Case Report

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Relapse of enterococcal prosthetic valve endocarditis with aortic root abscess following treatment with daptomycin in a patient not fit for surgery

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Daptomycin is a novel lipopeptide with activity against Gram-positive organisms including enterococci. It is licensed for the treatment of *Staphylococcus aureus* bacteraemia and right-sided endocarditis, but not endocarditis due to *Enterococcus* spp. We report a case of enterococcal prosthetic valve endocarditis with an aortic root abscess in an elderly patient who was not fit for surgery. The patient's endocarditis relapsed 9 weeks after a 6 week course of daptomycin.

Case report

An 84-year-old lady presented with breathlessness and chest pain of 1 days duration, with right middle zone consolidation and left pleural effusion on a chest radiograph. She was febrile (38 °C) with raised inflammatory markers [58 mg C-reactive protein (CRP) l⁻¹, 18.7 × 10⁹ white cells l⁻¹ and renal impairment (creatinine clearance rate 30 ml min⁻¹]. She was in atrial fibrillation. Her past medical history included an aortic valve replacement and triple vessel coronary artery bypass graft 11 months previously for moderate aortic regurgitation with aortic stenosis and ischaemic heart disease. She was commenced on intravenous (IV) co-amoxiclav, which was changed to 1 g IV amoxicillin at 8 hourly intervals for 12 days for presumed urosepsis after blood cultures taken on admission grew *Enterococcus faecalis*. The organism was identified by APIstrep (bioMérieux) and had amoxicillin and daptomycin MICs of 3 mg l⁻¹ (Etest). It was vancomycin and gentamicin susceptible. Urine culture was negative. She promptly recovered but in view of the history of aortic valve replacement a transthoracic echocardiogram and subsequently a transoesophageal echocardiogram (TOE) were performed, which showed no rocking or dehiscence, and no obvious vegetations or aortic regurgitation. Duke criteria for endocarditis at this point included one major and two minor criteria, which did not fully confirm the diagnosis of endocarditis. Three days after the antibiotics were stopped, blood cultures again grew *E. faecalis* but there was a negative urine culture. A second course of 2 g amoxicillin at 6 hourly intervals was commenced for 8 days. Gentamicin was omitted due to the

patient's renal impairment. A computed tomography scan of the abdomen and pelvis showed no intra-abdominal fluid collection or vertebral infection. Blood cultures taken 1 week after the stopping of the second course of antibiotics grew *E. faecalis*. A third 9 day course of amoxicillin also failed. Blood cultures still grew *E. faecalis* 10 days after stopping the therapy.

A fourth course of 2 g IV amoxicillin at 6 hourly intervals was started after a repeat TOE showed thickening of the superior aspect of the aortic valve and aortic root abscess cavity surrounding one third of the aortic root, which was suggestive of an aortic root abscess and para-prosthetic infection. Therefore, two major Duke criteria were fulfilled (typical micro-organism with endocardial involvement) confirming the diagnosis of endocarditis. Amoxicillin (8 g per day) as a continuous IV infusion was commenced and the patient was referred for surgery. This amoxicillin dose was chosen as her creatinine clearance rate had deteriorated to 17 ml min⁻¹ at this time. The patient was considered too high an operative risk due to her renal impairment and poor cardiac function. Amoxicillin was continued for 4 weeks and thereafter treatment with 8 mg daptomycin kg⁻¹ once daily was commenced for a total of 6 weeks (2 weeks as an inpatient and 4 weeks as an outpatient). CRP, renal function and creatine kinase (CK) levels were monitored closely. A transthoracic echocardiogram showed no abnormality prior to the stopping of antibiotics. Blood cultures tested 5 days after therapy was stopped were negative.

The patient returned 9 weeks later with a recurrence of *E. faecalis* bacteraemia. The daptomycin MIC remained at 3 mg l⁻¹. She was recommenced on 8 g amoxicillin per day by continuous infusion and 1 mg gentamicin kg⁻¹ twice daily (dependent on levels) was added for 6 weeks.

Abbreviations: BNF, British National Formulary; CK, creatine kinase; CRP, C-reactive protein; IV, intravenous; TOE, transoesophageal echocardiogram; VR, vancomycin resistant; VS, vancomycin susceptible.

Problems with gentamicin dosing were encountered and her renal function transiently deteriorated. A decision was made to commence her on long-term oral amoxicillin treatment in an attempt to suppress any further relapses. No blood cultures were taken subsequent to this but her CRP level was monitored monthly and was consistently within the normal range. She remained well after 9 months of treatment with 500 mg oral amoxicillin at 8 hourly intervals.

Discussion

Infective endocarditis was considered as a possible diagnosis after the patient's first positive blood culture due to the presence of a prosthetic valve. However, the initial TOE was negative. Further sources of the bacteraemia were explored. Subsequent positive blood cultures supported an endovascular source but echocardiography failed to support it until a TOE 2 months later confirmed the diagnosis of endocarditis [thus fulfilling two major criteria for infective endocarditis (Durack *et al.*, 1994)]. There was no rise in amoxicillin MIC (3 mg l⁻¹) that led to antibiotic failure.

High dose amoxicillin as a continuous infusion was commenced as gentamicin was contraindicated due to the patient's renal impairment. UK guidelines suggest 12 g per day for the treatment of enterococcal endocarditis (Elliott *et al.*, 2004). The lower dose of 8 g per day was chosen due to the patient's poor and deteriorating renal function (BNF, 2008). Options included adding gentamicin to the regimen and continuing amoxicillin. In view of the patient's renal function it was decided to commence treatment with daptomycin so as to allow her to be discharged home. Daptomycin is a novel lipopeptide (Enoch *et al.*, 2007). When the patient was stabilized daptomycin was chosen for the long-term therapy at home required to treat the inoperable aortic root abscess. Daptomycin has previously been successfully used to treat a perivalvular abscess due to methicillin-resistant *Staphylococcus aureus* (Mohan *et al.*, 2005), and has been successfully used to treat enterococcal bacteraemia (Cunha *et al.*, 2007; Mohr *et al.*, 2009). Unfortunately, in this latter study endocarditis cases were excluded. A higher daptomycin dose (8 mg kg⁻¹) was chosen due to the higher MIC that enterococci typically exhibit. Unfortunately, the presence of the prosthetic material with an associated abscess and the patient not being fit for valve replacement led to treatment failure. She was thus prescribed life-long suppressive therapy.

Data regarding the treatment of enterococcal endocarditis with daptomycin are currently limited to case series and case reports. These studies have several limitations, including variation in diagnostic methods and variation in treatment duration; one dose typically allows entry into the registries. MIC data were also frequently missing. These studies are summarized in Table 1.

The largest case series involved 30 patients (Levine & Lamp, 2007a). Twenty-four had left-sided endocarditis. A total of 15 involved vancomycin-resistant (VR) strains (8 *Enterococcus faecium*, 2 *E. faecalis* and 6 non-speciated, including 1 patient with dual infection) and 13 involved vancomycin-susceptible (VS) strains (11 *E. faecalis*, 1 *E. faecium* and 1 non-speciated). Two patients (one *E. faecalis* and one non-speciated) had no vancomycin susceptibility data provided. Twenty-seven had received prior antibiotics (most frequently vancomycin) and twenty received concomitant antibiotics. Six patients received 4 mg antibiotic kg⁻¹, twenty-one patients received 6 mg antibiotic kg⁻¹ and one patient received 8 mg antibiotic kg⁻¹. The median duration of therapy was 31 days (range 4–62 days). No MIC data were provided. CK levels rose in one patient. No differences were ascertained in terms of outcome in relation to vancomycin susceptibility and location of the endocarditis. Five patients died; two of these deaths were thought to be due to daptomycin failure and three were assessed as non-evaluable.

Fourteen patients with enterococcal endocarditis [VS *E. faecalis* (6), VR *E. faecium* (1), *Enterococcus* spp. (7: VR 5 and VS 2)] were included in one study (Levine & Lamp, 2007b). There were ten successes and two failures (two were non-evaluable). One failure received 6 mg daptomycin kg⁻¹ for 5 days and the other patient received 4 mg daptomycin kg⁻¹ for 62 days. No further information was included to describe the reasons for treatment failure such as presence of abscesses or prosthetic valves.

Two patients with left-sided endocarditis due to VR enterococci (species/MIC not stated) were included in a case series (Segreti *et al.*, 2006). One patient was undergoing haemodialysis and had a prosthetic mitral valve *in situ*. She received 22 days of daptomycin (6 mg kg⁻¹) in total before dying, during which time her CK level rose >10 fold. The other patient, a 51-year-old male, died despite 27 days of daptomycin (6 mg kg⁻¹). This patient had received vancomycin prior to this. It is not clear from the report whether the patients died because of daptomycin failure or their underlying condition, nor whether they were also inoperable.

A 60-year-old diabetic man required treatment with vancomycin for 12 weeks for a groin wound secondary to a right aorto-femoral bypass graft infection growing methicillin-resistant *S. aureus*. He developed native mitral valve endocarditis, with blood cultures growing VR *E. faecium* (Arias *et al.*, 2007). He received 6 mg daptomycin kg⁻¹ monotherapy for 6 weeks (daptomycin MIC=6 mg l⁻¹) but this proved inadequate. He subsequently responded to 6 weeks of daptomycin (8 mg kg⁻¹) with ampicillin (16 g per day) and gentamicin (1 mg kg⁻¹ twice daily). Resistance to daptomycin developed in a dialysis-dependent diabetic patient with aortic valve endocarditis. *E. faecalis* was grown from blood cultures, which was initially susceptible to amoxicillin, vancomycin and daptomycin. The patient received daptomycin at 6 mg kg⁻¹ (due to a penicillin

Table 1. Summary of case series/reports of daptomycin treatment of enterococcal endocarditis

Organism (no. of patients)	Patient age (years)/sex	Daptomycin MIC	Vancomycin resistance	Site/valve (no. of patients)	Previous antibiotics	Concomitant antibiotics	Daptomycin dose (no. of patients)	Duration of daptomycin treatment	Adverse event	Outcome	Reference
<i>E. faecalis</i> (13) <i>E. faecium</i> (9) Non-speciated (8)	NA	NA	15/30 (16 isolates)	L (24) R (6)	27/30 had prior antibiotics	20/30	4 mg kg ⁻¹ (6), 6 mg kg ⁻¹ (21), 8 mg kg ⁻¹ (1)	4–62 days (median 31 days)	1 patient had CK rise	5 died: 2 possibly due to daptomycin failure, 3 non-evaluable	Levine & Lamp (2007a)
<i>E. faecalis</i> (6) <i>E. faecium</i> (1) Non-speciated (7) Non-speciated (2)	NA	NA	6/14	L (6) L (1) L (5), R (2) Mitral (P)	NA	NA	NA	NA	NA	2 failed, 2 non-evaluable	Levine & Lamp (2007b)
<i>E. faecium</i> (1)	51/M 64/F	NA	2/2	Mitral (P)	1 had previous vancomycin	Amikacin, tobramycin	6 mg kg ⁻¹ (2)	27 days 22 days	1 patient had CK rise	Both died: non-evaluable	Segreti <i>et al.</i> (2006)
<i>E. faecium</i> (1)	60/M	6 mg l ⁻¹	1/1	Mitral	Vancomycin	–	6 mg kg ⁻¹ (1)	42 days	Nil	Required change to vancomycin	Arias <i>et al.</i> (2007)
<i>E. faecalis</i> (1)	55/F	NA	0/1	Aortic	No	No	6 mg kg ⁻¹ (1)	18 days		Required change to amoxicillin and valve replacement	Kanafani <i>et al.</i> (2007)
<i>E. faecium</i> (1)	70/M	2 mg l ⁻¹	1/1	Mitral	Linezolid	Gentamicin & doxycy- cline	6 mg kg ⁻¹ , then 8 mg kg ⁻¹ (1)	27 days		Required change to quinupristin/ dalfopristin	Fraher <i>et al.</i> (2007)

F, Female; L, left-sided endocarditis; M, male; NA, not available; P, prosthetic; R, right-sided endocarditis.

allergy) but blood cultures remained positive, and the MIC to daptomycin had risen to 32 mg l⁻¹. Valve replacement and ampicillin (after penicillin desensitization) were required to affect a cure (Kanafani *et al.*, 2007). Daptomycin was ineffective in a patient with mitral valve endocarditis due to VR *E. faecium* despite treatment with 6 mg kg⁻¹ and then 8 mg kg⁻¹. The MIC remained at 2 mg l⁻¹ throughout (Schwartz *et al.*, 2008). Further testing suggested that failure occurred as a result of low levels of free daptomycin due to protein binding.

A phase IV study is currently under way using daptomycin at a dose of 8 mg kg⁻¹ per day. The aim is to determine the safety and efficacy of daptomycin when used in addition to standard care in the treatment of proven native valve endocarditis compared to standard therapy (<http://clinicaltrials.gov/show/NCT00401960>). Toxicity and efficacy will be assessed.

Several further cases have been described in which resistance to daptomycin has developed in patients with VR strains of enterococcus whilst undergoing treatment. Daptomycin resistance (MIC 16 mg l⁻¹) emerged in a blood culture from a dialysis-dependent 64-year-old with cryptogenic cirrhosis (Lewis *et al.*, 2005; Long *et al.*, 2005; Munoz-Price *et al.*, 2005). De novo resistance to daptomycin in *E. faecium* has also been described in two case reports (Lesho *et al.*, 2006; Fraher *et al.*, 2007). In our case, the daptomycin MIC remained unchanged suggesting that failure was due to inadequate source control rather than resistance to daptomycin.

This report describes what is believed to be the first use of daptomycin for the treatment of an aortic root abscess due to *E. faecalis*. Daptomycin was given for 6 weeks (4 weeks as an outpatient) to a patient with multiple co-morbidities and renal impairment, and was well tolerated despite the higher dose used. Despite the higher dose, recurrence occurred as the patient was unfit for surgery and source control was, therefore, not possible. Whilst daptomycin is a useful agent for the treatment of serious infections due to Gram-positive bacteria, its use must be carefully monitored in view of the emergence of resistance and treatment failure, especially in cases where there is a persistent source.

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