

Letter to the Editor

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Emergence of daptomycin-resistant *Enterococcus faecium* in a critically ill patient with postoperative intra-abdominal sepsis

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Sir,

Daptomycin is a lipopeptide antibiotic with a potent bactericidal activity against a large number of Gram-positive bacteria. The mechanism of action of this antibiotic is unique since, in presence of calcium, daptomycin molecule inserts into the cell membrane, disrupts its homeostasis, and causes rapid bacterial death. In clinical practice, daptomycin is used for the treatment of serious *Staphylococcus aureus* and *Enterococcus* infections, particularly those caused by vancomycin- or linezolid-resistant strains¹.

Overall, daptomycin exhibits a good *in vitro* activity against enterococci. An extensive review of the literature estimated that only 0.6% of clinical isolates were resistant to daptomycin² while resistance is rarely observed *in vitro*³. However, only two years after its approval in the U.S. in 2003, the first case of daptomycin-resistant *Enterococcus* infection (DREI) was already reported⁴. Subsequently, some additional cases have been described². Initial reports on DREI involved patients that had been previously treated with daptomycin, but DREI can also occur in patients in which this antibiotic has not been previously employed⁵. Recently, several retrospective case series have been published showing that the more frequent types of DREI are associated with bacteraemia, intra-abdominal infections and urinary tract infections⁶⁻⁷.

Most of well-documented cases of DREI (those including clinical, microbiological, treatment and outcome data) have been described in the USA. Here we report a case of DREI in a patient from Spain that developed an intra-abdominal sepsis after bariatric surgery.

A 57-year-old woman with morbid obesity (body mass index 46.64 kg/m²) and a medical history of hypertension, type 2 diabetes, hyperuricemia, rheumatoid arthritis and appendectomy, underwent an elective laparoscopic gastrojejunal bypass. In the early postoperative period she developed abdominal

distention and respiratory distress. Laboratory data showed a white blood cell count of 11.8x10⁹/L with 89.8% polymorphonuclear (PMN) leukocytes and C-reactive protein, glucose and creatinine levels of 488 mg/L, 34.4 mmol/L and 189 µmol/L, respectively. Three days after surgery, she was febrile (38.5°C), her condition worsened rapidly and she developed a septic shock with respiratory and renal failures. She was admitted to the ICU under endotracheal intubation and mechanical ventilation. Fluid replacement, hemodynamic support, intravenous insulin and hemofiltration were started. An urgent laparotomy was performed, revealing perforation of the sigma and faecal peritonitis. A sigmoidectomy with terminal colostomy was performed and intravenous piperacillin/tazobactam was prescribed. Blood cultures were positive for a viridans group *Streptococcus*, *Bacteroides fragilis* and *Clostridium paraputrificum*. A mixed aerobic and anaerobic microbiota was isolated in peritoneal pus. On postoperative day 8 the patient became febrile again and a purulent exudate was found in the surgical wound. The blood white cell count raised to 41.3 x10⁹/L with 88% PMN leukocytes. Culture of the wound exudate was positive for a daptomycin-susceptible *Enterococcus faecium* (MIC=4 mg/L). Blood cultures were negative. Piperacillin/tazobactam was stopped and the patient was given daptomycin (8 mg/kg of body weight intravenously every 24 hours) for 14 days, but fever persisted. Meropenem and amikacin were used instead of daptomycin for an additional period of 14 days, but wound infection worsened and total breakdown occurred. Moreover, a colonic fistula was detected. On postoperative day 36 patient's fever subsided. Blood cultures yielded an *E. faecium* isolate which was resistant to daptomycin (MIC=24 mg/L).

The microorganism was also resistant to ampicillin, levofloxacin, gentamicin (MIC>500 mg/L), rifampicin and imipenem, and susceptible to vancomycin and linezolid. Linezolid was started and fever abated. However, on the following weeks, the patient suffered a complicated course; her condition deteriorated gradually and finally went into multiple organ failure. She died on 80 day after the initial gastric bypass procedure.

Susceptibility testing was performed using a Wider broth microdilution system (Francisco Soria Melguizo, SA, Madrid, Spain). Non susceptibility to daptomycin was confirmed using

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the E-test method (AB Biodisk), supplemented with additional calcium. Clinical and Laboratory Standards Institute (CLSI) guidelines were used for interpretation of MIC results⁹.

Intra-abdominal infection, the disease that our patient suffered, is one of the more frequently described types of DREI. Together with previous daptomycin exposure, significant risk factors for DREI infection are a previous abdominal surgery, the use of bactericidal antibiotics and a prolonged stay in the ICU^{6,9,10}. All of these medical conditions were found in the present case. The duration of daptomycin therapy in patients having DREI with previous daptomycin use, is usually higher than 10 days⁵. The patient also accomplished this condition, since she received daptomycin for a total period of 14 days.

Molecular typing has shown that there is a great genetic variability among the different strains of daptomycin resistant enterococci that can be isolated in hospitals. This point indicates that daptomycin resistance emerges separately among diverse strains of enterococci with no clonal identity. Daptomycin resistance is more likely to result from mutations that occur in the patient's intestinal microbiota instead of patient-to-patient transmission in an outbreak of clonally related bacteria⁶.

The mechanisms of daptomycin resistance in enterococci are not completely understood. They involve alterations in the structure and the functions of the cell membrane caused by mutations in several genes that are associated with cell envelope homeostasis or related to the phospholipid metabolism modulating the cell membrane ionic charge¹¹.

An increase of DREI incidence has been reported with the development of the clinical use of daptomycin⁶. As daptomycin prescription is likely to expand in the next years, clinicians and microbiologists must be aware of DREI occurrence in order to promptly implement the appropriate control measures.

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