Evaluation of Tedizolid and Comparators' Activity Against Gram-Positive Bacterial Isolates Causing Skin and Skin Structure Infections from Paediatric Patients in Europe and Surrounding Countries (2015–2019)

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Introduction

- Tedizolid is an oxazolidinone that exhibits activity against a broad array of gram-positive cocci, including those demonstrating multidrug-resistance phenotypes, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and some linezolid-resistant phenotypes.
- Tedizolid is approved by the US-FDA and EMA for treating acute bacterial skin and skin structure infections (SSSI) in adults.
- The pharmacokinetics, efficacy, safety, and tolerability of tedizolid in paediatric patients are under investigation in multiple clinical trials in Europe (MK-1986-013; MK-1986-012; and MK-1986-018).
- The activity of tedizolid and comparators was evaluated against clinical surveillance isolates collected from paediatric patients with SSSI in Europe and Israel during a 5-year period.

Materials and Methods

Organism Collection

- A total of 861 non-duplicate, Gram-positive isolates were included.
  - Isolates were collected from paediatric patients (<18 years) with SSSIs as a part of the surveillance of Tedizolid Activity and Resistance (STAR) Program during 2015–2019.
  - Contributing sites include 36 medical centres located in 19 European countries and Israel (Table 1).
- Isolates were initially identified by the participating laboratory and submitted to a central monitoring facility (JMI Laboratories, North Liberty, Iowa, USA) where bacterial identifications were confirmed using standard algorithms and supported by matrix assisted laser desorption ionization time-of-flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility testing

- Broth microdilution tests were performed according to the Clinical and Laboratory Standards Institute (CLSI) guidelines to determine antimicrobial susceptibility of tedizolid and numerous comparator antimicrobials used to treat patients with SSSI.
  - Reference broth microdilution method used 96-well panels manufactured by JMI Laboratories (North Liberty, Iowa, USA) containing cation-adjusted Mueller-Hinton broth (CAMHB) as testing media.
  - CAMHB supplemented with 2.5-5% lysed horse blood was used for streptococci.
  - CAMHB supplemented with 50 mg/L calcium (Ca^{2+}) was used for testing daptomycin.
- Quality control (QC) strains included *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619.
- Breakpoint criteria for tedizolid and comparator agents were those from EUCAST (2019). CLSI breakpoint was applied for tedizolid against *E. faecalis*.

Table 1 List of participating countries and medical centres

Country	No. of medical centres	No. of isolates	% isolates
UK	3	156	18.1%
Turkey	2	128	14.9%
Belarus	1	79	9.2%
France	4	69	8.0%
Italy	3	63	7.3%
Sweden	2	58	6.7%
Germany	4	54	6.3%
Russia	3	48	5.6%
Slovenia	1	42	4.9%
Czech Republic	1	35	4.1%
Ireland	2	29	3.4%
Belgium	1	24	2.8%
Spain	2	23	2.7%
Portugal	1	22	2.6%
Poland	1	13	1.5%
Hungary	1	8	0.9%
Romania	2	5	0.6%
Israel	1	4	0.5%
Greece	1	1	0.1%

Results

- Among 861 Gram-positive isolates recovered from paediatric patients with SSSI:
  - *S. aureus* comprised the majority (633; 73.5%) of the isolates, followed by β-haemolytic streptococci (BHS; 141; 16.4%), *E. faecalis* (25; 2.9%), and Viridans group streptococci (VGS; 21; 2.4%).
  - Other aerobic gram-positive organisms (11 species; mainly coagulase-negative *Staphylococcus*) consisted of a small number of isolates (62; 7.2%).
  - Similar frequency of pathogens was observed when stratified by age group, <12y and 12-18y (Figure 1).
- Tedizolid was highly active against *S. aureus* ($MIC_{50/90}$, 0.12/0.25 mg/L; Table 2).
  - Overall methicillin-resistant *S. aureus* (MRSA) rate was 12.5% (13.5% and 10.1% for the <12 and 12-18-year-old subsets, respectively).
  - Equivalent tedizolid $MIC_{50/90}$ values were observed against MRSA ($MIC_{50/90}$, 0.12/0.25 mg/L) and MSSA ($MIC_{50/90}$, 0.12/0.25 mg/L; Table 2).
  - Susceptibility rate of 100% was obtained for tedizolid, linezolid, vancomycin, and daptomycin against MRSA isolates (Figure 2).
- Tedizolid was also very active against BHS ($MIC_{50/90}$, 0.12/0.25 mg/L) and VGS ($MIC_{50/90}$, 0.12/0.12 mg/L; Table 2).
  - *S. agalactiae, S. dysgalactiae*, and *S. pyogenes* isolates were all inhibited (100% susceptible) by tedizolid at ≤0.25 mg/L, ≤0.25 mg/L, and ≤0.5 mg/L, respectively (Table 3).
  - Comparator agents, such as linezolid, daptomycin, vancomycin, and ceftaroline inhibited 100% of BHS isolates at the respective breakpoints (Figure 2).
  - Clindamycin susceptibility varied from 96.8% against *S. pyogenes* to 75% against *S. agalactiae* isolates (Figure 2).
- Low $MIC_{50/90}$ values (0.25/0.25 mg/L) were observed for tedizolid against *E. faecalis* isolates.
  - Tedizolid inhibited all *E. faecalis* isolates at the CLSI breakpoint (≤0.5 mg/L; 100% susceptible; Table 3).
- Ceftaroline and clindamycin showed susceptibility rates of >90% against MRSA, MSSA, *S. pyogenes*, and *S. dysgalactiae*, but lower susceptibility rates were observed for clindamycin tested against VGS (85.0%) and *S. agalactiae* (75.0%) (Figure 2).

Figure 1 Distribution of Gram-positive bacterial species and pathogen groups causing SSSI by age group

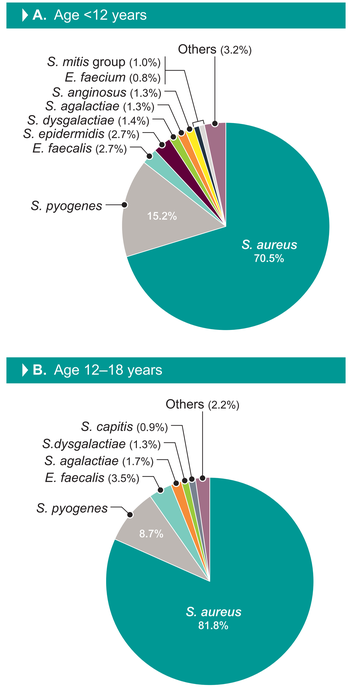
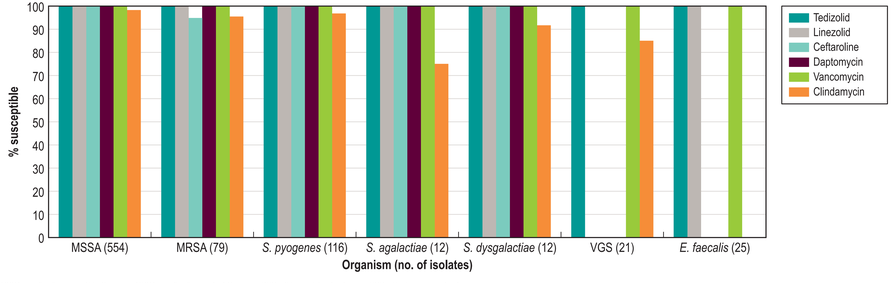


Figure 2 Tedizolid and comparators susceptibility rates against Gram positive pathogens causing SSSI in paediatric patients in Europe and surrounding countries (2015–2019)



MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; BHS = β-haemolytic streptococci; VGS = Viridans group streptococci.
Susceptibility rates according to published EUCAST breakpoints (EUCAST, 2019). CLSI breakpoint was applied for tedizolid against *E. faecalis*.
Ceftaroline other than pneumonia breakpoint was applied for MRSA and MSSA isolates.
Tedizolid breakpoint for *S. anginosus* group used for VGS isolates.
Breakpoint not available for some agent/organism combinations.

Table 2 Activity of tedizolid and comparators against Gram-positive pathogens causing SSSI in paediatric patients (2015–2019)

Organism (no. tested)	Tedizolid		Linezolid		Ceftaroline		Daptomycin		Vancomycin		Clindamycin	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
S. aureus (663)	0.12	0.25	1	2	0.25	0.25	0.25	0.5	1	1	≤0.25	≤0.25
MSSA (554)	0.12	0.25	1	2	0.25	0.25	0.25	0.5	1	1	≤0.25	≤0.25
MRSA (79)	0.12	0.25	1	2	0.5	1	0.25	0.5	1	1	≤0.25	≤0.25
E. faecalis (25)	0.25	0.25	1	2	2	4	1	1	1	2	NA	NA
BHS (141)	0.12	0.25	1	2	≤0.008	≤0.008	≤0.06	0.12	0.5	0.5	≤0.25	≤0.25
S. pyogenes (116)	0.12	0.25	1	2	≤0.008	≤0.008	≤0.06	0.12	0.5	0.5	≤0.25	≤0.25
S. agalactiae (12)	0.25	0.25	1	1	0.015	0.015	0.12	0.25	0.25	0.5	≤0.25	NA
S. dysgalactiae (12)	0.12	0.25	1	1	≤0.008	≤0.008	≤0.06	0.12	0.25	0.5	≤0.25	≤0.25
VGS (21)	0.12	0.12	1	1	0.015	0.06	0.25	0.5	0.5	1	≤0.25	2

MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; BHS = β-haemolytic streptococci; VGS = Viridans group streptococci. NA, not available

Conclusions

- Tedizolid was equipotent or more potent than comparators against MSSA and MRSA isolates causing SSSI in paediatric patients in Europe and Israel recovered in a 5-year period.
- Tedizolid was highly active against BHS, VGS, and *E. faecalis* isolates responsible for SSSI.
- Tedizolid may represent a valuable option for treating paediatric patients with SSSI caused by Gram-positive pathogens, if granted clinical approval.

Table 3 Tedizolid MIC distribution against Gram-positive pathogens causing SSSI in paediatric patients in Europe and surrounding countries (2015–2019)

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:						
	≤0.015	0.03	0.06	0.12	0.25	0.5	>0.5
MSSA (554)	0 0.0	1 0.2	35 6.5	288 58.5	216 97.5	14 100.0	
MRSA (79)		0 0.0	4 5.1	45 62.0	29 98.7	1 100.0	
Enterococcus faecalis (25)		0 0.0	1 4.0	4 20.0	19 96.0	1 100.0	
β-haemolytic streptococci (141)		0 0.0	3 2.1	78 57.4	55 96.5	5 100.0	
Streptococcus pyogenes (116)		0 0.0	3 2.6	63 56.9	45 95.7	5 100.0	
Streptococcus agalactiae (12)			0 0.0	5 41.7	7 100.0		
Streptococcus dysgalactiae (12)			0 0.0	9 75.0	3 100.0		
Viridans group streptococci (21)	0 0.0	2 9.5	7 42.9	10 90.5	2 100.0		

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