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RESEARCH ARTICLE

Optimizing vancomycin therapeutic drug monitoring compliance in pediatric oncology: towards personalized medication management

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Abstract

Aim: Vancomycin, a crucial treatment for Gram-positive bacteria, necessitates therapeutic drug monitoring (TDM) to prevent treatment failures. We investigated the healthcare professional's compliance toward TDM of vancomycin recommendations and follow-up levels. **Materials & methods:** We collected data from 485 patients who received vancomycin in the Children's Cancer Hospital Egypt 57357 medical records system (Cerner) over 4 months, from January to April 2020. **Results:** Our data shows that only 54% of patients had TDM requests from healthcare professionals for the total patients who received vancomycin treatment. The healthcare professionals' compliance with the recommendations was 91.7%, while the follow-up levels were 66.7%. **Conclusion:** While overall adherence to recommendations is strong, enhancing compliance with follow-up levels remains a priority for improvement.

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KEYWORDS
healthcare team compliance; pediatric oncology; personalized medication management; personalized medicine; precision medicine; TDM recommendations; vancomycin

1. Background

Vancomycin is a tricyclic glycopeptide with poor oral bioavailability [1,2]. It is the first line in treating methicillin-resistant *staphylococcus aureus* and ampicillin-resistant enterococci [1–4]. Vancomycin induces significant toxicities, including ototoxicity and nephrotoxicity. Vancomycin is usually prescribed in cases of fever, neutropenia, and soft tissue infections which are usually related to catheters, pneumonia, and hemodynamic instability [5]. The recommended daily dose of vancomycin is 40–60 mg/kg/day in the pediatric population, but higher doses may be needed [5,6]. Moreover, pediatric patients with normal renal function may need higher vancomycin doses than standard doses to reach the therapeutic level [6]. Vancomycin TDM is generally recommended due to the narrow therapeutic range as well as the poor correlation between the given dose and the drug concentration in the blood, which causes a wide range of adverse effects such as nephrotoxicity, ototoxicity, and infusion-related toxicities [7–9]. It is imperative in settings with pharmacokinetics variability, including pediatric populations, critically ill patients, patients with hematologic malignancies, and patients undergoing hematopoietic stem cell transplantation [10–12]. Interindividual variation is expected in the pediatric population compared with the adult population [10].

The toxicity of vancomycin might be upsurged due to various factors such as long-term treatment or concomitant administration of other nephrotoxic agents [13–15]. Therefore, monitoring vancomycin serum levels is crucial, mainly when administered with other nephrotoxic or ototoxic drugs, often concomitantly administered in pediatric oncology settings [16]. Patients with Gram-positive infections treated with vancomycin and adjusted according to therapeutic drug monitoring (TDM) levels exhibit superior clinical efficacy rates and a decline in the toxicity rate compared with those who take vancomycin without TDM guidance to personalize their doses [7]. Vancomycin trough level is highly recommended to ensure optimum dosing in pediatric patients with a 10–20 mg/l target range [8,17]. Although vancomycin is prescribed according to hospital guidelines in most cases, the TDM recommendations must be followed in all patients to prevent treatment failure, drug adverse events, and the risk of developing bacterial resistance due to subtherapeutic or toxic levels [9,18]. Neonates, critically ill patients, hemodialysis patients, patients with severe burns or

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sepsis and cancer patients are in compelling need of vancomycin dose optimization using TDM compared with normal patients [7]. TDM is a valuable monitoring approach to optimize the outcome of the treatment regimen by ensuring efficacy and minimizing toxicity by measuring the drug concentration in the plasma of the patients at a specific time interval to verify that it is within the recommended therapeutic range, as well as patient's adherence to the drug [18–21]. Ensuring adherence to TDM recommendations, especially antimicrobials, remains challenging for pharmacists. Compliance is crucial to prevent treatment failures and achieve therapeutic goals with maximum efficacy and minimal toxicity. One study reported that compliance with the recommendation in patients using aminoglycosides decreased the length of hospitalization, therapy, and the period where the patients were febrile [22].

In this study, we aim to investigate the healthcare team's compliance toward vancomycin TDM recommendations and follow-up, highlight the reasons for noncompliance, and suggest solutions to improve compliance.

2. Materials & methods

2.1. Study design

The current study is a prospective observational study performed including 485 pediatric oncology patients receiving intravenous (iv.) vancomycin at the Children's Cancer Hospital Egypt 57357 (CCHE). The study was approved by the Institutional Review Board (IRB) and the CCHE Scientific Medical Advisory Committee at CCHE (IRB approval number: 192020).

During the 4 months of the study, a chart review was conducted for all eligible subjects from January to April 2020. The study included all pediatric oncology patients receiving iv. vancomycin with potentially subtherapeutic or toxic vancomycin trough levels (levels require dose individualization). All patients within the normal range (10–20 mg/l) were excluded.

2.2. Inclusion & exclusion criteria

Our analysis includes pediatric patients receiving vancomycin as part of their support treatment. They experienced toxic levels defined as vancomycin concentration in the blood >20 mg/l or subtherapeutic levels defined as vancomycin concentration in the blood <10 mg/l. Patients with normal vancomycin levels (10–20 mg/l) were excluded from compliance with the recommendation analysis. For the follow-up analysis, patients with follow-up levels done or not done were included, while patients with vancomycin discontinued before reaching the steady state or noncompliant to the initial recommendation were excluded from the follow-up analysis.

2.3. Data collection

Data were extracted from the Cerner Health Facts Electronic Medical Record system (Cerner corporation). Healthcare workers' compliance with applying vancomycin TDM recommendations and adherence to the follow-up level were assessed. The adherence of the healthcare teams to the suggested recommendation by adjusting the dose or frequency of the vancomycin was considered compliance with the recommendation. Furthermore, reordering vancomycin TDM after attaining the steady state is deemed compliance with the follow-up.

2.4. Statistical analysis

Data were collected and analyzed using the software Statistical Package for Social Sciences (SPSS, version 20, IBM Corporation, Armonk, NY, USA). Data are presented in percentages.

3. Results

Over the 4 months of the study, the total number of levels measured was 522 for the total of 485 patients taking vancomycin. Out of the 485 patients on vancomycin, we found that only (54%, n = 262) patients had TDM orders, while (46%, n = 223) patients had no TDM order, as represented in (Figure 1). Our data shows that out of the 522 TDM results, the level was normal in (45.6%, n = 238), subtherapeutic in (35.2%, n = 184) and toxic in (19.2%, n = 100). Patients with normal TDM results or who have a level of subtherapeutic or toxic but need their samples checked (n = 18) were excluded, as depicted in (Figure 1).

3.1. Compliance & noncompliance to the primary recommendation

To examine healthcare professionals' compliance to the vancomycin TDM primary recommendation generated by the lab pharmacist, we find that the vancomycin level was subtherapeutic in 63.5% (n = 169) patients. In contrast, the level was toxic in 36.5% (n = 97). Sample was rechecked, and a new sample was withdrawn in 18 cases. The vancomycin level will be judged according to the follow-up level in which the total number of subtherapeutic cases were 8.1% (n = 15), and the toxic cases were 3% (n = 3). The action taken by the healthcare professional in response to the recommendation was modifying the vancomycin dose in 91.7% (n = 244) of the cases; hence, they have considered as compliant with the recommendation. Where the total number of subtherapeutic cases compliant to recommendation were 90.5% (n =

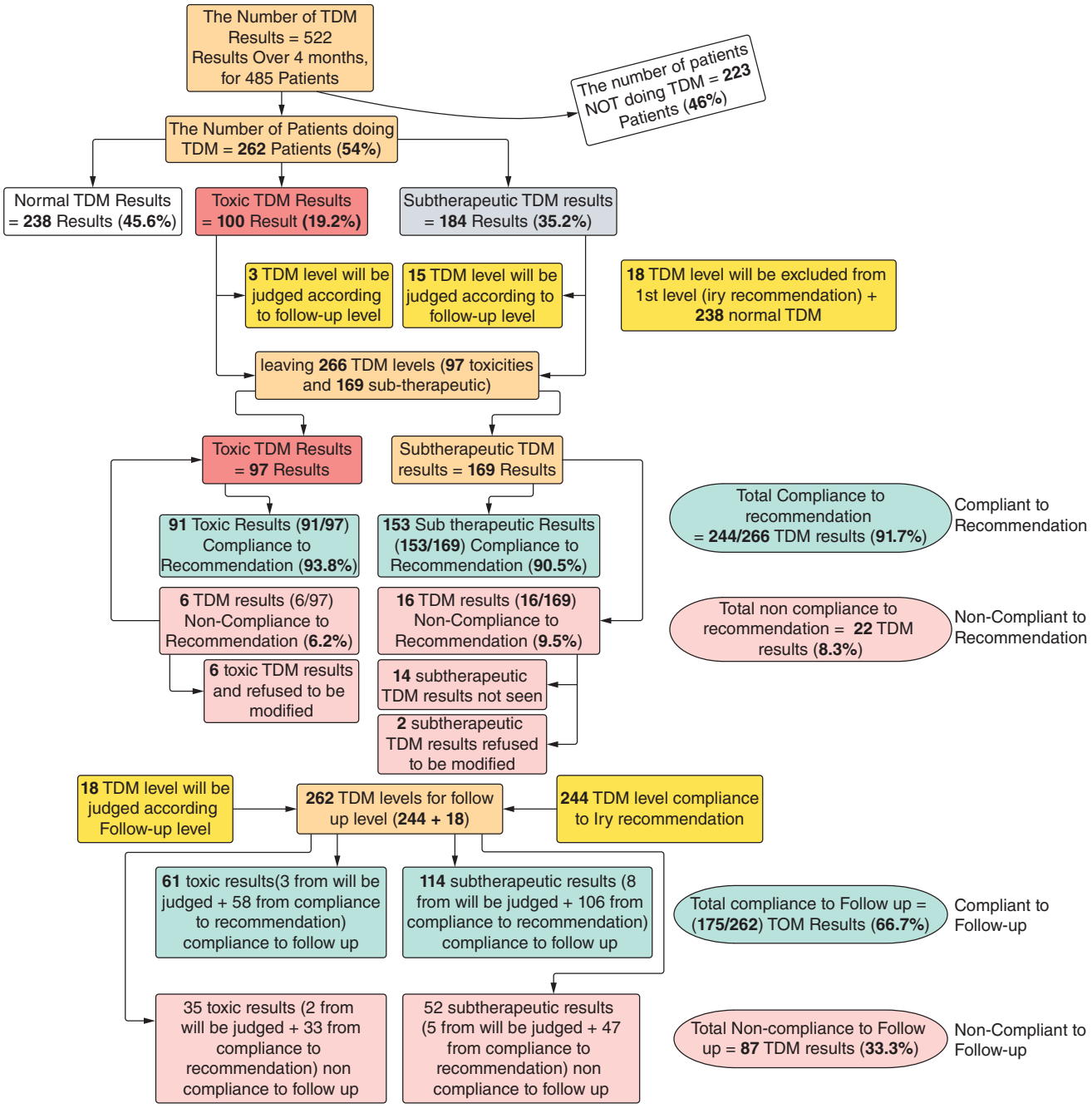

Figure 1. Depicts the total number of patients involved in the study; out of them, 485 patients have 522 therapeutic drug monitoring levels measured and divided into three main categories: normal, subtherapeutic and toxic. We also include the total number of TDM requests in each category and whether healthcare professionals are compliant to TDM or not. In addition, we define the excluded TDM requests in each case.
TDM: Therapeutic drug monitoring.

153/169) and the toxic cases were 93.8% (n = 91/97) of the total subtherapeutic and toxic cases studied, respectively. In addition, healthcare professionals did not modify the vancomycin dose in 8.3% (n = 22) of cases and therefore they considered as non-compliant to recommendation. Where the total number of subtherapeutic cases non-compliant to recommendation were 9.5% (n = 16/169) and the toxic cases were 6.2% (n = 6/97) as depicted in (Figure 2).

3.2. Compliance & noncompliance to the follow-up level

We proceeded to investigate healthcare professionals' compliance with the follow-up level ordered by the lab

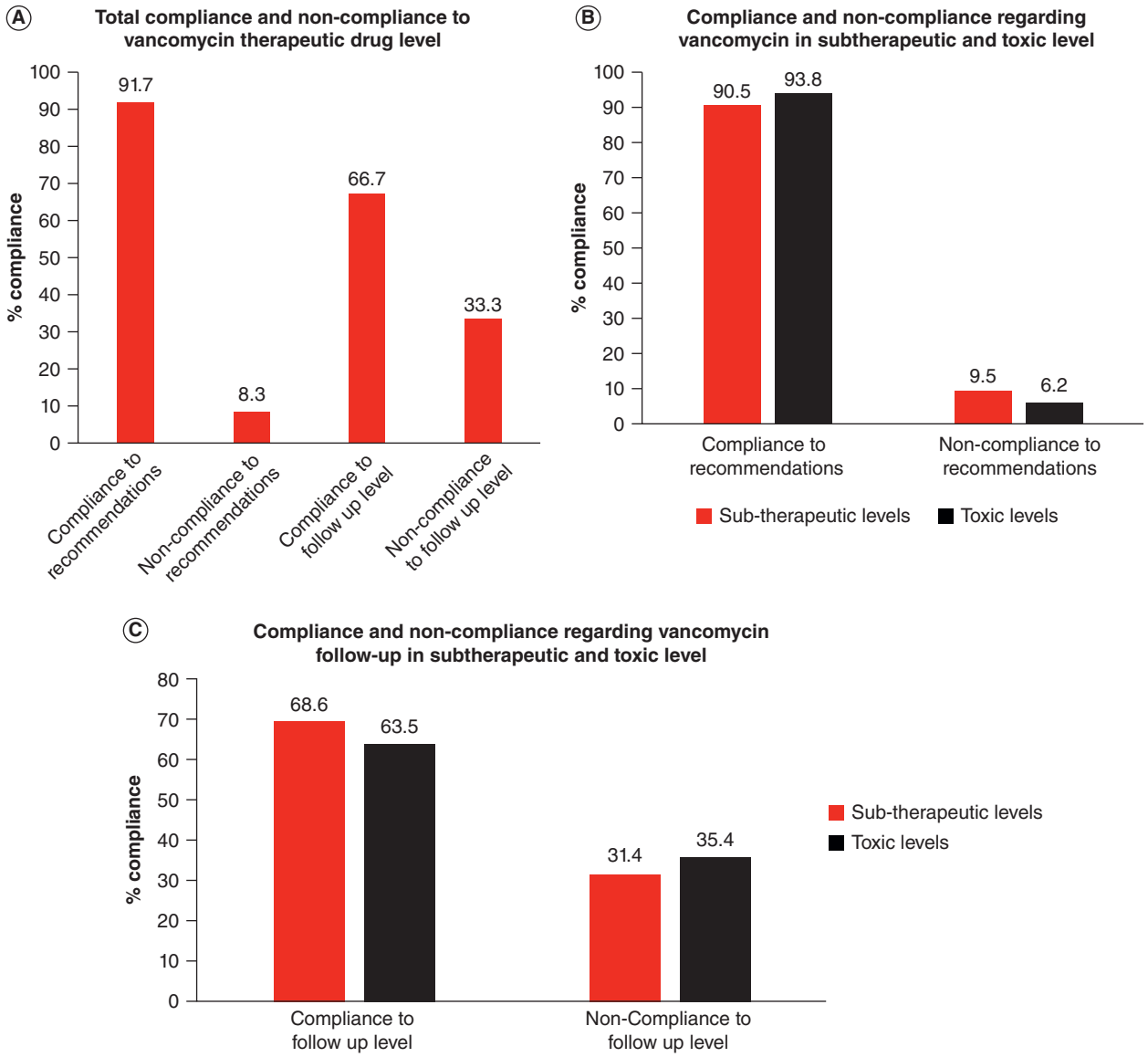

Figure 2. Compliance and noncompliance of healthcare professionals to primary vancomycin therapeutic drug monitoring primary recommendation and follow-up levels. **(A)** Healthcare professionals were compliant to the recommendation in 91.7% of cases and noncompliant in 8.3% of cases. While the total number of TDM results compliant to follow-up level is 66.7%, the total number of TDM results non-compliant to follow-up levels is 33.3%. **(B)** Highlights vancomycin compliance and non-compliance to TDM recommendation in relation to the total subtherapeutic and toxic levels. **(C)** Illustrates vancomycin compliance and non-compliance to TDM follow up levels in relation to the total subtherapeutic and toxic levels.
TDM: Therapeutic drug monitoring.

pharmacist. Our data shows that out of 262, including 244 compliant cases and 18 recheck sampling cases, in patients who have vancomycin level and included in our analysis to recommendation, the total number of TDM results compliant to follow-up level is 66.7% (n = 175/262). Where 68.6% (n =114/166) of subtherapeutic cases and 63.5% (n= 61/96) of toxic cases were compliant to follow up in relative the total subtherapeutic and toxic cases respectively. Moreover, The total number of TDM results non compliant to follow-up levels 33.3% (n = 87). Where 31.4% (n=52/166) of the subtherapeutic cases and 35.4% (n=35/96) of the toxic cases were non compliant to follow up in relative to the total subtherapeutic and toxic cases respectively (Figure 2).

4. Discussion

Conducting vancomycin TDM is essential for improving its efficacy, minimizing toxicity and decreasing the probability of bacterial resistance [23]. It is imperative to note that pediatric oncology patients undergoing chemotherapy and other treatments may experience kidney func-

tion and clearance changes. Such alterations can significantly impact the effectiveness of vancomycin due to the combined usage of other nephrotic and ototoxic drugs, leading to pharmacokinetic and toxicity issues [9,23]. Moreover, the risk of toxicity is not exclusively limited to intravenous vancomycin only, but also oral vancomycin can lead to supra-therapeutic levels in the bloodstream, which might result from prolonged administration and accumulation due to high total dosing [24]. Therefore, the healthcare team must comply with the TDM process [21,25,26]. Our study aims to thoroughly investigate the healthcare team's level of adherence to vancomycin TDM recommendations and follow-up protocols, discuss the reasons and provide practical solutions to improve compliance and ensure optimal patient care.

Our data reveals that out of the 485 patients who received vancomycin and had a total of 522 levels, only 54% (262) had TDM orders. Among those, 238 had normal results (45.6%), 184 had subtherapeutic results (35.2%) and 100 had toxic results (19.2%). Several reports demonstrate that empirical dosing is ineffective in achieving the desired therapeutic level of vancomycin, especially in pediatric populations [27–29]. Our research shows that nearly half of the patients, 46% (223) taking vancomycin, did not have their vancomycin levels checked. This could be attributed to various factors, such as insufficient awareness of TDM guidelines, inadequate communication among healthcare professionals, high workload, delayed sampling and a negative perception of TDM guidelines [30]. This lack of monitoring could contribute to higher mortality rates and the emergence of bacterial resistance [30]. The compliance rate can be further improved through increasing awareness among healthcare professionals regarding the significance of adhering to vancomycin TDM recommendations and follow-up guidelines. It is essential to highlight the adverse effects of poor compliance, such as increased patient mortality and the development of bacterial resistance, and reduce the negative perceptions regarding vancomycin TDM.

We investigated compliance regarding vancomycin TDM by measuring the compliance rate to recommendations and follow-up guidelines. Out of those who received vancomycin, our results show that the healthcare professionals were compliant to the recommendation guidelines in 91.7% of cases. In comparison, the percentage of poor compliance to the recommendation guidelines was only 8.3% of cases. For subtherapeutic levels, the compliance rate was 90.5% for recommendations, while the noncompliant rate was only 8.3%, as shown in (Figure 2). The reasons for noncompliance were that either the healthcare worker refused the advice to modify vancomycin dosing based on the recommendations in two cases out of 16 cases or missed the TDM results in 14 cases out of 16 cases. In cases where toxic levels were present, healthcare providers refused the advice to modify in only six cases. We found that the compliance rate to the follow-up level is lower than the compliance to the recommendations guidelines. Where the compliance rate to the follow-up level was 66.7%, and the noncompliance rate was 33.3%. However, the current study found that in most cases, when the pharmacist is aware that the vancomycin will be discontinued later in the day or the next day or that it will be switched to another antibiotic, they do not perform the follow-up level because the vancomycin will be discontinued in any case. Still, the discontinuation may not happen, and the dose modification or follow-up level is delayed.

Furthermore, our data reveals that the compliance rates have exceeded 90% thanks to our multi checkpoint approach, which involves a team of lab pharmacists, infectious disease pharmacists, and clinical pharmacists working in coordination with other healthcare professionals. In addition, the hospital's electronic system has many pop-up alerts, reminders and notes to help the healthcare team during the TDM process [31]. Our data suggests that the compliance rate is higher compared with other institutions in various countries that report low compliance rates to the institutional guidelines, including Jordan, Belgium, and Australia [30,32,33].

Moreover, adherence to TDM in our study was influenced by the efforts and contributions of a multidisciplinary team of pharmacists, who facilitated communication with other healthcare professionals by reviewing critical results and ensuring all recommendations were implemented. If the responsible pharmacist had a valid reason for noncompliance, it would be documented, and this service positively impacted the compliance rate. Although the current approach has its benefits, there is one drawback to consider. Currently, only toxic results are deemed critical, but including subtherapeutic results in this category could potentially enhance compliance rates and ultimately improve treatment outcomes. Pharmacists can have a more prominent role in TDM programs, which entails establishing teaching programs about pharmacokinetics, pharmacodynamics and TDM of specific antimicrobials, along with clinical case studies for pharmacists.

Finally, vancomycin can exhibit harmful effects if taken for a long time or in combination with other drugs. Monitoring vancomycin levels in pediatric cancer patients is crucial to prevent adverse drug reactions. Our data reveals that compliance to recommendations surpassed 90% while compliance to follow-up levels is lower. Therefore, we recommend establishing TDM-focused educational programs such as a pharmacist-led TDM credentialing program, facilitating access to decision-support tools,

adopting a multidisciplinary team approach which can improve communication among healthcare professionals, and reduce healthcare professionals workload, could result in higher adherence rates, improve drug monitoring and enhance patient outcomes.

5. Conclusion

To summarize, vancomycin is a commonly prescribed medication for serious illnesses. However, it can have toxic effects on patients, especially if taken for extended periods or in combination with other harmful drugs. Therefore, it is recommended to regularly monitor vancomycin levels in pediatric cancer patients to detect any potential adverse reactions. Our research found that healthcare providers are more likely to follow recommendations in toxic results than subtherapeutic results. However, even subtherapeutic results can lead to bacterial resistance, so it is essential to prioritize monitoring and follow-up. Unfortunately, compliance with follow-up recommendations is lower due to varying factors such as missing the recommendations and healthcare providers refused the advice to modify the vancomycin dose. To address these issues, we suggest implementing an electronic alert system for pharmacists to perform follow-up monitoring after the fourth dose of vancomycin. Additionally, we recommend a pharmacist-led TDM accrediting program to enhance the TDM process and increase the involvement of clinical pharmacists in healthcare settings.

Article highlights

- Vancomycin therapeutic drug monitoring (TDM) is crucial for effective and safe medication.
- Nearly half of the patients on vancomycin do not get their levels checked.
- Our results show that the healthcare professionals complied with the recommendation guidelines in 91.7% of cases.
- Compliance with the recommendation among total subtherapeutic cases were (90.5%) and among total toxicity cases were (93.8%).
- The compliance rate to follow-up is lower than the recommendations, with 66.7% compliance compared with 33.3% noncompliance.
- Our comprehensive approach has resulted in over 90% compliance rates. The hospital's electronic system (Cerner) also provides helpful pop-up alerts and reminders to support the TDM process.
- We recommend establishing TDM-focused educational programs such as a pharmacist-led TDM credentialing program, facilitating access to decision-support tools and adopting a multidisciplinary team approach, which can improve communication among healthcare professionals.

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Institutional review board statement

CCHE's Human Research Ethics Committee granted ethics approval for this project.

Data availability statement

The data represented in this article are available on request from the corresponding author.

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