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# Comparison between conventional dosing versus personalized pharmacokinetic dosing of vancomycin: a pilot study from a Malaysian private hospital

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ABSTRACT

Pharmacist led vancomycin dosing is not a common practice in private hospital settings of the Malaysian healthcare system. The lack of this pharmacist led system has led to conventional vancomycin dosing without considering the differences in patients pharmacokinetic parameters. This study aims to compare the differences in vancomycin doses between conventional dosing and pharmacist-led personalized pharmacokinetic dosing. A retrospective pilot study was conducted on inpatient adults who were prescribed with intravenous vancomycin in a private hospital. Personalized vancomycin doses were retrospectively calculated by using the pharmacokinetic parameters and was then compared with the actual conventional doses used in the patients. The area under concentration curve over 24 hours/minimum inhibitory concentration ($AUC_{24}$/MIC) ratio achieved by the doses was also compared. The targeted $AUC_{24}$/MIC ratio was 400-600 to ensure efficacy and safety of the therapy. A total of 24 patients with a median age of 55.50 years were conveniently sampled. The patients were mostly male (58.3%) and were admitted to the neurosurgical ward (33.3%). Vancomycin was mainly prescribed as empirical treatment (58.3%) for a median treatment period of 5.00 days (IQR 4.00 – 7.00 days). The conventional doses had significant ($p < 0.001$) lower median total daily dose (2000 mg versus 2500 mg) and lower $AUC_{24}$/MIC ratio (385 versus 495) as compared to personalized doses. In conclusion, the personalized pharmacokinetic dosing method was significantly more able to achieve the targeted $AUC_{24}$/MIC ratio. Vancomycin personalized dosing should be considered in the Malaysian private hospital setting.

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## INTRODUCTION

Vancomycin is the key therapeutic option for the treatment of highly resistant gram positive infections caused by methicillin resistant *Staphylococcus aureus* (MRSA) and methicillin resistant coagulase negative *Staphylococcus* species (Liu *et al.*, 2011). A previous study from Malaysia reported that 21% of nosocomial bacteraemia were caused by MRSA (Ahmad *et al.*, 2010). Besides, there was an increase in the prevalence of MRSA in Malaysia from 17% to 44.1% in around 20 years (Ahmad *et al.*, 2009; Rohani *et al.*, 2000). Vancomycin is a large

glycopeptide compound that is not absorbed orally and is eliminated primarily through kidney (Matzke *et al.*, 1986). During haemodialysis, the vancomycin dialysability was minimal (0-5%) with conventional low flux dialyser. Most dialysis centres nowadays use high flux dialysers with a median percentage of dialysability around 31% (Petejova *et al.*, 2012). Vancomycin is a drug with narrow therapeutic window. Serum drug concentration must achieve specific therapeutic range to ensure optimum treatment (Pharmacy Practice & Development Division, 2019). Serum trough concentration is one of the methods to monitor vancomycin toxicity and efficacy as vancomycin poses a time dependent bactericidal effect. Area under concentration curve over 24 hours/minimum inhibitory concentration ($AUC_{24}$/MIC) ratio is another method of vancomycin therapeutic effect monitoring (Rybak *et al.*, 2020). $AUC_{24}$/MIC ratio of $\geq$ 400 is recommended as it has been associated with greater clinical success and more rapid bacterial eradication (Moise-Broder *et al.*, 2004).

Serum trough concentration of 15–20 mg/L is the surrogate marker for $AUC_{24}$/MIC of $\geq$ 400 for a MIC of $\leq$ 1.0 mg/L (Álvarez *et al.*, 2016). Hence, the Infectious Disease Society of America (IDSA) recommended 15–20 mg/L as the targeted trough concentration of vancomycin for critically ill adults and >10 mg/L for all other adult patients (Liu *et al.*, 2011). Currently, increasing MIC value of MRSA strains has been observed in Malaysian hospitals. A total of 95% of the MRSA strains found to have a vancomycin MIC of $\geq$ 1.0 mg/L (Ahmad *et al.*, 2010). Therefore, optimal vancomycin dosing is important as newer and effective agents to target highly resistant gram-positive organisms is limited. The conventional dosing regimen of vancomycin is a daily dose of 2000 mg divided to either 500 mg every 6 hourly or 1000 mg every 12 hourly for adults with normal kidney function (Pfizer, 2018). The dose can be given as 15-20 mg/kg of actual body weight every 8 to 12 hourly as an alternative if the patient's weight data is available (Rybak *et al.*, 2009).

The above mentioned conventional method of vancomycin dosing is a common practice among private hospitals in Malaysia which generally do not establish a therapeutic drug monitoring system for personalized pharmacokinetic dosing. The personalized dosing method considers the patient's kidney function and pharmacokinetic parameters such as the volume of distribution and elimination rate constant in the determination of vancomycin dosing regimen (Matzke *et al.*, 1984). This ensures the dose can achieve the targeted serum concentration and $AUC_{24}$/MIC to optimize the therapeutic effect (Pharmacy Practice & Development Division, 2019). The personalized dosing is routinely practiced among the government hospitals in Malaysia by the clinical pharmacists (Pharmacy Practice & Development Division, 2019). The pharmacist-led clinical pharmacokinetic services are well-established among the Malaysian government hospitals in which therapeutic drug monitoring on narrow therapeutic index drugs are performed (Rahman *et al.*, 2013). The serum drug concentrations are monitored in therapeutic drug monitoring. Subsequently, personalized pharmacokinetic parameters can be determined from the serum concentrations. The patient's dosing regimen can be adjusted accordingly to the serum concentration and the personalized pharmacokinetic parameters (Pharmacy Practice & Development Division, 2019).

Personalized dosing method allows patients with specific disease states and conditions to have an individualized target serum concentration and a customized pharmacokinetic parameter (Bauer, 2008). Pharmacokinetic monitoring of vancomycin was cost effective for those who received concomitant nephrotoxins, intensive care and oncology patients (Darko *et al.*, 2003). Besides, a systematic review suggested that patients who underwent therapeutic drug monitoring have higher rates of therapeutic efficacy and reduced rates of kidney toxicity than those who not under the monitoring (Ye *et al.*, 2013). Personalized dosing method has been shown to improve treatment outcomes, reduce adverse effects and costs (Darko *et al.*, 2003; Ye *et al.*, 2013). A prospective randomized trial suggested personalized pharmacokinetic dosing over conventional dosing method of aminoglycosides (Begg *et al.*, 1989). Besides, a previous study concluded that personalized dosing method significantly reduced time to attain desire vancomycin trough concentration (Miller *et al.*, 2018).

In the presence of pharmacy-led vancomycin dosing and monitoring system, the percentage of patients achieving vancomycin serum therapeutic levels were increased while the percentage of acute kidney injury was decreased (Momattin *et al.*, 2016). Nevertheless, the Malaysian private hospitals are generally using conventional dosing method for vancomycin. There is a lack of pharmacists led therapeutic drug monitoring in private hospitals to guide the dosing of vancomycin. Without the monitoring of serum drug concentration, the vancomycin dose can still be personalized by performing a pharmacokinetic calculation based on a patient's kidney function and body weight (Pharmacy Practice & Development Division, 2019). There is a need to compare the use of conventional versus pharmacist

led personalized pharmacokinetic dosing method for vancomycin in the Malaysian private hospital setting. This pilot study, therefore, aimed to evaluate the differences in the dose by using a conventional dosing method compared to personalized pharmacokinetic dosing method for vancomycin therapy in a private hospital in Malaysia. The difference in $AUC_{24}$/MIC ratio achieved by these two dosing methods was also assessed.

## MATERIALS AND METHODS

### Study design

This was a single centre retrospective observational pilot study conducted at KPJ Johor Specialist Hospital, a 243 bedded private hospital in southern part of peninsular Malaysia, consisting of intensive care units, pediatric, orthopedic, surgical, oncology, geriatrics, obstetrics and gynecology specialties. This study has granted ethics approval from KPJ Research Ethics Review Committee and Human Ethics Committee of Universiti Sains Malaysia (ethics approval number: USM/JEPeM/18100612). The inclusion criteria were adult patients admitted to the ward and received intravenous vancomycin treatment as part of inpatient therapy. Patients who were below the age of 18 years old, without documented body weight or serum creatinine level, received continuous renal replacement therapy at the same time as vancomycin administration were excluded from the study.

### Data collection

Warded patients who received vancomycin therapy from $1^{st}$ January 2016 to $31^{st}$ August 2018 were identified through pharmacy records. The patients' case notes and medication charts were traced from the medical report department and retrospectively screened for eligibility to be recruited in the study. Convenient sampling was used in patient recruitment. The patients data were collected and recorded in a specifically designed data collection form. The data collected were including patients age, gender, ethnicity, height, body weight, infection type and site of the positive MRSA culture, serial blood urea nitrogen, serial serum creatinine, fluid balance, serial vancomycin dosage regimes and duration of therapy. Additionally, patient's exposure to nephrotoxic agents, including radiographic contrast agents, aminoglycosides, diuretics, cyclosporin, tacrolimus, nonsteroidal inflammatory drugs, cyclooxygenase-2 (COX-2) inhibitors, as well as angiotensin converting enzyme inhibitors and angiotensin receptor blocking agents were recorded. The patient's comorbidity information was also collected to calculate the Charlson Comorbidity Index scores.

### Personalized pharmacokinetic dose calculation

The personalized vancomycin doses were manually calculated by the principle investigator (first author) by using pharmacokinetic formulae listed below. The elimination rate constant ($k_e$) was computed using Equation (1) from Matzke *et al.* (1984).

Elimination rate constant,

$$k_e = 0.00083\ \text{ClCr} + 0.0044 \quad (1)$$

Creatinine clearance (ClCr) was calculated using Cockcroft–Gault equation as showed in Equations (2) and (3) (Cockcroft and Gault, 1976).

Male ClCr =

$$\frac{(140 - \text{Age})\ \text{x Body weight}}{\text{SrCr}\ \left(\mu\text{molL}^{-1}\right)} \times 1.23 \quad (2)$$

Female ClCr =

$$\frac{(140 - \text{Age}) \times \text{Body weight}}{\text{SrCr}\ \left(\mu\text{molL}^{-1}\right)} \times 1.04 \quad (3)$$

The body weight used for Cockcroft-Gault equation was varied (Winter, 2010). Actual body weight was used in underweight patients and ideal body weight in patients of normal weight as showed in Equations (4) and (5) (Winter *et al.*, 2012). For overweight, obese, and morbidly obese patients, adjusted body weight as showed in Equation (6) was used (Winter *et al.*, 2012). The body weight categories were based on the following body mass index (BMI) structure: underweight patients, BMI of less than 18.5 kg/m$^2$; normal weight patients, 18.5-22.9 kg/m$^2$; overweight patients, 23.0-27.4 kg/m$^2$; obese patients, 27.5-39.9 kg/m$^2$; and morbidly obese patients, 40 kg/m$^2$ or greater (Ministry of Health Malaysia, 2004).

$$\text{Male IBW} = 50 + 0.9\ (\text{Ht in cm} - 152) \quad (4)$$

$$\text{Female IBW} = 45.5 + 0.9\ (\text{Ht in cm} - 152) \quad (5)$$

Adjusted body weight =

$$\text{IBW} + 0.4\ (\text{Actual body weight} - \text{IBW}) \quad (6)$$

Vancomycin clearance (Cl) was assumed as equal to creatinine clearance as vancomycin is mainly excreted by the kidney in adults $\geq$ 18 years old (Winter *et al.*, 2012). The volume of distribution (Vd) was calculated using the patient's personalized vancomycin Cl (in L/h unit) and elimination rate constant as showed in Equation (7) (Winter *et al.*, 2012).

$$\text{Volume of distribution, Vd} = \frac{\text{Cl}}{\text{K}_e} \quad (7)$$

Peak serum concentration (Cmax) was set at 25–30 mg/L whereas trough serum concentration (Cmin) was set at 14–16 mg/L in accordance with the recommendation to achieve $AUC_{24}$/MIC ratio of $\geq$ 400 (Álvarez *et al.*, 2016). In cases where the organism's MIC was available, the target Cmin would be based on the MIC, with a target of 8 to 10 times the reported MIC (Pharmacy Services UK Health Care, 2017). The infusion time ($t_{inf}$) of vancomycin was assumed as one hour for doses $\leq$ 1000 mg and two hours for doses that were > 1000 mg (Malaysian Society of Intensive Care, 2017). New dosing interval was calculated using the formula in Equation (8) (Matzke *et al.*, 1984) and was rounded up to 8, 12, 18, 24, 36, 48 and 72 hours.

Dosing interval,

$$\tau = \frac{\ln\left(C_{max}/C_{min}\right)}{K_e} + t_{inf} \quad (8)$$

New personalized vancomycin dose was then calculated using the pharmacokinetic infusion formula based on one compartmental model as listed in Equation (9) (Winter *et al.*, 2012) below and was rounded up to the nearest 50 mg.

Dose (in $mgh^{-1}$) =

$$C_{max}.k_e.Vd.\left[\frac{\left(1-e^{-k_e\tau}\right)}{\left(1-e^{-k_e t_{inf}}\right)}\right] \quad (9)$$

The $AUC_{24}$/MIC ratio was calculated as listed in Equation (10) (Pharmacy Practice & Development Division, 2019). The daily $AUC_{24}$/MIC ratio was computed based on patient's 24-hour daily dose for both conventional and personalized dosing method as showed in Equation (9), vancomycin clearance as showed in Equations (2) and (3) in L/h unit and the MIC of the infecting pathogen. Any missing MIC value from the data will be assumed as 1.0 mg/dL. This assumption was based on Malaysian local data (Ahmad *et al.*, 2010).

$$AUC_{24}/MIC = \frac{\text{Total daily dose}}{Cl \times MIC} \quad (10)$$

### Data analysis

The completed calculated personalized vancomycin pharmacokinetic doses were reviewed and double checked by the co-investigator (second author) for the completeness and accuracy of the data. All statistical analyses were performed using IBM SPSS® version 24. Mann-Whitney U test was used to compare the actual administered doses (conventional dosing) and calculated pharmacokinetic doses (personalized dosing) in the context of dose differences and $AUC_{24}$/MIC ratio differences. The Wilcoxon signed rank test was used to compare the differences between kidney function at baseline and at the end of therapy in the patients received conventional vancomycin doses. A $p$ value of < 0.05 was deemed statistically significant.

## RESULTS

A total of 24 patients were recruited in the study (Table 1). The median age of the patients was 55.50 years (IQR: 36.75 – 63.00). Majority of the patients were male (58.3%) with neurosurgical (33.3%) as the most frequent prescribing discipline for vancomycin. Vancomycin was mainly used as an empirical treatment (58.3%) for respiratory tract infections (20.8%) and bloodstream infections (8.3%). As definitive therapy (41.7%), vancomycin was primarily prescribed for respiratory tract infection (12.5%) as well. The median duration of vancomycin therapy was 5.00 days (IQR: 4.00 – 7.00). Meanwhile, the patients' median Charlson Comorbidity Index score was 2.5 (IQR: 2.0 – 6.0).

Comparison between dosing method showed that the average total daily dose of vancomycin received by the patients (using conventional dosing) was significantly lower than if personalized pharmacokinetic dosing were used. The patients in this study received a median fixed dose of vancomycin 2000 mg daily (IQR: 1500 – 2000 mg). When calculated using the personalized pharmacokinetic method, a higher median total daily dose requirement of 2500 mg (IQR: 1900 – 3300 mg) was observed. This trend was also observed when evaluating the total daily dose on a day-by-day basis, whereby the patients were consistently being prescribed significantly lower conventional doses than the calculated personalized pharmacokinetic doses (Table 2).

Vancomycin $AUC_{24}$/MIC ratio achieved in both dosing method is illustrated in Table 3. There was a significant difference in average $AUC_{24}$/MIC ratio between the two dosing methods with the median value of 385 (IQR: 244 – 463) in the conventional dosing method versus 495 (IQR: 472 – 514) in the personalized pharmacokinetic dosing method. Attainment of $AUC_{24}$/MIC ratio of > 400 was observed only on the first two days of treatment in the patients who received conventional dosing in this study. Meanwhile, if the patients were receiving personalized pharmacokinetic dosing, the $AUC_{24}$/MIC ratio would be > 400 throughout the treatment days. Considering the patients kidney function, the median baseline serum creatinine was 71.0 $\mu$mol/L (IQR: 64.0 – 99.0) and creatinine clearance was 79.8 mL/min (IQR: 52.7 – 108.00). Meanwhile, the median baseline blood urea nitrogen was

**Table 1: Patients baseline demographic characteristics**

| Demographic characteristics | n (%) | Demographic characteristics | n (%) |
|---|---|---|---|
| **Gender** | | **Indication for vancomycin** | |
| Male | 14 (58.3) | **Empirical** | 14 (58.3) |
| Female | 10 (41.7) | Respiratory tract infection | 5 (20.8) |
| | | Bloodstream infection | 2 (8.3) |
| **Age** | | Skin and soft tissue infection | 1 (4.2) |
| 21 – 30 years | 2 (8.3) | Bone and joint infection | 1 (4.2) |
| 31 – 40 years | 6 (25.0) | Central nervous system infection | 1 (4.2) |
| 41 – 50 years | 2 (8.3) | Intra-abdominal infection | 1 (4.2) |
| 51 – 60 years | 8 (33.3) | Surgical site infection | 1 (4.2) |
| > 60 years | 6 (25.0) | Others | 2 (8.3) |
| | | **Definitive** | 10 (41.7) |
| **Ethnicity** | | Respiratory tract infection | 3 (12.5) |
| Malay | 7 (29.2) | Central nervous system infection | 2 (8.3) |
| Indian | 8 (33.3) | Skin and soft tissue infection | 2 (8.3) |
| Chinese | 6 (25.0) | Surgical site infection | 2 (8.3) |
| Others | 3 (12.5) | Bone and joint infection | 1 (4.2) |
| **Body Mass Index** | | **Site of positive MRSA culture** | |
| 20.0 – 25.0 kg/m2 | 12 (50.0) | Skin tissue or pus swab | 5 (20.8) |
| 26.0 – 30.0 kg/m2 | 8 (33.3) | Respiratory tract | 3 (12.5) |
| > 30 kg/m2 | 4 (16.7) | Tip of catheter | 2 (8.3) |
| | | No culture | 14 (58.3) |
| **Discipline** | | | |
| Neurosurgical | 8 (33.3) | Duration of vancomycin therapy | |
| Orthopaedic | 5 (20.8) | 2 – 5 days | 17 (70.8) |
| Internal medicine | 4 (16.7) | > 5 days | 7 (29.2) |
| Intensive care | 2 (8.3) | | |
| Nephrology | 2 (8.3) | Concurrent nephrotoxic drugs | |
| Respiratory | 2 (8.3) | Diuretics | 4 (16.7) |
| Other | 1 (4.2) | Angiotensin II receptor blockers | 3 (12.5) |
| | | COX-2 inhibitors | 3 (12.5) |
| | | Aminoglycosides | 1 (4.2) |
| | | Nil | 13 (54.2) |

COX-2 inhibitors = cyclooxygenase-2 inhibitors

6.1 mmol/L (IQR: 3.8 – 19.2). Regarding adverse effects monitoring, the kidney function trend of the patients who were prescribed conventional vancomycin doses were reviewed. The results showed that the median blood urea nitrogen, serum creatinine, creatinine clearance, and urine output at day 4 were not differed significantly compared to baseline (day 1) (Table 4).

## DISCUSSION

This study observed a significant difference in total daily vancomycin doses between conventional and personalized pharmacokinetic dosing method. The patients were more likely to receive lower doses through conventional vancomycin dosing method.

This result was consistent with the study findings from Begg *et al.*, conducted on another nephrotoxic drug class aminoglycosides whereby conventional doses or 'physician intuition' doses were reportedly much lower than the personalized pharmacokinetic doses (Begg *et al.*, 1989). Without guidance from serum drug concentrations monitoring, physicians tend to be rather cautious in dosing vancomycin in patients with intact kidney function. However, in critically ill patients with increased volume of distribution and the presence of augmented renal clear-

 

**Table 2: Dose differences between vancomycin conventional dosing and personalized pharmacokinetic dosing in the patients**

| | Total daily dose (mg/day) | | | | |
|---|---|---|---|---|---|
| | Conventional dosing | | Personalized pharmacokinetic dosing | | Mann-Whitney U test results |
| | Median [IQR] | Number of patients | Median [IQR] | Number of patients | |
| Day 1 | 1750 [1000 - 2000] | 24 | 2300 [1285 - 3000] | 24 | $p$=0.066; Z=-1.838 |
| Day 2 | 2000 [1500 - 2000] | 22 | 2400 [1775 - 3075] | 18 | $p$=0.025; Z=-2.249 |
| Day 3 | 2000 [1625 - 2000] | 20 | 2450 [1775 - 3300] | 16 | $p$=0.024; Z=-2.249 |
| Day 4 | 2000 [1875 - 2000] | 18 | 2550 [1798 - 3075] | 14 | $p$=0.035; Z=-2.105 |
| Day 5 | 2000 [1500 - 2000] | 14 | 2700 [2350 - 3450] | 10 | $p$=0.003; Z=-3.002 |
| Day 6 | 2000 [1500 - 2000] | 7 | 3300 [2775 - 3900] | 5 | $p$=0.006; Z=-2.738 |
| Day 7 | 2000 [1500 - 2000] | 7 | 3600 [2962 - 4125] | 6 | $p$=0.004; Z=-2.905 |
| Average* | 2000 [1500 – 2000] | 24 | 2500 [1900 – 3300] | 24 | $p$<0.001; Z=-6.013 |

*Average total daily dose for the seven days of vancomycin therapy (from day 1 to day 7).

ance, standardized dosing of vancomycin is insufficient (Mustafa *et al.*, 2018). Subtherapeutic dosing will lead to inadequate bactericidal killing effect and possible treatment failure. Furthermore, insufficient dosing may facilitate the development of drug-resistant microorganisms (Appelbaum, 2007).

Average attainment of $AUC_{24}$/MIC ratio of <400 was observed in the prescribed conventional vancomycin doses in this study. Based on the American Society of Hospital System Pharmacists guideline, an $AUC_{24}$/MIC ratio of $\geq$ 400 is a predictor of successful vancomycin therapy in organism eradication (Rybak *et al.*, 2009). $AUC_{24}$/MIC ratio of < 400 has been notoriously associated with treatment failure for MRSA in adults (Men *et al.*, 2016). The low $AUC_{24}$/MIC ratio of <400 could increase all-cause mortality and treatment failure rates by 50% as compared to the ratio of $\geq$ 400 (Men *et al.*, 2016). A simple evaluation of conventional dosing practice of 1000 mg every 12 hours for a young adult with normal kidney function (creatinine clearance of $\geq$ 100 mL/min) and average weight (70 kg) would only yield a 24-hour drug AUC of approximately 300 mgh/L. Unless the microorganism has a vancomycin MIC of 0.5 mg/L, this dosage regimen will not generate the targeted $AUC_{24}$/MIC ratio of $\geq$ 400. Indeed, the recent revised consensus guideline recommended that the vancomycin MIC should be assumed as 1.0 mg/L and the $AUC_{24}$/MIC ratio should be achieved 400-600 to ensure the efficacy and safety of vancomycin therapy (Rybak *et al.*, 2020). Vancomycin MIC determination was not routinely carried out on clinical isolates of MRSA at the present study in the private hospital unless the patients did not respond to their initial treatment. However, it is justifiable to assume MIC as 1.0 mg/L based on a previous multicentre study in Malaysia which demonstrate 95% of MRSA had vancomycin MIC of $\geq$ 1 mg/L (Álvarez *et al.*, 2016). Based on the personalized pharmacokinetic calculation in the present study, an average daily dose of 2500 mg would be required to achieve $AUC_{24}$/MIC ratio of > 400. Nevertheless, this daily dosage requirement is slightly lower than the daily dosage of 3000–4000 mg reported by a previous study which involves more critically ill patients in ICU (del Mar Fernández de Gatta Garcia *et al.*, 2007).

Nephrotoxicity is the main concern of vancomycin therapy. Lodise *et al.*, directly examine the relationship between AUC and nephrotoxicity and found that in 27 patients with $AUC_{24}$/MIC > 1300, 26% (7 patients) had developed nephrotoxicity (Lodise

**Table 3: $AUC_{24}$/MIC ratio differences between vancomycin conventional dosing and personalized pharmacokinetic dosing in the patients**

| | $AUC_{24}$/MIC ratio by day | | | | |
|---|---|---|---|---|---|
| | Conventional dosing | | Personalized pharmacokinetic dosing | | Mann-Whitney U test results |
| | Median [IQR] | Number of patients | Median [IQR] | Number of patients | |
| Day 1 | 421 [231-514] | 24 | 493 [467-509] | 24 | $p$=0.017; Z=-2.380 |
| Day 2 | 424 [212-479] | 22 | 504 [482-514] | 18 | $p$=0.002; Z=-3.086 |
| Day 3 | 386 [243-445] | 20 | 496 [481-514] | 16 | $p$<0.001; Z=-3.948 |
| Day 4 | 369 [260-531] | 18 | 482 [470-505] | 14 | $p$=0.038; Z=-2.070 |
| Day 5 | 318 [243-452] | 14 | 495 [472-514] | 10 | $p$=0.001; Z=-3.309 |
| Day 6 | 263 [214-418] | 7 | 492 [463-507] | 5 | $p$=0.004; Z=-2.842 |
| Day 7 | 253 [188-416] | 7 | 484 [466-504] | 6 | $p$=0.004; Z=-2.857 |
| Average* | 385 [244-463] | 24 | 495 [472-514] | 24 | $p$<0.001; Z=-7.703 |

*Average $AUC_{24}$/MIC ratio for the seven days of vancomycin therapy (from day 1 to day 7)

**Table 4: Patients' kidney functions during actual therapy with conventional vancomycin doses**

| | Blood urea nitrogen* (mmol/L) | | Serum creatinine* ($\mu$mol/L) | | Creatinine clearance* (mL/min) | | Urine output* (mL/kg/hour) | |
|---|---|---|---|---|---|---|---|---|
| | Median [IQR] | Number of patient | Median [IQR] | Number of patient | Median [IQR] | Number of patient | Median [IQR] | Number of patient |
| Day 1 | 6.1 [3.8 - 10.4] | 24 | 71 [64 - 99] | 24 | 79.8 [53 - 108] | 24 | 0.83 [0.44 - 1.13] | 21 |
| Day 2 | 7.5 [4.8 - 20.1] | 13 | 65 [60 - 111] | 12 | 77.0 [45 - 114] | 12 | 0.85 [0.47 - 1.32] | 18 |
| Day 3 | 5.6 [3.6 - 21.2] | 11 | 69 [59 - 86] | 11 | 80.9 [45 - 88.7] | 11 | 1.01 [0.56 - 1.27] | 16 |
| Day 4 | 6.1 [4.2 - 24.8] | 9 | 74 [64 - 101] | 9 | 94.4 [46.3 - 102] | 9 | 0.70 [0.36 - 0.90] | 14 |

*All the variables showed no significant difference between baseline (day 1) and day 4 (p values: 0.26 for blood urea nitrogen, 0.813 for serum creatinine, 0.953 for creatinine clearance and 0.074 for urine output; Z scores from Wilcoxon signed-rank tests: -1.125 for blood urea nitrogen, -0.237 for serum creatinine, -0.059 for creatinine clearance and -1.789 for urine output).

*et al.*, 2009). Meanwhile, Neely *et al.*, proposed an $AUC_{24}$/MIC of 700 as the upper level of safe vancomycin exposure with minimal nephrotoxicity risk for the treatment of infections with MIC $\leq$ 1.5 mg/L (Neely *et al.*, 2014). Besides, the recent revised consensus guideline stated that the $AUC_{24}$/MIC ratio (with MIC assumed as 1.0 mg/L) of 400 - 600 would ensure the efficacy and safety of vancomycin therapy (Rybak *et al.*, 2020). In the present study, the conventional dosing resulted in a lower $AUC_{24}$/MIC ratio and a lower risk of nephrotoxicity than personalized dosing, but at the expense of reduced efficacy. Conversely, the personalized dosing method managed to achieve the $AUC_{24}$/MIC ratio in the range of 400 to 600, which could avoid the risk of nephrotoxicity and at the same time maintain the efficacy of treatment.

In this study, the patients have received conventional vancomycin doses and the kidney functions at the end of therapy did not differ significantly from the baseline. This is not surprising as the majority of vancomycin in this study were used as empirical treatment with an average duration of five days. Studies have demonstrated the strong relationship between acute kidney injury and vancomycin exposures (Bamgbola, 2016). Longer duration of therapy exceeding seven days correlate with a higher risk of nephrotoxicity (Contreiras *et al.*, 2014). There was 12% greater incidence of acute kidney injury for each additional day of treatment with vancomycin (Cano *et al.*, 2012). Besides a duration of therapy, the high dosage used is another factor that results in increased vancomycin exposures and vancomycin-induced acute kidney injury (Wong-Beringer *et al.*, 2011). This often poses a clinical dilemma as aggressive dosing is required to curb the trend of MIC creep. A study by Lodise *et al.* demonstrated a dose-toxicity relationship with a daily dose of vancomycin in excess of 4000 mg increases the likelihood of acute kidney injury by more than threefold (Lodise *et al.*, 2008). In another study, 21% of patients on high-dose therapy (achieved trough serum concentration of 15−20 mg/L) for more than one week, and 30% of those treated for more than two weeks sustained nephrotoxicity (Hidayat *et al.*, 2006). In the present study, an average of 2000 mg per day of conventional vancomycin dosage used with a relatively short duration of therapy could explain the retainment of baseline kidney function throughout the therapy. Nevertheless, the personalized dosing using pharmacokinetic method showed an average total daily dose of only 2500 mg, which is far less than the maximum dose of 4000 mg which could lead to increases risk of nephrotoxicity (Lodise *et al.*, 2008).

Susceptibility to vancomycin nephrotoxicity is profoundly confounded by other clinical events that compromise glomerular filtration, such as haemodynamic instability and concurrent administration of nephrotoxic agents - most notably, aminoglycosides (Rybak *et al.*, 1990). In a prospective trial of 168 patients that compared three treatment modalities, acute kidney injury was noted in 5% of those treated with vancomycin, 22% of those who had vancomycin and aminoglycoside, and 11% of those treated with gentamicin only (Rybak *et al.*, 1990). In the present study, merely one out of 24 patients received concomitant aminoglycosides therapy. Coadministration with other nephrotoxic agents, including loop diuretics, COX-2 inhibitors and ARB were found in a few patients. However, the majority of the patients did not receive any concomitant nephrotoxic drugs. This study may not have captured the vancomycin renal toxicity synergism relationship with other nephrotoxic agents, because of the short duration of vancomycin treatment.

### Limitations

It is important to note that there were limitations to this pilot study. The retrospective analysis allowed only written clinical considerations to be assessed, hence open it up to confounding and bias that may well be avoided with prospective study methods. Besides, there was a lack of therapeutic drug monitoring of the vancomycin serum concentration and clinical outcomes assessment in the study. Despite the above-mentioned limitations, this pilot study has gained insight into the efficacy of vancomycin treatment which can be considerably improved by personalized dosing using pharmacokinetic methods. The study findings are valuable as baseline data for future prospective study in Malaysian private hospital settings in the area of personalized dosing approach, particularly the assessment on clinical outcomes and cost-effectiveness of the vancomycin treatment.

## CONCLUSIONS

This study observed a significant difference in total daily vancomycin doses between conventional and personalized pharmacokinetic dosing method. The patients were generally received vancomycin at a conventional standard dosage of 1000 mg every 12 hourly, which failed to achieve the target $AUC_{24}$/MIC ratio. Whereas, personalized pharmacokinetic dose prediction method allows individual dosage adjustment to achieve the goal of a target for vancomycin effectiveness. The results of this study highlight the importance of dosing personalization to avoid any potential delay in efficacy or development of resis-

tance from sub-therapeutic vancomycin dose. As there is variability in vancomycin dose requirement, the Malaysian private hospital should consider using personalized pharmacokinetic rather than conventional weight-based or fixed-dose to optimize vancomycin therapy.

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**Conflict of Interest**

The authors declare that they have no conflict of interest for this study.

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