Dear Reviewers and Editors,

Thank you for your work and for giving us an opportunity to resubmit an updated version of our manuscript. We thank for the reviewers' comments concerning our manuscript entitled "Vancomycin dosing in an obese patient with acute renal failure: A case report and systematic review" (ID: 73503). Their comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have made every effort to concern comments carefully and have made correction which we hope meet with approval.

Our article reports the medical records of dose adjustment of vancomycin in an obese patient (body mass index (BMI) 78.4kg/m^2). Adjustment of loading dose and maintenance dose is critical for the antibiotic treatment in obese patients using vancomycin. We should make appropriate dose adjustments based on the patient's therapeutic drug monitoring and renal function. At the same time, Adjustment of loading dose and maintenance dose is critical for the effective concentration in obese patients using vancomycin. In addition, this article reviews the current literatures on the application of vancomycin in the obese population and provides recommendations on how to make dose adjustments based on the available evidence.

According to reviewers' advices, we tried best to correct and improve our English. **It has been edited by a professional editing service (UNIWINSCI Team) which we hope meet with approval. All changes were highlighted in yellow in the manuscript.**

The responds to the reviewers' as well as editors' comments are as following.

Reviewer 1:

1 Response to comment: Dear Authors, thank you very much for reviewing the Vancomycin dosing in obesity with acute renal failure. Please check the manuscript for invalid writing again. Reviewer

Response: Thanks for your advice. We have revised the redundant descriptions in the article. In addition, we tried best to correct English and it has been edited by a professional editing service (UNIWINSCI Team) for improving English.

Reviewer 2:

1 Response to comment: Dear Authors Congratulations on this wonderful piece of

work on vancomycin titration for obese individuals. I would recommend the authors to give a summary table on the standard dosing regimen for various category of individuals based on their weight and comorbidis and the parameters that has to be monitoring to determine the adequacy of dosing for ease of understanding to the readers

Response: Thanks for your comments. According to The Evidence-based Guideline for Therapeutic Drug Monitoring of Vancomycin (2020): although 3 studies showed that vancomycin dosing based on actual weight (15–20 mg/kg, every 8–12 hours) might increase the risk of supratherapeutic concentrations and nephrotoxicity in obese patients (BMI >30 kg/m^2), the revised dose regimens were different between the 3 studies. And the pharmacokinetics in patients receiving CRRT are complicated and difficult to predict. As there is limited evidence and great heterogeneity in clinical settings between studies. These recommendations are essentially based on small sample-sized PK studies with no evaluation of outcome, and must be considered with caution. Thus, we are sorry that it is difficult to make the standard recommendation concerning the vancomycin dose regimen for these patients. Studies suggest that incorporate assessment of renal function and trough concentrations are needed to identify the optimal dosing strategies for infections in obese patients. We recommend maintaining vancomycin serum trough concentrations at 10 to 20mg/L in obese patients. We tried best to clearly described the pharmacokinetic changes in obese patients in detail. It is helpful for clinicians and may be a good reference.

Reviewer 3:

1 Response to comment: Can you explain why this study is new or telling new things?

Response: Thanks for your comments. Due to the increasing prevalence of obesity, dose-finding studies in this population are essential to ensure appropriate vancomycin administration. Physiological changes in obese patients pose challenges for clinicians. Although vancomycin pharmacokinetics is well described in the general population. To our knowledge, there are no current studies specifically evaluating vancomycin

dosing in severely obese, critically ill patients. Current population pharmacokinetic approaches used for vancomycin dosage selection are limited for these populations. We describe in detail the patient's vancomycin blood levels, renal function, and clinical outcomes, it is a rare but successful case of a severely obese, critically ill patient (BMI 78.4kg/m^2). It is helpful for clinicians and may be a good reference.

2 Response to comment: Line 73-79: You keep repeating about obesity. Please summarize the new sentence to make it easier to understand. Please re-write again about “obesity”.

Response: Thanks for your advice. According to your advice, we have reorganized the paragraph in lines 79-84 and highlighted it. In this way, it is consistent with the text and may be easier for readers to understand. In addition, our manuscript has been edited by a professional editing service (UNIWINSCI Team) for improving English. If fail to meet with approval, we are very willing to continue to revise.

3 Response to comment: In this case, how do you deferential diagnosis between *Staphylococcus hemolyticus* infection and colonization. How about your criteria for diagnosis?

Response: Thanks for your comments. The diagnosis of infection usually is based on clinical signs; infectious indexes and microbial culture. Classic indexes of infection include C-reactive protein (CRP), calcitoninogen (PCT) and white blood cell (WBC) and so on.

The main infection sites were the left lower limb and scrotum accompanied by drainage of purulent fluid. There were signs of infection: Persistent fever, sometimes even the heart rate is fast. There were indexes to infection (PCT:9.170ng/mL; CRP:183.51mg/L and WBC:14.02X10^9). In addition, the culture of secretion revealed *Staphylococcus hemolyticus* at the local hospital. Therefore, we consider it as a bacterial infection rather than colonization.

4 Response to comment: Line 147; For treatment *Staphylococcus hemolyticus*, why

do you discontinue linezolid and start intravenous infusion of vancomycin? How about the effect of linezolid PK on a severely obese patient?

Response: Thanks for your comments. The patient was treated with linezolid for three days, therapy subsequently was changed to vancomycin. Because the patient's clinical status worsened, with persistent fever (40.2℃) and the high-sensitivity C-reactive protein (hs-CRP) rose to 183.51mg/L. According to our clinical experience, considering individual patient differences and medication factors, vancomycin has higher clinical efficacy than linezolid in some patients. The results supported the hypothesis that vancomycin had significantly better clinical efficacy in this obesity patients.

5 Response to comment: Line 149-150: Due to infusion-related reaction peculiar to vancomycin, please add details about the administration time of vancomycin in a dosage of 1-2 g.

Response: Thanks for your comments. we increased the administration time of vancomycin infusion in line 155-157: we determined the dosing regimen of a loading dose (vancomycin administered as continuous infusion of 2g over 2h) and a maintenance dose (vancomycin 1g infused over 60 min every 8h). Red man syndrome is a rare but possibly serious adverse reaction during treatment with intravenous vancomycin. The reaction is often associated with rapid (<1 h) infusion of the first dose of vancomycin. In order to prevent red man syndrome, vancomycin requires a prolonged infusion process.

6 Response to comment: Line 221…obtaining optimal target blood concentrations, and improve clinical efficacy. The next paragraph, I suggest adding more reference and detailed description of serum trough concentrations as a surrogate marker correlation of vancomycin AUC/MIC. Please see: Issaranggoon Na Ayuthaya S, et al. Correlation of the vancomycin 24-h area under the concentration-time curve (AUC_{24}) and trough serum concentration in children with severe infection: A clinical pharmacokinetic study. Int J Infect Dis. 2020;92: 151-159.

doi:10.1016/j.ijid.2019.12.036

Response: Thanks for your comments. I have read this and related literature carefully. In addition, we describe in detail the relevance of serum trough concentration as a surrogate marker for vancomycin AUC/MIC in lines 234-245 and highlighted it.

7 Response to comment: Line 223: The authors mention about vancomycin in critically ill patients. Could you please insert/use/discuss about vancomycin parameters in critically ill (e.g.CL) patients? Please see: doi.org/10.2147/IDR.S121513

Response: Thanks for your comments. According to your advice, I have read the literature related to vancomycin in obese, critically ill patients carefully. However, despite the growing number of obese patients, PK studies on antibiotics in this patient population are greatly lacking. Furthermore, there are a number of limitations in the studies already performed. Pharmacokinetics alterations may be further increased in obese critically ill patients where both conditions together (obesity and critical illness) may further cause enhanced pathophysiological changes. Thus, vancomycin was more likely to exhibit altered pharmacokinetics in the obese, critically ill patient. For this special patient population, we discuss about V_d in lines 191-196 and CL in lines 207-213 with highlights.

8 Response to comment: Please provide more data of importance of physician around the world to recognize vancomycin dosing adjustment in an obese patient.

Response: Thanks for your comments. The importance of dose adjustment of vancomycin for obese patients by clinicians has been added in lines 77-79,84-85 of the article and highlighted it.

9 **Response to comment:** Please write "*Acinetobacter baumannii*" in italics. Line 36: Please write "*Staphylococcus hemolyticus*" in italics.

Response: Thanks for your advice. It has been modified in the revised manuscript. I am truly sorry for the error. We tried best to correct English and it has been edited by a professional editing service (UNIWINSCI Team) for improving English.

10 **Response to comment:** Please add initial serum creatinine and GFR of this patient in treatment section.

Response: Thanks for your comments. According to your advice, initial serum creatinine and creatinine clearance rate of this patient have been added to the treatment section: His initial serum creatinine is 63.3μmol/L and creatinine clearance (CrCl)>90 mL/min.

The glomerular filtration rate (GFR) is a dynamic function that can change almost instantaneously in response to stressors. Despite its central role in nephrology, there are no techniques available to the clinician for monitoring GFR in real time. The creatinine clearance (CrCl) is the usual technique employed by physicians as a clinical measurement of GFR. In clinical practice, the renal function of patients was reflected by the calculated CrCl, and then the dosage was adjusted by CrCl (doi: 10.1016/s0272-6386(82)80091-7). To our knowledge, the correction formula for obese patients still cannot accurately reflect the renal function for the severely obese patient. It is important to adjust the dose by monitoring the change in the patient's 24h urine output. Real-time and accurate monitoring of urine output could improve the clinical management of patients in the ICU, and enable clinicians to early recognition of kidney injury.

Science editor:

1 Response to comment: This manuscript reports a case of vancomycin doing adjustment in an obese patient (body mass index 78.4kg/m^2) with necrotizing fasciitis of the screw and left lower extreme achieved with acute renal failure. Please supple the summary of standard dosing regimens for various categories of individuals according to their weight and comorbidity and the parameters that must be monitored to determine dose adequacy.

Response: Thanks for your comments. According to The Evidence-based Guideline for Therapeutic Drug Monitoring of Vancomycin (2020): although 3 studies showed that vancomycin dosing based on actual weight (15–20 mg/kg, every 8–12 hours) might increase the risk of supratherapeutic concentrations and nephrotoxicity in obese patients (BMI>30kg/m^2), the revised dose regimens were different between the 3 studies. And the pharmacokinetics in patients receiving CRRT are complicated and difficult to predict. As there is limited evidence and great heterogeneity in clinical settings between studies. These recommendations are essentially based on small sample-sized PK studies with no evaluation of outcome, and must be considered with caution. Thus, we are sorry that it is difficult to make the standard recommendation concerning the vancomycin dose regimen for these patients. Studies suggest that incorporate assessment of renal function and trough concentrations are needed to identify the optimal dosing strategies for infections in obese patients. We recommend maintaining vancomycin serum trough concentrations at 10 to 20mg/L in obese patients. We tried best to clearly described the pharmacokinetic changes in obese patients in detail. It is helpful for clinicians and may be a good reference.

2 Response to comment: Please provide more data on the importance of doctors identifying vancomycin dose adjustments in obese patients.

Response: Thanks for your comments. The importance of dose adjustment of vancomycin for obese patients by clinicians has been added in lines 77-79,84-85 of the article and highlighted it.

Company editor-in-chief:

1 Response to comment: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please

prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response: Thanks for your comments. We have revised the manuscript according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. In addition, we have provided the original figure and table, and the figure was prepared and arranged using PowerPoint.

Thank you for giving us an opportunity to resubmit an updated version of our manuscript.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Sincerely,

Jing Bai.