Case Report

A Novel Way of Treating Multidrug-resistant Enterococci

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Abstract

Context: Daptomycin is the only antibiotic available with *in vitro* bactericidal activity against vancomycin-resistant enterococci (VRE). Its increased use has resulted in cases of decreased daptomycin efficacy. Recent *in vitro* studies have shown effective use of beta (β)-lactam and daptomycin antibiotics, as a combination therapy, in the treatment of VRE. We describe a case of effective treatment in a patient with VRE infection using dual ampicillin and daptomycin therapy that shows bench-to-bedside application of the abovementioned finding. **Case Report:** A 76-year-old gentleman with a history of bilateral arthroplasty was admitted with a swollen left knee. Blood cultures were positive for *Enterococcus faecium*. Left knee joint aspiration showed leukocytosis and alpha defensins. Extensive imaging did not show any other source of infection. Culture sensitivity results showed multidrug-resistant enterococci sensitive to daptomycin. The patient was started on intravenous (IV) daptomycin. His left knee prosthesis was explanted and a spacer was placed. The patient continued to be bacteremic for 10 days after removing the knee prosthesis. The patient was trialed on combination IV ampicillin and daptomycin. His blood culture turned negative 2 days later. The patient was discharged home to continue 6 weeks of IV ampicillin and daptomycin. **Conclusion:** The exact mechanism of the daptomycin/ampicillin synergy effect is unclear. Current hypothesis suggests that ampicillin causes a reduction in the net positive charge of the bacterial surface, possibly by releasing lipoteichoic acid (LTA) from the cell wall. This process increases the ability of the cationic daptomycin/calcium complex to bind to the cell wall more effectively. Our case shows the clinical application of the same. A prospective randomized control trial to explore the effectiveness of dual antibiotic therapy *in vivo* is needed. If proven, daptomycin/β-lactam can become a standard of care to treat VRE and decrease daptomycin nonsusceptibility.

Keywords: Daptomycin/beta (β)-lactam, daptomycin nonsusceptibility, vancomycin-resistant enterococci

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Context

Accounting for almost 10% of total bloodstream infections, *Enterococcus* is the fourth most common pathogen responsible for bloodstream infections in North America.[1] Of those total number of *Enterococcus* infections, 25% are resistant to vancomycin.[2] Vancomycin-resistant enterococci (VRE) infections have been associated with increased mortality and morbidity.[3,4] In patients infected with VRE, the odds of death are 2.5 times higher compared with vancomycin-susceptible enterococci.[3] Most of these antibiotics are bacteriostatic and associated with extensive drug-drug interactions.[5-7] Daptomycin is the only antibiotic available with *in vitro* bactericidal activity against VRE.[8-10] Daptomycin is being increasingly used, especially in the critically ill and immunosuppressed, even though it is not approved by the Food and Drug Administration (FDA).[11] There have been reports of

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daptomycin nonsusceptible enterococci emergence during monotherapy.[12,13] Studies have shown that 2–3% of VRE cases may be nonsusceptible to daptomycin.[13] In those cases of resistant organisms, there are no other antibiotic treatment options. There have been recent *in vitro* studies showing effective use of beta (β)-lactams and daptomycin on daptomycin nonsusceptible enterococci.[14-16] We describe a case of effective treatment in a patient with vancomycin-resistant *Enterococcus faecium* with dual ampicillin and daptomycin therapy that shows bench-to-bedside application of the abovementioned finding.

Case Presentation

A 76-year-old gentleman with a past medical history significant for extensive coronary artery disease and bilateral arthroplasty was admitted with the complaint of left knee swelling. He was afebrile on presentation. His left knee was erythematous, tender, and swollen compared to the right knee. Arthrocentesis was positive for alpha defensins with white blood cell (WBC) count of 18,000/uL. Fluid culture was negative. No crystalopathy was identified. Blood cultures were positive for *Enterococci faecium*. Transesophageal echocardiogram (TEE) was performed to rule out infective endocarditis and was negative.

The VRE, found in blood culture, were sensitive to daptomycin with 1:2 dilutions and resistant to ampicillin with 1:32 dilution. The patient was started on intravenous (IV) daptomycin 6 mg/kg daily. His left knee prosthesis was explanted and a spacer was placed on the fourth day of admission. Blood cultures were performed every other day to assess the antibiotic response. His blood cultures continued to grow VRE for 10 days after the explantation of the prosthesis. Extensive imaging was performed to find the source of infection. A whole body nuclear-tagged WBC scan did not show any signs of persistent infection. Magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis with and without contrast failed to show any focus of infection. Arthrocentesis of the right knee and repeat TEE were negative as well. Due to persistent bacteremia, the patient was tried on a combination of IV ampicillin and daptomycin. On the second day of the combined therapy, the next set of blood cultures were obtained and were negative for the first time since admission. Repeat blood cultures continued to be negative for 7 more days. He was eventually discharged with the peripherally inserted central catheter (PICC) line to continue 6 weeks of IV ampicillin and daptomycin.

Discussion

This case showed an interesting clinical application of combination ampicillin and daptomycin to combat daptomycin nonsusceptible organisms. This phenomenon had been described mostly in *in vitro* studies.

Sakoulas *et al*. demonstrated a threefold decrease in daptomycin minimum inhibitory concentration (MIC), when VRE strain was grown in a medium containing 50 mg/L ampicillin and 100 mg/L ampicillin.[14] However, the exact mechanism of the daptomycin/ampicillin synergistic effect is unclear at this time. The current hypothesis suggested that ampicillin causes a reduction in the net positive charge of the bacterial surface by releasing lipoteichoic acid (LTA) from the cell wall. The loss of LTA released cell autolysins that caused bacterial cell wall destabilization. More importantly, the reduction in cell wall positive charge appeared to allow the cationic daptomycin/calcium complex to bind more effectively to the cell wall. In a fluorescence-labeled daptomycin assay, this mechanism was supported as ampicillin pretreatment that resulted in an increase in daptomycin binding.[14,16]

Although, difficult to prove that in the current case, the clearance of bacteremia was related to the abovementioned mechanism, the patient continued to be bacteremic for 10 days while being treated with daptomycin monotherapy. With the addition of ampicillin, blood cultures drawn a couple of days after were negative and remained negative. This was similarly described in the report by Sakoulas *et al*., where a patient with persistent bacteremia refractory to 7 days of daptomycin/linezolid cleared the infection within 24 h of starting dual high-dose daptomycin and ampicillin.[14] In a multiple hospitals study, Moise *et al*. showed a significantly higher daptomycin monotherapy failure when daptomycin MIC values were 3–4 μg/L, compared to MIC <2 μg/L ($P = 0.005$). When comparing the two different MIC groups in patients treated with β-lactam/daptomycin dual therapy, treatment failure was not significantly different ($P = 0.417$).[15] This may be evidence to suggest that adjunct ampicillin may be indicated in infections where daptomycin MIC is 3–4.

Additionally, our case shows that *in vitro* drug susceptibility testing may not accurately translate into clinical potency. Even though the enterococcus isolate was resistant to ampicillin, the addition of ampicillin resulted in effective clearance of the patient's bacteremia, increasing the *in vivo* potency of daptomycin.

Other studies have described increased daptomycin efficacy with the addition of ceftaroline, a cephalosporin to which enterococci are intrinsically resistant.[17] Dual antibiotic therapy with ampicillin and daptomycin additionally appeared to be effective in treating methicillin-resistant *staphylococcus aureus*.[18]

Conclusion

Daptomycin is a potent bactericidal antibiotic. With the increased prevalence of VRE related infections, daptomycin may be the last line of defense against enterococci. Increasing prevalence of daptomycin nonsusceptible enterococci presents an added challenge for treating such life-threatening infections. A few *in vitro* experiments have studied the increased efficacy of daptomycin in the presence of β-lactam antibiotics. A prospective randomized control trial to explore the effectiveness of dual antibiotic therapy *in vivo* is needed. Further studies to assess synergistic effect of different antibiotics with daptomycin should be assessed. As multidrug-resistant organisms are becoming more common, it would be worthwhile to investigate synergistic antibiotic therapy. If proven, daptomycin/β-lactam can become a standard of care to treat VRE and can decrease daptomycin nonsusceptibility.

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Conflicts of interest

There are no conflicts of interest.

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