Combination Therapy with Ceftazidime-Avibactam and Amikacin for Multidrug-Resistant *Pseudomonas aeruginosa* Infection with Fulminant Myocarditis in a Younger Patient: A Case Report and Literature Review

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Abstract

**Introduction:** Fulminant myocarditis is a life-threatening disease among young patients. *Pseudomonas aeruginosa* is distributed in nature and is often spread as an opportunistic pathogen to cause hospital-acquired infections in patients with underlying diseases and low immunity.

**Case Presentation:** This report presented a case of a 28-year-old woman with fulminant myocarditis followed by *P. aeruginosa* infection. After hospitalization, she received veno-arterial extracorporeal membrane oxygenation (ECMO) and continuous renal replacement treatment (CRRT). Initially, piperacillin sodium tazobactam combined with amikacin was used for anti-infection therapy, which had a poor clinical effect. Subsequently, it was recommended to use ceftazidime-avibactam and amikacin for treatment. Finally, the infection index of the patient returned to normal.

**Conclusions:** It is necessary to select correct and effective drugs according to etiology, considering the influence of ECMO and CRRT on the patient’s antimicrobial pharmacokinetics/pharmacodynamics (PK/PD). This case could provide a reference for safe and rational drug use in clinical practice.

**Keywords:** Myocarditis, Multidrug-Resistant, *Pseudomonas aeruginosa*, ECMO, CRRT

1. Introduction

Fulminant myocarditis is the most serious and unique type of myocarditis, characterized by sudden onset, rapid progression, rapid occurrence of hemodynamic abnormalities and severe arrhythmias, and multiple organ failure (1). *Pseudomonas aeruginosa* is a gram-negative bacterium widely distributed in nature and healthcare facilities. In hospitals, *P. aeruginosa* is often spread as an opportunistic pathogen to cause hospital-acquired infections (2). The infections are difficult to treat due to the complex mechanism of drug resistance (3). This study analyzed the anti-infection treatment process and pharmaceutical care of a patient with *P. aeruginosa* infection secondary to fulminant myocarditis.

2. Case Presentation

A previously healthy 28-year-old woman weighing 55 kg was admitted to emergency intensive care unit (EICU) on January 12, 2022, with a dry cough for 3 days, subxiphoid pain for 1 day, and dampness and cold limbs for 2 hours. Three days before admission, the patient developed an itchy throat, accompanied by a dry cough, sore throat, nasal congestion, runny nose, fear of cold, and fever. The laboratory examination results were as follows: White blood cell (WBC) count, $7.58 \times 10^9$/L; neutrophil ratio (N%), 64.3%; platelet count, $129 \times 10^9$/L; C-reactive protein (CRP), 1.5 mg/L; cytokine (CK), 457 U/L; CK-MB, 29 U/L; cardiac troponin I (cTnI), 2,170 mg/L; N-terminal pro-B-type natriuretic peptide (NTpro-BNP), 6510 ng/L; and creatinine (Cr), 66.9 µmol/L. After emergency treatment with piperacillin sodium tazobactam sodium 4.5 g q8h, esomeprazole sodium 40 mg bid, and intermittent rehy-
On the 13th to 16th days after admission, the patient's high-dose CRRT continued. The drug sensitivity results showed that the organism was sensitive to ceftazidime. The 24h urine output was 105 mL. Thus, ceftazidime-avibactam was replaced with cefazidime-avibactam 2.5 g q8h (maintenance infusion over 2 hours) combined with amikacin 0.4 g qd. On the 13th to 16th days after admission, the patient's high-temperature was 39°C, and there was a small amount of thin white sputum in the airway. Laboratory tests showed a WBC count of 16.99 × 10^9/L, N% of 83.6%, CRP level of 69.8 mg/L, and PCT level of 0.82 g/mL. On the 23rd day after admission, the patient's highest temperature was 38.4°C, and laboratory tests showed a WBC count of 13.7 × 10^9/L. The levels of CRP and PCT were 28.4 mg/L and 1.79 ng/mL, respectively.

The 24h urine volume was 5 mL, and the patient had intermittent mental symptoms. The clinical pharmacologist believed that the psychiatric symptoms might be related to ceftazidime-avibactam, and the poor renal function recovery might be related to amikacin. Therefore, it was suggested that the dose of ceftazidime-avibactam should be adjusted to 1.25 g q8h, and amikacin should be stopped. The patient showed no obvious psychiatric symptoms again. On the 27th day after admission, the patient stopped CRRT. On the 29th day after admission, the patient's body temperature was maintained at about 36.5°C. The beta-D-glucan test and bacterial culture were both negative. On day 2 of hospitalization, the ECG showed ST elevation, low voltage, and right axis deviation (Figure 1). On the sixth day after admission, the 24h urine volume of the patient was only 70 mL. The WBC count was 20.24 × 10^9/L, N% was 88.7%, CRP was 161 mg/L, and PCT was 3.21 ng/mL. The chest radiograph showed exudative changes in both lungs and aggravation of pulmonary edema (Figure 2A). At the EICU, the patient was given fasting, gastrointestinal decompression, emergency, and tracheal intubation respirator-assisted ventilation. Then, ECMO and CRRT were applied with other supportive measures. The routine blood examination showed a WBC of 21.56 × 10^9/L, N% of 93.6%, CRP of 85.7 mg/L, and procalcitonin (PCT) of 5.82 ng/mL. During days 1 to 6 after admission, the patient's body temperature was maintained at about 36.5°C. The beta-D-glucan test and bacterial culture were both negative. On day 2 of hospitalization, the ECG showed ST elevation, low voltage, and right axis deviation (Figure 1). On the sixth day after admission, the 24h urine volume of the patient was only 70 mL. The WBC count was 20.24 × 10^9/L, N% was 88.7%, CRP was 161 mg/L, and PCT was 3.21 ng/mL. The chest radiograph showed exudative changes in both lungs and aggravation of pulmonary edema (Figure 2A). On the seventh day after admission, the patient had a large amount of white sputum in the airway. Laboratory tests showed a WBC count of 13.7 × 10^9/L, N% of 93.6%, CRP of 182.2 mg/L, and procalcitonin (PCT) of 1.29 g/mL. On the 23rd day after admission, the patient's highest temperature was 38.4°C, and laboratory tests showed a WBC count of 13.7 × 10^9/L. The levels of CRP and PCT were 28.4 mg/L and 1.79 ng/mL, respectively. The 24h urine volume was 5 mL, and the patient had intermittent mental symptoms. The clinical pharmacologist believed that the psychiatric symptoms might be related to ceftazidime-avibactam, and the poor renal function recovery might be related to amikacin. Therefore, it was suggested that the dose of ceftazidime-avibactam should be adjusted to 1.25 g q8h, and amikacin should be stopped. The patient showed no obvious psychiatric symptoms again. On the 27th day after admission, the patient stopped CRRT. On the 29th day after admission, the patient's body temperature was maintained at about 36.5°C. The beta-D-glucan test and bacterial culture were both negative. On day 2 of hospitalization, the ECG showed ST elevation, low voltage, and right axis deviation (Figure 1). On the sixth day after admission, the 24h urine volume of the patient was only 70 mL. The WBC count was 20.24 × 10^9/L, N% was 88.7%, CRP was 161 mg/L, and PCT was 3.21 ng/mL. The chest radiograph showed exudative changes in both lungs and aggravation of pulmonary edema (Figure 2A). On the seventh day after admission, the patient had a large amount of white sputum in the airway. Laboratory tests showed a WBC count of 13.7 × 10^9/L, N% of 93.6%, CRP of 182.2 mg/L, and procalcitonin (PCT) of 1.29 g/mL. On the 23rd day after admission, the patient's highest temperature was 38.4°C, and laboratory tests showed a WBC count of 13.7 × 10^9/L. The levels of CRP and PCT were 28.4 mg/L and 1.79 ng/mL, respectively.

Table 1. Drug Sensitivity Test of *Pseudomonas aeruginosa*

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>MIC (µg/ml)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>≥ 16</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>≥ 32</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ampicillin/Sulbactam</td>
<td>≥ 32</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>≥ 64</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>16</td>
<td>Intermediary</td>
</tr>
<tr>
<td>Cefepime</td>
<td>16</td>
<td>Intermediary</td>
</tr>
<tr>
<td>Ceftotetan</td>
<td>≥ 64</td>
<td>Resistant</td>
</tr>
<tr>
<td>Amikacin</td>
<td>4</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>4</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≥ 4</td>
<td>Resistant</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>≥ 8</td>
<td>Resistant</td>
</tr>
<tr>
<td>SMZco</td>
<td>≥ 120</td>
<td>Resistant</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>64</td>
<td>Intermediary</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≤ 1</td>
<td>Sensitive</td>
</tr>
</tbody>
</table>
26.2 mmol/L, and she was discharged after renal function improved. The clinical course of the patient's laboratory findings during admission is demonstrated in Figure 3.

3. Discussion

In this case, the young woman had no previous systemic disease. The onset of this disease was sudden, with the precursor symptoms of upper respiratory tract virus infection and the rapid emergence of severe hemodynamic disorders. The laboratory test showed that the myocardial zymogram and troponin were significantly increased, indicating that the myocardium was seriously damaged. The bedside echocardiography showed that the diffuse ventricular wall movement was weakened. After admission, *P. aeruginosa* was detected, and mNGS confirmed its sequence. The three aspects could be used to determine whether *P. aeruginosa* is a pathogenic bacterium. First,
the patient received ECMO combined with CRRT support therapy, indwelling internal jugular vein, femoral vein catheters, intubation, and ventilator-assisted ventilation. The skin and mucosal barrier were destroyed, and methylprednisolone sodium succinate regulated immunotherapy for 15 days. Therefore, there were risk factors for *P. aeruginosa* infection. Second, mNGS can detect a variety of pathogenic microorganisms without bias by sequencing and analyzing microbial and host nucleic acids in clinical samples (4). Huang et al. showed that mNGS had higher accuracy and sensitivity (5). The patient’s mNGS results showed that *P. aeruginosa* was detected in both BALF and blood samples. Three consecutive sputum cultures showed *P. aeruginosa*, consistent with the mNGS results. Finally, according to the combined drug sensitivity results, the treatment protocol was adjusted to ceftazidime-avibactam combined with amikacin. After about 2 weeks of treatment, the patient’s inflammatory indicators returned to normal. No *P. aeruginosa* was detected again.

The drug sensitivity results showed that *P. aeruginosa* was not sensitive to cephalosporins, carbapenems, quinolones, and common β-lactamase inhibitor compound preparations, which could be considered multidrug-resistant *P. aeruginosa* (6). The combination regimen for the treatment of multidrug-resistant *P. aeruginosa* infections was recommended by Tamma et al., and the β-lactam combined with aminoglycosides, quinolones, or fosfomycin was most commonly used against *P. aeruginosa* (7). Considering drug sensitivity results, clinical pharmacists suggested piperacillin sodium tazobactam combined with amikacin for anti-infection therapy. During CRRT treatment, drugs with water solubility, low
After 5 days of anti-infection treatment, the patient’s body temperature was higher than before, and there was still a large amount of yellow mucus in the airway. The following reasons might exist for the poor anti-infection efficacy: First, under ECMO combined with CRRT treatment, Vd significantly increased, leading to a decrease in plasma concentration, which could not reach the expected PK/PD target value. Second, the drug sensitivity results showed that the MIC of piperacillin sodium tazobactam against *P. aeruginosa* (16 mg/L < minimum drug concentration (MIC) ≤ 64 mg/L) was recommended by Gilbert et al. (11). Therefore, the patient was initially given piperacillin sodium tazobactam 4.5 g q8h combined with amikacin 0.4 g qd anti-infective therapy.

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3.1. Conclusions

We presented a case of fulminant myocarditis secondary to multidrug-resistant *P. aeruginosa* infection. Clinical pharmacists actively assisted the doctors in developing an anti-infection regimen. Initially, piperacillin sodium tazobactam combined with amikacin was used for anti-infection therapy, which had a poor clinical effect. Subsequently, combined with the drug sensitivity test and relevant guidelines, it was recommended to use ceftazidime-avibactam and amikacin for anti-infection. Meantime, adverse reactions were found in time to adjust the dose to ensure the safety of medication for patients. In clinical practice, selecting correct and effective drugs according to etiology is necessary, considering the influence of patient life support on antimicrobial PK/PD. However, more randomized studies are still needed to demonstrate the efficacy and safety of ceftazidime-avibactam and amikacin for multidrug-resistant *P. aeruginosa* infection patients during ECMO and CRRT therapy.

Footnotes

**Authors’ Contribution:** Study concept and design: W. Q.; analysis and interpretation of data: X. Z., S. C., and Q. W.; drafting of the manuscript: X. Z. and S. C.; critical revision of the manuscript for important intellectual content: C. C. and W. Q.

**Conflict of Interests:** The authors declare that they have no competing interests.

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Informed Consent: Written informed consent was obtained from the patient.

References


