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

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Arena et al. describe in this issue a case of a young patient admitted to the intensive care unit for an acute subdural hematoma who developed bacteremia due to *Enterococcus faecalis* under linezolid treatment (1). They measured linezolid concentrations after 6 h of the last administration on 2 occasions, and both were close (2.13 mg/liter) or below (1.47 mg/liter) the MIC of *E. faecalis* (2 mg/liter). The low concentrations achieved in this patient could explain, at least in part, the breakthrough bacteremia due to linezolid-susceptible *E. faecalis*. Indeed, previous experience in orthopedic infections has documented clinical failure associated with low linezolid concentrations (2). These results are in agreement with pharmacodynamic studies showing that linezolid is a time-dependent antibiotic (3, 4).

Linezolid has a higher volume of distribution (*V*) than beta-lactams do (0.7 liters/kg versus 0.2 to 0.4 liters/kg); it is mainly eliminated by a nonenzymatic pathway in the liver, and the kidneys eliminate 30% of unmodified linezolid. According to these characteristics, it would not be expected that variations in the *V* or in the glomerular filtration (GF) modify serum linezolid concentrations, and there are no recommendations for adjusting linezolid dose in clinical situations where these parameters varied significantly (5). However, some authors have reported low linezolid concentrations in patients with sepsis (6, 7), cystic fibrosis (8), severe burn injuries (9, 10), or morbid obesity (11). Recently, we have studied the risk factors associated with low trough linezolid concentrations (minimum concentration of drug [C_{min}] of $<$2 mg/liter, the MIC_{50} of *Staphylococcus aureus* and *Enterococcus* spp.). Patients with a C_{min} of $<$2 mg/liter more frequently had an estimated GF (eGF) of $>$80 ml/min (78.3%) than those patients with a C_{min} of $\geq$2 mg/liter (32.7%) (this difference was statistically significant [$P = 0.0001$]), and eGF was an independent predictor of low linezolid trough serum concentrations (12). The patient described by Arena et al. (1) did not receive concomitant drugs and had no comorbidity (liver cirrhosis) that could potentially modify the kinetics of linezolid, but interestingly, this patient had an eGF of 121 ml/min. Indeed, high glomerular filtration is a common feature in critically ill patients (13–15). On the other hand, recent studies have shown a higher linezolid concentration (16) and a higher risk of hematological adverse events (17–19) in patients with renal failure, suggesting that renal function impacts significantly on linezolid clearance. Therefore, it is necessary to consider monitoring serum concentrations in patients with sepsis or renal failure to improve efficacy and to avoid toxicity. In addition, to optimize linezolid exposure, a continuous infusion of 1,200 mg daily has demonstrated more stable serum linezolid concentrations and better pharmacodynamic parameters than intermittent administration (7).

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