Activity of Tedizolid and Comparator Agents Against Gram-positive Isolates Causing Skin and Skin Structure Infections in Pediatric Patients in United States Hospitals (2015–2019)

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Background: Tedizolid was approved by the United States Food and Drug Administration to treat acute bacterial skin and skin structure infections in adults in 2014, and in 2020, United States Food and Drug Administration expanded the approval of tedizolid to treat pediatric patients 12 years of age and older. This study assessed the activity of tedizolid and comparator agents against clinical surveillance isolates collected from pediatric patients with skin and skin structure infection in the United States.

Methods: A total of 2747 gram-positive organisms (1 per patient) were collected in 2015 to 2019 from pediatric (≤17 years old) patients with skin and skin structure infections. The isolates were collected from 33 US medical centers and susceptibility tested against tedizolid and comparators by reference broth microdilution methods. Susceptibility results for main pathogens were stratified by patient age: ≤1 years old (851 isolates), 2 to 5 years old (623), 6 to 12 years old (754) and 13 to 17 years old (519).

Results: *Staphylococcus aureus* (n = 2163) was the main pathogen recovered from all age groups, followed by β-hemolytic streptococci (n = 460). Tedizolid inhibited all *S. aureus*, including methicillin-resistant *S. aureus* (MRSA) isolates (41.0%), regardless of the age group. MRSA rates varied by age group; MRSA was highest among ≤1 years old (45.0%) and lowest in the 13 to 17 years old (32.7%) groups. Linezolid, daptomycin and vancomycin also displayed susceptibility rates of 100% against *S. aureus* isolates. Clindamycin (81.3%–98.5%), tetracycline (91.6%–97.1%) and trimethoprim-sulfamethoxazole (97.0%–100%) susceptibility rates varied among age groups and methicillin resistance profiles. Overall, tedizolid, linezolid, daptomycin and vancomycin inhibited all gram-positive pathogens in this collection.

Conclusions: Tedizolid was very active against a large collection of gram-positive pathogens causing skin and skin structure infection in pediatric patients, including MRSA isolates.

Key Words: Tedizolid, oxazolidinone, *S. aureus*

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Acute bacterial skin and skin structure infections (ABSSSI) are common in children. Frequently, these patients are referred to emergency departments, leading to a large number of hospitalizations. ABSSSI consist of a large spectrum of diseases, from those that impair the skin exclusively to those that involve deep skin structures, such as subcutaneous tissues, fascia and muscles, causing cellulitis, abscesses and wound or burn infections that may be life-threatening.[1,2] These infections are most frequently caused by gram-positive bacteria, mainly *Staphylococcus aureus*.[1] In this context, the emergence and dissemination of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) drastically changed the epidemiology of SSSI and narrowed the available therapeutic options.[3]

Administration of systemic antimicrobial agents along with incision and drainage remains the suggested treatment of purulent SSSIs. Appropriate coverage for MRSA is recommended in moderate and severe cases.[4] Vancomycin, daptomycin, linezolid, telavancin or ceftaroline are among options to treat severe ABSSSI caused by MRSA in adults, but only vancomycin, ceftaroline and linezolid are currently approved for use in children. However, these antimicrobials may pose significant risk of adverse events. Among others, vancomycin can be nephrotoxic and requires drug-level monitoring, while linezolid can be associated with the development of myelosuppression.[1] In addition, antimicrobial dosing guidelines in children are inconsistent, most likely due to the lack of pharmacokinetic/pharmacodynamic (PK/PD) data in this population.[5]

Tedizolid is an oxazolidinone class of antimicrobial that inhibits protein synthesis and exhibits potent activity against *Staphylococcus*, *Streptococcus* and *Enterococcus* species, including MRSA and vancomycin-resistant *Enterococcus*. Tedizolid, the active metabolite of the parenteral prodrug tedizolid phosphate, acts by binding to the 23S ribosomal RNA of the 50S subunit, thereby preventing the formation of the 70S initiation complex and thus inhibiting protein synthesis.[6] Tedizolid is approved by the United States Food and Drug Administration (US-FDA), the European Medicines Agency, and other regulatory agencies for the treatment of ABSSSI in adults (Sivextro) and is currently under clinical evaluation for treating ABSSSI in pediatric patients. Recently, studies evaluating the PK and safety of tedizolid in the pediatric population have been completed,[7,8] and the US-FDA has recently expanded the approval of tedizolid to treat pediatric patients 12 years of age and

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older with ABSSSI. The aim of this study was to evaluate the in vitro activity of tedizolid and comparator agents against contemporary (2015–2019) gram-positive isolates causing SSSI in pediatric patients from US medical centers as part of the Surveillance of Tedizolid Activity and Resistance Program.

MATERIALS AND METHODS

Bacterial Isolates

A total of 2747 gram-positive isolates were collected from pediatric patients (≤17 years old) with SSSIs between 2015 and 2019 as part of the Surveillance of Tedizolid Activity and Resistance Program. Only bacterial isolates determined to be clinically significant by local criteria as the reported probable cause of an infection were included in this investigation. The isolates were collected from 33 US medical centers in 23 states from all 9 US Census Bureau divisions. Bacterial identification was performed by the participating centers and confirmed by the monitoring laboratory (JMI Laboratories, North Liberty, IA) using standard biochemical tests and matrix-assisted laser desorption ionization–time of flight mass spectrometry using the MALDI Biotyper (Bruker Daltonics, Billerica, MA) according to the manufacturer's instructions.

Susceptibility Testing

Broth microdilution methods were performed according to Clinical and Laboratory Standard Institute (CLSI) guidelines to determine the antimicrobial susceptibility of tedizolid and comparator agents.[9] Frozen-form broth microdilution panels were manufactured by JMI Laboratories and contained cation-adjusted Mueller-Hinton broth with 2.5% to 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). CLSI susceptibility breakpoints (M100-S30) were used to determine susceptibility/resistance rates for tedizolid and comparator agents.[10] In addition, susceptibility results were analyzed by stratifying isolates based on the age of the patient, as follows: ≤1, 2 to 5, 6 to 12 and 13 to 17 years old.

Data Analysis

The data for this project were analyzed using R Studio version 2022.02.0. Statistical analysis used χ^2 tests to compare proportions between groups of isolates. A logistical regression model was also used to determine the significance of the change in the proportions of isolates between the age groups. *P* values ≤0.05 were considered significant.

RESULTS

S. aureus (n = 2163; 78.4%) was the main pathogen recovered from all age groups (≤1; 2–5; 6–12 and 13–17 years old), followed by β-hemolytic streptococci (BHS; n = 460; 16.7%), coagulase-negative staphylococci (CoNS; n = 70; 2.5%), *Enterococcus* spp. (n = 37; 1.3%) and Viridans group streptococci (n = 17; 0.6%). The age group of patients with the highest number of isolates was ≤1 years old (851 isolates; 31.0%), followed by 6 to 12 years old (754 isolates; 27.4%), 2 to 5 years old (623 isolates; 22.6%) and 13 to 17 years old (519 isolates; 18.9%).

Tedizolid [minimal inhibitory concentration ($MIC)_{50/90}$, 0.12/0.25 mg/L; Table 1] inhibited all *S. aureus* at the susceptible breakpoint of ≤0.5 mg/L, regardless of age group (Table 2). Linezolid ($MIC_{50/90}$, 1/2 mg/L), daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L) and vancomycin ($MIC_{50/90}$, 1/1 mg/L) also inhibited all *S. aureus* isolates at their respective susceptibility breakpoints (Table 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 *S. aureus* (MSSA; $MIC_{50/90}$, 0.12/0.25 mg/L, Table 1) isolates, regardless of age group. MRSA rates significantly decreased as the age groups increased in age (*P* value = 0.0002). MRSA rate was higher in the ≤1 years old age group (45.0%), followed by the 6 to 12 years old (41.7%), 2 to 5 years old (41.3%) and 13 to 17 years old (32.7%) groups. Overall, MRSA rates among the pediatric population progressively decreased (*P* value = 0.003) from 2015 (47.7%) to 2018 (34.8%) but resumed to 41.1% in 2019 (Fig. 1). Tedizolid MIC_{50} and MIC_{90} values were 4- to 8-fold lower than those values displayed by linezolid ($MIC_{50/90}$, 1/1 mg/L; 100% susceptible) against MRSA isolates. Although linezolid, daptomycin, vancomycin (100% susceptible) and trimethoprim-sulfamethoxazole (97.0%–99.3% susceptible) remained active against MRSA isolates, susceptibility rates varied for tetracycline (91.6%–95.8%) among the age groups (Table 2). Notably, the susceptibility rate for clindamycin (90.3% overall) against MRSA was lower than that obtained against MSSA (97.2%). Likewise, clindamycin exhibited lower susceptibility rate against MRSA isolates recovered from patients in the 13 to 17 years old age group (81.3%) compared with all other groups (90.5%–93.7%).

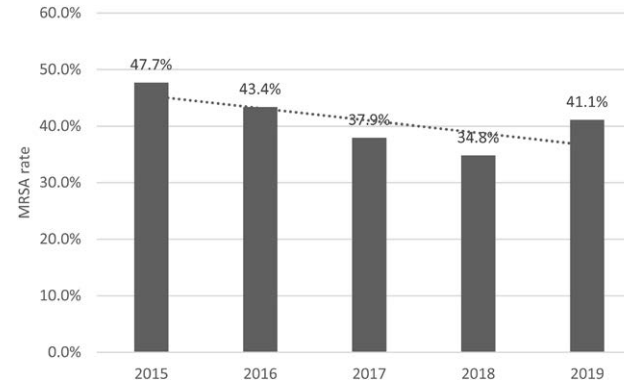

FIGURE 1. MRSA rates among the pediatric population between 2015 and 2019. Regression slope coefficient of –2.2% (*P* value = 0.0002).

Tedizolid was also active ($MIC_{50/90}$, 0.12/0.12 mg/L) against CoNS (70 isolates; Table 1), regardless of the methicillin resistance phenotype. Although linezolid, daptomycin and vancomycin were active against CoNS, other comparators such as clindamycin (75.7% susceptible) and trimethoprim-sulfamethoxazole (88.6% susceptible) showed susceptibility rates <90% (Table 3). Furthermore, methicillin resistance was noted in 32.9% of the CoNS isolates.

BHS (460 isolates; 16.7% of all isolates) was the second most common pathogen group causing SSSI in pediatric patients. BHS isolates were more frequently recovered from patients in the 6 to 12 years old (24.8%) and 2 to 5 years old (22.2% of isolates) age groups compared with the 13 to 17 years old (11.8%) and ≤1 years old (8.7%) age groups (*P* values < 0.001). Organisms in these groups included *Streptococcus pyogenes* (409 isolates), *S. agalactiae* (39) and *S. dysgalactiae* (12). Tedizolid inhibited all BHS isolates at ≤0.5 mg/L (Table 1); furthermore, MIC_{50} and MIC_{90} values were within 2-fold (0.12/0.25 mg/L) against all BHS species included in this collection. These pathogens were also susceptible to comparator agents (Table 2). Penicillin, ceftriaxone, linezolid, daptomycin and vancomycin displayed susceptibility rates of 100%. The clindamycin susceptibility rate was 95.4% overall, ranging from 90.2% to 97.8% in the 13 to 17 and 2 to 5 years old age groups, respectively. Tetracycline susceptibility rates showed great variability among the age groups, from 68.9% to 92.5% in the 13 to 17 and 6 to 12 years old age groups. Tedizolid was highly active

TABLE 1. Antimicrobial Activity of Tedizolid Tested Against the Main Organisms and Organism Groups of Isolates From Pediatric (≤17 Years Old) Patients (United States, 2015–2019)

	No. and Cumulative % of Isolates Inhibited at MIC (mg/L) of:							MIC_{50}	MIC_{90}
Organism/Organism Group (No. of Isolates)	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5		
Staphylococcus aureus (2163)		0	2	222	1225	668	46	0.12	0.25
		0.0	0.1	10.4	67.0	97.9	100.0		
Methicillin-susceptible (1277)			0	102	648	485	42	0.12	0.25
			0.0	8.0	58.7	96.7	100.0		
Methicillin-resistant (886)		0	2	120	577	183	4	0.12	0.25
		0.0	0.2	13.8	78.9	99.5	100.0		
Coagulase-negative staphylococci (70)		0	1	19	44	6		0.12	0.12
		0.0	1.4	28.6	91.4	100.0			
Methicillin-susceptible (47)		0	1	15	28	3		0.12	0.12
		0.0	2.1	34.0	93.6	100.0			
Methicillin-resistant (23)			0	4	16	3		0.12	0.25
			0.0	17.4	87.0	100.0			
Enterococcus spp. (37)			0	1	16	18	2	0.25	0.25
			0.0	2.7	45.9	94.6	100.0		
β-hemolytic streptococci (460)			0	12	252	188	8	0.12	0.25
			0.0	2.6	57.4	98.3	100.0		
Viridans group *streptococci* (17)	1	0	3	3	9	1		0.12	0.12
	5.9	5.9	23.5	41.2	94.1	100.0			

TABLE 2. Activity of Tedizolid and Comparator Antimicrobial Agents Stratified by Age Group (United States, 2015–2019)

	% Susceptible by CLSI criteria* (No. of Tested)				
Organism/Antimicrobial Agent	≤1 Years Old	2–5 Years Old	6–12 Years Old	13–17 Years Old	All Isolates (≤17 Years Old)
MSSA	(410)	(272)	(309)	(286)	(1277)
Tedizolid	100.0	100.0	100.0	100.0	100.0
Linezolid	100.0	100.0	100.0	100.0	100.0
Clindamycin	98.5	97.1	97.1	95.5	97.2
Daptomycin	100.0	100.0	100.0	100.0	100.0
Tetracycline	93.2	96.0	97.1	93.0	94.7
TMP-SMT	100.0	99.3	100.0	99.7	99.8
Vancomycin	100.0	100.0	100.0	100.0	100.0
MRSA	(335)	(191)	(221)	(139)	(886)
Tedizolid	100.0	100.0	100.0	100.0	100.0
Linezolid	100.0	100.0	100.0	100.0	100.0
Clindamycin	93.7	90.6	90.5	81.3	90.3
Daptomycin	100.0	100.0	100.0	100.0	100.0
Tetracycline	91.6	95.8	95.0	92.1	93.5
TMP-SMT	97.0	99.0	98.2	99.3	98.1
Vancomycin	100.0	100.0	100.0	100.0	100.0
β-hemolytic streptococci†	(74)	(138)	(187)	(61)	(460)
Tedizolid	100.0‡	100.0‡	100.0‡	100.0‡	100.0‡
Linezolid	100.0	100.0	100.0	100.0	100.0
Ceftriaxone	100.0	100.0	100.0	100.0	100.0
Clindamycin	94.6	97.8	95.7	90.2	95.4
Daptomycin	100.0	100.0	100.0	100.0	100.0
Penicillin	100.0	100.0	100.0	100.0	100.0
Tetracycline	71.6	89.9	92.5	68.9	85.2
Vancomycin	100.0	100.0	100.0	100.0	100.0

*Criteria as published by CLSI.[10]

†Organisms include: *Streptococcus agalactiae* (39), *S. dysgalactiae* (12) and *S. pyogenes* (409).

‡Tedizolid CLSI breakpoints for *S. pyogenes* and *S. agalactiae* applied to all β-hemolytic streptococci.

TMP-SMT indicates trimethoprim-sulfamethoxazole.

against *Enterococcus* spp. (37 isolates, $MIC_{50/90}$, 0.25/0.25 mg/L; highest MIC, 0.5 mg/L) and Viridans group *streptococci* (17 isolates, $MIC_{50/90}$, 0.12/0.12 mg/L; highest MIC, 0.25 mg/L; Table 1).

DISCUSSION

While skin and skin structure infections affect both outpatients and inpatients, a significant increase in ambulatory visits and hospital admissions for SSSIs has been observed over the last 2 decades due to these infections.[11,12] It has been estimated that 385,000 pediatric patients present to the US emergency departments annually with SSSI.[13] Using the Kids' Inpatient Databases, Lautz et al[14] observed that SSTI admissions among children younger than 3 years increased from 32.5% in 2000 to 49.6% in 2006. Hospital admissions for pediatric patients with ABSSSI have similarly become more frequent in the past decade.[15] SSSI in hospitalized

TABLE 3. Antimicrobial Activity of Tedizolid and Comparator Agents Against Gram-positive Pathogens Causing SSSI in Pediatric Patients in US Medical Centers (2015–2019)

	mg/L		CLSI*	
Antimicrobial Agent	MIC_{50}	MIC_{90}	%S	%R
S. aureus (n = 2163)				
Tedizolid	0.12	0.25	100.0	0.0
Linezolid	1	2	100.0	0.0
Clindamycin	≤0.25	≤0.25	94.4	5.5
Daptomycin	0.25	0.5	100.0	0.0
Oxacillin	0.5	>2	59.1	41.0
Tetracycline	≤0.5	≤0.5	94.2	3.8
TMP-SMT	≤0.5	≤0.5	99.1	0.9
Vancomycin	1	1	100.0	0.0
β-hemolytic streptococci (n = 460)				
Tedizolid	0.12	0.25	100.0†	0.0
Linezolid	1	2	100.0	0.0
Ceftriaxone	≤0.03	0.06	100.0	0.0
Clindamycin	≤0.25	≤0.25	95.4	4.3
Daptomycin	≤0.06	0.25	100.0	0.0
Penicillin	≤0.03	≤0.03	100.0	0.0
Tetracycline	≤0.25	>4	85.2	14.1
Vancomycin	0.5	0.5	100.0	0.0
Coagulase-negative *Staphylococcus*‡ (n = 70)				
Tedizolid	0.12	0.12	100.0§	0.0
Linezolid	0.5	1	100.0	0.0
Clindamycin	≤0.25	>2	75.7	22.9
Daptomycin	0.25	0.5	100.0	0.0
Oxacillin	0.5	>2	67.1	32.9
Tetracycline	≤0.5	1	92.9	4.3
TMP-SMT	≤0.5	4	88.6	11.4
Vancomycin	1	2	100.0	0.0
Enterococcus spp¶ (n = 37)				
Tedizolid	0.25	0.25	100.0‖	0.0
Linezolid	1	2	100.0	0.0
Ampicillin	≤0.5	1	91.9	8.1
Daptomycin	0.5	2		
Tetracycline	>8	>8	18.9	81.1
Vancomycin	1	2	94.6	5.4
Viridans group *Streptococcus*** (n = 17)				
Tedizolid	0.12	0.12	100.0††	0.0
Linezolid	1	1	100.0	0.0
Ceftriaxone	0.12	1	94.1	5.9
Clindamycin	≤0.25	>2	88.2	11.8
Daptomycin	0.12	1	100.0	0.0
Penicillin	≤0.03	0.25	88.2	5.9
Tetracycline	≤0.25	>4	76.5	23.5
Vancomycin	0.5	0.5	100.0	0.0

*Criteria as published by CLSI.[10]

†Tedizolid CLSI breakpoints for *S. pyogenes* and *S. agalactiae* applied to all β-hemolytic streptococci.

‡Organisms include *Staphylococcus capitis* (5), *S. caprae* (3), *S. epidermidis* (30), *S. hominis* (2), *S. intermedius* (1), *S. lugdunensis* (24), *S. pseudintermedius* (1), *S. simulans* (2) and *S. warneri* (2).

§Tedizolid CLSI breakpoints for *S. aureus* applied to all staphylococci.

¶Organisms include *Enterococcus avium* (2), *E. casseliflavus* (2), *E. faecalis* (30) and *E. faecium* (3).

‖Tedizolid CLSI breakpoints for *E. faecalis* were applied to all *Enterococcus* spp.

**Organisms include *Streptococcus anginosus* (5), *S. anginosus* group (3), *S. constellatus* (1), *S. cristatus* (1), *S. intermedius* (5), *S. massiliensis* (1) and *S. mitis* group (1).

††Tedizolid CLSI breakpoints for *S. anginosus* group were applied to all Viridans group streptococci.

patients increases the length of hospital stay, causes considerable morbidity with significant attributable mortality, and likely has an important role in the development of antimicrobial resistance.[16,17]

S. aureus remains the major cause of SSSI in adult and pediatric patients. MRSA strains emerged in the 1960s and were found predominantly in patients exposed to health care facilities. However, the epidemiology of SSSI has changed with the surge of CA-MRSA strains in the mid-1990s. Now, CA-MRSA is the leading identifiable cause of SSSI in US emergency departments in pediatric and adult patients.[18] In this study, MRSA was observed in 41.0% of all *S. aureus* causing SSSI in pediatric patients in US medical centers and showed a progressive decrease over the study period but for the last year, 2019. This evidence aligns with the substantial decreases in the community-onset MRSA bloodstream infection rates from 2005 to 2016 published by Kourtis et al[19] using the National Healthcare Safety Network and the Emerging Infections Program surveillance system. Although there are several agents active against MRSA that are approved for the treatment of adults with SSSI, antimicrobial options for treating pediatric patients with SSSI continue to be problematic as some antimicrobials have been poorly studied in children or have significant intrinsic limitations for their use in pediatrics, including antimicrobial resistance and the risk of significant adverse events.[1]

Tedizolid is an oxazolidinone antimicrobial agent with more potent in vitro activity than linezolid against several gram-positive pathogens, including MRSA, due to its increased number of active binding sites to the target ribosomal subunit.[20] Although several acquired resistance mechanisms to linezolid have been described, which mainly prevent its interaction with the ribosomal target, resistance to this class of antimicrobial is rarely reported in clinical practice.[21–24] Nevertheless, limited data exist on resistance profiles for bacterial pathogens isolated from children.

In the present study, the antimicrobial susceptibility of 2747 gram-positive pathogens collected from pediatric patients hospitalized in US medical centers was evaluated, and tedizolid was active in vitro against 100% of *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp. isolates. Resistance to oxazolidinones was not observed in this collection. Overall, susceptibility rates to comparator agents were high. Linezolid, daptomycin and vancomycin also displayed activity against all *S. aureus* isolates, including MRSA, and β-hemolytic streptococci, regardless of the age group. Other available antimicrobial agents, such as clindamycin, tetracyclines and trimethoprim-sulfamethoxazole inhibited >90% of MSSA and MRSA isolates, except for clindamycin, which displayed a susceptibility rate of 81.3% when tested against MRSA isolates from the 13 to 17 years old group.

In 2020, the US-FDA has expanded the approval of tedizolid to include pediatric patients 12 years of age to <18 years of age for the treatment of ABSSSI. Differently from other recently approved antimicrobials for treating skin and skin structure infections in adults that have limited evidence of PK, safety and efficacy in children, tedizolid is under an investigational plan for all pediatric age groups, including newborns.[8] Clinical trials in infants are especially needed because the PK, safety and efficacy may differ significantly from that observed in adults and older children. A Phase 3 clinical trial recently evaluating the safety and efficacy of tedizolid in 121 adolescents (12–<18 years of age) with ABSSSI was completed.[7] This study compared tedizolid (oral and intravenous, 200 mg once daily for 6 days) to an investigator-selected active comparator per the local standard of care for 10 days. Results from this study suggested that the safety and efficacy of tedizolid was comparable to active comparators. In addition, no clinically significant differences were observed between treatment groups regarding hematologic parameters. In adults, the efficacy of tedizolid for the treatment of SSSI was assessed in 2 Phase 3 randomized clinical trials (ESTABLISH-1 and ESTABLISH-2).[25,26] In both studies, noninferiority results for early clinical response were obtained when a 6-day course of intravenous tedizolid was compared with a 10-day course of intravenous linezolid.[27] Although linezolid can be associated with the development of myelosuppression and tedizolid is a more

potent inhibitor of mitochondrial protein synthesis than linezolid, the risks of adverse effects related to mitochondrial dysfunction (ie, lactic acidosis, myelosuppression and neuropathy) were found to be inferior for tedizolid than linezolid in studies carried out in animal models.[28]

In summary, data from this study demonstrated that a large collection of gram-positive organisms causing SSSI in pediatric patients was susceptible to tedizolid and that tedizolid was consistently active in vitro against organisms isolated from all age groups. Although these results support further evaluation of tedizolid for treating pediatric patients, including infections caused by MRSA, there are no studies in children under 2 years of age with this antibiotic.

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