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Case Report

Novel Salvage Regimen for Extremely Persistent Vancomycin-Resistant *Enterococcus faecium* Bloodstream Infection: A Case Report

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Abstract

Background: Treatment of vancomycin-resistant Enterococcus (VRE) infection is challenging due to the limited number of safe and effective antibiotic therapies available. We report a patient with persistent VRE bacteremia.

Case Presentation: A 75-year-old patient was admitted to the hospital after four months of persistent *Enterococcus faecium* bacteremia. After an additional five months of persistent *E. faecium* bacteremia, despite extensive source control attempts and various antibiotic regimens, a novel regimen consisting of oritavancin, ceftaroline, and tigecycline resulted in successful clearance of blood cultures.

Conclusions: This novel antibiotic combination can be considered for the treatment of persistent VRE bacteremia that fails to resolve with commonly used antibiotics.

Keywords: Vancomycin Resistant; Enterococcus *faecium*; Bacteremia; Case Report

Abbreviations: AUMC: Augusta University Medical Center AUMC; D5W: 5% Dextrose in Water; HFHS: Henry Ford Health System; IV: Intravenously; MIC: Minimum Inhibitory Concentration; PFGE: Pulsed-Field Gel Electrophoresis; R: Resistant; TTE: Transthoracic Echocardiogram; VRE: Vancomycin-Resistant Enterococcus; VSE: Vancomycin-Susceptible Enterococcus

Introduction

Treatment of vancomycin-resistant Enterococcus (VRE) infection is challenging due to the limited number of safe and effective antibiotic therapies available [1]. We present a case of multidrug-resistant VRE bacteremia that failed multiple antibiotic regimens. Salvage therapy using a novel combination of antibiotics resulted in eventual clearance of blood cultures, after nine months of persistent bacteremia.

Case

A 75-year-old male presented to our hospital, Augusta University Medical Center (AUMC) in April 2016 with persistent VRE bacteremia. His medical history was significant for hypertension, type 2 diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, and atrial fibrillation. The patient presented to an external health system in December 2015 with fevers, weight loss and dysuria. It was at this time that he

was first diagnosed with VRE bacteremia. Information about the patient's hospital course is limited due to incomplete access to medical records. The patient presented to the same health system again in January 2016. Blood cultures were once again growing VRE, for which he was discharged on daptomycin. In February, blood cultures obtained during a follow-up appointment once again identified VRE, which prompted a hospital readmission. During this readmission, a transesophageal echocardiogram was negative for infective endocarditis. A colonoscopy was performed, during which 18 polyps were removed. The patient received daptomycin before transitioning to linezolid for a total of 25 days. Blood cultures collected prior to discharge, turned positive for VRE after discharge.

In April, the patient presented again to the health system with hypoglycaemia. Blood cultures were still positive for VRE. Indium leukocyte imaging was performed, which failed to identify a focus of infection. Cholecystectomy was performed due to the concern that the gallbladder could be the source of bacteremia. However, blood cultures remained positive. At this time, the patient was transferred to our facility. Upon transfer, the patient was receiving ceftaroline 600 mg intravenously (IV) every 12 hours and daptomycin 6 mg/kg IV every 24 hours. The patient was afebrile, asymptomatic, and hemodynamically stable. Laboratory analysis identified a white blood cell count of 6.5 thousand/mm3, haemoglobin of 9.2 g/dL, and platelets of 222 thousand/mm3 and serum creatinine of 1.08 mg/dL. The patient's blood cultures were positive for VRE susceptible only to chloramphenicol (MIC ≤ 8 µg/mL), gentamicin for synergy (MIC ≤ 500 µg/mL), and streptomycin for synergy (MIC ≤ 1000 µg/mL). A transthoracic echocardiogram (TTE) was performed, which showed no obvious infection. Since endocarditis could not be ruled out, antibiotics were continued for presumed aortic valve endocarditis. Ceftaroline and daptomycin were continued but the daptomycin dose was increased to 10 mg/kg IV every 24 hours and the ceftaroline frequency increased to 600 mg IV every 8 hours. Ampicillin was also added for synergy. Due to continued bacteremia, the combination of ampicillin, ceftaroline, and daptomycin was switched to quinupristin-dalfopristin 150-350 mg IV every 8 hours and gentamicin for synergy (goal peak: 3-4 µg/mL; goal trough < 1 µg/mL). After 19 days, the regimen was discontinued due to debilitating myalgias. Antibiotics were switched back to daptomycin 10 mg/kg IV every 24 hours, ceftaroline 600 mg IV every 8 hours and ampicillin 2 g IV every 6 hours. As blood cultures did not clear after 9 days, antibiotics were switched to oritavancin 1200 mg IV every 48 hours and ampicillin 2 g every 6 hours. Unfortunately, the patient experienced respiratory distress due to the volume associated with oritavancin preparation (each dose is prepared in one liter of 5% dextrose in water [D5W]). Despite reducing the volume of D5W to 750 mL along with diuresis, his respiratory distress did not improve. Due to continued VRE bacteremia, ampicillin was switched to chloramphenicol 12.5 mg/kg IV every 6 hours. After initiation of chloramphenicol, the patient's platelets decreased from 209 thousand/mm3 to 103 thousand/mm3. A chloramphenicol peak (23.1 µg/mL; target range of 10-20 µg/mL) and trough (11.8 µg/mL; target range of 5-10 µg/mL) were obtained. The frequency of chloramphenicol was reduced from every 6 hours to every 8 hours. Due to the respiratory distress secondary to oritavancin, it was switched to minocycline 100 mg IV every 12 hours, for which susceptibilities were not available. A TTE was repeated which showed an 8 x 4 mm mass on the aortic valve. The patient underwent an aortic valve replacement. The aortic valve tissue culture grew VRE. With aortic valve replacement and antibiotic therapy, the blood cultures finally cleared. However, after 20 days of negative blood cultures, they became positive again for VRE. After 8 months of recalcitrant VRE bloodstream infection, now with recurrence despite multiple source control interventions and attempted salvage regimens, the patient's antibiotics were switched to a novel combination of oritavancin 1200 mg IV every 72 hours, ceftaroline 600 mg IV every 12 hours, and tigecycline 50 mg IV every 12 hours (Figure 1). After receiving this therapy for 4 days, the blood cultures cleared. The patient remained on this regimen for 4 weeks, during which the blood cultures remained negative. Despite having successfully cleared his VRE bacteremia, the patient continued to experience respiratory distress. Upon his transfer to the medical intensive care unit, the patient required intubation. After discussion with the patient's family and considering his poor quality of life during the 5-month hospital admission, a decision was made to withdraw care, after which the patient passed away.

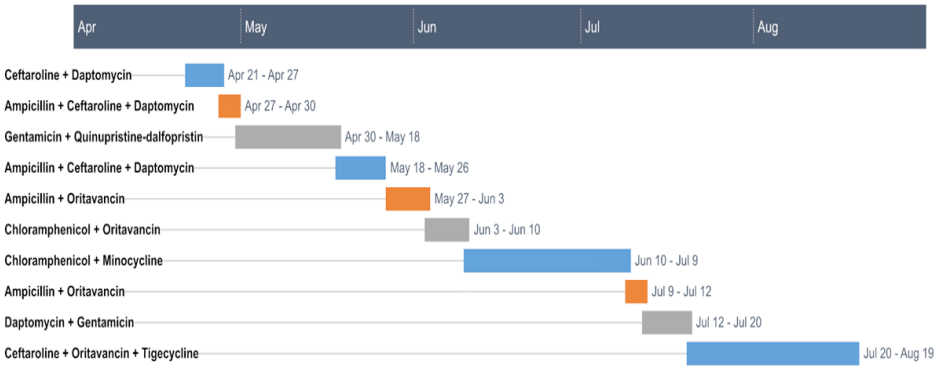

Figure 1: Time line of antibiotic treatment course.

Microbiology

During this patient's hospital course, the *E. faecium* strains that were isolated for this patient displayed variable susceptibility over time. Thirteen *E. faecium* isolates (collected between April and May 2016) were sent to the Infectious Disease Research Lab at the Henry Ford Health System (HFHS) in Detroit, Michigan for further investigation. Of the thirteen isolates, AUMC had identified (utilizing the VITEK®2 system; bioMérieux Inc., Durham, North Carolina) 6 isolates that were vancomycin-resistant (MIC >16 µg/mL). However, after undergoing further investigation at the HFHS laboratory, it was found that two of the VRE isolates were in fact vancomycin-susceptible, with MICs of 1.5 µg/mL (assessed by vancomycin E-test, bioMérieux Inc., Durham, North Carolina). In addition, five isolates had daptomycin susceptibilities repeated at the HFHS lab. Of the five, four were found to be daptomycin-resistant (assessed by daptomycin E-test, bioMérieux Inc., Durham, North Carolina), with MICs ranging from 12 µg/mL to 24 µg/mL. One isolate had a daptomycin MIC of 4 µg/mL when tested at AUMC, but when susceptibility was repeated at HFHS, the MIC for this same isolate was 24 µg/mL (Table 1).

Isolate #	Culture Date	Daptomycin MIC via VITEK® (AUMC)	Vancomycin MIC via VITEK® (AUMC)	AUMC result	HFH Result	Vancomycin MIC via E-test (HFH)	Daptomycin MIC via E-test (HFH)	Ceftaroline MIC via E-test (HFH)	Tigecycline MIC via E-test (HFH)
95180	4/21/2016	>4	>16	VRE	VSE	1.5	12	>32	0.125
95181	4/25/2016	>4	1	VSE	VSE	1.5	12	>32	0.125
95182	4/25/2016	>4	1	VSE	VSE	1.5	--	--	--
95183	4/26/2016	>4	1	VSE	VSE	1.5	--	--	--
95184	4/26/2016	>4	>16	VRE	VRE	>256	24	>32	0.125
95185	4/27/2016	>4	1	VSE	VSE	1.5	--	--	--
95186	4/27/2016	>4	1	VSE	VSE	2	--	--	--
95205	4/21/2016	>4	>16	VRE	VSE	1.5	--	--	--
95206	4/24/2016	>4	1	VSE	VSE	1.5	--	--	--
95207	5/3/2020	>4	>16	VRE	VRE	>256	--	--	--
95208	5/10/2020	>4	>16	VRE	VRE	>256	--	--	--
95209	5/15/2020	>4	>16	VRE	VRE	1.5 plus R (mixed)	24	--	--

95210	5/18/2020	4	1	VSE	VSE	1.5 plus R (mixed)	24	--	--
VSE = vancomycin-susceptible Enterococcus R = resistant									

Table 1: Comparison of MIC results from AUMC and HFH on 13 isolates.

Pulsed-field gel electrophoresis (PFGE) was performed on each isolate to evaluate strain typing in order to determine relatedness between strains. Genomic DNA was prepared as previously described [2] and was digested with SmaI restriction endonuclease. A CHEF-DR III system (Bio-Rad, Hercules, CA) was used to perform all PFGE. Data for the enterococcal isolates were entered into a Gel Doc XR+ Gel Documentation System (Bio-Rad, Hercules, California) database and PFGE patterns were compared using BioNumerics software (Applied Maths, St-Martens-Latem, Belgium). Isolates were placed in the same PFGE group if SmaI restriction patterns were ≥ 80% similarity using the Dice coefficient. Overall, it was found that all 13 strains were ≥ 80% similar, which can be seen in the dendogram below (Figure 2).

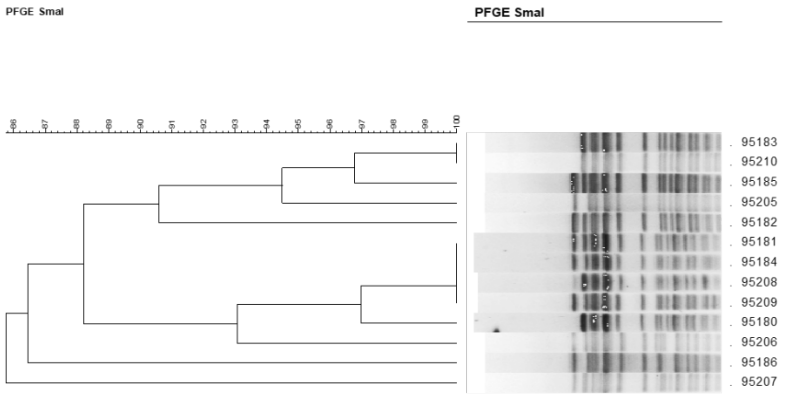

Figure 2: Pulsed-field gel electrophoresis profiles and dendogram of 13 isolates of E. *faecium*.

Discussion

This case illustrates the difficulties that are encountered in the management of VRE bacteremia. Despite persistent bacteremia, the source of bacteremia was never identified. Various combinations of antibiotics were utilized, but only two were successful in the clearance of bacteremia. Clinical experience with using prolonged oritavancin for severe infections is limited. Our oritavancin dosing regimen was derived from a case report which described a patient with VRE prosthetic valve endocarditis [3]. This patient was treated with oritavancin 1200 mg IV every other day for three doses and subsequently once weekly for 6 weeks. With regrowth of VRE from blood cultures, the patient received oritavancin at 1200mg IV twice weekly for 10 weeks. At the end of therapy as well as 17 months after completion of oritavancin, the blood cultures remained negative [3]. The time-kill studies performed by Smith and colleagues demonstrated synergy between oritavancin and beta-lactams. Similar to daptomycin and vancomycin, the synergy between oritavancin and beta-lactams increases as the susceptibility to vancomycin and daptomycin decreases [4]. Another case report describes a patient with VRE infective endocarditis who was successfully treated with daptomycin and tigecycline [5]. As the mechanism of action of tigecycline is similar to that of gentamicin, it is inferred that combining daptomycin with tigecycline could also result in synergy [6]. As far as we know, this is the first case of prolonged VRE bacteremia that had lasted for a total of 9 months, which was treated with a novel combination regimen of ceftaroline, oritavancin, and tigecycline. Unfortunately, the source of VRE bacteremia was unable to be identified. This case exhibits the dilemma that is often faced in the treatment of multidrug-resistant VRE infections. Further studies utilizing this novel antibiotic regimen is warranted. We present this case in honor of our patient. The only thing he had wanted was that we learn something from his experience and learn more about this resistant "bug". He wished to be able to contribute himself to the study of medicine, for which we are forever thankful.

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