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In Vitro Activity of Tedizolid and Key Comparators Against *Staphylococcus aureus* Isolated from Latin America: 2014-2015

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Revised Abstract

Background: *Staphylococcus aureus* (SA) is the predominant cause of acute bacterial skin and skin structure infections (ABSSSI) and frequently of nosocomial pneumonia. The prevalence of methicillin-resistant SA (MRSA) ranges between 20 and 70% worldwide. Development of any new agent for the treatment of infections caused by MRSA must be accompanied by on-going monitoring of that drug's *in vitro* activity. Tedizolid (TZD) is a novel oxazolidinone with potent activity against Gram-positive pathogens, including MRSA. This study investigated the *in vitro* activity of TZD versus linezolid (LZD), vancomycin (VAN), and teicoplanin (TEC) against SA from five Latin American countries. **Material/methods:** SA isolates (527 MRSA and 694 MSSA) were collected throughout 2014-2015 from sites in five countries. All isolates were tested centrally by broth microdilution and interpretive criteria according to CLSI guidelines. **Results:** The Table shows MIC_{90} MIC values (mg/L) (%S)[a] for TZD and three gram-positive comparators.

Country	Organism (n)	Tedizolid	Linezolid	Vancomycin	Teicoplanin
Argentina	MSSA (62)	0.5 (100)	2 (100)	1 (100)	1 (100)
	MRSA (86)	0.5 (100)	2 (100)	1 (100)	1 (100)
Brazil	MSSA (294)	0.5 (100)	4 (100)	1 (100)	1 (100)
	MRSA (182)	0.5 (100)	4 (100)	1 (100)	1 (100)
Chile	MSSA (65)	0.5 (100)	2 (100)	1 (100)	1 (100)
	MRSA (87)	0.5 (100)	2 (100)	1 (100)	2 (100)
Colombia	MSSA (29)	0.5 (100)	2 (100)	1 (100)	1 (100)
	MRSA (46)	0.5 (100)	2 (100)	1 (100)	1 (100)
Mexico	MSSA (244)	0.5 (100)	2 (100)	1 (100)	1 (100)
	MRSA (126)	0.5 (100)	4 (100)	1 (100)	2 (99.2)

a. FDA breakpoints were applied for TZD and EUCAST breakpoint were applied for LZD, VAN, and TEC.

In all LA countries, TZD has shown the highest potency against the overall collection of SA. Based on MIC_{90} values in the overall collection of SA isolates, TZD was 8-fold more potent than LZD and 2-fold more potent than VAN, TEC, and daptomycin. **Conclusions:** TZD exhibited the most potent *in vitro* activity among the agents analyzed against both MRSA and MSSA in all Latin American countries. The findings support the global clinical development of TZD for severe infections caused by MRSA such as ABSSSIs and nosocomial pneumonia.

Introduction

Staphylococcus aureus is the predominant cause of acute bacterial skin and skin structure infections (ABSSSI) and frequently of nosocomial pneumonia. The prevalence of methicillin-resistant *S. aureus* (MRSA) ranges between 20 and 70% worldwide. Development of any new agent for the treatment of infections caused by MRSA must be accompanied by on-going monitoring of that drug's *in vitro* activity. Tedizolid is a novel oxazolidinone with potent activity against Gram-positive pathogens, including MRSA. This study investigated the *in vitro* activity of tedizolid versus linezolid, vancomycin, and teicoplanin against *S. aureus* from five Latin American countries.

Materials & Methods

- *S. aureus* isolates were collected from patient infections in Argentina (148 isolates), Brazil (476), Chile (152), Colombia (75), and Mexico (370).
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method and interpretive criteria [1,2]. MIC values were read at 100% inhibition, ignoring the occasional pinpoint trailing end point that *S. aureus* can generate when tested against oxazolidinones.
- Quality control (QC) was performed on each day of testing using appropriate ATCC strains, following CLSI and manufacturer guidelines. Results were included in the analysis only when corresponding QC results were within the acceptable ranges [2].

Results

Table 1. Overall Susceptibility Profiles of *S. aureus* from Latin American Countries.

		CLSI interpretation[a]			MIC (mg/mL)		
Organism (n)	**Drug**	**% Susceptible**	**% Intermediate**	**% Resistant**	**MIC_{50}**	**MIC_{90}**	**MIC range**
S. aureus (1,221)	**Tedizolid**	100	0.0	0.0	0.25	0.5	0.12-0.5
	Linezolid	100	0.0	0.0	2	4	0.5-4
	Clindamycin	72.6	0.7	26.7	0.12	> 2	≤0.03->2
	Daptomycin	99.9	0.0	0.1	0.5	1	0.25-1
	Erythromycin	54.1	2.1	43.8	0.5	> 4	≤0.12->4
	Oxacillin	56.8	0.0	43.2	0.5	> 4	0.12->4
	Teicoplanin	100	0.0	0.0	0.5	1	≤0.12-4
	SXT	98.4	0.0	1.6	≤0.5	≤0.5	≤0.5->2
	Vancomycin	100	0.0	0.0	1	1	≤0.25-2
S. aureus, MRSA (527)	**Tedizolid**	100	0.0	0.0	0.25	0.5	0.12-0.5
	Linezolid	100	0.0	0.0	2	4	0.5-4
	Clindamycin	42.1	0.8	57.1	> 2	> 2	≤0.03->2
	Daptomycin	99.8	0.0	0.2	0.5	1	0.25-2
	Erythromycin	32.1	1.7	66.2	> 4	> 4	≤0.12->4
	Teicoplanin	100	0.0	0.0	1	1	≤0.12-4
	SXT	97.7	0.0	2.3	≤0.5	≤0.5	≤0.5->2
	Vancomycin	100	0.0	0.0	1	1	≤0.25-2
S. aureus, MSSA (694)	**Tedizolid**	100	0.0	0.0	0.5	0.5	0.12-0.5
	Linezolid	100	0.0	0.0	2	4	1-4
	Clindamycin	95.8	0.6	3.6	0.12	0.12	0.06->2
	Daptomycin	100	0.0	0.0	0.5	0.5	0.25-1
	Erythromycin	70.8	2.2	27.0	0.5	> 4	0.25->4
	Teicoplanin	100	0.0	0.0	0.5	1	≤0.12-2
	SXT	99.0	0.0	1.0	≤0.5	≤0.5	≤0.5->2
	Vancomycin	100	0.0	0.0	1	1	0.5-2

a. Susceptibility % was based upon CLSI breakpoint criteria.

Figure 1. Distribution of Tedizolid and Linezolid MIC Values Against 148 *S. aureus* Isolates from Argentina.

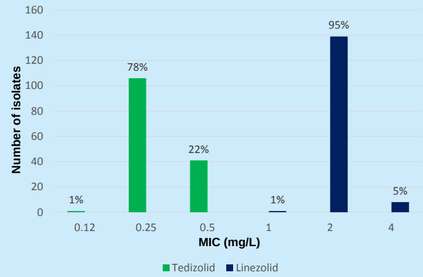


Figure 2. Distribution of Tedizolid and Linezolid MIC Values Against 476 *S. aureus* Isolates from Brazil.

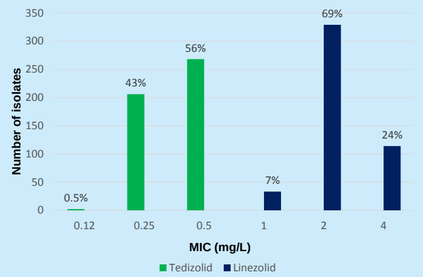


Figure 3. Distribution of Tedizolid and Linezolid MIC Values Against 152 *S. aureus* Isolates from Chile.

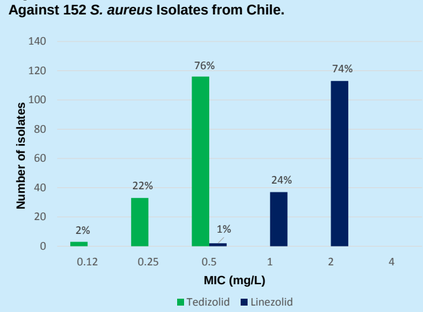


Figure 4. Distribution of Tedizolid and Linezolid MIC Values Against 75 *S. aureus* Isolates from Colombia.

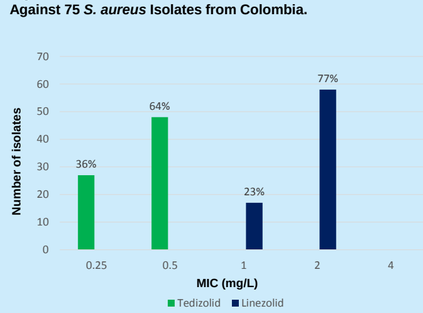
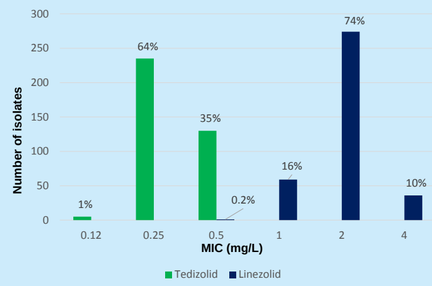


Figure 5. Distribution of Tedizolid and Linezolid MIC Values Against 370 *S. aureus* Isolates from Mexico.



Conclusions

- Tedizolid exhibited the most potent *in vitro* activity among the agents analyzed against all *S. aureus* in all Latin American countries.
- Tedizolid was more potent than linezolid, vancomycin, and teicoplanin.
- The findings support the global clinical development of tedizolid for severe infections caused by MRSA such as ABSSSIs and nosocomial pneumonia.

References and Acknowledgments:

1. Clinical Laboratory Standards Institute. 2015. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards -- Tenth Edition. CLSI document M07-A10 Wayne, PA.
2. Clinical and Laboratory Standards Institute. 2016. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Sixth Informational Supplement. CLSI Document M100-S, 26E. Wayne, PA.

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