IMPROVING THE APPROPRIATENESS OF THERAPEUTIC DRUG MONITORING SAMPLING IN HOSPITAL SULTANAH NUR ZAHIRAH, KUALA TERENGGANU

Lukman Nul Hakim Md Khairi, Farah Syakirah Ahmad, Aimi Shazana Muhammad Anuar, Nurul Ain Wan Omar, Nurul Najmi Muhammad, Nurulhayati Abd. Jamal, Wan Najiah W. Mokhtar @ W. Moxtor, Maznuraini Zainuddin.

Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu.

Corresponding Author: Lukman Nul Hakim Md Khairi
Email: lukmankhairi@gmail.com

Abstract

Therapeutic drug monitoring (TDM) is a valuable clinical tool in optimisation of drug regimens. However, improper utilisation of TDM may lead to significant resource wastage and expose patients to avoidable trauma, toxicity, therapeutic failure and prolonged hospitalisation. This study aimed to reduce the percentage of inappropriate TDM sampling to our proposed standard of less than 20% within a four-month intervention period. A cross-sectional study was undertaken from January to December 2015 at the inpatient setting of Hospital Sultanah Nur Zahirah. Gentamicin and Vancomycin analytes were studied because these analytes accounted for 69.2% of total samples received in 2014. TDM Monitoring Form was used to collect sampling and dosage information to assess sampling appropriateness. A closed-ended self-administered questionnaire was distributed to a group of medical doctors to assess their knowledge on appropriate Gentamicin and Vancomycin TDM sampling method pre- and post-intervention. Prior to the intervention phase in October to December 2014, 79.4% of TDM were inappropriately sampled. The main contributing factors were inadequate knowledge among medical doctors, lack of sampling reminders for new TDM requests, and misunderstanding on sampling information for repeated TDM requests. 60-minute face-to-face educational sessions on TDM sampling method were conducted specifically for staff at the General Medical and Paediatric Departments, and two continuing medical education (CME) slots were held at the hospital level. Guidelines on TDM sampling was initiated and laminated copies were distributed to all wards. Implementation of TDM Alert System which consisted of digital reminders and physical stickers was also introduced. The interventions were able to reduce the inappropriate sampling percentage from 79.4% to 41.8% post-intervention, and to 19.1% in the recent monitoring phase of January until June 2019. Continuous close monitoring and sustainable implementation of the measures are vital as TDM sampling appropriateness may affect clinical interpretation of the results.

KEYWORDS: Therapeutic drug monitoring, sampling, appropriateness

Problem

Improper utilisation of therapeutic drug monitoring (TDM) is inclusive of inappropriateness in its indication, sampling time and application of results. This may lead to significant wastage of resources and expose patients to trauma, toxicity, therapeutic failure and prolonged hospitalisation. In 2012, inappropriate Vancomycin TDM alone was reported to result in an excess of USD 13,080 (MYR 53,366) per year of unnecessary hospital expenditure in the United States of America (1). As a comparison, in 2014, inappropriate sampling of Gentamicin and Vancomycin TDM was associated with an extrapolated annual avoidable cost of MYR 21,664 in Hospital Sultanah Nur Zahirah (HSNZ). This highlights the importance of an improvement of quality in our institution where resources are highly valued.

HSNZ is a state general hospital situated in the district of Kuala Terengganu with a population of 343,282 people. HSNZ has a maximum capacity of 1,107 beds and 43 wards. HSNZ serves as a reference hospital for district hospitals and health clinics throughout the state of Terengganu with an estimated population of 1,250,000.

Pharmacy Department is one of the key clinical support units in HSNZ. This department provides a wide range of pharmaceutical care services including ambulatory pharmacy, inpatient pharmacy, ward pharmacy, clinical pharmacokinetics, manufacturing, logistics, pharmacy resources and information centre. The Clinical Pharmacokinetic Unit (CPU) is responsible for processing TDM requests i.e. screens TDM requests and blood samples, interprets the results based on patients' clinical status, communicates interpretation of the results, and recommends appropriate action to the requesting physician (2). The unit is led by a pharmacist and supported by provisionally registered pharmacists. In HSNZ, sample analysis is carried out by the Pathology Department. Results and recommendations of TDM requests will be relayed between laboratory staff to pharmacists and ultimately to medical doctors through the Laboratory Information System (LIS) and Hospital Information System (HIS), respectively. As a reference hospital, the unit accepts both internal and external TDM requests, including from district hospitals and health clinics. In 2014, CPU received a total of 5,327 TDM requests of 13 different analytes of narrow therapeutic window drugs (3) including Amikacin, Gentamicin, Vancomycin, Carbamazepine, Digoxin, Phenobarbitone, Valproic Acid, Cyclosporine, Methotrexate, Phenytoin, Theophylline, Paracetamol and Salicylate. Out of these samples, 69.2% were Gentamicin and Vancomycin requests, and were mainly received from General Medicine and Paediatrics Department.

During the pre-intervention phase of this study in HSNZ, 79.4% (n=677/853 samples) of the internal TDM samplings were inappropriate, which highlighted the urgent need to solve the problem. This study was designed to reduce the inappropriateness of internal TDM sampling in HSNZ to less than 20% within a 4-month intervention period (a 50% reduction from a local study by Hamzah et al. (4) which reported 45.2% of inappropriate sampling).

Background

TDM is an important pharmaceutical care service for optimisation of drug regimens with a narrow therapeutic index. It aids in identifying alterations in drug disposition and possible drug-drug interactions, designing patient-specific drug regimen and minimising adverse effects (5). Appropriate sampling of TDM is vital as accurate interpretation of TDM results by TDM pharmacists depends on the concise information on the sampling (6,7).

A local cross-sectional study in 2008 evaluated TDM sampling inappropriateness in HSNZ. Eighty four TDM requests, including Digoxin, Gentamicin and antiepileptic analytes were screened and 45.2% of them were found to be inappropriately sampled (4). Since ordering of TDM requests by a computerised order system had yet to be available during that time, the study suggested comprehensive and long term educational programs for medical doctors and nurses, along with active roles of ward

pharmacists during clinical rounds as the corrective intervention (4). Another study conducted at the Singapore General Hospital in 2014 stated that 61.5% of Vancomycin TDM samples were inappropriately withdrawn (8). An analysis of the inappropriately sampled Vancomycin showed 41 unnecessary dose withholds, 24 dose changes, and 102 unchanged doses. The associated cost due to inappropriate interpretation was USD 7,286 (MYR 29,727) (8).

Through an audit in a Hong Kong government hospital laboratory, Kwok et al. (9,10) found multiple reasons for inappropriate orders of laboratory tests. These included medical doctors making a mistake, inadequate knowledge on appropriate use of the tests, lack of experience, and repetitive ordering of tests prior to checking the results of the previous test.

Effective educational programme and accessible guideline for TDM sampling are vital. By educating nurses and phlebotomists about the appropriate timing of Vancomycin sampling, the timing appropriateness improved significantly from 37% to 78% post intervention (11). The percentage of Vancomycin trough sampled at steady state concentration also increased from 36% to 55% (11). Intervention of 60-minute face-to-face educational sessions and provision of printed Vancomycin dosing and monitoring guideline to junior medical officers and pharmacists increased the appropriate sampling time from 72.6% to 80.6% (12).

Utilisation of digital reminders for TDM tests ordered through computerised physician order system is another means to improve the appropriateness of TDM sampling. In a study conducted in Brigham and Women's Hospital in Boston, Massachusetts in 2011, an information technology based intervention that provided educational instructions and linked the timing of medication administration to nurses who were responsible for Vancomycin trough blood withdrawal reduced the Vancomycin timing errors percentage from 39% to 32% (6). A pop up alert message when Vancomycin test was ordered including a timing guide and a justification for routine monitoring increased the percentage of appropriate Vancomycin trough order from 58% to 68% (13).

Measurement

The primary outcome of the study was the percentage of inappropriate TDM sampling, calculated as the number of inappropriate TDM samples over the total number of TDM samples received. Inappropriate sampling was defined as TDM blood withdrawal which was inconsistent with our local TDM sampling guidelines in terms of timing, completeness and steady state achievement at point of sampling (14). The study included new and repeated TDM requests. New TDM requests are samples from patients who have not been sampled for TDM investigations, while repeated TDM requests are samples withdrawn based on recommendation of previous TDM result interpretation. Each TDM request was clerked by pharmacists at CPU using HSNZ TDM Monitoring Form before results interpretation was provided. These forms were used as our data collection tool to examine information on sample timing, medication dosing, and time interval.

Initial data was obtained retrospectively with samples received throughout 2014. It was found that out of a total of 5,327 samples and 13 different analytes, Gentamicin topped the list of the most requested TDM analytes (52.0%; n=2,772), followed by Vancomycin (17.2%; n=916). Therefore, all new and repeated samples of Gentamicin and Vancomycin were included to prevent probable resistant strains that could have resulted from improper sampling. All inpatients were included in the study, except those with stage 5 Chronic Kidney Disease.

A pre-intervention analysis of Gentamicin and Vancomycin TDM samples received between October and December 2014 showed that 79.4% (677/853 samples) of these samples were inappropriately withdrawn. Based on a group consensus, our team agreed to propose a standard of up to 20% of inappropriate sampling based on availability and capability of existing human resource, a 50% reduction from a local

study by Hamzah et al. (4) which reported 45.2% of inappropriate sampling.

Initial Assessment of the Problem

A cause-and-effect analysis was performed during the problem analysis phase to gain an early understanding on the possible contributing factors to the problem (Figure 1). The identified factors involved inadequate knowledge among medical doctors, lack of sampling reminder for new TDM requests, and misunderstanding of the sampling information for repeated TDM requests.

We started our study by evaluating the knowledge of TDM sampling among medical doctors, as they were responsible for ordering TDM requests on our computerised physician order system of Hospital Information System (HIS) and executing blood withdrawal thus ample knowledge on TDM sampling information is vital. A closed-ended self-administered questionnaire was developed to assess medical doctors' knowledge on Gentamicin and Vancomycin TDM sampling methods pre- and post-intervention. The questionnaire consisted of 10 questions: four questions on sampling time, three questions on sampling components, and three questions on time to steady state. A respondent would be categorised as having 'Good Knowledge' if he/she scores at least 80%. A number of 95 medical doctors responded to the questionnaire and only 61.1% (n=58) of them had 'Good Knowledge' in the pre-intervention phase.

Based on the training record review, there was no documented department-driven seminar or short educational lectures provided to medical doctors from the period of 2012 till 2014. The existing local clinical pharmacokinetic protocol which contained information on sampling, pharmacokinetics, adverse drug reaction, monitoring parameter, dosage and interaction was last reviewed in 2008. In addition to that, a simplified version of the sampling guideline for quick reference to the ward staff was also not available, explaining the reason for a lack of reference for TDM sampling at wards.

Despite having a computerised physician order system of HIS for TDM investigations, there was under-utilisation of digital reminders to guide medical doctors on new and repeated sampling instructions. No planned provision of sampling guide was made available for new TDM requests as information was given upon request by medical doctors and by clinical pharmacists during ward rounds. On the other hand, all repeated TDM requests were dependent on the pharmacy team through phone reminders on the correct sampling time.

Strategy

Based on the contributing factors identified, four improvement strategies were formulated. An institutional TDM sampling guideline was introduced with specific sampling time and elements (e.g. peak and trough concentrations). The sampling information in the 2008 institutional protocol was improvised based on previously published reference and with input from our TDM pharmacist. The new version was complete with sampling details on timing for steady state achievement for Gentamicin and Vancomycin. Unnecessary TDM sampling of Vancomycin peak concentration was removed. Additionally, the sampling guideline was simplified into a single-page reference and the laminated form of the guidelines was distributed to all wards.

Secondly, the project team provided face-to-face 60-minute educational sessions on Gentamicin and Vancomycin TDM sampling guidelines, especially on its clinical applications to medical doctors. Four sessions were held at different hospital platforms; individual sessions for General Medical and Paediatrics Department staff, and two continuing medical education (CME) slots for hospital staff and medical housemen. Focus was given on the appropriate sampling in terms of specific timing and steady state of Gentamicin and Vancomycin, importance of accurate sampling, and possible complications of non-compliance. The educational sessions received positive feedback from the audience.

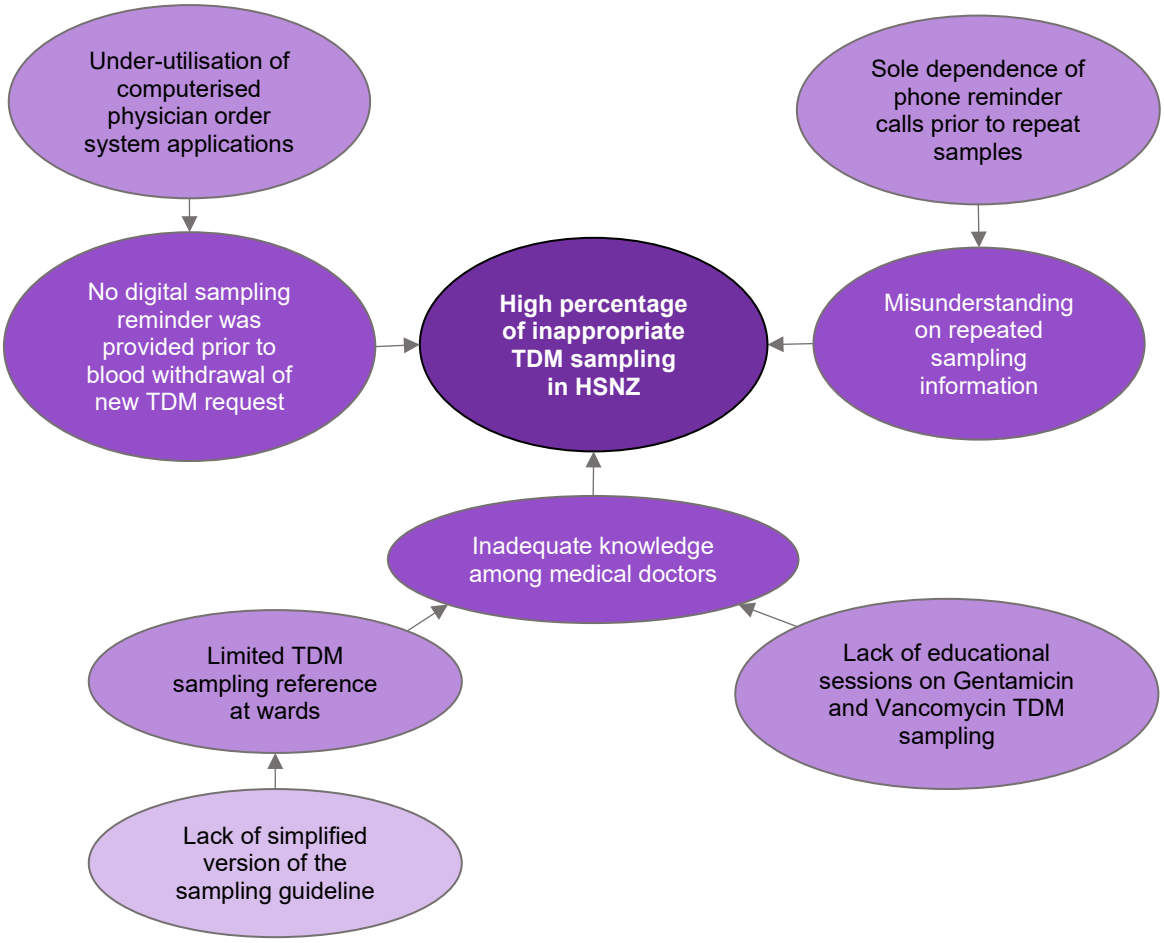

Figure 1: Cause-and-effect chart of high percentage of inappropriate TDM sampling.

The senior doctors indicated that the intervention provided them with good insight into the issue and how they could contribute to solving the problem.

The current process of care was reviewed and was found to be insufficient to support a TDM request handling, which led to an appropriate sampling. Thus, the process of care was updated with additions of a few critical steps, particularly in providing sampling reminder (Figure 2).

A reminder system named 'TDM Alert' was created and prompted medical doctors to execute blood withdrawal in new and repeated cases at the right time, with complete TDM request, and after the steady state had been achieved. The reminder would appear at two points of work process prior to blood sampling. The first point was during the ordering step of TDM drugs and request on HIS. An on-screen pop-up would appear to guide medical doctors on the general sampling information for the drug. The second point was when planning for repeated Gentamicin and Vancomycin sampling. To ensure accurate repeated sampling, a physical sticker with the information of planned and actual timing, and elements of repeated blood taking was introduced. This measure, named 'TDM Alert Sticker', would be filled and pasted onto the patient's bed head ticket (BHT) by the CPU pharmacist a day prior to the planned sampling date.

Results

Each intervention implemented led to a substantial improvement in the percentage of TDM sampling appropriateness.

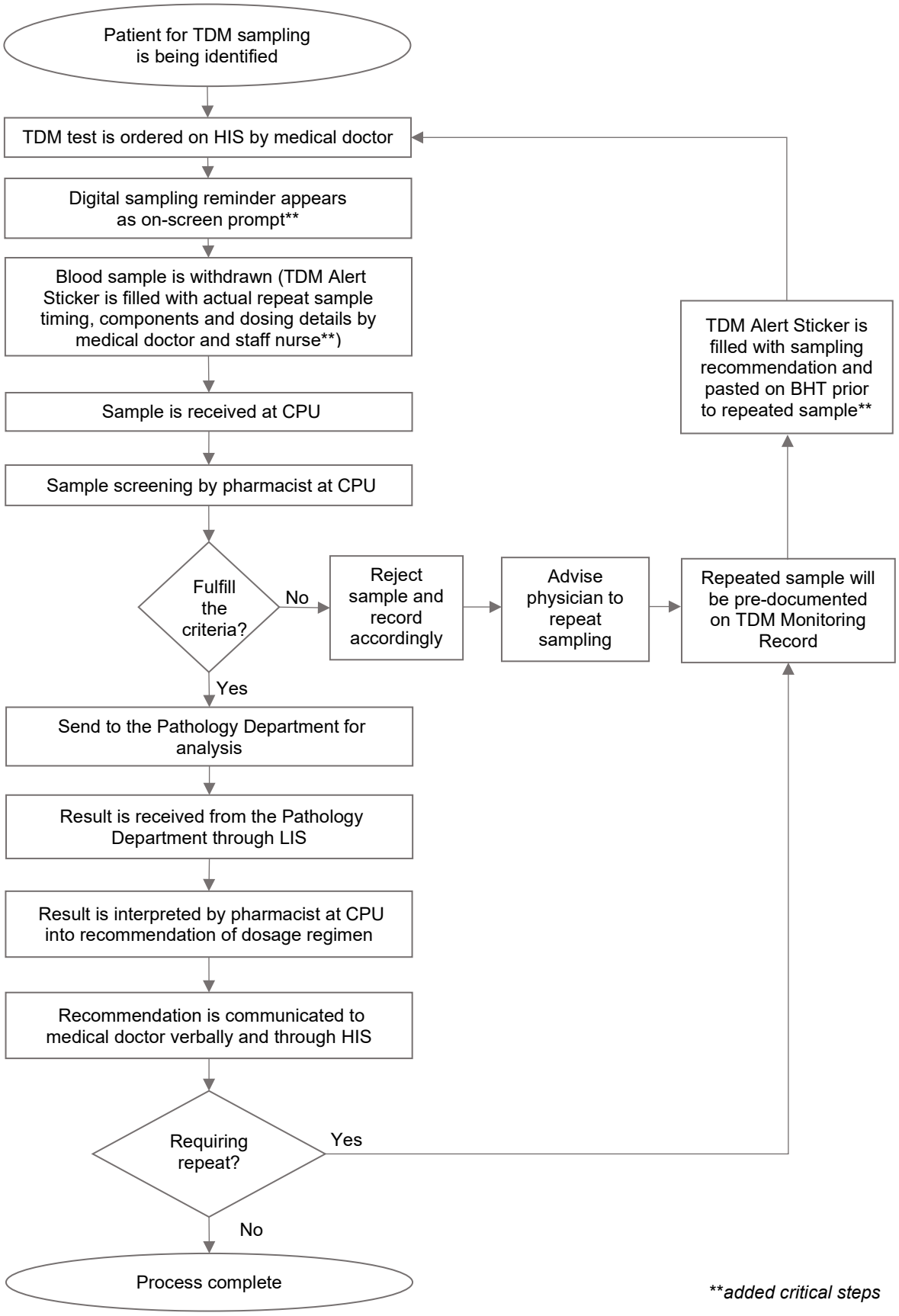

Figure 2: Improved standard operating procedure or point of care to enhance TDM sampling.

The percentage of Gentamicin and Vancomycin TDM inappropriate sampling was reduced to 41.8% (666/1,594 samples) following the intervention between July to December 2015. The monitoring phase continued and recent results showed that the inappropriateness level further decreased to a level lower than the standard set (20% of inappropriate sampling) (Figure 3).

Cost saving was calculated in terms of extrapolated annual avoidable cost attributed to the reagent test kit expenditure. This was inclusive of reagent test kit cost associated with inappropriate sampling (Cost per Gentamicin and Vancomycin test: MYR 8.00). In 2014, the extrapolated annual avoidable cost of inappropriate TDM sampling was MYR 21,664 per year (3-month pre-intervention inappropriate samples of 677) and in 2015, post intervention, the cost reduced by 50.8% to MYR 10,656 per year (6-month post-intervention inappropriate samples of 666).

There was an improvement in the level of knowledge on TDM sampling of Gentamicin and Vancomycin among medical doctors. During the face-to-face educational lectures, medical doctors were requested to answer self-administered questionnaire on Gentamicin and Vancomycin sampling method before and after the session. Of the 95 participants who consisted of 5 specialists, 15 medical officers, and 75 medical housemen, the percentage of medical doctors who had 'Good Knowledge' i.e. a score of at least 80%, increased from 61.1% (58 subjects) to 88.4% (84 subjects) following the intervention.

In addition to that, the project resulted in the pharmacy department being given permanent slots at the medical housemen' orientation week and once-a-year session at the medical housemen' educational slots in HSNZ from 2016. These sessions serve as an update sharing platform on TDM for new medical doctors.

Lessons and Limitations

Engaging a multi-disciplined team was imperative to initiating and sustaining successful change.

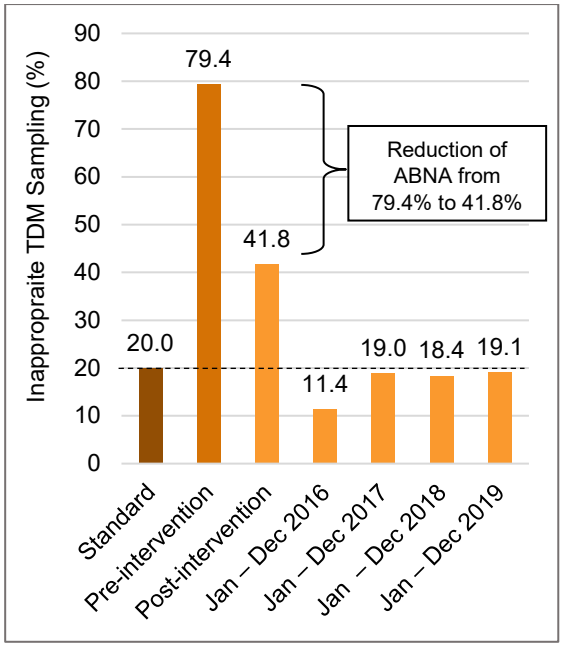

Figure 3: Percentage of inappropriate TDM sampling pre (October – December 2014) and post (July – December 2015) intervention phases

Senior doctors played a vital role in encouraging the medical housemen to improve their quality of TDM blood taking. Nurses on the other hand assisted with blood sampling, particularly in synchronising the medication administration time with sampling. Pharmacists were in the lead position to monitor the appropriateness and ensure sustainable improvement.

This project was limited by the inclusion of only two TDM analytes of Gentamicin and Vancomycin. Comparatively, other studies covered other analytes including anti-epileptics, Cyclosporine and Digoxin (5)(4). Thus, our project could have underestimated or overestimated the inappropriateness.

Conclusion and the Next Steps

The reduction in the percentage of inappropriate TDM sampling was contributed by the introduction of multiple measures including an educational program and sampling reminder system. This project has proven to be sustainable since its commencement in 2015 until 2019, with the reduction of percentage of TDM sampling inappropriateness to lower than the target of 20%. To ensure

sustainability of the project, our team appointed our TDM pharmacist as the head of project to ensure project continuation, regular audit management, and to teach. The digital reminder system can be implemented at facilities equipped with similar computerised physician order system.

Acknowledgements

We would like to thank the Director General of Health Malaysia for his permission to publish this article, and the State Health Director and the Deputy State Health Director (Pharmacy) of Terengganu for their support in this project. We also wish to express our gratitude and appreciation to the Director of HSNZ, Chief Pharmacist, all medical doctors, pharmacists, and nurses for their involvement and contribution to this project.

Conflict of Interest

None

Funding

None

References

1. Suryadevara M, Steidl KE, Probst LA, Shaw J. Inappropriate vancomycin therapeutic drug monitoring in hospitalized pediatric patients increases pediatric trauma and hospital costs. J Pediatr Pharmacol Ther. 2012 Apr;17(2):159–65.

2. Ministry of Health Malaysia. Policy and Guideline of Clinical Pharmacokinetic Pharmacy Services. 2015.

3. Ministry of Health Malaysia. Pharmacy Management Report (PF) 6.7. 2014.

4. Hamzah A, Fatah AB, Rahman AB. Evaluation of blood sampling times and indications for therapeutic drug monitoring services. Malaysian J Pharm Sci. 2008;6(1):1–11.

5. Al Za'abi M, Al Muqbali J, Al-Waili K. Sampling time and indications appropriateness for therapeutically monitored drugs at a teaching university hospital in Oman. Saudi Pharm J. 2015;23:458–62.

6. Melanson SEF, Mijailovic AS, Wright APM, Szumita PM, Bates DW, Tanasijevic MJ. An Intervention to Improve the Timing of Vancomycin Levels. Am J Clin Pathol. 2013 Dec;140(6):801–6.

7. Coleman LK, Wilson AS. Impact of Nursing Education on the Proportion of Appropriately Drawn Vancomycin Trough Concentrations.

8. Seng JJB, Yong MHA, Peh ZX, Soong JL, Tan MH. Appropriateness of vancomycin therapeutic drug monitoring and its outcomes among non-dialysis patients in a tertiary hospital in Singapore. Int J Clin Pharm. 2018 Oct;40(5):977–81.

9. Kwok J, Jones B. Unnecessary repeat requesting of tests: An audit in a government hospital immunology laboratory. J Clin Pathol. 2005;58(5):457–62.

10. Hovinga CA, Rose DF, Phelps SJ. Appropriateness of Anticonvulsant Concentration Monitoring In Hospitalized Pediatric Patients. J Pediatr Pharmacol Ther. 2003;8(3):200–9.

11. Swartling M, Gupta R, Dudas V, Guglielmo BJ. Short term impact of guidelines on vancomycin dosing and therapeutic drug monitoring. Int J Clin Pharm. 2012 Apr;34(2):282–5.

12. Phillips C, Gordon D. Pharmacist-led implementation of a vancomycin guideline across medical and surgical units: impact on clinical behavior and therapeutic drug monitoring outcomes. Integr Pharm Res Pract. 2015 Oct;4:145.

13. Traugott KA, Maxwell PR, Green K, Frei C, Lewis JS. Effects of therapeutic drug monitoring criteria in a computerized prescriber-order-entry system on the appropriateness of vancomycin level orders. Am J Heal Pharm. 2011 Feb;68(4):347–52.

14. Hospital Sultanah Nur Zahirah. HSNZ TDM Sampling Guidelines. 2015.