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Original article

Daptomycin versus linezolid for the treatment of vancomycin-resistant enterococcal bacteraemia: implications of daptomycin dose

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ABSTRACT

Treatment options for vancomycin-resistant enterococci (VRE) bloodstream infection are limited. Studies comparing daptomycin or linezolid in treating VRE bloodstream infection have conflicting results and suggest daptomycin underdosing. The responses to different daptomycin doses have not been studied. We conducted a multicentre prospective cohort study to compare linezolid and daptomycin (≥6 mg/kg) for the treatment of VRE bloodstream infection. The primary outcome was 14-day mortality. We used multivariate logistic regression analysis for outcome analysis and a generalized additive model for dose-dependent response estimation. Two hundred twelve patients were included (daptomycin, $n = 141$; linezolid, $n = 71$). All-cause 14-day mortality was higher in the daptomycin group (36.9% vs. 21.1%; p 0.03). After adjusting for confounders in logistic regression, mortality was lower in the linezolid group (adjusted odds ratio (aOR), 0.45; 95% confidence interval (CI), 0.21–0.96; p 0.04). The generalized additive model showed that higher-dose daptomycin (≥9 mg/kg) was associated with better survival than lower-dose daptomycin (6–9 mg/kg). Logistic regression showed that linezolid (aOR, 0.36; 95% CI, 0.17–0.79; p 0.01) and higher-dose daptomycin (aOR, 0.26; 95% CI, 0.09–0.74; p 0.01) independently predicted lower mortality compared to lower-dose daptomycin. Linezolid was not superior to higher-dose daptomycin in terms of mortality (aOR, 1.40; 95% CI, 0.45–4.37; p 0.57). Higher-dose daptomycin had lower mortality than lower-dose daptomycin. Despite higher mortality for lower-dose daptomycin than linezolid, linezolid conferred no survival benefit compared to higher-dose daptomycin. Our findings suggest that the recommended daptomycin dose is suboptimal for treating VRE bacteraemia. **Y.-C. Chuang, CMI 2016;22:890.e1–890.e7**

Introduction

Vancomycin-resistant enterococci (VRE) has emerged as an important pathogen causing nosocomial infections [1] after it was first described in 1986 [2,3]. Vancomycin resistance is an important predictor of mortality of enterococcal bacteraemia [4]. However, treatment options are limited [5]. Linezolid is approved for VRE infection [6]. However, because of its bacteriostatic nature, there are concerns about using linezolid for treating VRE bacteraemia [7].

Daptomycin has rapid bactericidal activity against enterococci [7]. Although the recent study by Britt *et al.* [8] showed that daptomycin is superior to linezolid in treating VRE bacteraemia, their results differed from those of other studies [9,10]. Several important limitations of previous studies should be noted [8,11–16]. All of the previous studies were retrospective and may have been affected by recall bias. In addition, the recommended daptomycin dose was 6 mg/kg [17] and was based on the treatment of *Staphylococcus aureus* bacteraemia. One case series demonstrated daptomycin-treated VRE bacteraemic patients receiving a daptomycin dose of

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>6 mg/kg had a better outcome than those receiving a lower dose [18]. The daptomycin dose has varied widely in previous studies [19]. Because daptomycin exhibits concentration-dependent bacterial killing, underdosing may lead to underestimation of the efficacy of daptomycin [19]. However, it is unclear whether the dose differences can explain the conflicting results. To our knowledge, the responses to different doses of daptomycin have not been studied in patients who received daptomycin at a dose ≥6 mg/kg.

The primary aim of this multicentre prospective cohort study was to examine whether daptomycin at a dose ≥6 mg/kg would be associated with a higher survival rate compared to linezolid. Our secondary aim was to analyse whether higher daptomycin dose would result in better survival outcomes.

Methods

Hospital setting and patients

The study was conducted at the National Taiwan University Hospital (NTUH), a 2200-bed medical centre located in Taipei City and NTUH Yun-Lin Branch, a 600-bed teaching hospital in Yun-Lin county. The study was approved by the research ethics committee of the NTUH (NTUH 201011023RB). The informed consent process was waived by the ethics committee.

We used a previously collected database originally designed to follow VRE bacteraemic patients. Patients with VRE bacteraemia were enrolled prospectively from January 2010 through July 2015. Patients were identified through computer-generated daily microbiology reports. The patients who had blood culture reports of VRE on weekends or holidays were followed from the nearest workday. VRE bacteraemia was defined as the growth of VRE in one or more blood culture from a patient with fever (body temperature ≥38°C). If the patient had multiple episodes of VRE bacteraemia during the study period, only the first episode was included. Patients who had VRE bacteraemia and were prescribed parenteral daptomycin or linezolid were included. The decision about which drug to use and the dose for each patient was made by the primary care physician. There were no local guidelines for using a higher dose of daptomycin for the treatment of more severe infection. If a patient initially received daptomycin but this was later changed to linezolid, that patient was placed into the daptomycin group, and vice versa. Patients who were younger than 18 years of age, who were not admitted to hospital, who received <6 mg/kg of daptomycin or who received daptomycin and linezolid in combination were excluded.

Microbiologic studies and antimicrobial susceptibility testing

Blood cultures were processed by the clinical microbiology laboratory. VRE was identified using the VITEK-2 identification system (bioMérieux, Marcy l'Etoile, France). Vancomycin resistance was defined as an enterococcus isolate with a minimum inhibitory concentration (MIC) of vancomycin of ≥32 mg/L. The blood isolates were preserved for subsequent microbiologic characterization. The MICs of linezolid and daptomycin against enterococci were determined using the broth microdilution method and interpreted according to the Clinical and Laboratory Standards Institute [20].

Clinical data collection and definitions

We prospectively followed the patients daily by reviewing the electronic medical records and recorded the patients' demographic data, underlying diseases and sites of infection. The sites of primary infection were identified according to the definitions of the US Centers for Disease Control and Prevention [21]. If no infectious focus of bacteraemia could be identified, the bacteraemia was classified as primary bacteraemia. The Charlson comorbidity index was used to adjust for underlying conditions [22]. Bacteraemia severity was assessed using the Pitt bacteraemia score at the onset of bacteraemia [23].

Bacteraemia onset was defined as the day when the VRE-positive sample for blood culture was drawn. The daptomycin dose was calculated according to the subject's actual body weight. Use of immunosuppressive agents was defined as the receipt of antineoplastic drugs, cyclophosphamide or other immunosuppressive agents within 6 weeks, or as receipt of prednisolone at a dosage of ≥20 mg daily for ≥2 weeks or 30 mg daily for ≥1 week before onset of bacteraemia. Thrombocytopaenia was defined as a platelet count <80 000/μL. We recommended that the creatine phosphokinase (CPK) level be measured at least once a week during daptomycin treatment [24] and if symptomatic in either group of patients. Elevated CPK was defined as CPK higher than the upper limit of normal. High elevation of CPK was defined as CPK more than tenfold the upper limit of normal. Creatinine clearance was estimated using Cockcroft-Gault equation [25,26]. Augmented renal clearance (ARC) was defined as creatinine clearance ≥130 (mL/min/1.73 m^2) [26]. The primary outcome was all-cause in-hospital 14-day mortality after the onset of VRE bacteraemia. Secondary outcomes included infection-related mortality, adverse events such as thrombocytopaenia and elevated CPK. Infection-related mortality was defined as death within 14 days after onset of VRE bacteraemia without another explanation and without resolution of infection symptoms or signs, or persistent VRE bacteraemia before death.

Statistical analysis

The mean and SD were calculated for continuous variables and percentages for categorical variables. Student's *t* test and Fisher's exact test were used to compare continuous and categorical variables, respectively, between two groups. Multivariate logistic regression was used for outcome analysis. Variables with p ≤0.2 in the univariate regression were included in the multivariate analysis. Multivariable models were developed by backward stepwise minimizing Akaike's information criterion (AIC) [27]. After stepwise AIC selection, only variables with p ≤0.05 were considered significant and were retained in the final multivariate prediction model. The dose–response relationship between the daptomycin dose and mortality was estimated using the generalized additive model (GAM) [28]. Propensity score–matched analyses were performed as sensitivity analysis [29]. Stata 14 (StataCorp, College Station, TX, USA) was used. Two-sided p values of ≤0.05 were considered significant.

Results

Two hundred twelve patients were enrolled in 2010–2015 (Fig. 1). All patients had vancomycin-resistant *Enterococcus faecium* infection, and three had vancomycin-resistant *Enterococcus faecalis* coinfection. The mean (SD) age of the study cohort was 65.1 (17.1) years, and Pitt bacteraemia score was 3.7 (2.8) points. One hundred twenty-three patients (58%) were men, and 89 (42.0%) used an immunosuppressive agent (Table 1). Linezolid and daptomycin MICs were available in 177 VRE isolates. No linezolid resistance was found in VRE isolated from patients receiving linezolid treatment, but two VRE isolates from patients receiving daptomycin showed daptomycin resistance.

Five of the 141 daptomycin-treated patients had changed to linezolid treatment because of a lack of improvement (five patients had microbiology-documented failure and persistent VRE bacteraemia under daptomycin treatment). Seven of the 71 linezolid-treated patients had changed to daptomycin treatment (four due to thrombocytopaenia, one due to suspicious linezolid-related