Five Years of Analysis of the *In Vitro* Activity of Tedizolid against a Worldwide Collection of Indicated Species Causing Clinical Infections: Results from the Surveillance of Tedizolid Activity and Resistance (STAR) Program

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INTRODUCTION

- Gram-positive pathogens frequently cause community and healthcare associated infections (HAIs).
- *Staphylococcus aureus* and *Enterococcus faecalis* are common HAI organisms that challenge antimicrobial therapy due to intrinsic or acquired resistance mechanisms.
- Tedizolid is an oxazolidinone-class antimicrobial that inhibits protein synthesis and exhibits activity against staphylococci, streptococci, and enterococci, including methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus spp.* (VRE).
- Tedizolid was approved by the European Medicines Agency (EMA), the United States Food and Drug Administration (US FDA), and other regulatory agencies for the treatment of acute bacterial skin and skin structure infection (ABSSSI) and has been considered as a therapy candidate for other infection types.
- The Surveillance of Tedizolid Activity and Resistance (STAR) Program monitored tedizolid activity against staphylococci, streptococci, and enterococci.
- This study reports STAR Program results obtained in the last five years.

MATERIALS AND METHODS

- A total of 47,400 Gram-positive unique isolates from indicated species were collected between 2015 and 2019 as part of the STAR Program.
- Isolates were recovered from 107 medical centers in the United States (21,243 isolates), Europe (17,674 isolates), the Asia-Pacific region (4,954 isolates), and Latin America (3,529 isolates).
- Pathogens included *S. aureus* (n=35,978; 75.9%), *E. faecalis* (n=4,992; 10.5%), *Streptococcus pyogenes* (n=3,240; 6.8%), *Streptococcus agalactiae* (n=2,509; 5.3%), and *Streptococcus anginosus* group (n=681; 1.4%). Pathogen distribution and respective types of infections are shown in Figures 1 and 2, respectively.
- Bacterial identification was performed by the participating centers and confirmed by the monitoring laboratory (JMI Laboratories, North Liberty, IA) using matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF; Bruker Daltonics, Massachusetts, USA) following the manufacturer's instructions.
- Susceptibility testing was performed by broth microdilution according to Clinical and Laboratory Standard Institute M07 (2018) guidelines.
  - Frozen-form panels were manufactured by JMI Laboratories and contained cation-adjusted Mueller-Hinton broth, with 2.5–5% lysed horse blood added for streptococci.
- Quality control reference strains (*S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619) were tested concurrently.
- Breakpoint criteria for MIC interpretations were from EUCAST (2021) and CLSI (2021). For comparison, tedizolid and daptomycin CLSI (2021) breakpoints were applied.
- Screening of *cfr, cfr*(B), *cfr*(C), *optrA*, and *poxtA* genes by whole genome sequencing, along with an *in silico* analysis, were performed on linezolid non-susceptible (NS; MIC, ≥4 mg/) isolates.
- Additionally, DNA sequences associated with the 23S rRNA and ribosomal proteins (L3, L4, and L22) were analyzed for the presence of mutations, as previously described.

RESULTS

- Tedizolid $MIC_{50/90}$ values were 0.12/0.25 mg/L against *S. aureus* (>99.9% susceptible), including MRSA isolates (Table 1).
- MRSA was observed in 32.7% of *S. aureus*. Tedizolid activity against MRSA isolates ($MIC_{50/90}$, 0.12/0.25 mg/L) was equivalent to that observed against methicillin-susceptible *S. aureus* isolates ($MIC_{50/90}$, 0.12/0.25 mg/L; Table 1).
- Tedizolid (>99.9% susceptible) was 4- to 8-fold more active than linezolid ($MIC_{50/90}$, 1/2 mg/L; >99.9% susceptible) and vancomycin ($MIC_{50/90}$, 1/1 mg/L; 100% susceptible) against MRSA (Table 2).
  - Susceptibility rates for ceftaroline and clindamycin were 92.9% and 73.3%, respectively, among MRSA isolates.
- A single linezolid-NS *S. aureus* (MIC, >8 mg/L) was noted. This isolate was recovered from a patient in a US (Louisiana) hospital, and it showed a tedizolid MIC of >1 mg/L and G2576T mutations in the 23S rRNA (Table 3).
- Tedizolid MIC values for *E. faecalis* ($MIC_{50/90}$, 0.25/0.25 mg/L) were 4- to 8-fold lower than those values observed for linezolid ($MIC_{50/90}$, 1/2 mg/L) and vancomycin ($MIC_{50/90}$, 1/2 mg/L; Table 2).
- All the vancomycin-resistant *E. faecalis* isolates tested (n=95, >16 mg/L) were susceptible to tedizolid ($MIC_{50/90}$, 0.12/0.25 mg/L) at ≤0.5 mg/L.
- Similarly, tedizolid was highly active against linezolid-NS *E. faecalis* (n=26; $MIC_{50/90}$, 0.5/1 mg/L), with 73.1% of the isolates classified as susceptible using CLSI breakpoint (Table 1).
  - 25 out of 26 (96.2%) linezolid-NS *E. faecalis* isolates carried *optr*A (Table 3).
  - The remaining linezolid-NS *E. faecalis* isolate had G2576T mutations and displayed a tedizolid MIC of >1 mg/L.
  - Linezolid-NS isolates were recovered from the Asia-Pacific region (10 isolates), Europe (9), North America (4), and Latin America (3). Table 3 displays the country of origin for each isolate.
- No linezolid-NS isolate carrying *cfr* or *poxtA* genes were detected (Table 3).
- All *S. pyogenes* ($MIC_{50/90}$, 0.12/0.25 mg/L; 100% susceptible) and *S. agalactiae* ($MIC_{50/90}$, 0.25/0.25 mg/L; 100% susceptible) isolates were susceptible to tedizolid, with MIC_{90} values 8-fold lower than linezolid (MIC_{90}, 2 mg/L for both species).
  - Clindamycin and erythromycin susceptibility rates against *S. pyogenes* were 96.3% and 88.2%, respectively, and 69.9% and 56.4% against *S. agalactiae* (Table 4).
- *S. anginosus* group susceptibility rates for tedizolid, penicillin, and clindamycin were 100%, 99.1%, and 86.4%, respectively (Table 4).
- Additional analysis showed that tedizolid had consistent *in vitro* activity, regardless of geographic region or study year.

CONCLUSIONS

- Tedizolid was active against ≥99.9% of *S. aureus, E. faecalis, S. pyogenes, S. agalactiae,* and *S. anginosus* group isolates collected worldwide in 2015–2019, with MIC_{50} values ranging from 0.12 to 0.25 mg/L and MIC_{90} values of 0.25 mg/L.
- No resistance trends were observed for tedizolid during the study years.
- Among linezolid-NS isolates, 23S rRNA mutations (G2576T) were detected in only 1 *S. aureus* and 1 *E. faecalis isolate.*
- The *cfr* or *poxtA* genes were not detected among linezolid-NS *S. aureus* or *E. faecalis* isolates.
- Linezolid-NS *E. faecalis* isolates carried mostly the *optrA* gene.

Table 1. Activity of tedizolid against indicated Gram-positive species causing infections worldwide (2015–2019)

Organism/group	Number of isolates tested and percentage of tedizolid susceptible isolates overall and per year													
	2015		2016		2017		2018		2019		Total			
	n	%S [a]	*n*	%S [a]	*n*	%S [a]	*n*	%S [a]	*n*	%S [a]	*n*	%S [a]	MIC_{50}	MIC_{90}
S. aureus	7,406	100	8,307	100	6,948	100	6,691	>99.9	6,626	100	35,978	0.12	0.25	>99.9
MSSA	4,886	100	5,675	100	4,543	100	4,529	100	4,577	100	24,210	0.12	0.25	100
MRSA	2,520	100	2,632	100	2,405	100	2,162	>99.9	2,049	100	11,768	0.12	0.25	>99.9
E. faecalis [b]	966	99.9	1,016	99.9	898	100	1,062	99.6	1,050	99.9	4,992	0.25	0.25	99.9
LZD-NS [b,c]	2	50.0	4	75.0	2	100	10	60.0	8	87.5	26	0.5	1	73.1
VRE [b]	24	100	18	100	17	100	21	100	15	100	95	0.12	0.25	100
S. pyogenes	643	100	735	100	646	100	654	100	562	100	3,240	0.12	0.25	100
S. agalactiae	532	100	584	100	533	100	439	100	421	100	2,509	0.25	0.25	100
S. anginosus group	158	100	178	100	105	100	125	100	115	100	681	0.12	0.25	100

[a] Using EUCAST 2021 breakpoints.
[b] Using CLSI 2021 breakpoints.
[c] LZD-NS isolates were recovered from the US (4), Mexico (3), Taiwan (3), Australia (2), Malaysia (2), Vietnam (2), Poland (2), Philippines (1), France (1), Germany (1), Hungary (1), Ireland (1), Italy (1), Sweden (1), and Turkey (1).
Abbreviations: MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; LZD-NS, linezolid non-susceptible; VRE, vancomycin-resistant *Enterococcus*.

Table 2. Activity of tedizolid and comparators agents against *S. aureus* and *E. faecalis* isolates and resistance phenotypes causing infections worldwide (2015–2019)

Organism (no. tested)	MIC (mg/L)		EUCAST[a]	
Antimicrobial agent	MIC_{50}	MIC_{90}	%S	%R
MSSA (*24,210*)				
Tedizolid	0.12	0.25	100.0	0.0
Linezolid	1	2	100.0	0.0
Ceftaroline	0.25	0.25	100.0 [b]	0.0
Clindamycin	≤0.25	≤0.25	96.7	3.0
Daptomycin	0.25	0.5	>99.9	<0.1
Erythromycin	0.25	>8	76.4	21.7
TMP-SMT	≤0.5	≤0.5	99.5	0.4
Vancomycin	1	1	100.0	0.0
MRSA (*11,768*)				
Tedizolid	0.12	0.25	>99.9	<0.1
Linezolid	1	2	>99.9	<0.1
Ceftaroline	1	1	92.9 [b]	<0.1
Clindamycin	≤0.25	>2	73.3	26.5
Daptomycin	0.25	0.5	>99.9	<0.1
Erythromycin	>8	>8	24.3	74.4
TMP-SMT	≤0.5	≤0.5	96.4	3.1
Vancomycin	1	1	100.0	0.0
E. faecalis (*4,992*)				
Tedizolid	0.25	0.25	99.9 [c]	
Linezolid	1	2	99.9	0.1
Ampicillin	1	1	>99.9	0.0
Daptomycin	0.5	1	99.6 [c]	0.0
Vancomycin	1	2	98.1	1.9
LNZ-NS *E. faecalis* (*26*)				
Tedizolid	0.5	1	73.1 [c]	
Linezolid	4	8	84.6	15.4
Ampicillin	1	1	100.0	0.0
Daptomycin	1	1	100.0 [c]	0.0
Vancomycin	1	1	100.0	0.0
VRE (*95*)				
Tedizolid	0.12	0.25	100.0 [c]	
Linezolid	1	2	100.0	0.0
Ampicillin	1	2	98.9	0.0
Daptomycin	0.5	1	100.0 [c]	
Vancomycin	>16	>16	0.0	100.0

a Criteria as published by EUCAST 2021.
b Using other than pneumonia breakpoints.
c Using CLSI 2021 breakpoint.
Abbreviations: MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; LZD-NS, linezolid non-susceptible; VRE, vancomycin-resistant *Enterococcus*; TMP-SMT, trimethoprim-sulfamethoxazole.

Table 3. Characterization of oxazolidinone resistance mechanisms in linezolid-NS *E. faecalis* and *S. aureus* isolates (2015–2019)

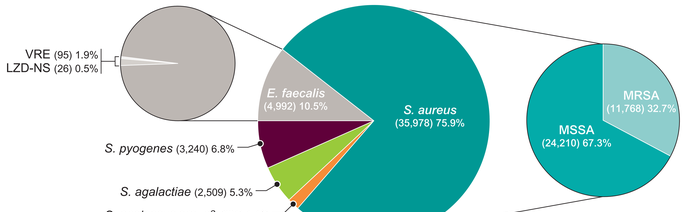
Organism	Year	Country	MIC (mg/L)		Resistance mechanism			
			Linezolid	Tedizolid	23S rRNA gene/ L3-L4-L22 amino acid alterations	methyltransferase *cfr*	ribosomal protection *poxtA*	ribosomal protection *optrA*
S. aureus	2018	USA	>8	>1	G2576T	-	-	-
E. faecalis	2015	Ireland	8	>1	-	-	-	+
E. faecalis	2015	USA	4	0.5	-	-	-	+
E. faecalis	2016	Taiwan	4	0.5	-	-	-	+
E. faecalis	2016	France	4	0.25	-	-	-	+
E. faecalis	2016	Mexico	4	0.5	-	-	-	+
E. faecalis	2016	Mexico	4	1	-	-	-	+
E. faecalis	2017	Germany	4	0.5	-	-	-	+
E. faecalis	2017	Mexico	4	0.5	-	-	-	+
E. faecalis	2018	Australia	8	1	-	-	-	+
E. faecalis	2018	Malaysia	4	0.5	-	-	-	+
E. faecalis	2018	Malaysia	4	0.5	-	-	-	+
E. faecalis	2018	Philippines	4	0.5	-	-	-	+
E. faecalis	2018	Taiwan	4	0.5	-	-	-	+
E. faecalis	2018	Taiwan	4	0.5	-	-	-	+
E. faecalis	2018	Vietnam	4	1	-	-	-	+
E. faecalis	2018	Vietnam	4	1	-	-	-	+
E. faecalis	2018	Italy	>8	>1	G2576T	-	-	-
E. faecalis	2018	USA	4	0.5	-	-	-	+
E. faecalis	2019	Australia	4	0.5	-	-	-	+
E. faecalis	2019	Hungary	4	0.5	-	-	-	+
E. faecalis	2019	Poland	4	0.5	-	-	-	+
E. faecalis	2019	Poland	4	0.5	-	-	-	+
E. faecalis	2019	Sweden	4	0.5	-	-	-	+
E. faecalis	2019	Turkey	4	0.5	-	-	-	+
E. faecalis	2019	USA	8	1	-	-	-	+
E. faecalis	2019	USA	4	0.5	-	-	-	+

Table 4. Activity of tedizolid and comparators agents against *S. pyogenes, S. agalactiae*, and the *S. anginosus* group causing infections worldwide (2015–2019)

Organism (no. tested)	MIC (mg/L)		EUCAST[a]	
Antimicrobial agent	MIC_{50}	MIC_{90}	%S	%R
S. pyogenes (3,240)				
Tedizolid	0.12	0.25	100.0	0.0
Linezolid	1	2	100.0	0.0
Clindamycin	≤0.25	≤0.25	96.3	3.7
Daptomycin	≤0.06	0.12	100.0	0.0
Erythromycin	≤0.03	1	88.2	10.9
Levofloxacin	0.5	1	0.0	0.2
Penicillin	≤0.03	≤0.03	100.0	0.0
Vancomycin	0.25	0.5	100.0	0.0
S. agalactiae (2,509)				
Tedizolid	0.25	0.25	100.0	0.0
Linezolid	1	2	100.0	0.0
Clindamycin	0.25	>2	69.9	30.1
Daptomycin	0.25	0.25	100.0	0.0
Erythromycin	0.06	>4	56.4	42.0
Levofloxacin	1	1	0.0	3.4
Penicillin	0.06	0.06	99.9	0.1
Vancomycin	0.5	0.5	100.0	0.0
S. anginosus group (*681*)				
Tedizolid	0.12	0.25	100.0	0.0
Linezolid	1	1	100.0	
Clindamycin	≤0.25	>2	86.4	13.6
Daptomycin	0.25	0.5	99.8 [b]	
Erythromycin	≤0.03	4	78.0 [b]	19.4
Levofloxacin	0.5	1	99.0 [b]	1.0
Penicillin	≤0.03	0.06	99.1	0.3
Vancomycin	0.5	1	100.0	0.0

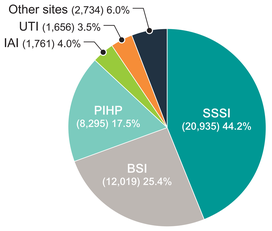
a Criteria as published by EUCAST 2021.
b Using CLSI 2021 breakpoints.

Figure 1. Distribution of organisms and resistant phenotypes causing infections worldwide (2015–2019)



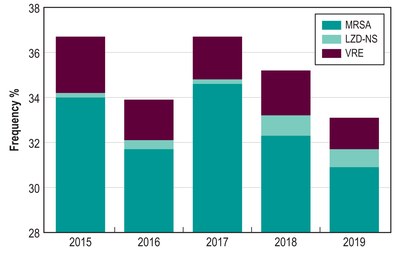
Abbreviations: MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; LZD-NS, linezolid non-susceptible; VRE, vancomycin-resistant *Enterococcus*.
[a] Organisms included: *Streptococcus anginosus* (404), *Streptococcus constellatus* (82), *Streptococcus intermedius* (37), and *Streptococcus anginosus* group (158).

Figure 2. Distribution of organisms by infection type (2015–2019)



Abbreviations: SSSI, skin and skin structure infection; BSI, bloodstream infection; PIHP, pneumonia in hospitalized patients; IAI, intra-abdominal infection; UTI, urinary tract infection.

Figure 3. Frequency of resistant phenotypes among *S. aureus* (n = 35,978) and *E. faecalis* (n=4,992) by study year



Abbreviations: MRSA, methicillin-resistant *S. aureus*; LZD-NS, linezolid non-susceptible *E. faecalis*; VRE, vancomycin-resistant *E. faecalis*.

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