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A case of fatal daptomycin-resistant, vancomycin-resistant enterococcal infective endocarditis in end-stage kidney disease

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Introduction: Ireland currently has the highest reported rate in Europe of vancomycin-resistant *Enterococcus* (VRE) isolated from the bloodstream, but data regarding the prevalence of VRE endocarditis remain scarce. Treatment options for *Enterococcus*-mediated endocarditis are limited, and therefore daptomycin is commonly used off licence in this setting.

Case presentation: A 60-year-old male with end-stage kidney disease (ESKD) presented with VRE bacteraemia secondary to a gangrenous right foot colonized with vancomycin-resistant *Enterococcus faecium*. Aortic valve endocarditis was confirmed using transoesophageal echocardiography. Treatment was commenced with linezolid and subsequently modified to combination therapy with daptomycin and rifampicin. High-dose daptomycin therapy was employed unsuccessfully and, after 20 days of therapy, daptomycin resistance emerged, which proved fatal.

Conclusion: The case was ethically challenging and involved a refusal of amputation and, ultimately, any form of treatment by the patient. In summary, however, daptomycin-resistant VRE bacteraemia complicated by recalcitrant daptomycin-resistant VRE endocarditis proved fatal for this patient. Further evaluation of the efficacy and safety of high-dose daptomycin for the treatment of VRE infective endocarditis is needed.

Keywords: Daptomycin; end-stage kidney disease (ESKD); resistance; rifampicin; vancomycin-resistant *Enterococcus* (VRE).

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Introduction

Enterococci are Gram-positive organisms that form part of the commensal gut flora. A common nosocomial pathogen resistant to many antimicrobials, enterococci can reside and survive in the clinical environment for prolonged periods with an associated risk of contaminating healthcare workers and the potential for cross-transmission to patients (Biedenbach *et al.*, 2004). Enterococci are the second most common nosocomial bloodstream pathogen isolated in the USA with the prevalence of vancomycin-resistant *Enterococcus* (VRE) in intensive care units currently exceeding 30% (Wisplinghoff *et al.*, 2004). *Enterococcus faecalis* and *Enterococcus faecium* are the predominant pathogens associated with VRE infections (Carmeli *et al.*, 2002). Ireland has the highest proportion

of VRE bloodstream isolates in Europe, as reported to the European Centre for Disease Prevention and Control. In 2013, 176 VRE were identified among 408 *E. faecium* isolates from bloodstream infections in Ireland (43.1%). VRE results in significant increases in length of hospital admission and mortality (DiazGranados *et al.*, 2005).

For patients aged ≤ 60 years, enterococci account for up to 10% of cases of native valve infective endocarditis, rising to almost 20% in those >60 years. In prosthetic valve endocarditis, 5–10% of cases that occur in the first 60 days post-operatively and up to 15% of cases occurring after 60 days are secondary to enterococcal infection (Mylonakis and Calderwood, 2001). The first case of VRE infective endocarditis was reported in 1996 (Bishara *et al.*, 1999), but subsequent reports in the literature have been rare (Forrest *et al.*, 2011). A study involving a review of 107 cases of enterococcal endocarditis noted no cases secondary to vancomycin resistance (McDonald

Abbreviations: ESKD, end-stage kidney disease; i.v., intravenous; VRE, vancomycin-resistant *Enterococcus*.

et al., 2005). Haemodialysis patients and renal transplant recipients are at relatively high risk of VRE infective endocarditis (Humphreys *et al.*, 2004), and rates of intestinal VRE colonization have been shown to be higher in these groups than in other patient populations (Patel *et al.*, 2001).

There are limited effective antimicrobial treatment options for VRE infections including infective endocarditis. Daptomycin is a concentration-dependent bactericidal lipopeptide antibiotic, licensed in the Republic of Ireland for the treatment of skin and soft tissue infections. It is also licensed for use in the management of *Staphylococcus aureus* bacteraemia, including right-sided endocarditis, at doses of 4 and 6 mg (kg body weight)⁻¹, respectively (Boucher and Sakoulas, 2007). Dose adjustment is required for patients with renal impairment. It is used off label in Ireland to treat patients infected with VRE. It is excreted renally (Hawkey, 2008) and is rapidly bactericidal (Mascio *et al.*, 2007), and had demonstrated *in vitro* concentration-dependent killing with a half-life of 8–9 h (LaPlante and Rybak, 2004). The drug acts on the cell membrane causing membrane depolarization and also inhibits the synthesis of lipoteichoic acid, which is necessary for cell wall synthesis (Enoch *et al.*, 2007). Daptomycin displays *in vitro* activity against >90 % of *Enterococcus* spp., including those resistant to other antibiotics, such as vancomycin, linezolid and quinupristin-dalfopristin (Sader and Jones, 2009). Thickening of the cell wall associated with vancomycin intermediate-susceptible *S. aureus* isolates has been shown to decrease susceptibility to daptomycin and, while an exact resistance mechanism in enterococci has not yet been determined, a similar mechanism secondary to reduced daptomycin diffusion through a thickened enterococcal cell wall has been proposed (Cui *et al.*, 2006; Kelley *et al.*, 2011).

To the best of our knowledge, this is the first report of daptomycin-resistant VRE aortic valve infective endocarditis complicated by end-stage kidney disease (ESKD) in Ireland and one of only nine reports of daptomycin-resistant infective endocarditis globally based on a Pubmed search completed in July 2015. In that search, no reports of such endocarditis complicated by kidney disease could be found.

Case report

The right big toe of a 60-year-old Irish male with ESKD secondary to diabetic nephropathy on haemodialysis became gangrenous secondary to peripheral vascular disease, and he underwent a toe amputation in May 2010. Samples taken from the wound were determined to be positive for VRE (*E. faecium*) and a surveillance rectal swab detected that the patient was VRE colonized. He was commenced on a 5-week course of intravenous (i.v.) linezolid 600 mg twice daily followed by 7 days of oral linezolid 600 mg twice daily with limited resolution. A right mid-foot amputation was performed in September 2010 followed by wound debridement in October 2010. The history of this infected foot dated back to 2008 when he had his first episode of cellulitis requiring antimicrobials. With each

progressively worsening foot infection, the patient was very reluctant to undergo any surgical procedure to remove the nidus of infection, necessitating prolonged antimicrobial exposure. Between October 2009 and January 2010, a 16-week admission occurred for a *Klebsiella pneumoniae* and *Candida albicans* continuous ambulatory peritoneal dialysis-associated peritonitis requiring a protracted prescription of broad-spectrum bacterial and fungal cover. Ultimately, the patient was commenced on haemodialysis.

On 15 July 2011, he was admitted from the dialysis unit with sepsis. Blood samples were taken from the dialysis permacath, which were positive for VRE. Laboratory testing again demonstrated the presence of *E. faecium*, demonstrating the same antibiogram as the earlier VRE cultured in 2010. He was commenced on i.v. linezolid 600 mg twice daily. A transthoracic echocardiogram was performed, which did not show any vegetations suspicious for infective endocarditis. Consecutive blood cultures, 48 h apart, demonstrated evidence of continuous VRE bacteraemia. Sterility of blood was achieved for 22 days until a set of blood cultures taken in early August 2011 again yielded VRE. A transoesophageal echocardiogram identified vegetations on the aortic valve. A decision was made to switch from linezolid 600 mg twice daily to daptomycin 6 mg kg⁻¹ i.v. administered following dialysis sessions. Seven days later, with blood cultures still VRE positive, rifampicin 600 mg twice daily i.v. was added for additional synergistic bactericidal activity as the patient also had an ongoing active foot infection, for which source control had not been achieved. An interdialytic daptomycin dosing regimen was commenced with daptomycin at 8, 8 and 10 mg kg⁻¹ administered post-dialysis at 48, 48 and 72 h, respectively (following consultation with the suppliers of the antimicrobial agents and a review of available literature) (Salama *et al.*, 2009). The patient consistently declined amputation of his right leg during his final admission. Following 17 days of therapy (29 August 2011), we noted daptomycin resistance (MIC > 8 mg l⁻¹) during routine in-house susceptibility testing.

In early September 2011, with worsening necrosis and gangrene of his right leg, confirmed aortic valve endocarditis, unresolving VRE bacteraemia and rising C-reactive protein, together with refusal to consent to a right leg amputation, the patient undertook his own discharge from hospital with rifampicin 600 mg twice daily *per os* and daptomycin 6 mg kg⁻¹ i.v. once daily to be administered intravenously in the community. He continued to deteriorate with persistent VRE bacteraemia. Dialysis was subsequently withdrawn following consultation with the patient and his family, as there was consensus that, given ongoing sepsis from multiple sources, the patient was too unwell to continue with haemodialysis. Antimicrobial therapy also ceased at this time. Palliative care services reviewed the patient and he was admitted to a local hospice where he died 2 weeks later.

Discussion

Patients undergoing outpatient haemodialysis are at high risk of VRE acquisition due to repeated close contact

between patients in the dialysis unit, repeated exposure of patients to antimicrobials including vancomycin for treatment of dialysis line infections (at least in Ireland), shared transport to dialysis units and frequent hospital admissions (Kee *et al.*, 2012). The reliance on central catheters in the dialysis population is thought to be a key factor contributing to the rise of resistant enterococcal isolates (Boucher *et al.*, 2009). To place this case in context, at the time of writing, the University Hospital Limerick dialysis unit is attended by 67 patients of whom 37 are VRE positive. A further 78 attend a satellite dialysis unit in the nearby city centre of whom 11 are known to be VRE positive.

Mortality rates in patients with VRE bloodstream infections are high, ranging between 20 and 46 % (Han *et al.*, 2009; McKinnell *et al.*, 2011; Twilla *et al.*, 2012), and bacterial endocarditis in dialysis patients is associated with poor prognosis (Leither *et al.*, 2013). Surgical management of VRE infective endocarditis is rarely employed, as most patients have significant co-morbidities that would prohibit such invasive intervention (Salgado and Farr, 2003). As a consequence, medical management is the preferred treatment approach. The use of daptomycin as monotherapy for the treatment of VRE endocarditis is not recommended due to increased risk of resistance (Linden, 2007; Schulte *et al.*, 2008). Various mechanisms for enterococcal daptomycin resistance have been described including altered cell membrane composition, altered ability of daptomycin to depolarize the cell (Steed *et al.*, 2011) and the risk of gene transfer of daptomycin-resistant determinants (Kelesidis *et al.*, 2011; Diaz *et al.*, 2014). Concern has also been raised as to whether a tendency to provide empiric VRE cover to at-risk patients with daptomycin and linezolid, while awaiting final culture results, may also be contributing to the development of resistance secondary to overuse (Short *et al.*, 2014).

A published analysis of infective endocarditis cases warned that daptomycin monotherapy for enterococcal infective endocarditis could not be advocated and recommended combination therapy of daptomycin with another antimicrobial such as rifampicin, gentamicin, linezolid or a β -lactam for treatment of VRE endocarditis (Cerón *et al.*, 2014). Similarly, synergistic therapy with daptomycin and rifampicin has been advocated (Leclercq *et al.*, 1991). However, the addition of rifampicin 600 mg twice daily *per os* proved ineffective in our patient.

The appropriate dose of daptomycin for VRE infective endocarditis has not been defined but, as *in vivo* and *in vitro* studies have revealed that using higher doses of daptomycin increases the degree and speed of bactericidal activity due to its concentration-dependent pharmacodynamic mechanism, higher doses than recommended for *S. aureus* bacteraemia (6 mg kg⁻¹ day⁻¹) have been suggested (Cunha *et al.*, 2007; Hall *et al.*, 2012). At 6 mg kg⁻¹ day⁻¹, sterility of blood cultures was not achieved. The use of daptomycin at higher doses of ≥ 8 mg kg⁻¹ day⁻¹ (Kullar *et al.*, 2011, 2013) and 14 mg kg⁻¹ day⁻¹ (Moise *et al.*, 2009) for the treatment of

infective endocarditis have been demonstrated with no adverse patient outcomes. Reported cases of daptomycin resistance have been associated with complicated infections (e.g. osteomyelitis, medical device infections and endocarditis) at doses of ≤ 6 mg kg⁻¹ (Kelesidis *et al.*, 2011). Our attempt at using intradialytic daptomycin at 8, 8 and 10 mg kg⁻¹ post-dialysis at 48, 48 and 72 h, respectively, also failed. There was no rise in creatinine phosphokinase levels with daptomycin therapy over 20 days, which was a positive finding given that rising creatinine phosphokinase levels can often prohibit the use of daptomycin, particularly in those with renal impairment.

We are unaware of any randomized controlled trials that have evaluated the management of VRE infective endocarditis. Linezolid is a bacteriostatic antimicrobial licensed by the US Food and Drug Administration for treatment in this setting, but cure rates remain disappointing (Birmingham *et al.*, 2003; Chuang *et al.*, 2014) and resistance rates of 20 % have been reported (Pogue *et al.*, 2007). The side-effect profile of linezolid with associated myelosuppression, including neutropenia, thrombocytopenia and anaemia (Hachem *et al.*, 2003) is particularly problematic in the dialysis population. Tigecycline has been used in combination with other agents for the treatment of vancomycin-resistant *E. faecium* infections, but it achieves low serum levels and reports of its use are scarce (Florescu *et al.*, 2008; Schutt and Bohm, 2009).

Conclusion

In conclusion, VRE endocarditis is a very uncommon nosocomial infection but is clinically challenging when it arises, given the lack of licensed treatment options. In this case, the same *E. faecium* isolate persisted from multiple sites despite antimicrobial therapy, having probably initially been a rectal colonizer. High-dose daptomycin is generally well tolerated (and we observed no adverse effects in our patient). Ultimately, without amputation and definitive source control, this patient was unlikely to clear his VRE bacteraemia, affording some potential to cure his infective endocarditis. The ethical issues associated with this case are multi-faceted and deserve discussion elsewhere. The rapid emergence of daptomycin resistance following only 20 days of therapy should heighten the awareness of other centres to this possibility in complicated VRE infections. No linezolid resistance was observed in this case.

We continue to monitor for resistance in all patients receiving treatment with daptomycin. The prescription of daptomycin within our institution remains restricted, and is permissible following consultation with clinical microbiology or infectious diseases staff only. To date, no further cases of VRE infective endocarditis or daptomycin resistance have been identified in our institution.

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