Evaluation of Tedizolid Activity against Gram-Positive Clinical Isolates Causing Pneumonia in Europe and Surrounding Areas (2014–2017)

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INTRODUCTION

- Bacterial pneumonia is a leading cause of morbidity and mortality in the United States and Europe that results in substantial antibiotic usage
- Delaying pathogen-appropriate antimicrobial therapy to patients with either community-acquired bacterial pneumonia (CABP) or nosocomial pneumonia (NP) (including hospital-acquired bacterial pneumonia [HABP] and ventilator-associated pneumonia [VABP]) results in excess mortality
- Given that timely, sensitive, and specific means of diagnosing bacterial pneumonia are not readily available yet, initial antibiotic selection remains empiric for most patients while considering the suspected etiology, pathogen-directed therapy changes, and antibiotic resistance
- Although the causes of bacterial pneumonia may vary according to the onset of infection, *Streptococcus pneumoniae* and *Staphylococcus aureus* are the predominant gram-positive pathogens in CAP and HAP, respectively
- Tedizolid is currently approved to treat acute bacterial skin and skin structure infections (ABSSSI) and is in an ongoing Phase 3 clinical trial for nosocomial pneumonia (NCT02019420)
- This study evaluated tedizolid and comparator *in vitro* activities against gram-positive isolates causing pneumonia in hospitalised patients

MATERIALS AND METHODS

Organism collection

- A total of 1,824 gram-positive non-duplicate single-patient isolates were collected from the respiratory tract of patients hospitalised with pneumonia
  - Isolates originated from 19 European countries/regions (37 sites) and were submitted to a monitoring laboratory as part of the Surveillance of Tedizolid Activity and Resistance (STAR) program
- 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 technology mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Bremen, Germany)

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following guidelines from the Clinical and Laboratory Standards Institute (CLSI) M07 document (2018)
  - Broth microdilution used 96-well reference 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
- MIC readings for tedizolid and linezolid were performed according to the CLSI guidelines—ie, the first well at 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 strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* 29212, and *S. pneumoniae* ATCC 49619)
  - All QC results were within published acceptable ranges
- Breakpoint criteria for tedizolid and comparator agents were those from EUCAST (2018)
- The onset of pneumonia (CABP versus NP) caused by methicillin-resistant *S. aureus* (MRSA) was defined according to CDC criteria

Table 1 Antimicrobial activity of tedizolid tested against the main gram-positive organisms and organism groups of isolates in 2014–2017

Organism / organism group (no. of isolates)	Number of isolates and cumulative % inhibited at MIC (mg/L) of:						MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5		
Staphylococcus aureus (1,534)		7 0.5	203 13.7	1016 79.9	293 99.0	15 100.0	0.12	0.25
MRSA (400)		5 1.2	67 18.0	269 85.2	58 99.8	1 100.0	0.12	0.25
HAP (191)		3 1.6	36 20.4	131 89.0	20 99.5	1 100.0	0.12	0.25
CAP (140)			23 16.4	93 82.9	24 100.0		0.12	0.25
MSSA (1,134)		2 0.2	136 12.2	747 78.0	235 98.8	14 100.0	0.12	0.25
Coagulase-negative staphylococci[a] (46)			19 41.3	25 95.7	2 100.0		0.12	0.12
Streptococcus pneumoniae (101)		1 1.0	7 7.9	60 67.3	31 98.0	2 100.0	0.12	0.25
Enterococcus faecalis (46)				24 52.2	22 100.0		0.12	0.25
Enterococcus faecium (26)			3 11.5	15 69.2	8 100.0		0.12	0.25
β-haemolytic streptococci[b] (46)			2 4.3	32 73.9	11 97.8	1 100.0	0.12	0.25
Viridans group streptococci[c] (25)		2 8.0	7 36.0	12 84.0	4 100.0		0.12	0.25

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; HAP, hospital-acquired pneumonia; CAP, community-acquired pneumonia.
[a] Includes: *Staphylococcus epidermidis* (26), *S. haemolyticus* (16), *S. lugdunensis* (1), *S. warneri* (3).
[b] Includes: *Streptococcus agalactiae* (26), *S. dysgalactiae* (1), *S. pyogenes* (19).
[c] Includes: *Streptococcus anginosus* (6), *S. constellatus* (1), *S. cristatus* (1), *S. mitis* (1), *S. mitis group* (7), *S. mitis/ oralis* (5), *S. oralis* (2), *S. parasanguinis* (1), *S. vestibularis* (1).

RESULTS

- Gram-positive isolates included in this study were recovered from patients with pneumonia requiring hospitalisation
  - S. aureus comprised the majority (84.1%) of the isolates, of which 26.1% were MRSA (Table 1)
  - Other gram-positive organisms consisted of a small number of isolates
- Overall, tedizolid showed MIC_{50} and MIC_{90} values of 0.12 and 0.25 mg/L against all *S. aureus*, or the methicillin-susceptible, -resistant, CA- or HA-MRSA subsets (Table 1)
- Tigecycline ($MIC_{50/90}$, 0.06/0.12 mg/L), tedizolid ($MIC_{50/90}$, 0.12/0.25 mg/L), and vancomycin ($MIC_{50/90}$, 0.5/1 mg/L) were the most active agents against MRSA (Table 2)
- Tedizolid ($MIC_{50/90}$, 0.12/0.12 mg/L) inhibited all coagulase-negative staphylococci (84.8% methicillin-resistant) at ≤0.25 mg/L
  - Tedizolid and tigecycline ($MIC_{50/90}$, 0.06/0.25 mg/L; 100.0% susceptible) showed the lowest MIC values against coagulase-negative staphylococci (Tables 1 and 2)
- Tedizolid (MIC_{90}, 0.25 mg/L), ceftaroline (MIC_{90}, 0.12 mg/L), and vancomycin (MIC_{90}, 0.25 mg/L) showed the lowest MIC_{90} results against *S. pneumoniae* (Table 2)
  - A total of 29.8% and 17.8% of *S. pneumoniae* were non-susceptible to penicillin and ceftriaxone, respectively

Table 2 Activity of tedizolid and comparator antimicrobial agents against clinical isolates causing pneumonia in hospitalised patients (2014–2017)

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	EUCAST[a]		
				%S	%I	%R
MRSA (400)						
Tedizolid	0.12	0.25	0.03 to 0.5	100.0		0.0
Linezolid	1	1	≤0.12 to 2	100.0		0.0
Ceftaroline	1	2	0.25 to 4	82.2	17.6	0.3
Clindamycin	≤0.25	>2	≤0.25 to >2	74.0	0.3	25.7
Erythromycin	>8	>8	≤0.12 to >8	32.0	1.5	66.5
Levofloxacin	>4	>4	≤0.12 to >4	14.2		85.8
Teicoplanin	≤2	≤2	≤2 to 4	99.5		0.5
Tetracycline	≤0.5	1	≤0.5 to >8	90.8	0.0	9.2
Tigecycline	0.06	0.12	≤0.015 to 0.25	100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	98.8	0.5	0.8
Vancomycin	0.5	1	≤0.12 to 2	100.0		0.0
CoNS[b] (46)						
Tedizolid	0.12	0.12	0.06 to 0.25	100.0		0.0
Linezolid	0.5	1	0.25 to 2	100.0		0.0
Ceftaroline	0.5	2	≤0.06 to 2			
Clindamycin	≤0.25	>2	≤0.25 to >2	78.3	4.3	17.4
Erythromycin	>8	>8	≤0.12 to >8	21.7	0.0	78.3
Levofloxacin	4	>4	≤0.12 to >4	28.3		71.7
Oxacillin	>2	>2	≤0.25 to >2	15.2		84.8
Teicoplanin	≤2	4	≤2 to >16	91.3		8.7
Tetracycline	≤0.5	>8	≤0.5 to >8	76.1	4.3	19.6
Tigecycline	0.06	0.25	≤0.015 to 0.5	100.0		0.0
Trimethoprim-sulfamethoxazole	2	>4	≤0.5 to >4	54.3	15.2	30.4
Vancomycin	1	2	0.5 to 2	100.0		0.0
S. pneumoniae (101)						
Tedizolid	0.12	0.25	0.03 to 0.5			
Linezolid	1	1	0.25 to 2	100.0	0.0	0.0
Amoxicillin-clavulanic acid	≤1	2	≤1 to >4			
Ceftaroline	≤0.015	0.12	≤0.015 to 0.5	99.0		1.0
Ceftriaxone	≤0.06	1	≤0.06 to >2	82.2	16.8	1.0
Clindamycin	≤0.25	>1	≤0.25 to >1	82.2		17.8
Erythromycin	≤0.12	>2	≤0.12 to >2	75.2	0.0	24.8
Levofloxacin	1	1	0.5 to >4	98.0		2.0
Penicillin[c]	≤0.06	2	≤0.06 to 4	70.3	24.8	5.0
Tetracycline	≤0.5	>4	≤0.5 to >4	78.2	1.0	20.8
Trimethoprim-sulfamethoxazole	≤0.5	4	≤0.5 to >4	79.2	5.9	14.9
Vancomycin	0.25	0.25	≤0.12 to 0.5	100.0		0.0
E faecalis (46)						
Tedizolid	0.12	0.25	0.12 to 0.25			
Linezolid	1	2	0.5 to 2	100.0		0.0
Ampicillin	1	2	≤0.5 to 4	100.0	0.0	0.0
Levofloxacin[d]	1	>4	0.5 to >4	68.4		31.6
Teicoplanin	≤2	≤2	≤2 to ≤2	100.0		0.0
Tigecycline	0.06		0.06 to 0.12	100.0	0.0	0.0
Vancomycin	1	2	≤0.5 to 2	100.0		0.0
E faecium (26)						
Tedizolid	0.12	0.25	0.06 to 0.25			
Linezolid	1	1	0.5 to 2	100.0		0.0
Ampicillin	>8	>8	>8 to >8	0.0	0.0	100.0
Levofloxacin[d]	>4	>4	>4 to >4	0.0		100.0
Teicoplanin	≤2	>16	≤2 to >16	88.5		11.5
Vancomycin	≤0.5	>16	≤0.5 to >16	84.6		15.4
BHS[e] (46)						
Tedizolid	0.12	0.25	0.06 to 0.5	100.0		0.0
Linezolid	1	2	0.5 to 2	100.0	0.0	0.0
Amoxicillin-clavulanic acid	≤1	≤1	≤1 to ≤1			
Ceftaroline	≤0.015	≤0.015	≤0.015 to 0.03			
Ceftriaxone	≤0.06	0.12	≤0.06 to 0.25			
Clindamycin	≤0.25	≤0.25	≤0.25 to >2	95.2		4.8
Erythromycin	≤0.12	2	≤0.12 to >16	84.8	0.0	15.2
Levofloxacin	0.5	1	0.25 to 2	100.0		0.0
Penicillin	≤0.06	≤0.06	≤0.06 to ≤0.06	100.0		0.0
Teicoplanin	0.12		0.12 to 0.25	100.0		0.0
Tetracycline	≤0.5	>4	≤0.5 to >4	54.8	0.0	45.2
Tigecycline	0.03		0.03 to 0.06	100.0	0.0	0.0
Vancomycin	0.25	0.5	0.25 to 0.5	100.0		0.0
VGS[f] (25)						
Tedizolid	0.12	0.25	0.03 to 0.25			
Linezolid	0.5	1	0.25 to 1			
Amoxicillin-clavulanic acid	≤1	4	≤1 to >4			
Ceftaroline	0.03	0.12	≤0.015 to 0.5			
Ceftriaxone	0.25	2	≤0.06 to >2	80.0		20.0
Clindamycin	≤0.25	>2	≤0.25 to >2	84.0		16.0
Erythromycin	≤0.12	>4	≤0.12 to >4			
Levofloxacin	1	4	0.25 to >4			
Penicillin	≤0.06	2	≤0.06 to >8	72.0	20.0	8.0
Tetracycline	≤0.5	>4	≤0.5 to >4			
Vancomycin	0.5	0.5	0.25 to 1	100.0		0.0

MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative streptococci; BHS, β-haemolytic streptococci; VGS, viridans group streptococci
[a] Criteria as published by EUCAST (2018).
[b] Includes: *Staphylococcus epidermidis* (26), *S. haemolyticus* (16), *S. lugdunensis* (1), *S. warneri* (3).
[c] Using parenteral (non-meningitis) breakpoints.
[d] Uncomplicated UTI only.
[e] Includes: *Streptococcus agalactiae* (26), *S. dysgalactiae* (1), *S. pyogenes* (19).
[f] Includes: *Streptococcus anginosus* (6), *S. constellatus* (1), *S. cristatus* (1), *S. mitis* (1), *S. mitis group* (7), *S. mitis/oralis* (5), *S. oralis* (2), *S. parasanguinis* (1), *S. vestibularis* (1).

- Tedizolid ($MIC_{50/90}$, 0.12/0.25 mg/L) was active against *E. faecalis*, and all isolates remained susceptible to ampicillin, vancomycin, and the oxazolidinones (Table 2)
- A total of 15.4% of *E. faecium* isolates were vancomycin-resistant and only tedizolid ($MIC_{50/90}$, 0.12/0.25 mg/L) and linezolid ($MIC_{50/90}$, 1/1 mg/L) were active *in vitro* (Table 2)
- Ceftaroline (MIC_{50}, ≤0.015 mg/L), penicillin (MIC_{50}, ≤0.06 mg/L), ceftriaxone (MIC_{50}, 0.12 mg/L), and tedizolid (MIC_{50}, 0.25 mg/L) were the most potent agents against β-haemolytic streptococci (Table 2)
- Tedizolid (MIC_{90}, 0.25 mg/L), ceftaroline (MIC_{90}, 0.12 mg/L), and vancomycin (MIC_{90}, 0.5 mg/L) had the lowest MIC_{90} values against viridans group streptococci (28.0% and 20.0% penicillin- and ceftriaxone-nonsusceptible, respectively)

CONCLUSIONS

- *S. aureus* remains the main gram-positive pathogen responsible for pneumonia in hospitalised patients, while occurrences of other organisms were less prevalent
- In general, tedizolid showed potent and greater activity than comparator agents against isolates causing pneumonia in hospitalised patients in Europe and surrounding regions
- These data support the clinical development of tedizolid for treating pneumonia patients infected with gram-positive organisms

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