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Incidence, management and outcomes of the first *cfr*-mediated linezolid-resistant *Staphylococcus epidermidis* outbreak in a tertiary referral centre in the Republic of Ireland

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SUMMARY

Aim: To report the first Irish outbreak of *cfr*-mediated linezolid-resistant *Staphylococcus epidermidis*.

Methods: Linezolid-resistant *S. epidermidis* isolated at University Hospital Limerick from four blood cultures, one wound and four screening swabs (from nine patients) between April and June 2013 were characterized by pulsed-field gel electrophoresis (PFGE), multilocus sequence typing (MLST) and staphylococcal cassette chromosome (SCC*mec*) typing. Antibiotic susceptibilities were determined according to the guidelines of the British Society for Antimicrobial Chemotherapy. The outbreak was controlled through prohibiting prescription and use of linezolid, adherence to infection prevention and control practices, enhanced environmental cleaning, isolation of affected patients, and hospital-wide education programmes.

Findings: PFGE showed that all nine isolates represented a single clonal strain. MLST showed that they belonged to ST2, and SCC*mec* typing showed that they encoded a variant of SCC*mec*III. All nine isolates were *cfr* positive, and eight isolates were positive for the G2576T 23S rRNA mutation commonly associated with linezolid resistance. Isolates exhibited multiple antibiotic resistances (i.e. linezolid, gentamicin, methicillin, clindamycin, ciprofloxacin, fusidic acid and rifampicin). The adopted infection prevention intervention was effective, and the outbreak was limited to the affected intensive care unit.

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Conclusions: This is the first documented outbreak of *cfr*-mediated linezolid-resistant *S. epidermidis* in the Republic of Ireland. Despite this, and due to existing outbreak management protocols, the responsible micro-organism and source were identified efficiently. However, it became apparent that staff knowledge of antimicrobial susceptibilities and appropriate hygiene practices were suboptimal at the time of the outbreak, and that educational interventions (and re-inforcement) are necessary to avoid occurrence of antimicrobial resistance and outbreaks such as reported here.

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Introduction

Linezolid is a bacteriostatic oxazolidinone antibiotic that binds to the 50S subunit of bacterial ribosomes and inhibits protein synthesis.[1] It is licensed for use in 70 countries worldwide, and has been used to treat over four million patients since its introduction in 2000.[2] Linezolid is currently approved for use in the Republic of Ireland for treatment of multi-drug-resistant Gram-positive infections, including nosocomial and community-acquired pneumonia and skin and soft tissue infections, including those caused by meticillin-susceptible and -resistant staphylococci, coagulase-negative staphylococci and vancomycin-resistant enterococci.

Recent surveillance data indicate that <1% of *Staphylococcus aureus* and 2% of coagulase-negative *Staphylococcus* spp. (CoNS) are resistant to linezolid.[3–5] Mutations in chromosomal genes encoding the central loop of domain V of the 23S rRNA, with the G2576T substitution, are the most commonly reported resistance mechanism.[6] Substitutions for T2500A, T2504A and G2215A have also been identified in some staphylococci from clinical infections, as have mutations in the genes for ribosomal proteins L3, L4 and L22.[7,8] In contrast with mutational resistance, the *cfr* (chloramphenicol-florfenicol resistance) gene encodes a transferable 23S rRNA methyltransferase conferring resistance to linezolid.[9] The *cfr* gene encodes resistance to phenicols, lincosamides, oxazolidinones, pleuromutilins and streptogramin A antimicrobials (the so-called 'PhLOPS$_A$ phenotype') and selected macrolides, thus conferring multi-drug resistance.[10] *cfr*-positive isolates pose an emerging global health threat,[11] and prompt recognition of this pattern of resistance is needed to prevent the establishment of reservoirs of *cfr*-positive bacteria in skin and gut flora.[12]

Outbreaks of *cfr*-mediated linezolid-resistant *S. aureus*[13,14] and *Enterococcus faecalis*[15] have been described previously. However, this paper describes the molecular epidemiology, management and outcomes of the first documented outbreak of *cfr*-mediated linezolid-resistant *Staphylococcus epidermidis* in the Republic of Ireland.

Methods

Setting

University Hospital Limerick (UHL) is a tertiary referral university teaching hospital with 483 inpatient beds. Patients are admitted from the community and from other hospitals located in the Mid-West of Ireland. The catchment population of the hospital is 300,000. The intensive care unit (ICU) is a medical-surgical unit that caters for patients over 16 years of age. At the time of this outbreak, the ICU had seven beds (including two isolation rooms). There were three handwashing stations located within the ICU, with alcohol hand gels at each bedspace. Two full-time consultant microbiologists and two infection prevention and control nurses were employed directly by UHL, and worked on-site at the time of the outbreak.

Index case identification

The index case patient for this outbreak was identified as a male in his twenties admitted to UHL in April 2013 following a deliberate self-poisoning. He was diagnosed with an aspiration pneumonia, and antimicrobial therapy was commenced with piperacillin-tazobactam 4.5 g TDS IV and clarithromycin 500 mg

Table I
Antibiotic susceptibility profiles (minimum inhibitory concentrations, mg/l)

Patient	Sex	PHE MIC Lin	Gent	Ox	Pen	Tei	Van	Clin	Ery	Cip	Moxi	Quin/Dalf	Tet	Dap	Fus	Rif
Patient A	M	>8	128	>16	>8	4	2	>8	0.5	>8				0.5	8	>2
Patient B	M	>8	128	>16	>8	4	4	>8	0.5	>8				0.5	8	>2
Patient C	M	>8	128	>16	>8	8	2	>8	0.5	>8		0.5		≤0.25	16	>2
Patient D	F	>8	128	>16	>8	8	2	>8	0.5	>8		0.5		≤0.25	16	>2
Patient E	M	>8	128	>16	>8	8	2	>8	0.5	>8		0.5		0.5	16	>2
Patient F	F	>8	256	>16	>8	4	2	>8	1	>8				0.5	8	>2
Patient G	F	>8	256	>16	>8	8	2	>8	1	>8				0.5	8	>2
Patient H	F	>8	256	>16	>8	8	2	>8	1	>8				0.5	8	>2
Patient I	M	>8	256	>16	>8	8	2	>8	0.5	>8	4	0.5	4	0.5	8	>2

PHE MIC, Public Health England minimum inhibitory concentration; Gent, gentamicin; Ox, oxacillin; Pen, penicillin; Tei, teicoplanin; Van, vancomycin; Clin, clindamycin; Ery, erythromycin; Lin, linezolid; Cip, ciprofloxacin; Moxi, moxiflocaxin; Quin/Dalf, quinopristin/dalfopristin; Tet, tetracycline; Dap, daptomycin; Fus, fuscidic acid; Rif, rifampicin; M, male; F, female.

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