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Activity of Tedizolid and Comparator Agents against Gram-Positive Bacterial Isolates Causing Skin and Skin Structure Infections in Pediatric Patients during 2015–2019 in the US

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Introduction

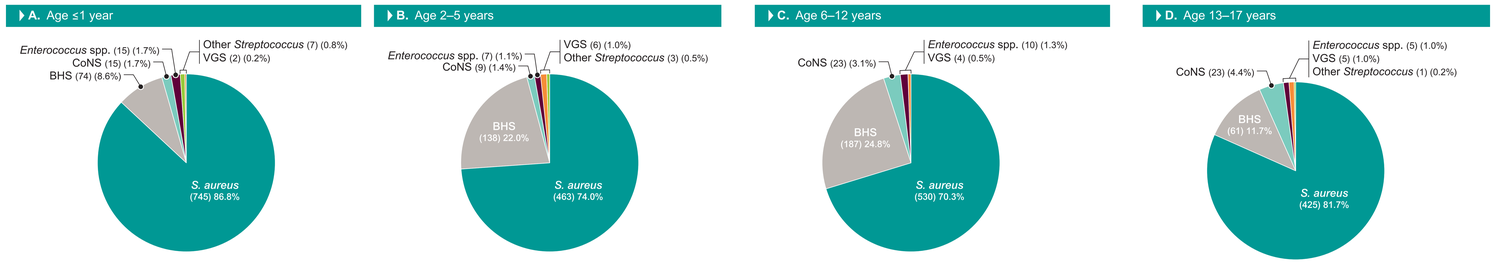
- New strategies to treat acute bacterial skin and skin structure infections (ABSSSI) are needed due to the spread of methicillin-resistant *Staphylococcus aureus* (MRSA), a common multidrug-resistant pathogen of ABSSSIs in the overall population and in pediatric patients.
- Tedizolid is an oxazolidinone-class of antimicrobial that inhibits protein synthesis and exhibits activity against *Staphylococcus, Streptococcus,* and *Enterococcus* species.
- Tedizolid is approved by the European Medicines Agency, the United States Food and Drug Administration, and other regulatory agencies for the treatment of ABSSSI in adults. Tedizolid is under clinical evaluation for treating ABSSSI in pediatric patients.
- This study assessed the activity of tedizolid and comparators against clinical surveillance isolates collected from pediatric patients with SSSI in the US.

Materials and Methods

Organism collection

- A total of 2,758 Gram-positive isolates were collected from pediatric patients with SSSIs between 2015 and 2019 as part of the Surveillance of Tedizolid Activity and Resistance (STAR) Program.
- The isolates were recovered from 33 medical centers in the US, including all 9 Census regions; Figure 1 lists the percentage of isolates per participating region.

Figure 2 Pathogen distribution by age group



- Pathogens mostly included *S. aureus* (n=2,163; 78.4%), which was the main *species* recovered from all age groups (≤1y; 2-5y; 6-12y; 13-17y), β-hemolytic streptococci (BHS; n=460; 16.7%), and coagulase-negative staphylococci (CoNS; n=70; 2.5%). Pathogen distribution by age group is shown in Figure 2.
- Only Gram-positive isolates (1 per patient per infection episode) determined to be clinically significant by local criteria as the probable cause of infection were included.
- 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 (Bruker Daltonics, Massachusetts, USA) following the manufacturer's instructions.

Antimicrobial susceptibility testing

- Susceptibility testing was performed by broth microdilution according to Clinical and Laboratory Standard Institute M07 (2018) guidelines.
- Frozen-form broth microdilution panels were manufactured by JMI Laboratories and contained cation-adjusted Mueller-Hinton broth with 2.5–5% lysed horse blood added for streptococci.
- Quality assurance was performed by concurrently testing CLSI-recommended quality control reference strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619).
- Breakpoint criteria for MIC interpretations were those criteria from the CLSI M100 (2020) document.

Results

- Tedizolid was active against all *S. aureus* ($MIC_{50/90}$, 0.12/0.25 mg/L; 100% susceptible), and MIC_{50} and MIC_{90} values were 4- to 8-fold dilutions lower than those values displayed by linezolid ($MIC_{50/90}$, 1/1 mg/L; 100% susceptible; Figure 3).
  - Equivalent tedizolid $MIC_{50/90}$ values (0.12/0.25 mg/L) were observed against MRSA (n=886; 41.0% of all *S. aureus*) and methicillin-susceptible (MSSA; $MIC_{50/90}$, 0.12/0.25 mg/L, Table 1) isolates, regardless of age group.
- All CoNS isolates were inhibited by tedizolid at MIC value of ≤0.25 mg/L, and 32.9% were methicillin resistant.
- Tedizolid also was very active against BHS ($MIC_{50/90}$, 0.12/0.25 mg/L; 100% susceptible), regardless of species, and against Viridans group streptococci (VGS; $MIC_{50/90}$, 0.12/0.12 mg/L; 100% susceptible; Table 1).
- Tedizolid was the most potent agent (MIC_{90}, 0.25 mg/L; 100% susceptible) against *E. faecalis* (n=37, 1.1% of all SSSI pathogens).
  - Only 1 vancomycin-resistant *E. faecalis* isolate was observed in this collection; its tedizolid MIC value was 0.12 mg/L.
  - Tedizolid inhibited all *E. faecalis* causing SSSI in pediatric patients at ≤0.5 mg/L (Table 1).
- Tedizolid, linezolid, and daptomycin inhibited all *S. aureus*, *E. faecalis*, and *Streptococcus* spp. isolates recovered from SSSI in pediatric patients at their respective susceptibility breakpoints (Table 1).
- Ceftaroline and clindamycin showed susceptibility rates of >90% against MRSA, MSSA, *S. pyogenes,* and *S. dysgalactiae.*
- Lower susceptibility rates were observed for clindamycin against CoNS (75.7%), VGS (88.2%), and *S. agalactiae* (64.1%).

Conclusions

- *S. aureus* and BHS were responsible for >95% of the isolates causing SSSI in pediatric patients across US hospitals during a 5-year period.
- Tedizolid was highly active against all *S. aureus* and BHS isolates from this collection, but also was active against the less common species of CoNS, enterococci and VGS.
- Tedizolid was equipotent or more potent than comparators against MSSA and MRSA isolates.
- Tedizolid was 4- to 8-fold more active against *Staphylococcus* spp., *Enterococcus* spp., and *Streptococcus* spp. isolates than linezolid.
- Tedizolid may be considered an option for treating pediatric patients with ABSSSI caused by Gram-positive pathogens.

Figure 3 MIC distribution of oxazolidinones against *S. aureus* (*n* = 2,163) and beta-hemolytic streptococci (*n* = 460) isolates

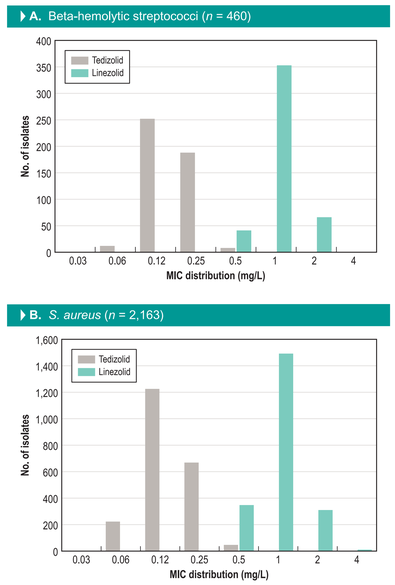
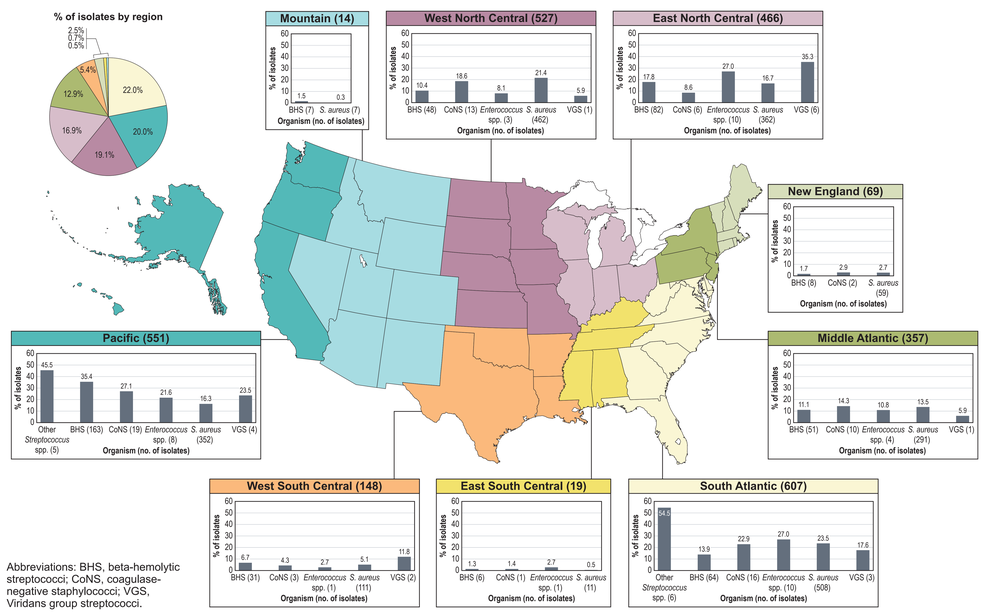


Figure 1 Percentage of isolates recovered by participating centers according to US Census region



Abbreviations: BHS, beta-hemolytic streptococci; CoNS, coagulase-negative staphylococci; VGS, Viridans group streptococci.

Table 1 Activity of tedizolid and comparators against Gram-positive cocci causing SSSI in pediatric patients

Organism[a] (no. tested)	MIC_{50} / MIC_{90} (%S, CLSI[b])											
Phenotype	Tedizolid		Linezolid		Ceftaroline		Daptomycin		Clindamycin		Vancomycin	
MSSA (1,277)	0.12 / 0.25	(100)	1 / 2	(100)	0.25 / 0.25	(100)	0.25 / 0.5	(100)	≤0.25 / ≤0.25	(97.2)	1 / 1	(100)
MRSA (886)	0.12 / 0.25	(100)	1 / 1	(100)	0.5 / 1	(99.0)	0.25 / 0.5	(100)	≤0.25 / ≤0.25	(90.3)	0.5 / 1	(100)
CoNS (70)	0.12 / 0.12	(100)[c]	0.5 / 1	(100)	0.12 / 0.25	(100)[f]	0.25 / 0.5	(100)	≤0.25 / >2	(75.7)	1 / 2	(100)
E. faecalis (30)	0.25 / 0.25	(100)	1 / 2	(100)	1 / 4	—	0.5 / 1	(100)	—		1 / 2	(96.7)
BHS (460)	0.12 / 0.25	(100)	1 / 2	(100)	≤0.008 / ≤0.008	(100)	≤0.06 / 0.25	(100)	≤0.25 / ≤0.25	(95.4)	0.5 / 0.5	(100)
S. pyogenes (409)	0.12 / 0.25	(100)	1 / 2	(100)	≤0.008 / ≤0.008	(100)	≤0.06 / 0.12	(100)	≤0.25 / ≤0.25	(98.5)	0.5 / 0.5	(100)
S. agalactiae (39)	0.12 / 0.25	(100)	1 / 1	(100)	0.015 / 0.015	(100)	0.12 / 0.25	(100)	≤0.25 / >2	(64.1)	0.5 / 0.5	(100)
S. dysgalactiae (12)	0.12 / 0.25	(100)[d]	1 / 1	(100)	≤0.008 / ≤0.008	(100)	≤0.06 / ≤0.06	(100)	≤0.25 / ≤0.25	(91.7)	0.25 / 0.5	(100)
VGS (17)	0.12 / 0.12	(100)[e]	1 / 1	(100)	≤0.008 / 0.06	—	0.12 / 1	(100)	≤0.25 / >2	(88.2)	0.5 / 0.5	(100)

[a] MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative *Staphylococcus*; BHS, β-hemolytic streptococci; VGS, Viridans group streptococci.
[b] %S = percentage susceptible (CLSI, 2020), according to breakpoint availability.
[c] Tedizolid breakpoint for *S. aureus* used for CoNS.
[d] Tedizolid breakpoint for *S. pyogenes* and *S. agalactiae* used for *S. dysgalactiae.*
[e] Tedizolid breakpoint for *S. anginosus* group used for VGS.
[f] Ceftaroline breakpoint for *S. aureus* used for CoNS

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