J Antimicrob Chemother 2010; **65**: 1126–1136
doi:10.1093/jac/dkq087 Advance publication 2 April 2010

Journal of Antimicrobial Chemotherapy

A potential role for daptomycin in enterococcal infections: what is the evidence?

Rafael Cantón[1,2]*, Patricia Ruiz-Garbajosa[1,2], Ricardo L. Chaves[3] and Alan P. Johnson[4]

[1]*Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain;* [2]*CIBER en Epidemiología y Salud Pública (CIBERESP), Madrid, Spain;* [3]*Novartis Pharma AG, Novartis Campus, CH-4056 Basel, Switzerland;* [4]*Department of Healthcare-Associated Infection and Antimicrobial Resistance, Health Protection Agency Centre for Infections, London NW9 5EQ, UK*

*Corresponding author. Tel: +34-91-336-8330; Fax: +34-91-336-8809; E-mail: rcanton.hrc@salud.madrid.org

Nosocomial infections caused by enterococci present a challenge for clinicians because treatment options are often limited due to the widespread occurrence of strains resistant to multiple antibiotics, including vancomycin. Daptomycin is a first-in-class cyclic lipopeptide that has proven efficacy for the treatment of Gram-positive infections. Although methicillin-resistant *Staphylococcus aureus* has been the most prominent target in the clinical development of daptomycin, this agent has demonstrated potent bactericidal activity in enterococcal infection models and has been used for the treatment of enterococcal infections in humans. In recent years, large-scale susceptibility studies have shown that daptomycin is active against >98% of enterococci tested, irrespective of their susceptibility to other antibacterial agents. This lack of cross-resistance reflects the fact that daptomycin has a mode of action distinct from those of other antibiotics, including glycopeptides. While there are limited data available from randomized controlled trials, extensive clinical experience with daptomycin in enterococcal infections (including bacteraemia, endocarditis, skin and soft tissue infections, bone and joint infections and urinary tract infections) has been reported. This growing body of evidence provides useful insights regarding the efficacy of daptomycin against enterococci in clinical settings.

Keywords: Gram-positive bacteria, cyclic lipopeptide antibiotics, nosocomial infections, vancomycin resistance

Introduction

Enterococci, particularly *Enterococcus faecalis* and *Enterococcus faecium*, are among the leading pathogens isolated from nosocomial infections.[1,2] Despite the availability of a number of antimicrobial agents to treat enterococcal infections, a substantial proportion of patients do not achieve adequate outcomes,[1,3–5] due in part to an increase in the proportion of enterococcal strains that are resistant to one or more of these agents.[6–10] Additional therapeutic options are, therefore, required for effective management of such patients.

Daptomycin is a cyclic lipopeptide that has rapid bactericidal activity against a broad spectrum of Gram-positive bacteria.[11,12] It is indicated for the treatment of complicated skin and soft tissue infections (cSSTIs) caused by susceptible Gram-positive bacteria, right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*, and *S. aureus* bacteraemia (SAB) when associated with RIE or cSSTI.[12] In clinical practice, daptomycin is commonly used to treat enterococcal infections (often in patients with multiple co-morbidities), occasionally at doses higher than 6 mg/kg, the approved dosage to treat SAB.[12]

There is a growing body of *in vitro* and clinical evidence suggesting that daptomycin has good activity against enterococci. This article evaluates the evidence for the role of daptomycin in this clinical setting.

In vitro activity of daptomycin against enterococci

Several studies have compared the activity of daptomycin against clinical isolates of enterococci with those of currently licensed agents (Table 1).[8,9,13–18] In a surveillance study of clinical isolates recovered during 2002–08 in the USA, >99.9% of 4496 *E. faecalis* and >99.5% of 2875 *E. faecium* isolates were susceptible to daptomycin, with MIC_{90}s of 1 and 4 mg/L, respectively.[18] These results were confirmed by European surveillance carried out between 2005 and 2007 that included 3385 strains of enterococci, which showed a daptomycin susceptibility rate of 100%, with the MIC_{90}s of daptomycin for *E. faecalis* and *E. faecium* being 1 and 2 mg/L, respectively.[15] In both studies, the MIC_{90} of daptomycin was at or below the CLSI daptomycin susceptibility breakpoint for enterococci of ≤4 mg/L, which also corresponds to the epidemiological cut-off values for *E. faecalis* and *E. faecium* established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[19,20] Daptomycin demonstrated

Table 1. Susceptibility of enterococci to antibiotic agents in multicentre, comparative studies worldwide

Study year	Region	Source of isolates	*Enterococcus* species	No. of isolates	Daptomycin		Linezolid		Vancomycin		Quinupristin/dalfopristin		Reference
					MIC_{90}	% susceptibility	MIC_{90}	% susceptibility	MIC_{90}	% susceptibility	MIC_{90}	% susceptibility	
2006	USA	bacteraemia, wound or other infections	enterococci	547	2	99.8	2	97.4	>16	71.7	>2	31.1	8
2004–05	Europe	various infection types	VSE	484	4	100	2	99.8	0.5	99.8	ND	ND	9
			VRE	195	4	100	2	100	≥64	21.7	ND	ND	
2007	Europe	various infection types	VSE	542	4	100	2	95.4	0.5	100	ND	ND	9
			VRE	187	4	100	2	95.7	≥64	21.4	ND	ND	
2005–07	Europe	bloodstream, skin or other infections	VSE										15
			E. faecium	853	2	100	2	99.8	1	100	>2	70.6	
			E. faecalis	2133	1	100	2	100	2	100	>2	0.9	
			VRE										
			E. faecium	267	2	100	2	99.3	>16	0	>2	78.3	
			E. faecalis	18	1	100	2	100	>16	0	>2	0	
2002–05	USA/Canada	various infection types	VSE	3336	2	99.9	2	99.8	ND	ND	>2	11.2	14
			VRE	1560	4	99.4	2	98.5	ND	ND	2	86.9	
2005–08	Europe	bloodstream infections	vancomycin-resistant *E. faecium*	134	2	99.3	2	98.5	ND	ND	>2	73.1	16
2005–06	Canada	various infection types in ICU patients	*E. faecalis*	91	1	100	2	92.3	2	97.8	ND	ND	17
			E. faecium	29	2	100	8	34.5	>64	72.4	ND	ND	
			VRE	17	1	100	4	64.7	>64	0	ND	ND	
			other enterococci	135	1	100	2	97.2	2	94.7	ND	ND	
2007–08	USA/Korea	blood or skin infections	*E. faecalis* (USA/Korea)	455	2	100	2	96.9	4	96.0	32	0.9	13
			E. faecium (Korea)	184	4	100	2	95.7	>128	73.4	4	78.8	
			E. faecium (USA)	205	4	98.5	4	85.9	>128	20.0	2	71.7	

ICU, intensive care unit; ND, not determined; VRE, vancomycin-resistant enterococci; VSE, vancomycin-susceptible enterococci.
All MIC data were measured using broth microdilution.

excellent *in vitro* activity against enterococcal isolates recovered from patients at high risk of developing infections due to antibiotic-resistant bacteria, such as patients with cancer or in intensive care units.[17,21] Studies have also shown that other enterococcal species, including *Enterococcus durans, Enterococcus avium, Enterococcus casseliflavus, Enterococcus gallinarum* and *Enterococcus raffinosus*, are susceptible to daptomycin.[22–24]

Activity of daptomycin against enterococci growing as biofilms

Biofilms are populations of bacterial cells attached irreversibly on various human and artificial surfaces and encased in a hydrated matrix mainly composed of exopolymeric substances and polysaccharides. According to the NIH in the USA, biofilms account for >80% of microbial infections in the body.[25] It has been suggested that the ability of enterococci to form biofilms may be facilitated by the production of enterococcal surface protein.[26–28] Enterococci develop persistent biofilms on a wide variety of medical devices that are commonly used in hospitalized patients, and this may partially explain why they are one of the leading causes of nosocomial infections.

Biofilms are difficult to eradicate because they restrict the diffusion and target accessibility of antimicrobial agents. Moreover, bacterial cells in biofilms (sessile bacteria) have slower growth rates and can tolerate 10- to 1000-fold higher concentrations of antibiotics than planktonic bacteria.[27] Therefore, the biofilm matrix is generally considered as a platform for the development of drug-resistant bacteria. The persistence of biofilms on medical devices may contribute to prolonged infection, thereby increasing the opportunity for patient-to-patient transmission.

The eradication of biofilms requires an antibiotic that can effectively penetrate the biofilm matrix and is active against slow-growing bacteria. Daptomycin is bactericidal against stationary-phase bacteria and has good penetration into the biofilm matrix to effectively reduce bacterial growth.[29,30] In contrast, some reports have shown ineffective killing of *E. faecalis* growing in biofilms using vancomycin.[31,32] In an *in vitro* biofilm model (using silicone discs), daptomycin was significantly superior to quinupristin/dalfopristin and linezolid in reducing the growth of vancomycin-resistant *E. faecalis* isolated from patients with catheter-related bacteraemia ($P<0.01$; Table 2).[33]

Table 2. Daptomycin demonstrated superior activity over comparator antibiotics in reducing the growth of 22 vancomycin-resistant *E. faecalis* isolates from catheter-related bacteraemia patients in biofilms (extracted from the study by Raad *et al.*[33])

Antibiotic or control	MIC range (mg/L)	Biofilm (mean cfu per disc ± SEM)[a]
Daptomycin	2.0–8.0	$1.3\times10^2\pm2.7\times10^1$
Minocycline	≥0.06–8.0	$5.6\times10^2\pm1.2\times10^2$
Quinupristin/dalfopristin	≥0.06–2.0	$3.0\times10^3\pm1.8\times10^2$
Linezolid	0.5–2.0	$4.3\times10^3\pm1.4\times10^2$
Control (water)	NA	$5.0\times10^3\pm0$

NA, not applicable; SEM, standard error of the mean.
[a]Colonization data are after 24 h of exposure to 2000 mg/L antibiotic. All antibiotics significantly reduced biofilm colonization compared with the control ($P\leq0.01$). Daptomycin was more effective than minocycline ($P<0.001$). Minocycline was significantly more effective than quinupristin/dalfopristin ($P<0.01$) and quinupristin/dalfopristin was significantly more effective than linezolid ($P<0.01$). A total of 660 discs were tested using six discs per isolate plus a particular antibiotic or water.

Activity of daptomycin against antibiotic-resistant enterococci

The increasing prevalence of infections caused by vancomycin-resistant enterococci (VRE) has been documented globally.[10,34] Enterococcal strains resistant to several non-glycopeptide antibiotic agents, including ampicillin, quinupristin/dalfopristin and/or linezolid, have also been reported.[7–9]

In a recent surveillance study performed across 50 medical centres in the USA, 28% of enterococci isolates were resistant to vancomycin.[8] Moreover, surveillance of enterococcal infections in the USA showed that between 2002 and 2008, only 20.2% of *E. faecium* isolates ($n=2875$) were susceptible to vancomycin.[18] In Europe, the VRE rate increased from 4.5% in 2006 to 10.2% in 2007, although the prevalence varied significantly from country to country. For example, in 2007 there were no reports of VRE in either Switzerland or Spain, but the prevalence of VRE was 25.8% and 23.8% in Ireland and Poland, respectively. Among *E. faecium* strains, the vancomycin resistance rate in Europe increased from 17.9% in 2005 to 26.3% in 2007.[15] Similar trends were seen in the European Antimicrobial Resistance Surveillance System (EARSS).[10,35]

Resistance to vancomycin is conferred by a number of *van* genes, of which *vanA* and *vanB* are the most prevalent.[7,10] In 2007, 76% of VRE isolates in North America and 40% of isolates in Europe exhibited the VanA phenotype.[7] Although the majority of clinical enterococcal isolates are *E. faecalis*, *E. faecium* is the more prevalent species among VRE.[7,28] The increase in the incidence of VRE in the hospital setting is mainly due to the emergence of vancomycin resistance among a subpopulation of *E. faecium* known as clonal complex 17 (CC17).[7,28] Nearly all *E. faecium* isolates belonging to CC17 are resistant to ampicillin and partially resistant to quinolones. CC17 *E. faecium* isolates also possess additional genetic determinants, including putative virulence genes, such as those encoding different cell wall-anchored surface proteins.[28] It appears that a large number of genes acquired by CC17 *E. faecium* contribute to its selective advantage; this, together with its inherent antibiotic resistance, facilitates the further dissemination of VRE in the hospital environment.[28,36] Daptomycin has effective *in vitro* activity against *E. faecium* isolates belonging to CC17 (P. Ruiz-Garbajosa, T. M. Coque, F. Baquero and R. Cantón, unpublished data).

As the mode of action of daptomycin is distinct from that of glycopeptides, its activity against enterococci is unaffected by the presence of the *van* genes. Studies have shown that most enterococci are susceptible to daptomycin, irrespective of their resistance towards vancomycin.[8,14–16,22,37] Among VRE, daptomycin MICs ranged from 1 to 4 mg/L for isolates with the VanA phenotype,[38] and daptomycin was also active against those with VanB or VanC phenotypes.[22] In an analysis of the antimicrobial susceptibility of Gram-positive bacteria collected in European and Israeli medical centres from 2005 to 2007, all 285 VRE

isolates were susceptible to daptomycin. The MIC_{90}s of daptomycin for vancomycin-non-susceptible *E. faecalis* and *E. faecium* were 1 and 2 mg/L, respectively.[15] When tested against bloodstream isolates, 99.3% of vancomycin-resistant *E. faecium* isolates were susceptible to daptomycin, 98.5% to linezolid and 73.1% to quinupristin/dalfopristin.[16] Daptomycin showed greater inhibitory activity against glycopeptide-resistant enterococci (GRE) than linezolid (MIC_{90} 1.5 mg/L versus 4.0 mg/L),[37] and was also more active against VRE than linezolid or quinupristin/dalfopristin in time–kill studies.[11]

Furthermore, *in vitro* time–kill, agar diffusion and chequerboard studies demonstrated synergistic effects of daptomycin with rifampicin or ampicillin against VRE, including linezolid-resistant strains. No antagonism of daptomycin with these agents was seen.[39–41] Other *in vitro* data also showed that daptomycin has non-antagonistic effects with gentamicin and β-lactams against vancomycin-susceptible enterococci and VRE,[42] suggesting that combination therapy may be beneficial in certain clinical situations, such as in neutropenic patients.[43] Nevertheless, clinical data for this beneficial effect are still scarce.

Additional reports have documented that enterococci are frequently also resistant to antibiotics other than vancomycin. In the 2005 SENTRY antimicrobial surveillance programme, which evaluated 953 enterococci isolates from medical centres in 10 European countries, Turkey and Israel, 49.5% and 29.2% of the isolates were resistant to ciprofloxacin and ampicillin, respectively.[44] This could possibly be a consequence of CC17 *E. faecium* expansion.[28] The programme also found quinupristin/dalfopristin to be inactive against 10% of *E. faecium* isolates.[7] As expected, daptomycin activity against enterococci was not influenced by their susceptibility to ampicillin or quinupristin/dalfopristin.[22,45] Furthermore, of 1000 *E. faecium* clinical isolates tested in Greece, 2.5% were resistant to linezolid and 15% were resistant to quinupristin/dalfopristin, but none was resistant to daptomycin. As in previous studies, there were no differences in daptomycin MICs for isolates that were resistant or susceptible to other antibiotics. In particular, the activity of daptomycin was not reduced against enterococci resistant to vancomycin or linezolid.[45] Daptomycin also demonstrated rapid bactericidal activity against ampicillin-resistant enterococci, and its activity was not compromised when tested simultaneously with aminoglycosides.[46] Other *in vitro* studies also showed daptomycin to be bactericidal against aminoglycoside-resistant or penicillinase-producing enterococci.[47]

Linezolid-resistant enterococci have been isolated from clinical specimens.[8,9,48] Surveillance in the USA during 2006 showed that nearly 2% of enterococci tested were resistant to linezolid,[8] while in Europe the frequency of enterococci non-susceptible to linezolid increased from 0.1% in 2004/2005 to 4.7% in 2007.[9] A German study of 60 clinical isolates reported that a high proportion of glycopeptide-resistant *E. faecium* (82%) exhibited intermediate susceptibility to linezolid,[37] which could be due to over-representation of specific GRE strains due to clonal spread.[49,50] In all these studies, daptomycin remained active against enterococci regardless of the susceptibility to linezolid, with MICs ranging from 0.06 to 4 mg/L.[9] In a separate *in vitro* study of linezolid-resistant clinical isolates, daptomycin inhibited all enterococcal isolates ($n=68$) at ≤4 mg/L, and the majority of *E. faecalis* (93.3%) and *E. faecium* (94.3%) strains had daptomycin MICs of ≤1 and ≤2 mg/L, respectively.[51]

Evidence from animal models

In vivo evidence further suggests the efficacy of daptomycin in enterococcal infections, including those involving GRE. In a rat model of endocarditis, daptomycin at standard recommended human doses (6 mg/kg every 24 h) showed similar efficacy to amoxicillin and vancomycin, and was significantly ($P<0.05$) more effective than teicoplanin against glycopeptide-susceptible *E. faecalis* isolates. Moreover, daptomycin was also superior to teicoplanin in the treatment of endocarditis due to VanB vancomycin-resistant *E. faecium*.[52] These results are consistent with the findings of an *in vitro* model of simulated endocardial vegetations. In this model, a simulated regimen of daptomycin at 6 mg/kg every 24 h demonstrated significant bactericidal activity against a strain of vancomycin-resistant *E. faecium*.[53] Another study showed that high-dose daptomycin (12 mg/kg), alone or in combination with gentamicin, was effective in a rabbit model of endocarditis caused by *E. faecium*.[54] Daptomycin also showed rapid bactericidal activity against vancomycin-resistant *E. faecium* in a pharmacodynamic model, with no development of resistance despite subinhibitory antimicrobial activity.[55] In addition, studies with murine renal and thigh infection models showed that clinically relevant exposure to daptomycin was effective against enterococci.[56,57]

Complementing data from *in vitro* time–kill studies, daptomycin demonstrated excellent bactericidal activity and dose-dependent reductions in bacterial counts in these animal models, supporting the potential benefits for the treatment of enterococcal infections in humans.

Clinical experience with daptomycin in enterococcal infections

Considerable clinical experience with daptomycin in enterococcal infections is available in the form of published case reports, case series and the Cubicin Outcomes Registry and Experience (CORE®) database. CORE is a retrospective, post-marketing database that includes information on prescribing patterns and outcomes with daptomycin therapy in the USA.[58]

Bacteraemia

Using the CORE database, Mohr *et al.*[59] analysed clinical outcomes of patients with enterococcal bacteraemia who were treated with daptomycin. A total of 159 patients with enterococcal bacteraemia, comprising 120 patients with *E. faecium* (91% vancomycin resistant) and 39 with *E. faecalis* (23% vancomycin resistant), were treated with daptomycin either as first-line therapy (17%) or after prior treatment with other antibiotic agents.[59] The overall clinical success rate was 87%, with similar rates between patients infected with *E. faecium* (87%) and those infected with *E. faecalis* (90%). Clinical outcomes were not influenced by the use of concomitant antibiotic therapy, and clinical success was reported in 87% of those patients who received prior vancomycin and 88% of patients who did not. The clinical outcome in relation to dosage schedule for daptomycin was not reported.[59]

Vancomycin resistance is independently associated with increased mortality among patients with bacteraemia due to

enterococci.[60,61] The fact that patients with bacteraemia due to VRE are also less likely to receive appropriate therapy than those with vancomycin-susceptible enterococcal bloodstream infections[62,63] highlights a lack of appropriate therapeutic options for these patients. The Infectious Diseases Society of America 2009 guidelines recommend the use of daptomycin for the treatment of catheter-related bacteraemia due to VRE or ampicillin-resistant enterococci in patients with or without dialysis.[64]

A recent retrospective chart review included the medical records of 30 patients with bacteraemia due to VRE who received a median daptomycin dose of 6 mg/kg (range, 3.7–8 mg/kg). All isolates were susceptible to daptomycin, with MICs ranging from <1 to 4 mg/L, and this is reflected in the microbiological cure rate of 80%, while clinical success was observed in 17 patients (59%). The authors suggested that the efficacy rate of daptomycin would have been higher if all patients received a 6 mg/kg/dose.[65] Segreti *et al.*[66] also reported a retrospective series of patients with bacteraemia due to Gram-positive bacteria who were treated with daptomycin. Among nine patients with bacteraemia without endocarditis due to VRE (most of whom had received previous therapy with vancomycin or linezolid), five achieved successful resolution of infection after treatment with daptomycin at 4–6 mg/kg (four received monotherapy and one received daptomycin in combination with tobramycin). Treatment was not successful in the remaining four patients who received 6 mg/kg daptomycin (three received concomitant aminoglycosides). All four of these patients died, but they all had other serious co-morbidities.[66] Two cases of bacteraemia due to VRE successfully treated with daptomycin at a dosage of 4 mg/kg were reported by Kvirikadze *et al.*;[67] a further case reported a patient with bacteraemia caused by a vancomycin-susceptible strain of *E. faecalis* unresponsive to vancomycin therapy who was also treated successfully with 12 mg/kg daptomycin.[68] Although daptomycin is not approved for the treatment of enterococcal bacteraemia, there is growing evidence from clinical practice that doses higher than the currently approved dose (e.g. 8–12 mg/kg once a day) may be required for optimal treatment of complicated enterococcal infections.[69–71]

Several reports have focused on the use of daptomycin for the treatment of enterococcal bacteraemia in neutropenic patients. In a study of 92 allogeneic haematopoietic stem cell recipients, 34 patients developed bloodstream infections, of which 14 (41%) were due to VRE (13 *E. faecium* and 1 *E. avium*). Ten of these patients received daptomycin, three of whom were reported as microbiological failures; however, the infecting strains remained susceptible to daptomycin *in vitro* in all three cases. This observation, coupled with the fact that all 10 patients treated with daptomycin had also received linezolid or other antibiotics, highlights the inherent difficulty in interpreting microbiological outcomes. In addition, the clinical picture was complicated by the presence of underlying conditions in these patients and the absence of a comparator group.[72] Nine febrile neutropenic patients with bacteraemia due to VRE (eight *E. faecium* and one *E. faecalis*) were treated with daptomycin in an open-label emergency-use trial. Four patients (44%) achieved clinical and/or microbiological cure; two patients died within 3 days of commencement of treatment, indicating the severity of their illnesses. No correlation between clinical or microbiological outcome and daptomycin dose (4 or 6 mg/kg) was apparent; in fact, the small number of patients makes it difficult to draw meaningful conclusions from this study.[69] More recently, treatment failure was observed in 13 of 31 bacteraemic patients treated with daptomycin, 6 of which were due to relapses within 1 month of initiation of initial infection.[73]

Successful treatment with daptomycin combination therapy in patients with bacteraemia has also been reported.[43,74] In one case, a 21-day-old full-term infant developed bacteraemia due to vancomycin-resistant *E. faecium* 10 days after heart surgery (endocarditis was suspected but not confirmed). Bacteraemia persisted despite the removal of vascular catheters and treatment with antibiotics (including linezolid, quinupristin/dalfopristin, ampicillin/sulbactam and rifampicin). Microbiological cure was achieved with a combination regimen that initially included daptomycin (4 mg/kg every 48 h) in combination with gentamicin, but with the dose of daptomycin subsequently increased to 6 mg/kg every 24 h in combination with gentamicin and doxycycline.[74]

Two retrospective studies have attempted to compare daptomycin with linezolid for the treatment of bacteraemia due to VRE. In a study by Mave *et al.*[75] in 98 adult patients, 68 of whom received linezolid and 30 of whom received daptomycin, the microbiological cure rates were 88.2% and 90%, respectively. No statistically significant differences in clinical outcomes were observed. Differences in the baseline characteristics of the treatment groups (significantly higher proportions of patients in intensive care units and patients with concomitant SAB in the daptomycin group) precluded any conclusive statements about the comparative performance of the two compounds. Similar results were described for daptomycin and linezolid in a study of neutropenic cancer patients by Marion *et al.*[76] Clearance of blood cultures was seen in 17 (81%) of 21 patients who received daptomycin, and 8 (80%) of 10 patients who were treated with linezolid. Relapse of infection was seen in 19.1% and 20% of the patient treatment groups, respectively. Overall mortality in the two patient cohorts was 52.3% and 60%, respectively.[76]

Infective endocarditis (IE)

In an analysis of the CORE database, *Enterococcus* was identified as the primary pathogen in 14 of 49 patients with IE. Clinical success was reported in 10 of 14 patients [9 with left-sided IE (LIE) and 1 with RIE], and 2 patients failed daptomycin therapy (1 with LIE and 1 with RIE). Outcomes were not evaluable for the remaining two patients.[77] Case reports of daptomycin for IE caused by *Enterococcus* spp. have yielded various outcomes, including death in some cases (Table 3). It should be noted, however, that all patients in these cases had significant underlying co-morbidities, with the majority failing prior antibiotic treatment. Daptomycin was usually given in combination with other antibiotics with no standardization as to concomitant treatment, and it was unclear whether cases of mortality were attributable to endocarditis or the underlying co-morbidity.

One recent case report detailed successful combination treatment with high-dose daptomycin (8 mg/kg every 24 h), gentamicin (1 mg/kg every 12 h) and ampicillin (16 g every 24 h) in a patient with LIE caused by a strain of *E. faecium* 'heteroresistant' to vancomycin, but susceptible to daptomycin (MIC < 4 mg/L). Previous treatment with daptomycin (6 mg/kg) monotherapy cleared blood cultures, but persistent vegetation was detected 5 weeks after the start of treatment and the patient refused

Table 3. Case reports of endocarditis due to vancomycin-resistant enterococci treated with daptomycin

Patient			Dose	Pathogen	Concomitant			
age	sex	Underlying conditions	(mg/kg)	(all VAN-resistant)	antibiotics	Prior antibiotics	Outcome	Reference
64	F	haemodialysis, prosthetic valve	6	*Enterococcus* spp.[a]	TOB	none	died	66[b]
51	M	not reported	6	*Enterococcus* spp.[a]	AMK	VAN	died	66[b]
25	F	SLE, ESRD	8	*E. faecium*	GEN, RIF	LZD	died	103
62	M	diabetes, coronary and peripheral arterial disease, ESRD	6	*E. faecium*	TGC	VAN, LZD, MEM, FLC	recovered	104
60	M	diabetes	6/8[c]	*E. faecium*	AMP, GEN	FEP, VAN	recovered	78
13	M	GVHD, pancreatitis	6/8[c]	*E. faecium*	NR	VAN, MEM, GEN	died	105
70	M	renal failure (receiving haemodialysis)	6/8[c]	*E. faecium*	GEN, DOX	LZD	failure	106

AMK, amikacin; AMP, ampicillin; DOX, doxycycline; ESRD, end-stage renal disease; F, female; FEP, cefepime; FLC, fluconazole; GEN, gentamicin; GVHD, graft-versus-host disease; LZD, linezolid; M, male; MEM, meropenem; NR, not reported; RIF, rifampicin; SLE, systemic lupus erythematosus; TGC, tigecycline; TOB, tobramycin; VAN, vancomycin.
[a]Species not stated.
[b]Patients who were included in a CORE analysis.
[c]Initial dose of 6 mg/kg increased to 8 mg/kg.

valve replacement. Daptomycin monotherapy was halted and substituted by vancomycin plus gentamicin. These therapies were subsequently stopped after detection of VRE in blood cultures. Finally, the combination of high-dose daptomycin (8 mg/kg every 24 h), gentamicin and high-dose ampicillin (16 g every 24 h), given over 6 weeks, cured the infection.[78] In a separate case of endocarditis due to a strain of linezolid-resistant VRE (MICs: linezolid, 12 mg/L; and daptomycin, 3 mg/L), and the patient was successfully treated with high-dose daptomycin (started at 6 mg/kg every 24 h and subsequently increased to 8 mg/kg every 24 h) in combination with rifampicin, gentamicin and tigecycline.[79] Despite this evidence, more clinical data are needed to define the role of daptomycin (alone or in combination) therapy in enterococcal endocarditis.

Skin and soft tissue infections (including surgical site infections)

In the pivotal studies, *E. faecalis* was the third most frequently treated pathogen (11.8%), and the clinical success rate among patients with cSSTI due to *E. faecalis* was 73.0% for daptomycin and 75.5% for the comparators (cloxacillin, flucloxacillin, nafcillin, oxacillin or vancomycin).[80] A report from the CORE database analysing patients with surgical site infections found that *Enterococcus* spp. were the second most common pathogen, being isolated from 23 (22%) of 104 evaluable patients. Eight of these 23 patients had VRE (7 *E. faecium*), of which 5 had organ/space infection. *Enterococcus* was considered to be the primary pathogen in 16 of these 23 patients, with clinical success reported for 14 (88%) patients. The success rate for patients with any VRE was 63% (five of eight patients). VRE was found to be an independent risk factor for treatment failure (odds ratio 14.2; 95% confidence interval 1.3–154).[81]

In an analysis of 522 evaluable patients with skin and soft tissue infections registered in the CORE database in 2004, 337 patients (65%) yielded Gram-positive pathogens on culture, 63 (19%) of which were *Enterococcus* spp. that included 28 VRE cases. In 48 patients where an *Enterococcus* sp. was considered to be the primary pathogen, clinical success was noted in 44 patients (92%).[82]

Bone and joint infections

The CORE database also collects data for patients receiving daptomycin for the treatment of osteomyelitis.[83] Clinical outcomes were evaluated at the end of therapy (EOT group) and for patients who had one or more follow-up post-treatment assessments 3–13 months after the end of therapy (PT group). Of 148 patients with osteomyelitis registered during 2004, 12 and 8 patients in the EOT and PT groups, respectively, had infections due to enterococci. Outcomes for patients in the EOT group with enterococcal infections were not reported, but six of the eight patients in the PT group where enterococci were considered to be the primary pathogen were reported as having successful clinical outcomes, while two patients failed therapy. This was similar to the overall clinical success rate of 82% (55 of 67 patients) in the PT group.

Other infections

A small number of publications documenting the use of daptomycin for the treatment of other enterococcal infections have appeared recently in the literature. Two reports concerned lower urinary tract infections (UTIs), which is a potential area of interest because ~50% of the daptomycin dose is excreted as unchanged drug in urine over 24 h following intravenous administration.[84] One open-label, single-blinded study compared daptomycin and ciprofloxacin for the treatment of adults with complicated UTIs caused by Gram-positive pathogens.[85] A total of 68 patients were randomized to receive daptomycin (4 mg/kg every 24 h) or ciprofloxacin (400 mg every 12 h) for 5–14 days. Of 45 patients treated for enterococcal UTI,

Table 4. Case reports of infections with daptomycin-non-susceptible enterococci isolates

Patient		Underlying conditions	Indication for DAP use		DAP treatment	DAP MIC, mg/L	Other antibiotic used/surgery	Final outcome	Reference
age	sex		pathogen	type of infection					
53	M	NR	VAN-resistant *E. faecalis*	endocarditis (mitral valve)	6 mg/kg every 24 h for 8 weeks (followed by mitral valve replacement)	>8 (Etest)	prior: NAF, VAN follow-on: LZD	bacteraemia 10 days after discharge and died soon afterwards	96
55	F	diabetes mellitus, haemodialysis, AICD	*E. faecalis*	endocarditis (aortic valve)	6 mg/kg every 48 h	32 (microdilution)	follow-on: AMP, GEN, aortic valve replacement, tricuspid valvuloplasty, removal of AICD	cured	97
22	M	Hodgkin's lymphoma, AML, testicular carcinoma	VAN-resistant *E. faecium*, *E. coli*	bacteraemia	6 mg/kg every 24 h for 17 days	>32 (microdilution)	prior: DOX, FEP, VAN, metronidazole concomitant: MEM follow-on: LZD, DOX, catheter removal	cured	98
37	F	AML	VAN-resistant *E. faecium*	bacteraemia	6 mg/kg for 17 days	>32 (microdilution)	prior: TZP, GEN, VAN, AMB, VRC follow-on: LZD, catheter removal	recurrence of VRE bacteraemia	99
62	F	myelofibrosis, GVHD	VAN-resistant *E. durans*	bacteraemia	6 mg/kg every 48 h for 20 days	32 (Etest)	prior: FEP, LVX follow-on: LZD, catheter removal	cured	95
NR	M	Crohn's disease	VAN-resistant *E. faecium*	bacteraemia	NR	16 (Etest)	prior: Q/D	NR	94
64	F	cryptogenic cirrhosis, haemodialysis	VAN-resistant *E. faecalis*	bacteraemia	400 mg every 48 h for ~14 days	16 (microdilution)	prior: LZD concomitant: AMK follow-on: LZD, AMP	died	100

AICD, automated implantable cardioverter-defibrillator; AMB, amphotericin B; AMK, amikacin; AML, acute myeloid leukaemia; AMP, ampicillin; DAP, daptomycin; DOX, doxycycline; F, female; FEP, cefepime; GEN, gentamicin; GVHD, graft-versus-host disease; LVX, levofloxacin; LZD, linezolid; M, male; MEM, meropenem; NAF, nafcillin; NR, not reported; Q/D, quinupristin/dalfopristin; TZP, piperacillin/tazobactam; VAN, vancomycin; VRC, voriconazole; VRE, vancomycin-resistant enterococci.

22 patients with *E. faecalis* infections received daptomycin and 23 (21 with *E. faecalis* and 2 with *E. faecium* infections) received ciprofloxacin. The microbiological eradication rate was 81.8% (18 of 22 patients) for daptomycin and 78.3% (18 of 23 patients) for ciprofloxacin.[85] In a separate report, five hospitalized patients with UTIs due to multidrug-resistant VRE (species not indicated) were treated with 250 mg/day of daptomycin (equivalent to 1.4–3.7 mg/kg) for 5 days, because the authors speculated that urinary accumulation of daptomycin should allow for lower dosing. In all five patients, urine cultures 2 days after completion of therapy were negative, and follow-up 10–14 days after therapy revealed no recurrence of bacteriuria.[86] It should be noted that patients with enterococcal UTIs may be at risk of complications such as bacteraemia, and no strong rationale exists for the use of daptomycin doses lower than those doses shown to be safe in clinical studies,[80,87] and subsequently approved for cSSTI (4 mg/kg) and SAB with or without IE (6 mg/kg).[12]

Daptomycin has also been used successfully in two patients receiving peritoneal dialysis for end-stage renal disease who developed peritonitis due to VRE.[88] Each patient was treated for 10 or 14 days with intraperitoneal daptomycin (20 mg/L), given every 4 h through peritoneal dialysate exchanges. The treatment was successful despite the known degradation of daptomycin in dextrose solution. A separate case report also showed that intraperitoneal daptomycin (15 mg/kg once weekly) was successful in the treatment of continuous ambulatory peritoneal dialysis-related peritonitis due to vancomycin-resistant *E. faecium*.[89]

Successful treatment of external ventricular drain-associated ventriculitis caused by *E. faecalis* with intraventricular daptomycin has also been reported.[90]

Resistance of enterococci to daptomycin

Neither the CLSI nor the EUCAST committees have defined resistance breakpoints for enterococci to daptomycin. According to the CLSI, enterococci isolates with daptomycin MICs ≤4 mg/L are considered susceptible to the drug. Only rare occurrences of isolates displaying MIC values higher than the susceptible breakpoint have been described.[20,91] Moreover, enterococci with daptomycin MICs >4 mg/L (CLSI susceptible breakpoint of ≤4 mg/L) are often designated as resistant or as non-susceptible.

Few *in vitro* resistance studies have been performed with daptomycin and enterococci, and the mechanism underpinning this resistance remains to be elucidated. Spontaneous resistance to daptomycin in enterococci occurs rarely *in vitro*, with frequencies $<10^{-9}$.[92] In one study, enterococci and staphylococci obtained from agar plates that contained daptomycin (at concentrations above the MIC) failed to grow when subcultured on daptomycin-containing agar plates. After purification on agar plates without daptomycin, these bacteria exhibited MICs identical to those for the parent strains. This suggested that susceptibility to daptomycin is heterogeneous.[92]

Daptomycin-non-susceptible *E. faecium* (with an MIC of 6 mg/L) was recovered from a patient with bacteraemia who had no previous exposure to daptomycin.[93] However, the study did not investigate the potential mechanisms underlying the reduced susceptibility of daptomycin. Treatment failures of enterococcal infections associated with reduced daptomycin susceptibility have been reported (Table 4),[94–100] including five cases of bacteraemia[94,95,98–100] and two cases of endocarditis.[96,97] The majority of these infections were due to VRE.[94–96,98–100] In six out of these seven treatment failure cases, patients had received daptomycin treatment prior to the detection of a resistant strain, suggesting that the resistance developed during treatment;[95–100] however, it is difficult to draw firm conclusions regarding this because baseline MICs for daptomycin were not available in most cases.[94–97,99,100] The daptomycin MICs for these *E. faecium* and *E. faecalis* isolates ranged from >8 to >32 mg/L[94,98,99] and from >8 to 32 mg/L,[96,97,100] respectively. The conditions of these patients were complicated by other underlying diseases. Five of these cases involved foreign bodies,[95–98,100] and the removal of prosthetic devices was delayed in four cases.[95–98] Furthermore, the daptomycin doses used in three of six cases with a known dosing regimen were <6 mg/kg every 24 h, which may be suboptimal for the treatment of enterococcal endocarditis or bacteraemia (the CLSI susceptibility breakpoint and the EUCAST epidemiology cut-off value for enterococci are greater than that for *S. aureus*).[12,19,20,87,101,102]

Conclusions

Treatment for enterococcal infections is becoming increasingly challenging, because enterococci may develop resistance to existing therapies and there is a paucity of therapeutic options against multidrug-resistant enterococci. Using the CLSI breakpoint of ≤4 mg/L and the EUCAST epidemiological cut-off value of 4 mg/L, microbiological data show that the large majority of clinical enterococcal isolates are susceptible to daptomycin. Furthermore, daptomycin is not associated with cross-resistance to other antimicrobials and is active against most isolates of antibiotic-resistant enterococci, including VRE. Current clinical practice suggests that daptomycin alone or combined with other agents can achieve favourable outcomes in patients with enterococcal infections, including those with multiple co-morbidities. Further clinical experience, including additional safety and efficacy studies with higher doses of daptomycin (8–12 mg/kg), will be useful in better characterizing the role of daptomycin in enterococcal infections.

Funding

This work, including writing support, was funded by Novartis Pharma AG.

Transparency declarations

R. C. and A. P. J. have received honoraria for speaking from Novartis and Pfizer. P. R.-G. has no conflicts of interest to declare. R. L. C. is an employee of Novartis Pharma AG, and as such owns stock options with the company. R. L. C. has no other conflicts of interest to declare.

The authors did not receive honoraria for writing this article.

A. P. J. is Editor-in-Chief of *JAC*, but took no part in, and did not influence, the editorial process.

Writing support for the preparation of this manuscript was provided by Magdalene Chu, of Chameleon Communications International.

References

1 Fisher K, Phillips C. The ecology, epidemiology and virulence of *Enterococcus*. *Microbiology* 2009; **155**: 1749–57.

2 Hidron AI, Edwards JR, Patel J *et al*. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. *Infect Control Hosp Epidemiol* 2008; **29**: 996–1011.

3 Birmingham MC, Rayner CR, Meagher AK *et al*. Linezolid for the treatment of multidrug-resistant, Gram-positive infections: experience from a compassionate-use program. *Clin Infect Dis* 2003; **36**: 159–68.

4 Florescu I, Beuran M, Dimov R *et al*. Efficacy and safety of tigecycline compared with vancomycin or linezolid for treatment of serious infections with methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci: a Phase 3, multicentre, double-blind, randomized study. *J Antimicrob Chemother* 2008; **62** Suppl 1: i17–i28.

5 Moellering RC, Linden PK, Reinhardt J *et al*. The efficacy and safety of quinupristin/dalfopristin for the treatment of infections caused by vancomycin-resistant *Enterococcus faecium*. Synercid Emergency-Use Study Group. *J Antimicrob Chemother* 1999; **44**: 251–61.

6 Arias CA, Murray BE. Emergence and management of drug-resistant enterococcal infections. *Expert Rev Anti Infect Ther* 2008; **6**: 637–55.

7 Deshpande LM, Fritsche TR, Moet GJ *et al*. Antimicrobial resistance and molecular epidemiology of vancomycin-resistant enterococci from North America and Europe: a report from the SENTRY antimicrobial surveillance program. *Diagn Microbiol Infect Dis* 2007; **58**: 163–70.

8 Jones RN, Fritsche TR, Sader HS *et al*. LEADER surveillance program results for 2006: an activity and spectrum analysis of linezolid using clinical isolates from the United States (50 medical centers). *Diagn Microbiol Infect Dis* 2007; **59**: 309–17.

9 Morrissey I. Daptomycin susceptibility of contemporary Gram-positive pathogens circulating in Europe between 2004 and 2007. In: *Abstracts of the Nineteenth European Congress of Clinical Microbiology and Infectious Diseases, Helsinki, 2009*. Abstract P1626. European Society of Clinical Microbiology and Infectious Diseases, Basel, Switzerland.

10 Werner G, Coque T, Hammerum A *et al*. Emergence and spread of vancomycin resistance among enterococci in Europe. *Euro Surveill* 2008; **13**: 19046.

11 Rybak MJ, Hershberger E, Moldovan T *et al*. *In vitro* activities of daptomycin, vancomycin, linezolid, and quinupristin-dalfopristin against staphylococci and enterococci, including vancomycin-intermediate and -resistant strains. *Antimicrob Agents Chemother* 2000; **44**: 1062–6.

12 Novartis Europharm Ltd. *Cubicin (daptomycin) Summary of Product Characteristics*. 2009. http://www.ema.europa.eu/humandocs/PDFs/EPAR/cubicin/emea-combined-h637en.pdf/ (9 February 2010, date last accessed).

13 Badal R, Bouchillon S, Hoban D *et al*. A multicenter evaluation of *in vitro* activity of oritavancin and comparators against staphylococci, enterococci and streptococci—the ORION study. In: *Abstracts of the Nineteenth European Congress of Clinical Microbiology and Infectious Diseases, Helsinki, 2009*. Abstract P1618. European Society of Clinical Microbiology and Infectious Diseases, Basel, Switzerland.

14 Pfaller MA, Sader HS, Jones RN. Evaluation of the *in vitro* activity of daptomycin against 19615 clinical isolates of Gram-positive cocci collected in North American hospitals (2002–2005). *Diagn Microbiol Infect Dis* 2007; **57**: 459–65.

15 Sader HS, Moet GJ, Jones RN. Update on the *in vitro* activity of daptomycin tested against 17,193 Gram-positive bacteria isolated from European medical centers (2005–2007). *J Chemother* 2009; **21**: 500–6.

16 Sader HS, Mendes RE, Jones RN. Prevalence and antimicrobial susceptibility patterns of methicillin-resistant *S. aureus* and vancomycin-resistant *E. faecium* causing bloodstream infections in European hospitals (2005–2008). In: *Abstracts of the Nineteenth European Congress of Clinical Microbiology and Infectious Diseases, Helsinki, 2009*. Abstract P1720. European Society of Clinical Microbiology and Infectious Diseases, Basel, Switzerland.

17 Zhanel GG, DeCorby M, Nichol KA *et al*. Antimicrobial susceptibility of 3931 organisms isolated from intensive care units in Canada: Canadian National Intensive Care Unit Study, 2005/2006. *Diagn Microbiol Infect Dis* 2008; **62**: 67–80.

18 Sader HS, Jones RN. Evaluation of daptomycin activity tested against 35,058 bacterial strains from hospitalized patients: summary of a 7 year surveillance program for North America (2002–2008). In: *Abstracts of the Forty-seventh Annual Meeting of the Infectious Diseases Society of America, Philadelphia, PA, 2009*. Abstract P199. Infectious Diseases Society of America, Arlington, VA, USA.

19 Data from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) web site. http://www.eucast.org/ (1 November 2009, date last accessed).

20 Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing: Eighteenth Informational Supplement M100-S18*. CLSI, Wayne, PA, USA, 2008.

21 Sader HS, Fritsche TR, Jones RN. Frequency of occurrence and daptomycin susceptibility rates of Gram-positive organisms causing bloodstream infections in cancer patients. *J Chemother* 2008; **20**: 570–6.

22 Jorgensen JH, Crawford SA, Kelly CC *et al*. *In vitro* activity of daptomycin against vancomycin-resistant enterococci of various Van types and comparison of susceptibility testing methods. *Antimicrob Agents Chemother* 2003; **47**: 3760–3.

23 Streit JM, Jones RN, Sader HS. Daptomycin activity and spectrum: a worldwide sample of 6737 clinical Gram-positive organisms. *J Antimicrob Chemother* 2004; **53**: 669–74.

24 Piper KE, Steckelberg JM, Patel R. *In vitro* activity of daptomycin against clinical isolates of Gram-positive bacteria. *J Infect Chemother* 2005; **11**: 207–9.

25 NIH. *Research on Microbial Biofilms*. http://grants.nih.gov/grants/guide/pa-files/PA-03-047.html/ (18 June 2009, date last accessed).

26 Heikens E, Bonten MJ, Willems RJ. Enterococcal surface protein Esp is important for biofilm formation of *Enterococcus faecium* E1162. *J Bacteriol* 2007; **189**: 8233–40.

27 Mohamed JA, Huang DB. Biofilm formation by enterococci. *J Med Microbiol* 2007; **56**: 1581–8.

28 Willems RJ, Bonten MJ. Glycopeptide-resistant enterococci: deciphering virulence, resistance and epidemicity. *Curr Opin Infect Dis* 2007; **20**: 384–90.

29 Mascio CT, Alder JD, Silverman JA. Bactericidal action of daptomycin against stationary-phase and nondividing *Staphylococcus aureus* cells. *Antimicrob Agents Chemother* 2007; **51**: 4255–60.

30 Stewart PS, Davison WM, Steenbergen JN. Daptomycin rapidly penetrates a *Staphylococcus epidermidis* biofilm. *Antimicrob Agents Chemother* 2009; **53**: 3505–7.

31 LaPlante KL, Mermel LA. *In vitro* activities of telavancin and vancomycin against biofilm-producing *Staphylococcus aureus*, *S. epidermidis* and *Enterococcus faecalis*. *Antimicrob Agents Chemother* 2009; **53**: 3166–9.

32 Sandoe JA, Wysome J, West AP *et al*. Measurement of ampicillin, vancomycin, linezolid and gentamicin activity against enterococcal biofilms. *J Antimicrob Chemother* 2006; **57**: 767–70.

33 Raad II, Hanna HA, Boktour M *et al*. Vancomycin-resistant *Enterococcus faecium*: catheter colonization, *esp* gene, and decreased susceptibility to antibiotics in biofilm. *Antimicrob Agents Chemother* 2005; **49**: 5046–50.

34 Johnson AP, Uttley AH, Woodford N *et al*. Resistance to vancomycin and teicoplanin: an emerging clinical problem. *Clin Microbiol Rev* 1990; **3**: 280–91.

35 European Antimicrobial Resistance Surveillance System (EARSS). http://www.rivm.nl/earss/database/ (1 September 2009, date last accessed).

36 Coque TM, Willems RJ, Fortun J *et al*. Population structure of *Enterococcus faecium* causing bacteremia in a Spanish university hospital: setting the scene for a future increase in vancomycin resistance? *Antimicrob Agents Chemother* 2005; **49**: 2693–700.

37 Abb J. *In vitro* activities of tigecycline, daptomycin, linezolid and quinupristin/dalfopristin against glycopeptide-resistant *Enterococcus faecium*. *Int J Antimicrob Agents* 2007; **29**: 358–60.

38 Stylianakis A, Tsiplakou S, Papaioannou V *et al*. *In vitro* activity of daptomycin against various VanA VRE species derived from clinical specimens. In: *Abstracts of the Eighteenth European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, 2008*. Abstract P1720. European Society of Clinical Microbiology and Infectious Diseases, Basel, Switzerland.

39 Pankey G, Ashcraft D, Patel N. *In vitro* synergy of daptomycin plus rifampin against *Enterococcus faecium* resistant to both linezolid and vancomycin. *Antimicrob Agents Chemother* 2005; **49**: 5166–8.

40 Rand KH, Houck H. Daptomycin synergy with rifampicin and ampicillin against vancomycin-resistant enterococci. *J Antimicrob Chemother* 2004; **53**: 530–2.

41 Steenbergen JN, Mohr JF, Thorne GM. Effects of daptomycin in combination with other antimicrobial agents: a review of *in vitro* and animal model studies. *J Antimicrob Chemother* 2009; **64**: 1130–8.

42 Snydman DR, McDermott LA, Jacobus NV. Evaluation of *in vitro* interaction of daptomycin with gentamicin or β-lactam antibiotics against *Staphylococcus aureus* and enterococci by FIC index and timed-kill curves. *J Chemother* 2005; **17**: 614–21.

43 Barber GR, Lauretta J, Saez R. A febrile neutropenic patient with *Enterococcus gallinarum* sepsis treated with daptomycin and gentamicin. *Pharmacotherapy* 2007; **27**: 927–32.

44 Sader HS, Watters AA, Fritsche TR *et al*. Daptomycin antimicrobial activity tested against methicillin-resistant staphylococci and vancomycin-resistant enterococci isolated in European medical centers (2005). *BMC Infect Dis* 2007; **7**: 29.

45 Malli E, Spiliopoulou I, Kolonitsiou F *et al*. *In vitro* activity of daptomycin against Gram-positive cocci: the first multicentre study in Greece. *Int J Antimicrob Agents* 2008; **32**: 525–8.

46 el Mady A, Mortensen JE. The bactericidal activity of ampicillin, daptomycin, and vancomycin against ampicillin-resistant *Enterococcus faecium*. *Diagn Microbiol Infect Dis* 1991; **14**: 141–5.

47 Wanger AR, Murray BE. Activity of LY146032 against enterococci with and without high-level aminoglycoside resistance, including two penicillinase-producing strains. *Antimicrob Agents Chemother* 1987; **31**: 1779–81.

48 Allen GP, Bierman BC. *In vitro* analysis of resistance selection by linezolid in vancomycin-susceptible and -resistant *Enterococcus faecalis* and *Enterococcus faecium*. *Int J Antimicrob Agents* 2009; **34**: 21–4.

49 Theilacker C, Jonas D, Huebner J *et al*. Outcomes of invasive infection due to vancomycin-resistant *Enterococcus faecium* during a recent outbreak. *Infection* 2009; **37**: 540–3.

50 Schulte B, Heininger A, Autenrieth IB *et al*. Emergence of increasing linezolid-resistance in enterococci in a post-outbreak situation with vancomycin-resistant *Enterococcus faecium*. *Epidemiol Infect* 2008; **136**: 1131–3.

51 Mendes RE, Jones RN, Deshpande LM *et al*. Daptomycin activity tested against linezolid-nonsusceptible gram-positive clinical isolates. *Microb Drug Resist* 2009; **15**: 245–9.

52 Vouillamoz J, Moreillon P, Giddey M *et al*. Efficacy of daptomycin in the treatment of experimental endocarditis due to susceptible and multidrug-resistant enterococci. *J Antimicrob Chemother* 2006; **58**: 1208–14.

53 Akins RL, Rybak MJ. Bactericidal activities of two daptomycin regimens against clinical strains of glycopeptide intermediate-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium*, and methicillin-resistant *Staphylococcus aureus* isolates in an *in vitro* pharmacodynamic model with simulated endocardial vegetations. *Antimicrob Agents Chemother* 2001; **45**: 454–9.

54 Caron F, Kitzis MD, Gutmann L *et al*. Daptomycin or teicoplanin in combination with gentamicin for treatment of experimental endocarditis due to a highly glycopeptide-resistant isolate of *Enterococcus faecium*. *Antimicrob Agents Chemother* 1992; **36**: 2611–6.

55 Cha R, Grucz RG Jr, Rybak MJ. Daptomycin dose-effect relationship against resistant Gram-positive organisms. *Antimicrob Agents Chemother* 2003; **47**: 1598–603.

56 Alder J, Li T, Yu D *et al*. Analysis of daptomycin efficacy and breakpoint standards in a murine model of *Enterococcus faecalis* and *Enterococcus faecium* renal infection. *Antimicrob Agents Chemother* 2003; **47**: 3561–6.

57 Dandekar PK, Tessier PR, Williams P *et al*. Pharmacodynamic profile of daptomycin against *Enterococcus* species and methicillin-resistant *Staphylococcus aureus* in a murine thigh infection model. *J Antimicrob Chemother* 2003; **52**: 405–11.

58 Rolston KV, Segreti J, Lamp KC *et al*. Cubicin Outcomes Registry and Experience (CORE) methodology. *Am J Med* 2007; **120**: S4–5.

59 Mohr JF, Friedrich LV, Yankelev S *et al*. Daptomycin for the treatment of enterococcal bacteraemia: results from the Cubicin Outcomes Registry and Experience (CORE). *Int J Antimicrob Agents* 2009; **33**: 543–8.

60 Diaz Granados CA, Zimmer SM, Klein M *et al*. Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: a meta-analysis. *Clin Infect Dis* 2005; **41**: 327–33.

61 Vergis EN, Hayden MK, Chow JW *et al*. Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia. A prospective multicenter study. *Ann Intern Med* 2001; **135**: 484–92.

62 Nannini EC. Vancomycin-resistant enterococcal bloodstream infection-related mortality: focus on the lack of appropriate therapy. *Clin Infect Dis* 2006; **42**: 1203–4.

63 Diaz Granados CA, Jernigan JA. Reply to Nannini and to a previous letter by Hurley. *Clin Infect Dis* 2006; **42**: 1204–5.

64 Mermel LA, Allon M, Bouza E *et al*. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **49**: 1–45.

65 Gallagher JC, Perez ME, Marino EA *et al*. Daptomycin therapy for vancomycin-resistant enterococcal bacteremia: a retrospective case series of 30 patients. *Pharmacotherapy* 2009; **29**: 792–9.

66 Segreti JA, Crank CW, Finney MS. Daptomycin for the treatment of Gram-positive bacteremia and infective endocarditis: a retrospective case series of 31 patients. *Pharmacotherapy* 2006; **26**: 347–52.

67 Kvirikadze N, Suseno M, Vescio T *et al*. Daptomycin for the treatment of vancomycin resistant *Enterococcus faecium* bacteremia. *Scand J Infect Dis* 2006; **38**: 290–2.

68 Cunha BA, Mickail N, Eisenstein L. *E. faecalis* vancomycin-sensitive enterococcal bacteremia unresponsive to a vancomycin tolerant strain

successfully treated with high-dose daptomycin. *Heart Lung* 2007; **36**: 456–61.

69 Poutsiaka DD, Skiffington S, Miller KB *et al*. Daptomycin in the treatment of vancomycin-resistant *Enterococcus faecium* bacteremia in neutropenic patients. *J Infect* 2007; **54**: 567–71.

70 Figueroa DA, Mangini E, Amodio-Groton M *et al*. Safety of high-dose intravenous daptomycin treatment: three-year cumulative experience in a clinical program. *Clin Infect Dis* 2009; **49**: 177–80.

71 Cosgrove SE, Corey GR. A balancing act: microbe versus muscle. *Clin Infect Dis* 2009; **49**: 181–3.

72 Weinstock DM, Conlon M, Iovino C *et al*. Colonization, bloodstream infection, and mortality caused by vancomycin-resistant *Enterococcus* early after allogeneic hematopoietic stem cell transplant. *Biol Blood Marrow Transplant* 2007; **13**: 615–21.

73 Grim SA, Hong I, Freeman J *et al*. Daptomycin for the treatment of vancomycin-resistant enterococcal infections. *J Antimicrob Chemother* 2009; **63**: 414–6.

74 Beneri CA, Nicolau DP, Seiden HS *et al*. Successful treatment of a neonate with persistent vancomycin-resistant enterococcal bacteraemia with a daptomycin-containing regimen. *Infect Drug Resist* 2008; **1**: 9–11.

75 Mave V, Garcia-Diaz J, Islam T *et al*. Vancomycin-resistant enterococcal bacteraemia: is daptomycin as effective as linezolid? *J Antimicrob Chemother* 2009; **64**: 175–80.

76 Marion C, Kennedy L, High K. Daptomycin or linezolid in the treatment of vancomycin-resistant enterococcal bacteraemia in neutropenic cancer patients. In: *Abstracts of the Forty-eighth Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 2008*. Abstract L-2120, p. 618. American Society for Microbiology, Washington, DC, USA.

77 Levine DP, Lamp KC. Daptomycin in the treatment of patients with infective endocarditis: experience from a registry. *Am J Med* 2007; **120**: S28–33.

78 Arias CA, Torres HA, Singh KV *et al*. Failure of daptomycin monotherapy for endocarditis caused by an *Enterococcus faecium* strain with vancomycin-resistant and vancomycin-susceptible subpopulations and evidence of *in vivo* loss of the *vanA* gene cluster. *Clin Infect Dis* 2007; **45**: 1343–6.

79 Schutt AC, Bohm NM. Multidrug-resistant *Enterococcus faecium* endocarditis treated with combination tigecycline and high-dose daptomycin. *Ann Pharmacother* 2009; **43**: 2108–2.

80 Arbeit RD, Maki D, Tally FP *et al*. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. *Clin Infect Dis* 2004; **38**: 1673–81.

81 Chamberlain RS, Culshaw DL, Donovan BJ *et al*. Daptomycin for the treatment of surgical site infections. *Surgery* 2009; **146**: 316–24.

82 Owens RC Jr, Lamp KC, Friedrich LV *et al*. Postmarketing clinical experience in patients with skin and skin-structure infections treated with daptomycin. *Am J Med* 2007; **120**: S6–12.

83 Lamp KC, Friedrich LV, Mendez-Vigo L *et al*. Clinical experience with daptomycin for the treatment of patients with osteomyelitis. *Am J Med* 2007; **120**: S13–20.

84 Dvorchik BH, Brazier D, DeBruin MF *et al*. Daptomycin pharmacokinetics and safety following administration of escalating doses once daily to healthy subjects. *Antimicrob Agents Chemother* 2003; **47**: 1318–23.

85 Naber KG, Eisenstein BI, Tally FP. Daptomycin versus ciprofloxacin in the treatment of complicated urinary tract infections due to Gram-positive bacteria. *Infect Dis Clin Pract* 2004; **12**: 322–7.

86 Fisher L, North D. Effectiveness of low-dose daptomycin in the treatment of vancomycin-resistant enterococcal urinary tract infections. *Int J Antimicrob Agents* 2009; **33**: 493–4.

87 Fowler VG Jr, Boucher HW, Corey GR *et al*. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med* 2006; **355**: 653–65.

88 Huen SC, Hall I, Topal J *et al*. Successful use of intraperitoneal daptomycin in the treatment of vancomycin-resistant *Enterococcus* peritonitis. *Am J Kidney Dis* 2009; **54**: 538–41.

89 Hassoun AA, Coomer RW, Mendez-Vigo L. Intraperitoneal daptomycin used to successfully treat vancomycin-resistant *Enterococcus* peritonitis. *Perit Dial Int* 2009; **29**: 671–3.

90 Elvy J, Porter D, Brown E. Treatment of external ventricular drain-associated ventriculitis caused by *Enterococcus faecalis* with intraventricular daptomycin. *J Antimicrob Chemother* 2008; **61**: 461–2.

91 EUCAST. EUCAST technical note on daptomycin. *Clin Microbiol Infect* 2006; **12**: 599–601.

92 Silverman JA, Oliver N, Andrew T *et al*. Resistance studies with daptomycin. *Antimicrob Agents Chemother* 2001; **45**: 1799–802.

93 Lesho EP, Wortmann GW, Craft D *et al*. *De novo* daptomycin nonsusceptibility in a clinical isolate. *J Clin Microbiol* 2006; **44**: 673.

94 Fraher MH, Corcoran GD, Creagh S *et al*. Daptomycin-resistant *Enterococcus faecium* in a patient with no prior exposure to daptomycin. *J Hosp Infect* 2007; **65**: 376–8.

95 Green MR, Anasetti C, Sandin RL *et al*. Development of daptomycin resistance in a bone marrow transplant patient with vancomycin-resistant *Enterococcus durans*. *J Oncol Pharm Pract* 2006; **12**: 179–81.

96 Hidron AI, Schuetz AN, Nolte FS *et al*. Daptomycin resistance in *Enterococcus faecalis* prosthetic valve endocarditis. *J Antimicrob Chemother* 2008; **61**: 1394–6.

97 Kanafani ZA, Federspiel JJ, Fowler VG Jr. Infective endocarditis caused by daptomycin-resistant *Enterococcus faecalis*: a case report. *Scand J Infect Dis* 2007; **39**: 75–7.

98 Lewis JS, Owens A, Cadena J *et al*. Emergence of daptomycin resistance in *Enterococcus faecium* during daptomycin therapy. *Antimicrob Agents Chemother* 2005; **49**: 1664–5.

99 Long JK, Choueiri TK, Hall GS *et al*. Daptomycin-resistant *Enterococcus faecium* in a patient with acute myeloid leukemia. *Mayo Clin Proc* 2005; **80**: 1215–6.

100 Munoz-Price LS, Lolans K, Quinn JP. Emergence of resistance to daptomycin during treatment of vancomycin-resistant *Enterococcus faecalis* infection. *Clin Infect Dis* 2005; **41**: 565–6.

101 Cubist Pharmaceuticals. *Cubicin (daptomycin) Prescribing Information*. 2008. http://www.cubicin.com/pdf/PrescribingInformation.pdf/ (9 February 2010, date last accessed).

102 EUCAST. *Daptomycin - EUCAST Clinical MIC Breakpoints*. 2006. http://www.srga.org/eucastwt/MICTAB/MICdaptomycin.html/ (9 February 2010, date last accessed).

103 Stevens MP, Edmond MB. Endocarditis due to vancomycin-resistant enterococci: case report and review of the literature. *Clin Infect Dis* 2005; **41**: 1134–42.

104 Jenkins I. Linezolid- and vancomycin-resistant *Enterococcus faecium* endocarditis: successful treatment with tigecycline and daptomycin. *J Hosp Med* 2007; **2**: 343–4.

105 Akins RL, Haase MR, Levy EN. Pharmacokinetics of daptomycin in a critically ill adolescent with vancomycin-resistant enterococcal endocarditis. *Pharmacotherapy* 2006; **26**: 694–8.

106 Schwartz BS, Ngo PD, Guglielmo BJ. Daptomycin treatment failure for vancomycin-resistant *Enterococcus faecium* infective endocarditis: impact of protein binding? *Ann Pharmacother* 2008; **42**: 289–90.