resistance among Streptococcus pyogenes. 2008; 46
Chemother the subset of 45 macrolide-resistant isolates with an MIC 90 of compounds. S. H. was employed by Arpida AG. K. M. has companies for research and consultancy on antimicrobial I. M. has received funds from numerous pharmaceutical
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Congress of Clinical Microbiology and Infectious Diseases Preliminary data were presented at the Eighteenth European
Resistence to several clinically used antibiotics,1–4 these streptococcal species in the aetiology of cSSTIs and the emergence of resistance to several clinically used antibiotics,1–4 these
for infections due to Streptococcus pyogenes.3 In contrast, in two Phase III clinical trials of cSSTIs, iclaprim exhibited good eradication rates for Streptococcus pyogenes.9,10 Considering the importance of β-haemolytic streptococcal species in the aetiology of cSSTIs and the emergence of resistance to several clinically used antibiotics,1–4 these data further demonstrate the potential for iclaprim to treat infections caused by Streptococcus pyogenes and Streptococcus agalactiae in cSSTIs.

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Daptomycin for the treatment of vancomycin-resistant enterococcal infections
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Sir,
Vancomycin-resistant enterococci (VRE) are an important cause of nosocomial bloodstream infection (BSI) due to increased mortality compared with vancomycin-susceptible strains1 and limited
treatment options. Quinupristin/dalfopristin and linezolid are FDA-approved for the treatment of VRE. Quinupristin/dalfopristin is limited by lack of activity against *Enterococcus faecalis* and toxicities including myalgia, arthralgia and infusion site pain.\(^2\) Linezolid has activity against *E. faecalis* and *Enterococcus faecium*; however, its use is associated with myelosuppressive effects.\(^3\) Tigecycline is a newer agent with anti-VRE activity, but clinical data regarding its use for treatment of VRE infections are lacking.\(^6\) Daptomycin is an intravenous antibiotic with FDA approval for the treatment of complicated skin infections at a dose of 4 mg/kg/day and *Staphylococcus aureus* bacteraemia at a dose of 6 mg/kg/day. Daptomycin has *in vitro* activity against VRE,\(^7\) including strains exhibiting resistance to quinupristin/dalfopristin and linezolid,\(^8\) but there are insufficient data to support an FDA indication for its use in treating VRE infections.\(^8\) We sought to describe the outcomes of patients with VRE who were treated with daptomycin at our institution.

Hospitalized patients ≥18 years of age receiving at least 72 h of daptomycin for the treatment of VRE from 1 September 2003 through 18 June 2007 were identified through a pharmacy database. Patients were excluded if daptomycin was initiated at an outside institution. Demographic, clinical and laboratory data were collected. A successful outcome was defined as: (i) resolution of signs and symptoms of VRE infection; and (ii) culture-confirmed eradication or radiographic resolution of intra-abdominal infections where culture data were absent within 10 days of daptomycin therapy. Failure was defined as the absence of these endpoints with no relapse of infection within 1 month of initial infection. Death during VRE therapy was also recorded. Institutional review board approval was obtained.

Thirty-four patients received daptomycin for treatment of VRE; the mean age was 52.9 years (range 20–75 years) and 50% were male. The majority of patients were Caucasian (17, 50%) with nine (26%) Hispanic, seven (21%) African American and one (3%) Asian. The mean and median duration of daptomycin were 15.6 and 11 days, respectively. Co-morbid health conditions included: malignancy, 12 (35%); diabetes mellitus and solid organ transplantation, 11 (32%) each; end-stage hepatic disease, 7 (21%); end-stage renal disease, 6 (18%); and haematopoietic stem cell transplantation, 5 (15%). Thirty-two out of 34 infections were caused by *E. faecium* and two by *E. faecalis*, and 36% of the isolates exhibited decreased linezolid susceptibility (MIC ≥4 mg/L). Daptomycin MICs were obtained for seven isolates, all of which were susceptible with MICs ranging from 0.5 to 2 mg/L.

Thirty of 34 patients (88%) received daptomycin for VRE BSI. Four of the 30 patients with BSI also had intra-abdominal infection and two had infective endocarditis (IE). In 12 patients, daptomycin was the first anti-VRE therapy received; nine of these patients had baseline thrombocytopenia and three had linezolid-intermediate or -resistant isolates despite lack of linezolid exposure. Of the remaining patients, 11/34 (32%) received daptomycin for clinical and/or microbiological failure of initial anti-VRE therapy, 8/34 (24%) received daptomycin for myelosuppression due to linezolid therapy and 3/34 (9%) received daptomycin based on Infectious Diseases consultation. Three patients had culture-confirmed resolution of their VRE infection prior to daptomycin and were not included in the outcome assessment. Of the remaining 31 patients, 18 (58%) patients had resolution while 13 (42%) experienced failure (Table 1), six due to relapse of infection within 1 month. Patients with failure had a younger median age (42 versus 57.5 years, \(P = 0.015\)) and a higher incidence of malignancy (62% ...
versus 22%, \( P = 0.065 \) compared with patients with successful outcomes. These risk factors appeared to be related, as seven of 12 patients with malignancy had leukaemia, and these patients were of a relatively young age (mean age 37 versus 57 years, \( P = 0.001 \)) and had a high rate of treatment failure (86%, \( P = 0.012 \)). The dose of daptomycin and the timing of its administration were evaluated as risk factors for failure. Among the eight patients who received daptomycin at a dose of >6 mg/kg/day, six (75%) experienced failure compared with 30% of those receiving lower daily doses of daptomycin (\( P = 0.043 \)). Of note, the two patients who had success on receiving lower daily doses of daptomycin were given \( \geq 7 \) mg/kg/day as an initial dose rather than escalating the dose from 6 mg/kg/day after a range of 3–10 days of therapy. Time to appropriate therapy did not impact the outcome of infection. Multivariate analysis did not provide any insight into independent risk factors, likely due to small sample sizes.

Ten out of 31 (32%) died while receiving anti-VRE therapy; seven of these patients were on daptomycin at the time of death and two patients and one patient died while receiving linezolid and quinupristin/dalfopristin, respectively, after daptomycin therapy. There was no difference in age, gender, daptomycin dose or duration, timing of anti-VRE therapy or co-morbidities with the exception of increased malignancy among patients who died (58% versus 16%, \( P = 0.021 \)). There was a borderline significant trend towards increased risk of death on therapy among patients with clinical failures compared with those with successful outcomes (54% versus 17%, \( P = 0.052 \)).

There were no clinically significant adverse effects of daptomycin noted. One patient developed an increased creatine phosphokinase to four times the baseline; however, the patient was asymptomatic and this finding resolved upon discontinuation of daptomycin.

There are limited data describing the use of daptomycin for treatment of VRE BSIs.\(^9\)--\(^12\) Most of these reports are available only in abstract form, limiting the ability to draw conclusions regarding patient types that might benefit most from daptomycin therapy. Clinical cure rates range from 45%\(^\text{12}\) to 71%,\(^9\)\(^10\) although Mave et al.\(^11\) reported microbiological clearance of VRE among 88% of daptomycin recipients. Our study found a success rate of 58% with daptomycin. Daptomycin is very active against \( \textit{S. aureus} \), with MIC values generally in the range of \( \leq 1 \) mg/L.\(^7\) However, daptomycin has less \textit{in vitro} activity against enterococci, with MICs ranging from 2 to 4 mg/L for \( \textit{E. faecalis} \) and \( \textit{E. faecium} \), respectively.\(^7\) Given the concentration-dependent antimicrobial activity of daptomycin, it is possible that the administration of higher doses may have an effect on the outcome of enterococcal infections. In our study, patients who received >6 mg/kg/day of daptomycin more often had treatment failure, but it is likely that this dose escalation was performed in patients who were more critically ill or doing poorly. Of the two patients in our study who were started on daptomycin at \( >7 \) mg/kg/day, both had resolution of infection, although this is obviously too small a sample size from which to draw conclusions. In the study by Alam and Jimenez,\(^8\) there was a 70% success rate in 10 patients with BSI or IE, all of whom received 8 mg/kg/day of daptomycin. The studies by Mave et al.\(^11\) and El-Lababidi et al.\(^10\) did not report dosing information, but Segreti et al.\(^12\) noted a 45% success rate in 11 patients with BSI or IE; a dose of 6 mg/kg/day was administered to these patients.

The above data highlight the fact that additional therapies are needed for the treatment of serious VRE infections, particularly in critically ill patients with serious co-morbidities, as the patients included in this study were. Furthermore, additional studies regarding optimal dosing of daptomycin for VRE may be useful.

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Transparency declarations

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References