Drug Utilization Evaluation of Vancomycin among Patients in Jafar Ibn Auf Pediatric Hospital, 2018 [version 2; peer review: 2 approved]

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Abstract

Background: Vancomycin is an antibiotic of growing importance in the treatment of hospital-acquired infections; with a particular emphasis on its value in the fight against Methicillin-resistant Staphylococcus aureus. Increasing reports of Vancomycin resistance have raised concerns about the effectiveness of this drug. Drug utilization evaluation has an important role in controlling rational use of antibiotics to prevent the emergence of resistance.

Methods: We conducted a retrospective 6-months study at Jafar Ibn Auf pediatric hospital. Data including patient's demographics, diagnosis, Dosage regimen, and treatment duration were reviewed. The concordance of practice with the Hospital Infection Control Practices Advisory Committee (HICPAC) guidelines and principles of antibiotic therapy was assessed.

Results: 127 medical records were reviewed in this study. Sepsis (29%) and Pneumonia (19.6%) were the most common indications. Culture test was requested in 20.5% of patients. Monitoring of serum creatinine was carried in 81.1% of patients. Based on HICPAC guidelines vancomycin was administered appropriately in 67.7% percent of cases. Considering the infusion rate, most of patients with specific order were received vancomycin in 1 hour.

Conclusions: The results showed that vancomycin was used empirically without subsequent adjustment of the antimicrobial agent according to culture and sensitivity data and lack of paying enough attention to the infusion rate and serum creatinine monitoring.

Keywords
Vancomycin, Drug utilization evaluation, Pediatrics

Open Peer Review

Invited Reviewers

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01 Oct 2019

Invited Reviewers
1. Ghulam Jilany Khan, University of Central Punjab, Lahore, Pakistan
2. Khalid O. Alfarouk, Hala Alfarouk Cancer Center, Khartoum, Sudan

Any reports and responses or comments on the article can be found at the end of the article.
Introduction
The majority of admitted inpatients are given antimicrobials as therapy or prophylaxis during their hospitalization. It has been shown that at least 50% of antimicrobial prescriptions are unnecessary. Antimicrobial over prescription increases the costs of health care, increases super-infection due to antimicrobial-resistant bacteria, and may increase the likelihood of an unwanted side-effects1.

As one critical challenge that health care faces is resistance to vancomycin, which is antibiotic that has a definite indications and a crucial role in treating infections in patients allergic to beta-lactam antibacterial medications or in bacterial infections that are resistant to other antibiotics2. Vancomycin acts by inhibiting the earlier stage of development of the bacterial cell wall compared to beta-lactams, it blocks cell wall phospholipid synthesis by inhibiting transglycosylase enzymes3-5. Vancomycin has a narrow antibacterial spectrum against Methicillin-Resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Enterococcus* and *Streptococcus pneumonia* infections, thus is saved for these serious public health concerns6-7.

MRSA has become one of the predominant health care issues, and its resistance to vancomycin is growing. Cases of MRSA have increased in the US from 35.9% in 1992 to 64.4% in 2003, mainly due to inappropriate prescribing of broad spectrum antibiotics8. Additionally, 10 to 30% of nosocomial infections in US were caused by vancomycin-resistant enterococci (VRE)9. The increase in VRE has led to the development of recommendations for the use of vancomycin by the Hospital Infection Control Practices Advisory Committee (HICPAC)10, a part of the Centers for Disease Control and Prevention (CDC), published in 1995. They indicate what constitutes appropriate and inappropriate usage of vancomycin, and advises physicians to use the guidelines to decrease the emergence of vancomycin-resistant strains11.

Drug utilization evaluation (DUE) studies have an important role in controlling rational use of antibiotics to prevent resistance12. Since we did not have any data regarding how rationally vancomycin is being prescribed in Jafar Ibn Auf Pediatric Hospital, we conducted this DUE study to determine the rate of rational use of vancomycin according to the standard guidelines.

Methods
Study design and setting
We performed a retrospective cross-sectional record-based study of vancomycin use in Jafar Ibn Auf Pediatric Hospital, Khartoum, Sudan. From January 2018 to June 2018

Participants and study size
Medical records of all patients hospitalized during the study period were reviewed.

Inclusion criteria included: any pediatric patients receiving vancomycin during their hospitalization.

Exclusion criteria included: patients who received vancomycin orally because the infusion rate is one of the variables that should be measured and/or patients with incomplete data.

Variables
Medical records were reviewed, and the following data was extracted using a check list (see extended data12): dose of vancomycin; duration of infusion; duration of treatment with vancomycin; serum creatinine monitoring; culture and sensitivity test results; concurrent antimicrobials and nephrotoxic drugs; and adverse drug reactions.

Data sources/ measurements
The study was carried out by reviewing all medical records of patients who were admitted and received vancomycin during the study period. A data collection form was used to gather patients’ information. Patients were grouped according to their age into: neonates (1–28 days), infants (1–24 month) and children (2–14 years). Appropriate or inappropriate use of vancomycin was classified according to the guidelines issued by HICPAC. The reasons for appropriate use include: the treatment of β-lactams-resistant gram-positive infections, treatment of patients allergic to β-lactams with gram-positive infections, discontinuation of vancomycin therapy when microbial cultures are negative, and empiric therapy in patients with risk factors; such as patients with co-morbidities and intensive care unit patient’s or confirmed gram-positive infections by culture. Cases in which the use was empiric in patients with risk factors has been justified by hospital epidemiology – due to a high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA).

Statistical analysis
Statistical analysis SPSS version 20.0 was used to analyze the data. Continuous variables were analyzed using Student’s t-test. Chi-square test was used to compare qualitative variables. P values less than 0.05 were considered to be statistically significant.

Ethical statement
Ethical clearance (FPEC-07-2018) was obtained from the Ethical Committee of the Faculty of Pharmacy, University of Khartoum. Additional approval for checking the medical records was obtained from Jafar Ibn Auf Pediatric Hospital.

Results
During the study period, 127 patients (61 females and 66 males) received vancomycin (Underlying data13). As shown in Table 1, about a quarter of patients were hospitalized in a period of 11 to 15 days. Culture tests were performed in 20.5% of patients, with blood being the most common sample taken for microbiology study. Moreover, about 38.6% of patients received vancomycin for 4 to 7 days. (Table 1)
According to clinical indication, vancomycin was used to treat sepsis and pneumonia in 29% and 19.7% of patients respectively (Table 2). However, around 55% of patients had received vancomycin without specific instructions from physicians to the nurses regarding the duration of infusion, while 26.8% and 18.1% of patients were receiving vancomycin with specific instructions stated from the physician in the medical records to give vancomycin for duration of 1 hour or 30 min, respectively (Table 2).

Results for the monitoring of serum creatinine are presented in Table 3. Appropriate dose (dosing and frequency) was observed in 81% of the patients (including renal dose adjustment), the need for dose adjustment was essential in 21 patients, but only 11 cases were adjusted. Recorded adverse drug reactions and drug-drug interactions are shown in Table 3. Only 5% of patients developed nephrotoxicity, and furosemide was the most common prescribed drug recorded to have a potential drug-drug interaction.

According to the HICPAC guidelines, vancomycin use was considered appropriate in 86 participants (67.8%) (Table 4). Of these, 27.6% of cases (35) were empiric therapy in patients with risk factors; such as patients with co-morbidities and intensive care unit patients, 22.8 % (29) was for the treatment of β-lactams-resistant gram-positive infections treatment, 12.6% (16) for confirmed gram positive infections by culture, 2.4% (3) for treatment of patients allergic to β-lactams with gram-positive infections and 2.4% (3) for discontinuation of vancomycin therapy when microbial cultures are negative. Moreover, there was a significant difference in the appropriateness of vancomycin

| Table 1. Demographic and clinical data of patients who received vancomycin. |
|---------------------------------|-----------------|-----------------|-----------------|
| Demographic & clinical characteristics | Number (Frequency %) |
| Age group | | |
| 1–28 days (neonates) | 35 (27.56%) |
| 1–24 month (infants) | 42 (33.07%) |
| 2–14 years (children) | 50 (39.37%) |
| Hospital units | | |
| General | 67 (52.76%) |
| Cardiology | 7 (5.51%) |
| Respiratory | 6 (4.72%) |
| Hematology | 3 (2.36%) |
| Gastroenterology | 4 (3.15%) |
| Nephrology | 5 (3.94%) |
| Nursery | 35 (27.56%) |
| Outcome | | |
| Improved | 119 (93.70%) |
| Failed | 3 (2.36%) |
| Referred | 5 (3.94%) |
| Treatment duration | | |
| 1 to 3 days | 13 (10.24%) |
| 4 to 7 days | 49 (38.58%) |
| 8 to 14 days | 46 (36.22%) |
| 15 to 21 days | 14 (11.02%) |
| More than 21 days | 5 (3.94%) |

| Table 2. Indications for vancomycin and instructions by physicians regarding the duration of infusion use among the study participants. |
|---------------------------------|-----------------|-----------------|-----------------|
| Indications | Number (Frequency %) |
| Meningitis | 18 (14.17%) |
| Pneumonia | 25 (19.69%) |
| Sepsis | 37 (29.13%) |
| Febrile neutropenia | 2 (1.57%) |
| Osteomyelitis | 1 (0.79%) |
| Endocarditis | 1 (0.79%) |
| Others | 43 (33.86%) |
| Instructions regarding duration of infusion | Number (Frequency %) |
| Without any specific order | 70 (55.12%) |
| Half an hour | 23 (18.11%) |
| One hour | 34 (26.77%) |

| Table 3. Monitoring of serum creatinine among the study participants, and adverse drug reactions and drug-drug interactions among the study participants. |
|---------------------------------|-----------------|-----------------|-----------------|
| Monitoring of serum creatinine | Number (Frequency %) |
| Once | 77 (60.63%) |
| Twice weekly | 26 (20.47%) |
| Not done | 24 (18.90%) |
| Adverse drug reactions | Number (Frequency %) |
| Anaphylaxis | 1 (0.79%) |
| Nephrotoxicity | 6 (4.72%) |
| None | 120 (94.49%) |
| Drug-drug interactions | Number (Frequency %) |
| Furosemide | 16 (12.60%) |
| Amikacin | 3 (2.36%) |
| NSAID | 6 (4.72%) |
| Furosemide & Amikacin | 2 (1.58%) |
| No | 100 (78.74%) |

NSAID – nonsteroidal anti-inflammatory drugs
Table 4. Number and percent of appropriate and inappropriate use of vancomycin based on age.

<table>
<thead>
<tr>
<th>Age</th>
<th>Appropriate</th>
<th>Inappropriate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Frequency %</td>
</tr>
<tr>
<td>1–29 days</td>
<td>30</td>
<td>85.7%</td>
</tr>
<tr>
<td>1–24 months</td>
<td>28</td>
<td>66%</td>
</tr>
<tr>
<td>2–14 years</td>
<td>28</td>
<td>56%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>86</td>
<td>67.7%</td>
</tr>
</tbody>
</table>

use in the three groups based on age (neonates, infants and children), with P value = 0.015 (Table 4).

Discussion

Vancomycin is an antibiotic used to treat serious infections in patients hypersensitive to β-lactam antibiotics, or those caused by bacteria resistant to β-lactams such as MRSA. In this study, sepsis (29%) and pneumonia (19.6%) were the most common indications for vancomycin use; a similar finding has been reported in Oman. On the other hand, an Iranian study showed that vancomycin was mostly used to treat febrile neutropenia (87.9%) and sepsis (74.5%), which was similar to results reported in Hong Kong. Considering the duration of vancomycin therapy, the maximum duration (40 days) was prescribed in one patient suffering from pneumonia due to he suffered from other diseases; the minimum period of administration was one day. Most infections, including gram-positive bacteria, can be treated for less than 15 days with vancomycin, but the duration of treatment with vancomycin for endocarditis and osteomyelitis can last for up to an 8-week period.

Our study demonstrated that most patients received vancomycin empirically without following culture and sensitivity testing. The rate of requesting culture and sensitivity tests was low (20.5%), similar to Salehifar et al. In which culture and sensitivity test was performed in 30.1% of cases. The main reason for the low rate of requesting culture is that most patients had no health insurance to cover the cost of culture.

According to the HICPAC guidelines, 67.7% of the vancomycin prescriptions were appropriate; the reasons for its appropriate use included the treatment of β-lactams-resistant gram-positive infections, treatment of patients allergic to β-lactams with gram-positive infections, and discontinuation of vancomycin therapy when microbial cultures have been negative. Empiric therapy is also in patients with risk factors and confirmed gram-positive infections by culture. The rate of adherence to HICPAC recommendations was lower in our study compared to other trials, including Alfandari et al. and Melo et al. studies, in which the rate of appropriate use was 71% and 95% respectively. However, in Askarian et al’s study out of 200 vancomycin prescriptions, only 12 (6%) were considered appropriate; which was very low compared to our results.

Given the importance of infusion rate, and the occurrence of “red man syndrome” by vancomycin (a hypersensitivity reaction characterized by flushing, erythema and pruritus, particularly of the upper body), the guidelines recommend that the time of infusion should be ≥ 30 minutes per 500 mg dose of vancomycin to avoid this infusion-related anaphylaxis–like reaction. The results showed that in more than half of the patients (55%) there were no specific instructions regarding the duration of infusion. An anaphylactic reaction occurred in two patients.

Nephrotoxicity is one of the most common adverse drug reactions, so daily monitoring of serum creatinine and estimated creatinine clearance, in addition to ensuring the proper vancomycin dose can be effective while preventing renal toxicity. Multiple risk factors influencing the occurrence of nephrotoxicity include; treatment duration beyond one week, pre-existing renal insufficiency, concurrent administration of nephrotoxic drugs, sepsis and critical illnesses, as well as infusion rate. In this study, nephrotoxicity occurred in 4.7% of patients, although serum creatinine testing was performed in 81% of patients.

Concerning serum creatinine monitoring, guidelines recommend that it should be monitored at least twice weekly, and weekly for long term therapy. In this study, in 60.6% of patients; serum creatinine was monitored once (75% of them before initiating vancomycin therapy and 25% during treatment with vancomycin therapy), while only 20% of patients were monitored twice weekly. 19% of cases had no serum creatinine monitoring. In Oliveira and Ribeiro’s study, serum creatinine was monitored to 93.4% patients which was higher compared to our results.

Regarding dosing of vancomycin; in neonates, 15mg/kg is the suggested starting dose, then 10 mg/kg every 12 hours up to the first week after birth, followed by 10 mg/kg every 8 hours up to the age of one month; for children ≥1 month 15 mg/kg every 8 hours (maximum daily dose 2 g) is recommended. Appropriate dosing was observed in 81% of the patients, which was higher than an Iranian study in which 52% of the participants were given an appropriate dose. Since 80% to 90% of vancomycin is excreted unchanged in the urine, dose adjustment is required in renal insufficient/failure patients. In this study, the need for dose adjustment was essential in 21 patients, but only 11 of cases were adjusted.

Regarding drug-drug interactions, the most common interactive drugs used were furosemide (12.6%), amikacin (2.4%) and non-steroidal anti-inflammatory drugs (NSAID) (4.7%). Two patients were receiving vancomycin, furosemide and amikacin concomitantly. All these medications have been reported to increase the risk of vancomycin-induced nephrotoxicity. Specially, the combination of aminoglycosides with vancomycin dose can be effective while preventing renal toxicity. According to the HICPAC guidelines, 67.7% of the vancomycin prescriptions were appropriate; the reasons for its appropriate use included the treatment of β-lactams-resistant gram-positive infections, treatment of patients allergic to β-lactams with gram-positive infections, and discontinuation of vancomycin therapy when microbial cultures have been negative. Empiric therapy is also in patients with risk factors and confirmed gram-positive infections by culture. The rate of adherence to HICPAC recommendations was lower in our study compared to other trials, including Alfandari et al. and Melo et al. studies, in which the rate of appropriate use was 71% and 95% respectively. However, in Askarian et al’s study out of 200 vancomycin prescriptions, only 12 (6%) were considered appropriate; which was very low compared to our results.

According to the HICPAC guidelines, 67.7% of the vancomycin prescriptions were appropriate; the reasons for its appropriate use included the treatment of β-lactams-resistant gram-positive infections, treatment of patients allergic to β-lactams with gram-positive infections, and discontinuation of vancomycin therapy when microbial cultures have been negative. Empiric therapy is also in patients with risk factors and confirmed gram-positive infections by culture. The rate of adherence to HICPAC recommendations was lower in our study compared to other trials, including Alfandari et al. and Melo et al. studies, in which the rate of appropriate use was 71% and 95% respectively. However, in Askarian et al’s study out of 200 vancomycin prescriptions, only 12 (6%) were considered appropriate; which was very low compared to our results.
85.7%. Dehghan et al. also showed a significant difference in the appropriateness of vancomycin use in three groups based on age (neonates, infants, and children) with P value of 0.017, however, the most appropriate use was observed in infants (68.1%)10. The recorded irrational use of vancomycin in this study indicates deficiencies in utilization practices at the level of this hospital and perhaps the entire region. Such practices require further restrictive measures on vancomycin prescribing.

Limitations of the study
One of the major limitations was the poor documentation in the medical records used. Thus, information such as therapeutic monitoring of serum vancomycin concentrations was not available; therefore, we exclude it from the variables to be measured and we recommend that it is essential to document serum concentration levels when using vancomycin.

Conclusion
Our findings confirmed that more than 30% of patients received vancomycin without fulfilling the HICPAC criteria. Insufficient attention to monitor the rate of infusion of vancomycin and serum creatinine, in addition to low rate/lack of requesting culture and sensitivity testing are collectively indicated the reasons for inconsistency to HICPAC guidelines.

References


Data availability

Underlying data

- Vancomycin Data.xlsx (Extracted data from medical records)

Extended data

- Check-list.doc (Checklist used for data extraction from medical records)

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication)

Acknowledgments
The authors would like to acknowledge all members of Jafar Ibn Auf Pediatric Hospital for their contributions.


Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 12 November 2021
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✔ Khalid O. Alfarouk
Department of Evolutionary Pharmacology, and Tumor Metabolism, Hala Alfarouk Cancer Center, Khartoum, Sudan

Approved.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pharmacology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 09 November 2021
https://doi.org/10.5256/f1000research.21233.r98730

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✔ Khalid O. Alfarouk
Department of Evolutionary Pharmacology, and Tumor Metabolism, Hala Alfarouk Cancer Center, Khartoum, Sudan

Dear Editor,
Thank you very much for the current work titled: Drug Utilization Evaluation of Vancomycin among Patients in Jafar Ibn Auf Pediatric Hospital, 2018.

The authors performed a drug utilization study to determine the rational use of vancomycin according to the standard guidelines at Jafar Ibn Auf Hospital. The topic is crucial and describes how vancomycin is prescribed, which provides the basis for utilizing an antimicrobial regimen against diseases.

However, before betting the house, some points should addressed in this manuscript:

○ Was the study reported according to the STROBE statement for writing a cross-sectional study?

○ Regarding the exclusion criteria for the participants. Are there any other exclusion criteria in addition to who received vancomycin orally and/or patients with incomplete data?

○ The authors should represent both the number and frequency % for each variable in the tables for the table.

Sincerely,

Khalid

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pharmacology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 09 Nov 2021
Bashir Yousef, Sudan International University, Khartoum, Sudan

1- Was the study reported according to the STROBE statement for writing a cross-sectional study?
   Reply: Authors appreciate the reviewer for this valuable comment. We want to inform you that the study was conducted according to the STROBE statement.

2- Regarding the exclusion criteria for the participants. Are there any other exclusion criteria in addition to who received vancomycin orally and/or patients with incomplete data?
   Reply: The authors would like to thanks the reviewer for this important question about the exclusion criteria for the participants. As we mentioned in this study, the only exclusion criteria were patients who received vancomycin orally and/or patients with incomplete data.

3- The authors should represent both the number and frequency % for each variable in the tables for the table.
   Reply: We thanks the reviewer for this suggestion that further simplify the tables.
   As a response: All Tables in the manuscript were modified by adding the number of the participants and frequency % for each response or answer.

Competing Interests: None

Reviewer Report 15 April 2020

https://doi.org/10.5256/f1000research.21233.r59899

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Ghulam Jilany Khan

1 Faculty of Pharmacy, University of Central Punjab, Lahore, Pakistan
2 State Key Laboratory of Bioelectronics, School of Biological Science and Medical Engineering (BME), Southeast University, Nanjing, China

Vancomycin is an important antimicrobial drug particularly against MRSA however its growing development of resistance against the microbes has made it an important drug for further studies and a higher level of understanding for its utility and mode of usage.

In present study, the authors conducted a retrospective study at Jafar Ibn Auf Hospital which is one of the good health care facility for infectious and other diseases. The results concluded that 86 patents (67.8%) were receiving the Vancomycin therapy appropriately against Sepsis (29%) and Pneumonia (19.6%) as most common indication.

1. The authors have reported that the therapy was given to a pneumonia patient for 40 days and alternatively it was recommended for another patient for one day only, here I would suggest the authors to update the record for this duration of one day as well and whether it
was discontinued for some medical reason OR due to treatment success OR due to something else. As per my understanding Vancomycin therapy should not be given for that much limited duration.

2. The authors have reported that in most of the cases vancomycin therapy was given as an imperial treatment, and culture sensitivity testing rate is very low, The authors should explain (in discussion) why they have this much low rate of culture sensitivity testing?

3. I highly recommend the acceptance of this manuscript for publication as it will provide the basis for antimicrobial regimen design against certain diseases.

**Is the work clearly and accurately presented and does it cite the current literature?**
Yes

**Is the study design appropriate and is the work technically sound?**
Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**
Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**
Yes

**Are all the source data underlying the results available to ensure full reproducibility?**
No

**Are the conclusions drawn adequately supported by the results?**
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Antimicrobials, Tumor Metastasis, Non Small Cell Lung Cancer, Diabetes, Basic and Clinical Pharmacology/Oncology, MDR Nanocareer Drug Deliver System

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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**Author Response 09 Nov 2021**

**Bashir Yousef**, Sudan International University, Khartoum, Sudan

1- The authors have reported that the therapy was given to a pneumonia patient for 40 days and alternatively it was recommended for another patient for one day only, here I would suggest the authors to update the record for this duration of one day as well and whether it was discontinued for some medical reason OR due to treatment success OR due to something else. As per my understanding Vancomycin therapy should not be given for that much limited duration.
Reply: The authors would like to thank the reviewer for this important comment. This patient was suffered from many diseases that made him stay for 40 days in the hospital.
As a response: We have added the explanation in the discussion section
  ○ Considering the duration of vancomycin therapy, the maximum duration (40 days) was prescribed in one patient suffering from pneumonia due to he suffered from other diseases.

2- The authors have reported that in most of the cases vancomycin therapy was given as an imperial treatment, and culture sensitivity testing rate is very low, The authors should explain (in discussion) why they have this much low rate of culture sensitivity testing?
Reply: The authors appreciate this important suggestion and we agree about the importance of explanations of the low rate of culture. The main reason for this is high cost of the culture, and many patients couldn't afford to do it.
As a response: we added the explanation in the discussion part
  ○ The main reason for the low rate of requesting culture is that most patients had no health insurance to cover the cost of culture.

3- I highly recommend the acceptance of this manuscript for publication as it will provide the basis for antimicrobial regimen design against certain diseases
Reply: We appreciate your words about the importance of this study.

Competing Interests: None