Pediatr Infect Vaccine. 2022 Aug;29(2):105-109
https://doi.org/10.14776/piv.2022.29.e11
pISSN 2384-1079·eISSN 2384-1087

PIV PEDIATRIC INFECTION & VACCINE

Case Report

Successful Treatment of Vancomycin-Resistant Enterococcus Bacteremia With a Combination of Daptomycin and Tigecycline in an Infant who Underwent Heart-Lung Transplantation

Jeong Eun Kang, Joung-Hee Byun, Younga Kim, Su Eun Park

Department of Pediatrics, Pusan National University Children's Hospital, Yangsan, the Republic of Korea

Received: Apr 5, 2022
Revised: Aug 4, 2022
Accepted: Aug 18, 2022
Published online: Aug 26, 2022

Correspondence to
Su Eun Park
Department of Pediatrics, Pusan National University Children's Hospital, 20 Geumo-ro, Meulgeum-eup, Yangsan 50612, the Republic of Korea.
Email: psepse@naver.com

ORCID iDs
Jeong Eun Kang
https://orcid.org/0000-0001-5710-8926
Joung-Hee Byun
https://orcid.org/0000-0003-2088-4029
Younga Kim
https://orcid.org/0000-0002-8332-5200
Su Eun Park
https://orcid.org/0000-0001-5860-821X

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

The treatment of invasive infections caused by multidrug-resistant vancomycin-resistant enterococci (VRE) is challenging, particularly in pediatric patients with underlying medical conditions. Newer antibiotics used to treat VRE infections in pediatric patients are insufficiently studied. This report presents the case of a 6-month-old infant who underwent heart–lung transplantation and was successfully treated with a combination of daptomycin and tigecycline for recurrent VRE bacteremia shortly after the discontinuation of linezolid.

Keywords: Vancomycin; *Enterococcus faecium*; Bacteremia; Daptomycin; Tigecycline

INTRODUCTION

Established antibiotics are lacking for the proper treatment of multidrug-resistant vancomycin-resistant enterococci (VRE) bacteremia, especially in pediatric patients. Although quinupristin-dalfopristin, linezolid, daptomycin, and tigecycline have not been sufficiently studied in pediatric patients, they are generally considered acceptable options for treating VRE bacteremia in children.[1] Among them, linezolid is the recommended first-line antibiotic for the treatment of VRE bacteremia in children. However, in cases when linezolid cannot be used, appropriate antimicrobial therapy choices are much more limited.

Here, we report a case of successful treatment of VRE bacteremia using combination daptomycin and tigecycline in an infant who underwent heart-lung transplantation.

CASE

A 6-month-old boy diagnosed with total anomalous pulmonary venous return at birth underwent heart–lung transplantation for aggravated pulmonary vein stenosis and pulmonary hypertension. Three days after cardiopulmonary transplantation, he developed fever, hypotension, and oliguria; white blood cell count was 4,440/mm^3, hemoglobin level

Author Contributions

Conceptualization: Park SE; Data curation: Kang JE; Project administration: Park SE, Kang JE; Resources: Kim Y; Software: Byun JH; Supervision: Park SE; Validation: Park SE; Writing - original draft: Kang JE; Writing - review & editing: Park SE.

was 9.4 g/dL, and platelet count was 16,000/mm^3. Blood chemistry tests showed a blood urea nitrogen level of 6.4 mg/dL, creatinine level of 0.21 mg/dL, and progressive increase in blood C-reactive protein (CRP) level of up to 10.44 mg/dL. Vancomycin and meropenem were empirically administered. *Enterococcus faecium* was isolated from each pair of blood cultures obtained from peripheral and central venous catheters. Antibiotic susceptibility analysis revealed that the isolate was resistant to penicillin (minimum inhibitory concentration, MIC>64 μg/mL), erythromycin (MIC>8 μg/mL), gentamicin (high-level resistance, SYN-R), ciprofloxacin (MIC>8 μg/mL), vancomycin (MIC>32 μg/mL), and teicoplanin (MIC=8 μg/mL) but susceptible to linezolid (MIC=2 μg/mL) and tigecycline (MIC<0.12 μg/mL). The central catheter was also changed. Delayed sternal closure surgery was performed on post operative day (POD) 5, and the presence of VRE was confirmed in the wound culture performed together. Hence, we changed the vancomycin and meropenem to linezolid (30 mg/kg/day), gentamicin, and cefepime, respectively. After 2 days of antibiotic treatment, the blood culture remained VRE positive; thus, the antimicrobial agents were changed from gentamicin and cefepime to doxycycline, rifampicin, and ertapenem.

On the day after the antibiotic changes, VRE was isolated in the central blood culture without peripheral blood culture. Computed tomography (CT) angiography and chest radiography were performed to evaluate endocarditis or mediastinitis. On the CT images, a tissue-like liquefaction pocket pressing upon the right atrium was observed for which, removal surgery was performed. The operative finding was hematoma, and fluid culture was VRE positive.

Three days after the initiation of linezolid in combination with doxycycline and rifampicin, the blood culture result was negative. However, 11 days after linezolid administration, the patient's activity decreased, and he no longer responded. As peripheral neuropathy could not be excluded, linezolid treatment was discontinued. Follow-up blood culture showed no growth. His upper and lower extremity movements gradually recovered for 3 weeks after the cessation of linezolid.

On POD 26, there were no findings suggestive of infection such as fever, but the CRP level was elevated; blood cultures were performed daily and cefepime was administered. Four days after the administration of cefepime, VRE was isolated in the blood cultures from both the peripheral and central venous catheters for 2 consecutive days. High-dose daptomycin (10 mg/kg/dose every 24 hour) with tigecycline was selected to the treatment of VRE bacteremia. VRE was not detected in repeated blood cultures 2 days after the use of this antibiotic combination; therefore, the antibiotics were continued for 14 days and then discontinued, and no VRE was noted in subsequent blood cultures.

After successful treatment of VRE, ventilator support was gradually reduced; the patient was extubated at 9 months of age, and he was discharged at 10 months of age. He is currently 21 months old and is undergoing follow-up at an outpatient clinic without VRE relapse. **Fig. 1** summarizes the antibiotic treatment course and VRE status.

DISCUSSION

In this case, VRE bacteremia recurred after the early discontinuation of linezolid due to drug-related peripheral neuropathy. Although the optimal antibiotic choices for the treatment of VRE bacteremia in cases in which linezolid cannot be used are limited, daptomycin is

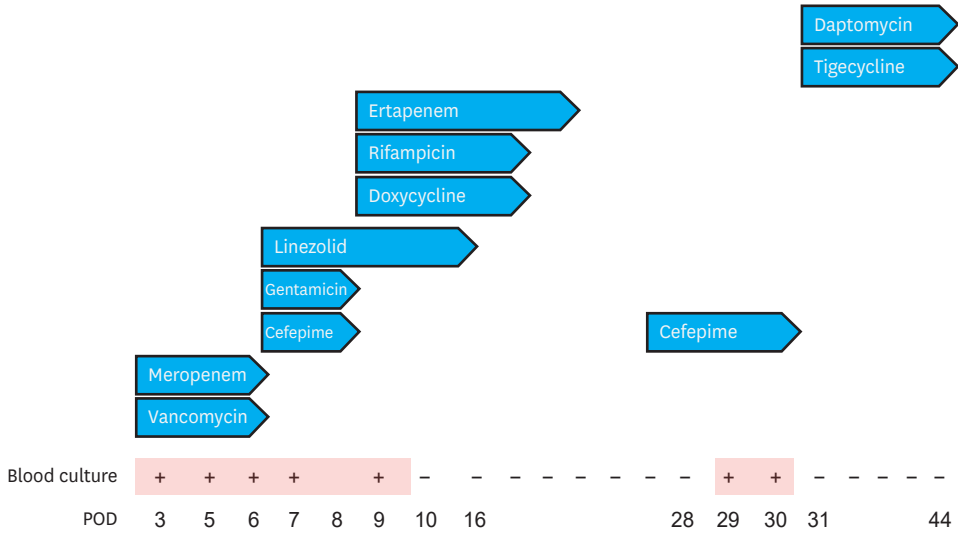

Fig. 1. Antibiotic treatment course.
Abbreviations: POD, post operative day.

often considered as an alternative treatment for VRE infections.[2] A combination of high-dose daptomycin and tigecycline was selected for the treatment of relapsed VRE bacteremia in this case, and VRE bacteremia was successfully cleared after the administration of the combination of daptomycin and tigecycline.

Ampicillin is recommended for the treatment of bacteremia caused by enterococci that are resistant to vancomycin but susceptible to ampicillin.[3] However, since most VRE are resistant to ampicillin, the appropriate antibiotics for VRE bacteremia in the setting of ampicillin resistance is uncertain. Quinupristin-dalfopristin, linezolid, daptomycin, and tigecycline have good in vitro activity against *E. faecium* and are considered alternatives if VRE is resistant to ampicillin.[4] Of them, linezolid and daptomycin are commonly used in children with VRE bacteremia. Quinupristin-dalfopristin showed no differences in clinical response, mortality, or relapse rates compared to linezolid in adult cancer patients with VRE infections,[5] but its use in children is extremely limited due to the need for central venous catheter insertion and the high rate of adverse drug reactions.[1] Tigecycline monotherapy is not recommended for the treatment of VRE bacteremia because of its low serum concentrations.[6]

Although linezolid, the only antimicrobial agent approved by the US Food and Drug Administration for VRE infection, is the recommended first-line drug for the treatment of VRE infection in adults and children,[3] the main concerns regarding the use of linezolid are its bacteriostatic activity and toxicity. Peripheral neuropathy is one of the most important adverse reactions of linezolid because it is rare and sometimes irreversible.[7] The reported incidence of peripheral neuropathy is 0.4–9%,[1] mainly due to its prolonged use. Our patient developed peripheral neuropathy even after a relatively short period of use, which was possibly related to the prolonged administration of sedatives and muscle relaxants. We decided to use higher doses of a combination of daptomycin and tigecycline to treat relapsed VRE bacteremia in this infant who underwent heart–lung transplantation. The reasons for this decision are as follows. First, there is a possibility of the development of VRE endocarditis in this case because of the underlying conditions and prolonged hospitalization under mechanical ventilation. Second, recent systematic reviews reported that a higher dose

https://doi.org/10.14776/piv.2022.29.e11

(≥9 mg/kg) of daptomycin than the standard (6 mg/kg) in patients with VRE bacteremia is associated with reduced mortality and appears safe.[2] Third, combination therapy is usually recommended for the treatment of invasive enterococcal infections, such as bacteremia, endocarditis, and meningitis, despite the lack of clear evidence of the role of antimicrobial combinations. Although several recent in vitro studies[8,9] have shown that a combination of daptomycin and beta-lactam antibiotics such as ampicillin, ceftaroline, and ertapenem has a synergistic effect on the management of VRE infection, we selected tigecycline as a combination of daptomycin based on the opinion of expert group[4] and some case reports.[10-12] Finally, because our clinical laboratory services do not routinely provide daptomycin susceptibility testing for enterococci, daptomycin monotherapy poses a risk of treatment failure. The present case of relapsed VRE bacteremia was noted in a boy who underwent heart–lung transplantation and successfully treated with a combination of daptomycin and tigecycline. Thus, this combination may be an effective alternative treatment for invasive VRE infections in young children.

REFERENCES

1. Tamma PD, Hsu AJ. Optimizing therapy for vancomycin-resistant enterococcal bacteremia in children. Curr Opin Infect Dis 2014;27:517-27.
PUBMED | CROSSREF
2. Foolad F, Taylor BD, Shelburne SA, Arias CA, Aitken SL. Association of daptomycin dosing regimen and mortality in patients with VRE bacteraemia: a review. J Antimicrob Chemother 2018;73:2277-83.
PUBMED | CROSSREF
3. O'Driscoll T, Crank CW. Vancomycin-resistant enterococcal infections: epidemiology, clinical manifestations, and optimal management. Infect Drug Resist 2015;8:217-30.
PUBMED | CROSSREF
4. Arias CA, Contreras GA, Murray BE. Management of multidrug-resistant enterococcal infections. Clin Microbiol Infect 2010;16:555-62.
PUBMED | CROSSREF
5. Raad I, Hachem R, Hanna H, Afif C, Escalante C, Kantarjian H, et al. Prospective, randomized study comparing quinupristin-dalfopristin with linezolid in the treatment of vancomycin-resistant *Enterococcus faecium* infections. J Antimicrob Chemother 2004;53:646-9.
PUBMED | CROSSREF
6. Meagher AK, Ambrose PG, Grasela TH, Ellis-Grosse EJ. The pharmacokinetic and pharmacodynamic profile of tigecycline. Clin Infect Dis 2005;41 Suppl 5:S333-40.
PUBMED | CROSSREF
7. Bressler AM, Zimmer SM, Gilmore JL, Somani J. Peripheral neuropathy associated with prolonged use of linezolid. Lancet Infect Dis 2004;4:528-31.
PUBMED | CROSSREF
8. Sakoulas G, Bayer AS, Pogliano J, Tsuji BT, Yang SJ, Mishra NN, et al. Ampicillin enhances daptomycin- and cationic host defense peptide-mediated killing of ampicillin- and vancomycin-resistant *Enterococcus faecium*. Antimicrob Agents Chemother 2012;56:838-44.
PUBMED | CROSSREF
9. Sakoulas G, Rose W, Nonejuie P, Olson J, Pogliano J, Humphries R, et al. Ceftaroline restores daptomycin activity against daptomycin-nonsusceptible vancomycin-resistant *Enterococcus faecium*. Antimicrob Agents Chemother 2014;58:1494-500.
PUBMED | CROSSREF
10. Jenkins I. Linezolid- and vancomycin-resistant *Enterococcus faecium* endocarditis: successful treatment with tigecycline and daptomycin. J Hosp Med 2007;2:343-4.
PUBMED | CROSSREF
11. Polidori M, Nuccorini A, Tascini C, Gemignani G, Iapoce R, Leonildi A, et al. Vancomycin-resistant *Enterococcus faecium* (VRE) bacteremia in infective endocarditis successfully treated with combination daptomycin and tigecycline. J Chemother 2011;23:240-1.
PUBMED | CROSSREF

12. Munita JM, Mishra NN, Alvarez D, Tran TT, Diaz L, Panesso D, et al. Failure of high-dose daptomycin for bacteremia caused by daptomycin-susceptible *Enterococcus faecium* harboring LiaSR substitutions. Clin Infect Dis 2014;59:1277-80.
PUBMED | CROSSREF

요약

다제내성 반코마이신 저항성 장내구균(multidrug-resistant vancomycin-resistant enterococci, VRE)에 의한 침습감염의 치료는 특히 기저질환을 가진 소아 환자들에게 어려운 점이 있다. 소아환자들에게서 VRE 감염을 치료하기 위한 새로운 항생제에 대한 연구가 충분히 이루어지지 않았다. 본 증례는 심폐이식을 받은 생후 6개월 된 영아에서 linezolid 중단 이후 재발된 VRE 균혈증에 대해 daptomycin과 tigecycline 조합으로 성공적으로 치료하여 이를 보고하는 바이다.