In Vitro Activity of Tedizolid in Comparison With Other Oral and Intravenous Agents Against a US Collection of Community-Acquired Methicillin-Resistant *Staphylococcus aureus* (2014-2015)

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Mendes RE; Sader HS; Rhomberg P; Flamm RK

JMI Laboratories, North Liberty, Iowa, USA

Rodrigo E. Mendes, PhD
JMI Laboratories
345 Beaver Kreek Centre, Ste A
North Liberty, IA 52317, USA
319-665-3370
rodrigo-mendes@jmilabs.com

INTRODUCTION

- Methicillin-resistant *Staphylococcus aureus* (MRSA) has been an endemic nosocomial pathogen in many hospitals worldwide for the past 5 decades
- The 1980s and early 1990s saw the emergence and spread of community-associated MRSA (CA-MRSA) in the United States
  - This brought difficulties for the empiric treatment of community-acquired infections, and later guidelines were revised to provide appropriate MRSA cover
  - In addition, although CA-MRSA isolates were initially associated with distinct phenotypes, genotypes, and risk factors, the distinction between hospital-acquired MRSA (HA-MRSA) and CA-MRSA isolates has become blurred in recent years
- Tedizolid is a novel oxazolidinone prodrug antibacterial administered at a dose of 200 mg once daily for 6 days either orally (with or without food) or as an intravenous (IV) infusion in patients ≥18 years of age
  - Tedizolid is approved for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of *S. aureus* (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and *Enterococcus faecalis*
  - Tedizolid has high bioavailability and the benefit of a prolonged half-life, which allows for once-daily dosing
- Given that several studies have reported on the high incidence of CA-MRSA in the United States, this study was conducted to evaluate the activity of tedizolid compared with that of other agents with oral and/or IV formulations against CA-MRSA

MATERIALS AND METHODS

Bacterial strain collection

- A total of 2138 CA-MRSA isolates were collected during the Surveillance of Tedizolid Activity and Resistance (STAR) Program for 2014 and 2015
- Isolates were recovered from 30 medical sites located in 9 US census divisions
- Isolates were initially identified by the participating laboratory and submitted to a central monitoring facility (JMI Laboratories, North Liberty, Iowa), where bacterial identifications were confirmed using standard algorithms and supported by MALDI–TOF–MS (Bruker Daltonics, Bremen, Germany)
- For purposes of data analysis, isolates were classified according to age group (adult [≥18 years] and pediatric [≤17 years]). Community-acquired isolates were defined according to Centers for Disease Control and Prevention criteria
  - *S. aureus* isolates recovered either from an outpatient or from an inpatient <48 hours after hospital admission were selected for this study
  - However, because of the lack of further demographic information, it is not possible to differentiate between community-acquired and health care–associated community-onset infection

Antimicrobial susceptibility testing

- Isolates were tested for susceptibility by broth microdilution in accordance with guidelines from the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document
- Testing was performed using reference 96-well panels manufactured by JMI Laboratories
- Minimum inhibitory concentration (MIC) readings for tedizolid and linezolid were performed according to the CLSI guidelines (ie, the first well in which trailing begins without regard for pinpoint trailing in the wells)
  - Quality assurance was performed by concurrent testing of CLSI-recommended quality control (QC) reference strain (*S. aureus* ATCC 29213)
  - All QC results were within acceptable published ranges
- Breakpoint criteria for tedizolid and comparator agents were those from CLSI (M100-S26)

RESULTS

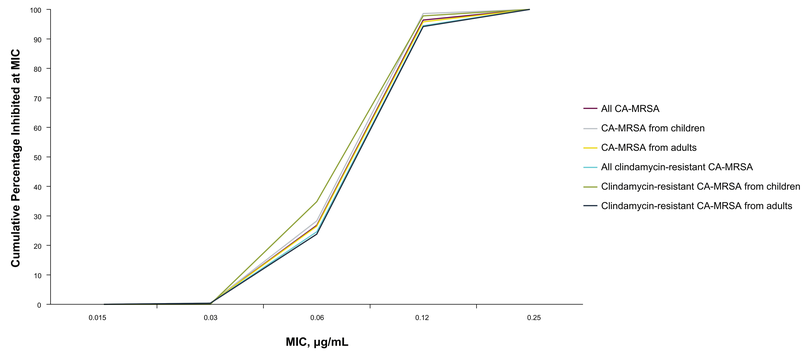
- Overall, tedizolid ($MIC_{50/90}$, 0.12/0.12 µg/mL) inhibited all CA-MRSA isolates at ≤0.25 µg/mL, below the breakpoint for susceptibility (ie, ≤0.5 µg/mL) (**Table 1**). Furthermore, tedizolid showed similar MIC distribution profiles ($MIC_{50/90}$, 0.12/0.12 µg/mL) against CA-MRSA, regardless of age group or clindamycin phenotype (**Table 1** and **Figure 1**)

Table 1. Activity of tedizolid against contemporary CA-MRSA isolates in the United States

CA-MRSA/Phenotype Populations (no. tested)	MIC, µg/mL		No. (cumulative %) Inhibited at MIC, µg/mL				
	50%	90%	≤0.015	0.03	0.06	0.12	0.25
All (2138)	0.12	0.12	0 (0.0)	8 (0.4)	566 (26.8)	1487 (96.4)	77 (100.0)
Pediatric (487)	0.12	0.12	0 (0.0)	2 (0.4)	136 (28.3)	342 (98.6)	7 (100.0)
Adult (1651)	0.12	0.12	0 (0.0)	6 (0.4)	430 (26.4)	1145 (95.8)	70 (100.0)
Clindamycin-resistant (541)	0.12	0.12	0 (0.0)	2 (0.4)	131 (24.6)	378 (94.5)	30 (100.0)
Pediatric (46)	0.12	0.12	0 (0.0)	0 (0.0)	16 (34.8)	29 (97.8)	1 (100.0)
Adult (495)	0.12	0.12	0 (0.0)	2 (0.4)	115 (23.6)	349 (94.1)	29 (100.0)

CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*; MIC = minimum inhibitory concentration.

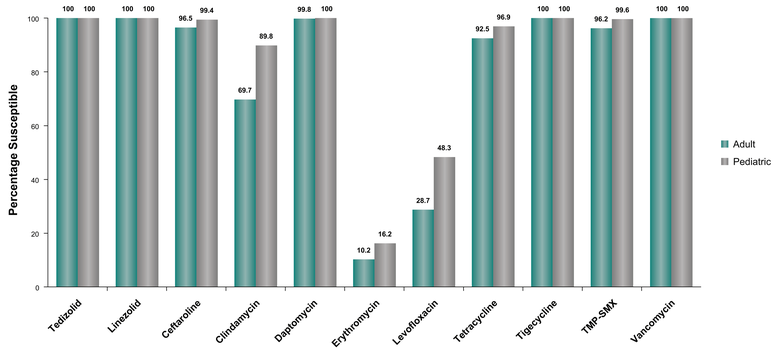
Figure 1. Tedizolid MIC distributions obtained against CA-MRSA (data are presented as the cumulative percentage of isolates inhibited at each MIC [µg/mL]).



CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*; MIC = minimum inhibitory concentration.

- Oral agents available for the treatment of MRSA, such as linezolid (100.0% susceptible), tetracycline (92.5–96.9% susceptible), and trimethoprim-sulfamethoxazole (TMP-SMX; 96.2–99.6% susceptible), were active against CA-MRSA subsets from adult and pediatric patients, whereas clindamycin (69.7–89.8% susceptible) had suboptimal antimicrobial coverage (**Figure 2**)
- Erythromycin (10.2–16.2% susceptible) and levofloxacin (28.7–48.3% susceptible) were not active against the CA-MRSA subsets; hence, they are not recommended for the empiric coverage of such pathogens (**Figure 2**)
- Tedizolid MIC results were 2- to 4-fold lower than those obtained for IV options such as daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL) and 8-fold lower than obtained for linezolid ($MIC_{50/90}$, 1/1 µg/mL), ceftaroline ($MIC_{50/90}$, 1/1 µg/mL), and vancomycin ($MIC_{50/90}$, 1/1 µg/mL) against CA-MRSA and population subsets (data not shown)

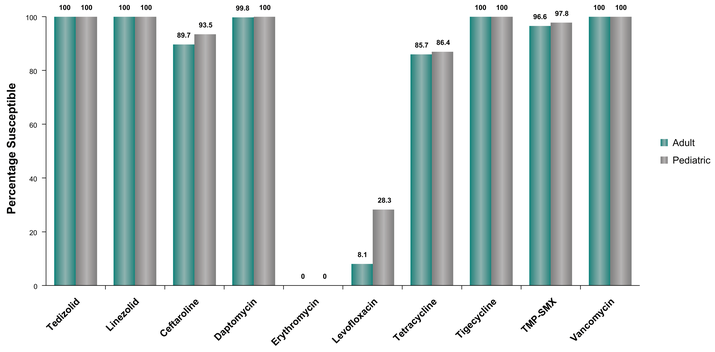
Figure 2. Susceptibility profile of CA-MRSA isolates causing infection in the United States.



CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*; TMP-SMX = trimethoprim-sulfamethoxazole.

- TMP-SMX (96.6–97.8% susceptible) remained active against the clindamycin-resistant CA-MRSA population, whereas tetracycline activity (85.7–86.4% susceptible) showed marginal coverage (**Figure 3**)
- Linezolid (100.0% susceptible), daptomycin (≥99.8% susceptible), tigecycline (100.0% susceptible), and vancomycin (100.0% susceptible) had consistent activities against clindamycin-resistant CA-MRSA populations from pediatric and adult patients (**Figure 3**)

Figure 3. Susceptibility profile of clindamycin-resistant CA-MRSA isolates causing infection in the United States.



CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*; TMP-SMX = trimethoprim-sulfamethoxazole.

CONCLUSIONS

- Tedizolid had potent and consistent activities against CA-MRSA, regardless of clindamycin phenotype or age of patient population. In addition, tedizolid potency was greater than that of comparators with oral and/or IV formulations
- With the exception of clindamycin against CA-MRSA and tetracycline against the clindamycin-resistant subset, other oral agents recommended for empiric coverage of CA-MRSA in outpatient settings also showed coverage against CA-MRSA

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