

Combination of Ceftazidime-Avibactam and Meropenem for the Treatment of Pneumonia and Bloodstream Infections Caused by Pan-Drug Resistant *Pseudomonas aeruginosa* ST244: A Case Report

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Case Presentation: We describe a challenging case of a woman with *Pseudomonas aeruginosa* pneumonia and bloodstream infections following cardiothoracic surgery. This strain exhibited a pan-drug resistance phenotype belonging to the high-risk clone ST244. Finally, she was successfully treated by antibiotic therapy with ceftazidime/avibactam (CAZ/AVI) and meropenem (MEPM).

Conclusion: This case suggests that the combination of CAZ/AVI and MEPM may represent a potential therapeutic option for severe infections caused by pan-drug-resistant *Pseudomonas aeruginosa* (PDR-PA).

Keywords: ceftazidime/avibactam, meropenem, pan-drug resistance, *Pseudomonas aeruginosa*

Introduction

Pseudomonas aeruginosa is a pervasive nosocomial pathogen that poses a substantial burden and challenge to healthcare systems. Among these strains, extensively drug-resistant/pan-drug-resistant *P. aeruginosa* (XDR/PDR-PA) has been reported worldwide in recent years, and the mortality rate associated with XDR/PDR-PA infection remains high.¹ Furthermore, ST244 is identified as one of the top 10 high-risk strains of *P. aeruginosa* worldwide.² The current range of therapeutic options for XDR/PDR-PA is limited.

In recent years, several in vitro and in vivo studies have demonstrated the synergistic potential when β -lactam/ β -lactamase inhibitors (BL/BLIs) are combined with carbapenems in treating drug-resistant *P. aeruginosa* infections. Ceftazidime-avibactam (CAZ/AVI), a novel BL/BLI, was approved and made available by the China Food and Drug Administration in 2019 to treat hospital-acquired bacterial pneumonia.³ Meropenem (MEPM), a traditional carbapenem, has shown strong efficacy against *P. aeruginosa*. In vitro studies conducted by Mikhail et al have indicated that combining CAZ/AVI and MEPM exerts a synergistic effect against carbapenem-resistant *P. aeruginosa* (CR-PA).⁴ Currently, there are no clinical reports on using CAZ/AVI in combination with MEPM to treat XDR/PDR-PA infections. Here, we present a challenging case of successful treatment of PDR-PA pneumonia and bloodstream infections using CAZ/AVI in combination with MEPM.

Case Presentation

A 53-year-old female patient presented with chest tightness and shortness of breath following physical exertion, occasionally accompanied by cardiac discomfort, nocturnal breath-holding, and telangiectasia in early August 2021. Cardiac ultrasound revealed severe mitral and tricuspid regurgitation. The patient was admitted to the Chinese People's Liberation Army General Hospital on 2 September 2021 for treatment of severe mitral valve insufficiency and atrial fibrillation. Time points (On day +X) are counted from the date of hospital admission.

On day +13, she underwent total thoracoscopic hypothermia-induced ventricular fibrillation with mitral valvuloplasty, tricuspid valvuloplasty, left auricle closure, and intra-aortic balloon pacemaker implantation. On day +14, she developed circulatory failure and poor tissue perfusion and received extracorporeal membrane oxygenation (ECMO) implantation via the femoral artery for circulatory assistance. Her circulation stabilized post-ECMO, and continuous administration of vasoactive drugs was initiated, with close monitoring of her vital signs. On day +17, a second thoracotomy was performed under bedside thoracoscopy, and on day +21, a second open thoracotomy was conducted for hemostasis. By day +23, her circulation had stabilized, and ECMO was withdrawn.

On day +32, the patient developed a fever (37.8°C). Blood cultures were processed using the BacT/ALERT system (bioMérieux, Marcy-l'Étoile, France). *P. aeruginosa* was isolated from both tracheal aspirate and blood samples. Identification and antimicrobial susceptibility tests were performed using the VITEK®2 automated system (bioMérieux, Marcy-l'Étoile, France). The isolate demonstrated resistance to multiple antimicrobial agents. The minimum inhibitory concentrations (MICs) were as follows: imipenem (≥ 16 mg/L), meropenem (≥ 16 mg/L), aztreonam (≥ 32 mg/L), ciprofloxacin (≥ 4 mg/L), gentamicin (≥ 16 mg/L), tobramycin (≥ 16 mg/L), piperacillin (≥ 128 mg/L), piperacillin–tazobactam (≥ 128 mg/L), ceftazidime (≥ 64 mg/L), and cefazolin (≥ 64 mg/L). Based on these results, the isolate was classified as PDR. Elevated C-reactive protein (CRP), interleukin-6 (IL-6), and procalcitonin (PCT) levels were observed, with values of 8.643 mg/dL, 89.18 pg/mL, and 1.41 ng/mL, respectively (Table S1). Chest radiographs demonstrated diffuse bilateral opacities, predominantly involving the right lung (Figure 1). Levofloxacin (0.5g/d), sulbactam sodium (1g/8h), and MEPM (1g/8h) were administered for anti-infective therapy (Figure S1). On day +33, the patient had a low-grade fever (37.5°C), and chest radiographs showed radiographic progression compared with the previous day (Table S2 and Figure 1). On day +34, levofloxacin was replaced with amikacin (0.4g/12h). On day +36, CAZ/AVI (2.5g/8h) was initiated for PDR-PA pneumonia and bloodstream infections, and on day +37, sulbactam sodium was discontinued (Figure S1).

On day +46, chest radiographs revealed multiple patchy shadows in both lungs, with an increase in the extent of the lesions compared to day +32. The patient's temperature returned to normal. On day +48, chest radiographs revealed large membranous ground-glass opacities in the right lung, with an increase in lesion extent and density compared to day +46. Simultaneously, the patient's temperature normalized to 36.5°C. These findings suggest that the anti-infective treatment was effective, and CAZ/AVI and MEPM were discontinued. By day +50, the ground-glass opacities in the right lung had decreased. On day +57, chest radiographs revealed a clear lung field with few remaining patchy opacities, suggesting moderate control of the pulmonary infection (Figure 1). On day +121, the patient's condition was stable, and she was discharged.

Antimicrobial Susceptibility Tests and Synergistic Tests

Antimicrobial susceptibility tests were performed using the broth microdilution method with twofold dilutions. The MICs were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (2021 edition). The MIC of CAZ/AVI was 32 mg/L, and that of MEPM was 16 mg/L. For combination test, a checkerboard assay was performed in 96-well microtiter plates. Serial twofold dilutions of CAZ/AVI and MEPM were prepared, and bacterial suspensions equivalent to approximately 5×10^5 CFU/mL were inoculated. Plates were incubated at 35°C for 18–24 hours. The fractional inhibitory concentration index (FICI) was calculated as follows: $FICI = (MIC \text{ of CAZ/AVI in combination} / MIC \text{ of CAZ/AVI alone}) + (MIC \text{ of MEPM in combination} / MIC \text{ of MEPM alone})$. In the combination, the MIC of CAZ/AVI decreased from 32 mg/L to 16 mg/L, and the MIC of MEPM decreased from 16 mg/L to 2 mg/L. According to the predefined criteria ($FICI \leq 0.5$, synergy; $0.5 < FICI < 1$, partial synergy), the calculated FICI was 0.625, indicating a partial synergistic effect of CAZ/AVI combined with MEPM against this isolate in vitro.

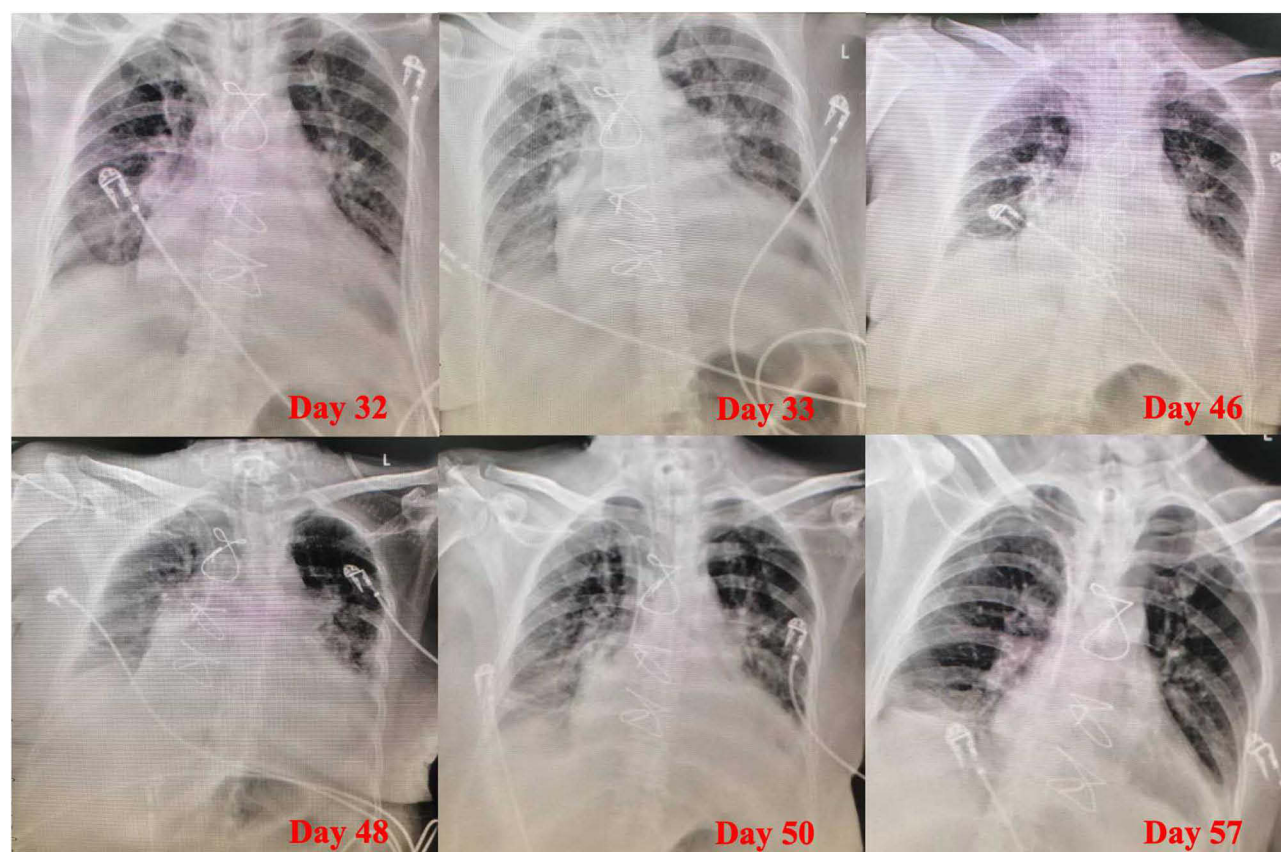


Figure 1 Serial changes in chest radiographs during hospitalization.

Molecular Characteristics

Genomic DNA was extracted using a commercial bacterial DNA extraction kit (Solarbio, China). Whole-genome sequencing was performed using the Illumina platform (Illumina, USA). Sequence assembly was conducted using SPAdes software, and antimicrobial resistance genes were identified using the ResFinder and CARD databases. Multilocus sequence typing (MLST) was performed to determine the sequence type. Whole genome sequencing identified this PDR-PA strain as belonging to high-risk clone ST244. Various virulence genes, including T3SS effectors (*exoS*, *exoT*, *exoY*, and *toxA*), T6SS effectors (*tse1*, *tse2*, and *tse3*), elastase (*lasB*), alkaline protease (*aprA*), adherence factors (*fliC* and *fleP*), and two-component sensor (*fleS*), were positive in this strain. Illumina sequencing results showed that this isolate contained 7 antimicrobial resistance genes, including *blaPDC-1*, *blaPER-1*, *blaOXA-101*, *blaOXA-847*, *APH(3'')-Ib*, *APH(6)-Id*, *AAC(6')-Ib10*, *aadA5*, explaining their resistance to all tested antibiotics.

Discussion

High-risk clones of *P. aeruginosa* are widely prevalent and spread worldwide, causing high mortality rates as well as low cure rates and bringing great challenges to clinicians.^{1,5} ST244 is one of the top 10 high-risk clones of *P. aeruginosa*, and it is currently found in East Asia (China, Korea), Europe (Spain, Portugal, Denmark, Poland), South America (Brazil, Colombia), etc. Besides, various horizontally acquired β -lactamases detected in ST244, such as class A β -lactamases (*blaCTX-M-2*, *blaPER-1*), class B β -lactamases (*blaVIM-2*, *blaIMP-1*), and class D β -lactamases (*blaOXA-101*, *blaOXA-10*).^{2,6-9}

In this article, we report a case of a woman who was successfully treated with CAZ/AVI in combination with MEPM for PDR-PA pneumonia and bloodstream infections after cardiothoracic surgery. When MEPM was used separately, her body temperature fluctuated between 37.5°C to 37.8 °C, which indicated that the pneumonia and bloodstream infection were poorly controlled. After 10 days of therapy of CAZ/AVI in combination with MEPM, her body temperature

returned to normal. At the same time, follow-up chest radiographs showed improvement of pulmonary opacities. Besides, synergistic tests by the checkerboard method in vitro suggested that the MIC of MEPM decreased to 2 mg/L when CAZ/AVI and MEPM were combined. After 12 days of CAZ/AVI and MEPM combination therapy, her body temperature stabilized, and her pneumonia and bloodstream infections resolved. In the end, her life was saved.

Several studies have demonstrated the synergistic effect of CAZ/AVI and MEPM against drug-resistant *P. aeruginosa* in vitro.^{4,10} However, there is a lack of in vivo experiments to prove the synergistic effect of CAZ/AVI and MEPM against drug-resistant *P. aeruginosa*. This paper serves as a case report to initially show the synergistic effect of CAZ/AVI and MEPM against drug-resistant *P. aeruginosa* infections in humans. In addition, in vivo experiments with large-scale samples are still needed to validate the synergistic effects of CAZ/AVI and MEPM against drug-resistant *P. aeruginosa*.

This case has several strengths. To support the therapeutic decision, detailed microbiological analyses were performed, including antimicrobial susceptibility tests, checkerboard synergy testing and whole-genome sequencing. These findings provide insight into the mechanisms underlying the observed clinical response. However, several limitations should be acknowledged. As this is a single case report, a definitive causal relationship between the combination therapy and clinical recovery cannot be established. Furthermore, in vitro synergistic activity does not necessarily translate into consistent clinical benefit.

Conclusion

This case suggests that the combination of CAZ/AVI and MEPM may represent a potential therapeutic option for severe infections caused by PDR-PA.

Data Sharing Statement

The data supporting the findings of this study are available from the first author (YK) upon reasonable request.

Ethical Approval

Ethical approval was waived by the Institutional Review Board of Chinese People's Liberation Army General Hospital due to the nature of a single case report. We have confirmed that the patient's informed consent form includes permission for the publication of case details and images.

Author Contributions

YK was responsible for the initial data collection and drafting of the manuscript. SK provided guidance on the radiological evaluation and interpretation of imaging findings. JC supervised the overall study, provided critical revisions, and guided the manuscript preparation. All authors made a significant contribution to the work reported; participated in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare for this work.

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