Arch Argent Pediatr 2016;114(6):e432-e435 / e432

Vancomycin-resistant *Enterococcus* bacteremia in a child with acute myeloid leukemia: Successful treatment with daptomycin

Ayşe Büyükcam[a], M.D., Eda Karadağ Öncel[a], M.D., Yasemin Özsürekçi[a], M.D., Prof. Ali B. Cengiz[a], M.D., Assoc. Prof. Barış Kuşkonmaz[b], M.D., and Prof. Banu Sancak[c], M.D.

ABSTRACT

Multiple-drug-resistant enterococcal infections can be a serious problem in pediatric patients particularly concomitance with severe underlying diseases and lead to significant morbidity and mortality. The treatment options in children are limited compared with adults. We report a 3-year old-boy with acute myeloid leukemia (AML)–M7 and vancomycin-resistant enterococcus bacteremia successfully treated with daptomycin. Daptomycin may be an alternative therapy for VRE infections in children; more studies are needed for extended usage.

***Key words**: vancomycin resistant Enterococci, child, daptomycin, linezolid.*

http://dx.doi.org/10.5546/aap.2016.eng.e432

BACKGROUND

Vancomycin-resistant *Enterococcus* (VRE) infections is a global clinical problem at the hospital settings and can cause infective endocarditis, catheter-related bloodstream infections, urinary tract infections and bacteremia of unknown source. VRE bacteremia is a major cause of nosocomial infections with a significant morbidity and mortality especially in children with underlying severe chronic diseases.[1-3] Daptomycin is a cyclic lipopeptide antimicrobial agent derived from *Streptomyces roseosporus* and it has *in vitro* bactericidal activity against gram-positive pathogens.[2,4] The clinical experience with daptomycin therapy in pediatric patients with VRE is limited. Moreover, drug dosage, safety and tolerability have not been definitely established in children.[2] We report our experience about treatment of a VRE bacteremia in a 3-year-old boy with acute myeloid leukemia (AML)-M7 and Down syndrome.

CASE REPORT

A 3-year-old patient with Down syndrome and AML-M7 was admitted to the Emergency Department due to fever at the fourth month of chemotherapy.

Medical history: When he was 23 months old, he was brought to the clinic with bone pain and inability to walk; he was diagnosed with pre B cell leukemia. St Jude's Total XV chemotherapy protocol was given for leukemia. The patient's foot pain repeated at the 28 weeks of chemotherapy; bone marrow aspiration revealed AML-M7. His treatment protocol was switched to AML BFM 2004. His past medical history was also remarkable for congenital heart disease (atrial septal defect and ventricular septal defect).

Physical examination: He was febrile (tympanic temperature was 38.5 °C), 2/6 systolic murmur was audible and hepatosplenomegaly was detected.

Laboratory data: Hemoglobin of 11.8 g/dL, platelet count of 190 × 10^3/µL and a white blood cell count of 6700/µL (neutrophils 68%, lymphocytes and blasts 14%, monocytes 18%), with normal liver enzymes, kidney function tests and urinalysis. His erythrocyte sedimentation rate was 43 mm/h and C-reactive protein was 27.2 mg/dL (normal: 0-0,8 mg/dL).

The diagnosis of AML relapse was confirmed with bone marrow biopsy examination.

Day 1: The patient was hospitalized and meropenem was started due to neutropenic fever.

Day 7: Teicoplanin, amikacin were empirically added to the treatment because of the persistence of the fever.

Day 8: Liposomal amphotericin B was added.

Day 10: On the following days, pneumonia was diagnosed under antibiotics and trimetroprime sulfamethaxazole started. The antibiotics were

a. Pediatric Infectious Diseases Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey.
b. Bone Marrow Transplantation Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey.
c. Department of Medical Microbiology, Hacettepe University Faculty of Medicine, Ankara, Turkey.

E-mail Address:
Ayşe Büyükcam, M.D.: dr.aysebaktir@gmail.com

Funding: None.

Conflict of interest: None.

Received: 3-16-2016
Accepted: 5-23-2016

going on due to the clinical deterioration and prolonged fever. It was known that the patient was colonized with vancomycin-resistant *Enterococcus faecium* for the last eight months as detected in the surveillance cultures of stool. VRE was isolated from blood cultures which were taken from the central venous port and the peripheral vein on admission (VRE susceptibilities are shown in *Table 1*).

Day 10: Linezolid (10 mg/kg/dose every 8 hours) was added and immunoglobulin M-enriched immunoglobulin (pentaglobulin 4.8 g/dose) was administered for four times.

Day 12: Ciprofloxacine was added for progression of pneumonia (*Figure 1*).

Day 13: VRE was still being isolated from blood cultures at the third day of linezolid treatment.

The central venous port was removed and replaced with a new vascular catheter on the 13th day of therapy. Both procedures were also performed at the same time because of the necessity of vascular access. Trans-thoracic echocardiogram did not reveal valve vegetation.

Day 21: Amikacin was switched with gentamycin and repeat blood cultures continued to grow VRE.

Day 22: Daptomycin (8 mg/kg/day, a single dose) was added to linezolid at the 12th day of therapy after consent of the parents and approval by The Ministry of Health of Turkey. Linezolid was continued after the beginning of daptomycin treatment.

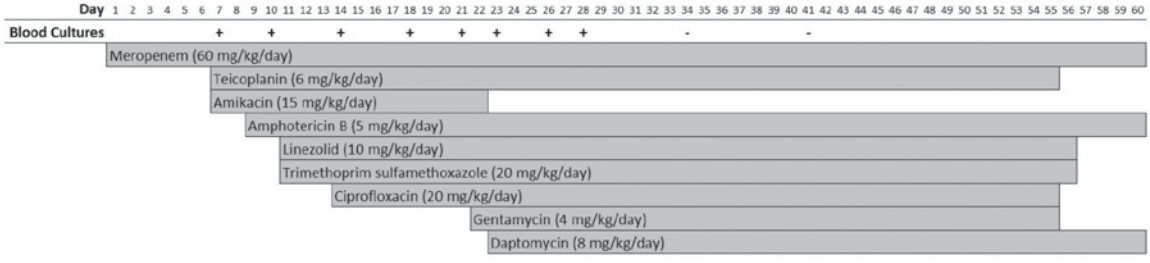
Day 32: The blood culture of the patient was sterile. Daptomycin therapy was continued for 5-weeks during which the blood culture were negative (*Table 2*).

TABLE 1. *VRE, susceptibilities*

Antimicrobial	Method of susceptibility Testing	MIC (µg/mL)	Susceptibility interpretation
Ampicillin	Vitek2 system(V2S)*	≥32	R
Imipenem	V2S	≥16	R
High levels of gentamicin	V2S	SYN-S	S
High levels of streptomycin	V2S	SYN-R	R
Ciprofloxacin	V2S	≥8	R
Erythromycin	V2S	≥8	R
Clindamycin	V2S	≥8	R
Linezolid	V2S	2	S
Teicoplanin	V2S	≥32	R
Vancomycin	V2S	≥32	R
Tetracycline	V2S	≥16	R
Tigecycline	V2S	≤12	S
Trimethoprim Sulfametoxazol	V2S	≥320	R
Daptomycin	E-test	2	S

Abbreviations: MIC, minimum inhibitory concentration.
*BioMerieux France.

FIGURE 1. *Antimicrobial therapy and blood culture results of patient during daptomycin treatment*



Serum CPK levels were in normal limits during the treatment. On 3th, 9th and 13th days after completion of daptomycin treatment the blood cultures were persistently negative. The previously planned FLAG IDA protocol for relapse AML was given. The patient died at the 77th day of hospitalization due to pulmonary infection, bleeding and progression of AML. No specific microorganism was detected during the last episode of pulmonary infection and progression of disease.

DISCUSSION

Vancomycin-resistant enterococcal bacteremia has an unfavorable outcome in children.[5] While the various agents including quinupristin-dalfopristin, daptomycin, and tigecyline are being used for VRE infections in adults, limited treatment options are significant problems for children. The clinical cure rate of infections with antibiotic resistant gram-positive pathogens was reported as 69.7% in children treated with linezolid.[6] In another study by Grazzino et al., the clinical cure or improvement of VRE infections with linezolid was achieved in 66.7% of the pediatric patients.[7] However, linezolid has bacteriostatic activity to enterococcci and treatment failure may be seen despite susceptibility of VRE and removal of central venous port as in our patient.[8] Daptomycin has appeared as another alternative for the treatment of VRE infections in pediatric population in recent years. The effectiveness of the treatment was shown in several reports in children with meningitis, bacteremia, sepsis, endocarditis, and urinary tract infections caused by VRE.[2,9,10] A certain number of combination therapy including ampicilline, aminogycosides, ceftalorine, tigecyline, rifampicin, and doxycycline with daptomycine has been used succesfully for VRE infections in the literature[3]. In addition synergy between daptomycin and gentamicin, for high-level gentamicin susceptible *E. faecium* has been already known[11] and it occured in our treatment. Therefore, we cannot generalize the potential benefit of multiantimicrobial usage.

Data are limited on the usage of daptomycin for pediatric patients. Also effective doses of daptomycin in children are different from adults and the optimal dosage is not well established. Daptomycin mostly binds a protein in circulation and is eliminated through kidneys.[2] Limited pharmacokinetic studies have manifested faster daptomycin clearance in children and it seems to have a shorter half-life in children aged 2-6 when compared to children aged 12-17.[10] Higher doses may be required in younger patients and the administration of 15 mg/kg/12 h was reported as a maximum dose in the literature in an infant.[2,8] Our patient was treated at a dose of 8 mg/kg/

TABLE 2. *The patient's cultures during the treatment*

Treatment day	Blood culture		Other cultures
	Central venous port/vasculer catheter*	Peripheral vein	
7 th	VRE (+)	VRE (+)	
8 th			Urine (-)
10 th	VRE (+)	VRE (+)	
14 th	VRE (+)	VRE (+)	
18 th	VRE (+)	VRE (+)	
21 th	VRE (+)		
23 th		VRE (+)	
26 th	VRE (+)	VRE (+)	
27 th			Pleural fluide (-)
28 th	VRE (+)	VRE (+)	
33th			Pleural fluide (-)
34 th	-	-	
41th	-		
63th**	-	-	

* Port was removed and replaced with a new vascular catheter on the 13th of therapy.

**Cultures were taken after three days the discontinuation of daptomycin.

day and the use of daptomycin resulting in microbiological and clinical cure of infection without the observation of any side effects.

Several factors have related to an increase in the incidence of VRE infection, which may be attributed to several factors that increase the risk of infection, such as colonization of gastrointestinal tract, prior vancomycin or fluoroquinolone therapy, higher Acute Physiology and Chronic Health Evaluation II (APACHE) score and previous corticosteroid usage. Furthermore, in many reports, underlying hematologic malignancy, receiving chemotherapy, and high-grade bacteremia have been reported; the isolation of VRE from blood is significantly correlated with mortality. However these risk factors were showed in adult population and we have insufficient data in pediatric patients.[12,13] The present case of persistent bloodstream VRE infection occurred in a boy with severe neutropenia following chemotherapy for relapsed AML-M7, and its clinical course shared similarities with those previously reported, particularly the poor outcome.

CONCLUSION

This report highlights the therapeutic approach of the persistent VRE bacteremia in a child with AML-M7 and Down syndrome, treated successfully with daptomycin. Despite susceptibility to linezolid, modification of antimicrobial therapy to daptomycin resolved the fever with favorable clinical and microbiological response in this case. We thought that more studies are needed to clarify the pharmacodynamics, pharmacokinetics, tolerability and toxicity of daptomycin in pediatric population, especially patients with underlying chronic diseases. ■

REFERENCES

1. Tamma PD, Hsu AJ. Optimizing therapy for vancomycin-resistant enterococcal bacteremia in children. *Curr Opin Infect Dis* 2014;27(6):517-27.
2. Principi N, Caironi M, Venturini F, Pani L, et al. Daptomycin in paediatrics: current knowledge and the need for future research. *J Antimicrob Chemother* 2015 Mar;70(3):643-8.
3. Munita JM, Murray BE, Arias CA. Daptomycin for the treatment of bacteraemia due to vancomycin-resistant enterococci. *Int J Antimicrob Agents* 2014;44(5):387-95.
4. Humphries RM, Pollett S, Sakoulas G. A current perspective on daptomycin for the clinical microbiologist. *Clin Microbiol Rev* 2013;26(4):759-80.
5. Diaz Granados CA, Zimmer SM, Klein M, Jernigan JA. Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: a meta-analysis. *Clin Infect Dis* 2005;41(3):327-33.
6. Jantausch BA, Deville J, Adler S, Morfin MR, et al. Linezolid for the treatment of children with bacteremia or nosocomial pneumonia caused by resistant gram-positive bacterial pathogens. *Pediatr Infect Dis J* 2003;22(9 Suppl):S164-71.
7. Garazzino S, Tovo PA. Clinical experience with linezolid in infants and children. *J Antimicrob Chemother* 2011;66 Suppl 4:iv23-iv41.
8. Beneri CA, Nicolau DP, Seiden HS, Rubin LG. Successful treatment of a neonate with persistent vancomycin-resistant enterococcal bacteremia with a daptomycin-containing regimen. *Infect Drug Resist* 2008;1:9-11.
9. Ardura MI, Mejias A, Katz KS, Revell P, et al. Daptomycin therapy for invasive Gram-positive bacterial infections in children. *Pediatr Infect Dis J* 2007;26(12):1128-32.
10. Durand C, Brueckner A, Sampadian C, Willett KC, et al. Daptomycin use in pediatric patients. *Am J Health Syst Pharm* 2014;71(14):1177-82.
11. Hindler JA, Wong-Beringer A, Charlton CL, Miller SA, et al. In vitro activity of daptomycin in combination with beta-lactams, gentamicin, rifampin and tigecycline against daptomycin-nonsusceptible enterococci. *Antimicrob Agents Chemother* 2015;59(7):4279-88.
12. Ornstein MC, Mukherjee S, Keng M, Elson P, et al. Impact of vancomycin-resistant enterococcal bacteremia on outcome during acute myeloid leukemia induction therapy. *Leuk Lymphoma* 2015;56(9):2536-42.
13. Kraft S, Mackler E, Schlickman P, Welch K, et al. Outcomes of therapy: vancomycin-resistant enterococcal bacteremia in hematology and bone marrow transplant patients. *Support Care Cancer* 2011;19(12):1969-74.