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Cefoperazone-sulbactam and ornidazole for *Gardnerella vaginalis* bloodstream infection after cesarean section: A case report

Mu Y *et al.* Bloodstream infections caused by *Gardnerella vaginalis*

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Abstract

BACKGROUND

Gardnerella vaginalis (*G. vaginalis*) is a facultative anaerobic bacteria known to cause bloodstream infections however, the cases are very rare in clinics. There is very limited clinical experience in the treatment of bloodstream infections caused by *G. vaginalis*. Therefore, there is an urgent need for effective antibacterial drugs to treat patients with bloodstream infections caused by *G. vaginalis*.

CASE SUMMARY

A woman who underwent a cesarean section presented with a sudden onset of high fever 1-day post-surgery. The blood cultures suggested an infection due to *G. vaginalis* and treatment with cefoperazone-sulbactam was started. After 5 d of treatment, there was a decrease in the hemogram, however, the temperature and C-reactive protein (CRP) levels remained high. Based on clinical experience and a review of literature, the treatment was modified to include ornidazole in combination with cefoperazone-sulbactam. Following a week of treatment, the temperature, hemogram, and CRP levels returned to normal, and blood cultures turned negative, suggesting a therapeutic effect of the combination treatment.

CONCLUSION

This case highlights the effective use of cefoperazone-sulbactam combined with ornidazole for bloodstream infection caused by *G. vaginalis* following a cesarean section.

Key Words: *Gardnerella vaginalis*; Bloodstream infections; Anti-infective; Cefoperazone-sulbactam; Ornidazole; Case report

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Core Tip: We analyzed a case of bloodstream infection caused by *Gardnerella vaginalis* (*G. vaginalis*) after cesarean section. We believe that our study makes a significant contribution to the literature because it indicates that cefoperazone-sulbactam combined with ornidazole is an effective therapy for bloodstream infection caused by *G. vaginalis* after cesarean section.

INTRODUCTION

Haemophilus vaginalis, is a gram-negative bacillus that was first isolated as early as 1953, from male patients with urethritis, prostatitis, and female patients with cervicitis^[1]. The development of electron microscopy helped scholars identify the characteristics of the bacterium as that resembling gram-negative bacteria. *Gardnerella* genus was officially included in Bergey's Handbook of Systematic Bacteriology in 1984, and *Gardnerella vaginalis* (*G. vaginalis*) is the only strain of this genus. *G. vaginalis* colonizes the anus and rectum of healthy adult men, women, and children and is mostly transmitted through sexual intercourse. It is reported that *G. vaginalis* is associated with a variety of infectious diseases and is the main causative pathogen of bacterial vaginosis (BV)^[2]. Clinicians have previously isolated *G. vaginalis* from the patient's amniotic fluid, prostatic fluid, semen, and ascites^[3-5]. Additionally, there are few reports of *G. vaginalis*-induced maternal bloodstream infection. In this report, a case of *G. vaginalis* bloodstream infection after a cesarean section (C-section) was analyzed to provide a reference for clinical treatment.

CASE PRESENTATION

Chief complaints

The patient (female, aged 31 years, height 165 cm, weight 65 kg, Han nationality) presented with sudden fever on the first day after a C-section, and the highest temperature was recorded at 39.7 °C.

History of present illness

The patient was admitted to the hospital for delivery at 38⁺² wk of pregnancy on November 17, 2021. Since the lower segment of the uterus was thin and the fetus was full-term, scar uterine rupture could occur during vaginal delivery. Therefore, after excluding surgical contraindications, the patient underwent a C-section under spinal anesthesia on November 19, 2021. During the surgery, abnormal proliferation of varicose blood vessels in the lower segment of the uterus was found, and dense adhesion was noted in the bladder. After decomposing a part of the adhesion, a baby boy (Apgar 10/10) was successfully delivered. Once the umbilical cord was cut, the patient was prophylactically administered cefoxitin 2 g to prevent post-surgical infections. The placenta and fetal membrane were delivered completely, and the postoperative bleeding was 300 mL. The patient was given misoprostol 0.4 mg anal plug and ergometrine maleate 0.2 mg intramuscular injection post-surgery, to strengthen uterine contraction, and she was started on 80 mg of sodium kalo sulfonate intravenous drip to stop the bleeding.

History of past illnesses

The patient was a healthy female with no significant ailments reported in her medical history. There was no history of dyslipidemia, hypertension, diabetes, or other diseases. The patient reported regular menstruation in the past, married at an appropriate age, and the spouse was healthy. Her pregnancy history is 1-0-3-1. The patient had previously given birth to a son by C-section in 2015.

Personal and family history

The patient reported no family history of inherited diseases or premature coronary heart disease.

Physical examination

The highest body temperature was recorded to be 37.7 °C on day 1 post-surgery.

Laboratory examinations

The following were the laboratory examination results after the C-section: White blood cell (WBC), $15.97 \times 10^9/L$; neutrophil count (NEUT), 84.7%; C-reactive protein (CRP), 93.96 mg/L; Blood culture suggested the presence of *G. vaginalis* in anaerobic bottles (left and right sides).

Imaging examinations

The patient did not have an imaging examination.

FINAL DIAGNOSIS

Postpartum bloodstream infection.

TREATMENT

One day post-C-section

The patient spiked a sudden fever in the afternoon, and the highest temperature of 39.7 °C was recorded at 10:00 pm. Routine blood examinations were as follows, WBC, $15.97 \times 10^9/L$; NEUT, 84.7%; CRP, 93.96 mg/L. A blood sample was collected from the patient (left and right sides) for bacterial culture (aerobic bottle + anaerobic bottle). The antibiotic was changed to cefoperazone sulbactam (2:1) 3 g q12h to strengthen anti-infective treatment.

Day 2 post-C-section

The patient's temperature was reported as 38.6 °C and 38 °C at 2:00 am and 6:00 pm respectively. The patient's uterine contractions were good, the uterine fundus recovered to the size of two fingers under the umbilicus, the abdominal incision was dry and clean, and the patient's intestinal function had been restored.

Day 3 post-C-section

The patient's temperature was normal. Routine blood examination indicated WBC, $10.38 \times 10^9/L$; NEUT, 71.3%; CRP, 93.96 mg/L. The microbiology lab noted that the bacterial cultures suggested the growth of small gram-negative bacilli, as a result, the dose frequency of cefoperazone-sulbactam was increased to q8h.

Day 4 post-C-section

The patient reported her highest temperature of 37.6 °C at 2:00 pm. A blood sample was collected from the patient (left and right sides) for bacterial culture (aerobic bottle + anaerobic bottle) for the second time.

Day 6 post-C-section

The patient's highest temperature was reported as 37.5 °C at 2:00 pm. The patient had a good uterine contraction and a reduced amount of lochia, no exudative induration in abdominal appetite, and no other complaints of discomfort. Routine blood examination indicated WBC, $8.11 \times 10^9/L$; NEUT, 63.9%; CRP, 77.88 mg/L. The results of the first blood bacterial culture showed that *G. vaginalis* and other gram-negative bacilli were found in the anaerobic bottle (left and right). The doctor planned to alter the antibacterial regimen to piperacillin-tazobactam combined with ornidazole, however, the penicillin skin test returned was positive for the patient. Therefore, the patient was treated with cefoperazone sulbactam (2:1) 3 g q8h combined with ornidazole 0.5 g q12h.

Day 9 post-C-section

The patient reported normal body temperature with an occasional spike up to 37.7 °C.

Day 10 post-C-section

The results of the second blood culture showed no bacterial growth. However, the doctor collected blood from the patient (left and right sides) for bacterial culture (aerobic bottle + anaerobic bottle) for the third time.

Day 12 post-C-section

The patient reported a normal temperature throughout the day, no discomfort noted, the vital signs were stable, the uterus was well restored, and there were lesser amounts of lochia and no peculiar smell. Blood examination reported WBC, $7.16 \times 10^9/L$; NEUT, 63.6%; CRP, 29.27 mg/L. The treatment history is shown in Table 1.

OUTCOME AND FOLLOW-UP

On the 14th day after the C-section, the patient had been treated with cefoperazone-sulbactam combined with ornidazole for 10 d. The results of the third blood culture showed no signs of bacterial growth. The patient was generally in good condition and recovered well post-surgery, reaching the discharge standard.

DISCUSSION

Obstetric characteristics of patients with *G. vaginalis* bloodstream infection

G. vaginalis has been isolated in a variety of patients and biological samples, however, bloodstream infections in pregnant women are rare^[3-7]. A literature search was conducted for publications in the past 30 years on *G. vaginalis* bloodstream infection in pregnant women. Taking "*Gardnerella vaginalis*, bloodstream infections, bacteremia, puerperium" as the keywords. PubMed, EMBASE, CNKI, VIP, and other databases were searched for relevant studies. Meta-analysis, review, and other types of literature were excluded, and a total of 3 studies were included, involving 5 cases of parturient women^[8-10]. Due to the low number of case reports found, a statistically significant susceptibility index was not established. In the medical history review, it was found that a total of 4 cases had related factors causing infection. Two patients underwent intrauterine operations and one patient had long-term prenatal bleeding, which may cause upward vaginal infection due to *G. vaginalis*. Another patient with a missed abortion developed a high fever three days before the delivery. When exploring the uterine cavity, inflammatory exudation and bleeding were found in the uterine cavity, and a large amount of neutrophil infiltration was found in the endometrium. From the

perspective of histomorphology, it is inferred that this phenomenon may be due to gram-negative infections, and blood culture further confirmed the presence of *G. vaginalis*. The most likely route of infection is that *G. vaginalis* first causes inflammatory changes in the uterine cavity through ascending vaginal infection, resulting in gradual separation of the placenta, followed by *G. vaginalis* entering the blood to cause bloodstream infection (Table 2).

Detection of G. vaginalis in blood

After the sudden high fever, the peripheral venous blood of both left and right upper limbs was extracted and cultured in aerobic and anaerobic bottles at the same time, this was done to improve the detection rate of pathogens and reduce the rate of false negatives in the bacterial culture. *G. vaginalis* has a variety of forms, has high nutritional requirements, and is difficult to cultivate and identify, resulting in a low rate of clinical isolation. Initial blood cultures may be positive for *G. vaginalis*, however, growth is not always guaranteed and therefore they cannot be identified nor can the cultures be considered as false positive and discarded after being transferred to the culture medium^[11]. With the development of molecular biology techniques and mass spectrometry, especially the wide applications of MALDI-TOF MS, the ability to identify aerobic and anaerobic has significantly improved, providing a good basis for the clinical diagnosis of infections. Although the blood culture of the 5 patients reported in the other studies was positive, there was some inconsistency noted in the results of bacterial morphology, such as gram-negative bacillus and gram-negative cocci^[8-10]. Five cases of blood cultures were transferred to a different culture media immediately after the culture bottle showed positive results, and the results were further verified using mass spectrometry or polymerase chain reaction (Table 3). Once the blood cultures showed gram-negative bacilli, the sample was immediately transferred to a different culture media, and finally confirmed that the bacteria was *G. vaginalis*. Therefore, it is our understanding that in such patients, bacterial blood culture must be done in bilateral double bottles. It is necessary to collect samples before antibiotic

administration or treatment modification, and appropriately extend the culture time. A variety of methods can be used for comparison and review during identification, to obtain more accurate results.

Early symptoms and laboratory examination of bloodstream infections caused by *G. vaginalis* post-parturition

The first symptom reported in the 5 patients with postpartum *G. vaginalis* bloodstream infections reported in the literature was fever. The temperature range of patients was noted to be 38.8-39.7 °C, and the temperature of 4 of the patients was more than 39 °C, with an average of (39.26 ± 0.35 °C). Case 1 was a patient with a missed abortion who presented with fever before delivery. Cases 2 and 3 had fever after balloon placement in the cervix and artificial membrane rupture, respectively. Cases 4 and case 5 had fever on days 1 and 2 post the C-section. Routine blood examinations were urgently performed on the 5 patients with a sudden high fever. The mean value of WBC was $18.21 \pm 4.96 \times 10^9/L$, the mean value of NEUT was $89.96\% \pm 1.77\%$, and the mean value of CRP was 150.35 ± 25.07 mg/L. The above results were much higher when compared with the normal threshold, for these indicators (Table 4). The patient had no fever before delivery, and the first symptom on the first-day post-surgery was a high fever of 39.7 °C. The WBC, NEUT, and CRP values in her laboratory examination were significantly higher than those before, which was consistent with previous studies. Since patients with *G. vaginalis* bloodstream infections are rare, especially in obstetrics, there are very few reports of *G. vaginalis* bloodstream infections. There are no typical clinical symptoms or changes in the laboratory test indicators, and there is still a lack of evidence to predict bloodstream infections due to *G. vaginalis*.

The anti-microbial strategy of postpartum *G. vaginalis* bloodstream infections

Currently, the Clinical and Laboratory Standards Institute has no recommended method to test for drug sensitivity against *G. vaginalis*, therefore most medical facilities are unable to carry out drug sensitivity testing on *G. vaginalis*. The treatment regimens

reported in the literature are mainly empirical drugs, treatment with β -lactams (enzyme inhibitors), nitroimidazoles, second/third generation cephalosporins, and quinolones. All patients were reported to have achieved satisfactory outcomes once the treatment cycle was complete (Table 5).

In vitro drug sensitivity test showed that anti-microbial resistance to *G. vaginalis* varied across antibiotics^[12]. The antibiotics with a sensitivity profile > 80% were piperacillin-tazobactam (96.6%), cefepime (87.2%), cefoperazone-sulbactam (86.3%), and sulfamethoxazole-trimethoprim (84.6%), while the sensitivity to gentamicin and ciprofloxacin was less than 50%. Studies have also shown that *G. vaginalis* was also less sensitive to lincomycin (52.3%), while the resistance rate to cefepime was as high as 78.79%^[13,14]. Combined with the results of several *in vitro* drug sensitivity testing on *G. vaginalis*, this study found that the sensitivity of *G. vaginalis* to cefepime, cefotaxime, cefazolin, ampicillin, and azithromycin was quite different^[12-16]. the drug resistance spectrum of various strains of *G. vaginalis* may be affected by the differences in epidemiology and the rate of antibiotic usage in different regions. As *G. vaginalis* is a facultative anaerobic bacteria, and it is detected in the anaerobic bottles of the cases reported in the literature and this case, it is necessary to consider covering anaerobic bacteria in the selection of antibiotics. Piperacillin-tazobactam and cefoperazone-sulbactam belong to the β -lactam (enzyme inhibitor) class of antibiotics, which have good antibacterial activity against anaerobic bacteria. Piperacillin-tazobactam has a strong anti-microbial activity against anaerobic bacteria and can cover both common gram-positive anaerobic bacteria (such as *Streptococcus digest*, *Clostridium non-difficile*, *actinomyces*, *etc.*) and gram-negative anaerobic bacteria (*Bacteroides fragilis*, *Clostridium necrotizing*, *Prevotella melanogenes*, *etc.*).

Based on drug sensitivity test reports and evidence from clinical practice, this study concluded that the treatment strategy should include a β -lactam (enzyme inhibitor) antibiotic. Piperacillin-tazobactam is generally the first-choice antibiotic followed by cefoperazone-sulbactam. After 5 d of treatment with cefoperazone-sulbactam, the hemogram of the patient decreased, but the temperature and CRP levels were still high,

suggesting that the treatment was not satisfactory and that the current anti infection strategy has insufficient activity against anaerobic bacteria. Referring to the guidelines, metronidazole or tinidazole is the first choice for the treatment of BV caused by *G. vaginalis*^[17]. The Sanford Guide to Antimicrobial Therapy 2018 (48th edition) and National antimicrobial treatment guidelines (2nd edition) both suggest that nitroimidazoles can cover common anaerobic bacteria, especially anaerobic gram-negative bacteria with strong antibacterial activity, such as *Bacteroides fragilis*, *Clostridium necrotizing* and *Proctor melanogenes*^[18,19]. Although *G. vaginalis* is not included in the above guidelines, it can be seen from previous studies and the blood culture results of this patient that *G. vaginalis* is a gram-negative small bacillus, and therefore may be susceptible to nitroimidazoles in accordance with what is recommended in the above guidelines. Among the 5 cases of postpartum *G. vaginalis* bloodstream infection reported in the literature, the antibiotic regimen of 4 patients included metronidazole or ornidazole^[8-10]. Although the antibacterial spectrum of β -lactam (enzyme inhibitor) drugs and nitroimidazoles against anaerobic bacteria is partially repeated, their mechanisms of action differ. At present, there is still very limited research on the characteristics of *G. vaginalis* bloodstream infections, and monotherapy with cefoperazone-sulbactam did not show promising results in this patient, the combination use of antibiotics with different mechanisms of action may have a beneficial additive effect. Therefore, we believe that for patients with *G. vaginalis* bloodstream infections after a C-section, the treatment plan also needs to include nitroimidazole drugs, such as metronidazole, ornidazole, and so on. Combination therapy of cefoperazone-sulbactam combined with ornidazole, returned the patient's temperature, hemogram, and CRP level to normal within a week of treatment. The results of the second and third blood cultures were negative, and the treatment was shown to be satisfactory.

CONCLUSION

In conclusion,² we report a case of bloodstream infection caused by *G. vaginalis* after a C-section¹ that was treated with a combination of cefoperazone-sulbactam and ornidazole. Our experience shows that the combination therapy of cefoperazone-sulbactam and ornidazole is an effective therapy for bloodstream infection caused by *G. vaginalis* after a C-section.

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