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In vitro activity of tedizolid against clinical isolates of *Staphylococcus lugdunensis* and *Staphylococcus haemolyticus* from Europe and the United States

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ABSTRACT

Staphylococcus lugdunensis and *Staphylococcus haemolyticus* are unique among CoNS in that the former often causes aggressive disease, while the latter consistently exhibits high rates of multidrug resistance. We evaluated the in vitro susceptibility of contemporary (2012–2013) isolates from both pathogens to tedizolid and comparators, using standard methodology. Results were interpreted using CLSI and EUCAST breakpoints. Overall, 106 *S. lugdunensis* and 103 *S. haemolyticus* isolates were collected from 51 medical centers in the United States and 30 centers in 18 European countries. Tedizolid showed good activity against *S. lugdunensis* (MIC_{50}/MIC_{90}: 0.12/0.12 mg/L) and *S. haemolyticus* (MIC_{50}/MIC_{90}: 0.12/0.12 mg/L), inhibiting all isolates at MIC ≤0.25 mg/L. Based on the EUCAST breakpoint for staphylococci and when substituting the CLSI breakpoint for *Staphylococcus aureus*, all isolates were tedizolid susceptible. All isolates were also susceptible to linezolid, but the in vitro potency of tedizolid was 4-fold greater than that of linezolid against both *S. lugdunensis* and *S. haemolyticus*, based on MIC_{90} values. *S. lugdunensis* exhibited ≥99% susceptibility to vancomycin, teicoplanin, gentamicin, levofloxacin, and trimethoprim-sulfamethoxazole; 7% of isolates were resistant to tetracycline, 11% to clindamycin, and 2% were methicillin-resistant. *S. haemolyticus* exhibited high rates of resistance to commonly used anti-staphylococcal agents: 71% of isolates were resistant to methicillin, 36%–37% to clindamycin, and 30%–50% to gentamicin. These in vitro findings suggest that tedizolid could be an alternative treatment option for infections due to these medically important CoNS pathogens. Additional clinical evaluation and continued surveillance of tedizolid in vitro activity against *S. lugdunensis* and *S. haemolyticus* are warranted.

Staphylococcus lugdunensis and *Staphylococcus haemolyticus* are clinically important coagulase-negative staphylococci (CoNS) that have emerged as significant pathogens in multiple infection types, including infections of the skin and soft-tissue (Barros et al., 2012; Bocher et al., 2009; Czekaj et al., 2015; Frank et al., 2008). In addition, these pathogens have been implicated in osteoarticular infections, bacteremia, sepsis, and endocarditis (Argemi et al., 2017; Czekaj et al., 2015). Both species have characteristics distinguishing them from other CoNS. *S. lugdunensis* infections can resemble those caused by *Staphylococcus aureus*, with an aggressive clinical course, rather than the generally less severe infections (in immunocompetent hosts) typically caused by other species of CoNS (Bocher et al., 2009; Frank et al., 2008). While *S. lugdunensis* generally remain susceptible to various antibacterial classes, *S. haemolyticus* isolates are frequently multidrug-resistant, even more so than other CoNS, which are known to exhibit resistance to multiple anti-staphylococcal agents (Barros et al., 2012; Bocher et al., 2009; Czekaj et al., 2015; Frank et al., 2008; Ma et al., 2011; Pinheiro et al., 2016; Shittu et al., 2004).

Tedizolid phosphate, the prodrug of the oxazolidinone tedizolid, is approved for treating skin and soft-tissue infections. Tedizolid has activity against a wide range of gram-positive pathogens, including CoNS, as shown in the 5 years Surveillance Tedizolid Activity and Resistance program (Bensaci and Sahm, 2017), but only limited data exist on its activity against *S. haemolyticus* and *S. lugdunensis* (Bensaci and Sahm, 2017; Brown and Traczewski, 2010; Zurenko et al., 2014). To address this knowledge gap, the in vitro susceptibility of contemporary isolates from both pathogens to tedizolid and comparator agents was evaluated.

This analysis comprised all *S. lugdunensis* and *S. haemolyticus* isolates collected (from hospitalized patients and outpatients) between January 2012 and December 2013 from medical centers in the United States and Europe that participated in the SENTRY antimicrobial surveillance program during that time. The methodology related to the SENTRY program has been described elsewhere (Bell and Turnidge, 2003; JMI

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Table 1
Activity of tedizolid and linezolid against *S. lugdunensis* and *S. haemolyticus* isolates.

	Number and cumulative percentage inhibited at MIC (mg/L)						
	0.06	0.12	0.25	0.5	1	MIC_{50}	MIC_{90}
***Staphylococcus lugdunensis* (n = 106)**							
Tedizolid	38 (3%)	67 (99%)	1 (100%)	0 (0%)	0 (0%)	0.12	0.12
Linezolid	0 (0%)	0 (0%)	35 (33%)	70 (99%)	1 (100%)	0.5	0.5
***Staphylococcus haemolyticus* (n = 103)**							
Tedizolid	2 (2%)	95 (94%)	6 (100%)	0 (0%)	0 (0%)	0.12	0.12
Linezolid	0 (0%)	0 (0%)	0 (0%)	98 (95%)	5 (100%)	0.5	0.5

MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration required to inhibit growth of 50% of isolates; MIC_{90}, minimum inhibitory concentration required to inhibit growth of 90% of isolates.

Laboratories; Jones, 2003; Pfaller and Jones, 2001). Isolates deemed responsible for infections were consecutively collected from patients (only one isolate per patient episode). Isolates were forwarded to a central laboratory (JMI Laboratories, North Liberty, IA, USA) for confirmation of bacterial identification and susceptibility testing, which was performed by broth micro-dilution according to standard Clinical and Laboratory Standards (CLSI) reference methods (Clinical and Laboratory Standards Institute (CLSI), 2015), using validated broth microdilution panels (Thermo Fisher Scientific, Cleveland, OH, USA). All quality control results, performed using ATCC 29213, fell within expected ranges. For oxazolidinones, MIC values were read as the lowest concentration where trailing began, ignoring tiny buttons of growth, as per current CLSI guidelines (Clinical and Laboratory Standards Institute (CLSI), 2015, 2017). For tedizolid, susceptibility was interpreted using the current EUCAST breakpoints for *Staphylococcus* spp. (i.e., ≤0.5 mg/L susceptible; >0.5 mg/L resistant) (European Committee on Antimicrobial Susceptibility Testing, 2017) and CLSI breakpoints for *S. aureus* (i.e., ≤0.5 mg/L susceptible; 1 mg/L intermediate; ≥2 mg/L resistant) (Merck & Co Inc., 2016), in the absence of tedizolid breakpoints specific to CoNS. Minimum inhibitory concentration (MIC) results for all comparator agents were interpreted according to CLSI and EUCAST breakpoints (Clinical and Laboratory Standards Institute (CLSI), 2017; European Committee on Antimicrobial Susceptibility Testing, 2017).

Overall, 106 *S. lugdunensis* and 103 *S. haemolyticus* isolates were collected from 51 medical centers in the United States and 30 in 18 European countries. Isolates were obtained from wounds (n = 50), blood cultures (n = 48), skin and skin structure (n = 32), and other sources (n = 79; mostly abscesses, catheters, cerebrospinal fluid, and urinary tract). Tedizolid showed potent activity against all *S. lugdunensis* (MIC_{50}/MIC_{90}: 0.12/0.12 mg/L) and *S. haemolyticus* isolates (MIC_{50}/MIC_{90}: 0.12/0.12 mg/L), inhibiting all at MIC ≤0.25 mg/L (Table 1). All isolates were susceptible to linezolid. *S. lugdunensis* exhibited ≥99% susceptibility to vancomycin, teicoplanin, gentamicin, levofloxacin, and trimethoprim-sulfamethoxazole; 7% of isolates were resistant to tetracycline, 11% to clindamycin, and 2% were methicillin-resistant (Table 2A). *S. haemolyticus* exhibited high rates of resistance to commonly used anti-staphylococcal agents: 71% of isolates were resistant to methicillin, 36–37% to clindamycin, and 30–50% to gentamicin (Table 2B). Based on the EUCAST breakpoint for staphylococci (≤0.5 mg/L) and when substituting the CLSI breakpoint for *S. aureus* (also ≤0.5 mg/L), all isolates were tedizolid susceptible. Based on MIC_{90} values, the in vitro potency of tedizolid was 4-fold greater than that of linezolid against both *S. lugdunensis* and *S. haemolyticus*, a pattern previously also seen with other gram-positive pathogens (Bensaci and Sahm, 2017; Brown and Traczewski, 2010; Schaadt et al., 2009; Thomson and Goering, 2013).

Table 2
Activity of tedizolid and comparator antibacterial agents against *S. lugdunensis* (Part A) and *S. haemolyticus* (Part B).

Drug	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S/I/R (EUCAST)	%S/I/R (CLSI)
Part A: *S. lugdunensis* (n = 106)					
Tedizolid	0.06 to 0.25	0.12	0.12	100/—[a]/0[b]	100/0/0[b]
Linezolid	0.25 to 1	0.5	0.5	100/—/0	100/0/0
Oxacillin	≤0.25 to >2	0.5	1.0	98/—/2	98/0/2
Gentamicin	≤1	≤1	≤1	100/—/0	100/0/0
Levofloxacin	≤0.12 to >4	0.25	0.25	99/—/1	99/0/1
Clindamycin	≤0.25 to >2	≤0.25	≤0.25	89/—/11	89/0/11
Tetracycline	0.06 to >32	≤0.03	>32	93/—/7	93/0/7
TMP-SMX	≤0.5 to 4	≤0.5	≤0.5	99/—/1	99/0/1
Vancomycin	≤0.12 to 2	1	1	100/—/0	100/0/0
Teicoplanin	≤2	≤2	≤2	100/—/0	100/0/0
Part B: *S. haemolyticus* (n = 103)					
Tedizolid	0.06 to 0.25	0.12	0.12	100/—/0[b]	100/0/0[b]
Linezolid	0.5 to 1	0.5	0.5	100/—/0	100/0/0
Oxacillin	≤0.25 to >2	>2	>2	29/—/71	29/0/71
Gentamicin	≤1 to >8	≤1	>8	51/—/50	55/15/30
Levofloxacin	≤0.12 to >4	4	>4	39/1/60	39/1/60
Clindamycin	≤0.25 to >2	≤0.25	>2	63/—/37	63/1/36
Tetracycline	0.06 to >32	1	>32	65/1/34	75/2/24
TMP-SMX	≤0.5 to >4	≤0.5	>4	62/—/38	62/0/38
Vancomycin	0.25 to 2	1	2	100/—/0	100/0/0
Teicoplanin	≤2 to >16	≤2	8	82/—/18	92/5/3

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration required to inhibit growth of 50% of isolates; MIC_{90}, minimum inhibitory concentration required to inhibit growth of 90% of isolates; S, susceptible; TMP-SMX, trimethoprim/ sulfamethoxazole.
[a]The dash indicates that no intermediate category exists. [b]There are no approved tedizolid breakpoints specific to these pathogens. This analysis used EUCAST breakpoints for staphylococci (≤0.5 mg/L susceptible, >0.5 mg/L resistant) and, CLSI breakpoints for *S. aureus* (≤0.5 mg/L susceptible, 1 mg/L intermediate, ≥2 mg/L resistant), for comparative purposes.

As evidenced from Table 2, tedizolid, linezolid, and vancomycin remained active against *S. lugdunensis* and *S. haemolyticus* isolates resistant to commonly used antibacterials, including against methicillin-resistant strains. The MIC_{50} and MIC_{90} were not impacted by methicillin susceptibility or resistance. While this study included a relatively small number of clinical isolates overall, *S. lugdunensis* and *S. haemolyticus* are less frequently recovered from clinical specimens, thus resulting in a limited sample size even in a large surveillance study, such as the SENTRY program. Of note, this is still one of the largest recent data sets evaluating antibacterial activity in *S. lugdunensis* and *S. haemolyticus* to date. Furthermore, geographic distribution was diverse, thus minimizing potential bias due to spread of local clones within institutions.

Linezolid is widely accepted as a treatment option for CoNS, especially methicillin-resistant infections. However, the substantial increase in linezolid use over time has led to the emergence of linezolid resistance in this pathogen group in local institutions and broader geographic areas (Balandin et al., 2016; Butin et al., 2017; Decousser et al., 2015; Morroni et al., 2016; Papadimitriou-Olivgeris et al., 2013; Ramirez et al., 2013). In this study, all isolates were susceptible to linezolid. An important linezolid resistance mechanism is mediated by the horizontally transferable *cfr* gene (Quiles-Melero et al., 2013), but *cfr* seems to not affect tedizolid activity, as long as no other oxazolidinone resistance mechanisms are present (Locke et al., 2014; Sahm et al., 2015). *Cfr*-mediated linezolid resistance has been reported in isolates from patients with methicillin-resistant *S. haemolyticus* infections. (Cai et al., 2012; Cui et al., 2013; Fessler et al., 2014; Flamm et al., 2013; Martinez-Melendez et al., 2016; Rajan et al., 2017) Resistance to oxazolidinones, which act as protein synthesis inhibitors, is frequently mediated by mutations in genes encoding for ribosomal DNA or ribosomal proteins (Gu et al., 2013; Quiles-Melero et al., 2013). Linezolid-resistant *S. haemolyticus* with such mutations has been reported previously (Chamon et al., 2014; Mazzariol et al., 2012; Quiles-Melero et al., 2013; Tewhey et al., 2014). Of note, in these cases there is significant cross-resistance between linezolid and tedizolid (Perez-Parra et al., 2017; Sahm et al., 2015; Silva-Del Toro et al., 2016; Zurenko et al., 2014). *S. lugdunensis* has much lower rates of drug resistance than *S. haemolyticus*, but is a virulent pathogen that can cause infections similar to *S. aureus*; oxazolidinones may be an effective treatment option even in serious *S. lugdunensis* infections (Merino et al., 2010), with linezolid resistance in *S. lugdunensis* only very rarely reported (Flamm et al., 2013).

There is limited clinical experience treating *S. haemolyticus* and *S. lugdunensis* with tedizolid to date. In phase 2 and 3 clinical trials with tedizolid, 13 patients each had infections due to *S. haemolyticus* or *S. lugdunensis* (Moran et al., 2014; Prokocimer et al., 2011, 2012, 2013; Shorr et al., 2015). All isolates had low MIC values to both tedizolid (MIC range: 0.12–0.25 mg/L) and linezolid (MIC range: 0.5–1 mg/L). For *S. haemolyticus*, favorable microbiologic response as well as clinical cure rates at test-of-cure were 100% (5/5) for tedizolid and 88% (7/8) for linezolid. For *S. lugdunensis*, microbiologic response and clinical cure rates were 100% (6/6) for tedizolid and 86% (6/7) for linezolid (Moran et al., 2014; Prokocimer et al., 2011, 2012, 2013; Shorr et al., 2015).

In summary, these in vitro findings suggest that tedizolid could be an alternative treatment option for infections due to *S. lugdunensis* and *S. haemolyticus*. Additional clinical evaluation with greater patient numbers and/or in other infection types than ABSSSI is warranted, as is continued surveillance of tedizolid in vitro activity against these medically important CoNS pathogens.

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Conflicts of Interest

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