

Daptomycin for highly resistant *Enterococcus faecium* infection

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Summary

We report a case series of 11 patients with severe *E. faecium* infections treated with daptomycin. All strains were resistant to ampicillin (MIC >8 mg/l), but susceptible to vancomycin. Seven out of 11 strains were also highly resistant to gentamicin (MIC >500 mg/l). All patients were treated with multiple broad-spectrum antibiotics prior to isolation of *E. faecium* and had severe underlying diseases. Our experience suggests that salvage therapy with daptomycin might be a safe and efficacious treatment for *E. faecium* infections.

Key words: *E. faecium*; daptomycin; antibiotic resistance

Mortality in invasive enterococcal (bloodstream) infections has been reported to be as high as 51% [1]. High-level resistance to gentamicin is an independent predictor of mortality in invasive enterococcal infections in addition to underlying disease and resistance to vancomycin [2, 3].

The treatment of invasive enterococcal infections is a challenge for clinicians due to the reduced susceptibility to penicillins reflected by high minimum inhibitory concentrations (MIC) compared to other streptococci [4, 5]. Treatment recommendations for invasive enterococcal infections advocate synergistic antibiotic combinations such as an aminopenicillin plus gentamicin. In recent years a shift from ampicillin-sensitive *E. faecalis* to ampicillin-resistant *E. faecium* was noted in many European centres, a development we also observed in our hospital. In the event of resistance by *E. faecium* to ampicillin and/or high level gentamicin, vancomycin therapy has been suggested although it is poorly bactericidal [6]. Whilst treatment options of vancomycin resistant enterococci (VRE) are addressed in the literature, studies on treatment of enterococci with resistance to penicillin and/or high-level gentamicin

are scarce and no information from controlled studies is available [7, 8]. In expert opinions linezolid, quinupristin-

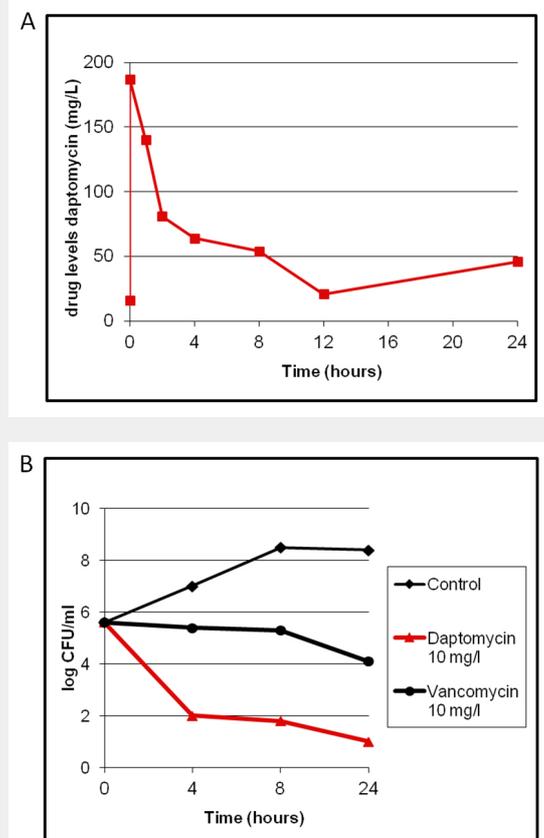


Figure 1 Therapeutic monitoring in one patient with high-dose daptomycin of 10 mg/kg/24 h (A) and in vitro killing curves showing a bactericidal effect of daptomycin at 10 mg/l in contrast to 10 mg/l vancomycin (B).

dalfopristin, tigecyclin, daptomycin, or the new antibiotics dalbavancin, telavancin, ceftobiprole and ceftaroline are under discussion as alternative treatments [6, 9–11]. Linezolid, a bacteriostatic agent which can be given orally due to its high oral bioavailability, is not approved for the treatment of endocarditis. Quinupristin-dalfopristin, a bactericidal combination of two synergistic working streptogramins, is not available in Switzerland. Furthermore, neither quinupristin-dalfopristin nor tigecyclin are approved for the treatment of endocarditis. For the new glycopeptides dalbavancin and telavancin, and the novel betalactams ceftobiprole and ceftaroline, only limited clinical data are available. Ceftobiprole showed high affinity to PBP5fm in vitro [12], but was withdrawn from the market by the company for further development.

Daptomycin, a cyclic lipopeptide with bactericidal activity against Gram-positive bacteria [13], is approved for complicated skin and soft tissue infections with Gram positive bacteria, as well as for *Staphylococcus aureus* bloodstream infections. Daptomycin has been shown to be efficient in

rat models of experimental endocarditis with *E. faecium* [14], but clinical data are scarce [15].

Here we report a case series of 11 retrospectively collected cases of severely ill patients with invasive *E. faecium* infections treated with daptomycin between 2007 and 2009. The study was approved by the local ethics committee. All strains were resistant to ampicillin (MIC >8 mg/l) but susceptible to vancomycin, and 7/11 strains were highly resistant to gentamicin (MIC >500 mg/l).

Table 1 summarises the underlying disease, the infectious focus, the dosage of daptomycin and the patients' outcome. All patients had severe underlying diseases: five had haematological malignancies, two had repeated episodes of cholangiosepsis, two had severe atherosclerosis after multiple vascular surgical procedures, and one had undergone liver transplantation. The majority of patients (10/11) were treated either on an intensive care unit or bone marrow transplant unit prior to isolation of the *E. faecium*.

Table 1: Patient characteristics, antibiotic treatment and outcome.

Age, sex, #	Underlying disease	Focus	Reason for daptomycin	Treatment (antibiotics, surgery)	Outcome 3 months after end of treatment
77, f	Acute leukaemia	Anorectal cellulitis (decubitus) associated bacteraemia	Acute renal failure	Daptomycin 6 mg/kg × 13 days + Meronem 2 × 1 g Surgery: no	Recovered
66, f, #	Acute leukaemia HSCT	Intracardial septic thrombosis	Ongoing fever despite vancomycin	Daptomycin 6 mg/kg × 6 weeks + vancomycin Surgery: no	Death (due to underlying disease: cerebral bleed)
54, m	Acute leukaemia HSCT Gall stone disease	Sepsis from cholecystitis with consecutive endocarditis, spondylodiscitis, pulmonary abscess	Ongoing bacteraemia despite vancomycin	Daptomycin 6 mg/kg + vancomycin Kill curves, TDM and daptomycin dose escalation to 10 mg/kg × 12 weeks Surgery: removal of choledochal stent	Death (due to underlying disease: gram neg sepsis)
61, m, #	Acute leukaemia Neutropenia	Bacteraemia of unknown origin	Renal and hepatic failure Haemofiltration Ongoing bacteraemia despite vancomycin	Daptomycin 6 mg/kg + meropenem Surgery: no	Death due to infection (after only 2 doses): Multiorgan failure
55, f	Chronic GvHD HSCT	Bacteraemia of unknown origin		Daptomycin 6 mg/kg + vancomycin Surgery: no	Recovered
65, f	Liver transplant	Cholangiosepsis	Relapse despite treatment with vancomycin Renal impairment Outpatient regimen	Vancomycin 7 days, then daptomycin 6 mg/kg × 7 days Surgery: removal of stent	Recovered
56, m, #	Colorectal cancer Neutropenia	Intraabdominal abscess	Once daily outpatient regimen	Daptomycin 6 mg/kg × 7 days + ciprofloxacin × 7 days Surgery: drainage of abscess	Recovered
91, m, #	Gallstone disease	Polymicrobial Bacteraemia from cholangitis (<i>E. coli</i> , <i>K. pneumoniae</i> , <i>E. faecium</i> , <i>Cl. perfringens</i>)	Relapsing cholangiosepsis	Daptomycin 6 mg/kg × 7 days Surgery: no	Recovered
81, m	Gallstone disease	Right sided endocarditis	Endocarditis developed despite vancomycin	Daptomycin 6 mg/kg + vancomycin × 10 days Then daptomycin monotherapy 10 mg/kg according to TDM × 6 weeks Surgery: no	Recovered
48, m	Aortic dissection vascular graft	Graft infection	Renal and hepatic impairment	vancomycin × 7 d until renal insufficiency, then daptomycin 6 mg/kg × 14 d Surgery: no	Death (due to underlying disease: postoperative bleeding)
78, m	Severe atherosclerosis Vascular graft	Vascular graft-associated deep tissue infection	Once daily outpatient regimen	Daptomycin 6 mg/kg × 14 days Surgery: surgical drainage of abscess with removal of foreign bodies	Recovered

f = female; m = male; HSCT = haematopoietic stem cell transplantation; GvHD = Graft-versus-host disease; strains susceptible to high level gentamicin are marked as follows: #.

All patients had been treated with multiple broad-spectrum antibiotics including betalactams, carbapenems and aminoglycosides prior to detection of *E. faecium*.

Five patients had bloodstream infections with *E. faecium* (3 of unknown origin, 1 graft infection, 1 septic thrombosis), 4 patients had relapsing cholangiosepsis (2 with consecutive endocarditis, 2 with infection of a biliary stent) and 2 patients had deep abscesses (1 intraabdominal abscess, 1 deep tissue abscess after angioplasty).

The rationales for the use of daptomycin were renal failure (3/11), vancomycin failure (4/11) in spite of vancomycin susceptibility (MIC \leq 4 mg/l), outpatient parenteral therapy (2/11) and ongoing septicemia (2/11).

In the majority of patients daptomycin was started in a dosage of 6 mg/kg/day. Two patients with endocarditis were treated with a higher dosage of 10 mg/kg/d according to therapeutic drug monitoring (TDM). In one patient with persistent bacteraemia, hypoproteinaemia and severe immunosuppression the dosage was increased to 10 mg/kg/d after *in vitro* kill-curves had shown a bactericidal effect defined by loss of \geq 3 log/CFU/24h with a concentration of 10 mg/l daptomycin (fig. 1B). It was noteworthy that vancomycin at a dose of 10 mg/l was bacteriostatic. In this patient TDM was performed (fig. 1A). In a second patient right-sided endocarditis developed whilst the patient was under treatment with vancomycin. Therapy was therefore switched to daptomycin 10 mg/kg/d and therapeutic drug monitoring was performed (data not shown).

Elevation of creatine kinase was noted in one patient with severe sepsis in multi-organ failure. Eosinophilic pneumonia did not occur.

Treatment outcomes are shown in table 1. Seven patients recovered and 4 died. Only in one case was death attributed to *E. faecium* infection. The patient died in severe sepsis after 2 doses of antibiotics. Death in the other three cases was attributed to the underlying condition.

Our case series illustrates that patients affected by bacteraemia with resistant enterococci suffer from severe underlying diseases. Monotherapy with vancomycin can result in treatment failure and bactericidal treatment is urgently needed.

Failures of daptomycin monotherapy for enterococcal infections have been described in case reports mainly for *E. faecalis* [16, 17]. The mechanisms of resistance are not yet elucidated and may potentially limit the use of daptomycin in the treatment of *E. faecium* [18]. Although we observed favourable effects with daptomycin at 6 mg/kg/d for the treatment of infections with *E. faecium*, the appropriate dosage remains to be elucidated in controlled studies.

Our case series indicates that salvage therapy with daptomycin was likely to be effective in 7/11 patients with refractory invasive infections due to multi-resistant *E. faecium*. Thus, daptomycin may be a reasonable alternative for *E. faecium* infections. However, it has not been proven superior in a comparative clinical study and retrospective cohort studies in patients with vancomycin-resistant enterococci show overlapping results [19–21]. Consequently, randomised controlled trials on the optimal dosage, efficacy and safety are urgently needed for these multiresistant bacteria which are difficult to treat [22].

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Figures (large format)

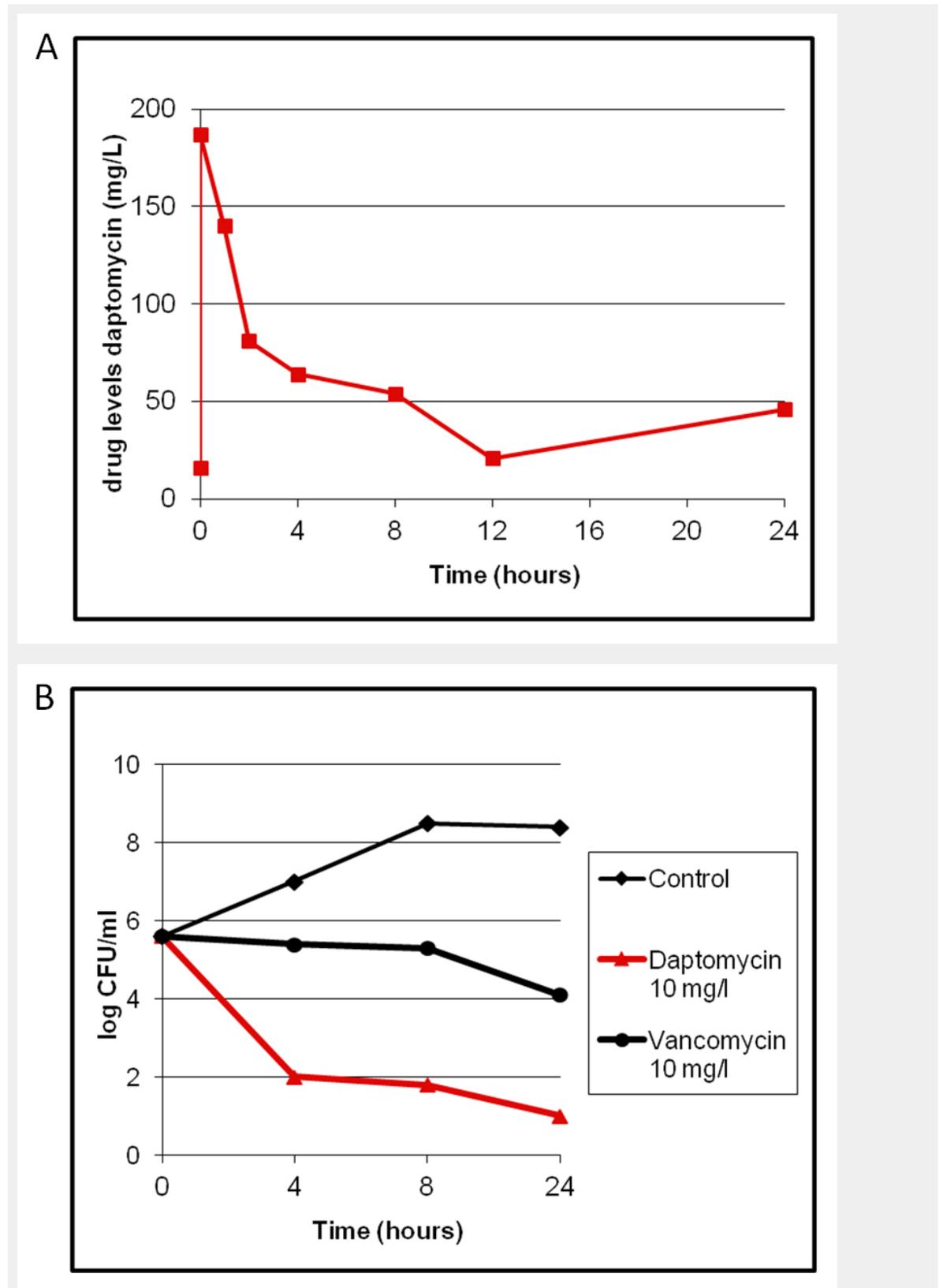


Figure 1

Therapeutic monitoring in one patient with high-dose daptomycin of 10 mg/kg/24 h (A) and in vitro killing curves showing a bactericidal effect of daptomycin at 10 mg/l in contrast to 10 mg/l vancomycin (B).