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Oxazolidinones: mechanisms of resistance and mobile genetic elements involved

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The oxazolidinones (linezolid and tedizolid) are last-resort antimicrobial agents used for the treatment of severe infections in humans caused by MDR Gram-positive bacteria. They bind to the peptidyl transferase centre of the bacterial ribosome inhibiting protein synthesis. Even if the majority of Gram-positive bacteria remain susceptible to oxazolidinones, resistant isolates have been reported worldwide. Apart from mutations, affecting mostly the 23S rDNA genes and selected ribosomal proteins, acquisition of resistance genes (*cfr* and *cfr*-like, *optrA* and *poxtA*), often associated with mobile genetic elements [such as non-conjugative and conjugative plasmids, transposons, integrative and conjugative elements (ICEs), prophages and translocatable units], plays a critical role in oxazolidinone resistance. In this review, we briefly summarize the current knowledge on oxazolidinone resistance mechanisms and provide an overview on the diversity of the mobile genetic elements carrying oxazolidinone resistance genes in Gram-positive and Gram-negative bacteria.

Background

Oxazolidinones are a synthetic class of antimicrobials developed over the past 30 years by numerous pharmaceutical companies.[1] Linezolid is the first member of the oxazolidinones introduced into clinical use in the early new century to treat serious infections by Gram-positive organisms, including MRSA, VRE, MDR pneumococci and MDR mycobacteria.[2] Clinical success of linezolid has driven considerable interest in developing new oxazolidinone molecules. Tedizolid is a second generation oxazolidinone designed to provide enhanced activity against Gram-positive pathogens that carry *cfr* genes[3] and approved for the treatment of acute bacterial skin and soft tissue infections in 2014.[4,5] Gram-negative pathogens are intrinsically resistant to oxazolidinones due to efflux pumps that force linezolid out of the cell faster than it can accumulate.[6,7] Currently, therapeutic recommendations for oxazolidinones include severe infections caused by the aforementioned pathogens, such as community-acquired and nosocomial pneumonia, bloodstream infections and skin and soft tissue infections involving MDR isolates, or in case of therapeutic failure. Despite the synthetic nature of oxazolidinones, linezolid resistance appeared shortly after its introduction,[8] representing a significant risk to public health and, therefore, attracting considerable attention.

This review presents the current knowledge about the mechanisms involved in oxazolidinone resistance, the resistance genes and the relevant mobile genetic elements (MGEs) responsible for their spread,[9–15] thereby providing an update on the latest findings on this topic.

Mode of action and mechanisms of resistance

Oxazolidinones inhibit both bacterial and archaeal protein synthesis by binding to the 50S ribosomal subunit; this mechanism of action differs from that of other protein synthesis inhibitors as it occurs at a very early stage. Oxazolidinones interact with the A-site pocket at the peptidyl transferase centre (PTC) by interfering with the binding and/or positioning of the amino acyl moiety of the incoming aminoacyl tRNA. As a result, these antibiotics prevent the formation of the ribosomal-fMet-tRNA initiation complex,[16,17] the translocation of peptidyl-tRNA from A site to P site and thereby the mRNA translation.[18] X-ray crystallography studies identified several conserved ribonucleotides that interact with oxazolidinones. The binding of linezolid stabilizes a distinct conformation of the universally conserved 23S rRNA nucleotide U2585 (*Escherichia coli* numbering) and induces a non-productive conformation of the PTC.[16] The PTC binding site for tedizolid is similar to the binding site for linezolid, although the D-ring of tedizolid may involve additional sites on the ribosome and is likely responsible for the better activity versus linezolid.[19] Several studies have in fact demonstrated that tedizolid is at

least 4-fold more active than linezolid against key Gram-positive pathogens.[20–23]

Linezolid resistance was first reported in enterococci in 2001,[24] then in *Staphylococcus aureus*[25] and later also in CoNS[26] and in *Streptococcus pneumoniae*.[27] Two programmes monitoring infections due to linezolid-resistant isolates are currently being conducted: LEADER (Linezolid Experience and Accurate Determination of Resistance) which gathers data in the USA and ZAAPS (Zyvox Annual Appraisal of Potency and Spectrum Program), operating worldwide. Although resistance to linezolid remains uncommon (>99% of Gram-positive pathogens are still susceptible),[28] different antimicrobial surveillance studies demonstrated that the number of linezolid-resistant isolates has increased during recent years.[28,29]

Currently, several mechanisms of resistance, or reduced susceptibility, to oxazolidinones have been identified. They can be summarized as follows: (i) ribosomal mutations in 23S rRNA and/or in L3 and/or L4 ribosomal proteins; (ii) loss of the *rlmN* gene activity; (iii) active efflux; and (iv) transferable mechanisms including the Cfr and Cfr-like methyltransferases and the ABC-F proteins OptrA, PoxtA and PoxtA2.

23S rRNA mutations

The linezolid binding site at the PTC is composed entirely of 23S rRNA and the binding pocket is lined with the universally conserved nucleotides which interact directly with the drug.[10,16] Several mutations of the 23S rRNA conferring oxazolidinone resistance have been described (induced *in vitro* and identified in resistant clinical isolates) that involve both nucleotides that directly interact with linezolid, such as G2061, C2452, A2503, U2504 and G2505, and nucleotides located more distally, such as A2062, G2447, A2453, C2499, U2500 and G2576.[10] The G2576U mutation, which is the most widespread in linezolid-resistant isolates, has been identified in both staphylococci and enterococci.[10] Reviews by Stefani *et al.*,[9] Long and Vester[10] and Mendes *et al.*[12] summarized the 23S rRNA mutations responsible for linezolid resistance. Studies carried out on *Mycobacterium smegmatis* have also shown that double mutations in 23S rRNA had remarkable synergistic effects on resistance leading to a 4–32-fold increase in linezolid MICs when compared with the single mutations.[30] Several authors reported that the MICs of linezolid for resistant *Enterococcus faecalis* and *S. aureus* isolates are related to the number of rDNA gene copies harbouring the G2576T mutation.[31,32]

However, these 23S rRNA alterations cause a considerable bacterial fitness cost, mainly when several alleles are mutated. Indeed, isolates containing alterations in 23S rRNA reverted to a WT genotype and phenotype once selective pressure was removed. In some cases the reversion was not complete and single alleles might remain mutated, providing a rapid selection of resistance phenotypes when selective pressure returned.[33] Cross-resistance between PTC-targeting antibiotics resulting from 23S rRNA mutations is not uncommon, for example, the G2576U mutation also confers resistance to chloramphenicol.[30] Interestingly, also a deletion of one 23S rDNA (*rrl*) copy can contribute to the development of linezolid resistance in *Staphylococcus capitis* and *Staphylococcus warneri*.[34,35]

Amino acid exchanges in the ribosomal proteins L3, L4 and L22

Other linezolid resistance mechanisms involve mutations in the genes coding for the ribosomal proteins L3, L4 and L22. Although these proteins are not part of the PTC, mutations in the respective genes that result in changes of amino acids that are located close to the PTC likely impact their conformation and stability.[36] Locke *et al.*[36] investigated the potential of MSSA and MRSA isolates to develop resistance to linezolid and tedizolid, obtaining several mutations both in 23S RNA and in the genes for the L3 and L4 ribosomal proteins. However, they found that only the 23S rRNA mutations resulted in high resistance to oxazolidinones.[36]

Amino acid substitutions in L3 and L4 able to cause reduced susceptibility to linezolid have been reported in several isolates either alone or in association with other resistance mechanisms.[10] Reviews by Stefani *et al.*,[9] Long and Vester[10] and Mendes *et al.*[12] summarized the linezolid resistance-mediating amino acid alterations in the ribosomal proteins. The majority of the amino acid exchanges are found in the L3 protein (encoded by the *rplC* gene) due to the close proximity of this protein to the PTC and F147L and/or A157R alterations appear to be the most widespread and associated with linezolid resistance.[10] Furthermore, a study suggested that amino acid exchanges in L3 could have a compensatory effect in terms of fitness in isolates that also have mutations in the 23S rRNA (for example G2576U).[37] In addition, a region of the L4 ribosomal protein (encoded by the *rplD* gene) is located close to the PTC and several studies indicated a higher frequency of insertions and deletions related to linezolid resistance in this region.[10,12] Wolter *et al.*[27] demonstrated that deletions in the *rplD* gene resulting in amino acid substitutions in the L4 protein (65WR66 and 68KG69) are responsible for a 4-fold increase in the linezolid MIC value. Moreover, the K86Q substitution found in *S. aureus*, plays a role in linezolid resistance.[36] Overall, data demonstrating the association of amino acid alterations in the L3 and L4 proteins with increased levels of linezolid resistance in staphylococci are rare;[38] only Locke *et al.*[36] by analysing laboratory-derived resistant isolates, have confirmed a correlation for selected mutations.

Mutations were also detected in the *rplV* gene which encodes the L22 protein. Little is known about the effects of these mutations and the resulting amino acid substitutions on linezolid resistance, although it is assumed that they play a role due to their close proximity to the linezolid binding site.[10,39,40]

Non-ribosomal linezolid resistance mechanisms

A decade ago, Gao *et al.*[41] described in a clinical MRSA isolate a mutation in the *rlmN* gene (encoding a RNA methyltransferase) that was thought to decrease the susceptibility to the linezolid. However, it was reported that a mutant lacking RlmN activity outcompeted those with active RlmN under selective pressure imposed by linezolid,[42] suggesting that loss of RlmN activity decreases susceptibility to linezolid.

Another reported non-ribosomal linezolid resistance mechanism is related to mutations increasing expression of ABC

transporter genes in *S. pneumoniae*.[37,43] In *S. aureus*, a major facilitator-superfamily-type multidrug efflux pump, encoded by the *lmrS* gene, was found to be able to extrude linezolid.[44]

Very recently, a novel mutation (A1345G) in the *rpoB* gene encoding the β subunit of bacterial RNA polymerase, has been implicated in resistance to tedizolid in MRSA after *in vitro* serial passages.[45]

Acquisition of transferable linezolid resistance genes and MGEs involved

The cfr gene

The onset of a new non-mutational and transmissible mechanism of linezolid resistance raised great concern within the scientific community about the future clinical efficacy of oxazolidinones. The *cfr* gene (**c**hloramphenicol and **f**lorfenicol **r**esistance) was firstly described in a bovine *Staphylococcus sciuri* (recently reclassified as *Mammaliicoccus sciuri*) isolate.[46]

The multiresistance *cfr* gene encodes an rRNA methyltransferase that adds a methyl group at the C-8 position of 23S rRNA nucleotide A2503.[47] The methylation confers combined resistance to five different classes of antimicrobial agents that bind at overlapping non-identical sites at the PTC.[48] The resulting phenotype is called $PhLOPS_A$, for resistance to phenicols, lincosamides, oxazolidinones, pleuromutilins and streptogramin A antibiotics. The gene *cfr* also confers significant increases in the MICs of selected 16-membered ring macrolides, such as josamycin and spiramycin, but not to tylosin.[49] Notably, the *cfr*-mediated methylation of A2503 of 23S rRNA does not interfere with the binding of tedizolid to the PTC—because of structural differences in A-ring C5 substituents between the two drugs—and therefore, does not confer resistance to tedizolid.[3]

A great potential for dissemination is underlined by the common location of *cfr* on MGEs, typically non-conjugative and conjugative plasmids, which are important vehicles for its spread not only among bacteria of the same species, but also among those of different species and genera.[11,15] In addition, the transduction mechanism can be considered an alternative pathway for transmission of the *cfr* gene between staphylococcal isolates.[50] The *cfr* spreading may also be promoted by other factors: (i) the presence of ISs next to the gene which can form so-called translocatable units;[15,51,52] (ii) the low fitness cost associated to its acquisition;[53] and (iii) the co-selection and persistence in the absence of a direct selective pressure (i.e. $PhLOPS_A$ agents) due to other antimicrobial resistance genes located on the same MGE.[15]

Several studies have confirmed this wide dissemination reporting on the occurrence of the *cfr* gene in a large number of Gram-positive genera (*Staphylococcus*, *Enterococcus*, *Bacillus*, *Macrococcus*, *Jeotgalicoccus* and *Streptococcus*) and even in Gram-negative genera (*Proteus*, *Escherichia*, *Morganella*, *Pasteurella*, *Providencia*, *Vibrio* and *Leclercia*).

Staphylococcus spp

The *cfr* gene, mainly found in staphylococcal isolates from animal origin, shows a great variability in its genetic contexts.[15] The gene is often flanked by IS elements: so far four different IS elements have been identified to bracket the *cfr* gene including IS*256*, IS*21-558*, IS*431* and IS*Enfa4*.[15] These elements can mediate the recombination/transposition events responsible for the *cfr* spread in staphylococci.[11,15] Stability tests confirmed that these *cfr*-containing regions could be looped out via IS-mediated recombination.[11,15,54] Initially identified in a bovine *S. sciuri*,[46] *cfr* was first described in 2005 in a clinical MRSA from sputum in Colombia.[55] The *cfr* gene and/or ribosomal mutations have also been reported in clinical staphylococcal isolates associated to hospital outbreaks.[56–60] These first reports were followed by several other studies showing the occurrence of the *cfr* gene in staphylococci isolated from both human and animal specimens (Table 1).

After the characterization of plasmid pSCFS1 from *S. sciuri* on which *cfr* was first detected,[61] the gene has been identified on a variety of other plasmids, but rarely in the chromosomal DNA. Interestingly, a truncated chromosomal *cfr* gene was detected in a livestock-associated MRSA (ST398) of porcine origin; the isolate was linezolid-susceptible owing to a frameshift mutation in the gene.[62]

Moreover, a non-truncated *cfr* gene was detected in MRSA-CC398 (where CC stands for clonal complex) isolates of pig origin,[63] as well as in MRSA-CC398 implicated in pig farmer colonization.[64] The *cfr* gene was also detected in *Staphylococcus equorum* and *Staphylococcus arlettae* from air sample of a swine farm with intensive-production.[65] To date, a plethora of different *cfr*-carrying plasmids have been reported in *Staphylococcus* spp., differing substantially in size and other features, such as backbone, cargo genes, transposase genes etc. (Table 1). A review by Schwarz *et al.*[15] showed and summarized the *cfr* genetic backbones in staphylococci.

Enterococcus spp

The first *cfr*-carrying plasmid (named pEF-01) in enterococci was identified in 2010 in an *E. faecalis* isolate of animal origin in China; the Cfr protein diverged from the WT of *S. sciuri* only by two amino acids.[94] The *cfr*-containing segment of pEF-01 is characterized by the presence of three copies of IS*1216* which probably play a key role in the gene dissemination by recombination processes into different plasmids and chromosomes, mainly of enterococci.[11,15] Enterococcal plasmids responsible for the spread of the *cfr* gene, as well as of other antimicrobial resistance genes, are typically mosaic structures which probably result from plasmid recombination and co-integration events involving replicative transposition of IS*1216*.[94–97]

Diaz *et al.*[98] first reported the characterization of a transferable *cfr*-carrying plasmid from a human isolate of *E. faecalis*. Later studies have identified several *cfr*-harbouring plasmids showing different features in enterococci of both animal and human origin (Table 1). A review by Schwarz *et al.*[15] showed and summarized the *cfr* genetic backbones in enterococci. However, to date the contribution of the *cfr* gene to linezolid resistance in *Enterococcus* spp. is still debated. It has been shown in single isolates that, probably due to yet unknown isolate-specific reasons, the Cfr protein failed to mediate linezolid resistance and a full $PhLOPS_A$ resistance phenotype in enterococci.[29,100,109]

Other Gram-positive bacteria

The *cfr* gene has been also found in other Gram-positive bacteria i.e.: *Bacillus* spp., *Streptococcus suis*, *Macrococcus caseolyticus* and *Jeotgalicoccus pinnipedialis*, all of animal origin.

Table 1. *cfr*-carrying genetic elements currently known

Bacterial species	Origin (Country)	Genetic element (kb)	Accession numbers	References
Staphylococcus spp.				
S. aureus	Pig (Germany)	pSCFS3 (~35.7)	AM086211 (partial sequence)	66
S. aureus 004-737X	Human (USA)	p004-737X (~55)	EU598691 (partial sequence)	67
S. aureus M05/0060	Human (Ireland)	pSCFS7 (~45)	FR675942 (partial sequence)	68
S. aureus CM05	Human (Colombia)	Chromosomal pSM19035-like (15.7)	JN849634	69
S. aureus 69371	Human (Spain)	pERGB (15.2)	JN970906	70
S. aureus SA16	Cow milk (China)	pMSA16 (7.0)	JQ246438	71
S. aureus 004-737X	Human (USA)	pSA737 (39.2)	KC206006	56
S. aureus 1128105	Human (USA)	p1128105 (~37.0)	KJ866414 (partial sequence)	72
S. aureus 417	Human (China)	pLRSA417 (39.5)	KJ922127	73
S. aureus 048-45547X	Human (Brazil)	p45547X (~48.5)	KJ192337 (partial sequence)	74
S. aureus 1518F	Pig (China)	Chromosomal SCCmec IVb (26.7)	KP777553	75
S. aureus M12/0145	Human (Ireland)	pSAM12-0145 (41.5)	KU521355	40
S. aureus M13/0401	Human (Ireland)	pSAM13-0401 (27.5)	KU510528	40
S. aureus AOUC 09-15	Human (Italy)	Tn*6349* (48.3)	MH746818.1	76
S. aureus GDC6P096P	Pig (China)	Unnamed plasmid 1 (37.5)	CP065195	77
S. aureus X2063	Pig (Spain)	pSCFS7 (~55)	FR675942 (partial sequence)	63
S. aureus X1761	Human (Spain)	pSCFS3 (~35.7)	AM086211 (partial sequence)	64
S. aureus GDY8P96A	Pig (China)	pY96A (39.2)	CP065516	15
S. aureus SR153	Human (China)	pSR01 (39.5)	CP048644	15
S. aureus CFSAN064038	Human (Denmark)	pGMI17-006 (45.8)	CP028164	15
S. aureus 2868B2	Food (China)	p2868B2 (39.1)	CP060142	78
S. aureus SA12	Pig (Korea)	pSA12 (38.1)	CP049977	79
S. epidermidis 426-3147L	Human (USA)	p7LC (~30.5)	JX910899 (partial sequence)	80
S. epidermidis 1243-07	Human (USA)	pSEPI8573 (39.3)	KC222021	56
S. epidermidis 12-00322	Human (Germany)	p12-00322 (36.7)	KM521836	38
S. epidermidis 12-00323	Human (Germany)	p12-02300 (38.8)	KM521837	38
S. epidermidis SP1	Human (Italy)	pSP01 (76.9)	KR230047	81
S. epidermidis M13/0451	Human (Ireland)	pSAM13-0451 (8.5)	KY579373	82
S. epidermidis	Human (France)	p-cfr-PBR-B (40.1)	PRJEB22222	59
S. epidermidis MB151	Human (USA)	pMB151a (49.0)	PRJNA434275	83
S. epidermidis 14-01514	Human (Germany)	p14-01514 (39.2)	KX520649	58
S. sciuri	Cattle (Germany)	pSCFS1 (17.1)	NC_005076	61
S. sciuri GN5-1	Pig (China)	pSS-04 (~40)	KF129410 (partial sequence)	52
S. sciuri W28-3	Pig (China)	pWo28-3 (60.5)	KT601170	84
S. sciuri Wo35-20	Pig (China)	pWo35-20 (NA)	KX982166 (partial sequence)	85
S. sciuri Wo28-1	Pig (China)	pWo28-1 (60.5)	KX982171	85
S. sciuri Wo27-9	Pig (China)	pWo27-9 (55.7)	KX982169	85
S. sciuri Wo33-7	Pig (China)	Chromosomal fragment (20.3)	KX982173	85
S. sciuri W33-13	Pig (China)	Chromosomal fragment (25)	KX982174	85
S. sciuri Wo48-2	Pig (China)	pWo48-2 (NA)	KX982175 (partial sequence)	85
S. sciuri Wo19-3	Pig (China)	pWo19-3 (NA)	KX982172 (partial sequence)	85
S. sciuri GDK8D55P	Duck (China)	pK8D55P-cfr (12.7)	CP065963	15
S. sciuri GDH8C110P	Animal feed (China)	pH8C110P-*cfr* (24.1)	CP065796	15
S. sciuri GDK8D6P	Duck (China)	pk8D6P-*cfr* (53.7)	CP065793	15
S. lentus LQQ47	Chicken (China)	pJP1-like (~40)	KF129408 (partial sequence)	52
S. lentus LQQ24-1	Chicken (China)	Chromosomal fragment (6.8)	KF029594	52
S. lentus LQW5	Chicken (China)	Chromosomal fragment (7.4)	KF129407	52
S. lentus LQQ9	Chicken (China)	Chromosomal fragment (8.6)	KF049005	52
S. lentus H29	Chicken (China)	Chromosomal DNA	CP059679	86
S. lentus H29	Chicken (China)	pH29-46 (46.1)	CP059680	86
S. cohnii 2-8	Pig (China)	pSS-01 (15.7)	JF834909	87
S. cohnii SS-03	Pig (China)	pSS-03 (7.0)	JQ219851	87

Continued

Table 1. *Continued*

Bacterial species	Origin (Country)	Genetic element (kb)	Accession numbers	References
S. cohnii SA17 1206047024	Human (China)	pHK01 (NA)	KC820816 (partial sequence)	88
S. saprophyticus DV3	Pig (China)	pSS-02 (~35.4)	JF834910 (partial sequence)	87
S. saprophyticus GDY8P168P	Pig (China)	pY8P168P-*cfr* (41.5)	CP065798	15
S. delphini 2794-1	Food (China)	Chromosomal fragment (20.3)	CP063367	89
S. delphini 245-1	Food (China)	Chromosomal fragment (20.3)	CP063368	89
S. warneri	Pig (Denmark)	pSCFS6 (~43.0)	AM408573 (partial sequence)	51
S. capitis MHZ	Human (China)	pMHZ (~54.7)	JX232067 (partial sequence)	90
S. equorum TLD18	Raw chicken (China)	pHNTLD18 (NA)	KF751702 (partial sequence)	91
S. equorum X109	Air (Spain)	pSP01-like (34.1)	MN6420001	65
S. rostri GT5	Duck (China)	pJP2 (~50)	KC989517 (partial sequence)	52
S. simulans DKCR35	Human (China)	pHNCR35 (9.8)	KF861983	92
S. arlettae SA-01	Chicken (China)	pSA-01 (63.5)	KX274135	93
S. arlettae X114	Air (Spain)	pSP01-like (30.1)	MN637835	65
S. xylosus 378	Pig (China)	pSX01 (39.9)	KP890694	15
Enterococcus spp.				
E. faecalis 603-50427X	Human (Thailand)	pHOU-cfr (~97)	JQ660368 (partial sequence)	98
E. faecalis EF-01	Cattle (China)	pEF-01 (32.3)	NC_014508	94
E. faecalis W9-2	Sewage (China)	pW9-2 (~55)	JQ911741 (partial sequence)	99
E. faecalis CPPF5	Pig (China)	pCPPF5 (12.2)	KC954773	100
E. faecalis S251	Pig (Italy)	Unnamed plasmid (~97)	MT723957 (partial sequence)	101
E. faecalis L9	Pig (Brazil)	pL9-A (7.7)	CP041775	102
E. faecalis EF02	Human (China)	pEF-L18/*cfr* (11.8)	MT874923	103
E. faecalis FC	Cattle (China)	Plasmid unnamed5 (11.9)	CP028840	15
E. faecalis 5ZG10E	Unknown (China)	pE30 (12.2)	KT717888	15
E. faecalis	Pig (China)	p4 (95.6)	MH830362	15
E. faecium F120805	Human (Ireland)	pF120805 (72.9)	KY579372	82
E. faecium E35048	Human (Italy)	pE35048-oc (41.8)	MF580438	104
E. faecium FSIS1608820	Cow (USA)	pFSIS1608820 (28.2)	CP028728	105
E. thailandicus W3	Sewage (China)	pW3 (~75)	JQ911739 (partial sequence)	99
E. thailandicus 3-38	Pig (China)	p3-38 (~72)	JQ911740 (partial sequence)	99
E. gallinarum 325	Pig (Italy)	Chromosomal fragment (9.5)	MT723959	101
E. gallinarum FS4	Pig (Italy)	pEgFS4-1 (34.6)	MZ291452	106
E. hirae Fas4-2	Pig (China)	pfas4-2 (85.6)	MK798156	107
E. casseliflavus DY31	Pig (China)	pDY31-cfr (12.3)	MW207672	108
Other Gram-positive bacteria				
Bacillus sp. BS-01	Pig (China)	pBS-01 (16.5)	GU591497	110
Bacillus sp. BS-02	Pig (China)	pBS-02 (16.5)	HQ128580	111
Bacillus sp. BS-03	Pig (China)	pBS-03 (7.4)	JQ394981	112
M. caseolyticus 207	Pig (China)	pJP1 (~53)	JQ320084 (partial sequence)	115
J. pinnipedialis 102	Pig (China)	pJP1 (~53)	JQ320084 (partial sequence)	115
S. suis S10	Pig (China)	pStrcfr (~100)	KC844836 (partial sequence)	113
S. suis SFJ44	Pig (China)	Genomic island (57.5)	CP031970	114
Gram-negative bacteria				
E. coli LYP-C-BCTb11	Pig (China)	pEC-01 (~110)	JN982327 (partial sequence)	116
E. coli SCEC2	Pig (China)	pSCEC2 (135.6)	KF152885	117
E. coli 8ZG6D	Pig (China)	pSD11 (37.6)	KM212169	118
E. coli GXEC6	Pig (China)	pGXEC6 (38.4)	KM580533	119
E. coli GXEC3	Pig (China)	pGXEC3 (41.6)	KM580532	119
E. coli FS-01	Pig (China)	pFSEC-01 (33.8)	KR779901	120
E. coli FS-02	Pig (China)	Chromosomal fragment (18.4)	KR779900	120
E. coli EP28	Pig (China)	pHNEP28 (108.8)	KT845955	121
E. coli SH21G	Pig (China)	pEC295*cfr* (67)	KY865320	122
E. coli LN310P	Pig (China)	pEC12 (70.1)	MG677985	122

Continued

Table 1. *Continued*

Bacterial species	Origin (Country)	Genetic element (kb)	Accession numbers	References
E. coli GDE6P124	Pig (China)	pHNEP124 (60.4)	MT667260	123
E. coli GDE6P129	Pig (China)	pHNEP129 (35.3)	MT667261	123
E. coli LHM10-1	Pig (China)	Plasmid unnamed4 (28.5)	CP037908	15
E. coli SY3018	Pig (China)	pEC14*cfr* (37.6)	KY865319	15
E. coli FT130	Bird (China)	pFT130-1 (52)	CP040091	15
E. coli FP671	Pig (China)	pHNFP671 (82.8)	KP324830	15
E. coli EP28	Livestock (China)	pHNEP28_*cfr* (108.8)	KT845955	15
P. vulgaris PV-01	Pig (China)	Chromosomal fragment (11.2)	JF969273	124
P. vulgaris PvSC3	Pig (China)	pPvSC3 (284.5)	CP034667	125
P. vulgaris BC22	Pig (China)	ICE*Pvu*ChnBC22 (148.7)	MH160822	126
P. vulgaris ZN3	Pig (China)	pZN3-cfr-121 kb (121.2)	CP047346	15
P. mirabilis BCP11	Pig (China)	ICE*PmiChnBCP11* (139.3)	MG773277	127
P. mirabilis STP3	Pig (China)	ICE*PmiChnSTP3* (118.9)	MT449450	128
P. mirabilis SCBX1.1	Pig (China)	plas1.1.1 (12.7)	CP047113	15
P. mirabilis YPM35	Duck (China)	pJPM35-2 (35.2)	CP053900	15
P. cibarius G32	Goose (China)	pG32-51 (51.6)	CP053373	129
P. cibarius G11	Goose (China)	pG11-51 (152.8)	CP047288	130
P. cibarius ZF1	Pig (China)	pZF1-*cfr* (59.1)	CP047341	15
P. cibarius ZF2	Pig (China)	pZF2-*cfr* (59.1)	CP045009	15
P. multocida FJ6671	Duck (China)	*cfr* plasmid (~40)	MK240189 (partial sequence)	131
P. multocida FJ6683	Duck (China)	*cfr* plasmid (~40)	MK240188 (partial sequence)	131
M. morganii BCMM24	Pig (China)	Tn*6451* (116.1)	MG832661	132
P. rettgeri YPR25	Duck (China)	pYPR25-2 (35.2)	CP060728	15
V. diabolicus NV27	*Mactra veneriformis* (China)	pNV27-cfr-208K (208)	CP085846	133
L. adecarboxylata	Pig feed (China)	pYUSHP29-3 (56.3)	NZ_CP087283	134

NA, not available.

In the genus *Bacillus*, three types of *cfr*-carrying plasmids have been described in isolates from swine faeces: (i) pBS-01 [also harbouring a complete copy of the *erm*(B)-carrying transposon Tn*917*];[110] (ii) pBS-02 (exhibiting a genetic background similar to that of pBS-01 but lacking of Tn*917*);[111] and (iii) pBS-03 (also co-carrying the streptomycin resistance gene *aadY*) (Table 1).[112]

In *S. suis*, the *cfr* gene was detected in the Tn*6644* transposon[76] located on the ~100 kb non-conjugative plasmid pStrcfr and on an antibiotic-resistance-associated genomic island (Table 1).[113,114]

In *M. caseolyticus*, the *cfr* gene was found on a plasmid highly related to pSS-03—widespread in porcine staphylococci—and on the pJP1 plasmid. In this latter plasmid, also detected in *J. pinnipedialis*, the *cfr* genetic context was very similar to the one of the staphylococcal plasmid pSCFS3 (Table 1).[115]

Gram-negative bacteria

Although the *cfr* gene is widespread in Gram-positive bacteria, it has also been identified in isolates, always of animal origin, belonging to different Gram-negative genera (*Escherichia*, *Proteus*, *Morganella*, *Pasteurella*, *Providencia*, *Vibrio* and *Leclercia*). The gene was located in the chromosomal DNA, or on plasmids, but also on integrative and conjugative elements (ICEs) (Table 1). A review by Schwarz *et al.*[15] showed the structural comparison of *cfr*-carrying plasmids detected in *E. coli* and in *Proteus* spp.

The first report of the *cfr* gene in a naturally occurring Gram-negative bacterium was from Wang *et al.*,[124] who found that a *cfr*-carrying segment with homology to a staphylococcal plasmid was found to be inserted into the chromosomal DNA of a florfenicol-resistant *Proteus vulgaris* isolate from swine. In this bacterial genus, *cfr* was also found on ICEs belonging to the family SXT/R391 in both *Proteus mirabilis* and *P. vulgaris*[126–128] and on conjugative MDR plasmids in *P. vulgaris* and *Proteus cibarius* (Table 1).[125,129,130]

The *cfr* gene was also detected in several *E. coli* isolates located on MDR conjugative plasmids exhibiting different backbones and sizes,[116–122,135] in *Morganella morganii* on a novel MDR Tn*6451* transposon derived from Tn*7*,[132] and in *Pasteurella multocida* isolates from sick ducks on two conjugative plasmids in China.[131] Several *cfr*-carrying plasmids have also been identified in some *Providencia rettgeri* isolates from duck and poultry samples,[15,136] in a *Vibrio diabolicus* from a clamshell of *Mactra veneriformis*[133] and in *Leclercia adecarboxylata* from pig feed.[134] Interestingly, IncP and IncX4 plasmids co-harbouring the *mcr-1* (responsible to colistin resistance) and *cfr* genes were detected in *E. coli* of swine origin in China.[123]

Most of the *cfr* genetic contexts were flanked by two IS*26* elements (IS*26*-*cfr*-IS*26*) with the same orientation; these ISs might

have a key role in the spread of the *cfr* gene among Gram-negative bacteria.[15]

cfr-like genes

The cfr(B) gene

Many years after the characterization of the *cfr* gene, a *cfr*-like determinant has been identified in seven linezolid-resistant human clinical isolates of *Clostridioides difficile* (formerly known as *Clostridium difficile* or *Peptoclostridium difficile*). Sequence analysis revealed that the clostridial Cfr showed an amino acid identity of 75.1% compared with the WT protein of *S. sciuri* (Table 2).[137] A following study named this novel resistance determinant *cfr*(B) and clarified that also this gene conferred a $PhLOPS_A$ phenotype.[138] The *cfr*(B) gene was not only detected in clinical *C. difficile* isolates,[137,139,140] but also in *E. faecalis*[141] and *Enterococcus faecium*[138,142,143] isolates from human specimens. The comparison between the Cfr(B) proteins found in *C. difficile*, *E. faecalis* and *E. faecium*, revealed an amino acid identity ranging from 99.7% to 100%.[15]

The *cfr*(B) gene was located both on the Tn*6218* transposon (or its variants)—a non-conjugative chromosomal transposon belonging to the Tn*916* family[15,142,144]—and on a not further characterized genetic element highly similar to a chromosomal fragment of *Faecalibacterium prausnitzii* L2/6.[140] The *cfr*(B) gene was also detected on mega plasmids larger than 200 kb in *E. faecium* isolates of human origin.[15,142] All *cfr*(B) genetic elements known to date are shown in Table 3.

The cfr(C) gene

In 2017, Tang *et al.*[145] identified and characterized a novel *cfr* variant emerged in the foodborne pathogen *Campylobacter* in five different US states. The protein exhibited a high similarity with enzymes of the S-adenosylmethionine superfamily and showed an amino acid identity of 55.4% and 52.2% with the Cfr of *S. sciuri* and with Cfr(B) of *E. faecium*, respectively (Table 2).[145] In addition, this novel *cfr*-like gene, named *cfr*(C), was able to confer a $PhLOPS_A$ resistance phenotype.

The *cfr*(C) gene was located on the conjugative plasmid pTx40 (48 kb) associated with the *tet*(O) and *aphA-3* genes responsible for tetracycline and aminoglycoside resistance, respectively.[145,146] Other studies carried out in China identified *cfr*(C) variants in *Campylobacter coli* isolates of porcine and chicken origin (Table 4).[147,148] Some of these genes, apparently dormant, failed to elevate MICs of phenicols for *C. coli*; however, when cloned and expressed in *Campylobacter jejuni*, they appeared to be fully functional. These *cfr*(C) variants were located on novel MDR genomic islands containing multiple antimicrobial resistance genes of Gram-positive origin or on five different chromosomal regions.[147,148]

The *cfr*(C) gene was also detected in Gram-positive—*C. difficile* and *Clostridium bolteae*—species and identified in three ICE-type organizations: ICE_{DA275}, ICE_{F548} and ICE_{90B3}.[149] In two *C. difficile* isolates from Greek hospitals, *cfr*(C) was located on a small pCd13-Lar plasmid,[139] while in *C. difficile* clinical isolates from Honduras and Costa Rica, it was detected on the ICE F548-like element.[140] Very recently, a chromosomal *cfr*(C) was also found in an isolate of *Clostridium perfringens* of cattle origin in China.[150]

Table 2. Percentage amino acid identities between the *cfr* variants

	cfr	*cfr*(B)	*cfr*(C)	*cfr*(D)	*cfr*(E)
cfr	100	75.14	55.39	65.29	52.37
cfr(B)	75.14	100	52.17	64.08	54.73
cfr(C)	55.39	52.17	100	49.13	57.77
cfr(D)	65.29	64.08	49.13	100	52.07
cfr(E)	52.37	54.73	57.77	52.07	100

All *cfr*(C)-carrying genetic elements known to date are indicated in Table 3 and the review by Schwarz *et al.*[15] showed the structural comparison of *cfr*(C)-carrying plasmids in *C. coli*.

The cfr(D) gene

The *cfr*(D) variant was first documented in France in a clinical *E. faecium* isolate[151] and shortly thereafter in an *E. faecium* isolated in a blood culture from of an Australian patient in 2020.[152] The *cfr*(D) gene encoded a 357 amino acid protein, which shared 65.3%, 64.1% and 49.1% amino acid identity with Cfr, Cfr(B) and Cfr(C), respectively (Table 2).

In *E. faecium* clinical isolates, *cfr*(D) was initially reported to be located on plasmids of different sizes (ranging from 11 to >100 kb). In these plasmids, the gene was flanked by IS*1216* located in the same orientation and associated with a complete, truncated or even missing *guaA* gene (encoding a glutamine-hydrolysing GMP synthase).[15,153,154] When expressed in *E. faecium* and *E. faecalis*, *cfr*(D) did not confer any resistance, whereas it was responsible for an expected $PhLOPS_A$ resistance phenotype in *E. coli*, suggesting that enterococci could constitute an unknown reservoir of *cfr*(D).[153] Some studies reported the occurrence of *cfr*(D)-carrying *E. faecalis* isolates in Spanish, Chinese and Scottish hospitals,[155–157] in enterococcal isolates from swine and manure in Italy,[101,158] and from food-producing animals in Korea.[159] The *cfr*(D) gene was also detected in *Streptococcus parasuis* and in *Vagococcus lutrae* isolates of swine origin in China.[160,161] All *cfr*(D) genetic elements known to date are indicated in Table 3.

The cfr(E) gene

The so far latest *cfr* variant, termed *cfr*(E), was recently discovered in a linezolid-resistant *C. difficile* clinical isolate collected in Mexico. Cfr(E) shares only 52.1%–57.8% amino acid identity with Cfr, Cfr(B), Cfr(C) and Cfr(D) proteins (Table 2). The putative new *cfr*-like gene was part of a not further described genetic element that shows partial hits to genomic sequences of various intestinal Firmicutes.[15,140]

The optrA gene

The *optrA* gene (**o**xazolidinone **p**henicol **t**ransferable **r**esistance) was initially identified in the linezolid-resistant *E. faecalis* E349 recovered from a Chinese patient in 2015. In this isolate, which lacked the *cfr*/*cfr*-like genes and ribosomal mutations, the *optrA* gene was located on a conjugative plasmid (pE349, 36 331 bp in size) that also carried the phenicol exporter gene *fexA*.[162] The *optrA* gene encodes an ABC-F protein resulting in resistance

Table 3. *cfr*-like-carrying genetic elements currently known

Bacterial species	Origin (Country)	Genetic element (kb)	Accession numbers	References
cfr(B)				
C. difficile Ox2167	Human (UK)	Tn*6218* (8.7)	HG002396	144
C. difficile Ox3196	Human (UK)	Tn*6218* (11.3)	HG002389	144
C. difficile PUC51	Human (Chile)	Unknown genetic element (NA)	CAADRH000000000	140
C. difficile PUC347	Human (Chile)	Unknown genetic element (NA)	CAADRI000000000	140
E. faecium 448-18961R	Human (USA)	Tn*6218* (8.4)	KR610408	138
E. faecium UW11590	Human (Germany)	Tn*6218* (~10.2)	SRP078305	142
E. faecium UW11733	Human (Germany)	Tn*6218* (~9.7)	SRP078305	142
E. faecium UW11858	Human (Germany)	ΔTn*6218* (~4.1)	SRP078305	142
E. faecium UW12712	Human (Germany)	ΔTn*6218* on plasmid (~300)	SRP078305	142
E. faecium UW10882	Human (Germany)	Tn*6218* on plasmid (~200)	SRP078305	142
E. faecium E7948	Human (Netherlands)	plasmid 2 (293.8)	LR135358	15
E. faecium 687669, 687671	Human (Panama)	Tn*6218*-like (8.4)	KR610408	29
E. faecalis KUB3006	Human (Japan)	Tn*6218* (11.3)	AP018538	141
cfr(C)				
C. coli Tx40	Cattle (USA)	pTx40 (48)	KX686749	145
C. coli SHP40	Pig (China)	Genomic island (20)	MF037584	147
C. coli SHP63	Pig (China)	Genomic island (17.7)	MF037585	147
C. coli SHP35	Pig (China)	Genomic island (12.7)	MF037586 (partial sequence)	147
C. coli CVM N61925F	Cattle (USA)	pN61925F (48)	MK541989	146
C. coli CVM N61740F	Cattle (USA)	pN61740F (48)	MK541988	146
C. coli CVM N46788F	Cattle (USA)	pN46788F (50.4)	MK541987	146
C. coli JZ_1_79	Pig (China)	pJZ_1_79 (62.4)	CP047213	148
C. coli SH89	Pig (China)	pSH89 (57.3)	CP047217	148
C. coli JP10	Pig (China)	Chromosomal fragment (19.5)	MT107515	148
C. coli SH96	Pig (China)	Chromosomal fragment (19.6)	MT107516	148
C. coli JZ_1_74	Pig (China)	Chromosomal fragment (9)	MT107517	148
C. coli JZ_1_53	Pig (China)	Chromosomal fragment (9.4)	MT107518	148
C. coli JZ_2_24	Pig (China)	Chromosomal fragment (10.8)	MT107519	148
C. difficile DA00275	Human (USA)	ICE_{DA275} (NA)	NA	149
C. difficile F548	Human (USA)	ICE_{F548} (NA)	NA	149
C. difficile Cd-13Lar	Human (Greece)	pCd13-Lar (6.9)	MH229772	139
C. difficile HON10	Human (Honduras)	F548-like ICE (NA)	NA	140
C. difficile LIBA5707	Human (Costa Rica)	F548-like ICE (NA)	NA	140
C. bolteae 90B3	Human (France)	ICE_{90B3} (24)	NA	149
C. perfringens 19TSBNCP	Cattle (China)	Chromosomal fragment (15.9)	CP073070	150
cfr(D)				
E. faecium 15-307-1	Human (France)	p15-307-1_02 (103)	CP044318	153
E. faecium E8014	Human (Netherlands)	Plasmid 4 (11.4)	LR135354	153
E. faecium M17/0314	Human (Ireland)	pM17/0314 (103.6)	MN831413	154
E. faecium BP5067	Human (India)	pBP5067_P1 (122.1)	CP059807	15
E. faecium BA17124	Human (India)	pBA17124_P1 (130.5)	CP059785	15
E. faecalis EF36	Food (Korea)	pEFS36_2 (35.8)	NZ_CP085293	159
E. faecalis EF108	Food (Korea)	pEFS108_1 (97.5)	NZ_CP085295	159
E. faecalis V386	Manure (Italy)	pV386 (33.4)	MZ603802	158
S. parasuis H35	Pig (China)	pH35-cfrD (7.5)	CP076722	160
V. lutrae BN31	Pig (China)	pBN31-cfrD (33.5)	CP081834	161
E. faecalis BX8117	Human (Scotland)	pBX8117-2 (NA)	PRJEB36950	157

NA, not available

to oxazolidinones (linezolid and tedizolid) and phenicols (chloramphenicol and florfenicol).[162] Some recent reports showed that OptrA, as well as other ABC-F proteins, is able to confer antimicrobial resistance through a ribosomal protection mechanism[163,164] unlike other ABC transporters using an active efflux.[165]

Table 4. General features of *cfr*(C)-positive *C. coli* and *C. difficile* isolates

Cfr(C) amino acid sequence			Isolates				MIC (mg/L)		
Variant	Amino acid substitution(s)	*cfr*(C) gene location	Species	Year of isolation	Source	ST	LZD	FFC	References
WT	—	P	*C. coli*	2017	a	ST1068	128	32	[142]
K	E94**K**	C	*C. difficile* DA00154	2010	h	NA	NA	NA	[146]
KV	T225**K**, I318**V**	C	*C. coli* SHP35	2015	a	ST7426	16	1	[144]
KV	T225**K**, I318**V**	C	*C. coli* SHP37	2015	a	ST7426	16	2	[144]
RV	K178**R**, I318**V**	C	*C. coli* SHP40	2015	a	ST828	32	4	[144]
SMQKRV[a]	R15**S**, I134**M**, K178**Q**, T225**K**, P298**R**, I318**V**	C	*C. coli* SHP63	2015	a	ST854	16	2	[144]
	ΔF247–S379	C	*C. coli* JP10	2018–19	a	ST854	8	1	[145]
RQ	K178**R**, R240**Q**	C	*C. coli* JZ_1_53	2018–19	a	ST5947	8	2	[145]
RQ	K178**R**, R240**Q**	C	*C. coli* JZ_1_74	2018–19	a	ST5947	128	32	[145]
ARV	E94**A**, K178**R**, I318**V**	P	*C. coli* JZ_1_79	2018–19	a	ST1058	128	32	[145]
AR	E94**A**, K178**R**	C	*C. coli* JZ_2_24	2018–19	a	ST828	128	32	[145]
RQ	K178**R**, R240**Q**	P	*C. coli* SH89	2018–19	a	ST828	128	64	[145]
ARV	E94**A**, K178**R**, I318**V**	C	*C. coli* SH96	2018–19	a	ST1450	128	64	[145]

P, plasmid; C, chromosome; a, animal origin; h, human origin; LZD, linezolid; FFC, florfenicol; NA, not available.
[a]Since this Cfr(C) protein variant is largely truncated it could be not functional.

Although the *optrA* gene was first detected in a human *Enterococcus*, its wide occurrence in bacteria from several sources, including animals, food of animal origin, vegetable products (even fresh flowers) and natural habitats, has been reported worldwide.[15,101,166–173] Overall, *optrA* has proven to be widespread especially in enterococci of animal origin which, therefore, represent an important reservoir for the dissemination of this resistance gene.[174] Though the 23S rRNA alterations remained the main oxazolidinone resistance mechanism in enterococci, a recent analysis on a global collection of enterococcal clinical isolates showed that *optrA* prevailed in *E. faecalis* species.[29]

A distinctive feature of *optrA* is its nucleotide variability consequently reflected in its amino acid sequence. Shortly after identification of the gene, two studies on the prevalence of the *optrA* gene in enterococci of clinical and animal origin in China displayed the presence of several gene variants compared with the WT.[175,176] All the allelic variants showed amino acid substitutions whose impact on the phenotype of resistance was not to date clarified. Very recently, Schwarz *et al.*[15] proposed that the WT OptrA and some protein variants (D, EDP, KD, KLDP, RD, RDK and RDKP) are commonly found in linezolid-resistant isolates, while other variants (DDTD, EYDM, EYDDK, EYDNDM and KDTP) are commonly identified in linezolid-susceptible ones. From the comparison of all the OptrA variants known so far, it was found that the Italian variant ($OptrA_{E35048}$) is much more dissimilar from the WT and from other variants showing a limited number of amino acid substitutions. Morroni *et al.*[177] and Schwarz *et al.*[15] listed the OptrA protein variants.

To date, a plethora of *optrA*-carrying genetic environments into the chromosomal DNA and on different plasmids, prophages and transposons have been reported (Table 5). The review by Schwarz *et al.*[15] showed the structural comparison of *optrA*-carrying plasmids in enterococci. In these platforms, the gene is often associated with *fexA*, responsible for phenicol resistance, and other resistance genes, suggesting that *optrA* may persist and spread also thanks to the selective pressure imposed by the use of antimicrobial agents other than phenicols and oxazolidinones.[15,212] Sex pheromone-responsive *optrA*-carrying plasmids have been found in *E. faecalis* isolates pointing out the huge flexibility of the *optrA* genetic background within the enterococcal population.[186,188] Notably, the *optrA* genetic contexts are often flanked by IS elements (mainly IS*1216*) in the same or opposite orientation, which could be able to form minicircles (also known as translocatable units), thereby promoting the *optrA* mobility.[15,178] Besides IS*1216*, *optrA* was also associated with IS*Efa15* in a novel composite transposon Tn*6628* and with IS*Chh1*-like in a porcine *C. coli* isolate from China.[104,209]

The spread of the *optrA* gene, besides to *Enterococcus* spp., also in other bacterial genera from several sources is a matter of great concern. The gene was in fact detected in other Gram-positive bacteria, such as *S. aureus*,[198,213] *S. sciuri* and *Staphylococcus simulans*,[84,85,169,196,197] *Streptococcus agalactiae*, *S. suis*, *S. parasuis* and *Streptococcus gallolyticus*,[28,114,160,179,199–201,214] *Aerococcus viridans*,[207] *Lactococcus garvieae*,[203] *Listeria monocytogenes*,[15] *Listeria innocua*,[204] *V. lutrae*[161] and *C. perfringens*,[205,206] and even in Gram-negative isolates, such as *C. coli* and *C. jejuni*[208–211] and *Fusobacterium* spp. and *Salmonella* spp.[15] In the most bacterial genera, the *optrA* genetic contexts are located on conjugative plasmids or, less frequently, on chromosomal transposons, such as Tn*6647*, Tn*6823*, Tn*6261*, Tn*7363* and Tn*6993*.[157,161,185,197,198] In

Table 5. *optrA*-carrying genetic elements currently known

Strain	Origin	Genetic element (kb)	Accession numbers	References
Enterococcus spp.				
E. faecalis E349	Human (China)	pE349 (36.3)	KP399637	162
E. faecalis 10-2-2	Pig (China)	p10-2-2 (~60)	KT862775	178
E. faecalis E121	Human (China)	pE121 (~80)	KT862776	178
E. faecalis E419	Human (China)	pE419 (~80)	KT862777	178
E. faecalis FX13	Pig (China)	pFX13 (~34)	KT862778	178
E. faecalis SF35	Chicken (China)	pSF35 (~65)	KT862779	178
E. faecalis XY17	Pig (China)	pXY17 (~30)	KT862780	178
E. faecalis E016	Human (China)	Chromosomal fragment (29.1)	KT862781	178
E. faecalis E079	Human (China)	Chromosomal fragment (14.2)	KT862782	178
E. faecalis E147	Human (China)	Chromosomal fragment (6.0)	KT862783	178
E. faecalis G20	Pig (Tibet)	Chromosomal fragment (17.5)	KT862784	178
E. faecalis LY4	Chicken (China)	Chromosomal fragment (13.1)	KT862785	178
E. faecalis 599	Human (USA)	NA	ALZI01000000	179
E. faecalis E1379A	Water (Tunisia)	pAF379 (45.6)	NHNF00000000	167
E. faecalis 6742	Human (Poland)	p6742_1 (36.3)	KY513280	180
E. faecalis UW13078	Human (Germany)	NA	SRP128637	181
E. faecalis UW14261	Human (Germany)	pE349-like (40.0)	SRP128637	181
E. faecalis UW15200	Human (Germany)	Unnamed plasmid (~75)	SRP128637	181
E. faecalis UW15335	Human (Germany)	Unnamed plasmid (~75)	SRP128637	181
E. faecalis UW15420	Human (Germany)	Unnamed plasmid (~80)	SRP128637	181
E. faecalis UW15589	Human (Germany)	Unnamed plasmid (~100)	SRP128637	181
E. faecalis UW15602	Human (Germany)	Unnamed plasmid (~75)	SRP128637	181
E. faecalis UW15712	Human (Germany)	Unnamed plasmid (~70)	SRP128637	181
E. faecalis KUB3006	Human (Japan)	pKUB3006-4 (36.3)	AP018542	141
E. faecalis KUB3007	Human (Japan)	pKUB3007-4 (36.3)	AP018547	141
E. faecalis N60443F	Cattle (USA)	pN60443F-2 (41.6)	CP028725	105
E. faecalis N48037F	Pig (USA)	pN48037F-3 (40.3)	CP028723	105
E. faecalis 29462	Human (China)	p29462 (21.6)	MH225419	182
E. faecalis 1203_10W003	Human (China)	p1203_10W003 (9.1)	MH225415	182
E. faecalis 1207_26W003	Human (China)	p1207_26W003 (8.1)	MH225416	182
E. faecalis WHXH	Human (China)	pWHXH (6.7)	MH225422	182
E. faecalis TZ2	Human (China)	Chromosomal fragment (75.1)	MH225421	182
E. faecium 19506	Human (China)	Chromosomal fragment (22.7)	MH225417	182
E. faecalis E035	Pig (China)	pE035 (121.5)	MK140641	183
E. faecalis C25	Pig (China)	Chromosomal fragment (16.6)	MK251150	184
		pC25-1 (45.6)	CP030043	
E. faecalis C54	Pig (China)	pC54 (64.5)	CP030046	184
E. faecalis E1731	Pig (China)	Tn*6674* (12.9)	MK737778	185
E. faecalis E211	Pig (China)	pE211 (77.5)	MK425644	186
E. faecalis E508	Pig (China)	pE508 (84.5)	MK425645	186
E. faecalis 190AC	Dog (China)	Unnamed plasmid (~60)	VWNX00000000	169
E. faecalis 3-8	Beef (China)	Unnamed plasmid (~60)	VWNN00000000	169
E. faecalis 82AC	Dog (China)	Unnamed plasmid (~100)	VWNU00000000	169
E. faecalis 114AC	Dog (China)	Unnamed plasmid (~100)	VRVK00000000	169
E. faecalis 8-2	Caraway seed (China)	Unnamed plasmid (~60)	VWOG00000000	169
E. faecalis 75AC	Dog (China)	Unnamed plasmid (~90)	VWNJ00000000	169
E. faecalis 131AC	Dog (China)	Unnamed plasmid (~60)	VRVN00000000	169
E. faecalis 109AC	Dog (China)	Chromosomal DNA	VWNK00000000	169
E. faecalis 11-7	Egg (China)	Chromosomal DNA	VWNO00000000	169
E. faecalis 52AC	Dog (China)	Chromosomal DNA	VWNR00000000	169
E. faecalis 121NS	Dog (China)	Chromosomal DNA	VWNW00000000	169
E. faecalis L9	Pig (Brazil)	pL9 (58.6)	CP041776	102

Continued

Table 5. *Continued*

Strain	Origin	Genetic element (kb)	Accession numbers	References
E. faecalis EF02	Human (China)	pEF-L13/optrA (8.3)	MT874924	103
E. faecalis M17/0149	Human (Ireland)	pM17/0149 (36.3)	MN831410	154
E. faecium strain M17/0314	Human (Ireland)	pM17/0314 (103.6)	MN831413	154
E. faecalis M17/0240	Human (Ireland)	plasmid optrA_I (10.5)	MN831414 (partial)	154
E. faecalis M18/0173	Human (Ireland)	plasmid optrA_II (9.7)	MN831415 (partial)	154
E. faecalis M18/0906	Human (Ireland)	plasmid optrA_IV (11.7)	MN831417 (partial)	154
E. faecalis M18/0497	Human (Ireland)	plasmid optrA_VI (12.6)	MN831419 (partial)	154
E. faecalis S7316	Human (Japan)	pS7316optrA (68.4)	LC499744	187
E. faecalis X526	Human (Spain)	Unknown genetic element (11.2)	MN731743 (partial)	155
E. faecalis C9952	Human (Spain)	Unknown genetic element (12.7)	MN731744 (partial)	155
E. faecalis C9901	Human (Spain)	Unnamed plasmid (21.5)	MN848142 (partial)	155
E. faecalis P10748	Human (China)	pEF10748 (53.2)	MK993385	188
E. faecalis F106	Water (Switzerland)	Chromosomal DNA	JAGMTZ00000000	172
E. faecalis F143	Water (Switzerland)	Chromosomal DNA	JAGMTY00000000	172
E. faecalis F162_1	Water (Switzerland)	plasmid (53)	JAMTX00000000	172
E. faecalis EN3	Water (Italy)	pEfs-EN3 (16.5)	MT683614	171
E. faecalis ES-1	Pig (China)	Chromosomal DNA	PRJNA609523	189
E. faecalis EFs17-1	Animal (South Korea)	pEFs17-1 (36.3)	MT223178	15
E. faecalis	Pig (China)	p1 (74.5)	MH830363	15
E. faecalis EF123	Chicken (China)	pEF123 (79.7)	KX579977	15
E. faecalis L15	Pig (Brazil)	pL15 (82.9)	CP042214	15
E. faecalis L8	Pig (Brazil)	pL8-A (91.5)	CP042217	15
E. faecalis E211	Pig (China)	pE211-2 (87.8)	MK784777	15
E. faecalis AR-0780	Human (USA)	Tn*6674* (12.9)	PRJNA523425	190
E. faecalis WE0851	Human (Scotland)	pWE0851-1 (59.7)	PRJEB36950	157
E. faecalis WE0254	Human (Scotland)	pWE0254-1 (80.5)	PRJEB36950	157
E. faecalis WE0438	Human (Scotland)	pWE0438 (61.3)	PRJEB36950	157
E. faecalis TM6294	Human (Scotland)	pTM6294-2 (52.8)	PRJEB36950	157
E. faecalis BX5936	Human (Scotland)	pBX5936-1 (68.6)	PRJEB36950	157
E. faecalis BX8117	Human (Scotland)	pBX8117-2 (41.8)	PRJEB36950	157
E. faecalis EFS17	Pig (South Korea)	Chromosomal DNA	NZ_CP085289	159
E. faecalis EFS108	Pig (South Korea)	Chromosomal DNA	NZ_CP085294	159
E. faecalis SY-1	Goat (China)	pSY-1-optrA (36.0)	CP078016	191
E. faecium C1904	Human (USA)	NA	AMBD01000000	179
E. faecium F120805	Human (Ireland)	pF120805 (72.9)	KY579372	82
E. faecium UW7931	Human (Germany)	Unnamed plasmid (~105)	SRP128637	181
E. faecium UW9805	Human (Germany)	Unnamed plasmid (~100)	SRP128637	181
E. faecium UW10156	Human (Germany)	Unnamed plasmid (~80)	SRP128637	181
E. faecium UW10862	Human (Germany)	Unnamed plasmid (~245)	SRP128637	181
E. faecium UW12119	Human (Germany)	Unnamed plasmid (~245)	SRP128637	181
E. faecium UW12227	Human (Germany)	Unnamed plasmid (~130)	SRP128637	181
E. faecium UW15425	Human (Germany)	Unnamed plasmid (~75)	SRP128637	181
E. faecium E35048	Human (Italy)	pE35048-oc (41.8)	MF580438	104
E. faecium FSIS1608820	Cattle (USA)	pFSIS1608820 (28.2)	CP028728	105
E. faecium GJA5	Pig (China)	Chromosomal fragment (16.1)	MK251151	184
E. faecium SC1	Pig (China)	Chromosomal fragment (26.0)	MK251152	184
E. faecium SC18	Pig (China)	Chromosomal fragment (26.7)	MK251153	184
E. faecium YG1	Pig (China)	Chromosomal fragment (26.7)	MK251154	184
E. faecium 15-307-1	Human (France)	p15-307-1_02 (103)	CP044318	153
E. faecium M17/0314	Human (Ireland)	plasmid optrA_III (8.0)	MN831416 (partial)	154
E. faecium M16/0594	Human (Ireland)	Chromosomal fragment (10.7)	MN831418	154
E. faecium O_03	Human (Ireland)	pEfmO_03 (58.6)	MT261365	192
E. faecium VB3025	Human (India)	Chromosomal DNA,	CP040236	193

Continued

Table 5. *Continued*

Strain	Origin	Genetic element (kb)	Accession numbers	References
		pV3240_2 (142.8)	CP040238	193
E. faecium VB3240	Human (India)	Chromosomal DNA	CP040369	193
E. faecium AVS0243	Water (Switzerland)	pAVS02435_2 (36.4)	CP072896	172
E. faecium F39	Water (Switzerland)	Chromosomal DNA	CP072881	172
E. faecium F88	Water (Switzerland)	pF88_1 (246.3)	CP072879	172
E. faecium DY28	Pig (China)	pDY28-optrA (54.9)	PRJNA673930	108
E. faecium DY32	Pig (China)	pDY32 (175.5)	PRJNA673930	108
E. faecium VB976	Human (India)	pVB976_p2 (123.6)	CP072588	194
E. faecium BP5067	Human (India)	pBP5067_P1 (122.1)	CP059807	194
E. faecium BA17124	Human (India)	pBA17124_P1 (130.5)	CP059785	194
E. casseliflavus 10-1	Beef (China)	Chromosomal DNA	VWOB00000000	169
E. casseliflavus DY31	Pig (China)	pDY31 (75.6)	PRJNA673930	108
E. gallinarum EG81	Pig (China)	Chromosomal Tn*554*-like (NA)	CP050816	195
		pEG81-1 (51.6)	CP050817	
E. gallinarum FS4	Pig (Italy)	pEgFS4-1 (34.6)	MZ291452	106
E. hirae F104	Water (Switzerland)	pF104_2 (56.9)	CP072892	172
E. hirae F105	Water (Switzerland)	Unnamed plasmid (36)	JAGMUA00000000	172
E. raffinosus F162_2	Water (Switzerland)	Chromosomal DNA	CP072888	172
Staphylococcus spp.				
S. sciuri S25-1	Pig (China)	Chromosomal fragment (23.9)	KX447566	196
S. sciuri MS58	Pig (China)	Chromosomal fragment (28.8)	KX447567	196
S. sciuri S13-1	Pig (China)	Chromosomal fragment (3.4)	KX447568	196
S. sciuri S031-25	Pig (China)	Chromosomal fragment (24.0)	KX447569	196
S. sciuri S032-3	Pig (China)	Chromosomal fragment (21.5)	KX447570	196
S. sciuri MS11-3	Pig (China)	Chromosomal fragment (28.2)	KX447571	196
S. sciuri S49-1	Pig (China)	Chromosomal fragment (21.8)	KX447572	196
S. sciuri W028-3	Pig (China)	pWo28-3 (60.5)	KT601170	84
S. sciuri Wo35-20	Pig (China)	pWo35-20, partial (31.3)	KX982166	85
S. sciuri Wo28-1	Pig (China)	pWo28-1 (60.5)	KX982171	85
S. sciuri Wo27-9	Pig (China)	pWo27-9 (55.7)	KX982169	85
S. sciuri Wo33-7	Pig (China)	Chromosomal fragment (20.3)	KX982173	85
S. sciuri Wo33-13	Pig (China)	Chromosomal fragment (25.0)	KX982174	85
S. sciuri W72	Pig (China)	Chromosomal fragment (29.1)	KX982167	85
S. sciuri Wo19-3	Pig (China)	Chromosomal fragment (12.3)	KY056650	85
S. sciuri Wo35-29	Pig (China)	Chromosomal fragment (14.6)	KX982168	85
S. sciuri BY05	Pig (China)	Chromosomal fragment (22.7)	MF805731	197
S. sciuri G07	Dog (China)	Chromosomal fragment (17.5)	MF805732	197
S. sciuri 53NC	Dog (China)	Chromosomal DNA	VWOD00000000	169
S. aureus SA01	Chicken (China)	Tn*6823* (16.3)	CP053075	198
S. simulans IY19	Pig (China)	Chromosomal fragment (18.8)	MF805730	197
Streptococcus spp.				
S. suis YS21	Pig (China)	Chromosomal DNA	ALMH01000001	179
S. suis YS35	Pig (China)	Chromosomal DNA	ALMN01000021	179
S. suis YS39	Pig (China)	Chromosomal DNA	ALMO01000001	179
S. suis YS49	Pig (China)	Chromosomal DNA	ALMT01000101	179
S. suis YS50	Pig (China)	Chromosomal DNA	ALMV01000119	179
S. suis YS57	Pig (China)	Chromosomal DNA	ALMZ01000078	179
S. suis YSJ17	Pig (China)	φSsuYSJ17-3 (56.7)	CP032064	199
S. suis SFJ44	Pig (China)	Genomic island (43.8)	CP031970	114
S. suis SC181	Pig (China)	φSC181 (54.8)	MK359990	200
S. suis SC216	Pig (China)	ICE*SsuSC216* (53.0)	MK359991	200
S. suis SC317	Pig (China)	ICE*SsuSC317* (103.3)	MK359989	200
S. suis CQ2B66	Pig (China)	Chromosomal DNA	PRJNA623715	201

Continued

Table 5. *Continued*

Strain	Origin	Genetic element (kb)	Accession numbers	References
S. suis BJCY50	Pig (China)	Chromosomal DNA	PRJNA623715	201
S. suis F5-1HN	Pig (China)	Chromosomal DNA	PRJNA623715	201
S. suis BJCY29	Pig (China)	Chromosomal DNA	PRJNA623715	201
S. suis BJAY75	Pig (China)	Chromosomal DNA	PRJNA623715	201
S. suis BS11F	Pig (China)	Chromosomal DNA	PRJNA623715	201
S. suis SC3B24	Pig (China)	Chromosomal DNA	PRJNA623715	201
S. suis CQ2B20R	Pig (China)	Chromosomal DNA	PRJNA623715	201
S. suis HNAY30	Pig (China)	Chromosomal DNA	PRJNA623715	201
S. suis HNBY23	Pig (China)	Chromosomal DNA	PRJNA623715	201
S. suis HNAY3	Pig (China)	Unamed plasmid (~40)	PRJNA623715	201
S. suis 1112S	Pig (China)	ICE*Ssu1112S* (74.3)	MW790610	202
S. parasuis H35	Pig (China)	Chromosomal DNA	CP076721	160
Other Gram-positive bacteria				
L. garvieae LG592	Human (China)	pLG592-optrA (42.0)	MW310586	203
L. garvieae LG606	Human (China)	pLG606-optrA (69.6)	MW310587	203
L. garvieae LG728	Human (China)	pLG728-optrA (77.6)	MW310588	203
L. garvieae LG791	Human (China)	pLG791-optrA (76.8)	MW310589	203
L. garvieae LG1074	Human (China)	pLG1074-optrA (85.8)	MW310590	203
L. garvieae LG1267	Human (China)	pLG1267-optrA (71.8)	MW310591	203
L. innocua LI42	Food (China)	Chromosomal DNA	SAMN18079989	204
L. innocua LI47	Food (China)	Chromosomal DNA	SAMN18080006	204
L. innocua LI203	Food (China)	Chromosomal DNA	SAMN18080009	204
C. perfringens 2C45	Chicken (China)	p2C45 (148.6)	NZ_JAAQTM010000004	205
C. perfringens QHY-2	Sheep (China)	Unknown	PRJNA735902	206
A. viridans 1417-4A	Pig (Italy)	pAv-optrA (37.8)	MW364930	207
V. lutrae BN31	Pig (China)	Tn*7363* (12.3)	CP081833	161
Gram-negative bacteria				
C. coli 1712SZ1KX20C	Chicken (China)	Genomic island (14.6)	PRJNA613634	208
C. coli 18QD2YX29C	Duck (China)	Genomic island (18)	PRJNA613634	208
C. coli JZ_1_15	Pig (China)	Chromosomal fragment (6.8)	CP047214	209
C. coli JZ_1_95	Pig (China)	Chromosomal fragment (6.8)	CP047197	209
C. coli SH52	Pig (China)	Chromosomal fragment (6.8)	MT780491	209
C. coli SH_72	Pig (China)	Chromosomal fragment (6.8)	MT780492	209
C. coli SH_22	Pig (China)	Chromosomal fragment (10.3)	MT780493	209
C. coli CC19CH075	Chicken (China)	Genomic island (18.5)	CP068581	210
C. coli CC19DZ036	Duck (China)	Genomic island (11.2)	CP068565	210
C. jejuni 542-1C	Pigeon meat (China)	Genomic island (21.3)	NA	211
C. jejuni CC19PF065	Pig (China)	Genomic island (18.2)	CP068567	210
C. jejuni ZS007	Duck meat (China)	Genomic island (22.7)	CP048771	210

NA, not available.

streptococci, *optrA* is instead carried by ICEs, prophages or pathogenicity islands,[114,179,199,200] though very recently, the first non-conjugative *optrA*-carrying plasmid was reported in a porcine *S. suis* isolate from China.[201] Of particular concern is the co-occurrence of *vanA* (associated with Tn*1546* variants) and *optrA* (located on a Tn*554*-related transposon) in linear plasmids that seem to have become increasingly important in the dissemination of Tn*1546* among *E. faecium* isolates.[194] Interestingly, a study demonstrated that the acquisition of an *optrA*-harbouring plasmid by *E. faecalis* did not affect the growth rates of the transconjugant compared with the recipient. Therefore, as assumed for the *cfr*-carrying plasmids, a low fitness cost could promote the spread and the maintenance of the *optrA* gene within the bacterial population.[180]

The poxtA gene

In 2018, Antonelli *et al.* described a novel transferable oxazolidinone resistance gene, named *poxtA* (**p**henicols, **ox**azolidinones and **t**etracyclines resistance), in a linezolid-resistant *cfr*-positive MRSA from a cystic fibrosis patient.[215,216] The *poxtA* gene encodes a ribosomal protection protein of the ARE ABC-F family (lineage F of the ABC superfamily proteins associated with antibiotic resistance),[163] which is distantly related to OptrA and able to

confer reduced susceptibility to phenicols, oxazolidinones and tetracyclines.[216] Very recently, Crowe-McAuliffe *et al*.[164] demonstrated that perturbation of the P-site tRNA by the PoxtA protein modifies the conformation of the attached nascent chain, thereby reducing the affinity of the antimicrobial agents to their binding site and leading to phenicol and oxazolidinone resistance. Furthermore, the same authors found no evidence for PoxtA conferring resistance to tetracycline, suggesting to reassigning the letters from the PoxtA acronym from **p**henicol-**ox**azolidinone **t**etracycline **A** to **p**henicol-**ox**azolidinone **t**ransmissible **A**, analogous to OptrA.[164]

The *poxtA* gene, flanked by two IS*1216* elements, was found to be associated with a 48 kb Tn*6349* composite transposon, inserted into a φN315-like prophage found in the chromosome of MRSA AOUC-0915. Tn*6349*, bounded by two IS*1216* elements, carried two transposons: the *poxtA*- and *fexB*-containing Tn*6657* and the *cfr*-carrying Tn*6644*.[76] Schwarz *et al*. suggested that Tn*6349* may not be considered a true composite transposons—since this transposon was bounded by IS*1216* (members of the IS*26* family) orientated in the same direction—thus, it should be termed as pseudo-compound transposon.[15,217]

In enterococci, a plasmid carrying *poxtA* was first detected in Italy from a porcine *E. faecium* isolate; the gene was able to confer linezolid resistance also in the absence of other known oxazolidinone resistance mechanisms.[218] Later, the *poxtA* gene was also detected in enterococci from humans,[15,154,219–222] from animals,[15,101,107,108,183,184,221,223,224] from food-producing animals[15,225–228] and from environmental sources.[15,171,172,229] Latest surveillances on the prevalence of the *poxtA* gene among clinical, animal or environmental linezolid-resistant enterococci collected in several countries reported that this resistance gene is the most prevalent oxazolidinone resistance mechanism in *E. faecium* independently from the presence of *optrA* gene and 23S rRNA alterations.[15,97,108,221,222,225,226]

Unlike the OptrA and Cfr(C) proteins, the amino acid sequence of PoxtA is essentially conserved, only five amino acid substitutions have been identified: R256H and I219L in *E. faecium* isolates[226,229] and E14K, E140K, F141L in a *Lactobacillus salivarius* strain.[230] Very recently, a new gene variant, named *poxtA2*, was found in *E. faecalis* and *Enterococcus casseliflavus* isolates of pig origin and in a human *Enterococcus gallinarum* isolate.[158,231,232] Unlike *poxtA*, *poxtA2* was not truncated by an IS*1216* insertion at the 3′ end, thus eight new amino acid (TPEEEQKY) replaced the six amino acid (GSVAKF) of WT protein. Baccani *et al*.[232] confirmed that *poxtA2* was functional in conferring protection against linezolid in the enterococcal background and hypothesized that this variant could be considered as a presumed *poxtA* ancestor. Another considerable difference between the *optrA* and *poxtA* genes concerns their diffusion: *optrA* is widespread in Gram-positive and even in Gram-negative bacteria, while to date *poxtA* was only identified in *Enterococcus* spp. except the first detection in an MRSA,[213] in *Staphylococcus haemolyticus* and *Staphylococcus saprophyticus* isolates[233] and very recently in a *L. salivarius* strain.[230] Interestingly, *L. salivarius* harboured two *poxtA* copies: one located on a non-conjugative MDR plasmid and another chromosomal copy, which was truncated by the insertion of an IS*Lasa1* element into the 3′-end of *poxtA*.[230] Some *poxtA* genetic contexts have been characterized, they were mainly found on different plasmids that seem to play a key role in the spread of this oxazolidinone resistance gene among enterococci (Table 6). The *poxtA* genetic contexts, often bracketed by IS*1216*-like elements in the same or in opposite orientation, were mobilizable as translocatable units.[15,234,221] On the other hand, Shan *et al*.[234] have suggested that IS*1216*E-mediated transposition and translocation processes can promote the spread of *poxtA* gene and ensure its persistence within the enterococcal population. The same authors also showed how mobilizable *poxtA*-carrying plasmids could transfer with the help of a conjugative plasmid by homologous recombination in *E. faecalis* and by replicative transposition in *Enterococcus lactis*.[96] Very recently, Xu *et al*.[97] observed that, during the conjugation process, *poxtA* plasmids can undergo recombination phenomena leading to the formation of mosaic structures that differ in size and organization from those of the parental isolates. The review by Schwarz *et al*.[15] showed the structural comparison of *poxtA*-carrying plasmids in enterococci.

Occurrence of multiple oxazolidinone resistance genes

The presence of two or more oxazolidinone resistance genes may account for higher oxazolidinone MICs both when genes are located on the same genetic element or co-harboured in the same bacterial host but on different genetic backgrounds. Immediately after the discovery of the *optrA* gene, two isolates carrying simultaneously *cfr* and *optrA*, the only characterized oxazolidinone resistance genes at that time, were identified.[109] Since then, a number of publications described the presence of two oxazolidinone resistance determinants on the same genetic element (Table 7). The co-location occurred both in plasmids and chromosomal elements and so far, has been reported in *Mammaliicoccus*, *Staphylococcus* and *Enterococcus* both of human and animal origin. The most common co-localization involved *cfr* and *optrA* or *cfr*(D) and *optrA* (Table 7).

Along with the co-locations, several publications described the presence of two or more oxazolidinone resistance genes (even a double copy of the same gene) in a single isolate but carried by diverse genetic elements (Table 8). In these cases, the combinations involved all genes other than *cfr*(E) and *poxtA2*. Such co-occurrences were reported in *Enterococcus*, *Clostridium*, *Streptococcus*, *Vagococcus* and *Lactobacillus* and mainly involved *cfr* and *optrA* or *optrA* and *poxtA* (Table 8). Interestingly, the *cfr*(D) gene is always associated with other oxazolidinone resistance genes: co-localized with *optrA* or *poxtA2* on enterococcal plasmids;[15,153,154,158,159] or co-harboured with a chromosomal *optrA*.[160,161] Worthy of note is the occurrence of the *cfr*, *optrA* and *poxtA* genes in two non-conjugative plasmids of an *E. gallinarum* isolate in Italy,[106] in three distinct plasmids of several sizes found in *E. casseliflavus* in China[108] and in an *E. faecalis* isolate in Belgium,[228] all of swine origin.

Moreover, various genetic lineages or CCs of *S. aureus*, *E. faecalis* and *E. faecium* isolates carrying *cfr*, *optrA* and *poxtA* genes have been detected during the past two decades all over the world. Due to the mobile character of these genes, their frequent association with MGEs and the observation that these MGEs can be exchanged across strain, species and genus boundaries, the oxazolidinone resistance genes are not found preferentially in a

Table 6. *poxtA/poxtA2*-carrying genetic elements currently known

Strain	Origin	Genetic element (kb)	Accession numbers	References
Enterococcus spp.				
E. faecium 25	Pig (China)	pC25-1 (67.6)	MH784601	223
E. faecium 27	Pig (China)	pC27-2 (62.3)	MH784602	223
E. faecium GZ8	Pig (China)	pGZ8 (36.9)	CP038162	226
E. faecium HB2-2	Chicken (China)	pHB2-2 (32.1)	CP038165	226
E. faecium SC3-1	Chicken (China)	pSC3-1 (36.8)	CP038167	226
E. faecium SCBC1	Pig (China)	pSCBC1 (41)	CP038169	226
E. faecium SDGJP3	Pig (China)	pSDGJP3 (51.6)	CP038171	226
E. faecium YN2-1	Pig (China)	pYN2-1 (41.3)	CP038173	226
E. faecium SDGJQ5	Chicken (China)	pSDGJQ5 (30.4)	CP038175	226
E. faecium HN11	Pig (China)	pHN11 (69.7)	CP038176	226
E. faecium M16/0594	Human (Ireland)	pM16/0594 (21.8)	MN831411	154
E. faecium E1077	Pig (China)	pE1077-23 (23.7)	MT074684	234
E. faecium T-E1077-31	Pig (China)	pT-E1077-31 (31.7)	MT074685	234
E. faecium F88	Surface water (Switzerland)	pF88_2 (41)	CP072880	172
E. faecium 18-465	Human (France)	p18-465_1 (24.3)	CP065753	222
E. faecium 18-276	Human (France)	p18-276_3 (35.6)	CP065757	222
E. faecium 18-042	Human (France)	p18-042_1 (9.4)	CP066216	222
E. faecium 17-318	Human (France)	p17-318_2 (38.4)	CP065772	222
E. faecium 16-164	Human (France)	p16-164 (27.2)	CP065776	222
E. faecium 16-021	Human (France)	p16-021_2 (38.7)	CP065779	222
E. faecium EF-3	Marine sediment (Italy)	pEfm-EF3 (27.7)	MT683615	171
E. faecium DY40	Pig (China)	pDY40-poxtA (21.2)	MW207677	108
E. faecium DY32	Pig (China)	pDY32-poxtA (27.3)	MW207676	108
E. faecium DY28	Pig (China)	pDY28-poxtA (43.3)	MW207671	108
E. faecium DY18	Pig (China)	pDY18-poxtA (34.9)	MW207668	108
E. faecium F179	Surface water (Switzerland)	pF179_3 (26.6)	CP072887	172
E. faecium F88	Surface water (Switzerland)	pF88_2 (41)	CP072880	172
E. faecium E843xGE-1-TC1	Pig (China)	pE843-TC-200 (200.5)	CP081503	96
E. faecium fac90	Pig (China)	pFac90-54 (54.3)	CP068246	97
E. faecalis E076	Pig (China)	pE076 (19.8)	MK140642	183
E. faecalis E035	Pig (China)	pE035 (121.5)	MK140641	183
E. faecalis C10	Pig (China)	pC10 (37.9)	MK861852	224
E. faecalis M18/0011	Human (Ireland)	pM18/0011 (18.2)	MN831412	154
E. faecalis V386	Manure (Italy)	pV386 (33.4)	MZ603802	158
E. faecalis 18-243	Human (France)	p18-243_2 (51.9)	CP065786	222
E. faecalis EF36	Food (South Korea)	pEFS36_2 (35.8)	NZ_CP085293	159
E. faecalis EF108	Pig (South Korea)	pEFS108_1 (97.5)	NZ_CP085295	159
E. faecalis E006	Pig (China)	pE006-19 (19.8)	CP082233	96
E. faecalis E006xJH2-2-TC1	Pig (China)	pE006-TC-121 (121.5)	CP081506	96
E. faecalis T90-3	Pig (China)	pT90-3 (71.1)	CP069131	97
E. faecalis T90-5	Pig (China)	pT90-5 (101.7)	CP069130	97
E. faecalis T90-6	Pig (China)	pT90-6 (149.5)	CP069129	97
E. hirae HDC14-2	Pig (China)	pHDC14-2.27K (27.3)	CP042294	15
E. hirae HDC14-2	Pig (China)	pHDC14-2.133K (133.3)	CP042290	15
E. hirae CQP3-9	Pig (China)	pCQP3-9_2 (33.1)	CP037957	184
E. hirae Fas4	Pig (China)	pFas4-1 (57.2)	MK798157	107
E. hirae GE-2	Marine sediment (Italy)	pEh-GE2 (24.8)	MT683616	171
E. hirae DY27	Pig (China)	pDY27-poxtA (53.5)	MW207669	108
E. hirae DY13	Pig (China)	pDY13-poxtA (25.2)	MW207667	108
E. gallinarum Eg-IV02	Human (Bolivia)	pIB-BOL (13.7)	MZ171245	232
E. gallinarum FS4	Pig (Italy)	pEgFS4-2 (38.3)	MZ291453	106
E. casseliflavus DY31	Pig (China)	pDY31-poxtA (16.5)	MW207674	108

Continued

Table 6. *Continued*

Strain	Origin	Genetic element (kb)	Accession numbers	References
E. lactis E843	Pig (China)	pE843-27 (27.8)	CP082268	96
Staphylococcus spp.				
S. aureus AOUC 09-15	Human (Italy)	Tn*6349* (48.3)	MH746818.1	76
S. haemolyticus GDY8P80P	Pig (China)	pY80 (55.7)	CP063444	233
Lactobacillus spp.				
L. salivarius BNS11	Pig (China)	Chromosomal fragment (10.9) pBNS11-37 kb (37.2)	CP089850 CP089852	230

Table 7. General features of strains containing co-located oxazolidinone resistance genes

Co-located oxazolidinone resistance genes	Species/isolate	Source (country)	Localization/genetic element (kb)	Accession numbers	References
cfr, *optrA*	*S. sciuri* W28-3	Pig (China)	pWo28-3 (60.5)	KT601170	84
	S. sciuri W35-20	Pig (China)	pWo35-20 (NA)	KX982166 (partial sequence)	85
	S. sciuri W28-1	Pig (China)	pWo28-1 (60.5)	KX982171	85
	S. sciuri W27-9	Pig (China)	pWo27-9 (55.7)	KX982169	85
	S. sciuri Wo33-7	Pig (China)	Chromosomal fragment (20.3)	KX982173	85
	S. sciuri W33-13	Pig (China)	Chromosomal fragment (25)	KX982174	85
	E. faecium F120805	Human (Ireland)	pF120805 (72.9)	KY579372	82
	E. faecium E35048	Human (Italy)	pE35048-oc (41.8)	MF580438	104
	E. faecium FSIS1608820	Cow (USA)	pFSIS1608820 (28.2)	CP028728	105
	E. faecalis S251	Pig (Italy)	Unnamed plasmid (~97)	MT723957 (partial sequence)	101
	E. avium S252	Pig (Italy)	Chromosomal fragment (16.4)	MT723957 (partial sequence)	101
	E. gallinarum FS4	Pig (Italy)	pEgFS4-1 (34.6)	MZ291452	106
cfr, *poxtA*	*S. aureus* AOUC 09-15	Human (Italy)	Tn*6349* (48.3)	MH746818.1	76
cfr(D), *optrA*	*E. faecium* 15-307-1	Human (France)	p15-307-1_02 (103)	CP044318	153
	E. faecium E8014	Human (Netherlands)	Plasmid 4 (11.4)	LR135354	153
	E. faecium M17/0314	Human (Ireland)	pM17/0314 (103.6)	MN831413	154
	E. faecium BP5067	Human (India)	pBP5067_P1 (122.1)	CP059807	15
	E. faecium BA17124	Human (India)	pBA17124_P1 (130.5)	CP059785	15
	E. faecalis BX8117	Human (Scotland)	pBX8117-2 (NA)	PRJEB36950	157
cfr(D), *poxtA2*	*E. faecalis* EFS0019	Pig (South Korea)	node #26 (31.8)	QUSQ00000000	231
	E. faecalis EF36	Food (South Korea)	pEFS36_2 (35.8)	NZ_CP085293	159
	E. faecalis EF108	Food (South Korea)	pEFS108_1 (97.5)	NZ_CP085295	159
	E. faecalis V386	Manure (Italy)	pV386 (33.4)	MZ603802	158
optrA, *poxtA*	*E. faecalis* E035	Pig (China)	pE035 (121.5)	MK140641	183
	E. faecalis S157	Pig (Italy)	Unnamed plasmid (~97)	MT723951 (partial sequence) MH746818[a]	101

NA, not available.

[a]Accession number of the *poxtA* genetic context of *S. aureus* AOUC 09-15 identical to the *poxtA* genetic background of *E. faecium* S157.

Table 8. General features of strains containing co-occurring oxazolidinone resistance genes

Species/isolate	Source (country)	Oxazolidinone resistance genes	Localization/genetic element (kb)	Accession numbers	References
E. faecalis 599799	Human (Thailand)	*cfr*	Chromosomal fragment (5.8)	JX910899[a]	29
		optrA	Unnamed plasmid (NA)	MF443373 (partial sequence)	
E. faecalis EF02	Human (China)	*cfr*	pEF-L18/*cfr* (11.8)	MT874923	103
		optrA	pEF-L13/*optrA* (8.3)	MT874924	
E. faecalis L9	Pig (Brazil)	*cfr*	pL9-A (7.7)	CP041775	102
		optrA	pL9 (57.5)	CP041776	
E. gallinarum 325	Pig (Italy)	*cfr*	Chromosomal fragment (9.5)	MT723959	101
		optrA	Chromosomal fragment (11.7)	MT723960	
E. hirae fas4	Pig (China)	*cfr*	pfas4-2 (85.6)	MK798156	107
		poxtA	pfas4-1 (57.2)	MK798157	
E. gallinarum FS4	Pig (Italy)	*cfr*, *poxtA*	pEgFS4-1 (34.6)	MZ291452	106
		poxtA	pEgFS4-2 (38.3)	MZ291453	
E. casseliflavus DY31	Pig (China)	*cfr*	pDY31-*cfr* (12.3)	MW207672	108
		optrA	pDY31-*optrA* (75.5)	MW207673	
		poxtA	pDY31-*poxtA* (16.5)	MW207674	
E. faecalis 687669, 687671	Human (Panama)	*cfr*(B)	Tn*6218*-like (8.4)	KR610408[b]	29
		optrA	Unnamed plasmid (NA)	MF443374 (partial sequence)	
E. faecalis KUB3006	Human (Japan)	*cfr*(B)	Tn*6218*-like (9.7)	AP018538	141
		optrA	pKUB3006-4 (36.3)	AP018542	
C. perfringens 19TSBNCP	Cattle (China)	*cfr*(C)	Chromosomal fragment (15.9)	CP073070	150
		optrA	Plasmid unnamed1 (63.8)	CP073071	
E. faecalis EF108	Food (South Korea)	*cfr*(D), *poxtA*2	pEFS108_1 (97.5)	NZ_CP085295	159
		optrA	Chromosomal fragment (NA)	SUB10526593	
E. faecalis X528	Human (Spain)	*cfr*(D)	Unknown genetic element (NA)	LR135354[c]	155
		optrA	Unknown genetic element (NA)	NA	
S. parasuis H35	Pig (China)	*cfr*(D)	pH35-cfrD (7.5)	CP076722	160
		optrA	Chromosomal fragment (10.4)	CP076721	
V. lutrae BN31	Pig (China)	*cfr*(D)	pBN31-cfrD (33.4)	CP081834	161
		optrA	Chromosomal Tn*7363* (13.6)	CP081833	
E. faecium M16/0594	Human (Ireland)	*optrA*	Chromosomal fragment (10.7)	MN831418	154
		poxtA	pM16/0594 (21.8)	NZ_MN831411	
E. faecium C10004	Air (Spain)	*optrA*	Unknown genetic element (NA)	NA	229
		poxtA	Unknown genetic element (NA)	NA	
E. faecium C10009	Air (Spain)	*optrA*	Unknown genetic element (NA)	NA	229
		poxtA	Unnamed plasmid (NA)	MN661250 (partial sequence)	
E. faecium F88		*optrA*	pF88_1 (246.3)	CP072879	172

Continued

Table 8. *Continued*

Species/isolate	Source (country)	Oxazolidinone resistance genes	Localization/genetic element (kb)	Accession numbers	References
	Surface water (Switzerland)	*poxtA*	pF88_2 (41)	CP072880	
E. faecium DY28	Pig (China)	*optrA*	pDY28-*optrA* (55)	MW207670	108
		poxtA	pDY28-*poxtA* (43.3)	MW207671	
E. casseliflavus DY32	Pig (China)	*optrA*	pDY32-*optrA* (175.5)	MW207675	108
		poxtA	pDY32-*poxtA* (27.3)	MW207676	
E. gallinarum EG81	Pig (China)	*optrA*	Chromosomal Tn*554*-like (NA)	CP050816	195
		optrA	pEG81-1 (51.6)	CP050817	
E. faecalis C25	Pig (China)	*optrA*	Chromosomal fragment (16.6)	MK251150	184
		optrA	pC25-1 (45.6)	CP030043	
E. faecium VB3025	Human (India)	*optrA*	Chromosomal DNA	CP040236	193
		optrA	pV3240_2 (142.8)	CP040238	
E. hirae HDC14-2	Pig (China)	*poxtA*	pHDC14-2.27K (27.3)	CP042294	15
		poxtA	pHDC14-2.133K (133.3)	CP042290	
L. salivarius BNS11	Pig (China)	Δ*poxtA*	Chromosomal fragment (10.9)	CP089850	230
		poxtA	pBNS11-37 kb (37.2)	CP089852	

NA, not available.

[a]Accession number of the *cfr* genetic context of *S. epidermidis* 426-3147L identical to the *cfr* genetic background of *E. faecalis* 599799.

[b]Accession number of the *cfr*(B) genetic context of *E. faecium* 448-18961R 98% identical to the *cfr*(B) genetic background of *E. faecalis* 687669 and 687671 isolates.

[c]Accession number of the *cfr*(D)-plasmid 4 of *E. faecium* E8014 100% identical to the *cfr*(D) genetic background of *E. faecalis* X528.

specific lineage of the aforementioned Gram-positive pathogens. The apparently disproportionately frequent occurrence of the gene *cfr* in the livestock-associated MRSA CC398 from livestock in Europe and North America is likely due to the fact that isolates of this CC are widespread among pigs, cattle and poultry and have—in contrast to isolates of other *S. aureus* CCs—been preferentially investigated for their antimicrobial resistance genes. The same is true for the *S. aureus* CC9 in Asian countries.

Concluding remarks

This review summarizes the current knowledge concerning the mechanisms of oxazolidinone resistance (ribosomal mutations and acquired resistance genes) and highlights the wide flexibility of all the genetic elements carrying the oxazolidinone resistance genes known to date. In particular, acquired resistance genes associated with MGEs, including plasmids, transposons, ICEs, prophages, genomic islands and ISs, pose a particular threat of dissemination of this type of resistance.[15] Our knowledge of the MGEs carrying oxazolidinone resistance genes points to the existence of a significant reservoir of such elements, especially among bacterial isolates from farm animals which in turn could easily end up in the food chain and thereby posing huge risks to public health.

Florfenicol, exclusively approved for use in veterinary medicine, is a broad-spectrum antimicrobial agent extensively used in livestock to prevent or to cure bacterial infections, but also as growth promoter in some countries.[15] It has a considerable impact on the dissemination of florfenicol resistance genes, including those also encoding resistance to oxazolidinones, despite the latter have not been approved for veterinary use.[15] Furthermore, it should be noted that *cfr*, *optrA* and *poxtA* are often co-localized on the same genetic element with genes that confer resistance to non-PhLOPS$_A$ antimicrobial agents, biocides and heavy metals.[15] Overall, both a direct and indirect selective pressure could play an important role in the selection, persistence and spread of the mobile oxazolidinone resistance genes in the bacterial population in human and veterinary settings.[15] The most efficient way of limiting the spread of these multiresistance genes is to reduce the selective pressure for acquired resistance determinants and other co-located resistance genes. This can only be achieved by the prudent use of phenicols, lincosamides and pleuromutilins, and also macrolides, tetracyclines and aminoglycosides, in animal production and veterinary medicine and of oxazolidinones in human medicine.[11,15] The knowledge of the genetic backgrounds of *cfr/cfr-like*-, *optrA*- and *poxtA*-mediated resistance—as summarized in this review—is essential for the understanding of the emergence and the spread of the mobile oxazolidinone resistance genes in several countries and in Gram-positive and Gram-negative bacteria.[11,15]

Further efforts, with consideration of the 'One Health' approach, are crucial to preserve the activity of oxazolidinones in clinical settings. An ongoing surveillance of the oxazolidinone-resistant isolates and distribution of *cfr* and its

variants, as well as *optrA* and *poxtA*, among Gram-positive and Gram-negative bacteria, is pivotal to limit their spread in environmental, animal and human settings.

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Transparency declarations

None to declare.

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