Activity of Tedizolid against Gram-Positive Clinical Isolates Causing Nosocomial- and Community-Acquired Infections in United States Hospitals (2014–2016)

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INTRODUCTION

- Tedizolid (previously known as torezolid or TR-700) is the second oxazolidinone to receive regulatory approval
  - This agent was approved by the United States (US) Food and Drug Administration (FDA) in 2014 and by the European Medicines Agency (EMA) and Health Canada in 2015 for the treatment of acute bacterial skin and skin structure infections (ABSSSI)
- This oxazolidinone is also approved for clinical use in other regions and is currently being evaluated for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia
- Both oxazolidinones, tedizolid and linezolid, inhibit protein synthesis by binding to the 50S subunit ribosome; however, tedizolid demonstrates enhanced potency compared with linezolid because molecule features enhance its binding to the target site (peptidyl transferase center)
- This study assessed the in vitro activities of tedizolid and comparator agents tested against gram-positive isolates responsible for SSSI, pneumonia, and bloodstream infections (BSI) in patients in the US and evaluated the in vitro activities against isolates causing infections in the community and hospital settings

MATERIALS AND METHODS

Bacterial isolates

- A total of 10,091 nonduplicate, single-patient gram-positive isolates were included
  - Isolates were recovered from patients hospitalized in 31 US sites during the Surveillance of Tedizolid Activity and Resistance (STAR) Program for 2014–2016
- 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)
- For this investigation, isolates were designated as hospital-acquired if they were cultured from a clinical specimen collected ≥48 hours after patient hospital admission, while community-acquired was defined as cultured from a clinical specimen collected <48 hours of admission

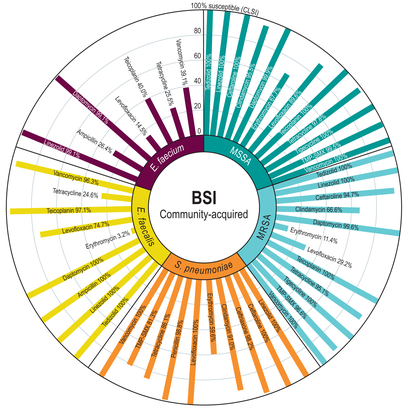
Antimicrobial susceptibility testing

- Isolates were susceptibility tested by broth microdilution following guidelines from the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document
- MIC reading for tedizolid and linezolid was performed according to the CLSI guidelines – ie, the first well at which trailing begins without regard to pinpoint trailing in the wells
- Quality assurance was performed by concurrently testing CLSI-recommended quality control reference strains (*Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* 29212, and *Streptococcus pneumoniae* ATCC 49169)
  - All QC results were within published acceptable ranges
- Breakpoint criteria for tedizolid and comparator agents were those from CLSI (2016), and tigecycline MIC interpretation used the FDA-approved breakpoints

RESULTS

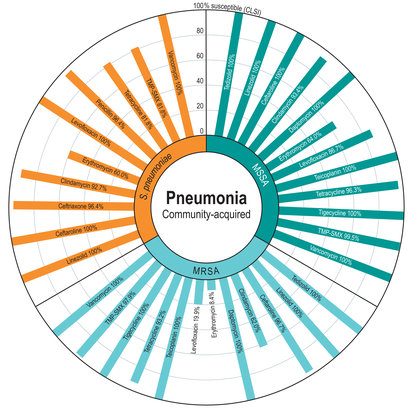
- Susceptibility profiles for methicillin-susceptible and -resistant *S. aureus* (MSSA and MRSA, respectively) were similar among isolates causing different infections (Figures 1–3)
- Overall, high susceptibility rates were noted for all antimicrobial agents tested against MSSA isolates, regardless of infection type, except for erythromycin, while MRSA exhibited low rates for erythromycin (8.4%–12.7%), clindamycin (57.2%–78.5%), and levofloxacin (16.8%–38.1%)

Figure 1 Activity of tedizolid and comparator agents tested against gram-positive isolates causing BSI in community and hospital settings



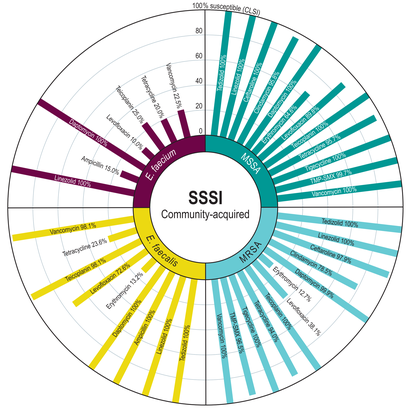
MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; TMP-SMX = trimethoprim-sulfamethoxazole.
Tedizolid susceptibility bars are not represented for *E. faecium* and *S. pneumoniae* due to the lack of breakpoints.

Figure 2 Activity of tedizolid and comparator agents tested against gram-positive isolates causing pneumonia in community and hospital settings



MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; TMP-SMX = trimethoprim-sulfamethoxazole.
Tedizolid susceptibility bars are not represented for *S. pneumoniae* due to the lack of breakpoints.

Figure 3 Activity of tedizolid and comparator agents tested against gram-positive isolates causing skin and skin structure infections in community and hospital settings



MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; TMP-SMX = trimethoprim-sulfamethoxazole.
Tedizolid susceptibility bars are not represented for *E. faecium* due to the lack of breakpoints.

- Tedizolid ($MIC_{50/90}$, 0.12/0.12-0.25 µg/mL; 100.0% susceptible) showed equivalent MIC_{50} and MIC_{90} values against MSSA and MRSA, regardless of infection type or origin of isolate
- Susceptibility profiles for *E. faecalis* isolates were similar among isolates causing BSI or SSSI from the community or hospital settings (Figures 1–3)
- Tedizolid ($MIC_{50/90}$, 0.12/0.25 µg/mL; 100.0% susceptible) potencies were consistent against *E. faecalis* causing various infection types in different settings, as were linezolid ($MIC_{50/90}$, 1/1 µg/mL; 100.0% susceptible), ampicillin ($MIC_{50/90}$, 1/1-2 µg/mL; 100.0% susceptible), daptomycin ($MIC_{50/90}$, 1/1-2 µg/mL; 100.0% susceptible), and vancomycin ($MIC_{50/90}$, 1/2 µg/mL; 94.9%–98.1% susceptible), although these agents had MIC_{50} and MIC_{90} values 4- to 8-fold higher than tedizolid (Figures 1–3)
- The proportion of *Enterococcus faecium* exhibiting a vancomycin-nonsusceptible phenotype was higher among isolates causing hospital infections compared to those from the community (Figures 1–3)
- Tedizolid ($MIC_{50/90}$, 0.12/0.25 µg/mL), linezolid ($MIC_{50/90}$, 1/1-2 µg/mL; 97.6%–100.0% susceptible), and daptomycin ($MIC_{50/90}$, 1/2-4 µg/mL; 97.4%–100.0% susceptible) were active in vitro against *E. faecium*, regardless of infection type (Figures 1–3)
- *S. pneumoniae* isolates were susceptible to several drugs tested, which showed consistent activity among isolates causing BSI or pneumonia, including tedizolid ($MIC_{50/90}$, 0.12/0.25 µg/mL) and linezolid ($MIC_{50/90}$, 1/2 µg/mL)
- Limited coverage was noted for erythromycin (59.6%–60.0%), tetracycline (81.8%–86.1%), and TMP-SMX (81.3%–81.8%) against *S. pneumoniae* (Figures 1–2)

CONCLUSIONS

- Susceptibility rates for pathogens causing infections in the community were not significantly different from those causing nosocomial infections
  - This may be due to the presence of a great number of isolates causing community-onset hospital-associated infections, which cannot be discriminated from pathogens causing community-acquired infections in this study
- Tedizolid had potent in vitro activity against gram-positive isolates causing infections in the community and hospital settings in the US, regardless of infection site or bacterial species
- The tedizolid in vitro potency was also generally higher than clinically available comparator agents when tested against *S. aureus* and enterococcal clinical isolates

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