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Tigecycline In Vitro Antibacterial Activity Against 249 Methicillin Resistant and 250 Methicillin Sensitive *Staphylococcus aureus* Isolates

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REVISED ABSTRACT

Background: Resistance of gram positive bacteria continue to be a therapeutic challenge for the clinician. Glycylcyclines are showing the promise of significant activity against many gram-positive pathogens. Tigecycline (GAR-936), a member of this new class of antimicrobials, has shown excellent activity against *Staphylococcus* spp. The activity of tigecycline was compared with those of other agents against methicillin resistant *Staphylococcus aureus* (MRSA) and methicillin sensitive *Staphylococcus aureus* (MSSA) from hospitals in Europe, Middle East and South Africa. **Methods**: A total of 499 clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Isolates were collected between January 2001 - September 2002. MIC's were determined by the central laboratory using broth microdilution panels from Dade Microscan according to NCCLS guidelines and manufacturer's instructions. **Results**: The susceptibility results of the 499 isolates of *Staphylococcus aureus* are listed in Table 1.

Table 1. In Vitro Activity (mcg/mL) of Tigecycline and Comparators Against MSSA and MRSA

	MSSA (n=250)			MRSA (n=249)		
	MIC (µg/ml)			MIC (µg/ml)		
Antibiotic	**Range**	**MIC_{50}**	**MIC_{90}**	**Range**	**MIC_{50}**	**MIC_{90}**
Tigecycline (GAR-936)	0.12-1	0.25	0.25	0.12-2	0.25	0.5
Amoxicillin/clav	0.25-64	1	1	0.25-64	32	64
Ampicillin/sulb	0.5->32	1	4	0.5->32	32	32
Imipenem	0.5->64	0.5	0.5	0.5->64	32	64
Cefepime	0.5->64	8	8	0.5->64	>64	>64
Ceftazidime	2->64	8	8	0.5->64	>64	>64
Ceftriaxone	0.5->64	4	4	0.5->64	>64	>64
Levofloxacin	0.25-16	0.25	0.25	0.25-32	8	16
Vancomycin	0.5->64	1	1	0.25->64	1	1
Quinupristin/dalfopristin	0.12->32	0.25	0.25	0.12->32	0.5	1
Linezolid	1->32	2	4	0.5->32	2	4

Conclusion: The in vitro activity of tigecycline was very good against both MSSA and MRSA and was more active than both vancomycin and quinupristin/dalfopristin. Tigecycline, a member of a new class of antimicrobials (glycylcyclines) activity was superior to linezolid, imipenem and the beta-lactam antimicrobials for both MSSA and MRSA.

BACKGROUND

Tigecycline is a novel antimicrobial with an expanded broad-spectrum of activity from a new class of compounds, glycylcyclines. Glycylcyclines were developed to avoid the two most prevalent tetracycline resistance mechanisms, ribosomal protection and efflux. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it's antibacterial activity is significant, it is considered to be bacteriostatic [1, 2]. While developed to provide activity against tetracycline- and multi-drug-resistant gram-positive pathogens, it has been demonstrated to possess significant broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative microorganisms [1,3-5]. Tigecycline MIC_{90} values of ≤0.5 mcg/ml have been demonstrated against methicillin-resistant *Staphylococcus aureus* (MRSA) [2, 4-6].

Tigecycline resistance is very infrequent and difficult to induce in the laboratory [7, 8] with a selection frequency observed at less than 10^{-9} [2, 3, 7]. Most tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [1-4, 6, 9-11]. The pharmacokinetics of parenteral tigecycline is linear with an unusually long half-life of 36 hours and a maximum serum concentration (C_{MAX}) of a 300 mg dose infused over 1 hour of 2.8 mcg/ml [12,13].

This study compared the activity of tigecycline with other agents against methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) from hospitals in Europe, Middle East and South Africa.

METHODS

- All isolates were derived from blood, respiratory tract, urine (no more than 30% of all isolates), skin, wound, fluids and other defined sources. Only one isolate per patient was accepted.
- Clinical isolates were collected between January 2001 - September 2002 from 34 study centers in 16 countries.
- Antimicrobial agents tested with concentrations (expressed in mcg/ml) were: Amoxicillin-clavulanic acid (0.25 - 64); Ampicillin-sulbactam (0.5 - 32); cefepime (0.5 - 64); ceftazidime (0.5 - 64); ceftriaxone (0.5 - 64); imipenem (0.5 - 64); levofloxacin (0.25 - 64); linezolid (0.12 - 32); doxycycline (0.06 - 32); quinupristin/dalfopristin (0.12 - 32); tigecycline (0.008 - 16) and vancomycin (0.12 - 64). MIC interpretive criteria followed published guidelines established by the NCCLS [15]. Tigecycline tentative breakpoints (in units of mcg/mL) are defined as susceptible ≤ 2; intermediate = 4; and resistant ≥ 8.
- Isolates were identified to genus and species at each site and confirmed by the central laboratory (Laboratories International for Microbiology Studies, Schaumburg, IL, USA).
- Organism collection, transport, confirmation of organism identification, antimicrobial susceptibility testing, as well as, construction and management of a centralized database was coordinated by Laboratories International for Microbiology Studies (LIMS).

Antimicrobial Susceptibility Testing

- MIC's were determined by the central laboratory using broth microdilution panels by Dade Microscan (Dade Behring Inc., Sacramento, CA. USA) according to NCCLS guidelines and manufacturer's instructions [15].
- Quality Control was performed using the following ATCC strains: *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213.

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RESULTS

Results are presented in the following tables and graphs.

Table 2. In Vitro Activity of Tigecycline and Comparator Agents Against 249 Isolates of Methicillin-resistant *Staphylococcus aureus*.

						MIC (mcg/ml)
Organism/ Phenotype	**Drug**	**NCCLS BP***	**% Sus**	**% Int**	**% Res**	**MIC_{90}**
S. aureus, MSSA (n=250)	Tigecycline	2*	100.0	--	--	0.25
	Amox/Clav	4/2	95.6	--	4.4	1
	Amp/Sulb	8/4	95.6	0.8	3.6	4
	Cefepime	8	95.2	0.8	4.0	4
	Ceftazidime	8	93.6	1.2	5.2	8
	Ceftriaxone	8	94.4	1.6	4.0	4
	Imipenem	4	96.4	--	3.6	0.5
	Levofloxacin	2	94.0	2.0	4.0	0.25
	Linezolid	4	99.2	--	0.8	4
	Quinu/Dalfo	1	99.2	0.4	0.4	0.25
	Vancomycin	4	99.6	--	0.4	1
S. aureus, MRSA (n=249)	Tigecycline	2*	100.0	--	--	0.5
	Amox/Clav	4/2	17.3	--	83	64
	Amp/Sulb	8/4	24.9	24	51	32
	Cefepime	8	10.4	7.2	82.3	>64
	Ceftaz	8	3.2	6.4	90.4	>64
	Ceftriax	8	6.0	13.3	80.7	>64
	Imipenem	4	24.9	2	73.1	64
	Levo	2	13.7	20.5	65.9	16
	Linezolid	4	99.2	--	0.8	4
	Quinu/Dalfo	1	99.2	0.4	0.4	1
	Vanco	4	99.6	--	0.4	1

* Breakpoints defined by the NCCLS 2003, document M100-S13; Tigecycline tentative breakpoints (in mcg/mL) defined as susceptible ≤ 2; intermediate = 4; resistant ≥ 8

MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*.

Table 3. Frequency Distribution (n) and Cumulative Percent Inhibition (%) at each MIC (mcg/mL) for Tigecycline and Comparative Agents Against 250 Methicillin-sensitive *Staphylococcus aureus*.

	MIC (mcg/mL) – n / Cumulative – (MIC_{90})										
Drug	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**>64**
Tigecycline	2	225	22	1							
	0.8	**90.8**	99.6	100							
Amox/Clav		50	44	133	11	1	1		5	5	
		20	37.6	**90.8**	95.2	95.6	96	96	98	100	
Amp/Sulb			57	74	92	14	2	2	9		
			22.8	52.4	89.2	**94.8**	95.6	96.4	99.6	100	
Cefepime			2		152	80	4	2			10
			0.8	0.8	61.6	**93.6**	95.2	96	96	96	100
Ceftaz					2	111	121	3	3		10
					0.8	45.2	**93.6**	94.8	96	96	100
Ceftriax			2		69	161	4	4			10
			0.8	0.8	28.4	**92.8**	94.4	96	96	96	100
Imipenem			238	1	1	1			1	6	2
			95.2	95.6	96	96.4	96.4	96.4	96.8	99.2	100
Levo		230	4	1		5	8	2			
		92	93.6	94	94	96	99.2	100			
Linezolid				2	175	71	1		1		
				0.8	70.8	**99.2**	99.6	99.6	99.6	100	
Quin/Dalfo	9	223	16		1				1		
	3.6	**92.8**	99.2	99.2	99.6	99.6	99.6	99.6	99.6	100	
Vanco			76	158	15						1
			30.4	**93.6**	99.6	99.6	99.6	99.6	99.6	99.6	100

Figure 1. In Vitro Activity of Tigecycline and Comparators Against 250 MSSA Showing Cumulative Percent Inhibited (%) at Each MIC (mcg/ml).

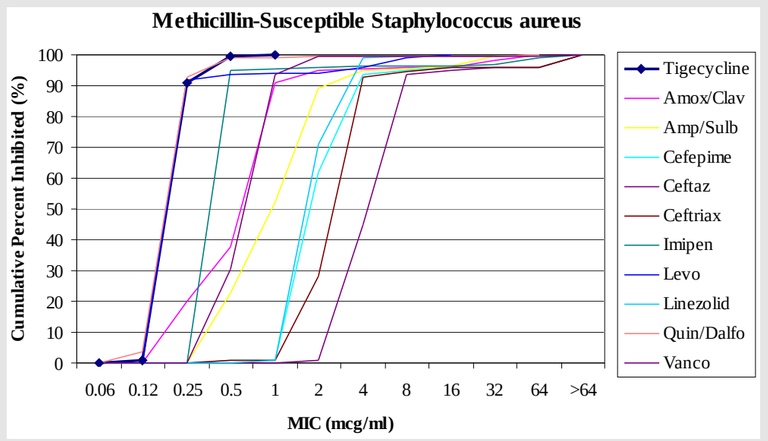
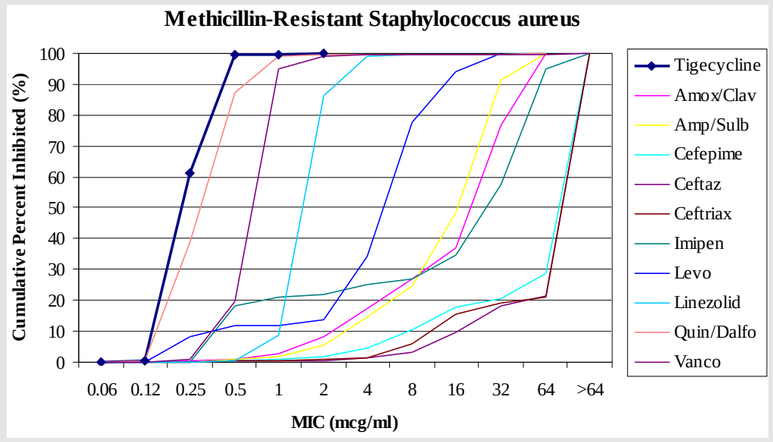


Table 4. Frequency Distribution (n) and Cumulative Percent Inhibition (%) at each MIC (mcg/mL) for Tigecycline and Comparative Agents Against 249 Methicillin-resistant *Staphylococcus aureus*.

	MIC (mcg/mL) – n / Cumulative % – (MIC_{90})										
Drug	**0.1**	**0.3**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**>64**
Tigecycline	1	152	95		1						
	0.4	61.4	**99.6**	99.6	100						
Amox/Clav		1	1	5	13	23	24	26	98	58	
		0.4	0.8	2.8	8	17.2	26.8	37.2	76.6	**100**	
Amp/Sulb			2	2	10	23	25	59	128		
			0.8	1.6	5.6	14.8	24.8	48.5	**91.5**	100	
Cefepime			1	1	3	6	15	18	7	21	177
			0.4	0.8	2	4.4	10.4	17.6	20.4	28.8	**100**
Ceftaz			1			2	5	16	22	8	195
			0.4	0.4	0.4	1.2	3.2	9.6	18.4	21.6	**100**
Ceftriax			1		1	1	12	24	9	5	196
			0.4	0.4	0.8	1.2	6	15.6	19.2	21.2	**100**
Imipen			45	7	3	7	5	20	56	94	12
			18.1	20.9	22.1	24.9	26.9	34.9	57.4	**95.2**	100
Levo		21	9		4	51	108	41	15		
		8.4	12	12	13.6	34.1	77.5	**94**	100		
Linezolid			1	21	193	32	1		1		
			0.4	8.8	86.3	**99**	99.6	99.6	99.6	100	
Quin/Dalfo	1	95	121	30	1				1		
	0.4	38.6	87.2	**99.2**	99.6	99.6	99.6	99.6	99.6	100	
Vanco		2	47	187	11	1					1
		0.8	19.7	**94.8**	99.2	99.6	99.6	99.6	99.6	99.6	100

Figure 2. In Vitro Activity of Tigecycline and Comparators Against 249 MRSA Showing Cumulative Percent Inhibited (%) at Each MIC (mcg/ml).



CONCLUSIONS

- Tigecycline inhibited the growth of all MSSA and MRSA at a MIC ≤ 2 mcg/ml.
- Tigecycline demonstrates in vitro activity comparable to or better than both vancomycin and quinupristin/dalfopristin against all MSSA and MRSA.
- Tigecycline demonstrates greater in vitro activity against MSSA and MRSA than linezolid, levofloxacin, imipenem and the beta-lactam antimicrobials.
- Tigecycline appears to be promising agent in the treatment of methicillin sensitive and methicillin resistant *Staphylococcus aureus*.