

CASE REPORT

Daptomycin for the treatment of daptomycin nonsusceptible *Enterococcus faecium* bacteremia

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ABSTRACT

The best therapeutic options for serious infections due to daptomycin nonsusceptible *Enterococcus faecium* (DNSE) remain unclear. We report the use of daptomycin for the treatment of DNSE bacteremia. To our knowledge, it is the first case of DNSE infection which successfully treated with daptomycin monotherapy in the literature. *J Microbiol Infect Dis* 2014;4(1): 36-38

Key words: Enterococcus, bloodstream infection, daptomycin

Daptomisine duyarlı olmayan *Enterococcus faecium* bakteriyemisinde daptomisin tedavisi: Olgu sunumu

ÖZET

Daptomisine duyarlı olmayan *Enterococcus faecium* (DNSE)'a bağlı ciddi enfeksiyonlarda en iyi tedavi seçeneği belirsizdir. Burada DNSE bakteriyemisi olan bir olguda daptomisin kullanımı tecrübemizi paylaştık. Bildiğimiz kadarı ile literatürde daptomisin monoterapisi ile başarılı tedavi edilen ilk olgudur.

Anahtar kelimeler: Enterokoklar, kanakımı enfeksiyonu, daptomisin

INTRODUCTION

Bacteremia caused by vancomycin-resistant enterococci (VRE) has been associated with higher morbidity and mortality than caused by vancomycin susceptible enterococci.¹ The optimal approach for treatment of enterococcal infection due to vancomycin-resistant *E. faecium* is uncertain.² Although daptomycin has not been approved by the FDA for *E. faecium*, some favor the use of daptomycin for treatment of *E. faecium* infections that are resistant in vitro to approved antibiotics.² Minimum dosing for bloodstream infections is 6 mg/kg intravenously once daily; in the setting of bloodstream infections some favor doses of 8 mg/kg intravenously once daily or higher. Higher dosing (8 to 12 mg/kg every 24 hours) may be more efficacious for life threatening infections due to *E. faecalis* or *E. faecium*.³ Daptomycin has concentration-dependent killing and in vivo data have shown that higher doses.⁴

The knowledge about the emergence of daptomycin nonsusceptible *Enterococcus* strains and the treatment of the associated infections is limited.⁵ Daptomycin nonsusceptibility among staphylococci has been reported in Turkey.^{6,7} We describe the first case which reported from Turkey of a patient with loss of daptomycin susceptibility among enterococci after daptomycin treatment.

CASE REPORT

In September 2010 a 36-year-old woman admitted to our neurosurgical intensive care unit (ICU) because she had a diffuse axonal injury due to a traffic accident. A subclavian nontunneled catheter was inserted and she was treated medically without any surgical intervention. On the ninth day of the admission she was found to have fever of 39°C and erythema at the catheter exit site. She was considered to have catheter related infection. Two blood

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cultures were obtained, the subclavian catheter was replaced and the catheter tip was sent for culture to our Clinical Microbiology Laboratory. Piperacillin-tazobactam (4.5 gm every 8 hours) intravenously was initiated on the same day while the culture result was pending. Vancomycin resistant *Enterococcus faecium* was isolated from both blood cultures and the catheter tip site. The Bact/Alert 3D (BioMerieux, Mercy Etoile, France) blood culture system was used. Identification was carried out by BBL CRYSTALTM Gram-Positive ID kit (Becton Dickinson, ABD). The antibiotic susceptibility performed by Kirby-Bauer disc diffusion test revealed resistance to penicillin, ampicillin, gentamicin, vancomycin, teicoplanin and rifampin. E test was also performed and the MIC breakpoints were found to be as follows: vancomycin >32 mg/L, teicoplanin >32 mg/L, linezolid 12 mg/L, daptomycin 1.5 mg/L. The strain was found to be susceptible to daptomycin. Piperacillin-tazobactam treatment was discontinued. Daptomycin (6 mg/kg per day) intravenously was initiated. The patient became afebrile on the second day of the treatment and daptomycin was continued for up to ten days. Approximately 15 days later she had fever, hypotension, and tachycardia although there were no signs of infection at her subclavian catheter exit site, the catheter was removed and the catheter tip was sent for culture again. Simultaneously two blood cultures were also obtained from the patient. Cefepime (2 g every 12 h) and daptomycin treatment (6 mg/kg per day) intravenously was initiated. The catheter tip culture remained sterile after the incubation but Vancomycin resistant *Enterococcus faecium* was isolated from both blood cultures. The Bact/Alert 3D (BioMerieux, Mercy Etoile, France) blood culture system was used. Identification was carried out by BBL CRYSTALTM Gram-Positive ID kit (Becton Dickinson, ABD). Cefepime treatment was discontinued. The antibiotic susceptibility performed by Kirby-Bauer disc diffusion test revealed resistance to penicillin, ampicillin, gentamicin, vancomycin, teicoplanin and rifampin. The MIC breakpoints established for different antibiotics by E test were as follows: vancomycin >32 mg/L, teicoplanin >32 mg/L, linezolid 32mg/L, daptomycin 8 mg/L. Although the strain was nonsusceptible to daptomycin we continued daptomycin 8 mg/kg treatment. We didn't find any vegetations on the performed trans-thoracic echocardiogram. The patient was considered to have primary bacteremia. The MIC breakpoint for daptomycin of the isolated strain was confirmed by a reference laboratory (Quotient Bioresearch, UK) to be 16 mg/L by both E-test and micro broth dilution methods. The patient became afebrile on the fifth day of treatment and the blood cultures

obtained on the same day remained sterile until the end of the incubation. The treatment was continued for 14 days. She was discharged on January 2011 with full recovery for her diffuse axonal injury and without any complications of the bacteremia.

DISCUSSION

Vancomycin resistant enterococci (VRE) are important cause of nosocomial bloodstream infection (BSI).^{8,9} There are limited treatment options currently available for the treatment of VRE infections.⁸ Daptomycin is a cyclic lipopeptide antibiotic with rapid bactericidal activity against drug-resistant bacteria including methicillin-resistant *Staphylococcus aureus* and VRE.¹⁰ Neither Clinical Laboratory Standards Institute (CLSI) nor the European Committee on Antimicrobial Susceptibility Testing (EUCAST) committees have defined resistance breakpoints for enterococci to daptomycin. EUCAST defined insufficient evidence to set a breakpoint for enterococci.¹¹ According to CLSI *Enterococcus* isolates with minimum inhibitory concentrations (MICs) ≤ 4 μg , determined by broth dilution are considered susceptible.¹² Moreover, enterococci with daptomycin MICs >4 $\mu\text{g/ml}$ are considered as non-susceptible (DNSE).¹¹ Strains with MICs above the established breakpoint are not often encountered. From 2003 through 2010 there are 23 studies reporting 150 DNSE. Of these 150 isolates, 140 (93.3%) were VRE, nine were vancomycin susceptible enterococci (VSE) and in one (0.7%) case, vancomycin susceptibility was not reported.⁵

Treatment of DNSE isolates was reported in nine cases. All cases had underlying diseases impairing the immune functions of the patients, were treated with alternative agents other than daptomycin and four of them were cured.^{5,12} The optimal management of serious DNSE infection is unknown.⁵ Currently there is no available literature comparing the efficacy of various doses of daptomycin in relation to MIC values.¹³

Daptomycin displays concentration-dependent activity that is best characterized by pharmacodynamic indexes AUC/MIC or $C_{\text{max}}/\text{MIC}$. The pharmacodynamics of daptomycin for *E. faecium* was characterized in the neutropenic mouse model. The AUC/MIC ratios required for bacteriostatic effect ranged from 0.94 to 1.67 for *E. faecium*. The free daptomycin concentrations needed were an average of one to two times the MIC over 24 hours to produce a bacteriostatic effect and two to four times the MIC over 24 hours to produce greater than 99% killing.⁴ For the human situation, it can be calculated that a mean AUC of approximately 858 mg h/l (as

reached with a dose 8 mg/kg in humans) and as our strain had MIC 16 mg/l, AUC/MIC ratio was calculated to be 53.6.^{14,15} This value might have been adequate for achieving bactericidal effect in our case.

Our case didn't have any co-morbidities causing immune impairment. This may also have contributed for the cure of our patient unlike the other reported cases of treatment failure. In our case *Enterococcus faecium* was resistant to all other antibiotic agents and we treated the patient with daptomycin as we didn't have any other choice. Although there are no defined MIC breakpoints for a resistant category for *Enterococcus* according to CLSI or EUCAST, to our knowledge it is the first case of DNSE infection successfully treated with daptomycin in the literature. As a result prospective studies are needed to fully understand the use of daptomycin in the treatment of DNSE bacteremia.

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