Risk factors associated with the acquisition of linezolid-resistant Enterococcus faecalis

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Abstract

Background Linezolid is used to treat vancomycin-resistant enterococcal infections. Vancomycin-resistant and -susceptible Enterococcus faecalis can develop resistance to linezolid in clinical settings with high linezolid consumption. Linezolid-resistant E. faecalis (LREF) has emerged as a major nosocomial pathogen in our hospital, in which linezolid use is considerable.

Aim To define risk factors and outcomes associated with LREF infections.

Methods A retrospective case-control study was designed to evaluate patients admitted to Hospital Civil de Guadalajara “Fray Antonio Alcalde” from January 2014 to October 2017. Fifty patients meeting case definitions for LREF infection and 100 controls hospitalized in the same rooms and dates as the cases were included. Clinical and demographic data were collected and analyzed.Results Risk factors for LREF, included hospitalization within the previous 6 months, intensive care unit admission, previous surgery, urinary catheterization, parenteral nutrition, and acute renal disease. Multivariate analysis identified prior exposures to linezolid [odds ratio (OR, 6.7] and clindamycin (OR, 6.7), previous hospitalization (OR, 2.8), previous surgery (OR, 5.7), and parenteral nutrition (OR, 3.4) as risk factors for LREF infection. The mortality rate for cases was 18% on the LREF versus 9% for controls.

Conclusion Risk factors for LREF infections include antibiotic exposures to linezolid, clindamycin, third-generation cephalosporins, meropenem, and colistin; previous hospitalization; intensive care unit admission; previous surgery; and the use of parenteral nutrition.

Introduction

Enterococci are ubiquitous healthcare-associated pathogens, with *Enterococcus* faecalis being isolated more often (85–90%) than *Enterococcus* faecium (10–15%). Frequently, enterococci are recovered from severely ill patients who have received multiple antibiotics and experienced prolonged hospitalization [1]. Enterococci exhibit intrinsic resistance to multiple antibiotic classes, including aminoglycosides, cephalosporins, streptogramins, and lincosamides [2, 3], with resistance noted more frequently in E. faecium than in E. faecalis. In addition, enterococci can develop resistance to linezolid, daptomycin, and vancomycin during treatment [4].

Although generally considered less capable of developing resistance than *E. faecium,* E. faecalis has emerged as a multidrug-resistant bacterium that may harbor linezolid resistance [5]. Linezolid-resistant *E. faecalis* (LREF) was first described in a 2002 report from the UK describing two E. faecium and one *E.* faecalis isolates with linezolid minimum inhibitory concentrations of 64 mg/L obtained from patients with prior linezolid exposures [6]. In the following years, multiple reports appeared, including two cases of LREF infections in patients who received linezolid previously for the treatment of vancomycin-resistant E. faecium infections [7] and in patients that received prolonged (>30 days) linezolid courses for enterococcal [8], and mycobacterial infections [9, 10]. The global impact of LREF was underscored by reports from Spain[11], Mexico[12], and Brazil of LREF isolates that were also vancomycin-resistant [13].

A collection of 730 clinical E. faecalis isolates contained 26 LREF isolates and 24 multidrug-resistant isolates [14].

Nosocomial outbreaks have occurred in numerous countries [15–17]. A five-year study correlated increasing annual LREF isolation frequency from 2011 to 2015 with increasing linezolid consumption rates measured in defined daily doses (DDD) per 100 bed-days [18].

Here, we aimed to define risk factors and outcomes associated with LREF infections.

Methods

Study design

A retrospective case-control study of patients hospitalized from January 2014 to October 2017 at the Hospital Civil de Guadalajara “Fray Antonio Alcalde” was designed. We evaluated 50 patients defined as cases (patients with a culture positive for LREF) and 100 defined as controls (patients hospitalized in the same rooms and dates as cases), with two controls per case.

Control patients were selected from the same source population the case-patients to prevent biased estimates of relative risk that occurs when designating patients with positive cultures for susceptible bacteria as the control group [19, 20]. We excluded patients hospitalized for <48 hours. Risk time was defined as the number of days from admission to being diagnosed as having a positive culture; for controls, exposure data were collected from the date of admission until the date of discharge or death.

The US Centers for Disease Control and Prevention/National Healthcare Safety Network surveillance definitions of healthcare-associated infections were used: the presence of purulent drainage in skin/soft tissue and surgical wound infections; bacterial isolates from more than one blood culture bottle for bloodstream infections; a positive culture from purulent material obtained during surgery for intra-abdominal infections; fever and a positive urine culture for urinary tract infections; and for respiratory tract infections, a positive respiratory specimen in the presence of fever, leukocytosis, increased respiratory secretions, and tachypnea.

Data and analysis

Clinical and demographic data were collected for cases and controls from clinical records. These included previous hospitalizations (within 6 months), prior antibiotic exposures (within 30 days), and time of discharge. The Charlson comorbidity index was used to assess comorbidities. Linezolid use was quantified by calculating DDD per 100 bed-days.

Identification and drug susceptibility were determined using the automated VITEK–2 system (Biomérieux, Lyon, France). Linezolid resistance was defined by a minimum inhibitory concentration >4 μg/mL. Data were analyzed using the T-test and 2 test in SPSS v. 24, and logistic regression analysis was conducted to calculate odds ratios (ORs).

P-values <0.05 were considered statistically significant.

Ethics statement

The local ethics and research committee Hospital Civil de Guadalajara. Fray Antonio Alcalde (121–17) and the ethics, research and biosafety committee (University of Guadalajara) approved the study (CI–058–18).

Results

The characteristics of the 50 cases and 100 controls are summarized in Table 1. Case-patients had a higher length of stay on average, 35.0 days compared to 11.1 days for controls ($p < 0.001$), with a risk time of 0.044. LREF was recovered from skin and soft tissues in 32% of case-patients, followed by blood (19%), intra-abdominal (16%), urine (14%), surgical wound (13%), and respiratory specimens (6%).

Risk factors for LREF, indicated by a significantly higher rate among cases than controls, included hospitalization within the previous 6 months, intensive care unit admission, previous surgery, urinary catheterization, parenteral nutrition, and acute renal disease (Table 1). Antibiotic exposures within the previous 30 days, particularly to third-generation cephalosporins, meropenem, linezolid, clindamycin, and colistin, were significantly increased among case-patients (Table 1).

Multivariate risk factor analysis indicated that LREF was more frequent in patients with previous hospitalization (OR 2.8), previous surgery (OR 5.7), parenteral nutrition (OR 3.4), exposure to clindamycin (OR 6.7), or exposure to linezolid (OR 6.7) (Table 2).

All LVEF isolates were sensitive to tigecycline, 98% to vancomycin, 80% to ampicillin, and 72% to high-level gentamicin. Meanwhile, 56% of the isolates were resistant to levofloxacin and 8% were resistant to quinupristin-dalfopristin.

The annual linezolid consumption DDDs per 100 bed-days during 2014–2017 were 30%, 30%, 30% and 40% respectively. The mortality rate for cases was 18% on the LREF versus 9% for controls.

Discussion

Infections due to drug-resistant bacteria including LREF are emerging as an important challenge in healthcare settings [21, 22]. The need for effective control policies to prevent drug-resistant nosocomial infections became apparent during increasingly frequent hospital outbreaks [23].

The predominant mechanism of enterococcal linezolid resistance is conferred by the G2576T mutation in the 23S rRNA gene. Other mechanisms include mutations in genes encoding the L3 and L4 ribosomal proteins, and in two plasmid-borne genes, *cfr* and *optrA* [1]. The *cfr* gene was first reported in 2000 in *Staphylococcus sciuri* [24]. Linezolid-resistant enterococcal infections were first identified during nosocomial outbreaks of *E. faecium* resistant to both vancomycin and linezolid [25–28].

Prior linezolid use was one the most significant risk factors for LREF infection identified in this study, similar to the findings of previous reports. Intensive care unit outbreaks of linezolid-resistant enterococci, including LREF, have occurred in the setting of prolonged linezolid treatment courses [12, 15, 17, 29, 30]. Other reported risk factors for linezolid-resistant enterococcal infections include immunosuppression, neutropenia, and invasive procedures [31]. In our cases, leading risk factors included the previous use of antibiotics (chiefly linezolid), previous hospitalization, and surgery.

Linezolid resistance can be acquired by multiple bacterial species through horizontal transmission of genetic elements [32–34]. The *cfr* gene was first documented in our hospital in 2009 in three LREF isolates [35]. All isolates were susceptible to tetracycline, tigecycline, daptomycin, and vancomycin. We detected linezolid-resistance in *Staphylococcus epidermidis,* and *Staphylococcus cohnii* [35], and *E. faecalis* in our hospital at approximately the same time, which suggests that *cfr* in staphylococci may act as a reservoir for this resistance factor.

Linezolid was approved for clinical use in the United States in 2000, two years after its approval in Mexico. Linezolid consumption in our hospital has increased progressively over the past 17 years owing to its use in tuberculosis treatment as a parenteral drug when oral administration is not available. Usually, the duration of the initial stabilization period is 15–30 days, within the time range identified in a 2018 report as risk factor for LVEF acquisition; the mean linezolid treatment duration was 29.8 ± 48.8 days [36]. Prolonged linezolid exposure was also documented as a risk factor for LVEF infections in 2004 and 2017 [8, 13].

In hospitals where vancomycin-resistant enterococci and linezolid-resistant enterococci co-circulate, extreme care should be taken to optimize empiric and directed therapies [37]. Delays in initiating appropriate therapy of enterococcal bloodstream infections can increase 30-day mortality significantly [37]. In our hospital, linezolid use is substantial, particularly during the initial, aggressive treatment of severe tuberculosis. Prolonged treatment courses for tuberculosis have likely facilitated the emergence of linezolid resistance in Gram-positive bacteria [18, 36]. A dedicated antimicrobial stewardship intervention intended to reduce linezolid use in our hospital is needed. A Spanish hospital reduced its linezolid consumption by 76%, while seeing a reduction in LREF isolation, after initiating a focused antimicrobial stewardship program [38].

Our study has several limitations. Firstly, stool cultures were not subjected to assess fecal carriage of LREF. Secondly, the mechanisms of resistance in our LREF isolates have not yet been defined.

Conclusions

LREF has emerged as a significant nosocomial pathogen in our hospital, in association with a high linezolid consumption load. Patients with previous hospitalization, surgery, parenteral nutrition, previous use of meropenem, prior use of clindamycin, and past linezolid exposure appear to be at increased risk of acquiring LREF infections.

Declarations

Data availability

The data used to support the findings of this study are included within the article. These data and further information are available on request.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Tables

Table 1. Characteristics of cases of patients infected with LVEF and controls.

Characteristic	Cases (N = 50) N (%)	Controls (N = 100) N (%)	p
Gender, males/females	23 (46)/27 (54)	55 (55)/45 (45)	0.298
Age (years) ± SD	44.54 ± 25	36.97 ± 22.6	0.227
Length of stay (days) ± SD	35.04 ± 33.3	11.12 ± 10.1	**<0.001**
Risk time (days)	12.42 ± 15.1	10.57 ± 9.8	0.110
Charlson score	2.2 ± 2.1	1.46 ± 1.8	0.114
Previous hospitalization	20 (40)	15 (15)	**0.001**
Previous surgery	15 (30)	5 (5)	**<0.001**
Intensive care unit stay	10 (20)	8 (8)	0.033
Central venous catheterization	18 (38)	23 (23)	0.092
Mechanical ventilation	15 (30)	17 (7)	0.067
Urinary catheterization	25 (50)	29 (29)	**0.012**
Parenteral nutrition	15 (30)	10 (10)	**0.002**
Acute renal disease	13 (26)	5 (5)	**<0.001**
Previous antibiotics	40 (80)	65 (65)	**0.021**
Third-generation cephalosporins	25 (50)	29 (29)	**0.006**
Meropenem	15 (30)	6 (6)	**<0.001**
Linezolid	18 (36)	6 (6)	**<0.001**
Clindamycin	17 (34)	8 (8)	**<0.001**
Fluoroquinolones	8 (16)	9 (9)	0.171
Amikacin	10 (20)	7 (7)	0.013
Vancomycin	3 (6)	4 (4)	0.546
Colistin	6 (12)	0	**< 0.001**

Significant p values are shown in bold.

Table 2. Multivariate analysis of risk factors associated with LVEF infection.

Characteristic	Cases (N = 50) N (%)	Controls (N = 100) N (%)	OR (95% CI)	p
Previous hospitalization	20 (40)	15 (15)	2.85 (0.944–8.62)	0.63
Previous surgery	15 (30)	5 (5)	5.79 (1.58–21.14)	0.008
Urinary catheter	25 (50)	29 (29)	0.760 (0.25–2.25)	0.620
Parenteral nutrition	15 (30)	10 (10)	3.45 (0.9–13.26)	0.071
Previous use of meropenem	15 (30)	6 (6)	1.11 (0.22–5.63)	0.895
Previous use of linezolid	18 (36)	6 (6)	6.74 (1.56–29.04)	**0.01**
Previous use of clindamycin	17 (34)	8 (8)	6.72 (2.23–20.19)	**0.001**

Significant p values are shown in bold.