*Case Report*

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# Successful Treatment Difficult-to-Treat Pseudomonas aeruginosa Endocarditis Using Cefiderocol: A Case Report

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## Abstract

Infectious endocarditis is the inflammation of the endocardium and the cardiac valves. It is primarily a disease caused by bacteria that can lead to rapid and significant morbidity and mortality if not efficiently diagnosed and treated. The current standard of care for treating IE is dependent on identifying the offending microorganism and its susceptibility to antimicrobials, sometimes requiring surgery. Infective endocarditis can pose an even more significant challenge when resistance to multiple antibiotics develops. We present a case of a 47-year-old female with difficult-to-treat Pseudomonas aeruginosa (DTR-PA) mitral and aortic valve infective endocarditis with a myriad of cardiac and extra-cardiac complications, treated with cefiderocol for six weeks. This case illustrates the first documented incidence of treatment efficacy with cefiderocol monotherapy in treating difficult-to-treat pseudomonas aeruginosa infective endocarditis.

## Keywords

Pseudomonas aeruginosa, Endocarditis, Cefiderocol, Difficult-to-treat infections, Antimicrobial resistance.

## INTRODUCTION

Infective endocarditis (IE) is caused by an infection of the endocardium and the cardiac valves. It arises via hematogenous spread or by direct mechanical trauma from the insertion of cardiac devices [1]. The causative microorganisms usually seed the valves and form vegetations. Normally, healthy endocardium is resistant to bacterial attachment; however, when the endocardium has been damaged and the microorganism is present in the bloodstream, an infection can occur. Risk factors for IE include injectable-drug-use (IDU), prosthetic valves, congenital or degenerative valvular disease, poor dental hygiene, indwelling cardiac devices, hemodialysis, immunosuppression, or frequent contact with healthcare facilities [1]. The risk factors and environmental setting of bacterial acquisition, healthcare versus community, provide hints towards the underlying infectious etiology. The most common causes of IE are gram-positive bacteria, primarily Staphylococci, Streptococci, and Enterococci, which consist of 80-90% of all cases [1]. Other less frequently causative organisms are the HACEK organisms (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella), the colonizers of the oropharynx. Other bacteria comprise only about 6% of total cases [1]. Finally, fungal IE represents only about 1% of cases but can be a typically fatal complication. A rare etiology of IE is Pseudomonas aeruginosa, accounting for approximately 1.5% of all cases. The origin of Pseudomonas aeruginosa IE can be from IDU, or healthcare associated, and treatment usually necessitates combination therapy with two IV anti-pseudomonal antibiotics from different classes to which the isolate is susceptible [2,3]. Without prompt intervention, IE can result in serious heart damage or death, with an overall mortality rate ranging from 20-25% [4].

## CASE PRESENTATION

Here we report a clinical case of a patient with DTR-PA IE of the mitral valve, managed with cefiderocol monotherapy.

A 47-year-old female with a past medical history of morbid obesity presented with the complaint of seven-day history of lethargy. The patient was evaluated and discovered to have septic shock with acute kidney injury (AKI) and encephalopathy, requiring crystalloid fluid challenges, vasoactive agents and empiric antibiotics with meropenem and vancomycin. She was found to have infected bilateral lower extremity and abdominal wounds. Two sets of blood cultures grew DTR-PA. The abdominal wound culture grew extended -spectrum beta-lactamase (ESBL) Klebsiella pneumoniae, multi-



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drug resistant (MDR) Escherichia coli, and Proteus mirabilis. The right lower extremity wound culture grew DTR-PA and carbapenem-resistant Acinetobacter baumannii (CRAB). Following culture and susceptibility results, the patient was started empirically on intravenous cefiderocol monotherapy, 2 grams every eight hours, which treated the bloodstream infection and the polymicrobial skin infections.

Due to persistent DTA-PA, a transesophageal echocardiogram (TEE) was ordered and demonstrated vegetations on the anterior mitral leaflet (1.0 cm x 0.4 cm) and aortic valve (1.4 cm x 0.7 cm) [Figures 1 and 2; Videos 1 and 2]. The patient was diagnosed with Pseudomonas aeruginosa infective endocarditis and was determined to not be a candidate for surgical intervention. Intravenous cefiderocol therapy was continued for a total duration of 6 weeks to cover for DTR-PA infective endocarditis and the MDR polymicrobial skin infections. A total of two dose adjustments were needed due to a transient rise in serum creatinine; otherwise, the patient tolerated IV cefiderocol therapy well. After one week of intravenous cefiderocol therapy, blood cultures from multiple different sites were obtained and demonstrated no bacterial growth. The patient completed three weeks of intravenous therapy inpatient and was discharged home in stable condition to complete the remaining three weeks of IV cefiderocol. Repeating the echocardiogram after discontinuation of therapy revealed no residual vegetations.

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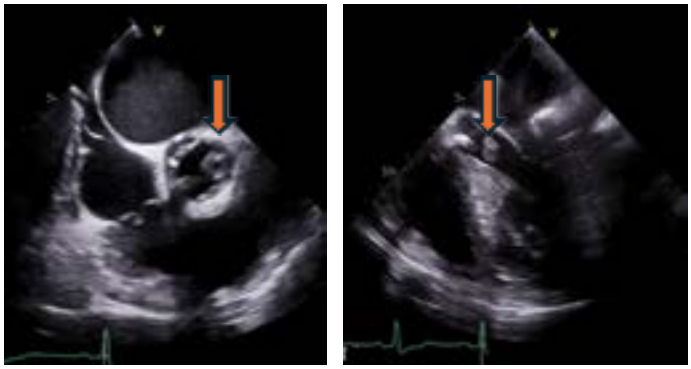


**Figure 1:** Echocardiography showing a large (1.4 x 0.7 cm) aortic valve vegetation (arrows).

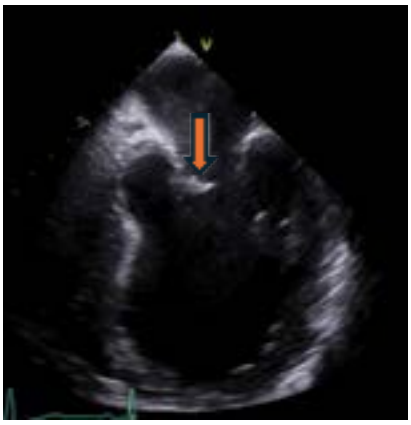
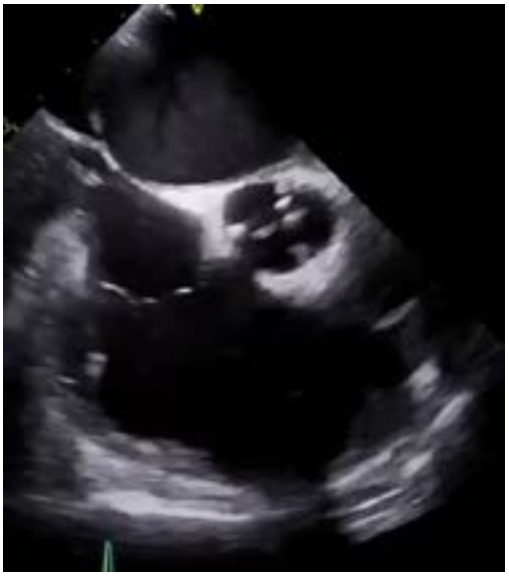
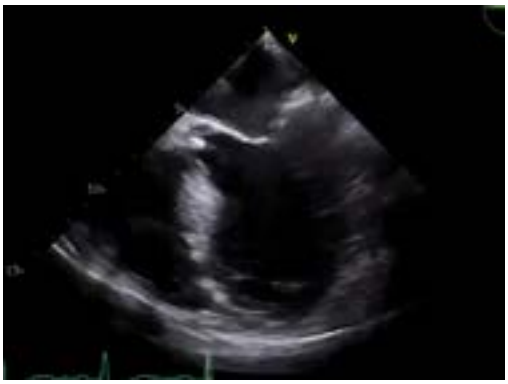


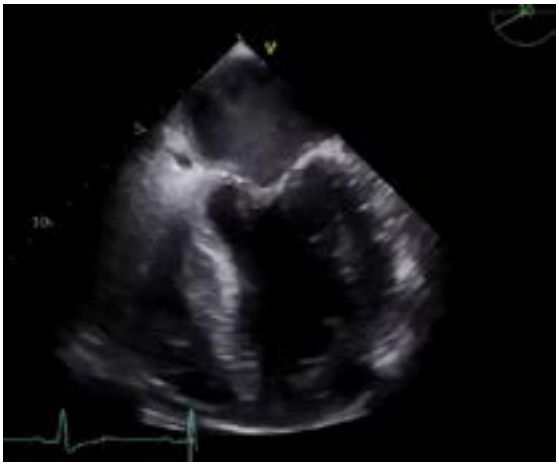
**Figure 2:** Echocardiography showing a large (1.0 x 0.4 cm) mitral valve vegetation (arrows).



**Vedio 1A**



**Vedio 1B**



**Vedio 2**

## DISCUSSION

This case presented above illustrates the challenges presented by infections caused by multidrug-resistant pathogens, particularly carbapenem-resistant Pseudomonas aeruginosa. As discussed earlier, the patient was diagnosed with DTR-PA IE complicated by additional polymicrobial skin infections. Amikacin, an aminoglycoside, was the only option for treatment on the standard panel. However, amikacin possesses toxic properties, including nephrotoxicity, and thus was not a suitable choice as the patient had suffered an AKI. The other monotherapy option with a favorable safety profile was cefiderocol which was initiated, resulting in major clinical improvement.

The novel antibiotic, cefiderocol, functions as a siderophore, binding ferric iron (Fe3+). This binding facilitates its transport across the outer membrane of gram-negative bacteria, which many other antibiotics struggle to penetrate. By utilizing the bacterial iron transport system, cefiderocol can bypass many common resistance mechanisms such as reduced permeability and efflux pumps. After entering the bacterial cell, cefiderocol functions like other cephalosporins, by binding penicillin binding proteins and inhibiting cell wall synthesis [5]. Cefiderocol displays effectiveness in treating beta-lactamase (ESBL and OXA) producing gram-negatives but has not shown any use in treating gram-positive or anaerobic organisms. The study conducted by Nakamura and colleagues investigated the pharmacodynamics of cefiderocol through in-vivo experiments using murine thigh and lung infection models. This research identified several important pharmacodynamic properties of cefiderocol, including susceptibility breakpoints, efficacy thresholds, and considerations for administration. The minimum inhibitory concentration (MIC) for susceptibility was determined to be 4 µg/mL for various gram-negative pathogens, including Pseudomonas aeruginosa. Cefiderocol exhibited a bacteriostatic effect when its concentration remained above the MIC for 40% to 70% of the dosing interval, and a bactericidal effect when this concentration was maintained for 55% to 88% of the dosing interval. Notably, cefiderocol demonstrated consistent success across different types of infection, including both lung and thigh infections. Additionally, the study found that a longer infusion time (3 hours versus 1 hour) improved the drug's efficacy [6]. The primary route of elimination of cefiderocol is through the kidneys via urinary excretion. Approximately 90.6% of the administered dose is recovered unchanged in the urine, indicating that renal clearance plays a crucial role in the drug's overall elimination. Given this reliance on kidney function, it is important to assess a patient's renal status when establishing correct dosing. Impaired renal function without dose adjustments could lead to decreased clearance of cefiderocol, increasing the risk of drug accumulation and potential toxicity [7]. In the case presented above, kidney function was frequently assessed, and two dose-adjustments were required due to transient increase in the patient's creatinine value.

Multiple clinical trials, notably the APEKS-NP and CREDIBLE-CR trials, have illustrated the efficacy of cefiderocol in treating complicated infections caused by DTR-PA and other gram-negative organisms. The APEKS-NP trial focused specifically on cefiderocol use in patients with gram-negative hospital-acquired and ventilator associated pneumonia, of which 16% of the intention-to-treat population's infection was caused by Pseudomonas aeruginosa. This study found that cefiderocol demonstrated comparable efficacy to high-dose, extended-infusion meropenem, with similar adverse events (88% for cefiderocol and 86% for meropenem) and similar all-cause mortality rates (12.4% for cefiderocol and 11.6% for meropenem) [8]. The CREDIBLE-CR trial compared the efficacy of cefiderocol to the best available therapy for patients with serious infections (pneumonia, bloodstream infections/sepsis, urinary tract infections) caused by carbapenem resistant gram-negative bacteria, including Pseudomonas aeruginosa (19% of the intention-to-treat group). Results of the CREDIBLE-CR trial showed that cefiderocol had similar efficacy against Pseudomonas aeruginosa and other carbapenem resistant gram negatives compared to the best available therapy. Clinical cure was achieved in 50% of the patients with pneumonia, 43% of patients with sepsis, and 53% of patients with UTIs who were treated with cefiderocol. Similarly, for those treated with the best available therapy, clinical cure was achieved in 53% of the patients with pneumonia, 43% of patients with BSI/sepsis, and 20% of patients with UTIs. Additionally, the bacteremia/sepsis treated with cefiderocol versus the best available therapy showed similar number of adverse events (91% and 96% respectively) and all-cause mortality (34% and 18% respectively) [9]. These two trials demonstrate comparable efficacy of cefiderocol to alternative treatment regimens and display similar safety profile to the alternative antimicrobial therapies.

Although only presently Food and Drug Administration (FDA) approved for the treatment of gram-negative hospital-acquired or ventilator-associated bacterial pneumonia and complicated urinary tract infections, cefiderocol demonstrated promising clinical results in the Pseudomonas aeruginosa infective endocarditis case presented above. Additionally, the use of cefiderocol monotherapy in this case is supported by the Infectious Disease Society of America (IDSA) guidelines, which recommend its use in clinical practice as an alternative treatment for DTR-PA [10].

## CONCLUSION

This case report illustrates the role of cefiderocol in treating difficult-to-treat Pseudomonas aeruginosa infective endocarditis. While cefiderocol does not have an FDA indication for this specific condition, multiple trials and existing literature suggest its effectiveness in managing challenging cases of resistant infections, reinforcing its possible role in treating infective endocarditis caused by resistant Gram-negative bacteria.

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