware of therapeutic drug monitoring but did not have comprehensive knowledge of vancomycin-specific guidelines. Cost and varied opinions on routine therapeutic drug monitoring hindered its implementation.

Keywords: Drug Monitoring, Knowledge-Attitudes-Practice study, Vancomycin.

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Introduction

Antimicrobial agents comprise 17.63% of all the drugs prescribed in daily practice (Joshi et al., 2022). Using antimicrobial agents faces an ever-increasing challenge of antimicrobial resistance, and hence, rational use of antimicrobial agents is required (Talbot et al., 2006). A precise dose adjustment is essential to maximise the therapeutic benefit and minimise the toxicity of antimicrobials. For this, a thorough understanding of their pharmacokinetic properties is useful. Fortunately, certain antimicrobials, such as aminoglycosides (Rea et al., 2008), vancomycin (Rybak et al., 2009), and antifungals like itraconazole (Ashbee et al., 2014) and voriconazole (Ebihara et al., 2022), exhibit a defined correlation between their plasma concentrations and therapeutic/toxic effects and hence are amenable to therapeutic drug monitoring (TDM) for optimisation of their doses.

TDM, which refers to the measurement of drug levels in the blood or any other biological fluid, helps in aiding personalised drug therapy to achieve maximum beneficial effect and minimise adverse effects due to the drug (Sjövall et al., 2023). At our institute, antimicrobial TDM facilities are available for vancomycin and voriconazole.

Vancomycin is a glycopeptide antibiotic that is commonly used in infections due to methicillin-resistant Staphylococcus aureus and in patients with penicillin allergy. However, its use has the risk of serious adverse reactions like nephrotoxicity, ototoxicity, and superinfections. A rapid infusion over a few minutes can also lead to infusion-related reactions like red man syndrome due to histamine release. Hence, TDM for vancomycin should be a part of its therapy, as monitoring of its trough concentrations (10 to 15 mcg/ml) has been conventionally used as a surrogate measure for its appropriate dosing (Vazquez-Guillamet & Kollef, 2014). However, the knowledge about the same is variable.

TDM for vancomycin was rolled out in 2021 at our institute, and the drug is being widely used in our intensive care units (ICU) and wards. However, since the inception of the TDM facility for vancomycin, only 30 patients over three years have been advised TDM for vancomycin. This shows that many patients are devoid of the facility of TDM, and to address it, baseline data on the hurdles has to be known. The hypothesis was that there are issues with the practice of clinicians towards TDM for vancomycin. This study is therefore planned to understand the knowledge, attitude, and practices of TDM for vancomycin among the doctor's prescribing vancomycin at our institute.

Methods

Questionnaire validation

A 13-item questionnaire was prepared by the authors, with a majority of the items being closed-ended multiple-choice questions. Two of them were multiple-response questions. This was submitted to a panel comprising ten experts for validation (face, content, and construct). During validation, the experts graded each item based on a four-point Likert scale from not relevant to highly relevant. The validators also provided their suggestions if they felt the questions were not framed properly or if any other relevant question could be added. Responses and suggestions were evaluated for content validity using the average congruency percentage (ACP) and content validity index (CVI), which included item-CVI (I-CVI) and scale-CVI (S-CVI). ACP was 90%, indicating that the questionnaire possessed content validity. I-CVI for all questions was 80% except for one question (60%) that was deleted from the final version (I-CVI of 78% was considered as the threshold (Shi et al., 2012) for retaining the questions). The S-CVI average and the S-CVI universal agreement were calculated to be 0.9 and 0.46, respectively. The inter-rater reliability was assessed using Fliess' kappa and Krippendorff's alpha, which were 0.059 and 0.067, respectively. The questions were reframed as per the experts' suggestions, and finally, a 12-item validated questionnaire was finalised and submitted for approval from the Institutional Ethics Committee (IEC).

Sample size estimation

To the best of the authors' knowledge, as no previous studies had been conducted in India at the time of planning the study to assess the knowledge, attitude, and practice of clinicians prescribing vancomycin in a tertiary care centre towards TDM of vancomycin, it was planned to enrol 100 clinicians from our institute (50 each from the departments of internal medicine and paediatrics) over six months.

Data collection

The study was conducted at a tertiary care hospital in India, as per ICMR guidelines 2017 and the Declaration of Helsinki 2013. All clinicians working in the departments of General Medicine and Paediatrics at our institute who were willing to provide written informed consent were eligible for the study. After obtaining approval from the IEC (EC/OA-194/2023), written informed consent was obtained from clinicians who agreed to take part in the study. The validated questionnaire was administered to the clinicians in paper form. The participant data were anonymised, thus maintaining their privacy and confidentiality. The responses provided by the participants were transcribed electronically for further analysis.

Statistical analysis

The data were analysed using descriptive statistical methods, with categorical data presented as proportions. Microsoft Excel version 2410 was used for data analysis.

Results

Among 126 clinicians approached, 100 consented to take part and completed the study. The designation of the participants is given in Table 1, and the years of experience after medical graduation are given in Table 2. Most participants were junior residents pursuing postgraduate medical degrees with one to three years of experience.

Table 1. Designation of the participants

Designation	No. of participants
Junior Resident (pursuing postgraduate medical degree)	79
Senior Resident (completed postgraduate medical degree)	14
Pursuing fellowship	2
Assistant Professor	4
Professor	1

Table 2. Number of years of experience after medical graduation

No. of years after medical graduation	No. of participants
<1	8
1 to 3	68
4 to 6	17
7-15	6
>15	1

All the participants were aware of the concept of TDM. Table 3 shows the drugs for which the participants routinely advised TDM. Each participant advised TDM for one or more than one drug, with antiepileptics being the most commonly advised drug.

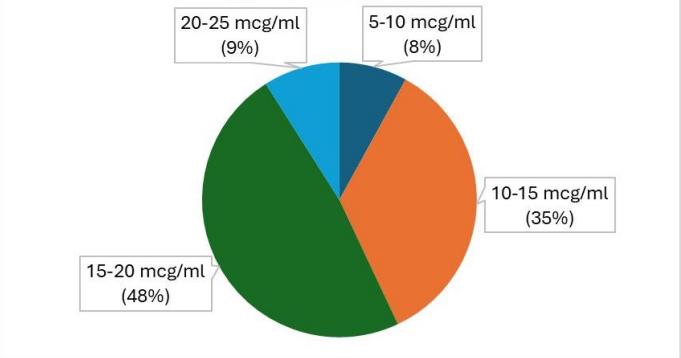
Table 3. Drugs for which the participants routinely advised TDM

Groups of drugs routinely advised for TDM	No. of participants
Antiepileptics	94
Antibacterials	29
Anticoagulants	18
Antitubercular drugs	8
Analgesic-Antipyretic	7
Immunosuppressants	7
Digoxin	7
Methotrexate	7
Lithium	6
Others[#]	17

#Others included Antipsychotics, Antiarrhythmics, Antifungals (n=3); Sedative Hypnotics, Methylxanthines (n=2); DMARDs, Antiretroviral drugs, Magnesium, Anti-Snake Venom (n=1)
TDM: Therapeutic Drug Monitoring

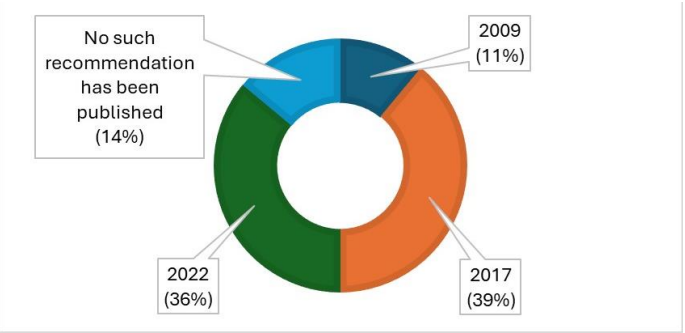
A majority (92%) of participants were aware of TDM facilities being available in the department of clinical pharmacology. Awareness of the therapeutic range of vancomycin is depicted in Figure 1. Most of the participants opined the therapeutic range of vancomycin as 15-20 mcg/ml.

Figure 1. Therapeutic Range of Vancomycin



Awareness about the year in which recent recommendations about TDM vancomycin were published is depicted in Figure 2. Only 36% of the participants were aware of the recent International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) 2022 guidelines.

Figure 2. Recent Recommendations by IATDMCT for TDM Vancomycin



The frequencies with which TDM for vancomycin should be practiced as opined by the clinicians, are given in Table 4, while the frequencies with which the clinicians actually

recommended TDM for vancomycin are given in Table 5. The practice of routine TDM of vancomycin was opined by 42% of the participants, as it is a drug with a narrow therapeutic index. However, 46% advised it only in case of toxicity.

Table 4. Frequencies with which TDM for vancomycin should be practised as opined by the clinicians

Frequencies with which TDM for vancomycin should be practised as opined by the clinicians	No. of participants
Routinely, as vancomycin is a highly toxic drug	17
Routinely, as vancomycin is a drug with a narrow therapeutic index	42
Only in patients with renal failure	31
Only in patients with an apparent lack of benefit due to vancomycin	10

TDM: Therapeutic Drug Monitoring

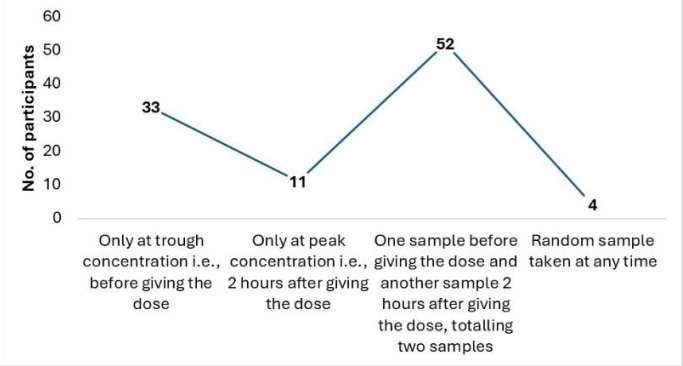
Table 5. Frequencies with which the clinicians actually recommend TDM for vancomycin

Frequencies with which the clinicians actually recommend TDM for vancomycin	No. of clinicians
Never	25
Daily	1
Every week	13
If there is no response after 3-5 days of therapy	15
Only if toxicity develops	46

TDM: Therapeutic Drug Monitoring

The awareness of the time of drawing the blood sample for TDM is depicted in Figure 3. A majority (52%) suggested drawing two samples; one before giving the dose and the other two hours after giving the dose.

Figure 3. Timing of Drawing Sample



A majority (93%) of the participants were aware of the adverse effects of vancomycin. Table 6 shows the adverse effects mentioned by the participants. Although each participant stated more than one adverse effect, 78 participants mentioned nephrotoxicity.

Table 6. Adverse effects of vancomycin as mentioned by the participants

Adverse effects of Vancomycin	No. of participants
Nephrotoxicity/Acute Kidney Injury	78
Red man syndrome	62
Hypersensitivity reactions	32
Ototoxicity	19
GI symptoms	15
Blood dyscrasias	13
Others*	13

*Others include CNS symptoms (n=4); cardiovascular symptoms (n=3); urinary symptoms (n=2); breathlessness, electrolyte disturbances, tachyphylaxis, antimicrobial resistance (n=1)

Figure 4 depicts the strategies used by the participants for managing a case of vancomycin toxicity. Initial clinical management followed by further management as per TDM levels was mentioned by 83% of participants.

Figure 4. Management of Patient with Vancomycin Toxicity

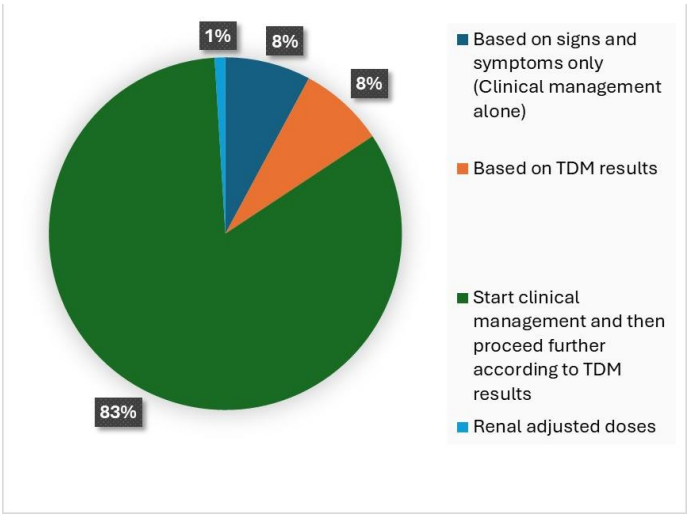
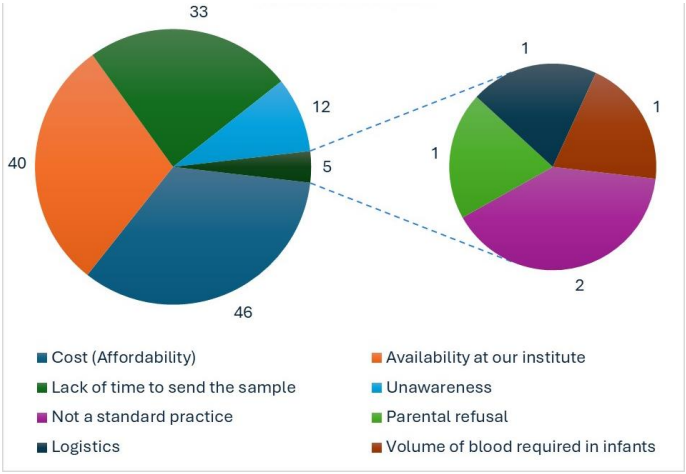


Figure 5 depicts the challenges to advising TDM for vancomycin. Among multiple barriers stated by each participant, 46 participants stated the cost of TDM vancomycin as a barrier.

Figure 5. Challenges for Advising TDM Vancomycin



Discussion

This study assessed the KAP of TDM for vancomycin among clinicians in the departments of internal medicine and paediatrics. As most of the participants (79%) were junior residents with one to three years of experience after graduation (68%), the study provides insight into the actual functioning of the referral process for TDM. The results reveal an intricate understanding of TDM practices, with several implications for improving vancomycin therapy and TDM utilisation.

The study found that all participants knew about TDM and 94% of them advised TDM for antiepileptics. However, the specific knowledge about TDM vancomycin was less. This is probably because of the ease with which an antimicrobial can be changed as compared to changing an antiepileptic drug. The department of clinical pharmacology has been offering antiepileptic drug TDM services for more than approximately 25 years, and being a government-run hospital, the cost is much less than other laboratories. Hence, patients are referred to our hospital even from other hospitals. This consolidates the awareness of the availability of TDM for antiepileptics.

TDM levels for vancomycin in critically ill patients are 15-20 mcg/ml; those in non-critical patients are 10-15 mcg/ml (Martin et al., 2010). Among the patients treated with vancomycin at our institute, most are critically ill and are admitted to the ICU. Hence, there was a mixed opinion among the clinicians regarding the therapeutic level of vancomycin. Additionally, the reference range of 10-15 mcg/ml (Reuter et al., 2022) identified by 35% of participants reflects a need for ongoing educational interventions to ensure that all practitioners are using the most current therapeutic targets.

Only 36% were aware of the 2022 IATDMCT guidelines for vancomycin (Reuter et al., 2022), indicating a gap in awareness of the current best practices. This finding is similar to the findings from other studies (Choi et al., 2019), where medical professionals show familiarity with general TDM concepts but lack up-to-date knowledge on specific drugs like vancomycin. Enhanced educational interventions focused on current guidelines could improve adherence to optimal vancomycin dosing strategies.

The mixed attitudes towards routine TDM for vancomycin are notable. While 42% of participants supported routine TDM because of vancomycin's narrow therapeutic index 46% recommended it only if toxicity occurred. This discrepancy highlights a prevalent issue in clinical practice where TDM is often underutilised unless adverse effects are evident (Rybak et al., 2009), especially for antimicrobials like vancomycin, where sub-therapeutic levels can increase the risk of treatment failure and drug resistance (Nataraj et al., 2019). Increasing awareness of the benefits of routine TDM could lead to more consistent and proactive vancomycin therapy.

The findings on TDM practices reveal that only 52% of participants correctly identified the need for two blood samples for accurate assessment of vancomycin levels (Rybak et al., 2009), like the findings in the study conducted by Wong et al. (Wong et al., 2014). This low percentage

suggests a significant gap in understanding among healthcare professionals regarding TDM principles, particularly for vancomycin. It highlights the need for targeted education on the pharmacokinetics of drugs and the importance of proper timing in blood sampling. Further, the fact that a significant proportion of participants do not recommend routine TDM suggests a need for further training on the importance of regular monitoring for therapeutic efficacy and safety.

Awareness of vancomycin's adverse effects was high, with 93% of participants recognising potential issues like nephrotoxicity. The fact that 83% would start clinical management and then proceed further based on TDM results in this study underscores a proactive approach to dealing with toxicity, aligning with best practices as given in the review by Zamoner et al. (Zamoner et al., 2019). This suggests that while knowledge about TDM might be lacking, there is a readiness to apply it effectively in managing vancomycin therapy.

The cost of TDM, cited by 34% of participants as a significant barrier, reflects a practical challenge in implementing TDM services in developing countries like India. This contrasts with the findings of Kim et al. (Kim et al., 2022), where elderly patients in the Republic of Korea, who were advised TDM vancomycin, had better economic benefits compared to those who were not advised the same. Further data in the Indian scenario can help in addressing this barrier. This can also help advocate for policy changes or explore cost-effective TDM strategies.

Conclusion and Recommendations

The findings of the study show that, while clinicians exhibit a general understanding of TDM and are aware of the TDM facilities available at the institute, their specific knowledge related to vancomycin TDM requires enhancement. Although they are very well aware of the practice essentials, they are unable to implement the same, especially for patients on routine care with vancomycin, because of significant barriers.

A multi-pronged approach is crucial for optimising vancomycin therapy. Group training sessions, followed by reinforcement in the form of reminders for addressing the gaps in knowledge about current guidelines and the benefits of routine TDM, may be required. Antimicrobial stewardship programs integrating TDM for antimicrobials like vancomycin can better support effective TDM practices by ensuring both the efficacy and safety of vancomycin treatment. Adopting sparse sampling strategies can address both the type and the volume of the body fluid sample required for estimating the drug levels, apart from reducing the costs, labour, and discomfort for patients and healthcare workers. By improving education, infrastructure, and resource allocation, we can eventually incorporate Bayesian software for AUC-guided TDM and dose adjustment of vancomycin.

Ethics Committee Approval: Approval from Institutional Ethics Committee, Seth G.S. Medical College and K.E.M. Hospital, Parel, Mumbai has been obtained with the approval number EC/OA-194/2023 dated 29 January 2024 .

Informed Consent:

1. I have read the information given in the Informed Consent Document for this study entitled "Knowledge, Attitude and Practices (KAP) of doctors prescribing Vancomycin in a tertiary care hospital towards Therapeutic Drug Monitoring (TDM) of Vancomycin."
2. I have received an explanation of the nature, purpose, duration, and foreseeable effects and risks of the study and what I will be expected to do. My questions have been answered satisfactorily.
3. I understand that my participation in the study is voluntary and that I may refuse to participate or may withdraw from the study at any time.
4. Institutional ethics committee authorities may wish to examine the information collected. By signing on this document, I give permission for such review of this document.
5. I understand that my identity will not be revealed in any report or publication.
6. I agree to take part in the above study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - MB, BK; Design- MB, BK; Supervision- MB, BK; Resources- VA, SB, MB, BK; Materials- VA, SB; Data Collection and/or Processing- VA, SB; Analysis and/or Interpretation- VA; Literature Search-- VA, SB, MB, BK; Writing Manuscript- VA; Critical Review- SB, MB, BK; Other-N/A

Conflict of Interest: The authors have no conflicts of interest to declare.

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