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The emerging problem of linezolid-resistant *Staphylococcus*

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The oxazolidinone antibiotic linezolid has demonstrated potent antimicrobial activity against Gram-positive bacterial pathogens, including methicillin-resistant staphylococci. This article systematically reviews the published literature for reports of linezolid-resistant *Staphylococcus* (LRS) infections to identify epidemiological, microbiological and clinical features for these infections. Linezolid remains active against >98% of *Staphylococcus*, with resistance identified in 0.05% of *Staphylococcus aureus* and 1.4% of coagulase-negative *Staphylococcus* (CoNS). In all reported cases, patients were treated with linezolid prior to isolation of LRS, with mean times of 20.0±47.0 months for *S. aureus* and 11.0±8.0 days for CoNS. The most common mechanisms for linezolid resistance were mutation (G2576T) to the 23S rRNA (63.5% of LRSA and 60.2% of LRCoNS) or the presence of a transmissible *cfr* ribosomal methyltransferase (54.5% of LRSA and 15.9% of LRCoNS). The emergence of linezolid resistance in *Staphylococcus* poses significant challenges to the clinical treatment of infections caused by these organisms, and in particular CoNS.

Keywords: antimicrobial resistance, staphylococci, MRSA, coagulase-negative *Staphylococcus*, healthcare-associated infection

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative *Staphylococcus* (MRCoNS) are major causes of both healthcare- and community-associated infections.[1–3] Linezolid, with both oral and parenteral formulations, is one of the few therapeutic options shown to be effective against MRSA, including treatment of complicated skin and soft tissue infections (SSTIs), osteomyelitis, and pneumonia.[4] Little is known regarding the efficacy of linezolid for the treatment of serious infections caused by MRCoNS. In particular, linezolid is not approved for the treatment of patients with catheter-site or catheter-related bloodstream infections or infections where coagulase-negative *Staphylococcus* (CoNS) are commonly implicated.

Data from the USA and global surveillance studies report <1% of *S. aureus* and 2% of CoNS[5–9] are linezolid resistant. Nonetheless, multifocal outbreaks of linezolid-resistant *Staphylococcus* (LRS) have been reported,[10–13] and both vertical and horizontal transmission of linezolid resistance determinants may occur. Very little data exist regarding treatment and clinical outcomes for LRS infections. A better understanding of the epidemiology and mechanisms of linezolid resistance are important to mandate judicious use of linezolid, both to preserve its clinical utility and prevent nosocomial transmission of LRS. Herein we systematically review the literature for all reported cases of LRS infection to document the current epidemiological, microbiological and clinical features of LRS infection.

Methods

A literature search was performed in PubMed and EMBASE through April 2012 using the National Library of Medicine's medical subject heading (MeSH) terms 'linezolid', 'staphylococcus', and 'resistance' for articles that reported linezolid-resistant *Staphylococcus*. The search was not restricted by language. The references cited in these articles were examined to identify additional reports. Linezolid resistance in *Staphylococcus* is defined by both the Clinical Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) as a linezolid MIC of ≥8 mg/L, and this breakpoint was used throughout interpretation of the literature.

Publications identified from the literature search were checked by title and abstract. If an article appeared relevant, the full text was reviewed. Articles included original articles, short communications, correspondences, letters or case reports that documented clinical isolates of linezolid-resistant *Staphylococcus*. Exclusion criteria were as follows: review articles, basic research on the mechanism of linezolid resistance, reports that described isolates with linezolid MICs <8 mg/L and duplicate isolates reported in multiple studies.

Statistical analysis was performed with χ^2 and Fisher's exact test when appropriate to compare rates of linezolid resistance among *S. aureus* and CoNS.

Results

Incidence and epidemiology of linezolid resistance

Linezolid susceptibility among clinically significant isolates is monitored through two surveillance programmes, the global Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS) and the USA Linezolid Experience and Accurate Determination of Resistance (LEADER). In these programmes, non-duplicate isolates from bacterial pneumonia and acute bacterial skin and skin-structure infections (ABSSSIs) are submitted by participating clinical laboratories and linezolid susceptibility is confirmed centrally using CLSI reference broth microdilution (BMD) MIC methods. *Staphylococcus* tested between 2002 and 2010 by both LEADER and ZAAPS were almost universally susceptible to linezolid (Table 1).[5,8,9,14–16] LEADER documented linezolid resistance in 0.05% of *S. aureus* ($n=13/23077$ isolates), and 1.4% of CoNS ($n=73/5202$ isolates).[5,7,15–18] The increased incidence of linezolid resistance in CoNS is significant ($\chi^2=249.6$, $P<0.0001$). In contrast, ZAAPS identified only one LRSA[8,9,14] and 10 LRCoNS[9] between 2002 and 2010, yielding an overall 0.14% rate of linezolid resistance among 8122 *Staphylococcus* tested. Denominator data on the number of *S. aureus* and CoNS isolates tested by ZAAPS have not been published.

Including those isolates documented above, a total of 812 citations were identified from PubMed and 2757 citations from EMBASE searches. A further five articles were identified through manual review of the references found in these publications. Following exclusion as defined in the methods, 22 publications describing clinical isolates of LRSA ($n=65$ cases; Table 2) and 28 of LRCoNS ($n=351$ cases) were included in this review. The majority of LRS were isolated from patients in North America and Europe. Overall, 46.2% (30/65) of LRSA were reported in North America, 30.8% (20/65) in Europe, 20.0% (13/65) in Asia, and 3.1% (2/65) in South America (Table 2 and Figure 1). LRCoNS were reported in Europe (53.6% of 351 isolates), North America (42.5%), South America (2.8%) and Asia (1.1%; Figure 1). LRCoNS comprised nine different species, among which 76.4% (268/351) were *Staphylococcus epidermidis*, 9.1% (32/351) were *Staphylococcus hominis* and 8.8% (31/351) were *Staphylococcus haemolyticus*.

Clonal spread of LRS

Three reports of LRSA (13.6% of 22 studies) and 14 reports of LRCoNS (50% of 28 studies) documented clonal dissemination of LRS within or across healthcare settings (Table 2). Two LRSA outbreaks were described in Spain, each involving a single hospital, and 15 or 12 patients, respectively.[13,19] The third LRSA outbreak was reported from Japan, and involved seven patients in six different hospitals.[20] Both outbreaks in Spain were caused by LRSA harbouring the mobile *cfr* resistance gene, whereas the Japanese study did not test for *cfr*. Five linezolid-resistant *S. epidermidis* with identical PFGE types were recovered from patients at two geographically disparate institutions in the USA between 2006 and 2008.[7] In Greece, two clones of LRCoNS were identified among 26 patients in four hospitals.[21] Neither the US nor the Greek isolates harboured *cfr*. These publications did not distinguish LRCoNS colonization versus infection.

Mechanisms of linezolid resistance

Linezolid resistance occurs by mutations in the linezolid 23S rRNA binding site, the ribosomal proteins L3 and/or L4 of the peptide translocation centre of the ribosome or by acquisition of a plasmid-borne ribosomal methyltransferase gene, *cfr*.[22,23] All three mechanisms have been documented in LRSA and LRCoNS.[24] Sixty-three LRSA (Figure 2) and 322 LRCoNS (Figure 2) were investigated for mechanisms of linezolid resistance. While every molecular study evaluated the presence of the 23S rRNA G2576T mutation, a significant portion of the studies did not investigate *cfr* or L3/L4. More specifically, 52.4% of LRSA ($n=33/63$ isolates tested) and 74.2% of LRCoNS

Table 1. Incidence of linezolid resistance among *Staphylococcus* from ZAAPS global (2002–2010) and LEADER USA (2004–2010) surveillance programs

	Number of isolates tested			Number of isolates resistant (*S. aureus*)		Number of isolates resistant (CoNS)	
		LEADER					
Year	ZAAPS[a]	*S. aureus*	CoNS	ZAAPS	LEADER	ZAAPS	LEADER
2002	502	ND	ND	0	ND	0	ND
2003	373	ND	ND	0	ND	0	ND
2004	419	2872	496	0	0	0	1
2005	465	3021	530	0	1	0	6
2006	657	2913	808	1	1	1	13
2007	1138	3318	1020	0	2	2	18
2008	1214	3156	856	0	3	3	15
2009	1184	3257	816	0	5	1	12
2010	3045	4540	676	0	1	3	8

ND, no data.
[a]Numbers of *S. aureus* or CoNS tested not separately noted.

Table 2. Clinical information for linezolid-resistant *S. aureus*

Author (Reference)	Number of patients	Sample type(s)	Year(s) isolated	Location	Treatment	Outcome
North America						
Endimiani A, 2011[19]	8	sputum, throat swab	2000–2009	USA	TMP/SXT+DOX (2/6, 33.3%); TMP/SXT+DOX+VAN (2/6, 33.3%); TMP/SXT+CAZ+VAN (1/6, 16.7%)	survived: 5/6 (83.3%)
					MEM+CLI (1/6, 16.7%)	died: 1/6 (16.7%)
					ND: 2 cases	ND: 2 cases
Farrell DJ, 2011[18]	5	ND	2009	USA	ND	ND
Farrell DJ, 2009[7]	3	ND	2008	USA	ND	ND
Jones RN, 2008[5]	2	ND	2007	USA	ND	ND
Jones RN, 2007[17]	1	ND	2006	USA	ND	ND
Zhu W, 2007[22]	5	ND	ND	USA	ND	ND
Roberts SM, 2006[33]	2	nares, drainage	Mar 2005	USA	CLI+LNZ	survived
Peeters MJ, 2005[34]	1	wound	ND	USA	VAN	infection resolved but died of ventricular tachycardia
Meka VG, 2004[35]	1	ND	ND	USA	VAN	survived
Meka VG, 2004[23]	1	blood	ND	USA	ND	
Tsiodras S, 2001[10]	1	peritoneal fluid	ND	USA	AZM+GEN+LVX+Q/D (with *Enterococcus faecalis* and *Pseudomonas aeruginosa* infection)	infection resolved but died of underlying disease
South America						
Gales AC, 2006[36]	1	sputum	Jul 2002	Brazil	ND	ND
Toh SM, 2007[37]	1	sputum	2005	Colombia	ND	ND
Europe						
Sánchez García M, 2010[29]	12[a]	ND	Apr 2008–Jun 2008	Spain	TGC (5/10, 50.0%); VAN (4/10, 40.0%); VAN+TGC (1/10, 10.0%); ND: 2 cases	survived: 7/10 (70.0%); died: 3/10 (30.0%); ND: 2 cases
Morales G, 2010[13]	15	ND	Apr 2008–Jun 2008	Spain	TGC (6/12, 50.0%); VAN (5/12, 41.7%); VAN+TGC (1/12, 8.3%); ND: 3 cases	survived: 9/12 (75.0%); died: 3/12 (25.0%); ND: 3 cases
Hill RL, 2010[38]	2	cystic fibrosis, sputum	ND	UK	ND	ND
Wilson P, 2003[39]	1	wound swab, empyema fluid	ND	UK	TEC+RIF	survived
Hentschke M, 2008[40]	1	stool	Jun 2005	Germany	ND	ND
Ross JE, 2011[9]	1	ND	2006	Ireland	ND	ND

Asia							
An D, 2011[41]	1	blood and pleural fluid	ND	Korea	TMP/SXT+MIN+TGC		died
Ikeda-Dantsuji Y, 2011[20]	11	ND	2006–2008	Japan	ND		ND
Yoshida K, 2009[42]	1	blood, catheter, stool	Sep 2008	Japan	ND		ND

Abbreviations: +, positive; −, negative; ND, not done; TMP/SXT, trimethoprim/sulfamethoxazole; DOX, doxycycline; VAN, vancomycin; CLI, clindamycin; MEM, meropenem; CAZ, ceftazidime; MIN, minocycline; TGC, tigecycline; CIP, ciprofloxacin; GEN, gentamicin; DAP, daptomycin; Q/D, quinupristin/dalfopristin; TEC, teicoplanin; AZM, azithromycin; RIF, rifampicin; LVX, levofloxacin.

[a]The 12 isolates in reference 29 were also included in reference 13, therefore the 12 isolates were not included in the total number of LRSA strains.

(*n*=239/322 isolates tested) were tested for the presence of the *cfr* gene, and 7.9% of LRSA (5/63 isolates tested) and 29.2% of LRCoNS (*n*=94/322 isolates) were tested for the L3 and/or L4 mutation (Figure 2). G2576T was found among the majority of LRSA (63.5%, *n*=63 isolates tested; Figure 2) and LRCoNS (60.2%, *n*=322 isolates tested; Figure 2). *cfr* was detected in 18 (54.5%) of the LRSA tested (Figure 2) and in only 38 (15.9%) of the LRCoNS tested (Figure 2). When bias imposed by testing of clonally related strains was removed, *cfr* was found in 10/25 (40%) unique LRSA and 10/54 (18.5%) unique LRCoNS.

In all cases (21/21) with available information, LRSA was isolated following linezolid treatment, the mean duration of which was 20.0±47.0 months. All cases of CoNS infection (74/74 cases) with available information were also in patients previously treated with linezolid, with a mean duration of therapy of 11.0±8.0 days. The difference in exposure times to linezolid prior to isolation of LRSA and LRCoNS was significant ($P<0.0001$, Student's *t*-test).

Susceptibility testing and in vitro susceptibility data

Nineteen of 22 (86.4%) studies reported the susceptibility testing method used to determine linezolid resistance in *S. aureus* and 27 of 28 (96.4%) in CoNS. The majority of studies used Etest (31/46, 67.4%), BMD (28/46, 60.9%), and disc diffusion (DD) (19/46, 41.3%). However, 19.6% (9/46) of studies used Vitek® or Vitek2® (bioMerieux, Durham, NC, USA), 10.9% (5/46) agar dilution, 8.7% (4/46) MicroScan (Siemens), and 2.2% (1/46) broth macrodilution. Most studies (32/46, 69.6%) used two or more methods to detect and confirm linezolid resistance.

In vitro susceptibility data for antimicrobial agents in addition to linezolid were reported for 56.3% (234/416) of LRS strains reviewed (Table 3). All LRSA tested were resistant to oxacillin (*n*=17), chloramphenicol (*n*=15), and minocycline (*n*=11) and susceptible to vancomycin (*n*=33), daptomycin (*n*=18), teicoplanin (*n*=33), tigecycline (*n*=15), amikacin (*n*=12) and quinupristin/dalfopristin (*n*=4). Variable resistance to clindamycin (20/21, 95.2%), gentamicin (17/19, 89.5%), ciprofloxacin (15/17, 88.2%), erythromycin (17/20, 85.0%), trimethoprim/sulfamethoxazole (5/17, 29.4%) and rifampicin (3/5, 60.0%) was reported (Table 3).

All LRCoNS isolates tested were resistant to oxacillin (*n*=94), levofloxacin (*n*=30), and tobramycin (*n*=46). LRCoNS strains also exhibited resistance to clindamycin (70/71, 98.6%), ciprofloxacin (66/69, 95.7%), gentamicin (54/57, 94.7%), amikacin (9/11, 81.8%), erythromycin (66/88, 75.0%) and tetracycline (50/56, 89.3%). Variable resistance rates were noted for rifampicin (19/46, 41.3%), teicoplanin (41/141, 29.1%) and quinupristin/dalfopristin (5/57, 8.8%). All but one LRCoNS tested (*n*=190) were susceptible to vancomycin; this isolate was vancomycin intermediate and emerged during treatment with vancomycin.[25] All LRCoNS tested were susceptible to daptomycin (*n*=176) and tigecycline (*n*=80).

Sites of infection

The type of infection was documented in 20 (30.8%) LRSA cases and 269 (76.6%) LRCoNS cases. For LRSA, 60.0% (12/20) were respiratory tract infections, 10.0% (2/20) were bloodstream

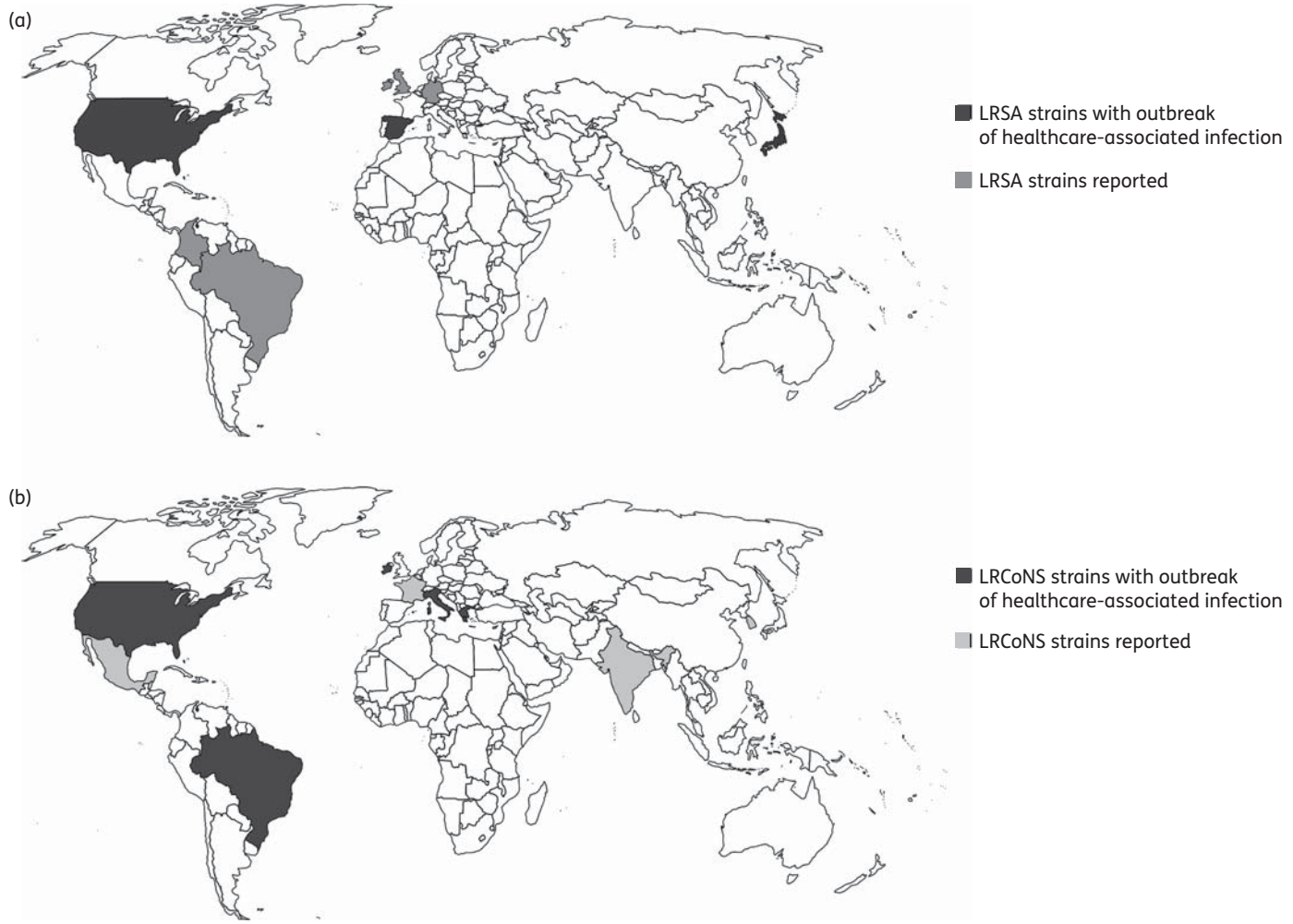

Figure 1. Distribution of linezolid resistance in *S. aureus* (a) and CoNS (b) worldwide. (a) Linezolid-resistant *S. aureus* (LRSA) strains reported in North America (USA), South America (Brazil, Colombia), Europe (Spain, UK, Germany, and Ireland), and Asia (Korea and Japan). (b) Linezolid-resistant CoNS (LRCoNS) reported in North America (USA, Mexico), South America (Brazil), Europe (Greece, Spain, Italy, France, and Ireland), and Asia (India.

infections (BSIs), 10.0% (2/20) were surgical site infections (SSIs) and 20.0% (4/20) were other sites. BSI was the most common infection documented for LRCoNS, with 98.6% (265/269) of the reported cases; 2 (0.7%) cases were reported each for SSI and other infections.

Discussion

In 2001, 1 year after linezolid was approved for clinical use, the first LRSA was reported in a US patient who had received a 1 month linezolid treatment for dialysis-associated peritonitis.[10] Since then, several cases of LRS have been reported in North and South America, Europe and Asia. While the incidence of linezolid resistance remains exceedingly low for *S. aureus*, more worrisome is the incidence of LRCoNS, which is roughly 28 times that of LRSA. One factor contributing to this increased incidence is the ability of CoNS to more readily develop resistance following linezolid exposure, although this has not been proven *in vitro* to our knowledge. The mean time of linezolid therapy reported prior to isolation of LRS was significantly shorter (11 days versus 20 months) for cases of LRCoNS. A second factor associated with selection for LRS is over-prescription of linezolid for staphylococcal bacteraemia, and in particular CoNS infections, as identified by the preponderance of LRCoNS isolated from the blood. However, this finding is likely biased by the fact that most clinical laboratories do not test antimicrobial susceptibility of CoNS unless isolated from a normally sterile site such as blood. Finally, significantly more LRCoNS were associated with outbreaks; 50% of the studies identified herein that investigated LRCoNS involved clonal LRCoNS, across one or more patients and facilities.

It is important to note that resistance rates among patients treated with linezolid for extended periods may be significantly elevated as compared with data reported in surveillance studies. For example, cystic fibrosis patients with respiratory tract infections caused by *S. aureus* have LRSA rates of up to 11%, directly related to the number and length of linezolid

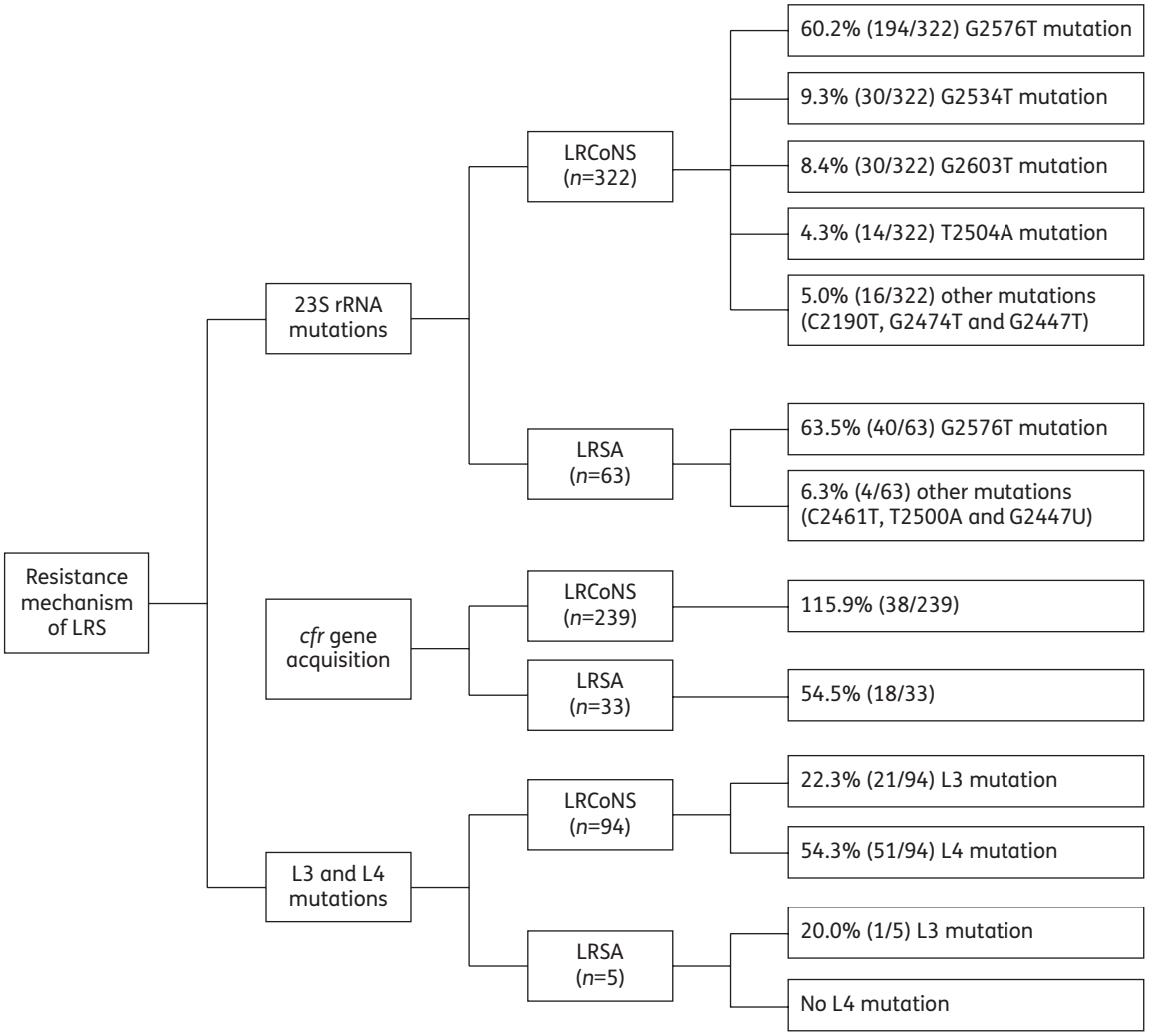

Figure 2. Resistance mechanisms of linezolid-resistant *Staphylococcus*. The percentage of isolates that harbour each mechanism of linezolid resistance among the number of isolates tested for each mechanism are shown.

treatments.[19] Linezolid is the only antibiotic with good activity against MRSA available as an oral formulation, making it desirable for outpatient treatment. However, up to a quarter of patients prescribed the oral formulation of linezolid are non-adherent with therapy.[26] While all cases of LRS with available clinical data indicated prior exposure to linezolid, the formulation was only reported in three studies: two studies described oral[10,19] and one parenteral dosing.[27] The relationship between compliance with linezolid therapy and linezolid resistance has not been formally evaluated, but may also be a factor driving linezolid resistance rates.

We identified a surprisingly high incidence of *cfr* among LRSA (40% of unique LRSA clones; Figure 2), a factor that strongly suggests horizontal gene transfer may be more common than previously appreciated. This finding raises significant concern about the possibility that isolates harbouring *cfr* may act as reservoirs for resistance.[28] Clonal spread of LRS with *cfr* has been documented in both institutional-level and multi-institutional outbreaks.[13,20,29,30] Infection control practices targeted to halt the spread of MRSA should be effective at preventing the dissemination of LRSA; in contrast, CoNS are rarely considered true pathogens and LRCoNS may go unrecognized. These isolates then have the potential to transfer *cfr* to more pathogenic organisms, such as *S. aureus*. This concern is more than theoretical; Mendes and colleagues documented transmission of a mobile *cfr* onto two plasmids that were then acquired by *Staphylococcus cohnii* and *Staphylococcus epidermidis* isolated from the blood of two patients with sepsis.[28]

Linezolid resistance may be under-reported based on technical hurdles in laboratory interpretation of both MIC and disc diffusion results. Compared with the standard CLSI BMD reference method, one study demonstrated 8/15 (53.3%) LRS were falsely reported susceptible by disc diffusion and 6/15 (40.0%) by Etest.[31] Errors in interpreting linezolid disc diffusion zones may be minimized by using endpoint reading recommendations published in the CLSI standards.[32] However, in our own unpublished observations, inter-user interpretation of the linezolid disc diffusion zones and MIC endpoints for the staphylococci

Table 3. Summary of antimicrobial susceptibility in linezolid-resistant *Staphylococcus*

	% Susceptible (number tested)	
Antimicrobial	LRSA	LRCoNS
Oxacillin	0.0 (17)	0.0 (94)
Erythromycin	15.0 (20)	25.0 (88)
Clindamycin	4.8 (21)	1.4 (71)
Tetracycline	ND	10.7 (56)
Minocycline	0.0 (11)	ND
Tigecycline	100.0 (15)	100.0 (80)
Amikacin	100.0 (12)	18.2 (11)
Gentamicin	10.5 (19)	5.3 (57)
Tobramycin	ND	0.0 (46)
Ciprofloxacin	11.8 (17)	4.3 (69)
Levofloxacin	ND	0.0 (30)
Trimethoprim/sulfamethoxazole	70.6 (17)	ND
Rifampicin	40.0 (5)	58.7 (46)
Quinupristin/dalfopristin	100.0 (4)	91.2 (57)
Vancomycin	100.0 (33)	99.5 (191)
Teicoplanin	100.0 (33)	70.9 (141)
Daptomycin	100.0 (18)	100.0 (176)

ND, no data.

varied significantly, even among seasoned technologists. To address this concern, it is advisable that clinical laboratories confirm any LRS, preferably by a second method, prior to reporting,[32] something that was done in only 72% of the studies evaluated.

Treatment options for LRS are limited, but based on current *in vitro* susceptibility data, LRS remain universally susceptible to vancomycin, daptomycin and tigecycline. It is clear that the preservation of these antimicrobials for the treatment of infections cause by highly resistant organisms such as LRS is critical.

The results reported herein may suffer from publication bias and other biases inherent in single studies. Furthermore, the spread of clonally related isolates may overestimate the prevalence of LRS infections in healthcare settings.

Conclusions

Linezolid remains highly active against most staphylococci, and its value in treating serious infections caused by MRSA has been well documented. Clinicians should remain cognizant that linezolid resistance may arise following prolonged treatment with linezolid and of the possibility of LRS in patients that have not been previously treated with linezolid, given the high incidence of LRSA carrying *cfr*. Susceptibility testing for linezolid resistance should be considered prior to using linezolid for serious infections. Further, judicious use of linezolid, accurate identification of resistance and application of strict infection control measures are essential to the preservation of linezolid as a therapeutic agent. To date, LRS remain susceptible to vancomycin, daptomycin and tigecycline. Further studies are needed to investigate the clinical outcome of LRS infections in order to optimize treatment of these infections.

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Transparency declarations

None to declare.

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