Molecular characteristics of oxazolidinone resistance in enterococci from a multicenter study in China

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Abstract

**Background:** Linezolid-resistant enterococci pose great challenges in clinical practice. The aim of this study is to study the mechanisms underlying the resistance and genetic environment of antimicrobial resistance gene of linezolid-resistant enterococci.

**Results:** The linezolid MICs of 16 enterococci were 4 mg/L to 16 mg/L. Four strains belonged to multi-drug resistant (MDR) bacteria. The sequence types (STs) of 13 enterococci strains performed WGS were diverse: 3 ST476, 1 ST86, ST116, ST480, ST59, ST416, ST21, ST67, ST16, ST585 and ST18. None of them carried multi-drug resistance gene cfr. Only one strain had the G2658 T mutation of target 23S rRNA gene. Thirteen (13/16, 81.3%) strains harbored the novel oxazolidinone resistance gene optrA. WGS analysis showed that the optrA gene was flanked by sequence IS1216E insertion in 13 strains, and optrA was adjacent to transposons Tn558 in two strains and Tn554 in one strain. The optrA gene was identified to be co-localized with fexA, the resistance genes mediated florfenicol resistance in 13 strains, and ermA, the resistance genes mediated erythromycin resistance in 9 strains, indicating that linezolid-resistant strains may be selected due to non-oxazolidinone antibiotics (i.e. macrolides and florfenicol) usage.

**Conclusion:** Our findings demonstrate the high diversity of optrA-carrying genetic platforms. The mobile genetic elements (MGEs) may play an important role in the dissemination of optrA into the enterococci isolates of human origin. The genetic evidence of transferable feature and co-selection of optrA should be gave more attention in clinical practice.

**Keywords:** optrA, Linezolid resistance, Oxazolidinone, Enterococci, Genetic environment

Background

Linezolid, which belongs to oxazolidinone, is the clinically last resort to treat vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and other multi-drug Gram-positive bacteria [1]. Linezolid exerts antibacterial effects by inhibiting the binding of mRNA to the ribosome, thereby affecting the synthesis of the protein [1]. It is generally considered that linezolid is a completely synthetic antibiotic, and theoretically, there should be no natural resistance phenomenon. Unfortunately, clinically resistant strains have emerged shortly after use of linezolid in clinical practice [2, 3]. The occurrence of linezolid-resistant strains show an increasing trend, especially in animal husbandry [4], which should attract sufficient attention.

The resistance to linezolid by gram-positive bacteria can be achieved by target-modified 23S rRNA mutations [5], acquiring exogenous chloramphenicol-florfenicol resistance (cfr) [6], optrA [7] or poxtA [8]. Targets 23S rRNA, L3, L4 and L22 mutations usually affect ribosome function and easily reverse in the absence of selective pressure. Therefore, chemical modifications (such as methylation) of rRNA are the more common resistance mechanisms of linezolid. The cfr gene encodes a methyltransferase that modifies the 23S rRNA at position A2503, which confers resistance to phenicols, lincomamide, oxazolidinones, pleuromutilin, and streptogramin A (PhLOPSA phenotype) [9]. The cfr gene has been identified in a variety of genera, including *Staphylococcus* [10], *Bacillus* [11], *Enterococcus* [12], *Macrococcus* [13],
Jeotgalicoccus [13], Streptococcus [14], Proteus [15] and Escherichia [16]. The cfr gene widely disseminates among oxazolidinone-resistant isolates from human [17] and animal [18] origin, which represents a serious threat to public health. Recently, two cfr variants, cfr(B) and cfr(C), have been found in Enterococcus faecium [19], Clostridium difficile [20] and Campylobacter [21]. The cfr gene was often found on a number of different plasmids [7, 15, 22], and integrated into transposons, leading to dissemination of this gene among the same or between different species of bacteria.

The transferable gene, optrA, has been identified, which confers cross-resistance to phenicols and oxazolidinones, including tedizolid [23]. This gene was identified in enterococci and staphylococci from clinical [24], healthy human and animal isolates [25, 26]. The resistance gene optrA can be located either on plasmid or chromosome [26]. Recently, one florfenicol-resistant Staphylococcus sciuri isolate, which carried both optrA and cfr, was identified in pig [27]. In this study, we investigated the oxazolidinones resistance genes among linezolid-resistant isolates among Chinese hospitals and utilized whole-genome sequencing (WGS), and further analyzed the genetic environment surrounding the resistance genes.

Materials and methods

Bacterial strains

A total of 15 non-duplicable linezolid-resistant enterococci strains and one linezolid intermediate-resistant enterococci strain (13 E. faecalis and 3 E. faecium) (1.5%, 16/1067) were collected from specimens of 16 patients from 9 hospitals between 2009 and 2013 in 6 provinces of China, including 5 samples from Beijing, 4 samples from Guangdong, 3 samples from Zhejiang, 2 samples from Fujian, 1 sample from Jiangsu and 1 sample from Hubei (Table 1). Among the 16 strains, 6 were recovered from patients with urinary tract infection, 5 from patients with bacteremia, 4 from patients with wound infection and 1 from patients with biliary tract infection. Among the 16 strains, 7 strains (1203_10W003, 1202_13E004, 1202_21W014, 19113, 19677, 19506 and SZ21494) were isolated in our previous study [28], and the 9 remaining strains were isolated in this study. Bacteria were first identified at the species level using the VITEK system (bioMerieux, Crapome, France), followed by a molecular method based on the 16S rRNA gene, and then by sequencing analysis.

Antimicrobial susceptibility testing

The minimal inhibitory concentrations (MICs) of 8 antimicrobial agents were determined by the agar dilution method, and tigecycline and daptomycin by broth microdilution. The antimicrobial agents tested included linezolid (Sigma Chemical Co., St. Louis, MO, USA), vancomycin (Sigma), teicoplanin (Sigma), levofloxacin (Sigma), erythromycin (Sigma), tigecycline (Pfizer, NY, USA), daptomycin (Cubist Pharmaceuticals, MA, USA), penicillin (Sigma), ampicillin (Sigma) and gentamycin (Sigma). E. faecalis ATCC 29212 was used for quality control in antimicrobial susceptibility testing. The results of susceptibility testing were interpreted according to CLSI guideline M100-S27. Isolates resistant to three or more antibiotics of different families were considered to be multi-drug resistant (MDR).

Molecular detection of resistance genes and mutations

The resistance genes cfr and optrA were determined by PCR as described previously. The mutation of domain V of the 23S rRNA gene was determined by PCR combined with sequencing as described previously [29]. Nucleotide sequences were compared with the linezolid-susceptible E. faecalis and E. faecium from Peking University People’s Hospital during the same period. The mutation was identified by the E. coli numbering.

Whole-genome sequencing (WGS)

Total genomic DNA of 13 enterococci strains carrying optrA gene was extracted by the standard phenol/chloroform method. The whole-genome sequencing was performed using Illumina technology. The sequences with read length of 150 bases were assembled into contigs using SPAdes (v.3.9.0) [30]. Plasmid content associated with optrA was analyzed using the contigs obtained by plasmidSPAdes. The assembled contigs were annotated by the Prokka v1.12 [31]. Insertion sequences (IS) were identified using ISFinder [32]. Multilocus sequence types (MLST) were assigned using the silico tool hosted by Center for Genomic Epidemiology (CGE) (www.genomicepidemiology.org). The resistance genes were identified by ResFinder 3.0 [33].

Maximum likelihood phylogenetic analysis of the core genome was performed using RAxML (Linux version v7.2.8) [34]. The sequences of the optrA-containing regions of 13 enterococci strains have been deposited at GenBank under the following accession numbers MH225413 (1202_13E004), MH225414 (1202_21W014), MH225415 (1203_10W003), MH225416 (1207_26W003), MH225417 (19506), MH225418 (19677), MH225419 (29462), MH225420 (SZ21494), MH225421 (TZ2), MH225422 (WHXH), MH225423 (XM2013_42321), MH225424 (XM2013_71028) and MH225425 (ZJ11066).

Results

 Susceptibility profiles of linezolid-resistant enterococci isolates

The susceptible breakpoint of enterococci to linezolid is defined as less than or equal to 2 mg/L, and the resistant breakpoint is defined as greater than or equal to 8 mg/L. The linezolid MICs of 16 enterococci were 4 mg/L to 16 mg/L, respectively. There were no significant
| Isolate no. | Organism      | Isolation year | Hospitalb | Isolation site | MICs (mg/L) | Linezolid resistance profiles | Antibiotic resistance genes | Other resistance genes |
|-------------|---------------|----------------|-----------|----------------|-------------|-------------------------------|-----------------------------|------------------------|
| 29462       | *E. faecalis*  | 2009           | ZRYH      | urine          | 86 8 4      | <=0.125 0.5 0.06 8 >4 R      | LVX, ERY                   | optrA –                |
| ZJ11066     | *E. faecalis*  | 2011           | ZJFY      | blood          | 116 8 2     | <=0.125 0.5 0.12 8 >4 R      | LVX, ERY                   | optrA –                |
| JS11041     | *E. faecium*   | 2011           | JSRM      | urine          | ND 8 >=64  >=32 0.5 0.25 2 0.06 8 >4 R | P, AMP, LVX, ERY –         | ND                      |
| 19113       | *E. faecalis*  | 2011           | SZRM      | bile           | ND 8 >=64  >=32 2 <=0.125 0.5 0.06 1 >4 R | P, AMP, LVX, ERY –         | –                       |
| ZJRE1       | *E. faecium*   | 2011           | ZJFE      | blood          | ND 16 >=64 >=32 1 0.5 1 0.06 8 >4 R | P, AMP, LVX, ERY –         | G2658 T                 |
| 1207_26W003 | *E. faecalis*  | 2012           | BJRM      | urine          | 476 4 2     | <=0.125 0.5 0.06 8 >4 R      | LVX, ERY                   | optrA –                |
| 1203_10W003 | *E. faecalis*  | 2012           | BJRM      | urine          | 480 8 2     | <=0.125 0.5 0.06 8 >4 R      | LVX, ERY                   | optrA –                |
| 19677       | *E. faecalis*  | 2012           | SZRM      | blood          | 59 8 2      | <=0.125 0.5 0.12 0.03 >4 R   | ERY                        | optrA –                |
| 19006       | *E. faecium*   | 2012           | SZRM      | wound          | 18 16 >=64 >=32 0.5 0.25 2 0.06 8 >4 S | P, AMP, LVX, ERY –         | –                       |
| 1202_13E004 | *E. faecalis*  | 2012           | BJRM      | wound          | 416 16 8    | <=0.125 0.5 0.12 8 >4 R      | LVX, ERY                   | optrA –                |
| 1202_21W014 | *E. faecalis*  | 2012           | BJRM      | urine          | 21 8 4      | <=0.125 0.5 0.12 8 >4 R      | LVX, ERY                   | optrA –                |
| SZ21494     | *E. faecalis*  | 2012           | SZRM      | wound          | 67 8 4      | <=0.125 1 0.06 1 >4 S        | ERY                        | optrA –                |
| XM2013_71028| *E. faecalis*  | 2013           | XMDY      | wound          | 16 8 2      | <=0.125 1 0.06 0.5 >4 R      | ERY                        | optrA –                |
Table 1: Clinical, phenotypic and genotypic data for the linezolid-resistant Enterococci isolates investigated (Continued)

| Isolate no. | Organism      | Isolation year | Hospitalb | Isolation site | ST c | MICs (mg/L)a | 23S rRNA gene mutations | Linezolid resistance genes | Other resistance genes |
|-------------|---------------|----------------|-----------|----------------|------|--------------|--------------------------|---------------------------|------------------------|
| XM2013_42321 | *E. faecalis* | 2013           | XMDY urine | 585            | 16   | <=2 1 <=0.125 0.5 0.06 8 >4 R LVX ERY | optrA – | emeA, APH(3′)-Ila, AAC(6′)-le-APH(2″)-Ia, aad(6), ANT(9)-Ia, dfrE, lnuD, lnuB, IsaI, IsaA, SAT-4, cat, fexA, ermA1, ermA2, tet(M), tet(L) |
| TZ2          | *E. faecalis* | 2013           | TZSY blood | 476            | 8    | <=2 1 <=0.125 0.5 0.12 8 >4 R LVX ERY | optrA – | emeA, AAC(6′)-le-APH(2″)-Ia, APH(3′)-Ila, aad(6), ANT(9)-Ia, dfrE, lnuB, IsaI, SAT-4, cat, fexA, ermA1, ermA2, tet(M), tet(L) |
| WHXH         | *E. faecalis* | 2013           | WHDS blood | 476            | 8    | <=2 1 <=0.125 0.5 0.12 8 >4 S LVX ERY | optrA – | emeA, AAC(6′)-le-APH(2″)-Ia, APH(3′)-Ila, aad(6), ANT(9)-Ia, dfrE, lnuB, IsaI, SAT-4, cat, fexA, ermA1, ermA2, tet(M), tet(C), tet(L) |

aMICs, the minimal inhibitory concentrations; LNZ, linezolid, susceptible (S): ≤2 mg/L, intermediate (I): 4 mg/L, resistant (R): ≥8 mg/L; P, penicillin, S: ≤2 mg/L, R: ≥8 mg/L; AMP, ampicillin, S: ≤2 mg/L, R: ≥8 mg/L; VAN, vancomycin, S: ≤4 mg/L, I: 8–16 mg/L, R: ≥32 mg/L; TEC, teicoplanin, S: ≤8 mg/L, I: 16 mg/L, R: ≥32 mg/L; DAP, S: ≤1 mg/L, susceptible-dose dependent (SDD): 2–4 mg/L; R: ≥8 mg/L; TGC, tigecycline, no breakpoint in CLSI M100; LVX, levofloxacin, S: ≤2 mg/L, I: 4 mg/L, R: ≥8 mg/L; ERY, erythromycin, S: ≤0.5 mg/L, I: 1–4 mg/L, R: ≥8 mg/L; HLG, high-level gentamycin (500 mg/L); –, negative; ND, not determined
bZRYH, China-Japan Friendship Hospital; ZJFY, 1st Affiliated Hospital of Zhejiang University; JSRM, Jiangsu Province Hospital; SZRM, Shenzhen People’s Hospital; ZJFE, 2nd Affiliated Hospital of Zhejiang University; BJRM, Peking University People’s Hospital; XMDY, 1st Affiliated Hospital of Xiamen University; TZSY, Taizhou Hospital of Zhejiang Province; WHDS, Wuhan Fourth Hospital
cST sequence type, ND not determined
differences in the linezolid MICs between optrA-positive strains (4–16 mg/L) and optrA-negative strains (8–16 mg/L). Most of the optrA-positive strains also exhibited resistance to erythromycin (16/16, 100%), levofloxacin (12/16, 75%) and high-level gentamycin (500 mg/L) (13/16, 81.3%). All strains were susceptible to vancomycin, teicoplanin, daptomycin and tigecycline. Three _E_.faecium and one _E_. faecalis strains (4/16, 25%) were resistant to penicillin and ampicillin, and all of 16 enterococci strains didn’t possess beta-lactamase. Four strains (4/16, 25%) belonged to MDR organism (Table 1).

**Distribution of antimicrobial resistance genes**

None of 16 linezolid-resistant enterococci strains contained cfr gene. Only one strain had the G2658T mutation in 23S rRNA gene with linezolid MIC of 16 mg/L. Most of the linezolid-resistant enterococci strains (n = 13) carried optrA gene (Table 1).

In addition to _optrA_ genes, all _optrA_ -positive strains harbored phenicols resistance gene _fexA_ (13/13, 100%), erythromycin resistance genes of different _erm_ gene classes ( _ermA1, ermB_ ) (13/13, 100%), trimethoprim resistant dihydrofolate reductase different _dfr_ gene classes ( _dfrE, dfrG_ ) (13/13, 100%), ATP-binding cassette (ABC) antibiotic efflux pump different gene classes ( _lsaA, lsaE, efrA, efrB_ ) (13/13, 100%). Further, majority _optrA_-positive strains carried tetracycline resistance genes of different _tet_ gene classes ( _tet[C], tet[L], tetM_ ) (12/13, 92.3%), multidrug and toxic compound extrusion (MATE) transporter _emeA_ gene (12/13, 92.3%) and aminoglycosides inactivating enzyme different gene classes ( _AAC(6)′-Ia, AAC(6)′-le-APH(2″)-Ia, APH(3′)-IIIa, aad [6], ANT(6)′-Ia, ANT(9)-Ia_ ) (10/13, 76.9%). Various additional resistance genes were identified including _cat, lnuB, lnuG, mdtF, SAT-4 and _efmA_.

**Core-genome phylogenetic analysis**

The 12 _E_.faecalis isolates performed WGS were classified into 10 sequence types (STs): 3 ST476, 1 ST86, ST116, ST480, ST59, ST416, ST21, ST67, ST16 and ST585, respectively. One _E_. faecium isolate belonged to ST18.

The phylogenetic tree of 12 _E_. faecalis isolates harboring _optrA_ gene showed that two of these isolates (29462 and XM2013_42321) were genetically unrelated with the rest isolates. Importantly, 1207_26W003 (Beijing), TZ2 (Zhejiang) and WHXH (Hubei) were recovered from different cities, were found very closely related (99.9%), and all of 3 strains belonged to ST476. In addition, strain 19677 recovered from Guangdong was closely related (99.4%) to strain 1202_13E004 recovered from Beijing. Further, strain 1203_10W003 isolated from Beijing and strain XM2013_71028 isolated from Fujian was closely related (99.3%) (Fig. 1).

**Genetic environment of _optrA_ on plasmids or chromosome**

Thirteen contigs containing the _optrA_ gene were blasted in the GenBank database, and 10 contigs were mapped against the plasmids (pE121 [GenBank accession number KT862776] and pE419 [KT862777]). The size of these 10 contigs was between 6372 bp and 21568 bp. According to the gene arrangements, the 10 contigs were divided into 4 groups: group 1 (29462 [MH225419], 1202_21W014 [MH225414]), group 2 (1203_10W003 [MH225415], SZ21494 [MH225420], ZJ11066 [MH225425]), group 3 (1207_26W003 [MH225416], 19677 [MH225418], XM2013_71028 [MH225424]), group 4 (WHXH [MH225422], XM2013_42321 [MH225423]). The genetic environment of _optrA_ in Group 1 was similar to that of plasmid pE121 (KT862776). Compared to the plasmid pE121, _ermA1_ gene was absent and the rest of the sequences were almost identical. The genetic environment of _optrA_ from Group 2 to Group 4 resembled that of plasmid pE419 (KT862777). Compared with pE419, the intergenic region between the left IS1216E and the first hypothetical protein was truncated in Group 2, two hypothetical proteins between _optrA_ gene and the right IS1216E were missing in Group 3, and _ermA1_ gene and two hypothetical proteins were missing in Group 4. The common feature of genetic environment of _optrA_ from Group 1 to Group 4 was flanked by IS1216E, and all of them carried phenicol resistance gene _fexA_ and erythromycin resistance gene _ermA1_ (Fig. 2a.).

The contigs containing _optrA_ gene of 1202_13E004 (MH225413) (29141 bp), 19506 (MH225417) (22720 bp) and TZ2 (MH225421) (75117 bp) were mapped on chromosomal (CP008816). The strains 1202_13E004 and 19506 contained a transposon Tn558 (A715531) with three transposases and the resistance gene _fexA_, and the resistance gene _optrA_ was adjacent to resistance gene _ermA1_. The strain TZ2 carried another transposon Tn554 (X03216) with three transposases and the resistance gene _ermA1_ and _optrA_ was adjacent to resistance gene _fexA_ (Fig. 2b.).

**Discussion**

This study indicates that the transferable resistance gene _optrA_ is very prevalent among linezolid-resistant enterococci strains isolated from human. Much more _optrA_ gene is located on plasmid than chromosome. The _optrA_ gene located on plasmid is flanked by IS1216E, while that located on chromosome is mediated by transposons.

In this study, none of linezolid-resistant enterococci strains carried _cfr_, while most of them harbored _optrA_. This suggests that acquiring _optrA_ is the main resistant mechanism in linezolid-resistant enterococci from human origin. The presence of _optrA_ was limited to a
few species of the genus *Enterococcus* [35] and only rare species of *Staphylococcus* [4]. The surveillance studies indicated that only 3.9–6.2% of staphylococci strains were positive for optrA [4, 25], which suggests a low prevalence of this oxazolidinone resistance gene in the genus *Staphylococcus*.

In present study, the optrA gene was located on plasmids in most of enterococci strains. The optrA gene is often surrounded by insertion sequences when located on plasmids from enterococci strains. Our data showed that all of optrA found on plasmids were flanked by IS1216E, which was similar to a previous study [26]. Other studies also found that co-localization of optrA and cfr was close to IS21–558 and IS257 in *S. sciuri* [4, 27]. IS1216E belongs to the IS6 family which among other mediates transmission of the vancomycin resistance gene vanA in *E. faecium*, the oxazolidinone resistance gene *cfr* in *E. faecalis* [36], the macrolide-lincosamide-streptogramin B resistance genes *erm*(B) and *erm*(T) in *E. hirae* [37] and *Streptococcus galolyticus* subsp. *pasteurianus* [38], respectively, and the tetracycline resistance gene *tet*(S) in *Streptococcus infantis* [39]. This indicates that optrA can be transferred between different genus bacteria by IS-mediated recombination events. Our study found that the optrA gene was located on chromosome in a few of enterococci strains. The optrA gene was adjacent to transposon Tn558 in two strains and to Tn554 in one strain. Tn558 and Tn554 could excise from their host DNA and produce circular forms which precede the integration of the transposon into a new target sequence [40]. The similar genetic arrangement of Tn554 and optrA was identified in both of staphylococci and enterococci, which suggest optrA can be disseminated mediated by transposon between different genus bacteria. The optrA gene was flanked by insertion sequences or transposons, indicating that mobile genetic elements mediate horizontal transfer of optrA among different genus bacteria, which should be given more attention to avoid this novel oxazolidinone resistance gene dissemination in hospitals.

Our data showed the co-localization of resistance genes *fexA* (*n* = 13) and *erm*(*A1*) (*n* = 9) with optrA. The gene *fexA* mediates resistance to fluorinated and non-fluorinated phenicols, which are widely used in livestock, but not in humans. The *fexA* gene was prevalent in florfenicol-resistant staphylococci [4] and enterococci [23] from animal origin. The evidence of co-localization of *fexA*, *erm*(*A1*) and optrA indicates that linezolid-resistant strains may be selected due to non-oxazolidinone antibiotics usage, such as macrolides (often used in hospital), florfenicol (often used in livestock) and et al.. The widespread use of florfenicol in livestock has exerted selective pressure on environmental bacteria and poses a significant public health threat to the increased resistance of the novel antibiotic linezolid.

In summary, optrA was found in most of linezolid-resistant enterococci. The high diversity of optrA-carrying genetic platforms was found even in a limited...
Fig. 2 (See legend on next page.)
The role of optrA in enterococci resistance to linezolid requires further investigation. The optrA gene was often flanked by inserton sequences or transposons, which might mediate the spread of optrA between different species or strains. The co-localization of fexA, ermA1 and optrA suggests that linezolid-resistant enterococci can be selected by other antibiotics such as macrolides and so on, which should be given more attention in clinical practice.

**Conclusion**

We discovered the high diversity of optrA-carrying genetic platforms in our limited number of analyzed isolates. MGE mediated the dissemination of optrA between different species or strains. The optrA gene was found in most of the linezolid-resistant enterococci. Further studies should be done to clarify the linezolid resistance mechanism of optrA gene in Enterococcus species.

**Abbreviations**

ABC: ATP-binding cassette; cfr: chloramphenicol-florfenicol resistance; IS: Insertion sequences; MATE: Multidrug and toxic compound extrusion; MDR: Multi-drug resistant; MGE: Mobile genetic element; MICS: Minimal inhibitory concentrations; MSSA: Methicillin-sensitive Staphylococcus aureus; MRSA: Methicillin-resistant Staphylococcus aureus; PFLOPS: Phenicol, lincomamide, oxazolidinones, pleuromutilin, and streptogramin A; VRE: Vancomycin-resistant enterococci; WGS: Whole-genome sequencing.

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