

Dear Editor:

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript again, we appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled “ Cefoperazone sulbactam and ornidazole for gardnerella vaginalis bloodstream infection after cesarean section: A case report and review of the literature ” (Manuscript NO.: 76549, Case Report).

We have studied reviewer`s comments carefully and have modified in the revision mode. We have tried our best to revise our manuscript according to the comments. We would like to express our great appreciation to you and reviewers for comments on our paper. We hope this article is of better quality, more scientific and reasonable results, and can meet your requirements.

Thank you and best regards.

Yours sincerely,

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List of Responses

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Cefoperazone sulbactam and ornidazole for gardnerella vaginalis bloodstream infection after cesarean section: A case report and review of the literature" (Manuscript NO.: 76549, Case Report). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our studies. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewers' comments are as follows:

Responds to the reviewers' comments:

Reviewer 1: An interesting case report. However, I would suggest to italicize the scientific names.

And also suggest to develop a timeline using a image or a table. Explain about penicillin

hypersensitivity and how it differ between piperacillin and cefoperazone. Explain why dose (cef-sul) was escalated?

Response: We are very thankful for your suggestions. We have italicized the scientific names according to your suggestions and developed a timeline using a table (Table 1).

Table 1 Clinical information and anti-infection treatment of the patient

Date	Basic information of patients	Antimicrobial treatment
2021-11-20 (Cesarean section day)		
Postoperative D1	The patient had a sudden fever on the afternoon, and had a highest temperature of 39.7 °C at 22:00. Blood routine examination indicates that WBC was $15.97 \times 10^9/L$, NE%	Cefoperazone sulbactam (2:1) 3g ivgtt q12h

	was 84.7% and CRP was 93.96 mg/L. Temperature was 38.6°C at 2:00 and 38°C at 18:00. The abdominal incision of the patient was dry and clean, and the patient's intestinal function had been restored. Temperature was normal and blood routine examination indicates that WBC was	
Postoperative D2		The treatment was the same as before
Postoperative D3	10.38×10 ⁹ /L, NEUT % was 71.3% and CRP was 93.96mg/L. Blood bacterial culture (first time) results suggested the possibility of gram-negative bacteria growth.	Cefoperazone sulbactam (2:1) 3g ivgtt q8h
Postoperative D4	Temperature was 37.6 degrees at 14:00 and was normal for the rest of the time. Temperature was 37.6 degrees at 14:00. Blood bacterial culture (first time) suggested the growth of <i>GV</i> (gram-negative microbacteria) in anaerobic bottles (left and right). Blood routine examination indicates that WBC was	The treatment was the same as before
Postoperative D6	8.11×10 ⁹ /L, NEUT % was 63.9% and CRP was 77.88mg/L.	Cefoperazone sulbactam (2:1) 3g ivgtt q8h combined with onidazole 0.5 q12h
Postoperative D9	Temperature occasionally reached 37.7°C, and was normal for the rest of the time.	The treatment was the same as before
Postoperative D10	The results of the blood bacterial culture (second time) showed that there was no bacterial growth	The treatment was the same as before
Postoperative D12	Temperature is normal today, without any discomfort, the uterus is well restored and blood routine tests of the patient's were basically normal	The treatment was the same as before
Postoperative D14 (Discharge day)	The results of the blood bacterial culture (third time) showed that there was no bacterial growth and the patient reached the discharge standard	Stopped antimicrobial treatment

Penicillins have a common mother nucleus, 6-aminopenicillanic acid, and there is a complete cross allergic reaction. According to the guiding principles for clinical application of antibiotics (2015 Edition): patients allergic to penicillin G or other penicillins are prohibited from using penicillins. It is generally believed that the R₁ side chain of cephalosporins is very important to predict the cross allergic reaction between penicillins and cephalosporins. The incidence of cross

allergic reactions between penicillins and the first / second generation cephalosporins were 4% and 1%, respectively, while the cross allergic reactions with the third / fourth generation cephalosporins were rare. According to the current clinical practice in China, cephalosporins should be the first choice for those who are allergic to penicillins (except those with anaphylactic shock). Therefore, this patient has the experience of mild penicillin allergic reaction. Therefore, cefoperazone sulbactam is preferred instead of piperacillin tazobactam when changing the anti infection regimen on the 6th day after cesarean section.

In recent years, some scholars put forward the concept of Augmented renal clearance (ARC). ARC has been defined as creatinine clearance $[(CrCl) > 130 \text{ ml/min/1.73 m}^2]$. Clinical pharmacists also gradually found that ARC is a common state in pregnant women. In the previous large sample regression analysis, the author's team has found that 47.1% of pregnant women are accompanied by ARC. Theoretically, the critically ill obstetric patients are younger and heavier, and the incidence of ARC may be higher than that in the general population. At present, it has been found that the antibacterial effects of many antibiotics such as vancomycin, meropenem and piperacillin tazobactam are affected by arc^[a-c]. Studies have shown that after giving conventional doses of carbapenems or β -lactam (enzyme inhibitor) or vancomycin to patients with severe infection, the pharmacokinetic / pharmacodynamic (PK/PD) target of 50% $fT > MIC$ and 100% $fT > MIC$ in patients with arc status are significantly lower than those in patients without arc status, with significant statistical difference^[d-e]. Therefore, patients with arc status need a larger dose. In patients with arc status, conventional drug dose will not only cause insufficient blood drug concentration and unable to achieve antibacterial effect, but also increase bacterial drug resistance^[f]. When the effect of antibiotics in pregnant patients is poor, when clinical pharmacists

judge that patients have ARC, they can consider increasing the dosage and / or frequency of time-dependent drugs and prolonging the time of drug infusion. Since urine creatinine was not determined, we used estimated glomerular filtration rate equations (CG formula) in the diagnosis of this patients with ARC. On the 6th day after delivery, the calculation result of estimated glomerular filtration rate was $167.46 \text{ ml} \cdot \text{min}^{-1}$, which was significantly higher than the critical value of $130 \text{ ml} \cdot \text{min}^{-1}$. Considering the existence of ARC, the daily administration frequency of cefoperazone sulbactam was increased (q12h→q8h).

- [a] Tang L, Ding XY, Duan LF, et al. A Regression Model to Predict Augmented Renal Clearance in Critically Ill Obstetric Patients and Effects on Vancomycin Treatment[J]. Front Pharmacol.2021 Jun 11; 12: 622948.
- [b] Bilbao-Meseguer I , A Rodríguez-Gascón, Barrasa H , et al. Augmented Renal Clearance in Critically Ill Patients: A Systematic Review[J]. Clinical Pharmacokinetics, 2018, 57(9): 1107-1121.
- [c] Tamatsukuri T, Ohbayashi M, Kohyama N, et al. The exploration of population pharmacokinetic model for meropenem in augmented renal clearance and investigation of optimum setting of dose[J]. J Infect Chemother, 2018, 24 (10): 834-840.
- [d] CARLIER M, CARRETTE S, ROBERTS J A, et al. Meropenem and piperacillin / tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic / pharmacodynamic target attainment when extended infusions are used[J]. Critical Care, 2013, 17(3): R84.
- [e] CAMPASSIL M L, GONZALEZ M C, MASEVICIUS L F D, et al. Augmented renal clearance in critically ill patients: incidence, associated factors and effects on vancomycin treatment[J]. Rev Bras TerIntensiva, 2014, 26(1): 13-20.
- [f] SIME F B, UDY A A, ROBERTS J A. Augmented renal clearance in critically ill patients: etiology, definition and implications for beta-lactam dose optimization[J]. Curr Opin Pharm, 2015, 24: 1-6.

Reviewer 2: Well written, good focused on *Gardnerella vaginalis* bloodstream infection.

Interesting case report for researchers. The authors can add the studies below as a references to increase the value of content in discussion section. Sarier M, Sepin N, Guler H, et al. Prevalence of Sexually Transmitted Disease in Asymptomatic Renal Transplant Recipients. *Experimental and Clinical Transplantation*. April 2018. doi: 10.6002/ect.2017.0232. Sarier M, Demir M, Goktas S, et al. Results of Real-time Multiplex Polymerase Chain Reaction Assay in Renal Transplant Recipients With Sterile Pyuria. *Transplant Proc*. 2017;49(6):1307-1311. doi:10.1016/j.transproceed.2017.02.051.

Response: We appreciate your advice very much. We have read the two literatures you recommended in detail and added the above two literatures to this manuscript, so as to increase the value of content in discussion section.

Other changes in the version of original manuscript with modification marks:

We have made some modifications to our manuscript according to the editor and reviewers' comments. The modifications led to changes in the order of references and two articles are added to the section of references and one articles is replaced.

The specific changes were: the former "6" was modified as "8"; the former "7" was modified as "9"; the former "8" was modified as "10"; the former "9" was modified as "11"; the former "12" was modified as "14"; the former "13" was modified as "15"; the former "14" was modified as "16"; the former "15" was modified as "17"; the former "16" was modified as "18"; the former "17" was modified as "19".

The former “2 Chang R, Wang N, Gao YY, Feng CX, Li N. Pathogenic bacteria distribution and drug resistance in patients with puerperal infection. *Chin J Nosocomiol*, 2017, 27(20): 4758-4760.” was replaced by “2 Schwebke JR, Muzny CA, Josey WE. Role of *Gardnerella vaginalis* in the pathogenesis of bacterial vaginosis: a conceptual model. *J Infect Dis*. 2014; 210: 338-43 [PMID: 24511102 DOI: 10.1093/infdis/jiu089]”.

“6 Sarier M, Demir M, Goktas S, Duman I, Buyukkinaci M, Yuksel Y, Tekin S, Yavuz AH, Sengul A. Results of Real-time Multiplex Polymerase Chain Reaction Assay in Renal Transplant Recipients With Sterile Pyuria. *Transplant Proc*. 2017, 49(6): 1307-1311.

7 Sarier M, Sepin Ozen N, Guler H, Duman I, Yuksel Y, Tekin S, Yavuz AH, Yucetin L, Erdogan Yilmaz M. Prevalence of Sexually Transmitted Diseases in Asymptomatic Renal Transplant Recipients. *Exp Clin Transplant*. 2018 Apr 4.” is added.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And all the changes were presented in the revision mode.

We appreciate for editor and reviewers` warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.