Evaluation of a Multi-disciplinary Medical Model in Vancomycin Treatment in Chinese Adult Patients: A Randomized Controlled Trial

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Abstract

Background

Acute kidney injury (AKI) is a common adverse drug reaction of vancomycin which is associated with increased mortality and morbidity. To investigate the roles of a multi-disciplinary medical model in preventing vancomycin-induced AKI (VI-AKI) through a standardized clinical path.

Methods

This study was a single center open-label randomized clinical trial which included adult pneumonia patients using vancomycin in Peking University First Hospital. In the intervention group (multi-disciplinary medical model), a standardized clinical path was conducted as (1) pharmacists-driven PopPK formula-based vancomycin regimen. (2) pharmacists-driven TDM monitor. (3) physicians-driven SCr monitor. (4) nephrologists-driven multi-disciplinary kidney protection. Pharmacists or nephrologists did not intervene patients; treatment in the control group (routine medical model). The primary outcome was the incidence of VI-AKI.

Results

145 patients including 72 in the intervention arm and 73 in the control arm, aged 69.0 (60.0-79.0) years with male in 74.5%, were included in the outcome analysis. The incidence of AKI was 23.6% (17/72) in the intervention arm and 34.2% (25/73) in the control arm ($P=0.16$). Among the 57 patients in the intervention arm who accepted PopPK based vancomycin regimen, AKI incidence was significantly decreased compared to patients in the control arm (15.8% vs. 34.2%, $P=0.02$).

Conclusions

Intervention with a multi-disciplinary medical model through standardized clinical path has the potential to reduce the incidence of VI-AKI. Multicenter and large sample size studies are warranted. This trial is registered with [chictr.org](http://www.chictr.org) (number ChiCTR1900021115, <http://www.chictr.org.cn/edit.aspx?pid=35376&htm=4>) on 29th Jan 2019 by retrospective registration.

1 Background

Vancomycin is the first-line treatment for methicillin-resistant staphylococcus aureus (MRSA) caused pneumonia, sepsis, infective endocarditis, central nervous system infections and skin and soft tissues infections. [1–4] Yet adverse drug reactions, especially vancomycin-induced acute kidney injury (VI-AKI) are still common [5–9], which significantly increase the mortality and medical expenses [10]. Our previous study showed that there was a significant insufficiency in the determination of serum creatinine (SCr) and the therapeutic drug monitoring (TDM) in those who were treated with vancomycin [9]. Moreover, in recent years, the minimum inhibitory concentration (MIC) of vancomycin has increased and vancomycin-resistant MRSA has appeared [11, 12], which lead to a rise in vancomycin dosage and an increased risk

for developing nephrotoxic AKI. The rational use of vancomycin to improve curative effect and reduce AKI remains a big challenge to both physicians and pharmacists.

There are several key factors in preventing VI-AKI, including timely SCr test for renal safety monitor, performing therapeutic drug monitoring (TDM) and using population pharmacokinetics (PopPK) to realize an individualized vancomycin administration. In the current study, we aimed to investigate the roles of a multi-disciplinary medical model, which included physicians in charge, nephrologists and pharmacists in preventing VI-AKI in adult pneumonia patients, through a standardized clinical path including PopPK models, TDM, and SCr monitor.

2 Methods

2.1 Study Design and Patients

This study was an open-label randomized clinical trial comparing a new work pattern on vancomycin usage to conditional ones in patients with pulmonary infections. The study was conducted at Peking University First Hospital. The participants were recruited from January 5th, 2017, to August 31st, 2018. The main study inclusion was aged ≥ 18 years, inpatients at the Respiratory Department, Respiratory Intensive Care Unit, Cardiac Intensive Care Unit and Surgery Intensive Care Unit, received intravenous vancomycin infusion due to pulmonary infections, and signed the informed consent. Principal exclusion criteria included multiple organ failure, renal replacement therapy, or chronic kidney disease stages 4 or 5. Patients withdrew when used vancomycin for less than 48 h.

The protocol was approved by the ethics committee at Peking University First Hospital. The study was conducted in accordance with the principles contained in the Declaration of Helsinki. All participants provided written informed consent before enrolling in the study. This trial is registered with [chictr.org](https://www.chictr.org/) (number ChiCTR1900021115). We indicate that your study adheres to CONSORT guidelines

2.2 Randomization

Patients were randomly assigned 1:1 to the intervention arm or control arm using randomized block design, which aimed to balance the number of participants between the intervention and control arms. The block randomization was managed by the statistical center of Peking University First Hospital.

2.3 Treatment and Follow-up

In the intervention group (multi-disciplinary medical model), a standardized clinical path was conducted as follows: (1) pharmacists used PopPK formulas [13] (see below) to develop treatment regimens. (2) pharmacists-driven TDM monitor 48 h after the first dosing. (3) physicians-driven SCr monitor 48 h and 7 d after vancomycin usage. (4) For patients developed VI-AKI, nephrologists-driven multi-disciplinary team working on kidney protection. In the control group (routine medical model), pharmacists or nephrologists did not intervene patients' treatment unless a professional referral was ordered by the physician in charge.

Patients in the intervention arm were assessed at baseline, 48h and 7d after vancomycin usage. Assessments included routine hematology, urinalysis, serum chemistry and TDM. eGFR was calculated using the CKD-EPI equation [14] using SCr level before vancomycin administration.

Two formulas were used to develop vancomycin regimens (see below), with formula 1 for adult patients (≥ 18 years, < 65 years) and formula 2 for elder patients (≥ 65 years) [15,16]. The steady-state serum trough concentrations were predicted according to the calculation formula (see formula 3), and pharmacists selected the appropriate dosing regimen according to the results.

$$CL \text{ (L/h)} = 2.45 \times (\text{CrCl}/56.28)^{0.542}, V \text{ (L)} = 154 \text{ (1)}$$

$$CL \text{ (L/h)} = 2.89 \times (\text{CrCl}/51.11)^{0.698}, V \text{ (L)} = 131 \text{ (2)}$$

$$C_{ssmin} = K_0 \times (1 - e^{-kt}) \times e^{-k(\tau - t)} / (CL \times (1 - e^{-k\tau})) \text{ (3)}$$

2.4 Outcomes

The prespecified primary outcome was the development of VI-AKI. We used the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) SCr definition [17] to define VI-AKI, which includes (1) increased SCr by 0.3 mg/dl (26.5 $\mu\text{mol/L}$) within 48 h during the use of vancomycin or 3 d following the discontinuation of vancomycin and/or (2) increased SCr to 1.5 times baseline over 7 d during the use of vancomycin or 3 d following drug discontinuation. For each case, the diagnosis of VI-AKI was further defined by a senior nephrologist according to the clinical relevance of AKI features and vancomycin administration. The severity of AKI was evaluated by peak SCr level and AKI stage, the following was described by stages 1, 2, and 3 according to the KDIGO criteria [17].

Prespecified secondary outcomes included all-cause in hospital mortality, clinical respiratory infection cure rate, prognosis of VI-AKI, inpatient days, vancomycin prescription days and total dosage. Clinical cure rate was defined with “Guiding Principles of Clinical Use of Antibiotics” in China and references [18]. When the symptoms, signs, laboratory tests and bacteriological tests of the infection returned to normal after the discontinuation of vancomycin, the patient would be defined as achieving recovery. When the improvement was significant, but one of the four items mentioned above was still abnormal, the patient would be defined as with significant effect. Both recovery and significant effect were classified as cure. Renal recovery of VI-AKI patients at hospital discharge was defined as (1) full recovery, with SCr decreased to baseline. (2) partial recovery, with SCr decreased by 25% or more from peak concentration but remaining higher than baseline. (3) failure to recover, with dialysis dependent or SCr decreased by less than 25% from peak concentration [17, 19–20]. We referred to three TDM guidelines from America and China [13,17,21]. The guidelines stated that vancomycin trough concentrations should be maintained within 10–20 mg/L. In patients with complex infections (endocarditis, meningitis, osteomyelitis, or hospital-acquired pneumonia caused by MRSA), vancomycin trough concentrations should reach 15–20 mg/L [22,23].

2.5 Statistical Analysis

Based on previously reported VI-AKI incidence [24] and the results of clinical trials [25], the putative incidences of primary outcomes were assumed 21.0% events in the control arm and 7.0% events in the intervention arm. With 80% statistical power and 5% α -error and allowing for a 20% dropout and withdrawal rate, we planned to recruit 99 patients per arm to the study.

Analyses were performed according to the intention-to-treat principle. Normally distributed data are shown as mean $\pm$ standard deviation, and non-normally distributed data as median and interquartile range (IQR). Categorical data are presented as count and percentage. Comparisons on variables of the 2 groups were conducted by using independent-samples t test for normally distributed continuous variables, Wilcoxon rank sum test for non-normally distributed continuous variables, and χ^2 test for nominal variables. Predefined subgroups were used for the primary outcome in stratified analyses, including whether accept PopPK assigned vancomycin regimen. $P < 0.05$ was considered statistically significant. Statistical analyses were conducted using IBM SPSS, version 20.0.

3 Results

3.1 Baseline Characteristics and Intention-to-treat Analysis

From January 5th, 2017, to August 31st, 2018, a total of 239 potentially eligible patients were screened, of whom 208 were eligible for the study and underwent random assignment (106 to the intervention arm and 102 to the control arm; Fig 1). 14 patients in the intervention arm and 11 patients in the control arm withdrew the study due to vancomycin usage for less than 48 h.

Altogether 183 patients were included in the intention-to-treat analysis, including 92 cases in the intervention arm and 91 cases in the control arm. The TDM monitoring rate was higher in patients of the intervention arm (81/92, 88.0%) than that of patients in the control arm (55/91, 60.4%) ($P < 0.001$). Among those who had TDM monitoring, 66.7% (54/92) of the patients in the intervention arm reached the standard of vancomycin concentration, which was much higher than that of patients in the control arm (31/91, 34.4%) ($P = 0.001$). However, in both groups, there were patients lacking baseline SCr measurements before vancomycin administration, including 20 cases in the intervention arm and 18 in the control arm (21.7% vs 19.8%, $P = 0.74$). As VI-AKI could not be determined in these cases, they were not included in the outcome analysis.

Finally, altogether 145 patients, aged 69.0 (60.0–79.0) years old with a male predominance (74.5%), including 72 patients in the intervention arm and 73 patients in the control arm, were included in the outcome analysis and the 2 randomized arms had similar characteristics at baseline (Table 1).

3.2 Primary End Point

In the primary outcome analysis, 42 (29.0%) patients developed VI-AKI in the 145 patients. The incidence was 23.6% (17/72) in the intervention arm and 34.2% (25/73) in the control arm ($P = 0.16$) (Table 2). 20

(47.6%) of 42 of AKI episodes were stage 1, 10 (23.8%) were stage 2, and 12 (28.6%) were stage 3. There was no obvious difference in the severity of AKI, evaluated by peak SCr levels (152.0 (101.3–258.5) vs. 135.6 (98.8–184.88), $P = 0.31$) or AKI stages between the two groups ($P = 0.95$).

We further focused on the effect of applying PopPK formula on the development of VI-AKI and compared primary outcome between the 57 patients in the intervention arm who accepted PopPK model to develop their vancomycin regimen, and the patients in the control arm. As it is shown in Table 3, there was a significant decrease in the AKI incidence in patients with PopPK formula intervention compared to those in the control arm (15.8% vs. 34.2%, $P = 0.02$). The severity of VI-AKI was likely to be reduced as patients with PopPK formula intervention tended to have a higher proportion of patients developed AKI stage 1 compared to those in the control arm, whereas the difference did not reach a statistical significance (66.7% vs. 48.0%, $P = 0.45$).

3.3 Secondary End Points

In the secondary outcome analysis, the all-cause in-hospital mortality was 14.5% (21/145), with no significant difference between patients in the intervention arm and those in the control arm (12.5% vs. 16.4%, $P = 0.50$). The clinical infection cure rate was 54.2% and 57.5%, respectively ($P = 0.68$). For the 42 patients with VI-AKI, we followed their renal prognosis until they were discharged (Table 4). Patients in the intervention arm tended to have a higher renal recovery rate (including both complete and partial recovery) compared to those in the control arm whereas the difference did not reach a statistical significance (58.8% vs. 40.0%, $P = 0.23$) (Table 4). There was no difference in the inpatient days and vancomycin using days. Yet, the total vancomycin dosage was significantly lower in intervention arm compared to the control arm. (11.0 (7.5–18.0) vs. 15.0 (9.0–27.0) mg, $P = 0.003$).

When we focused on the 57 patients with PopPK intervention, there was still no significant difference in the all-cause mortality compared to the patients in the control arm (10.5% vs. 16.4%, $P = 0.33$) (Table 5). The renal recovery rate tended to be increased by PopPK intervention compared to the control arm (77.8% vs. 40.0%, $P = 0.12$) (Table 5). And the total vancomycin dosage was significantly lower in patients with PopPK intervention compared to those in the control arm. (12.0 (8.7–18.0) vs. 15.0 (9.0–27.0) mg, $P = 0.02$).

4 Discussion

In this study, we examined the renal protective effect of a standardized clinical path performed by multi-disciplinary medical team in patients with pneumonia who received vancomycin therapy. We found that this multi-disciplinary medical model effectively improved the standardization of vancomycin administration. In patients who received PopPK formula estimation for vancomycin dosing, the rate of AKI was significantly reduced compared to patients treated with routine medical model.

Although alternative drugs with relatively less nephrotoxicity are available, vancomycin, due to its effectiveness and low cost, is still the preferred and widely used drug for the treatment of MRSA.

According to a multicenter study which included 103 hospitals in China, there were 357,225 cases of vancomycin prescription in the year of 2017[26], and the incidence of VI-AKI was 16.2%–30.8% [9, 27, 28]. Although it has been reported that vancomycin TDM facility is available in most academic hospitals in big cities, 76.5% of the patients in these hospitals had inadequate TDM [29]. Meanwhile, the preassessment of vancomycin dosage, as well as renal function monitoring were generally lacking [9]. It is thus critical to set up an executable standardized clinical path to improve vancomycin renal safety in China.

Some researchers have explored the multi-disciplinary cooperation to improve vancomycin administration. Smith AP et al [30] has showed that pharmacists helping physicians to test renal function for patients using vancomycin reduced the incidence of VI-AKI. Marquis KA et al [31] reported that pharmacists using weight-based-doses regimen helped improve the safety and effectiveness of vancomycin. In the current study, we set up a multi-disciplinary medical model, which included pharmacists performing vancomycin PopPK dosing assessment, pharmacists-driven TDM processing, physicians-driven SCr monitoring, and nephrologists leading kidney protective therapy. We reached an increased TDM rate (88.0% vs 60.4%, $P < 0.001$) with a higher proportion of patients achieving standard vancomycin plasma concentration (66.7% vs 34.4%, $P = 0.001$) through this medical model. In addition, 79.2% of patients in the multi-disciplinary intervention arm had vancomycin prescription based on PopPK formula dosing estimation while none of the cases in the control arm (routine medical model) got prescription dose assessment. These data indicated an improvement in the standardization of vancomycin administration. However, there was still an insufficiency in TDM monitor (12.0%), PopPK based dose assessment (20.8%), particularly SCr monitor (21.7%) in the intervention arm, which suggested a non-compliance existing in the physicians who were in charge of the patient. More work needs to be done to better execute this multi-disciplinary medical model.

PopPK has been shown as an efficacious tool for vancomycin administration. [19, 32–34] Previously, Leu WJ et al showed that dosing vancomycin with the help of PopPK tended to have a better outcome with regard to clinical efficacy and safety [35]. In the current study, patients who received PopPK formula estimation for vancomycin dosing had significantly reduced VI-AKI rate compared to patients treated with routine medical model (15.8% vs 34.2%, $P = 0.02$), with a likely reduced AKI severity and higher rate of renal recovery (77.8% vs. 40.0%, $P = 0.12$). Although there was a markedly decreased total vancomycin dosage (roughly by 20.0%) in patients with PopPK dosing assessment, the clinical cure rate had no significant difference with control arm. Our study reinforces the importance of individualized vancomycin dosing based on PopPK formula in preventing VI-AKI. Besides, active involvement of pharmacists in vancomycin therapeutic regimen facilitated PopPK formula implementing and TDM processing, which helped improve drug safety.

Our study has the limitation of a single-center trial with small sample size. The study lacks generalizability and mainly included patients in the intensive care units with pneumonia. The non-compliance of intervention in some physicians further limited the sample size and might result in further selecting bias. AKI was defined according to criteria based on changes in SCr independently of urinary

output, which might miss-diagnose patients with mild AKI who only presented transient urine volume decrease.

5 Conclusion

In conclusion, our study shows that intervention with a multi-disciplinary medical model through standardized clinical path effectively improves vancomycin administration, and has the potential to reduce the incidence and severity of VI-AKI. Multicenter and large sample size studies are warranted.

Abbreviations

Acute kidney injury = AKI;

vancomycin-induced AKI = VI-AKI;

methicillin-resistant staphylococcus aureus = MRSA;

therapeutic drug monitoring = TDM;

minimum inhibitory concentration = MIC;

population pharmacokinetics = PopPK;

SCr = Serum creatinine;

eGFR = Glomerular filtration rate;

WBC = White blood cell count;

NE = Neutrophil;

CHD = coronary heart disease;

CKD = chronic kidney disease;

CLD = chronic liver disease.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Peking University First Hospital Clinical Research Ethics Committee. We conducted this study in compliance with the principles of the Declaration of Helsinki. Consent to participate statement was obtained from all participants.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Methodology: XL; Formal analysis and investigation: CC, CQ, HJ, SL, XZ; Writing - original draft preparation: LM, FG; Writing - review and editing: LY, YC, YZ; Funding acquisition: LY; Supervision: LY and JL. All authors read and approved the final manuscript.

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Tables

Variable	Total n=145	Control n=73	Intervention n=72	P
Age (yr)	69.0 (60.0-79.0)	65.0 (58.5-78.0)	71.50 (61.0-79.7)	0.07
Male, n (%)	108 (74.5)	54 (74.0)	54 (75.0)	0.89
Body weight (kg)	65.0 (58.5-72.0)	65.0 (59.5-72.0)	64.0 (58.0-71.7)	0.47
Baseline SCr (mmol/L)	65.1±20.9	65.8±19.1	64.5±22.7	0.69
Baseline eGFR	87.4 (65.3-106.7)	87.4 (68.1-116.8)	86.7 (63.4-104.6)	0.49
WBC (10 ⁹ /L)	10.6 (7.3-14.3)	11.4 (8.4-14.4)	9.6 (6.3-14.2)	0.09
NE (%)	83.9 (76.7-89.3)	83.1 (76.3-88.1)	85.2 (76.7-90.7)	0.37
Hypertension, n(%)	75 (51.7)	35 (47.9)	40 (55.654)	0.36
Diabetes, n (%)	28 (19.3)	16 (21.9)	12 (16.7)	0.42
CHD, n (%)	31 (21.4)	12 (16.4)	19 (26.4)	0.14
CKD, n (%)	9 (6.2)	4 (5.5)	5 (6.9)	0.74
CLD, n (%)	10 (6.9)	3 (4.1)	7 (9.7)	0.21

Table 1. Patient baseline characteristics

Abbreviations: SCr= Serum creatinine; eGFR= Glomerular filtration rate; WBC= White blood cell count; NE= Neutrophil ; CHD= coronary heart disease; CKD= chronic kidney disease; CLD= chronic liver disease

Normal range: SCr (44-133) mmol/L; WBC (3.5-9.5) 10⁹/L; NE (40.0-75.0) %

Continuous data are shown as mean ± standard or median (IQR) as appropriate , categorical data are summarized as n (%) unless stated otherwise.

Table 2. Comparison of incidence and severity of VI-AKI between the two groups

Variable	Total n=145	Control n=73	Intervention n=72	P
Adoption of PopPK, n (%)		-	57 (79.2)	-
VI-AKI				
Incidence, n (%)	42 (29.0)	25 (34.2)	17 (23.6)	0.16
Peak SCr (mmol/L)	149.5 (101.6-220.6)	152.0 (101.3-258.5)	135.6 (98.8-184.88)	0.31
AKI stage, n (%)				0.95
1	20/42 (47.6)	12/25 (48.0)	8/17 (47.0)	-
2&3	22/42 (52.4)	13/25 (52.0)	9/17 (52.9)	-

Abbreviations: PopPK= Population pharmacokinetics; VI-AKI= Vancomycin-induced acute kidney injury; SCr= Serum creatinine; AKI=Acute kidney injury

Normal range: SCr (44-133) mmol/L; WBC (3.5-9.5) $10^9/L$; NE% (40.0-75.0) %

Continuous data are shown as mean $\pm$ standard or median (IQR) as appropriate , categorical data are summarized as n (%) unless stated otherwise.

Table3. Comparison of incidence and severity of VI-AKI between patients with PopPK intervention and the control group

Variable	Total n=130	Control n=73	PopPK Intervention n=57	P
VI-AKI incidence, n (%)	34 (26.1)	25 (34.2)	9 (15.8)	0.02
Peak SCr (mmol/L)	149.5 (101.6-220.6)	152.0 (101.3-258.5)	130 (98.8-153.9)	0.25
AKI stage, n (%)				0.45
1	18/34 (52.9)	12/25 (48.0)	6/9 (66.7)	-
2&3	16/34 (47.1)	13/25 (52.0)	3/9 (33.3)	-

Abbreviations: VI-AKI= Vancomycin-induced acute kidney injury; PopPK= Population pharmacokinetics; AKI=Acute kidney injury; SCr= Serum creatinine; AKI=Acute kidney injury

Normal range: SCr (44-133) mmol/L; WBC (3.5-9.5) $10^9/L$; NE% (40.0-75.0) %

Continuous data are shown as mean $\pm$ standard or median (IQR) as appropriate , categorical data are summarized as n (%) unless stated otherwise.

Table 4. Comparison of secondary outcomes between the two groups

Variable	Total n=145	Control n=73	Intervention n=72	P
All-cause mortality (%)	21 (14.5)	12 (16.4)	9 (12.5)	0.50
Clinical cure rate (%)	81 (55.9)	42 (57.5)	39 (54.2)	0.68
Renal recovery of VI-AKI, n (%)				0.23
Complete & partial	20/42 (47.6)	10/25 (40.0)	10/17 (58.8)	
None	22/42 (52.4)	15/25 (60.0)	7/17 (41.2)	
Inpatient days (d)	28.0 (18.0-43.0)	30.0 (20.0 44.0)	28.0 (15.2-42.7)	0.26
Use vancomycin days (d)	6.0 (4.0-9.0)	6.0 (4.0-11.0)	6.0 (4.0-8.0)	0.26
Total dosage (mg)	13.5 (8.2-21)	15.0 (9.0-27.0)	11.0 (7.5-18.0)	0.003

Abbreviations: VI-AKI= Vancomycin-induced acute kidney injury; AKI=Acute kidney injury ; SCr= Serum creatinine

Normal range: SCr (44-133) mmol/L; Vancomycin TMD (10-20) mg/L

Continuous data are shown as mean $\pm$ standard or median (IQR) , categorical data are summarized as n (%) unless stated otherwise.

Table 5. Comparison of secondary outcomes between patients with PopPK intervention and the control group

Variable	Total n=130	Control n=73	PopPK Intervention n=57	P
All-cause mortality (%)	18 (13.8)	12 (16.4)	6 (10.5)	0.33
Clinical cure rate (%)	74 (56.9)	42 (57.5)	32 (56.1)	0.87
Renal recovery of VI-AKI, n (%)				0.12
Complete & partial	17/34 (50.0)	10/25 (40.0)	7/9 (77.8)	
None	17/34 (50.0)	15/25 (60.0)	2/9 (22.2)	
Inpatient days (d)	29.0 (18.7-43.2)	30.0 (20.0 44.0)	29.0 (17.0-43.5)	0.53
Use vancomycin days (d)	6.0 (4.0-9.2)	6.0 (4.0-11.0)	6.0 (4.0-8.0)	0.40
Total dosage (mg)	14.7 (9.0-21.0)	15.0 (9.0-27.0)	12.0 (8.7-18.0)	0.02

Abbreviations: VI-AKI= Vancomycin-induced acute kidney injury; AKI=Acute kidney injury; SCr= Serum creatinine

Normal range: SCr (44-133) mmol/L; Vancomycin TMD (10-20) mg/L

Continuous data are shown as mean ± standard or median (IQR) , categorical data are summarized as n (%) unless stated otherwise.

Figures

Figure 1

Diagram of participant enrollment and analysis in the study

Supplementary Files

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- [CONSORT2010Checklist.doc](#)