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MINISTRY OF HEALTH MALAYSIA

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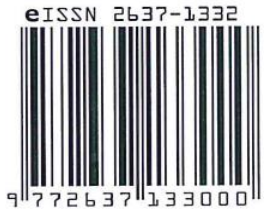

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Evaluation of Clinical and Cost Outcomes of the Antimicrobial Stewardship Programme in a Tertiary Referral Hospital in Perak, Malaysia

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Abstract

Introduction: The antimicrobial stewardship (AMS) programme has been implemented in most public healthcare facilities in Malaysia to promote judicious use of antimicrobials and to minimise antimicrobial resistance. Routine AMS ward rounds are one of the activities in the AMS programme.

Objective: This study aimed to evaluate the clinical outcomes of patients managed under the AMS programme in a Malaysian tertiary hospital, with the antimicrobial cost savings consequential to the recommendations provided by the AMS team during the routine AMS ward rounds.

Methods: This is a retrospective review of the AMS database in Hospital Raja Permaisuri Bainun, Perak from 1 January 2019 to 30 June 2019. The AMS clerking forms filled during ward rounds were reviewed and relevant data were collected. Cases with incomplete information or recommendations that had no direct impact on patients' clinical and cost outcomes were excluded.

Results: A total of 200 cases were referred to the AMS team for recommendations. Of those recommendations, 167 (83.5%) were accepted by the primary team. Most of the cases (76.0%) were discharged well. There was no association between duration of antimicrobial therapy ($p=0.147$), length of stay ($p=0.849$), 30-day infection-related mortality ($p>0.95$) and 30-day infection-related readmission ($p=0.329$) with acceptance of those recommendations. Accepting the recommendations contributed to a total antimicrobial cost saving of RM9,579.82 but rejection resulted in cost wastage of RM1,332.18 over the study period ($p<0.001$).

Conclusion: Recommendations provided by the AMS team resulted in cost savings without compromising other clinical outcomes. Future studies should evaluate the potential long-term benefits of AMS programme and the sustainability of these benefits.

Keywords: antimicrobial stewardship programme, AMS ward rounds, clinical outcomes, antimicrobial cost savings, Malaysian tertiary hospital

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Introduction

The development of antimicrobial agents provided a temporary solution in struggling pathogenic microorganisms (1). However, the inappropriate use of antimicrobial agents has been associated with antimicrobial resistance. Antimicrobial resistance is currently a serious threat to human health globally that requires urgent attentions and interventions (2). The most commonly reported resistant bacteria in Malaysia were *Staphylococcus aureus*, *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (3).

The antimicrobial management or stewardship programme has been developed as a response to antimicrobial resistance. Antimicrobial stewardship (AMS) has been defined as "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy and route of administration" (4). The AMS programme consists of various strategies such as education, formulary restriction, preauthorisation, prospective audit and feedback (1,4). Often, different strategies are combined in the AMS bundles. The objectives of the AMS programme are to improve patient outcomes, to optimise antimicrobial therapy, to limit any unintended consequences and to reduce healthcare costs without adversely impacting the quality of care (5). One of the AMS core activities is to formalise regular antimicrobial rounds by the

AMS team in hospitals (5). The AMS team of Hospital Raja Permaisuri Bainun (HRPB) in Ipoh, Perak, consisting of infectious diseases physicians, clinical pharmacists and clinical microbiologists, was established in October 2013.

It should be noted that the primary goal of any AMS programmes is not to reduce antimicrobial consumption, but instead is to improve the quality of patient care and subsequently to optimise antimicrobial costs. Several systematic reviews showed that AMS interventions increased compliance with local antimicrobial policies and improved patient outcomes (6,7). The Malaysian AMS protocol has also stated several process and outcome measures to evaluate the effectiveness of the AMS programme activities (5). Hence, in line with the placement of a dedicated pharmacist in the AMS team commencing January 2019 in HRPB, this study was performed to evaluate the impact of recommendations made by the AMS team during antimicrobial rounds on patients' clinical outcomes and antimicrobial cost savings.

Methods

Study Design and Setting

This study was conducted via retrospective review of the AMS database in HRPB. The AMS case clerking forms of all patients were reviewed and relevant data for each patient was collected. Cases reviewed by the AMS team between 1 January 2019 to 30 June 2019 involving patients with age 13 years old and above were included in this study. The cases were excluded if the AMS team provided recommendations that had no direct impact on patients' clinical and cost outcomes, such as to continue on existing antimicrobial regimen and any non-antimicrobial agent-related recommendations such as requirement of additional investigations, infection control measures or referral of complicated cases to the infectious diseases team.

Description of the AMS Programme

One of the activities implemented by the team was to conduct regular AMS ward rounds and this normally starts with case identification. Besides receiving case referral from the ward pharmacists, medication charts in the satellite pharmacies are reviewed by one of the AMS pharmacists on a daily basis. The details of all patients prescribed with carbapenems and vancomycin as well as cases with suspected inappropriate use of antibiotics were recorded in a screening list. Subsequently, cases in the screening list were reviewed in the ward. Cases with confirmed inappropriate use of antibiotics requiring infectious diseases physician assessment were referred to the AMS team. The use of antibiotics was considered to be inappropriate if one or more of the following criteria were met:

i. the hospital antibiotic guidelines (8) were not adhered without valid reasons
ii. the dosage, duration of therapy and/or empirical treatment choice was/were inappropriate according to the available guidelines
iii. a narrower- or broader-spectrum agent should be used based on the culture and sensitivity results
iv. infections did not present (i.e. due to bacteria colonization or an alternative explanation for the clinical presentation)

During the rounds, comprehensive discussions were performed on the identified cases. Following the discussion, the recommendations made by the AMS team were documented on an AMS sticker and it was then pasted on the patient's medical record. A direct feedback was also provided verbally to the primary team. The MAS team may provide one or more of the following recommendations:

i. continuation of the same regimen
ii. discontinuation of the antimicrobial agents
iii. de-escalating existing regimen based on culture and sensitivity results
iv. escalating existing regimen based on culture and sensitivity results
v. conversion of antimicrobial agents from parenteral route to oral route
vi. dose optimisation of the antimicrobial agents
vii. others (e.g. infection control measures, refer experts, re-investigate cultures etc.)

All cases were followed up for 30 days from the first day of the recommendation was made to determine the outcomes. The details of the cases were documented in an AMS clerking form.

Data Collection and Outcomes

The required information was collected from the AMS clerking forms and recorded in a data collection form. Data extracted included clinical characteristics, the reason of referral to the AMS team for review, recommendations made by the AMS team, the acceptance of the recommendations, clinical outcomes, and the change in antimicrobial cost.

The clinical characteristics included types of infection, antibiotics used and the prescribers. The reason of the cases to be referred to the AMS team for review was classified into the following categories:

i. inappropriate choice of antibiotics based on hospital antibiotic guidelines
ii. inappropriate duration of therapy
iii. inappropriate combination of antibiotics
iv. inappropriate antibiotic chosen for definitive therapy
v. others (e.g. infection was not present, inappropriate dosing regimen etc.)

For the purpose of this study, only recommendations made by the AMS team during ward rounds that had direct impact on patients' clinical and cost outcomes were evaluated. Those recommendations included:

i. discontinuation of the antibiotic regimen
ii. de-escalation of the existing antibiotic regimen
iii. escalation of the existing antibiotic regimen
iv. conversion of the antibiotic regimen from parenteral route to oral route
v. dose optimisation of the antibiotic regimen

The acceptance or rejection of the recommendations made by the AMS team during ward rounds was determined by reviewing the case in the ward within 24 hours after the recommendation was made. If the recommendations were accepted after this timeframe, they were still considered to be rejected for the purpose of this study.

The clinical outcomes evaluated were the duration of therapy with antimicrobial agents, the length of stay (LOS), the absence or presence of 30-day inpatient mortality and 30-day readmission. The duration of therapy was defined as the number of days the antibiotics were given in the ward. The LOS was defined as the number of days from the first day of admission to the day of discharge. The 30-day inpatient mortality was defined as patients who died, during hospitalisation, within 30 days from the first day of the recommendations made by the AMS team. If the cause of death was due to infection, then such death was defined as infection-related mortality. The 30-day infection-related readmission was defined as readmission due to infection that occurred within 30 days of the date of discharge. The clinical outcomes, especially the cause of death and cause of readmission, were obtained from the discharge summary of the patient.

The cost outcome for each case was evaluated in terms of the changes in antimicrobial cost. The change in antimicrobial cost was defined as the estimated difference between the cost incurred from the original prescription of the antimicrobial agents prior to the AMS recommendation and the cost after adopting the AMS recommendation (5). It was expressed in terms of Ringgit Malaysia (RM). The cost of an antimicrobial agent was calculated in terms of the number of ampoules / vials / tablets / capsules supplied multiplied by the government-approved unit price of that particular agent. The government-approved unit price was obtained from Pharmacy Information System (PhIS), Ministry of Health Malaysia, and the information was accessed on 1st November 2019. Figure 1 showed the calculation of the changes in antimicrobial costs.

Data Management and Statistical Analysis

The clinical characteristics of the cases, the reasons of referral to the AMS team for review, recommendations made by the AMS team, the acceptance of the recommendations, clinical outcomes and the change in antimicrobial cost were descriptively reported either in percentages or median (interquartile range, IQR). The Mann-Whitney test was used to compare the difference in the duration of antibiotic therapy, length of stay (LOS) and the change in antimicrobial cost between the recommendation acceptance and rejection groups. The Fisher's exact test was used to compare the difference in mortality and readmission between the recommendation acceptance and rejection groups. The significance level was set at $p<0.05$.

Ethics of the Study

Institutional approval to conduct this study was obtained from the head of department and hospital director before data collection. This study was also approved by Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia [KKM/NIHSEC/P19-2303(5)] (NMRR-19-2761-50838). All data obtained from the AMS database was kept confidential.

Calculation of Antimicrobial Cost

If an antimicrobial agent was discontinued

The change in cost = cost of the agent × cost saving days

If an antimicrobial agent was switched

The change in cost = (cost of the previous agent × cost saving days) – (cost of the new agent × cost saving days)

Cost saving days

- The number of days to the intended completion date of the antimicrobial agent.
- If the intended date of completion was not known, then the no. of days to the nearest multiple of 7 (e.g. 7 days, 14 days, 21 days etc.) was chosen based on the type of infection.

Note:

i. *A value with a positive sign indicated cost saving and that with a negative sign indicated cost wastage.*
ii. *The sign of the value obtained was reversed if the recommendations provided by the AMS team were not accepted.*

Figure 1: Calculation of the changes in antimicrobial cost with and without acceptance of the AMS team's recommendations

Results

Between January and June 2019, a total of 239 cases were reviewed by the AMS team. After excluding cases based on the exclusion criteria (33 continuation of existing antimicrobial regimen and 6 incomplete data), a total of 200 cases were included into the study. The total number of patients involved were 190 patients. Of those patients, 182 were reviewed once, 6 were reviewed twice and 2 were reviewed thrice, respectively, by the AMS team. Table 1 showed the five most encountered infections and reviewed antibiotics. Of the 200 cases, 150 (75.0%) were prescribed with one antibiotic, 45 (22.5%) were prescribed with two antibiotics and 5 (2.5%) were prescribed with three antibiotics. Almost one-half (49.5%) of the cases were reviewed from the Department of General Medicine followed by the Department of General Surgery (17.5%).

Table 2 showed the reasons of referral to the AMS team for review. Either one or two recommendations were made by the AMS team for each case referred. The number and types of the first recommendation made by the AMS team were summarised in Table 2. Fifteen cases (7.5%) had a second recommendation made. However, those recommendations were non-antibiotic-related such as recommendations to perform additional investigations, infection control measures or referral of complicated cases to the infectious diseases team. The overall acceptance of the recommendations made by the AMS team within 24 hours was 83.5% (167/200).

The cases in the study were followed up for 30 days from the first day of the recommendation made by the AMS team to determine their clinical outcomes. Of the 200 cases reviewed by the AMS team, 152 (76.0%) were discharged well, 10 (5.0%) were still hospitalized, 20 (10.0%) were transferred out to other healthcare facilities and 18 (9.0%) passed away. Of the 152 cases that were discharged well, 18 (11.8%) were re-admitted due to infection within 30 days of discharge. Of the 18 cases that died, 15 (83.3%) were due to infection.

Table 3 showed the comparison of clinical outcomes and antimicrobial cost savings between acceptance and rejection of AMS recommendations. Accepting the AMS recommendations did not affect the clinical outcomes in terms of the median duration of antibiotic therapy ($p=0.147$), length of stay ($p=0.849$), 30-day infection-related mortality rates ($p>0.95$) and 30-day infection-related readmission rates ($p=0.329$). However, it saved a total of RM9,579.82 (RM57.36 per case). Conversely, an extra cost of RM1,332.18 (RM40.37 per case) was spent as a result of rejecting the AMS recommendations ($p<0.001$).

Table 1: General characteristics of the reviewed cases (n=200)

Characteristic	n (%)
Five most encountered infections	
Community-acquired pneumonia	28 (14.0)
Hospital-acquired pneumonia	25 (12.5)
Surgical / traumatic wound infections	11 (5.5)
Urosepsis	10 (5.0)
Infective diarrhoea	8 (4.0)
Five most reviewed antibiotics	
Meropenem	44 (22.0)
Ceftriaxone	43 (21.5)
Piperacillin / tazobactam	14 (7.0)
Ceftazidime	14 (7.0)
Amoxicillin / clavulanic acid	13 (6.5)

Table 2: The reasons of referral to the AMS team and types of recommendation made (n=200)

Characteristic	n (%)
Reason	
Inappropriate choice of antibiotics based on hospital antibiotic guidelines	116 (58.0)
Inappropriate duration of therapy	21 (10.5)
Inappropriate combination of antibiotics	12 (6.0)
Inappropriate antibiotic chosen for definitive therapy	11 (5.5)
Others (infection was not present, inappropriate dosing regimen etc.)	40 (20.0)
Recommendation	
Discontinuation of the antibiotic regimen	83 (41.5)
De-escalation of the existing antibiotic regimen	91 (45.5)
Escalation of the existing antibiotic regimen	14 (7.0)
Conversion of the antibiotic regimen from parenteral route to oral route	9 (4.5)
Dose optimization of the antibiotic regimen	3 (1.5)

Table 3: Comparison of outcomes between the cases with acceptance and rejection of AMS recommendations

Variable	Recommendations accepted	Recommendations rejected	p-value
Mortality, n (%)			0.750 [a]
Yes	14 (10.1)	4 (12.5)	
No	124 (89.9)	28 (87.5)	
Infection-related mortality, n (%)			> 0.95 [b]
Yes	12 (85.7)	3 (75.0)	
No	2 (14.3)	1 (25.0)	
Infection-related readmission, n (%)			0.329 [c]
Yes	13 (10.5)	5 (17.9)	
No	111 (89.5)	23 (82.1)	
Duration of therapy (days), median (IQR)	11.00 (6.00, 16.75)	13.50 (7.25, 22.00)	0.147 [d]
Length of stay (days), median (IQR)	10.00 (6.00, 19.00)	9.50 (3.25, 25.75)	0.849 [d]
Cost savings (RM), median (IQR)	45.45 (14.37, 100.80)	-9.06 (-91.60, 11.16)	< 0.001 [e]

[a] Fisher's exact test, n=170; [b] Fisher's exact test, n=18; [c] Fisher's exact test, n=152; [d] Mann-Whitney test, n=152; [e] Mann-Whitney test, n=200

Discussion

Cases referred to the AMS team for ward rounds were mostly complicated and required infectious diseases physician assessment. Such cases were mainly referred due to inappropriate choice of antibiotics and duration of therapy or antibiotics not indicated. Hence, the types of recommendation made by the AMS team were mostly either discontinuation or de-escalation of the existing antibiotic regimen. Although prescribing

antibiotics for a longer duration than necessary or that were of broader spectrum than necessary could effectively treat the infections, such practices may result in the detrimental effects on ecological pressure and the emergence of antimicrobial resistance (2). Nevertheless, the AMS team occasionally recommended escalation of the existing antibiotic regimen based on patients' clinical presentation and the latest culture and sensitivity reports. Only 1.5% of the recommendations were dose optimisation of the antibiotic regimen. Such findings showed that the prescribers were generally aware of the dosing regimen of antibiotics in view of the availability of various materials of references. In the wards with ward pharmacists, they would have intervened prescriptions with inappropriate doses of antibiotics so that these cases need not be referred to the AMS team.

The overall acceptance of the recommendations made by the AMS team within 24 hours was 83.5%. A similar study conducted by Liew *et al*. in Singapore General Hospital showed that the acceptance of the recommendations by the primary management team was 77.8% (9). The recommendations made during AMS ward rounds, which were classified as a prospective audit and feedback strategy, were generally associated with a higher overall acceptance rate and less vulnerable to active rejection because the primary management team did not perceive the loss of autonomy in clinical decision and prescribing (10). The acceptance of recommendations was also voluntary rather than mandatory compared to other AMS strategies such as formulary restrictions and preauthorisation. This strategy had also provided opportunities for education and learning through case discussions and the feedback mechanism (10). This strategy also ensured individualisation of therapy, allowing patients' clinical characteristics and concomitant drugs to be considered (10).

There were no significant differences in the clinical outcomes, namely the median duration of antibiotic therapy, length of stay, 30-day mortality rates and 30-day infection-related readmission rates, between the recommendations acceptance and rejection groups in this study. In fact, such findings were heterogeneous among different studies conducted in different countries such as Africa, Hong Kong, Singapore, Spain and the United States (9,11-16) where some studies showed improvement in clinical outcomes among patients after accepting AMS interventions or recommendations while some studies showed no significant difference. However, direct comparison of the findings could not be made due to different study designs and different combination of AMS strategies used in these studies. Furthermore, the clinical outcomes of patients might be affected by many potential confounding factors such as the case mix of the patients, and it is therefore difficult to relate the impact of acceptance of AMS recommendations to the clinical outcomes.

The acceptance of AMS recommendations team was generally associated with significant antimicrobial cost savings in this study. Our findings were similar to those demonstrated in the studies conducted in Abu Dhabi, Hong Kong, Singapore, South Africa and Taiwan (13,15-18). AMS recommendations such as the discontinuation of existing antibiotic regimen reduced the duration of antibiotic therapy and therefore reduced the antimicrobial cost. De-escalation from a broad-spectrum antibiotic regimen to a relatively less costly narrow-spectrum antibiotic regimen also helped to reduce the antimicrobial cost.

The main objectives of the AMS activities are to ensure judicious use of antimicrobial agents and to minimise antimicrobial resistance. Some prescribers, however, were worried that accepting the AMS recommendations could adversely affect the clinical outcomes of their patients as they need to limit the use of broad-spectrum antimicrobial agents and reduce the duration of treatment (15). Some of them also believe that the AMS programme emphasises on the restriction of antimicrobial consumption and cost savings rather than improving the quality of patient care (15). Such an impression was not supported by the results of this study because accepting the AMS recommendations was not associated with unpredicted adverse clinical outcomes. Conversely, it was demonstrated that through rational selection and prescription of antibiotics, inappropriate consumption and expenditure could be reduced.

There are several limitations in this study. The retrospective nature of the study caused inadequate data to be collected. For example, we did not record the baseline demographic and clinical characteristics of the patients, which disallowed us to accurately assess the differences in the patient populations during data analysis. Secondly, we only assessed the clinical outcomes for inpatients within the same hospital. Hence, some of the important clinical outcomes, such as mortality in other facilities for patients who were transferred out from this hospital and readmissions to other healthcare facilities, were not captured. Thirdly, the government-approved unit price and the brand of the antibiotic might change with time and our data analysis was based on the unit price and brand on 1st November 2019. Therefore, the any changes in the unit prices and brands of antibiotics throughout the 6-month study period might cause discrepancy in terms

of cost savings estimation. Furthermore, the differences in purchasing agreements between institutions and variability in antimicrobial costs from country to country also did not allow any generalisation of our findings. Lastly, this study only assessed the impact of one type of AMS activity, namely the AMS ward rounds. A successful AMS bundle usually incorporates more than one activity or strategies. Hence, future studies should focus on the impact of different AMS strategies and to include other important outcomes such as improvement in appropriateness of antimicrobial prescriptions, infection-related hospitalisation rates, the prevalence of antimicrobial-related side effects and the impact of the AMS programme on antimicrobial susceptibility pattern.

Conclusion

The study demonstrated that the acceptance rate of recommendations provided by the AMS team during ward rounds was high. The acceptance of the recommendations had resulted in cost savings without compromising patients' clinical outcomes. This study highlighted the need of continuous efforts by the AMS team to ensure the sustainability of those outcomes in order to improve the quality of care of patients, to reduce healthcare costs and to minimise antimicrobial resistance.

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Conflict of interest statement:

All the authors have nothing to disclose regarding financial or personal relationships that may have a direct or indirect interest in the subject matter of this publication.

References

1. MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. Clin Microbiol Rev. 2005 Oct;18(4):638-56.
2. World Health Organisation. Global Antimicrobial Resistance Surveillance System (GLASS) report: Early implementation 2017-2018. Geneva, Switzerland: World Health Organisation; 2018.
3. Pharmaceutical Services Programme, Ministry of Health Malaysia. National antimicrobial guideline. 3rd ed. Selangor, Malaysia: Ministry of Health Malaysia; 2019.
4. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016 May;62(10):e51-77.
5. Ministry of Health Malaysia. Protocol on antimicrobial stewardship in healthcare facilities. Putrajaya, Malaysia: Ministry of Health Malaysia; 2014.
6. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017 Feb;2(2):CD003543.
7. Schuts EC, Hulscher MEJL, Mouton JW, Verduin CM, Stuart JWTC, Overdiek HWPM, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis. 2016 Jul;16(7):847-56.
8. Antimicrobial Stewardship Team, Hospital Raja Permaisuri Bainun. Antimicrobial guideline, Hospital Raja Permaisuri Bainun. 1st ed. Perak, Malaysia: Hospital Raja Permaisuri Bainun; 2017.
9. Liew YX, Lee W, Loh JC, Cai Y, Tang SS, Lim CL, et al. Impact of an antimicrobial stewardship programme on patient safety in Singapore General Hospital. Int J Antimicrob Agents. 2012 Jul;40(1):55-60.
10. Chung GW, Wu JE, Yeo CL, Chan D, Hsu LY. Antimicrobial stewardship: a review of prospective audit and feedback systems and an objective evaluation of outcomes. Virulence. 2013 Feb;4(2):151-7.
11. Teo J, Kwa AL, Loh J, Chlebicki MP, Lee W. The effect of a whole-system approach in an antimicrobial stewardship programme at the Singapore General Hospital. Eur J Clin Microbiol Infect Dis. 2012 Jun;31(6):947-55.

12. Güerri-Fernández R, Villar-García J, Herrera-Fernández S, Trenchs-Rodríguez M, Fernández-Morato J, Moro L, et al. An antimicrobial stewardship program reduces antimicrobial therapy duration and hospital stay in surgical wards. Rev Esp Quimioter. 2016 Jun;29(3):119-22.
13. Dunn K, O'Reilly A, Silke B, Rogers T, Bergin C. Implementing a pharmacist-led sequential antimicrobial therapy strategy: a controlled before-and-after study. Int J Clin Pharm. 2011 Apr;33(2):208-14.
14. Avdic E, Cushinotto LA, Hughes AH, Hansen AR, Efird LE, Bartlett JG, et al. Impact of an antimicrobial stewardship intervention on shortening the duration of therapy for community-acquired pneumonia. Clin Infect Dis. 2012 Jun;54(11):1581-7.
15. Ng CK, Wu TC, Chan WM, Leung YS, Li CK, Tsang DN, et al. Clinical and economic impact of an antibiotics stewardship programme in a regional hospital in Hong Kong. Qual Saf Health Care. 2008 Oct;17(5):387-92.
16. Boyles TH, Whitelaw A, Bamford C, Moodley M, Bonorchis K, Morris V, et al. Antibiotic stewardship ward rounds and a dedicated prescription chart reduce antibiotic consumption and pharmacy costs without affecting inpatient mortality or re-admission rates. PloS One. 2013 Dec;8(12):e79747.
17. El-Lababidi RM, Mooty M, Bonilla MF, Nusair A, Alatoom A, Mohamed S. Implementation and outcomes of an advanced antimicrobial stewardship program at a quaternary care hospital in the United Arab Emirates. J Am Coll Clin Pharm. 2019 Feb;2(5):515-23.
18. Lin YS, Lin IF, Yen YF, Lin PC, Shiu YC, Hu HY, et al. Impact of an antimicrobial stewardship program with multidisciplinary cooperation in a community public teaching hospital in Taiwan. Am J Infect Control. 2013 Nov;41(11):1069-72.

The Adequacy of Vancomycin Fixed-loading Dose Regimen in CRBSI for Patients Receiving Haemodialysis in Hospital Melaka

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Abstract

Introduction: Catheter-related bloodstream infection (CRBSI) is the major cause of mortality in haemodialysis patients. Vancomycin is the first-line treatment for Methicillin Resistant *Staphylococcus aureus* (MRSA). Inadequacy of vancomycin loading dose during initial treatment has been speculated as the cause of delayed achievement of vancomycin level within therapeutic range.

Objective: This study aimed to identify whether the vancomycin fixed-loading dose regime can produce vancomycin level within therapeutic range (15-20µg/mL) and to determine the total duration of vancomycin treatment required to achieve negative MRSA blood culture.

Methods: This was retrospective, non-randomised and one-year descriptive study. Patients with end-stage renal failure undergoing high-flux haemodialysis who were prescribed with vancomycin to treat MRSA CRBSI were included. The vancomycin fixed-loading dose protocol used was IV vancomycin 1,000mg on Day 1 and 750mg on Day 2 with the first vancomycin level monitoring on Day 3 or Day 4 (pre-haemodialysis sample). Subjects were stratified into three groups based on the first vancomycin level which were therapeutic level (15-20µg/mL), subtherapeutic level (<15µg/mL) and supratherapeutic level (>20µg/mL). Demographic details, descriptive data on duration to clearance of blood culture and the total duration of vancomycin treatment were collected and analysed.

Results: A total of 34 subjects were included (58.8% male, mean age 53.5 (standard deviation 12.9) years). Of these, 41.2% (n=14) had subtherapeutic, 35.3% (n=12) had supratherapeutic and 23.5% (n=8) had therapeutic vancomycin level. There was no difference in the duration to obtain clearance of MRSA from blood culture (p=0.660) and duration of vancomycin treatment (p=0.155) among these three groups of subjects.

Conclusion: This study showed that vancomycin fixed-loading dose protocol was unable to achieve first vancomycin level within the therapeutic range. Further clinical studies to identify suitable dosing regimen of vancomycin such as weight-based regimen in local population is warranted.

Keywords: fixed-loading dose, vancomycin, catheter-related bloodstream infection, Methicillin Resistant *Staphylococcus aureus*, haemodialysis

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Introduction

The prevalence of end-stage renal disease has been on an increasing trend and it is estimated to continue rising in the next decade. In 2010, around 2.6 million people received renal replacement therapy (RRT) worldwide, in which approximately 2 million people received dialysis (78%) and 0.6 million people received renal transplant. The number of people undergoing RRT was estimated to reach 5.4 million people by 2030 (1). In 2014, the total number of patients who required dialysis in Malaysia was 34,767 people and the annual death rate for patients with haemodialysis was 11.6% in year 2014 (2).

Catheter-related bloodstream infection (CRBSI) is common among end-stage renal failure (ESRF) patients undergoing haemodialysis via a catheter (3). With the incidence rate of 10% and mortality rate of 25%, CRBSI is a major complication resulting from long term use of catheter (4). The systemic progressions due to CRBSI include septic shock, multiorgan failure and deep-seated infection such as endocarditis and septic arthritis (5). One of the common pathogens found in CRBSI is staphylococcal species, with Methicillin Resistant *Staphylococcus aureus* (MRSA) being the emerging pathogen (6). Vancomycin is the first-line

treatment in CRBSI infection with MRSA (7). Trough level of vancomycin has been established to be within 15-20µg/mL to be able to achieve the area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio within 400 to 600 (8-9). The therapeutic range of AUC / MIC ratio is crucial to ensure adequate penetration of vancomycin into the infected sites and effective antibiotic exposure, hence improved clinical outcome and reduced mortality rate (10).

Vancomycin dosing in patients with ESRF who receive haemodialysis, however, is poorly defined currently with different approaches in initial loading dose being proposed for fast attainment of therapeutic vancomycin level (11). The delay in achieving therapeutic vancomycin level has been linked to the emergence of Vancomycin-intermediate *Staphylococcus aureus* (VISA) and Vancomycin-resistant *Staphylococcus aureus* (VRSA) infections, as well as treatment failure in MRSA bacteraemia from CRBSI (12).

The current protocol used in Hospital Melaka for CRBSI in haemodialysis patients is a fixed-loading dose of intravenous (IV) vancomycin 1,000mg on Day 1 followed by 750mg on Day 2. To ensure the clinical outcomes of our patients, it is highly crucial to investigate the effectiveness of this protocol. Therefore, our study aimed to identify whether the current vancomycin fixed-loading dose regime can produce vancomycin levels within the therapeutic range of 15-20µg/mL in ESRF patients receiving stable intermittent high-flux haemodialysis and to determine the total duration of vancomycin treatment required to achieve negative MRSA in blood culture.

Methods

This was a retrospective, non-randomised study conducted in Hospital Melaka, Malaysia. The study was approved by the Hospital Research Review Committee (HRRC) and the Ministry of Health (MOH) of Malaysia Medical Research & Ethics Committee (MREC). The study population involved of this study was admitted ESRF patients on regular high-flux haemodialysis who received vancomycin due to MRSA CRBSI during their stay in the hospital. The diagnosis of MRSA CRBSI was based on the blood culture from peripheral, red lumen, and blue lumen. Patients were excluded from the study if they did not complete the haemodialysis session while on vancomycin treatment and age below 18-years-old.

The vancomycin fixed-loading dose protocol used in Hospital Melaka was IV vancomycin 1,000mg on Day 1 followed by 750mg on Day 2. The first blood sampling for therapeutic drug monitoring (TDM) of vancomycin was conducted on Day 3 or Day 4 as pre-haemodialysis sample (Figure 1). The research team was alerted when patients were prescribed with vancomycin by the nephrologists and monitoring of serum vancomycin level was conducted for patients who were treated with vancomycin. The vancomycin was administered intravenously in normal saline and infused during the last hour of dialysis if the vancomycin dosing schedule fall on the haemodialysis day. The vancomycin serum concentrations were analysed in the Biochemistry Unit, Department of Pathology of Hospital Melaka using Viva-Pro E Siemens (immunoassay method). To evaluate this fixed-loading dose protocol, data on patient demographics, types of haemodialysis, duration of haemodialysis sessions, culture and sensitivity test data, dosing details of vancomycin, and serum concentration of vancomycin were collected using a pre-designed data collection form for the period of one year, from 1 December 2017 to 31 December 2018.

The sample size was calculated using Raosoft, an online calculator software for power analysis. All power analyses are assuming an alpha=0.05 with 95% power. From the calculation, the sample size required for this study was 30 patients. To cater for incomplete medical records, an additional 20% was added to the required sample sizes. The final sample size targeted was 36 patients.

The subjects were categorised into three groups based on their first TDM vancomycin level, which were subtherapeutic level (<15µg/mL), within therapeutic range (15-20µg/mL) and supratherapeutic level (>20µg/mL). The first blood culture monitoring was conducted after 3 days upon initiation of vancomycin treatment and repeated subsequently every 3 days until obtaining negative MRSA in the blood culture. These three groups of patients were compared in terms of duration to the clearance of blood culture from MRSA and the total duration of vancomycin treatment using one-way ANOVA test. Demographic data gathered were analysed using descriptive statistics in the form of frequency and percentages (mean ± SD or median ± IQR). All statistical analyses were performed using IBM Statistical Package for Social Science (IBM SPSS) programme version 22.0 and Microsoft Excel version 2013.

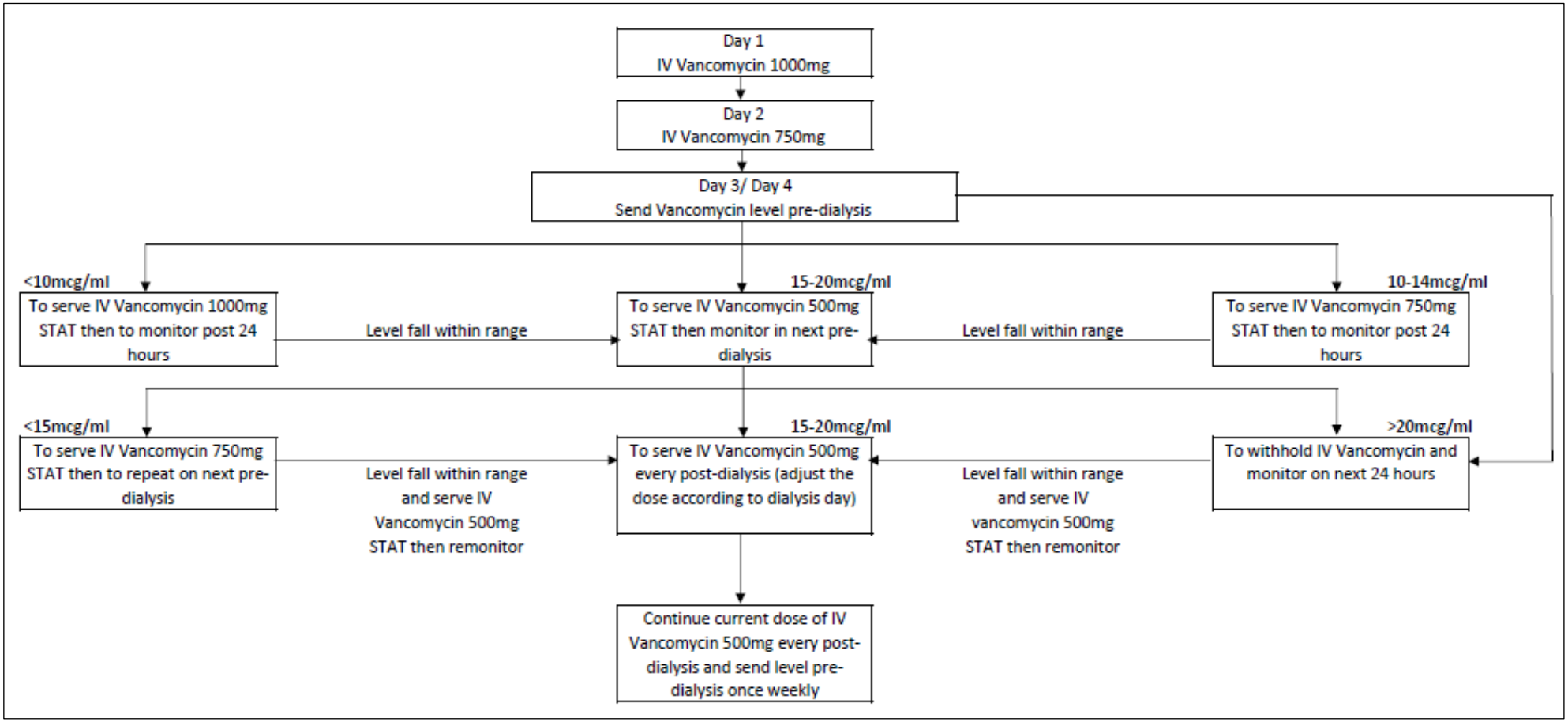

Figure 1: Vancomycin fixed-loading dose protocol in Hospital Melaka

Results

Thirty-four patients were included in this study instead of 36 targeted. The recorded adverse events of vancomycin were infusion-related side effects such as skin itchiness and redness if the rate of infusion was too fast. However, no patient was withdrawn from the study. The patient characteristics were shown in Table 1. The mean age of our patients was 53.5 (standard deviation (SD)12.9) years old, with 58.8% male patients. The common comorbidities of our patients were hypertension (88.2%) and diabetes (67.6%). In terms of the type of dialysis port used, most of the patients (61.8%) had internal jugular catheter (IJC) and femoral line(35.3%).

From the total of 34 patients, only eight (23.5%) patients achieved vancomycin level within the therapeutic range of 15-20µg/mL, 14 patients (41.2%) had subtherapeutic vancomycin level of <15µg/mL while 12 patients (35.3%) had supratherapeutic vancomycin level >20µg/mL. The mean duration for clearance of blood culture for the therapeutic range group was 12.9 (SD 6.5) days, subtherapeutic range group was 10 (SD 7.5) days and supratherapeutic range group was 10.4 (SD 10.2) days with no significant differences among these three groups (p =0.660).

The mean duration of vancomycin treatment for our patients who achieved therapeutic range 15-20µg/mL with the first TDM level was 25.8 (SD 19.8) days, group with subtherapeutic range was 32.7 (SD 14.4) days and group with supratherapeutic range was 20.9 (SD 12.4) days with no significant differences among these three groups (p =0.155) (Table 2).

Table 1: Patient demographics for vancomycin regimen in ESRF patients (n=34)

Variable	Value
Age, year, mean (SD)	53.5 (12.9)
Gender, n (%)	
Male	20 (58.8)
Female	14 (41.2)
Race, n (%)	
Malay	29 (85.3)
Chinese	4 (11.8)
Indian	1 (2.9)
Weight, kg, median (IQR)	63.5 (18)
Comorbidities, n (%)	
Hypertension	30 (88.2)
Diabetes	23 (67.6)
Dyslipedemia	4 (11.8)
Others *	21 (61.8)
Type of catheter, n (%)	
IJC	21 (61.8)
Femoral	12 (35.3)
FIstula	1 (2.9)

* liver cirrhosis, shoulder arthritis, gouty arthritis, young parkinsonism and glaucoma
Abbreviation: IJC - interjugular catheter; IQR - interquartile range; SD - standard deviation.

Table 2: Duration of vancomycin treatment and duration required to obtain first MRSA negative culture (n=34)

First vancomycin level	n (%)	Duration to MRSA negative culture, day, mean (SD)	F-statistic (df) [a]	P-value	Duration of vancomycin treatment, day, mean (SD)	F-statistic (df) [a]	P-value
<15µg/mL	14 (41.2)	12.9 (6.5)	0.421 (2,31)	0.660	32.7 (14.4)	1.983 (2,31)	0.155
15-20µg/mL	8 (23.5)	10.0 (7.5)			25.8 (19.8)		
>20µg/mL	12 (35.3)	10.4 (10.2)			20.9 (12.4)		

[a] One-way ANOVA

Discussion

Our analysis showed that 76.5% of the patients did not achieve first vancomycin level that was within the therapeutic range, with 41.2% had vancomycin level that was below while 35.3% was above the therapeutic range of 15-20µg/mL. This indicated that the current loading dose protocol was not able to attain targeted therapeutic vancomycin levels. The Infectious Diseases Society of America (IDSA) 2009 guidelines had established that the ideal duration for clearance of MRSA bacteraemia is 72 hours for the optimal clinical outcome. Therefore, vancomycin level needs to be within the therapeutic range on Day 3 or Day 4 as it is the surrogate marker for vancomycin exposure which translates to clinical progression, as therapeutic vancomycin level associates with better clinical outcome (7). In a study using a loading dose 1g, followed by a subsequent maintenance dose of 500mg or 1g, the targeted trough level of >15µg/mL was only 25.2% (13). Our study showed a similar result with only 23.5% of patients achieving the target range. The recent guideline suggested that weight-based vancomycin dosing appeared to be superior to fixed-dose dosing as the weght-based dosing considers patient's body size and may decrease the risk of subtherapeutic level on the first day of therapy (14). The National Antibiotic Guideline 2014 published by MOH Malaysia suggested vancomycin loading dose at 15-20mg/kg and then subsequently 500mg to 1000mg after each dialysis session (15). Furthermore, some studies demonstrated that the targeted vancomycin trough levels were more rapidly obtained by using a weight-based loading dose of 20mg/kg (11,16).

Our analysis showed that the first vancomycin level did not significantly affect the duration for clearance of MRSA from the blood culture and the total duration of vancomycin treatment. Factors that could have been significantly affecting these two clinical outcomes were the removal of the infected catheter or haemodialysis port, the involvement of deep-seated infection sites, and the presence of MRSA skin colonizer (17). However, our study showed that higher first vancomycin level did not associate with faster clearance of MRSA bacteraemia nor shorter duration of vancomycin treatment. Although the subtherapeutic level of vancomycin has not shown to affect clinical outcome, it is still important to maintain vancomycin trough at a minimum level of 10µg/mL to prevent treatment failure (8).

Vancomycin is a drug with high inter-individual and intra-individual variations in its pharmacokinetic parameters (18). Hence it is important to establish a loading dose protocol that is specific to the local population as an adaptation from other populations will not be suitable for drugs with a narrow therapeutic index. Vancomycin is substantially removed in patients who receive high-flux haemodialysis (19). Thus, the current fixed loading dose of vancomycin may not be suitable for patients undergoing high-flux haemodialysis in Hospital Melaka and more frequent dosing of vancomycin is needed to maintain the target serum concentrations.

The limitations of this study include the small sample size which might affect the significant effect of first vancomycin level on clinical outcomes. This study was also unable to determine whether the persistent subtherapeutic or supratherapeutic level of vancomycin will significantly affect the clinical outcomes. Nevertheless, the findings of this study would serve as a baseline to identify the best vancomycin initiation regimen for patients receiving haemodialysis. Further clinical studies can be carried out to identify other suitable dosing of vancomycin, such as the weight-based regimen, for patients undergoing haemodialysis with CRBSI.

Conclusion

Current vancomycin fixed-loading dose protocol for haemodialysis patients with MRSA induced CRBSI was unable to achieve therapeutic vancomycin level on Day 3 or Day 4 of vancomycin treatment. However, it was found that the first vancomycin level was not significantly associated with the clinical outcomes of CRBSI infection and the duration of vancomycin treatment.

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Conflict of interest statement

No external funding was received and the authors declared no conflict of interest.

References

1. Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: A systematic review. *Lancet*. 2015;385(9981):1975-1982.
2. Malaysian Society of Nephrology. 22nd Report of the Malaysian Dialysis & Transplant Registry 2014. Kuala Lumpur: Malaysian Society of Nephrology; 2015.
3. Hoen B, Paul-Dauphin A, Hestin D, Kessler M. EPIBACDIAL: a multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. *J Am Soc Nephrol*. 1998;9(5):869-876.
4. Fletcher S. Catheter-related bloodstream infection Authors. *Contin Educ Anaesth Crit Care Pain*. 2005;5(2):49-51.
5. Vandecasteele SJ, Boelaert JR, De Vriese AS. Staphylococcus aureus infections in hemodialysis: What a nephrologist should know. *Clin J Am Soc Nephrol* 2009;4(8):1388-1400.
6. Gafor AHA, Ping PC, Abidin AFZ, et al. Antibiogram for haemodialysis catheter related bloodstream infections. *Int J Nephrol* 2014;629459.
7. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection:2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009;49(1):1-45.
8. Rybak MJ, Lomaestro BM, Rotscahfer JC, et al. Vancomycin Therapeutic Guidelines: A Summary of Consensus Recommendations from the Infectious Diseases Society of America, the American Society of Health- System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin Infect Dis* 2009;49(3):325-327.
9. Vandecasteele SJ, De Vriese AS. Recent changes in vancomycin use in renal failure. *Kidney Int* 2010;77:760-764.
10. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by Infectious Disease Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis* 2011;52(3):285-292.
11. Vandecasteele SJ, De Vriese AS. Vancomycin dosing in patients on intermittent hemodialysis. *Semin Dial* 2011;24:50-55.
12. Jung Y, KH S, Je C, et al. Area under the concentration-time curve to minimum inhibitory concentration ratio as a predictor of vancomycin treatment outcome in methicillin-resistant Staphylococcus aureus bacteraemia. *Int J Antimicrob Agents* 2014;43(2);179-183.
13. Pai AB, Pai MP. Vancomycin dosing in high flux hemodialysis: a limited sampling algorithm. *Am J Health Syst Pharm* 2004; 61:1812–1816.
14. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin: A revised consensus guideline and review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Disease Society and the Society of Infectious Disease Pharmacists. *ASHP* 2019.
15. National antibiotic guidleline 2014. 2nd ed. Ministry of Health of Malaysia: Pharmacy Practice & Development Division; 2014.
16. Barth RH, DeVincenzo N. Use of vancomycin in high-flux hemodialysis: experience with 130 courses of therapy. *Kidney Int* 1996; 50: 929–936.
17. Heil EL, Claeys KC, Mynatt RP, et al. Making the change to area under the curve-based vancomycin dosing. *Am J Health-Syst Pharm* 2018;75:e828-37.
18. Matzke GR, McGory RW, Halstenson Ce, et al. Pharmacokinetics of vancomycin in patients with various degrees of renal function. *Antimicrob Agents Chemother* 1984;25:433-437.
19. Quale JM, O'Halloran JJ, DeVincenzo N, Barth RH. Removal of vancomycin by high-flux 1578 hemodialysis membranes. *Antimicrob Agents Chemother* 1992;36(7):1424-1426.

Vancomycin Initial Dosing in Adult Dialysis Patients in a Tertiary Care Hospital (VIDAD)

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Abstract

Introduction: Vancomycin is the drug of choice to treat methicillin-resistant *Staphylococcus aureus* infections in hospitalised patients. Guideline recommends a loading dose (LD) of vancomycin to rapidly achieve the targeted therapeutic concentration. However, in dialysis population there are conflicting opinions on whether LD is required.

Objective: The aims of the study were to identify the weight-based initial LD of vancomycin and time-to-first-sampling (TTFS) to achieve targeted serum vancomycin concentration (SVC) and the potential contributory factors affecting SVC at first sampling.

Methods: This was a prospective observational study conducted at a tertiary hospital over three months in 2016. All end-stage renal disease (ESRD) patients aged 18 years old and above, on dialysis and received intravenous vancomycin were included. Eligible patients were identified from the therapeutic drug monitoring (TDM) request forms. Demographic and clinical data were obtained from the medical records. Target SVC range was 15.0-20.0mg/L.

Results: Vancomycin dose prescribed ranged from 1,000-2,000mg with mean LD of 20.2 (standard deviation (SD) 5.8) mg/kg. This study found that the vancomycin TDM sampling was done either at TTFS less than 24 hours (49%) or 24-48 hours (51%). Only 18.4% of patients achieved the target SVC, while 65.3% were sub-therapeutic and 16.3% were above target. Factors that significantly influenced the SVC include LD ($p<0.001$) and TTFS ($p=0.003$). Target SVC was achieved in ESRD patients on dialysis when LD of 15.0-25.0mg/kg given and sampled at TTFS <24 hours. The linear regression equation describing the association is SVC = 0.616 (LD) - 0.213 (TTFS) + 7.487.

Conclusion: Weight-based LD and TTFS are important predictors that need to be considered when dosing vancomycin in dialysis patients to ensure its therapeutic effectiveness. LD of 20-25mg/kg is likely to achieve the target SVC at TTFS of 24 hours. The study findings may serve as a dosing guide of vancomycin in ESRD patients.

Keywords: vancomycin, dialysis, loading dose, TDM, sampling time

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are common infections in hospitalised patients. The prevalence of MRSA infections in the hospitals worldwide are high and MRSA rates of more than 50% were reported in the Asian and American continent (1). Meanwhile, local data in Malaysia showed increasing trend of MRSA infections, with 17% in 1986 to 44.1% in 2007 (2,3). Although MRSA can cause infections in multiple sites of body, the major concern has always been MRSA bacteraemia. This is because it can often progress to complicated metastatic MRSA infection, such as infective endocarditis, septic arthritis, osteomyelitis and multifocal collections or abscesses (4,5). In addition, complicated MRSA infections were associated with poorer clinical outcomes (6). The risk of MRSA infections among haemodialysis patients was 45.2 per 1,000 population compared to 0.2-0.4 per 1,000 population among the general population. This means that the risk of MRSA infections among haemodialysis patients was 100-fold higher (7).

There are a few antibiotics with anti-MRSA activities, including vancomycin, daptomycin, linezolid,

ceftaroline, teicoplanin, trimethoprim-sulfamethoxazole, rifampicin and fusidic acid. Although the Infectious Diseases Society of America guidelines recommended the use of intravenous vancomycin or daptomycin to treat MRSA bacteraemia, vancomycin has remained as the drug of choice in Malaysia as it is readily available and cheaper (8). Therapeutic drug monitoring (TDM) of vancomycin is important to ensure that sufficient drug concentration is achieved in the body to provide good bactericidal effect (9). It is thus crucial to achieve the recommended vancomycin serum trough concentrations of 15–20mg/L for maximal efficacy (9). This will improve drug penetration and increase the probability of clinical success (9). Recent study found that the guidelines advocated the practice of giving a loading doses (LD) of vancomycin to rapidly attain the therapeutic concentrations. The LD of 15-20mg/kg in patients with normal renal function and 25-30mg/kg in seriously ill patients were recommended (4,9).

In the dialysis population, however, there are conflicting opinions on whether a loading dose is required. Matzke *et al.* suggested LD of 25mg/kg regardless of renal function (10). On the other hand, Matsumoto *et al.* found that a vancomycin loading dose is required to promptly achieve targeted serum vancomycin concentration (SVC) because vancomycin has markedly prolonged plasma half-life in patient with renal dysfunction. However, no recommendation for the exact loading dose in dialysis patients was given to date (11). This may lead to the variations in vancomycin dosing among dialysis patient, which may affect the clinical outcomes. The current practice in Hospital Kuala Lumpur (HKL) is to use a standard initial dosing of 1,000mg for all dialysis patients. Even though this one-size-fits-all dosing offers convenience of dosing, the effectiveness is questionable. An internal audit by HKL Pharmacy Department revealed that almost 50% of SVC taken after the initial dose were sub-therapeutic at lower than 15mg/L. It was also noted that the SVC varied substantially among dialysis patients who received this standard LD of 1,000mg (12).

Renal function shown by creatinine clearance and residual renal function is known to affect the SVC. This is because vancomycin is primarily excreted through the kidney and therefore, changes in renal function would affect its clearance, indirectly influencing the SVC. In addition, renal replacement therapies such as haemodialysis, sustained low-efficiency dialysis (SLED) and peritoneal dialysis (PD) were shown to affect the vancomycin clearance (13). The dialysability of a drug varies based on the molecular weight, protein binding, type of dialysis membrane and mode of dialysis. The lower the molecular weight and protein binding, the higher the dialysability of the drug (14). Since the protein binding properties of vancomycin is reduced further to 20% in renal impairment, its clearance via dialysis is increased especially in high flux membrane haemodialysis (14,15). In addition, dialyser membrane surface area and blow flow rate would also affect the extraction of vancomycin during the dialysis (14). El Nekidy *et al.* reported weight-based LD, age and time between administration of LD and dialysis as significant factors affecting SVC among end-stage renal disease (ESRD) patients on haemodialysis (16). Another study by Oyaert *et al.* found albumin to be a significant predictor of unbound vancomycin concentration, regardless of patient's renal function (17).

There is limited evidence on the optimal method of vancomycin initial dosing among ESRD patients on dialysis, especially in the local setting. Therefore, it is important to assess the initial dosing of vancomycin, attainments of target SVC and the factors influencing SVC among this population. The aims of this study were to identify the weight-based initial dose of vancomycin and time-to-first-sampling (TTFS) to achieve targeted serum vancomycin concentration (SVC) among ESRD patients on dialysis, and to determine the factors affecting SVC at first sampling.

Methods

This was a prospective observational study at the nephrology and general medical wards of HKL, a tertiary hospital with nephrology specialty. The study was conducted from December 2015 to February 2016. Hospitalised ESRD patients aged 18 years old and above who were undergoing dialysis and receiving intravenous vancomycin during the admission as an empirical and/or definitive treatment for any infection were included in the study. Patients who were critically ill and admitted to the intensive care units or high-dependency wards, renal transplant patients, those who require continuous renal replacement therapy or cycler peritoneal dialysis and those who received vancomycin therapy without sampling of serum vancomycin level following the initial dose were excluded.

Universal sampling method was applied where all patients fulfilling the inclusion and exclusion criteria during the study period were included in the study. Initially, eligible patients were identified from the vancomycin TDM request forms sent to the pharmacy. Then, the identified patients' medical records were screened. Information such as socio-demographic, co-morbidities, dialysis prescriptions, vancomycin dosing and administration records were collected. Subsequently, TTFS and SVC following the initial dose

of vancomycin were obtained from the TDM forms. Data were collected using a structured data collection form.

Data analyses were conducted using IBM® SPSS® Statistics Version 20. Weight-based initial dose or LD of vancomycin prescribed, pattern of TTFS and the resulting SVC were analysed descriptively. Categorical data were reported in frequency (n) and percentage (%), while continuous variables were reported as mean and standard deviation (SD). Multiple linear regression was applied to determine the factors affecting the SVC after initial dose of vancomycin on first TDM sampling. The variables were included in the initial simple linear regression analysis, where those with $p<0.25$ were selected to be included in the multiple linear regression model. Final results were presented as regression coefficient, b (95% confidence interval (CI)), where p-value of <0.05 indicates statistical significance.

This study was conducted as per ethical standards of the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia. Ethics approval was obtained from the MREC (NMRR-15-2428-25002) prior to the commencement of the study. Patient's privacy and confidentiality was protected throughout the data collection, analyses, interpretation and publication processes as there were no patient identifiable data included.

Results

Demographic and Clinical Characteristics

During the study period, there were a total of 49 patients fulfilling the eligibility criteria and included in the study. The demographic and clinical characteristics were described in Table 1. The mean age of patients was 57.3 (SD 13.9) years old, where majority were male (65.3%) and of Malay ethnicity (73.5%). Approximately 80-85% of them had diabetes mellitus and hypertension. The mean creatinine clearance was 10.8 (SD 4.1) mL/min, where mostly (67.3%) had poor residual renal function. Mostly, vancomycin was prescribed for bloodstream infections (87.8%) as definitive therapy for MRSA infections (69.4%).

Initial Dose of Vancomycin and SVC

Initial dose of vancomycin administered ranged from 1,000 to 2,000mg, in which majority of the patients (59%) received 1,000mg and 22% received 1,500mg. The overall mean initial dose and weight-based LD were 1,227.6 (SD 300.5) mg and 20.2 (SD 5.8) mg/kg respectively.

The overall mean TTFS was 26.2 (SD 12.8) hours, where the samples of 49% patients were taken at less than 24 hours while the others were taken between 24 to 48 hours after the initial dose of vancomycin. Meanwhile, the overall mean SVC was 14.11 (SD 7.11) mg/L. Only 18.4% of patients achieved the targeted SVC of 15.0-20.0 mg/L, while 65.3% had sub-therapeutic and 16.3% had supra-therapeutic levels. The patterns of TTFS and LD given according to the SVC range achieved were summarised in Table 2. Figure 1 showed the mean SVC according to the LD and TTFS. Based on Figure 1, the SVC increased as the LD increased, at both TTFS of <24 hours and 24-48 hours. Despite that, the SVC was not within the targeted range at TTFS 24-48hours for any LD. In contrast, LD of 15.0-25.0mg/kg could achieve SVC of 15.0-20.0mg/L at TTFS <24 hours.

Factors Affecting SVC

Haemodialysis was a common mode of dialysis (81.6%) among the study population, while other dialysis were PD and SLED. 53% of the patients had at least one dialysis session between the initial dose and TDM sampling as shown in Table 1. Majority of patients (44.9%) who had pre-TDM dialysis had sub-therapeutic SVC as shown in Table 2, However, this group of patients also received a lower LD.

The factors affecting SVC following the administration of the initial dose of vancomycin among ESRD patients on dialysis were shown in Table 3. Simple linear regression performed at the initial step found that variables such as LD, TTFS, initial dose, creatinine clearance, age, type and number of dialysis to have $p<0.25$. These variables were included in the multiple linear regression analysis. However, only LD and TTFS was found to be significant independent factors that affects SVC in this population as shown by the model. A significant model ($p<0.001$) with r^2 value of 0.346 found a linear relationship between LD, TTFS and the resulting SVC achieved. When the LD is increased by 1mg/kg, the SVC will increase by 0.616mg/L (95% CI 0.317, 0.916; $p<0.001$). Meanwhile, when the TTFS is delayed by an hour, the SVC will drop by 0.213mg/L (95% CI -0.349, -0.077; $p=0.003$).

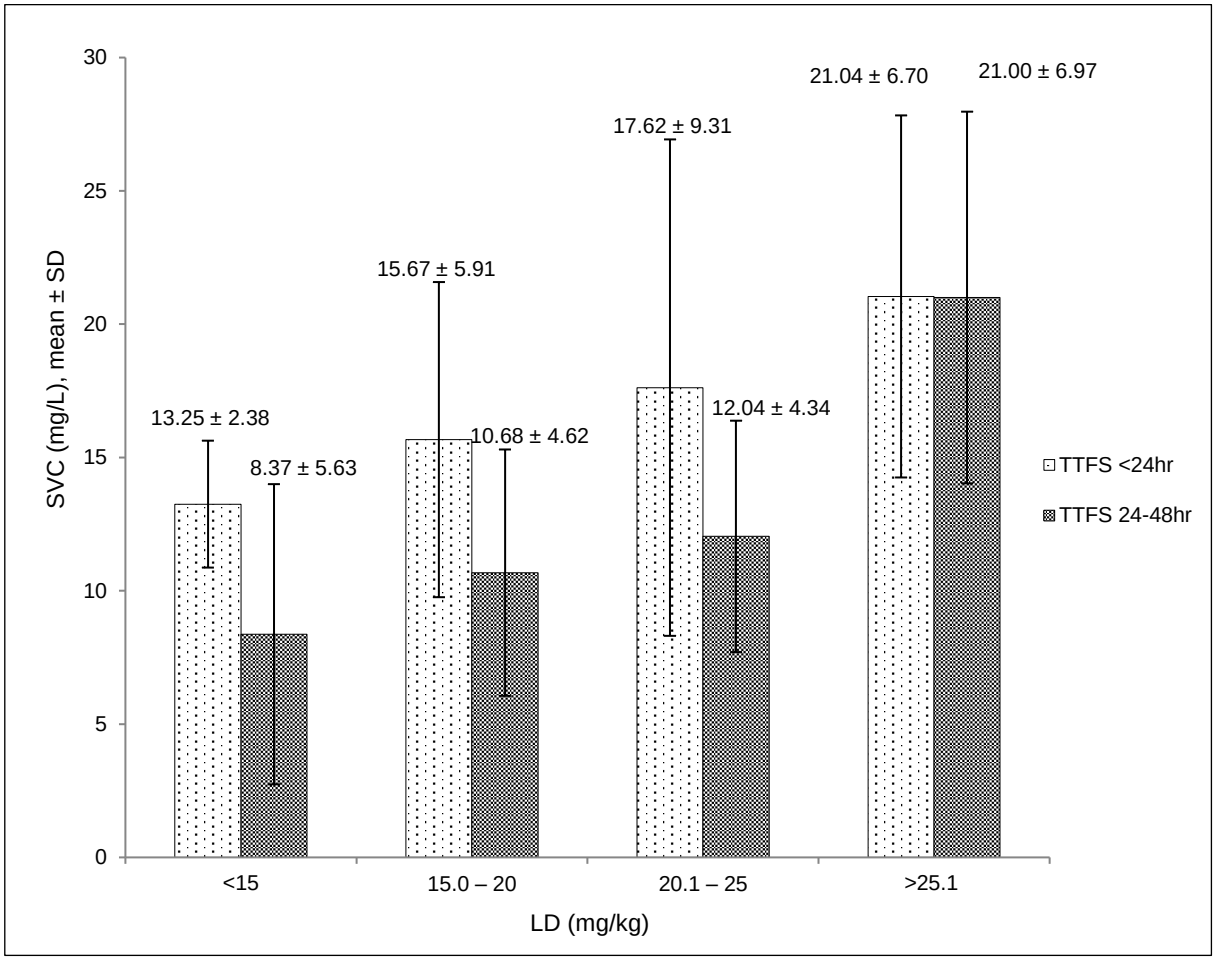
All the other variables; initial dose, creatinine clearance, age, albumin, residual renal function, type and number of dialysis were not significantly associated with the change in SVC. Based on the regression analysis, a linear equation showing the association between these factors were computed; SVC (mg/L) =

0.616 (LD in mg/kg) - 0.213 (TTFS in hours) + 7.487. Figure 2 showed the nomogram plotted based on the linear equation which can be used to predict the SVC. Based on the nomogram, a LD of 20-25 mg/kg and TTFS 24 hours after vancomycin administration would be able to produce an optimal initial SVC between 15.0 to 20.0 mg/L.

Table 1: Patient demographic and clinical characteristics (n=49)

Characteristics	Value
Age, year, mean (SD)	57.3 (13.9)
Age, year, n (%)	
≥ 60	27 (55.1)
< 60	22 (44.9)
Weight, kg, mean (SD)	62.7 (12.0)
Gender, n (%)	
Male	32 (65.3)
Female	17 (34.7)
Race, n (%)	
Malay	36 (73.5)
Chinese	2 (4.1)
Indian	9 (18.4)
Others	2 (4.1)
Comorbidities, n (%)	
Diabetes mellitus	42 (85.7)
Hypertension	41 (83.7)
Ischaemic Heart Disease	11 (22.4)
Heart failure	2 (4.1)
Malignancy	2 (4.1)
Serum creatinine, mg/L, mean (SD)	7.07 (3.23)
Creatinine clearance, mL/min, mean (SD)	10.8 (4.1)
Serum albumin, g/dL, mean (SD)	28.3 (6.2)
Residual renal function, n (%)	
≤100mL	33 (67.3)
>100mL	16 (32.7)
Type of dialysis, n (%)	
HD	40 (81.6)
PD	4 (8.2)
SLED	5 (10.2)
Number of dialysis session pre TDM, n (%)	
None	23 (46.9)
1 session	24 (49.0)
2 sessions	2 (4.1)
Indication of vancomycin, n (%)	
Empirical	15 (30.6)
Definitive	34 (69.4)
Site of infection, n (%)	
Bloodstream	43 (87.8)
Skin and soft tissue	2 (4.1)
Peritonitis	2 (4.1)
Urinary tract	1 (2.0)
Spine	1 (2.0)

Abbreviation: HD - haemodialysis, PD - peritoneal dialysis, SD – standard deviation, SLED - sustained low-efficiency dialysis, TDM – therapeutic drug monitoring



Abbreviation: LD - loading dose, TTFS - time-to-first-sampling, SVC - serum vancomycin concentration, SD – standard deviation

Figure 1: SVC according to LD and TTFS

Table 2: Vancomycin dosing according to the SVC (n=49)

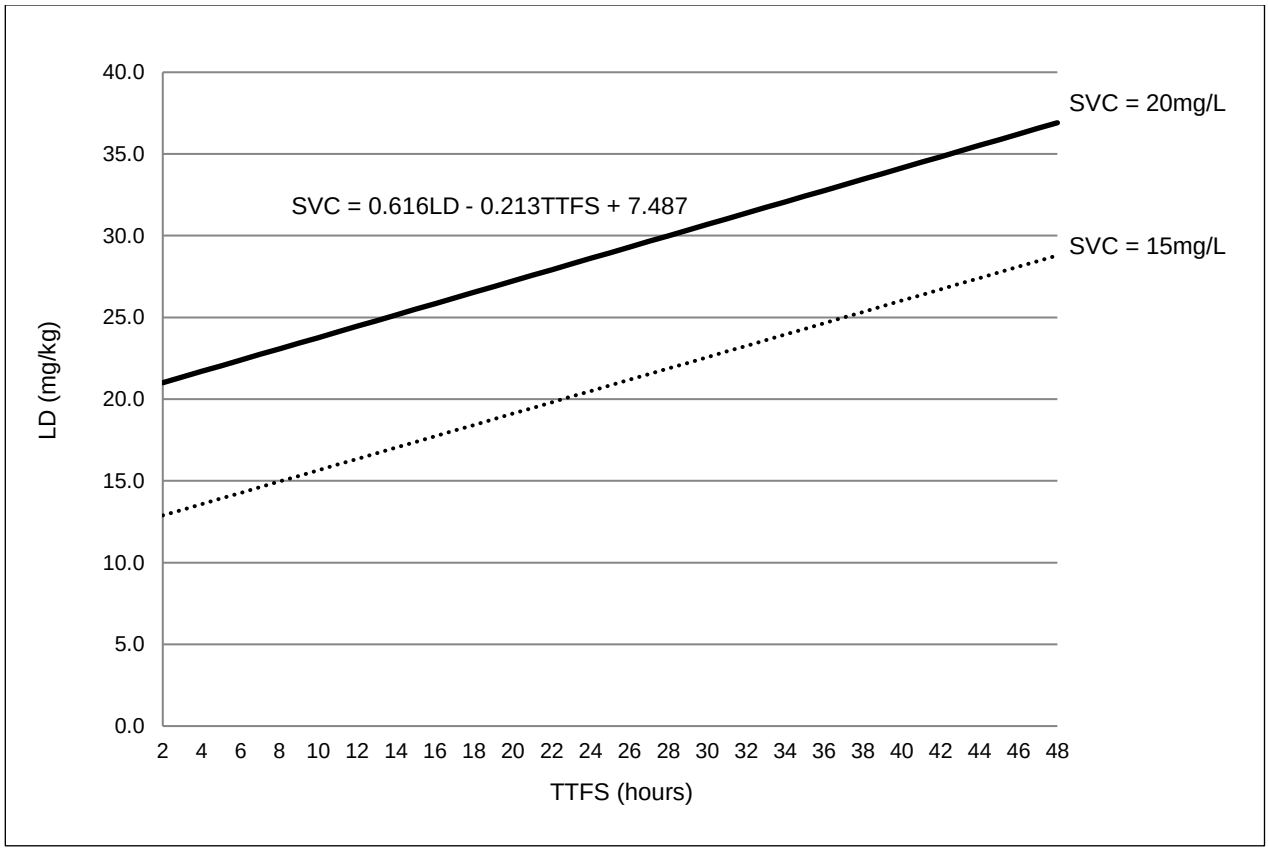
	SVC, mg/L		
	<15.0	15.0-20.0	>20.0
Total number of patients, n (%)	32 (65.3)	9 (18.4)	8 (16.3)
Number of patients who had dialysis prior to TDM, n (%)	22 (44.9)	1 (2.0)	3 (6.1)
SVC, mg/mL, mean (SD)	10.17 (3.5)	17.37 (1.6)	26.19 (6.2)
LD, mg/kg, mean (SD)	19.0 (5.4)	20.9 (4.3)	24.1 (7.4)
TTFS, hour, mean (SD)	28.5 (12.7)	22.5 (12.3)	21.2 (13.1)

Abbreviation: LD - loading dose, TDM – therapeutic drug monitoring, TTFS - time-to-first-sampling, SVC - serum vancomycin concentration, SD – standard deviation

Table 3: Factors affecting the SVC following initial dose of vancomycin among ESRF patients on dialysis (n=49)

Factors	Simple Linear Regression		Multiple Linear Regression	
	b^{ψ} (95% CI)	p-value	b^{ϵ} (95% CI)	p-value
LD	0.542 (0.218, 0.867)	0.002	0.616 (0.317, 0.916)	<0.001*
TTFS	-0.156 (-0.312, 0.000)	0.050	-0.213 (-0.349, -0.077)	0.003*
Initial dose	0.008 (0.002, 0.015)	0.012		
Number of dialysis session pre TDM	-3.442 (-6.913, 0.029)	0.052		
Creatinine clearance	-0.364 (-0.862, 0.134)	0.148		
Type of dialysis	-2.256 (-5.520, 1.007)	0.171		
Age	-0.093 (-0.240, 0.054)	0.209		
Albumin	0.049 (-0.289, 0.389)	0.771		
Residual renal function	0.007 (-3.033, 3.047)	0.996		

Abbreviation: ClCr – creatinine clearance, LD – loading dose, TDM – therapeutic drug monitoring, TTFS – time-to-first-sampling, SVC – serum vancomycin concentration, CI – confidence interval
Note: All variables except albumin and residual renal function were included in the multiple linear regression analysis.
b^{ψ} Crude regression coefficient; b^{ϵ} Adjusted regression coefficient; * p<0.05 denotes statistical significance.
Stepwise multiple linear regression method applied. Model assumptions are fulfilled.
Model is significant, p<0.001
No interactions and multi-collinearity detected
Coefficient of determination, $r^2 = 0.346$, constant = 7.487



Abbreviation: LD - loading dose, TTFS - time-to-first-sampling, SVC - serum vancomycin concentration

Figure 2: Nomogram predicting the LD and TTFS for SVC 15-20mg/L

Discussion

In this study, the initial vancomycin dose received by the patients ranged from 1,000mg to 2,000mg with LD 20.2 (SD 5.8) mg/kg. No specific weight-based calculations or dosing chart were used to determine the initial dose among our patients. El Nekidy *et al.* reported similar mean LD, although the range of the actual dose given was 1,000 – 3,000mg. This could be due to the higher mean weight of the patients included in their study compared to this study. In addition, El Nekidy *et al.* also used a pre-set dosing chart based on the body weight (LD 17.5mg/kg rounded to the nearest kilogram) to determine the initial dose (16).

There were equal proportion of TDM samples taken at <24 hours and 24-48 hours in this study, while the mean TTFS was closer to 24 hours. Similary, El Nekidy *et al.* and Brown *et al.* also reported mean sampling time between 23-29 hours (16, 18). Only a small proportion of patients in this study achieved the target SVC on the first TDM sampling, while majority had sub-therapeutic levels. However, El Nekidy *et al.* reported slightly higher proportion of patients with target SVC, while majority has supra-therapeutic levels (16).

This study also found that that weight-based LD and TTFS were significant predictors of SVC among ESRD patients on dialysis receiving vancomycin. Other studies also reported LD and sampling time or interval to be predictors of SVC (16,18-20). Our results also suggested that patients receiving a LD of 20-25mg/kg actual body weight of vancomycin with TTFS at 24 hours after vancomycin dose administration could achieve optimal initial SVC of 15.0-20.0 mg/L. El Nekidy *et al.* and Brown *et al.*, however, suggested a lower LD of 15-20 mg/kg of actual body weight and TTFS of 24 hours to achieve pre-haemodialysis SVC of 15.0-20.0mg/L (16,18). Barth *et al.*, on the other hand, suggested that vancomycin LD of 20mg/kg is more superior than a standard 1,000mg dosing to achieve the targeted pre-haemodialysis SVC of 10.0-25.0mg/L at TTFS 48 hours (19). On the other hand, Vandecasteele *et al.* proposed LD to be strategized as per the sampling interval, for example, 15mg/kg for one day interval, 25mg/kg for two days interval, and 35mg/kg for three days interval (20).

The optimal LD computed from this study are larger than others. This variation could be due to the differences in patient population studied, the type of dialysis and the presence of dialysis sessions between the LD and the first sampling of SVC. Studies by El Nekidy *et al.* and Brown *et al.* consist mostly of African Americans who may have different population pharmacokinetics compared to Asian population (16,18). Unlike the other studies which only included SVC taken pre-haemodialysis (16,18-20), our study included patients who had dialysis prior to SVC sampling and those who underwent SLED and PD. Given the fact that majority of the patients in this study were dialyzed using high flux dialyser, higher extent of removal of vancomycin resulted in higher requirement of LD (21).

Vancomycin has relatively low molecular weight of 1449 Dalton and dialysis using high flux dialyser made of membranes such as polysulfones, polyacrylonitrite and high efficiency cuprammonium rayon has been shown to effectively remove it (14,21). Apart from that, different mode of dialysis is shown to remove vancomycin to different extend. In the context of intermittent haemodialysis, supplementary dosing was generally proposed to achieve the target SVC. On the other hand, this was found to be not necessary for patients that were dialysed through PD (14). Removal rate by SLED however showed a 36% clearance over an eight-hours haemodialysis session (22). There were a small percentage of patients who underwent PD and SLED in this study, which may have contributed to variation in the results compared to the literatures.

Both El Nekidy *et al.* and Brown *et al.* did not study the effect of residual renal function on SVC but stated that as their study limitation instead. Pallota *et al.* suggested that the SVC of ESRD patient who have better residual renal function with creatinine clearance of 15mL/min would be double of that of a similar patient who is anuric. Thus, residual renal function has an impact towards SVC as it could influence vancomycin clearance and should be taken into consideration during dosing (15). Therefore, we included residual renal function in our analysis but found that it was not a significant predictor of SVC. This could be due to the majority of the study population had poor residual renal function as they were anuric or has urine output of ≤100mL. Hence, there was no significant predictive effect seen.

In addition to the factors suggested by this study, El Nekidy *et al.* and Brown *et al.* also found age to be another independent predictor of SVC in haemodialysis patient (16, 18). Our results did not find any significant correlation between age and SVC. Although the mean age of patients included in all three studies were similar, our study had equal proportion of elderly and non-elderly patients which is different from the other two studies. This may explain the lack of predictive value of age in our study. Aging is known to affect the pharmacokinetics of vancomycin, as study shown elderly haemodialysis subjects demonstrated 20% reduction in peak of concentration (Cmax), 23% reduction in systemic clearance and 45% higher volume of

distribution (Vd). This is attributed by higher tissue affinity in the elderly patients causing elevation of Vd (23).

In this study, the actual current weight was taken regardless of individual target dry weight. As vancomycin is a hydrophilic drug, weight differences between dry and wet body weights may influence the volume of distribution of vancomycin, and hence the SVC. Therefore, the time when the body weight measurement is taken (pre- or post-haemodialysis) is important assuming that all patients are dialysed up to their target dry weight. However, this was not taken into consideration in this study. In addition, three patients had their SVC taken within four hours post-dialysis. Since SVC taken within four hours of dialysis session might be inaccurate due to the incomplete distribution phase, the mean SVC reported could be affected (21).

Conclusion

Weight-based LD and TTFS are important factors that need to be taken into consideration when dosing vancomycin in ESRD patients on dialysis to ensure the achievement of therapeutic effectiveness of vancomycin. Vancomycin LD of 20-25mg/kg actual body weight is likely to yield desired SVC between 15.0-20.0 mg/L at TTFS of 24 hours. For future research, we recommend to investigate the significance of using dry and/or wet weight for dosing, type of dialysis and pre-dialysis vancomycin levels as the target SVC.

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Conflict of Interest Statement

No external funding was received and the authors declared no conflict of interest.

References

1. Stefani, S; Chung, D.R.; Lindsay, J.A;. Friedrich, A.W.; Kearns, A.M.; Westh, H; Mackenzie, F.M. Meticillin-resistant *Staphylococcus aureus* (MRSA): Global Epidemiology and Harmonisation of Typing Methods. *Int J Antimicrob Agents.* **2012**, *39(4)*, 273–82.
2. Rohani, M.Y.; Raudzah, A; Lau, M.G.; Zaidatul, A.A.; Salbiah, M.N.; Keah, K.C.; Noraini, A; Zainuldin, T. Susceptibility Pattern of *Staphylococcus aureus* Isolated in Malaysian Hospitals. *Int J Antimicrob Agents.* **2000**, *13(3),* 209–13.
3. Ahmad, N; Ruzan, I.N.; Abd Ghani, M.K.; Hussin, A; Nawi, S; Aziz, M.N.; Maning, N; Eow, V.L. Characteristics of Community- and Hospital- Acquired Meticillin- Resistant *Staphylococcus aureus* Strains Carrying SCCmec Type IV Isolated in Malaysia. *J Med Microbiol*. **2009,** *58(9),* 1213–8.
4. Liu, C; Bayer, A; Cosgrove, S.E; Daum, R.S; Fridkin, S.K; Gorwitz, R.J; *et al*. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children. *Clin Infect Dis*. **2011**, *52*, 285–92.
5. Tong, S.Y; Davis, J.S.; Eichenberger, E; Holland, T.L.; Fowler Jr, V.G. *Staphylococcus aureus* Infections: Epidemiology, Pathophysiology, Clinical Manifestations and Management. *Clin Microbiol Rev*. **2015**, *28*, 603–61.
6. van Hal, S.J.; Jensen, S.O.; Vaska, V.L.; Espedido, B.A.; Paterson, D.L.; Gosbell, I.B. Predictors of Mortality in *Staphylococcus aureus* Bacteremia. *Clin Microbiol Rev.* **2012,** *25,* 362–86.
7. Morbidity Mortality Weekly Report. **2007** Mar 9, *56(9),* 197-199
8. Ministry of Health Malaysia. National Antibiotic Guideline. 3rd ed. Kuala Lumpur: Pharmaceutical Services Programme, Ministry of Health Malaysia. **2019**.
9. Rybak, M; Lomaestro, B; Rotschaefer, J.C.; *et al.* Therapeutic monitoring of Vancomycin in Adult Patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Disease Society of America, and the Society of Infectious Disease Pharmacists. *Ann J Health Sys Pharm***. 2009,** *66,* 82-98.
10. Matzke, G.R; McGory, R.W.; Halstenson, C.E.; Keane, W.F. Pharmacokinetics of Vancomycin in Patients with Various Degrees of Renal Function*. Antimicrob Agents Chemother*, **1984**, *25*, 433-7
11. Matsumoto, K; Takesue, Y; Ohmagari. N; Mochizuki, T; *et al.* Practice Guideline for Therapeutic Drug Monitoring of Vancomycin: A Consensus Review of the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. *J Infect Chemother*. **2013**, *19(3)*, 365-380.

12. Therapeutic Drug Monitoring Vancomycin Report. **2014.** Pharmacy Department, Hospital Kuala Lumpur (personal communication)
13. Murphy, J.E. Clinical Pharmacokinetics. 6th ed. American Society of Health-System Pharmacists. **2017**.
14. Šefer; Siniša; VesnaDegoricija. About Drug Dialyzability. *ActaClinicaCroatica.* **2003***, 42(3),* 257-267
15. Pallotta, K.E.; Manley, H.J. Vancomycin Use in Patients Requiring Hemodialysis: A Literature Review. *Semin Dial*. **2008**, *21(1),* 63-70.
16. El Nekidy, W.S.; El Masri, M.M.; Umstead, G.S.; Dehoorne-Smith, M. Factors Influencing Vancomycin Loading Dose for Hospitalised Hemodialysis Patients: Prospective Observational Cohort Study. *Can J Hosp Pharm*. **2012**, *65(6),* 436-442
17. Oyaert, M; Spriet, I; Allegaert, K; *et al.* Factors impacting unbound vancomycin concentrations in different patient populations. *Antimicrob Agents Chemother*. **2015**, *59(11),* 7073-7079.
18. Brown, M; Pollisety, R; Greacely, E.J.; Cuhaci , B; Schlecht, H.P. Weight-based Loading of Vancomycin in Patients on Hemodialysis. *Clin Infect Dis.* **2011**, *53(2),* 164-166.
19. Barth, R.H.; DeVincenzo, N. Use of Vancomycin in High-flux Hemodialysis: Experience with 130 Courses of Therapy. *Kidney Int.* **1996**, *50*, 929-936
20. Vandecasteele, S.J.; De Bacquer, D; De Vriese, A.S. Implementation of a Dose Calculator for Vancomycin to Achieve Target Trough Levels of 15-20μg/mL in Persons Undergoing Hemodialysis. *Clin Infect Dis*. **2011**, *53*, 124-129
21. Launay-Vacher, V; Izzedine, H; Mercadal, L; Deray, G. Clinical Review: Use of Vancomycin in Haemodialysis Patients. *Crit Care*. **2002**, *6(4),* 313-6.
22. Vandecasteele, S.J.; De Vriese, A.S; Tacconelli, E. The Pharmacokinetics and Pharmacodynamics of Vancomycin in Clinical Practice: Evidence and Uncertainties. *J Antimicrob Chemother.* **2013,** *68(4),* 743-8*.*
23. Cutler, N.R.; Narang, P.K.; Lesko, L.J.; Ninos, M; Power, M. Vancomycin Disposition: The Importance of Age. *Clin Pharmacol Ther* .**1984**, 25, 433-7.

Effectiveness of *Skuad Cakna Ubat* Programme to Improve Medication Knowledge and Use among Community in Kuala Nerus, Terengganu: An Interventional Study

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Abstract

Introduction: It was reported that 55.6% of Malaysian consumers did not understand the proper use of their medicines. *Skuad Cakna Ubat* (SCU) was established to aid medication information delivery among community in Kuala Nerus, Terengganu. SCU utilised the concept of road tour to provide healthcare information services in a more casual approach.

Objectives: This study aimed to evaluate the effectiveness of SCU programme in terms of knowledge and practice of appropriate use of medicine among the community in Kuala Nerus, as well as to identify the association between demographic characteristics and knowledge and practice.

Methods: This was an interventional study involving consented participants from a few villages at selected eateries in the *Kuala Nerus* district from May to September 2019. The subjects were assessed on knowledge and practice of medication use through face-to-face interview using a *Malay* version validated questionnaire from the National Survey on the Use of Medicines (NSUM) III 2015. It was a 20-item questionnaire with eleven items in the knowledge domain and nine items in the practice domain. Pre- and post-interventional evaluations were done at 2-months interval.

Results: A total of 120 participants were recruited in this study. The mean age of the participants was 41.6 (standard deviation 14.8) years with the majority being male (66.7%) with secondary education and above (55.0%). There were significant improvements in the post-intervention mean knowledge and practice scores, with p=0.002 and p<0.001 respectively. Higher improvement in practice score (15.8%) was seen compared to knowledge score (5.7%). Knowledge and practice were negatively correlated with age (r_p=-0.205, p=0.025 and r_p=-0.127, p=0.167 respectively).

Conclusion: Findings revealed that the SCU programme imposed positive effects on the *Kuala Nerus* community's knowledge and practice on the appropriate use of medicines. Thus, extensive public engagement and collaboration with community pharmacy could be the future key in optimisation of pharmacy information delivery.

Keywords: National Survey on the Use of Medicines, pharmacist, *Skuad Cakna Ubat*, knowledge, practice

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Introduction

The proper diagnosis of disease and effective treatments are essential to an individual's prognosis and quality of life. Generally, the communities of developing countries have limited knowledge and awareness about the safety and proper storage of medicines commonly found at home (1). A few studies have shown that patients who use complementary medicines are unaware of the potential side effects and possible interactions with their prescribed medicines (2).

A national survey reported that 55.6% of Malaysian consumers did not understand the proper use of their medicines (4). A cross-sectional national survey among consumers in 2015 showed that 18.6% did not fully understand the proper use of their medicines, 46.8% were not able to identify the trade or generic name of their medicines, 17.0% had no knowledge on proper medicine storage, 29.7% were not aware of common side effects of their medicines and 31.6% were not aware of the possible interactions between traditional and modern medicines (3). Some individuals having difficulties in checking the expiry dates as well as lack of proper knowledge in disposing medications, often resulting in improper storage of medications

at home. This may lead to undesirable effects or unintentional risks like improper self-medication, accidental overdose and prescription drug abuse (5,6).

The *Skuad Cakna Ubat* (SCU) programme is an innovative programme founded by the pharmacy team from Kuala Nerus District Health Office (PKD), Ministry of Health Malaysia (MOH) in December 2016 in collaboration with the Pharmaceutical Service Division of Terengganu State Health Department (JKNT) and community pharmacies in the district. The SCU programme was established to aid medication information delivery in the community and enhance dissemination of healthcare information about the correct use of medications. By using the concept of road tour, SCU is able to provide health education to a wider population in a more relaxing approach. Correct usage of medications, antibiotic resistance, and the use of registered products are among the health information emphasised during the exposition. Participants are also encouraged to bring along their purchased health products to find out the status of product registration during the road tour.

In 2017, SCU had conducted activities in a total of 15 areas in the Kuala Nerus district, involving 1,328 participants. As the programme involved substantial efforts and commitment by the SCU team, it is important to ensure that it is able to produce its expected impact in the community. Therefore, this study was carried out to evaluate the effectiveness of SCU programme in terms of knowledge and practice on the appropriate use of medicines in the Kuala Nerus community, as well as to identify the association between demographic characteristics with knowledge and practice in Kuala Nerus.

Methods

Study Procedures

This study was conducted from May to September 2019. This study was conducted as a collaboration among the SCU team, JKNT, the Village Community Management Council (*Majlis Pengurusan Komuniti Kampung* (MPKK)) and the Non-Communicable Disease (NCD) team of Kuala Nerus district. The SCU programme was held bimonthly on Thursday from 8am to 12 noon. During every session, four trained pharmacists and one assistant pharmacist delivered the SCU programme and collected data for the study. Before the programme, all data collectors were briefed about the SCU module to ensure coherent interventions as well as standardised interview process. Layman terms were use throughout the process for better understanding by the participants.

Several locations of interests such as eateries with the most crowds were identified to carry out the SCU programme with the help of the village heads. Announcement such as promotions and banners about the details of SCU programme were made through social media, distribution of pamphlets at clinics, mosques and surrounding areas. A sample size of 120 participants was determined using PS Software version 3.1.6 based on literature review by Dawood et. al. (7). Approximately 25 recruitments were targeted in each SCU session during the study period. Subjects aged 18 years and above with no cognitive problem and with history of taking medicines were included into the study. Those who refused to participate or did not meet the inclusion criteria were given Meditips, an educational pamphlet on the proper use of medicines but were not counselled further.

Subjects who met the inclusion criteria were randomly selected and interviewed by the data collectors after obtaining their consent to participate in the study. Consented respondents first underwent a 10-minute one-on-one basis interview using the National Survey on the Use of Medicines (NSUM) III 2015 *Malay* version questionnaire as pre-intervention assessment. The SCU programme then began with self-introduction by the data collectors and brief introduction about the programme. SCU Interventions known as *Modul Sembang Santai* (Casual Conversation Module) was then delivered to the respondents. *Modul Sembang Santai* consists of five broad topics which are Know your medicines, 5B Concept, Registered medicines, Safe medicine storage and Drug allergy.

After two months, post-intervention evaluation was carried out using the same questionnaire by the same data collector via phone call. Those who cannot be reached by phone call after 2 months for post-intervention evaluation were counted as defaulted subjects and excluded from the final analysis. Figure 1 demonstrated the flow of study.

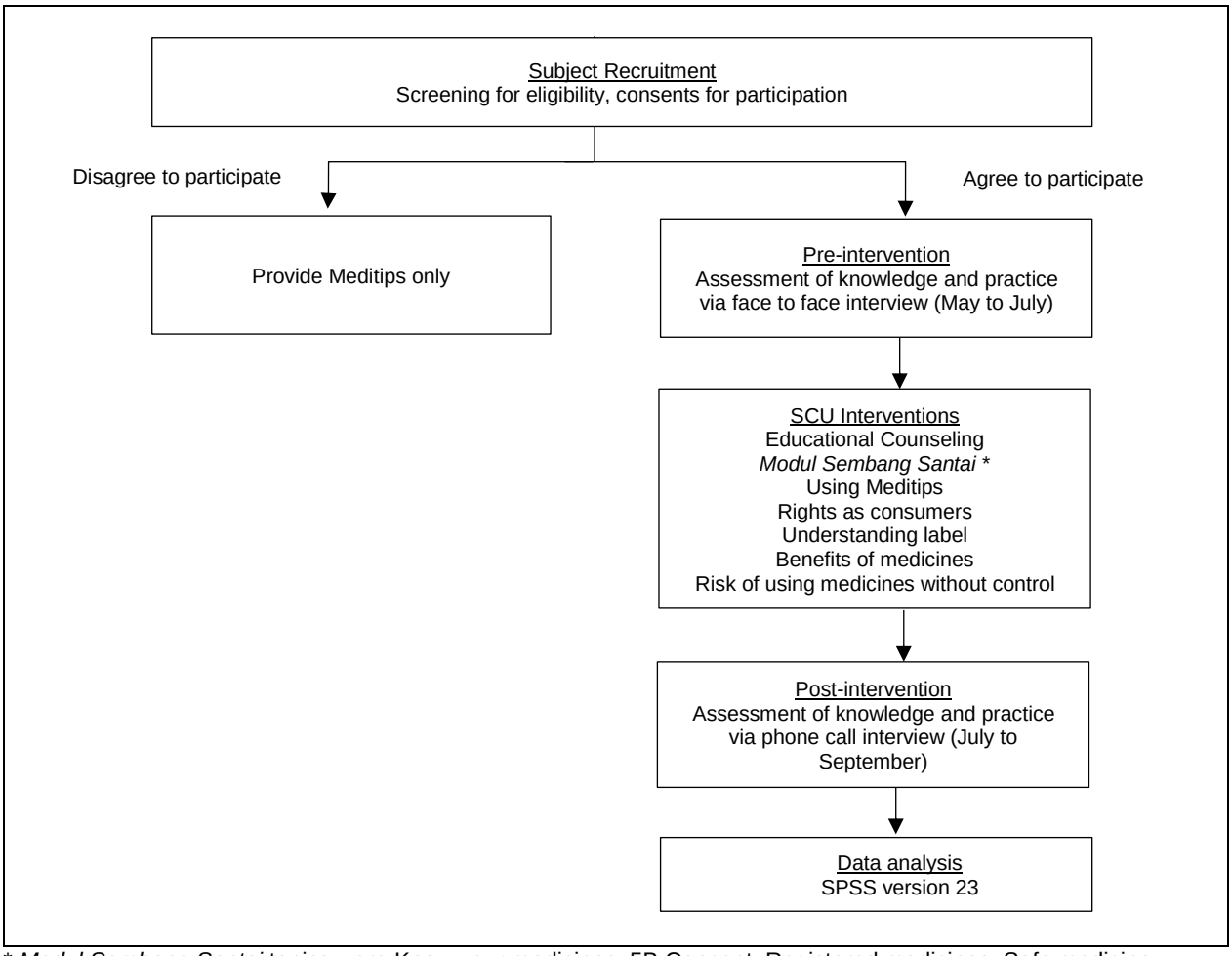
Data Collection Tool

The data collection tool was adopted from the validated NSUM by Malaysian Consumers III 2015 questionnaire. The questionnaire consists of respondents' demographic profile (seven items) - age, sex, ethnic group, education level, occupation, living status, monthly household income as well as contact number. The other two domains were knowledge (eleven items) and practice (9 items). The knowledge

domain contains eleven questions about generic name of medicines, understanding on proper use of medicines (5B), side-effects, contraindications and registered medicines. The practice domain contains nine questions about the storage of medicines and disposal of damaged / expired medicines. Every correct answer in both domains was given 1 score while incorrect answer was given 0 score. The maximum possible scores for the knowledge and practice domains were thus 11 and 9 respectively.

Statistical Analysis

Data were analysed using SPSS version 23. Descriptive statistics were used to describe the demographic characteristics of the respondents. Paired t-Test was used to determine the changes of mean knowledge and practice scores in the pre and post-interventions. The association between demographic factors and outcome variables were analysed using Pearson correlation coefficient test and one-way ANOVA. A value of $p<0.05$ was considered statistically significant.



* *Modul Sembang Santai* topics were Know your medicines, 5B Concept, Registered medicines, Safe medicine storage and Drug allergy

Figure 1: Study procedures and data collection during SCU

Results

A total of 155 respondents were recruited in this study initially but 35 participants were lost during follow up. Therefore, 120 respondents were included in the analysis. The mean age was 41.6 (standard deviation (SD) 14.8) years old and 66.7% of them were male. Majority of the participants were Malay (94.2%) while others were Chinese (5.8%). More than half of them had secondary education level (55%) and were currently employed (60%). Approximately 85.8% of them were living with their family members. Majority of the participants (73.3%) earn monthly income between RM501 to RM2,000 (Table 1).

Table 2 summarised respondents' knowledge and practice on medicines use scores. Our findings showed that the SCU participants had statistically significant increased mean knowledge score from pre-

intervention to post-intervention (p=0.002). Likewise, the same trend of result was found with the mean practice on medicines use score (p<0.001). The mean knowledge and practice on medicines use scores increased by 5.7% and 15.8% respectively.

Table 3 summarised the relationship between respondents' age and their knowledge and practice on medicine use (pre-SCU interventions). There was a statistically significant negative correlation between the respondents' age and knowledge (r=-0.205, p=0.025). Our study also analysed the association between respondents' demographic variables and their knowledge and practice on medicine use (pre-SCU interventions). There was no statistically significant association between the education level, living status and income with respondents' knowledge and practice on medicines use as shown in Table 4.

Table 1: Socio-demographic characteristics of study population (n=120)

Characteristics	Value
Age, year, mean (SD)	41.6 (14.8)
Gender, n (%)	
Male	80 (66.7)
Female	40 (33.3)
Ethnic, n (%)	
Malay	113 (94.2)
Chinese	7 (5.8)
Education level, n (%)	
Primary	6 (5.0)
Secondary	66 (55.0)
Tertiary	44 (36.7)
No education	4 (3.3)
Employment, n (%)	
Employed	72 (60.0)
Unemployed	48 (40.0)
Living status, n (%)	
Alone	14 (11.7)
With Family	103 (85.8)
Without Family	3 (2.5)
Monthly income, n (%)	
< RM500	24 (20.0)
RM501 – RM2,000	65 (54.2)
RM2,001 – RM3,500	18 (15.0)
RM3,501 – RM5,000	5 (4.2)
> RM5,000	8 (6.7)

Table 2: Knowledge and practice scores before and after taking part in SCU programme (n=120)

Domain	Pre-intervention score, mean (SD)	Post-intervention score, mean (SD)	P-value [a]
Knowledge on medicine use	8.283 (2.352)	8.758 (1.366)	0.002
Practice on medicine use	7.283 (1.330)	8.433 (0.877)	<0.001

[a] paired sample t-test, p<0.05 considered statistically significant
Abbreviation: SD – standard deviation

Table 3: Correlation between respondents' age and their knowledge and practice on medicines use (pre-SCU interventions) (n=120)

Domain	r	P-value [ß]
Knowledge	-0.205	0.025
Practice	-0.127	0.167

[ß] Pearson correlation coefficient, p<0.05 considered statistically significant
Abbreviation: r - Pearson correlation

Table 4: Association between respondents' demographic variables and their knowledge and practice on medicines use (pre-SCU interventions) (n=120)

Variable		n	Knowledge			Practice		
			Mean	(SD)	P-value[Ø]	Mean	(SD)	P-value[Ø]
Education level	Primary	6	8.167	(1.941)	0.091	7.000	(1.095)	0.426
	Secondary	66	7.893	(2.488)		7.151	(1.316)	
	Tertiary	44	8.977	(1.836)		7.546	(1.302)	
	No Formal	4	7.250	(4.349)		7.000	(2.160)	
Living status	Alone	14	8.714	(1.684)	0.321	7.143	(1.351)	0.602
	Family	103	8.175	(2.431)		7.282	(1.339)	
	Non-family	3	10.00	(1.732)		8.000	(1.000)	
Income	< RM500	24	8.208	(2.377)	0.973	7.209	(1.103)	0.516
	RM501–RM2,000	65	8.200	(2.545)		7.246	(1.370)	
	RM2,001–RM3,500	18	8.556	(2.036)		7.444	(1.247)	
	RM3,501–RM5,000	5	8.200	(1.643)		6.600	(2.510)	
	> RM5,000	8	8.625	(2.066)		7.875	(0.835)	

[Ø] One-Way ANOVA, $p<0.05$ considered statistically significant
Abbreviation: SD - standard deviation

Discussion

The mean scores of participants' knowledge and practice of medications use significantly improved after the SCU programme with increment of 5.7% and 15.8% respectively. This finding was supported by a study in Saudi Arabia which revealed that counselling by pharmacists improved the patients' medications knowledge with half of them showing good to excellent knowledge (52.9%) compared to those who did not received counselling (12.5%) (8). In addition, a 2014 study illustrated that educational interventions often resulted in better adherence and improved medication knowledge, and the most successful interventions used were behavioural support or coaching to support patients. (9)

In our findings, there was a statistically significant negative correlation between age and knowledge of medications use among the respondents suggesting poor knowledge was associated with increase of age. This finding showed that community in Kuala Nerus is very similar to other populations whereby elderly was less likely to understand some information about their medications (10) and the cognitive ability that was becoming low in advancing age could lead to inappropriate use of medicines (11). Meanwhile, medications knowledge among those age over 80 years was shown to be lower. (12).

Thus, policy makers should design specific programmes for the geriatric population in optimising the quality use of medicines as the elderlies are often subject to polypharmacy. One of the possible strategies is to synergize the SCU programme with the pharmacist-managed Geriatric Medication Therapy Adherence Clinics (MTAC) provided in MOH facilities. Besides, moving forward, SCU programme can also collaborate with other non-government organisations (NGO) that focused on geriatric interests such as Malaysia Society of Geriatric Medicines to design more effective approaches in delivering effective medication information to this target group.

In our study, no significant association was found between other demographic factors such as education level, income and living status with patient's knowledge and practice on medicines use. Likewise, a study done in 2016 revealed that there was no statistically significant association between patients' educational level and their medication knowledge in older patients (12). In contrary, patients living independently with a partner were shown to be significantly more knowledgeable than others. This study reported that elderly patients were found to be more likely to adhere to medications if they were highly educated, had diseases, were more satisfied with counselling, had received sufficient explanation of their medications, and were subject to lower frequency of dosing (13).

Our study, however, did not assess the SCU participants' medication adherence, which could be explored in future study. There were also a few limitations of this study such as lack of randomization during respondent recruitment so our study population might not represent the whole population of Kuala Nerus. This study is suggested to be carried out in larger populations as the SCU programme has been expanded at the national level. With more extensive public engagement, SCU programmes in collaboration with the community pharmacies can be the future key in enhancing public's knowledge and medication use. The

involvement of private sector could help to improve patients' access and utilisation of medications information resources in the community while promoting quality use of medicines.

Conclusion

Our study demonstrated that SCU programme had positive effects in the *Kuala Nerus* community in terms of knowledge and practice on the appropriate use of medicines. The counselling module in the SCU programme successfully improved patient's knowledge and practice on medicines use. Our study also showed that geriatrics has poor knowledge on medicines use compared to younger generation. Therefore, intervention measures in improving appropriate use of medicines especially in elderly group should be given more attention by the SCU programme.

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Conflict of Interest Statement

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References

1. Kheir N, Hajj ME, Wilbur K, Kaissi R, Yousif A. An exploratory study on medications in Qatar homes. Drug Healthc Patient Saf. 2011;3:99-106.
2. McD Taylor D, Walsham N, Taylor SE, Wong LF. Complementary and alternative medicines versus prescription drugs: perceptions of emergency department patients. Emerg Med J. 2006 Apr;23(4):266-8.
3. Mohamad Azmi, H, Fahad, S. A national survey on the use of medicines (NSUM) By Malaysian Consumers. (3RD ed). MALAYSIA: Quality Use of Medicines Pharmaceutical Services Division Ministry of Health Malaysia; 2016.
4. Bahri, S, Othman, NH, Mohamad Azmi, H, Shafie, AA, Izham, MIM. A national survey on the use of medicines (NSUM) by Malaysian consumers. (1st ed). MALAYSIA: Quality Use of Medicines Pharmaceutical Services Division Ministry of Health Malaysia; 2008.
5. Abou-Auda HS. An economic assessment of the extent of medication use and wastage among families in Saudi Arabia and Arabian Gulf countries. ClinTher. 2003 Apr;25(4):1276-92.
6. De Bolle L, Mehuys E, Adriaens E, Remon JP, Van Bortel L, Christiaens T. Home medication cabinets and self-medication: a source of potential health threats. Ann Pharmacother. 2008 Apr;42(4):572-9.
7. Dawood, O.T, Mohamed azmi, H, Fahad, S. Factors affecting knowledge and practice of medicine useamong the general public in the State of Penang, Malaysia. J Pharm Health Serv Res. 2017;8 : 51-57.
8. Alkatheri AM, Albekairy AM. Does the patients' educational level and previous counseling affect their medication knowledge. Ann Thorac Med. 2013 Apr;8(2):105-8.
9. Kuntz JL, Safford MM, Singh JA, Phansalkar S, Slight SP, Her QL, et al. Patient-centered interventions to improve medication management and adherence: a qualitative review of research findings. Patient EducCouns. 2014 Dec;97(3):310-26 .
10. Pérez-Jover V, Mira JJ, Carratala-Munuera C, Gil-Guillen VF, Basora J, López-Pineda A, et al. Inappropriate Use of Medication by Elderly, Polymedicated, or Multipathological Patients with Chronic Diseases. Int J Environ Res Public Health. 2018 Feb 10;15(2):E310.
11. Vrhovac R, Rojnic-Putarek N, Jaksic B. Knowledge of and attitudes to pharmacotherapy in medical inpatients. Int J ClinPharmacolTher. 2000 Sep;38(9):441-5.
12. Bosch-Lenders, D, Maessen, DWHA, Stoffers, HEJH, André Knottnerus, J, Winkens, B, Van Den Akker, M. Factors associated with appropriate knowledge of the indications for prescribed drugs among community-dwelling older patients with polypharmacy. Age And Ageing. 2016;45(3): 402–408.
13. Jin H, Kim Y, Rhie SJ. Factors affecting medication adherence in elderly people. Patient Prefer Adherence. 2016;10:2117-25.

Perception and Behaviour of Type 2 Diabetes Patients towards Diabetes Management during Ramadan

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Abstract

Introduction: Fasting during the holy month of Ramadan is one of the five pillars of Islam. There are exemptions for those who are not in a good health. Nevertheless, many Muslims still insist to fast even though their health conditions are discouraging and this could lead to health complications.

Objective: This study aimed to explore the perception and behaviour of Muslims with Type 2 Diabetes Mellitus (T2DM) in Hospital Tuanku Ampuan Najihah (HTAN) towards diabetes management during Ramadan.

Methods: Semi-structured interview sessions were conducted from August to October 2018 at HTAN medical clinic. Purposive sampling method was used to recruit Muslim respondents with T2DM aged 18 years and above who were prescribed with at least one antidiabetic agent. The interview topic guide consisted a series of open-ended questions related to diabetes management during Ramadan including perception of fasting, diabetes management, diet control and self-monitoring blood glucose (SMBG) practice. All the interviews were audio recorded and transcribed verbatim. Data collection was discontinued after saturation was achieved.

Results: A total of thirty T2DM patients were interviewed. Majority of the respondents were able to fast during Ramadan without difficulties. Many believed that fasting could improve general well-being. Most of them never experienced hypoglycaemia while fasting, but were aware of the symptoms and management of hypoglycaemia. Most respondents did not adjust their medications during fasting and reported either unchanged or reduced dietary intake. Only a few respondents owned glucometer and monitored blood glucose routinely although most respondents acknowledged the benefits of SMBG. Majority agreed that cost and logistic issues were the main barriers in practicing SMBG.

Conclusion: Generally, T2DM patients were positive about fasting. Nevertheless, these patients may not adjust their antidiabetic medications and monitor their blood sugar routinely during Ramadan although they were aware of the importance.

Keywords: perception, behaviour, Type 2 Diabetes Mellitus, diabetes management, Ramadan

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Introduction

Fasting during the holy month of Ramadan is one of the five pillars of Islam. Healthy Muslims are required to refrain from eating, drinking, smoking, using oral medications, sexual intercourse and other actions that should be abstained throughout the day, from sunrise until sunset. There are exemptions for those who are in a condition which does not allow them to fast, however, especially if fasting could worsen their health. These include pregnancy and nursing mothers, patients with uncontrolled chronic illnesses, elderlies and weak persons. For patients with uncontrolled diabetes, fasting during Ramadan has been consistently discouraged by healthcare providers as their risk of complications such as hypoglycaemia, hyperglycaemia, diabetic ketoacidosis, dehydration and thrombosis are high (1).

Fasting does not intend to create excessive hardship on the Muslims since individuals with conditions that do not allow them to fast are exempted. Nevertheless, many diabetic patients still insist on fasting and this could be challenging for themselves and the healthcare providers. In the Epidemiology of Diabetes and Ramadan (EPIDIAR) study which was conducted in 13 Islamic countries, high rate of acute complications was observed among the 12,243 diabetic individuals who fasted (2). Most of the patients

practice Ramadan fasting under the pressure of socio-cultural habits despite their doctors' disapproval (3) and healthcare professionals are rarely included in the decision-making process on whether or not to fast. Instead, friends and relatives, especially those with Type 2 Diabetes Mellitus (T2DM), are considered important to the decision-making process (4). These highlighted the difficulties to manage these patients.

A few guidelines and recommendations were published to guide patients with diabetes in managing their medications while fasting during Ramadan. In CREED study, almost all physicians reported providing fasting-specific advices to the patients and most of them reported using guidelines or recommendations for the management of diabetes during Ramadan (5). A patient's decision to fast should be made after ample discussions with a healthcare provider concerning the risks involved (6). For successful Ramadan fasting, attention must be paid to meal planning, glucose monitoring, daily activities and treatment adjustment (6,7). Thus, healthcare providers should play a pivotal role in giving advices and guiding these patients in adjusting to their temporary medications regimen changes during fasting in Ramadan.

There are multiple guidelines to aid healthcare providers in managing diabetic patients during Ramadan. However, limited data is available in Malaysia regarding the perception and behaviour of diabetic patients during the fasting month. Identification of the patients' experience and knowledge on diabetes management is important to aid healthcare providers to provide better care for diabetic patients (8). Therefore, this study aimed to explore the perception and behaviour of Muslim patients with T2DM in Hospital Tuanku Ampuan Najihah (HTAN) towards diabetes management during Ramadan. Findings from this study could provide a better understanding on the views and behaviours of T2DM patients thus improving patient care to ensure safe fasting.

Methods

This was a qualitative study aiming to comprehend from participants' own statements, what they believe concerning diabetes management and to explore how they behave towards handling their medications during Ramadan. Purposive sampling method was used. Muslim patients with T2DM aged 18 years old and above who were on at least one antidiabetic agent, fasting or not fasting during Ramadan, followed up at Medical Outpatient Department (MOPD) of HTAN for at least one year, and understood either Malay or English language were included in the study. Patients who were unable to comprehend the interview questions were excluded from the study.

Ethical approval (NMRR-18-3150-42652) was acquired from the Ministry of Health Malaysia Medical Review and Ethics Committee (MREC) prior to the commencement of the study. The investigators also obtained site approval prior to the initiation of the study. The participant's involvement in this study was on a voluntary basis and they were informed that they could quit the interview at any stage. Informed consent was obtained from all participants before the interview.

Data collection was conducted from August to October 2018 through face to face in-depth interview using an open-ended semi structured guide. The semi-structured interview guide was developed based on literature review and validated via peer review process. It explored a range of perceptions on fasting, diabetes management, diet control and self-monitoring blood glucose (SMBG) practice. A pilot study was conducted to pre-test the interview guide but the data was not included in the final analysis.

The interviews were conducted in a place where both the researcher and respondents considered as suitable and comfortable. The purpose of the study was explained to all respondents and they were informed that the interview sessions were audio recorded. Each session was held around 20 to 30 minutes. The respondents could freely answer any questions that they wanted to. General probing questions such as "Can you explain further?", "What is your opinion on this?" and "Can you further clarify?" were used during the interview sessions to facilitate the answering. The interviews were conducted in either Malay or English, which both researcher and participant can clearly understand each other.

All the interviews were audio recorded and transcribed verbatim by the primary investigator to avoid bias. Field notes taken during the interviews were compared to the transcripts. Each transcript was then repeatedly read by two other researchers. The main words and topics for each interview were highlighted and coded and these codes were identified and compiled into themes. Peer-reviewed translation of the quotes of the local Malaysian language interviews was conducted to make sure that the concepts were translated correctly. Commonalities and differences in the data were identified before the relationship between the data was made, and descriptive and explanatory conclusions were drawn (9,10). Data collection was discontinued when saturation was achieved, where no new information was obtained from subsequent interviews.

Results

A total of thirty T2DM patients were interviewed (Participant 1 to Participant 30). The respondents were equally distributed between males and females. Majority of the participants aged 50 and above (83.3%) and with monthly income below RM3,000 (90%). Most of the participants have a diabetes duration of 10 years and below (66.7%). More than half of the participants are insulin users (56.7%) and most of the participants do not own a glucometer at home (66.7%). The demographic and clinical characteristics of the respondents were summarised in Table 1.

The thematic content analysis identified four major themes and fourteen sub-themes as illustrated in Table 2. The four main themes identified in this study were perception of fasting, diabetes management, diet control and self-monitoring blood glucose (SMBG).

Table 1: Demographic and clinical characteristics of participants (n=30)

Characteristics	n (%)
Age range, year	
20 – 29	1 (3.33)
30 – 39	0 (0)
40 – 49	4 (13.33)
50 – 59	10 (33.33)
60 – 69	14 (46.67)
70 – 79	1 (3.33)
Gender	
Male	15 (50.00)
Female	15 (50.00)
Body Mass Index (BMI), kg/m^2	
18.5 – 24.9	9 (30.00)
25 – 29.9	11 (36.67)
Above 30	10 (33.33)
Educational Status	
Primary	12 (40.00)
Secondary	14 (46.67)
Certificate	2 (6.67)
No Formal Education	2 (6.67)
Working Status	
Working	16 (53.33)
Not Working	14 (46.67)
Monthly Income	
< RM999	3 (10.00)
RM1,000 – RM1,999	16 (53.33)
RM2,000 – RM2,999	8 (26.67)
RM3,000 – RM3,999	1 (3.33)
RM4,000 – RM4,999	1 (3.33)
RM5,000 – RM5,999	1 (3.33)
Duration of Diabetes, year	
1 – 5	13 (43.33)
6 – 10	7 (23.33)
11 – 15	5 (16.67)
16 – 20	1 (3.33)
21 – 25	4 (13.33)
Antidiabetic Agents	
Oral Anti-Diabetic Agents (OAD)	13 (43.33)
Insulin	10 (33.33)
OAD and Insulin	7 (23.33)
Own a Glucometer	
Yes	10 (33.33)
No	20 (66.67)

Table 2: Themes and sub-themes

Theme	Sub-theme
Perception of fasting	Ability to fast
	Knowledge on risk of fasting
	Issues with fasting
	Significance of fasting
Diabetes management	Behaviour during Ramadan
	Management of Hypoglycaemia
	Source of information
	Adjustment of medications
Diet control	Challenges in controlling diet
	Changes in eating habit
Self-Monitoring Blood Glucose (SMBG)	Practicing SMBG
	Benefits of SMBG
	Barriers in practicing SMBG

Theme 1: Perception of fasting

Sub-theme 1.1: Ability to fast

In this study, majority of the interviewed patients (n=22) were able to fast during Ramadan without any difficulties.

"I do not have any problem with fasting even though I have diabetes. Fasting is full." (Participant 13)

Participants did not experience any symptoms of hypoglycaemia even though they have diabetes for more than 5 years. Moreover, they confidently claimed that they could perform fasting during Ramadan since the first year they had been diagnosed with diabetes.

"It's full (fast for whole Ramadan month). Last time more difficult but I can survive. Even though I have diabetes, it is not a problem." (Participant 24)

Nevertheless, eight participants mentioned that they were unable to fully fast during Ramadan, but they still performed fasting for certain days during Ramadan.

"If I feel the signs of hypo (hypoglycaemia) ... About 5 days if I'm not mistaken ... I only fast for 25 days." (Participant 8)

Sub-theme 1.2 Knowledge on risk of fasting

Thirteen participants claimed that they knew the risk of fasting with diabetes. The most common risks reported were hypoglycaemia accompanied by lethargy, tremor, sweating and dizziness.

"The risk is the lack of sugar in the body. That's all. I'm afraid of hypo. That's what the doctor told me. Another symptom that I told you is tired. Less energy. That's what I experienced during the fasting month." (Participant 9)

Meanwhile, nine participants mentioned they did not know the risk of fasting and no one had ever told them about the risk of fasting. Some of the participants did not experience any difficulties during fasting thus they were unable to list out the risk of fasting.

"Ha. I do not know the risks... No one had ever told me what to do (if I get the risk of fasting)." (Participant 4)

"I'm not sure because I have no experience (of getting the risk during fasting month). Even though I have diabetes for so long, during fasting month, there is no problem." (Participant 29)

Sub-theme 1.3 Issues with fasting

Only seven participants had some issues with fasting. Some of them were confused on the timing of taking medications, while some of them tend to forget their medications due to the different routines during Ramadan.

> *"I'm a bit confused about taking the medications. Because some you need to take after breaking the fast and some to take after sahur. So it's a little bit confusing ..." (Participant 3)*

> *"During fasting month, it is hard to be compliant. Sometimes I'm not injecting insulin during the day because I tend to forget. During non-fasting month, it's easy as I remember to inject the insulin before I eat. While at night, sometimes I forgot to inject the insulin because I went to sleep earlier (in Ramadan)." (Participant 19)*

More than half of the participants (n=17) did not have any major issues with fasting. They experienced a few conditions such as hunger or thirst, but they were still able to manage the situation.

> *"For me there is no problem at all. It's normal to feel hungry during fasting month. But not to say until I am too weak (to continue fasting)." (Participant 15)*

> *"It is normal to feel hungry since I'm fasting. I did not experience any change (in my body) during fasting month." (Participant 27)*

Sub-theme 1.4 Significance of Fasting

Many (n=21) believed fasting can improve general well-being. Their body felt lighter, healthier and they could reduce weight through fasting.

> *"It's alright to fast. Because we have diabetes so everything must be controlled. Food, sugar, water. (Take care of) Our bodies, kidney. So, it is good if we fast." (Participant 1)*

> *"My body becomes healthier. Feel fresh while I'm fasting." (Participant 18)*

Two participants believed that they could gain *pahala* (reward) by following Islamic teaching.

> *"I will be rewarded. I can control my dietary intake especially sugar during the day. I can cleanse my stomach too (if I perform fasting)." (Participant 17)*

Theme 2: Diabetes management

Sub-theme 2.1 Behaviour during Ramadan

Slightly more than half of the participants (n=16) knew how to control their diet and how to manage their daily routines while fasting. Some believed that their behaviour might affect their fasting status during Ramadan.

> *"When start getting hypo (hypoglycaemia), we will feel shaking, sweating and going to faint. I'll quickly take sweet drinks and break the fast." (Participant 1)*

> *"I know what to do. Must control diet, take medications, inject insulin." (Participant 16)*

> *"We have to control our diet even though we can't eat during the day, but we must control food intake while breaking the fast. I only eat oat during Sahur and dates as usual." (Participant 20)*

Four participants did not aware their behaviour might affect their management of diabetes during fasting.

> *"…No idea. I've no experience." (Participant 25)*

Sub-theme 2.2 Management of hypoglycaemia

Most of the participants (n=22) had never experienced hypoglycaemia while fasting, whereas five participants had some episodes of hypoglycaemia during Ramadan. However, both groups were aware of hypoglycaemia symptoms and management of hypoglycaemia.

> *"If blood glucose level is below 4, I will break the fast. But sometimes, if time is nearly to breaking the fast at evening, I will wait until the time of breaking fast. I always ask myself whether I can fast or not, is there any problem. If no problem, I will continue fasting." (Participant 11)*

"If symptoms of hypoglycaemia appear, must take sugar. But for me, I had never experienced hypo so far." (Participant 12)

"There is no problem when fasting. I am already old and get used to fasting during Ramadan. If hypo, just break the fast will do." (Participant 28)

Sub-theme 2.3 Source of information

Half of the participants (n=15) gained the information from healthcare providers such as pharmacist, doctor, nurse, or medical assistant, while some participants (n=3) acquired the information from pamphlet.

"Pharmacist always provides the information regarding this matter." (Participant 22)

"I got a pamphlet from pharmacy, it contains information on how to take medication during fasting month." (Participant 23)

Only three participants claimed they never received any information regarding how to manage diabetes during Ramadan.

"No. Doctor never teach me, I do it by myself." (Participant 3)

Sub-theme 2.4 Adjustment of medications

More than half of the participants (n=18) did not adjust their medications during Ramadan. Some agreed that the doses of their medications were adequate during Ramadan, while some dare not adjust by themselves.

"I didn't change the dose (of my insulin). My (insulin) dose only little. My body also okay." (Participant 16)

"I do not dare to change the units (of insulin). I'm afraid not enough (dose) or over inject." (Participant 25)

Only seven participants adjusted their diabetic medications during Ramadan. Some of them did as instructed by the healthcare providers, while some adjusted the medications by their own based on their body condition.

"Let's say if usually we inject 30 (units of insulin) and 26 (units of insulin). You revert it (dose of insulin) when fasting. Morning can reduce a bit (dose) some more. Doctor told me to do so." (Participant 1)

"Yes. I increased 2 units before going for Raya feast. It's up to us how to adjust it." (Participant 10)

Theme 3: Diet control

Sub-theme 3.1 Challenges in controlling diet

Half of the participants (n=15) claimed that they had no problem in adjusting their diet during Ramadan since they were used to fast. There was not much difference in terms of food intake during fasting and non-fasting month.

"Nothing. Maybe I already get used to it. Whether fasting or not, it's the same. I don't feel hypo, dizzy, hungry, tired or anything." (Participant 4)

"For me is not a problem. We should know the risk (of not controlling diet) ourselves. We cannot eat extra. Same only (amount of food intake) fasting or not fasting." (Participant 5)

Some of the participants (n=5) agreed that there were challenges in controlling their diet during fasting, but they knew they must not have excessive food intake to ensure good glycaemic control. Two participants mentioned that the most challenging part was to resist their craving for food when they visited *Bazaar Ramadan* (local food market specially operating during Ramadan).

"It's hard to control what we eat. But since it is fasting month, we are forced not to eat during the day. Challenging but you have to accept it." (Participant 20)

Sub-theme 3.2 Changes in eating habit

Less than half of the participants (n=10) claimed that there were no changes in their eating habits. The amount of food intake was similar during fasting and non-fasting month.

> *"During non-fasting month, I did not eat much. I usually eat the same amount every day. I only eat half plate of rice. So as usual ... I only eat a little." (Participant 3)*

> *"Dietary intake is similar as always. Nothing changes." (Participant 7)*

Meanwhile, some of the participants admitted that there were changes in their food intake during the fasting month. They were able to reduce sugar intake, as in overall the amount of food intake is reduced during Ramadan.

> *"Reduce in dietary intake during fasting month. I only eat a little at night." (Participant 29)*

Theme 4: Self-monitoring blood glucose (SMBG)

Sub-theme 4.1 Practicing SMBG

One third of the participants (n=10) kept a glucometer at home. Among them, only eight participants performed blood glucose checking at home, while the other two participants claimed not checking blood glucose for a period of time because of financial constraint.

> *"I do it (SMBG) twice to three times daily ... If it's a fasting month, I check before sahur and before breaking the fast in the evening." (Participant 2)*

> *"I have a machine (glucometer) at home. Check 4 or 5 times a week. If I feel weak I will check too." (Participant 20)*

A few participants (n=5) carried out random blood glucose monitoring at health clinics or community pharmacy, based on symptoms and their body conditions.

> *"I check at health clinic once a week. Doctor asked me to go. (The clinic is) Near Palong." (Participant 6)*

Some of the participants (n=5) believed that examination during clinic appointment with doctor was adequate, thus further blood glucose monitoring was not required.

> *"I rarely go for blood sugar checking. Usually I check it when I have an appointment." (Participant 15)*

Sub-theme 4.2 Benefits of SMBG

More than half of the participants (n=18) believed they could benefit from SMBG practice. By monitoring own blood sugar, they could adjust the dose of insulin or amount of carbohydrate intake based on the blood glucose level. It also helped them to decide whether to continue fasting or to break the fast.

> *"First I can know how much of sugar (level) in my body is now. Second, I can know how many (insulin) to inject. For example, if high, add 2 units (of insulin)." (Participant 8)*

> *"If below 4 (blood glucose level) I'll break the fast because I'm scared of hypo, but if I feel hot, hunger, thirst, then I'll check the reflo (blood glucose level). If the level is high, I'll inject Actrapid." (Participant 11)*

> *"I can know the blood sugar level in the body. If the sugar is high, I'll control dietary intake, and take less sugar." (Participant 12)*

Sub-theme 4.3 Barriers in practicing SMBG

Cost and logistic issues were two main barriers to practicing SMBG among the participants (n=16). In addition, some participants who stayed in rural area and could not afford a glucometer need to travel a distance to the nearest health clinic or community pharmacy to check their blood sugar level, thus routine blood sugar monitoring was not feasible.

> *"Yes. Sometimes it's a problem to buy (test strips). Because I only have two children. Both are working, and I stay with my husband. If it (test strips) almost finish, I'll let them know earlier. It's*

difficult to buy, because it is not sold at the clinic, can only buy (the glucose test strips) from the pharmacy and the pharmacy is far, it's at Bahau." (Participant 2)

"No money. The needle (lancet) is expensive, the paper (test strip) also expensive. Sometimes I do it every week, sometimes not, it depends (on my financial status)." (Participant 13)

Some found that SMBG was time-consuming and difficult to perform on their own at home.

"Expensive. And I'm old, don't know how to do it by myself." (Participant 27)

One participant mentioned that it was difficult to buy the glucose strip for the brand of glucometer that he was using, thus limiting his practice of SMBG.

"The problem is very difficult to find the strip. Sometimes the brand is not available anymore." (Participant 12)

Only two participants did not have any issues in practicing SMBG.

"No. There is no obstacle. The clinic is near to my house and Alpro (pharmacy) also is not that far." (Participant 5)

Discussion

Previous studies reported that there were significant numbers of patients who did not consult a health professional prior to Ramadan fasting and some even fasted against medical advice, leading to unpleasure experiences during the Ramadan (2-4,11,12). The decision to fast might be influenced by family pressures and the overall social aspects of fasting (4,13). This study explores the perception and behaviour of T2DM patients towards diabetes management during the Ramadan. Understanding from the aspect of patients is extremely important, as this information could assist healthcare providers to structure their care plan according to patient's perspective of view, subsequently providing a more comprehensive care to ensure safe fasting.

The most common risks of fasting among diabetic patients are hypoglycaemia, hyperglycaemia and dehydration (1). It is therefore very important for patients to have the basic knowledge of diabetes to enable better self-management of diabetes during Ramadan. The EPIDIAR study showed that during the Ramadan, the risk of severe hypoglycaemia increased by 7.5 folds (0.4 to 3 events per 100 month) while causing a five-fold increase in the incidence of severe hyperglycaemia in T2DM patients. One of the main reasons was due to the lack of knowledge in managing diabetes during Ramadan (2).

The recent DAR 2020 Global Survey observed a high rate of Ramadan fasting regardless of fasting risk level (14). Although less than half of the participants in this study knew the risk of fasting, majority of them were able to fully fast throughout the Ramadan. This showed that Malaysia Muslims have a strong will in fasting. This finding is similar to a study by Salti *et al.*, in which the proportion of subjects fasting for at least 15 days is highest in Malaysia (89.8%) among the 13 countries studied (2). Although some of the participants were experiencing some issues such as thirst and hunger, they still continued to fast in view of their past experiences of fasting for years. Most of the participants chose to fast because they believed that fasting could help improving their general well-being. This was similar to another study by Lee *et al.*, where participants reported optimism towards fasting because they believed that fasting is beneficial to their overall well-being and family bonding (15). Some of our participants believed in the *pahala* (reward) and Allah gives them the willpower to abstain from food and drinks.

In order to minimise the adverse effects during fasting among diabetic patients and to maintain good glycaemic control, patient education and discussion of glucose monitoring and treatment regimens with their healthcare provider shall occur several weeks prior to Ramadan (16). Ramadan-focused education in diabetes empowers the patients to change their lifestyle during Ramadan, thus minimising the risk of hypoglycaemic events and preventing weight gains, which potentially benefits metabolic control (17). In this study, only half of participants claimed that they obtained right information from their healthcare providers prior to Ramadan and some of the participants acquired the information through pamphlet. Most of the participants in this study were educated with only two did not receive any formal education. Hence, this may explain why majority of the participants in this study had the knowledge on management of hypoglycaemia during Ramadan and did not experience any symptoms of hypoglycaemia while fasting.

A significant improvement in HbA1c was observed in patients who had adjustments made to their doses of antidiabetic agents during the Ramadan (18). However, there were only a few of our respondents

who adjusted the doses of insulin during fasting although most of them received relevant information from their healthcare providers. This was probably because the information provided focused more on non-pharmacological management. According to Beshyah *et al.*, physicians demonstrated inconsistencies in their level of knowledge, attitude and practices about the care of patients with diabetes during Ramadan (19). Therefore, it was recommended that simplified guidelines and educational materials could be dispensed to healthcare providers before Ramadan (20). To ensure that the patients are well equipped with the knowledge in pharmacological management, all diabetic patients should discuss with their healthcare providers regarding the need to change their medication regimen before Ramadan. This is especially true for all insulin users, as they should know how to adjust their insulin accordingly as most of the insulin regimes require adjustment according to the change of meal pattern in Ramadan.

Major changes in the dietary habits, daily physical activities and sleeping patterns during Ramadan have significant impact on glycaemic control, lipid profile, weight and dietary intake (21). In a study by Trepanowski and Bloomer in 2010, dietary changes pertaining to calorie intake may or may not differ over the period of Ramadan. These differences were responsible for the discrepancies in health-related outcome. Hence, whether or not Ramadan fasting elicits favourable health outcomes, it depends on the food choices of the fasters (22).

Lacking of food and water intake during the day along with heavy meals before and after fasting could create serious health issues as the routine diet pattern is disrupted. Most of the participants in this study seemed to understand this concept and thus reported an unchanged dietary intake, while less than half of the participants reported a reduction in dietary intake and there was no report of increased dietary intake. Majority of the participants in this study were more than 50 years old, thus they could have relatively poor appetite. Pilgrim *et al*. in 2015 found that many older people experience decreased appetite due to many factors including changes in physiological function, social circumstances, acute illness, chronic disease and use of medications (23).

SMBG is an important component of modern therapy for Diabetes Mellitus in order to achieve the targeted glycaemic control and to prevent hypoglycaemia (24-26). More detailed information on blood glucose level can be obtained by practicing SMBG. This information can help in the adjustment of a therapeutic regimen, modifying dietary intake and insulin dose on a regular basis (24). Most of the participants in this study also agreed that via SMBG, they could monitor their blood glucose level well during fasting month. SMBG can assist them in insulin adjustment, help them in making decision when to break the fast, and to modify their carbohydrate intake. A prospective study by Ahmedani *et al.* observed that with active glucose monitoring, alteration of drug dosage and timing, dietary counselling and patient education, majority of the patients did not have any serious acute complications during the Ramadan (27).

Although most of the participants in this study understood the benefits of SMBG practice, only a few of them owned a glucometer and performed SMBG routinely. The others only did random blood glucose checking when they felt unwell or during appointment with doctor. Cost was identified as the main barrier to SMBG in this study. As most of the participants in this study had low income (less than RM2,000 per month), they might not afford to buy the test strips and monitored blood sugar regularly. Considerable gaps persisted between the actual and recommended SMBG practices. Patients paying higher out-of-pocket expenditures for test strips were reported to have lower frequency of SMBG, which suggested that removing the financial barriers may probably increase the practice SMBG (28). Logistic issue was another common barrier to routine monitoring of blood glucose. Some of the participants stay in rural area, thus accessibility to nearest healthcare facilities or community pharmacy for blood glucose checking was an issue. Besides, the availability of glucose test strips was another obstacle in practicing SMBG. There were many brands of glucometers and glucose test strips available in the market. Whether or not a retail pharmacy keeps certain brands of glucose test strips was another factor in affecting SMBG practice.

By understanding patients' perception and behaviour during Ramadan, healthcare providers can optimise pre-Ramadan interventions to ensure safe fasting. Services can be expanded to incorporate other healthcare practitioners such as pharmacists, dieticians and nurses in giving advices on lifestyle modification, medication adjustment and active glucose monitoring during Ramadan. The main limitation of the study was that participants' responses were not correlated to clinical variables such as HbA1c and blood glucose readings. Future studies can focus on behavioural relationship with clinical variables to cater more insightful findings.

Conclusion

This study found that Muslim diabetic patients could be optimistic about Ramadan fasting as they believed that fasting can help to improve their general well-being. The patients, however, may not adjust their antidiabetic medications during the Ramadan. SMBG may not be widely practiced by the patients due to cost and logistic factors although they may be well aware of its importance. Therefore, healthcare providers should play a more active role in providing proper and adequate information to diabetic patients who wish to fast during Ramadan, with emphasis on the importance of medication adjustment and blood glucose monitoring. SMBG practice should be encouraged in all diabetic patients especially those on medications. This study outcome can assist healthcare providers to know better about patient's perspective of view, hence providing more comprehensive care to ensure safe fasting during Ramadan.

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Conflict of Interest

The authors declare that they have no competing interests.

References

1. International Diabetes Federation and the DAR International Alliance. Diabetes and Ramadan: Practical Guidelines. Brussels, Belgium: International Diabetes Federation, 2016. www.idf.org/guidelines/diabetes-in-ramadan and www.daralliance.org.
2. Salti I, Bénard E, Detournay B, Bianchi-Biscay M, Le Brigand C, Voinet C, Jabbar A. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. Diabetes care. 2004 Oct 1;27(10):2306-11.
3. Adarmouch L, Elansari N, Ouhdouch F, Amine M. The Behavior of Muslim Type 2 Diabetic Patients towards the Fasting of Ramadan. Ibnosina Journal of Medicine & Biomedical Sciences. 2013 Nov 1;5(6).
4. Mygind A, Kristiansen M, Wittrup I, Nørgaard LS. Patient perspectives on type 2 diabetes and medicine use during Ramadan among Pakistanis in Denmark. International journal of clinical pharmacy. 2013 Apr 1;35(2):281-8.
5. Babineaux SM, Toaima D, Boye KS, Zagar A, Tahbaz A, Jabbar A, Hassanein M. Multi-country retrospective observational study of the management and outcomes of patients with Type 2 diabetes during Ramadan in 2010 (CREED). Diabetic Medicine. 2015 Jun;32(6):819-28.
6. Al-Arouj M, Assaad-Khalil S, Buse J, Fahdil I, Fahmy M, Hafez S, Hassanein M, Ibrahim MA, Kendall D, Kishawi S, Al-Madani A. Recommendations for management of diabetes during Ramadan: update 2010. Diabetes care. 2010 Aug 1;33(8):1895-902.
7. Mohamed GA, Car N, Muacevic-Katanec D. Fasting of persons with diabetes mellitus during Ramadan. Diabetologia Croatica. 2002 Jan 1;31(2):75-84.
8. Al-Qazaz HK, Hassali MA, Shafie AA, Sulaiman SA, Sundram S. Perception and knowledge of patients with type 2 diabetes in Malaysia about their disease and medication: a qualitative study. Research in Social and Administrative Pharmacy. 2011 Jun 1;7(2):180-91.
9. Tracy SJ. Qualitative research methods: Collecting evidence, crafting analysis, communicating impact. John Wiley & Sons; 2019 Aug 20.
10. Straus A, Corbin J. Basics of qualitative research: grounded theory procedures and techniques. Newbury Park, CA: Sage, 1990.
11. Chowdhury TA. A survey of patients with type 2 diabetes and fasting outcomes during Ramadan 2016 in London: the East London Diabetes in Ramadan Survey. British Journal of Diabetes. 2017 Dec 15;17(4):149-51.
12. Gaborit B, Dutour O, Ronsin O, Atlan C, Darmon P, Gharsalli R, Pradel V, Dadoun F, Dutour A. Ramadan fasting with diabetes: an interview study of inpatients' and general practitioners' attitudes in the South of France. Diabetes & metabolism. 2011 Nov 1;37(5):395-402.
13. Patel NR, Kennedy A, Blickem C, Rogers A, Reeves D, Chew-Graham C. Having diabetes and having to fast: a qualitative study of British Muslims with diabetes. Health Expectations. 2015 Oct;18(5):1698-708.

14. Hassanein M, Hussein Z, Shaltout I, Seman WJ, Voon TC, Noor NM, Buyukbese MA, El Tony L, Shaker GM, Alamoudi RM, Hafidh K. The DAR 2020 Global survey: Ramadan fasting during COVID 19 pandemic and the impact of older age on fasting among adults with Type 2 diabetes. Diabetes research and clinical practice. 2021 Jan 23.
15. Lee JY, Wong CP, San San Tan C, Nasir NH, Lee SW. Type 2 diabetes patient's perspective on Ramadan fasting: a qualitative study. BMJ Open Diabetes Research and Care. 2017 May 1;5(1):e000365.
16. Ibrahim M, Al Magd MA, Annabi FA, Assaad-Khalil S, Ba-Essa EM, Fahdil I, Karadeniz S, Meriden T, Misha AA, Pozzilli P, Shera S. Recommendations for management of diabetes during Ramadan: update 2015. BMJ Open Diabetes Research and Care. 2015 Jun 1;3(1):e000108.
17. Bravis V, Hui E, Salih S, Mehar S, Hassanein M, Devendra D. Ramadan Education and Awareness in Diabetes (READ) programme for Muslims with Type 2 diabetes who fast during Ramadan. Diabetic Medicine. 2010 Mar;27(3):327-31.
18. Siaw MY, Chew DE, Dalan R, Shakoor A, Kamaldeen SA, Othman N, Choo CH, Shamsuri NH, Abdul Karim SN, Chan SY, Lee JY. Evaluating the effect of Ramadan fasting on muslim patients with diabetes in relation to use of medication and lifestyle patterns: a prospective study. International journal of endocrinology. 2014;2014.
19. Beshyah SA, Farooqi MH, Farghaly M, Abusnana S, Al Kaabi JM, Benbarka MM. Management of Diabetes during Ramadan Fasting: A Comprehensive Survey of Physicians' Knowledge, Attitudes and Practices. Ibnosina Journal of Medicine and Biomedical Sciences. 2017 Mar 1;9(2):28-36.
20. Hassanein M, Bashier A, Abdelgadir E, Al Saeed M, Alawadi F, Khalifa A. Survey of the knowledge and attitude of physicians toward the management of diabetes mellitus during Ramadan. Journal of Fasting and Health. 2016;4(3):117-21.
21. Hui E, Devendra D. Diabetes and fasting during Ramadan. Diabetes/metabolism research and reviews. 2010 Nov;26(8):606-10.
22. Trepanowski JF, Bloomer RJ. The impact of religious fasting on human health. Nutrition journal. 2010 Dec;9(1):57.
23. Pilgrim A, Robinson S, Sayer AA, Roberts H. An overview of appetite decline in older people. Nursing older people. 2015 Jun;27(5):29.
24. Benjamin EM. Self-monitoring of blood glucose: the basics. Clinical diabetes. 2002 Jan 1;20(1):45-7.
25. Lee JY, Wong CP, San San Tan C, Nasir NH, Lee SW. Telemonitoring in fasting individuals with Type 2 Diabetes Mellitus during Ramadan: A prospective, randomised controlled study. Scientific reports. 2017 Aug 31;7(1):10119.
26. Poolsup N, Suksomboon N, Rattanasookchit S. Meta-analysis of the benefits of self-monitoring of blood glucose on glycemic control in type 2 diabetes patients: an update. Diabetes technology & therapeutics. 2009 Dec 1;11(12):775-84.
27. Ahmedani MY, Haque MS, Basit A, Fawwad A, Alvi SF. Ramadan Prospective Diabetes Study: the role of drug dosage and timing alteration, active glucose monitoring and patient education. Diabetic Medicine. 2012 Jun;29(6):709-15.
28. Karter AJ, Ferrara A, Darbinian JA, Ackerson LM, Selby JV. Self-monitoring of blood glucose: language and financial barriers in a managed care population with diabetes. Diabetes care. 2000 Apr 1;23(4):477-83.

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