Characterization of daptomycin non-susceptible Enterococcus faecium producing urinary tract infection in a renal transplant recipient

ABSTRACT

Objectives. Characterization of a urine isolate of daptomycin non-susceptible Enterococcus faecium recovered from a patient with kidney transplantation and no history of daptomycin exposure.

Methods. After isolation in a urine sample, identification of E. faecium was confirmed by amplification of the E. faecium-specific gene encoding D-alanyl-D-alanine ligase (ddl) and daptomycin susceptibility testing was performed by E-test on cation-adjusted Mueller-Hinton agar. In order to determine the genetic bases of daptomycin resistance, the open reading frames of five genes previously associated with daptomycin resistance in enterococci were sequenced.

Results. Substitutions in the response regulator LiaR (S19F) and cardiolipin synthase (R218Q) were identified.

Conclusions. To the best of our knowledge, this is the first characterization of emerging daptomycin resistance in E. faecium in a Spanish hospital in the absence of daptomycin exposure and in a renal transplant recipient.

Keywords: Enterococcus faecium, daptomycin non-susceptible, liaR, cardiolipin synthase

INTRODUCTION

Daptomycin has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for skin and soft tissue infections and Staphylococcus aureus bacteremia. Although this antibiotic does not have an approved indication for multidrug-resistant enterococci, daptomycin has been extensively used against these organisms due to the paucity of other bactericidal options. However, reports of emergence daptomycin non-susceptibility during therapy of enterococci infections appear to be a problem with cases reported even in patients who have not received the antibiotic. Here, we report the detection of a clinical isolate of daptomycin non-susceptible Enterococcus faecium (MIC=12 mg/L) in a 46-years-old woman with kidney transplantation in Spain.

PATIENTS AND METHODS

In May 2005, this woman started hemodialysis due to chronic terminal kidney failure (National Kidney Foundation
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Daptomycin non-susceptible enterococci (DNSE) are emerging as important causes of healthcare-associated infections affecting patients with multiple comorbid conditions, patients exposed to antimicrobials in the previous three months (especially third-generation cephalosporins and metronidazole) or intra-abdominal disease. There have been reports of DNSE in immunocompromised patients with severe chronic disease, as in the present case, and recent intra-abdominal surgery. Interestingly, daptomycin resistance has been often associated with mutations in genes encoding two groups of proteins, regulatory systems that orchestrate the cell envelope response to antibiotics and antimicrobial peptides, and enzymes involved in phospholipid metabolism. The isolate of our patient exhibited a novel S19F in the predicted phospholipase domain of Cls that has been described before.

RESULTS

Daptomycin MIC by E-test on cation-adjusted Mueller-Hinton agar was 12 mg/L. Of note, neither the recipient nor the donor had documented exposure to daptomycin or other antimicrobials. The patient returned to the hospital with urinary complaints and a spontaneous urine sample was sent to the Clinical Microbiology Laboratory of the VNUH for microbiological diagnosis.

Study of the sample with the Sysmex UF-1000i system [TOA Medical Electronics, Kobe, Japan] revealed 44 white blood cells/μL in non-centrifuged urine and absence of yeast, erythrocytes or squamous epithelial cells. Culture yielded >10^4 CFU/mL of a single microorganism (isolate 3076755) that was identified as E. faecium by matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry and the MicroScan® system (Siemens Healthcare Diagnostics, Madrid, Spain). Confirmation of the identity of the microorganism was performed by PCR targeting the ddl gene encoding the E. faecium D-alanyl-D-alanine ligase, as described before. Susceptibility testing yielded a DAP MIC ≤4 mg/L and resistance to fluoroquinolones, tetracyclines, nitrofurantoin, macrolides (and lincosamides) and high-level resistance to streptomycin and gentamicin. The isolate was susceptible to fosfomycin (MIC ≤32 mg/L), glycopeptides (MIC ≤1 mg/L for vancomycin and for teicoplanin), linezolid (MIC = 2 mg/L) and quinupristin-dalfopristin (MIC ≤0.5 mg/L). E. faecalis ATCC 29212 and S. aureus ATCC 29213 served as controls for susceptibility testing.

DISCUSSION

Enterococci are gram-positive, facultative anaerobes that commonly colonize gastrointestinal and genitourinary tracts. They are generally considered to be of low virulence but are associated with hospital-acquired infections, including UTI, bacteremia, postsurgical wound infections, and gastrointestinal infections. E. faecium is frequently isolated in urine samples from UTI patients hospitalized in our Department of Nephrology, and phenotypes of resistance to beta-lactam antibiotics, fluoroquinolones, macrolides, and high-level resistance to aminoglycosides are commonly detected in these samples, although almost all (>99.9%) of clinical E. faecium isolates remain susceptible to linezolid, glycopeptides, and daptomycin (data not shown).

Daptomycin, a cyclic lipopeptide with in vitro bactericidal activity against Gram-positive bacteria including multidrug-resistant enterococci acts by causing important changes in the biophysical properties of the cell membrane of the bacterial cell membrane altering cell division and cell wall synthesis. Daptomycin is now widely used against severe multidrug-resistant enterococci (including VRE) infections, although it is not approved for these conditions. In our hospital, the utilization of daptomycin began in 2008 and has progressively increased over the past six years; however, daptomycin exposure was not identified as a risk factor in the present case, a phenomenon that has been reported previously.

Daptomycin MIC was 12 mg/L, indicating resistance to daptomycin. The isolate also exhibited high-level resistance to streptomycin and gentamicin. This is consistent with previous reports of daptomycin-resistant enterococci producing urinary tract infection in renal transplant recipients.
proteins have been previously shown to be important for the Daptomycin-non-susceptible phenotype and our results confirm previous observations.

In Spain, linezolid, daptomycin and tigecycline remain as therapeutic options against infections caused by multi-resistant enterococci. However, there have been reports of increases in daptomycin MIC in isolates of methicillin-resistant S. aureus treated with this antibiotic, although values remain within the susceptibility range, and resistance to linezolid has been documented in E. faecalis and E. faecium in some Spanish hospitals. To the best of our knowledge, this is the first case documented in a Spanish hospital in the absence of daptomycin exposure. Clinicians should be aware of the emergence of daptomycin non-susceptible enterococci in immunocompromised patients with or without a history of daptomycin exposure and check for daptomycin susceptibilities.

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TRANSPARENCY DECLARATIONS

All authors: None to declare.

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