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Breakthrough Bacteremia by Linezolid-Susceptible *Enterococcus faecalis* under Linezolid Treatment in a Severe Polytrauma Patient

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Linezolid has good activity against staphylococci and enterococci, inhibiting the majority of strains at concentrations between 1 and 4 μg/ml (1, 2). The susceptibility breakpoint for *Enterococcus* spp. is fixed by the European Committee on Antimicrobial Susceptibility Testing at ≤4 μg/ml (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables) and by the Clinical and Laboratory Standards Institute at ≤2 μg/ml (3).

The data in the literature suggest that, to obtain clinical success in the treatment of serious infections, the plasma linezolid concentration should remain above the MIC of the causative organism for more than 85% of the time over 24 h (4). Concerns have been expressed by Morata et al., who recently documented a wide interpatient variability in linezolid pharmacokinetic parameters in intensive care unit (ICU) patients (5).

We report the case of a breakthrough bacteremia during linezolid therapy, caused by a susceptible *Enterococcus faecalis* in a critically ill patient.

A previously healthy 21-year-old Caucasian male (body mass index, 21.6 kg/m^2), was admitted in the general ICU following a car accident polytrauma (score of 6 on the Glasgow coma scale).

A computed tomography scan revealed acute subdural hematoma, brain edema, and multiple fractures of the skull base. On day 1, the hematoma was evacuated, and a drainage was placed in the subdural space. Ceftriaxone (2,000 mg every 24 h) was administered from day 1 to day 8. On day 12, the patient presented hypothermia (35.3°C) and leukocytosis (white blood cell count, 20,530/μl) with neutrophilia (84%). An empirical intravenous treatment with linezolid (600 mg every 12 h) plus meropenem (1,000 mg every 8 h) was started, considering the possibility of a central nervous system infection by contiguity. Linezolid was administered intravenously (i.v.) over a 30-min period, at 1:00 a.m. and 1:00 p.m. Cultures of blood, urine, and bronchoalveolar lavage specimens, taken before the beginning of antibiotic treatment, yielded negative results. On day 15, the patient presented a rapid increase in body temperature (maximum 39.7°C) associated with an increased procalcitonin value (1.35 ng/ml), and an *E. faecalis* was isolated from blood culture. Identification and susceptibility testing were performed by matrix-assisted laser desorption ionization–time of flight mass spectrometry (Vitek MS, bioMérieux, Marcy l'Etoile, France) and the reference broth microdilution method, respectively (6). The isolate was susceptible to vancomycin (MIC, 2 μg/ml), ampicillin (MIC, 2 μg/ml), and linezolid (MIC, 2 μg/ml) and high-level resistant to gentamicin (MIC, >128 μg/ml). Cultures from the central venous catheter and urine and cerebrospinal fluid samples were negative. The antibiotic regimen was changed when identification of the blood isolate was available (on day 16), and the infection was successfully treated with 14 days of i.v. vancomycin (2,000 mg every 24 h in a continuous infusion) and meropenem (1,000 mg every 8 h).

Blood samples obtained on days 15 and 16, after 4 and 5 days of the start of linezolid, respectively, were analyzed for quantification of linezolid using high-performance liquid chromatography (HPLC). Plasma linezolid concentrations were determined by HPLC assay, with UV absorbance detection of 254 nm. The limit of quantification was 0.06 μg/ml. The intra-assay precision was >94%, and the interassay precision at 0.5 μg/ml was >90%. The correlation between drug concentration and area value was good for both aqueous and serum samples across the concentration range (r^2, 0.995 for both) (7).

Samples were obtained at 7:00 a.m., 6 h since the last administration. The two concentrations were 1.47 and 2.13 μg/ml, respectively. Therefore, plasma linezolid levels were lower than the MIC from 7:00 a.m. to 1:00 p.m. of day 15 (50% of the time in 24 h) and for an approximately similar period after 7:00 a. m. of day 16, meaning almost 50% of the time in 24 h. The patient had normal renal function (estimated glomerular filtration, 121 ml/min), liver function, and plasma protein values, and no concomitant drug interacting with linezolid was administered. No other features of the patient or of his medical conditions could be identified that could explain the low plasma linezolid values.

These findings underscore how standard dosing of linezolid could be inefficient in prevention of bacteremia caused by *Enterococcus* spp. with MIC values of ≥2 μg/ml, which correspond approximately to 45% of *Enterococcus faecalis* and 60% of wild-type *Enterococcus faecium* isolates (http://mic.eucast.org/Eucast2/).

Furthermore, under these circumstances, exposure to suboptimal drug concentration could play a role in the development of linezolid-resistant mutants.

The opportunity to perform therapeutic drug monitoring (TDM) for optimization of linezolid dose should be considered in similar cases. Where TDM is not applicable, a loading dose or continuous infusion should be considered to improve the efficacy of linezolid treatment (7, 8).

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For the author reply, see doi:10.1128/AAC.01587-13.

doi:10.1128/AAC.01112-13

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