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

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ABSTRACT

Objectives: Linezolid is a synthetic oxazolidinone antibiotic frequently used to treat vancomycin-resistant enterococcal infections. Vancomycin-susceptible *Enterococcus faecalis* can develop resistance to linezolid in environments with excessive linezolid use. The aim of this study was to define risk factors and outcome associated with the acquisition of linezolid-resistant *E. faecalis* (LREfs).

Methods: A retrospective case–control study was designed including patients hospitalised from January 2014 to October 2017 at Hospital Civil de Guadalajara 'Fray Antonio Alcalde' in Guadalajara, Mexico. A total of 50 patients culture-positive for LREfs and 100 control patients hospitalised in the same room and time as the cases were included. Clinical and demographic data were collected and analysed.

Results: Risk factors for the presence of LREfs included prior linezolid use [odds ratio (OR) = 6.74], prior clindamycin use (OR = 6.72) and previous surgery (OR = 5.79). The mortality rate was 18% for LREfs cases versus 9% for controls.

Conclusion: LREfs has emerged and spread in our hospital, an environment in which linezolid use is considerable. Risk factors for LREfs are prior antibiotic use, including linezolid, and previous surgery.

1. Introduction

Enterococci, notably *Enterococcus faecium* and *Enterococcus faecalis*, are common healthcare-associated pathogens, with *E. faecalis* being more frequent (85–90%) than *E. faecium* (10–15%). These bacterial species are frequently recovered from severely ill patients who have received multiple antibiotics and experienced prolonged hospitalisation [1].

Enterococci are intrinsically resistant to several antibiotics, a trait that is seen more frequently in *E. faecium* than in *E. faecalis*. The inherent resistance mechanisms of enterococci make them resistant to antibiotics such as aminoglycosides, β-lactams, cephalosporins and lincosamides [2,3]. The appearance and dissemination of vancomycin-resistant enterococci has resulted in the need for new modalities of treatment, with linezolid being one option [4].

Enterococci can develop resistance during treatment, including to linezolid, daptomycin and vancomycin [5]. Although seen as less capable of developing resistance, *E. faecalis* has evolved to become a multidrug-resistant bacterium, including to linezolid [6].

Linezolid resistance in enterococci was first reported in 2002 from the UK in two *E. faecium* and one *E. faecalis* with linezolid minimum inhibitory concentrations (MICs) of 64 mg/L that were obtained from patients with prior exposure to linezolid [7]. In the following years there have been multiple reports of this phenomenon, including two cases of linezolid-resistant *E. faecalis* (LREfs) obtained from patients who previously received linezolid for the treatment of infections caused by vancomycin-resistant *E. faecium* [8], in patients who received prolonged (>30 days) courses [9], from Spain [10], Mexico [11] and Brazil in *E. faecalis* also resistant to vancomycin [12], in patients receiving prolonged courses of linezolid for the treatment of mycobacterial infections [13,14], and of 26 *E. faecalis* found to be linezolid-resistant (with 24

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being multidrug-resistant) from a collection of 730 clinical *E. faecalis* isolates [15]. Nosocomial outbreaks began to occur in various countries [16–18]. In a 5-year surveillance study from 2011–2015, the relationship between antibiotic consumption and linezolid resistance in *E. faecalis* was studied [19]. The increasing annual detection of LREfs correlated with an increase in use of linezolid measured as defined daily doses (DDD) per 100 bed-days [19].

The aim of the current study was to define risk factors and outcomes associated with the acquisition of LREfs.

2. Methods

2.1. Study design

A retrospective case–control study among patients hospitalised from January 2014 to October 2017 at Hospital Civil de Guadalajara 'Fray Antonio Alcalde' (Guadalajara, Jalisco, Mexico) was designed. During this period, 50 case patients culture-positive for LREfs and 100 control patients hospitalised in the same room and time as the cases (i.e. two controls per case) were evaluated. Control patients were selected from the same source population as the case patients. The control patients were admitted during the same period as the case patients and were hospitalised in the same hospital service in which case patients were located to prevent biased estimates of relative risk that occurs when one decides patients with positive cultures for susceptible bacteria as the control group [20,21]. Patients hospitalised for <48 h were excluded. 'Risk time' was defined as the number of days from admission to being diagnosed with a positive culture; for controls, exposure data were collected from the date of admission until the date of discharge or death.

The National Healthcare Safety Network of the US Centers for Disease Control and Prevention (CDC/NHSN) surveillance definitions of healthcare-associated infection were used, as follows: for skin and soft-tissue infection and surgical wound infection, the presence of purulent drainage; for bloodstream infection, bacteria isolated from a blood culture bottle; for intra-abdominal infection, a positive culture from purulent material obtained during surgery; for urine tract infection, the presence of fever and a positive urine culture; and for respiratory tract infection, the presence of fever, leukocytosis, increase in respiratory secretions and tachypnoea.

Data obtained from the medical records, demographic information, previous hospitalisation, prior use of antibiotics and time of discharge were included. The Charlson comorbidity index was used to evaluate patients co-morbidities. Use of linezolid was determined as the DDD/100 bed-days.

2.2. Data and analysis

Clinical data were collected from the clinical records for cases and controls. Calculations were conducted to determine the Charlson comorbidity index. Species Identification and antimicrobial susceptibility were determined using a VITEK®2 automated system (bioMérieux, Lyon, France). The criteria of the Clinical and Laboratory Standards Institute (CLSI) were used for interpretation of the results of antimicrobial susceptibility testing. A linezolid MIC ≥ 8 μg/mL was considered resistant. Data were analysed using IBM SPSS Statistics v.24.0 (IBM Corp., Armonk, NY, USA), with logistic regression analysis conducted to calculate the odds ratio (OR). The *t*-test was used for independent variables and the χ^2 test was to evaluate differences between groups, with a *P*-value of <0.05 considered statistically significant.

2.3. Ethics statement

This study was approved by the local ethics, research and biosafety committee of the University of Guadalajara (Guadalajara, Mexico).

3. Results

LREfs 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%). Table 1 describes the characteristics of the 50 cases and 100 controls. Case patients had a longer mean length of stay compared with controls (35.0 days vs. 11.1 days; $P < 0.001$), with a risk time for cases of 12.42 days. Risk factors for LREfs included hospitalisation in the previous 6 months (40% vs. 15%; $P = 0.001$), stay in the

Table 1
Characteristics of cases patients infected with linezolid-resistant *Enterococcus faecalis* and controls.[a]

Characteristic	Cases (*N* = 50)	Controls (*N* = 100)	*P*-value[b]
Sex (male/female)	23 (46)/27 (54)	55 (55)/45 (45)	0.298
Age (years) (mean ± S.D.)	44.54 ± 25	36.97 ± 22.6	0.227
Length of stay (days) (mean ± S.D.)	35.0 ± 33.3	11.1 ± 10.1	**<0.001**
Risk time (days) (mean ± S.D.)	12.42 ± 15.1	10.57 ± 9.8	0.110
Charlson comorbidity index (mean ± S.D.)	2.2 ± 2.1	1.46 ± 1.8	0.114
Previous hospitalisation	20 (40)	15 (15)	**0.001**
Previous surgery	15 (30)	5 (5)	**<0.001**
ICU stay	10 (20)	8 (8)	**0.033**
Central venous catheter	18 (36)	23 (23)	0.092
Mechanical ventilation	15 (30)	17 (7)	0.067
Urinary catheter	25 (50)	29 (29)	**0.012**
Parenteral nutrition	15 (30)	10 (10)	**0.002**
Acute kidney disease	13 (26)	5 (5)	**<0.001**
Antibiotic use in previous 30 days	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**

S.D., standard deviation; ICU, intensive care unit.
[a] Data are *n* (%) unless otherwise stated.
[b] Significant *P*-values are shown in bold.

Table 2
Multivariate analysis of risk factors associated with linezolid-resistant *Enterococcus faecalis* infection.

Characteristic	*n* (%)		OR (95% CI)	*P*-value[a]
	Cases (*N* = 50)	Controls (*N* = 100)		
Previous hospitalisation	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**

OR, odds ratio; CI, confidence interval.
[a] Significant *P*-values are shown in bold.

intensive care unit (ICU) (20% vs. 8%; $P = 0.033$), previous surgery (30% vs. 5%; $P < 0.001$), presence of a urinary catheter (50% vs. 29%; $P = 0.012$), parenteral nutrition (30% vs. 10%; $P = 0.002$) and acute kidney disease (26% vs. 5%; $P < 0.001$).

In additional, use of antibiotics in the previous 30 days was significantly higher among case patients, including third-generation cephalosporins, meropenem, linezolid, clindamycin, amikacin and colistin (Table 1).

In the multivariate analysis of risk factors, LREfs was more frequent in patients with previous surgery (OR = 5.79), previous use of linezolid (OR = 6.74) and previous use of clindamycin (OR = 6.72) (Table 2).

All *E. faecalis* isolates were resistant to linezolid and over one-half of the isolates (56%) were resistant to levofloxacin, whereas 98% were susceptible to vancomycin, 80% were susceptible to ampicillin and 72% were susceptible to high-level gentamicin. The mortality rate was 18% for LREfs cases versus 9% for controls ($P = 0.003$). The DDD of linezolid in our hospital for the years 2014–2017 was 1.2, 5.1, 3.1 and 6.3, respectively.

4. Discussion

Infection with drug-resistant bacteria, including LREfs, is emerging as an important challenge in healthcare settings [3,22,23]. The need for adequate control policies on antibiotic-resistant bacteria became apparent when resistant bacteria began to achieve prominence in outbreaks [24].

This report describes the association of several risk factors with the development of LREfs infection.

Vancomycin resistance in enterococci was first described in 1988 and it has since been clinically encountered frequently both in community and nosocomial infections [4]. The predominant mechanism of linezolid resistance in enterococci involves the G2576T mutation in the 23S rRNA gene. Other mechanisms that have been reported are mutations in the L3 and L4 ribosomal proteins as well as two plasmid-borne genes (*cfr* and *optrA*) [1]. The *cfr* gene was first reported in 2000 in *Staphylococcus sciuri* [25], and linezolid-resistant enterococcal infections began to be detected among vancomycin-resistant *E. faecium* nosocomial infections, causing dissemination and outbreaks [26–29].

Prior use of linezolid was one the most significant risk factors for LREfs infection identified in this study, similar to the findings of previous reports. ICU outbreaks of linezolid-resistant enterococci, including LREfs, have occurred in the setting of prolonged linezolid treatment courses [13,16,18]. Among the risk factors significantly associated with the presence of a linezolid-resistant *Enterococcus* spp. is previous linezolid use, specifically its prolonged use [30,31].

Other risk factors for infection with linezolid-resistant *Enterococcus* spp. include immunosuppression, neutropenia and invasive procedures [32]. In the cases in the current study, primary risk factors included previous antibiotic use, mainly linezolid, as well as invasive procedures, previous hospitalisation and surgery.

Linezolid resistance can be acquired by many bacterial species through horizontal gene transfer [33–35]. The *cfr* gene was first documented in our hospital in 2009 in three linezolid-resistant staphylococcal isolates, all of which were susceptible to tetracycline, tigecycline, daptomycin and vancomycin [36]. In our hospital, linezolid resistance in *Staphylococcus epidermidis* and *Staphylococcus cohnii* [36] and in *E. faecalis* [11] was detected around the same time, which may suggest that the *cfr* gene present in staphylococci likely acted as a reservoir for this resistance.

Linezolid was approved for clinical use in 2000 in the USA, 2 years after its approval for human consumption in Mexico. During the past 17 years, linezolid consumption in our hospital has continuously increased secondary to its use in the treatment of tuberculosis (TB) as one of the intravenous drugs used when the oral route is not available. The duration of the initial stabilisation period is 15–30 days, a risk factor similar to a report in 2018 that prior to the isolation of LREfs the mean linezolid treatment duration was 29.8 ± 48.8 days [19] and to the prolonged linezolid exposure also documented in 2004 and 2017 [9,14].

In hospitals where both vancomycin-resistant enterococci and linezolid-resistant enterococci coexist, extreme care should be taken in choosing the best treatment option [37]. Enterococci infections can significantly increase the 30-day mortality rate [37].

Linezolid use is substantial in our hospital, particularly in the initial aggressive treatment of severe forms of TB. This practice has likely facilitated linezolid resistance in Gram-positive bacteria [19,38]. In an environment of excessive linezolid use, inappropriate use of clindamycin can enhance the selective pressure on enterococci to develop resistance to linezolid [39,40], as clindamycin promotes the development of *cfr* and *cfr*-like multiple resistance genes [40].

Linezolid resistance in *E. faecalis* is developing in other Mexican regions. In a recent report of antimicrobial resistance detected in 47 hospital centres in 20 Mexican states, resistance to linezolid occurred in 7.3% of 892 *E. faecalis* isolates and 2.4% of 124 *E. faecium* isolates [41].

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 LREfs isolation after initiating a focused antimicrobial stewardship programme [42].

The current study has several limitations, including the lack of faecal cultures to assess enterococcal carriage and detection of the linezolid resistance mechanism involved.

5. Conclusions

LREfs has emerged and spread in our hospital in Mexico, an environment in which linezolid use is considerable. LREfs

primarily causes infections in patients with previous hospitalisation, surgery and linezolid exposure.

Data availability

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

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None.

Competing interests

None declared.

Ethical approval

This study was approved by the local ethics, research and biosafety committee of the University of Guadalajara (Guadalajara, Mexico) [CI-058-18].

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