Rates of Antimicrobial Resistance in Latin America (2004-2007) and *in vitro* Activity of the Glycylcycline Tigecycline and of Other Antibiotics

Flávia Rossi[1], Patricia García[2], Bernardo Ronzon[3], Daniel Curcio[4], Michael J Dowzicky[5]

[1]Hospital das Clínicas da Faculdade de Medicina, University of São Paulo, LIM03, Rua Lee de Forest 32, São Paulo, São Paulo, Brazil; [2]Laboratorio de Microbiología, Departamento de Laboratorios Clínicos, Escuela de Medicina. Pontificia Universidad Católica de Chile; [3]Hospital Angeles del Pedregal, Camino a Santa Tersa 10 55, col. Heroes de Padierna, Mexico, D.F., Mexico; [4]Sanatorio San José, Infectología Institucional SRL; Buenos Aires, Argentina; [5]Wyeth Pharmaceuticals; Collegeville PA, USA

As a part of the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.), Gram-positive and Gram-negative bacterial isolates were collected from 33 centers in Latin America (centers in Argentina, Brazil, Chile, Colombia, Guatemala, Honduras, Jamaica, Mexico, Panama, Puerto Rico, and Venezuela) from January 2004 to September 2007. Argentina and Mexico were the greatest contributors of isolates to this study. Susceptibilities were determined according to Clinical Laboratory Standards Institute guidelines. Resistance levels were high for most key organisms across Latin America: 48.3% of *Staphylococcus aureus* isolates were methicillin-resistant while 21.4% of *Acinetobacter* spp. isolates were imipenem-resistant. Extended-spectrum β-lactamase were reported in 36.7% of *Klebsiella pneumoniae* and 20.8% of *E. coli* isolates. Tigecycline was the most active agent against Gram-positive isolates. Tigecycline was also highly active against all Gram-negative organisms, with the exception of *Pseudomonas aeruginosa*, against which piperacillin-tazobactam was the most active agent tested (79.3% of isolates susceptible). The *in vitro* activity of tigecycline against both Gram-positive and Gram-negative isolates indicates that it may be an useful tool for the treatment of nosocomial infections, even those caused by organisms that are resistant to other antibacterial agents.

Key-Words: Antibacterial resistance, Latin America, tigecycline, surveillance.

Increased resistance to antibacterial agents among clinically-important organisms has been widely reported in recent years [1]. In many cases, these organisms are resistant to multiple antibacterial agents [2], dramatically limiting available treatment options. High levels of antibacterial resistance among many key organisms have been reported in Latin America, particularly non-fermentative Gram-negative bacilli (including *Acinetobacter* spp. and *Pseudomonas aeruginosa*) and extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, but also among some Gram-positive organisms (including *Staphylococcus aureus*) [3]. Treatment of infections caused by these organisms is often complicated because of resistance to first-line antibacterial agents [4]. Surveillance studies are thus an essential component in the selection of appropriate empirical therapy, allowing for the monitoring of antibacterial resistance [5].

Tigecycline is the first commercially available member of a novel group of antibacterial agents, the glycylcyclines. The Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) is a global surveillance study designed to compare the *in vitro* activity of tigecycline with a panel of antibacterial agents used in daily clinical practice against a range of clinically important organisms. We report on four-year T.E.S.T. data (2004-2007) for Gram-positive and Gram-negative organisms collected from Latin America.

Received on 6 April 2008; revised 25 September 2008.

Address for correspondence: Dr. Flávia Rossi.Hospital das Clínicas da Faculdade de Medicina. University of São Paulo, LIM03. Rua Lee de Forest 32. São Paulo, São Paulo, Brazil. Phone. 55-11-5505-2480; Fax. 55-11-3758-0457. E-mail: ffrossi@attglobal.net.

The Brazilian Journal of Infectious Diseases 2008;12(5):405-415.

Material and Methods

Isolate Collection

For the T.E.S.T. study, Latin America is defined as including the following countries: Argentina, Brazil, Chile, Colombia, Guatemala, Honduras, Jamaica, Mexico, Panama, Puerto Rico and Venezuela (Table 1). Thirty-three Latin American centers participated in the T.E.S.T. study from January 2004 to September 2007 (Table 1). Data for 2007 are as yet incomplete.

Isolates that were determined by local criteria to be clinically significant were collected from in- and out-patients with documented nosocomial or community-acquired infections. Acceptable isolate sources included blood, the respiratory tract, urine (not exceeding 25% of isolates), skin, wounds and fluids. Only one isolate per patient was accepted in the study. Each center was required to contribute the following: 25 isolates each of *Staphylococcus aureus*, *Klebsiella* spp., *Escherichia coli* and *Enterobacter* spp.; 20 isolates of *Pseudomonas aeruginosa*; 15 isolates each of *Enterococcus* spp. and *Acinetobacter* spp.; and 10 isolates of *Serratia marcescens*. A maximum of 200 isolates was contributed by each center, after local determination of identity and antibacterial susceptibility.

Antimicrobial Susceptibility Testing

Minimum inhibitory concentrations (MICs) were determined locally using broth microdilution methodology, as defined by the Clinical Laboratory Standards Institute (CLSI, formerly NCCLS) [6], using either MicroScan® panels (Dade Behring Inc., CA, USA) or Sensititre® plates (TREK Diagnostic Systems, West Sussex, England). The test panel for Gram-negative isolates included (concentrations given in μg/mL): amikacin (0.5-64); amoxicillin-clavulanic acid (0.12/0.06-32/16);

Table 1. Number of centers participating in T.E.S.T. in Latin America from 2004-2007.

Year	Argentina	Brazil	Chile	Colombia	Guatemala	Honduras	Jamaica	Mexico	Panama	Puerto Rico	Venezuela	Latin America
2004	7	1	2	0	1	0	0	0	0	0	1	12
2005	9	1	3	1	0	0	0	2	0	0	0	16
2006	8	2	3	3	1	1	1	8	1	1	1	30
2007	1	1	1	0	1	0	0	8	0	0	0	12
Total*	25 (11)	5 (2)	9 (3)	4 (3)	3 (1)	1 (1)	1 (1)	18 (8)	1 (1)	1 (1)	2 (1)	70 (33)

*Some centers participated in multiple study years; numbers in parentheses indicate the number of unique centers participating in each country. Data for 2007 are incomplete.

ampicillin (0.5-32); cefepime (0.5-32); ceftriaxone (0.06-64); ceftazidime (8-32); imipenem (0.06-16, MicroScan® only); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); and piperacillin-tazobactam (0.06/4-128/4). Gram-positive organisms were tested against the following agents (in μg/mL): amoxicillin-clavulanic acid (0.03/0.0015-8/4), ampicillin (0.06-16), penicillin (0.06-8), linezolid (0.5-8), ceftriaxone (0.03-64), imipenem (0.12-16, MicroScan® only), levofloxacin (0.06-32), minocycline (0.25-8), tigecycline (0.008-16), piperacillin-tazobactam (0.25/4-16/4), and vancomycin (0.12-32). For tigecycline, interpretive criteria from the US Food and Drug Administration packaging insert were applied for *S. aureus* (susceptible ≤0.5 μg/mL), vancomycin-susceptible *E. faecalis* (susceptible ≤0.25 μg/mL) and the *Enterobacteriaceae* (susceptible ≤2 μg/mL, intermediate 4 μg/mL, resistant ≥8 μg/mL) [7]. For all other agents, CLSI interpretive criteria were applied [8].

MIC determinations were carried out using cation-adjusted Mueller-Hinton broth. Broth microdilution panels inoculated with Gram-negative organisms were incubated in ambient air at 35°C for 16-20 hours. *Staphylococcus aureus* and *Enterococcus* spp. were incubated in ambient air at 35°C for 20-24 hours. Quality control testing was carried out on each day of susceptibility testing, using the following ATCC strains: *E. coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, and *E. faecalis* ATCC 29212, when appropriate.

All isolates were sent to a single laboratory, International Health Management Associates, Inc. (IHMA, Schaumburg, IL, US), where confirmation of identification was carried out as well as inclusion of all data into a centralized database. MIC information was also returned to the central laboratory for inclusion in this centralized database using an OptiScan Data Collection Form, part of a proprietary optical character recognition system. MICs of approximately 10% of isolates from all centers were checked by IHMA as a part of standard quality control testing.

Antibacterial Resistance Determination

Confirmation of methicillin resistance was carried out by IHMA using the cefoxitin disk diffusion method, using 30 μg disks obtained from Remel, Lenexa, KS, USA.

The presence of ESBLs among *K. pneumoniae* and *E. coli* was detected according to CLSI methodology [8], for which cefotaxime (30 μg), cefotaxime-clavulanic acid (30/10 μg), ceftazidime (30 μg) and ceftazidime-clavulanic acid (30/10 μg) discs were used. An increase of ≥5 mm in inhibition zone on the combination disc compared to the cephalosporin only disc suggested an ESBL producing organism.

Results

The incidence of organisms, both resistant and susceptible, varied widely between species and between countries during the four-year study period. Most isolates came from Argentina or Mexico during this study interval (Tables 2 and 3).

Table 2. Distribution [% (number)] of *Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, Klebsiella pneumoniae, Escherichia coli,* and *Acinetobacter* spp. in Latin America between 2004-2007.

Pathogen	Year	Argentina	Brazil	Chile	Colombia	Guatemala	Honduras	Jamaica	Mexico	Panama	Puerto Rico	Venezuela	Latin America
S. aureus	2004	98.5 (64)	-	-	-	1.5 (1)	-	-	-	-	-	-	65
	2005	59.2 (157)	18.5 (49)	14.3 (38)	2.3 (6)	-	-	-	5.7 (15)	-	-	-	265
	2006	11.0 (55)	5.0 (25)	8.0 (40)	14.5 (72)	7.4 (37)	1.8 (9)	5.0 (25)	33.5 (167)	5.0 (25)	4.4 (22)	4.2 (21)	498
	2007	31.2 (24)	-	-	-	3.9 (3)	-	-	64.9 (50)	-	-	-	77
	Overall	33.1 (300)	8.2 (74)	8.6 (78)	8.6 (78)	4.5 (41)	1.0 (9)	2.8 (25)	25.6 (232)	2.8 (25)	2.4 (22)	2.3 (21)	905
E. faecalis	2004	100 (25)	-	-	-	-	-	-	-	-	-	-	25
	2005	53.8 (56)	26.0 (27)	15.4 (16)	3.8 (4)	-	-	-	1.0 (1)	-	-	-	104
	2006	18.8 (42)	3.6 (8)	9.8 (22)	12.5 (28)	4.5 (10)	2.2 (5)	5.8 (13)	31.3 (70)	5.8 (13)	2.2 (5)	3.6 (8)	224
	2007	15.0 (6)	-	-	-	2.5 (1)	-	-	82.5 (33)	-	-	-	40
	Overall	32.8 (129)	8.9 (35)	9.7 (38)	8.1 (32)	2.8 (11)	1.3 (5)	3.3 (13)	26.5 (104)	3.3 (13)	1.3 (5)	2.0 (8)	393
E. faecium	2004	100 (13)	-	-	-	-	-	-	-	-	-	-	13
	2005	50.0 (6)	25.0 (3)	25.0 (3)	-	-	-	-	-	-	-	-	12
	2006	14.1 (9)	6.3 (4)	1.6 (1)	15.6 (10)	3.1 (2)	1.6 (1)	-	48.4 (31)	1.6 (1)	1.6 (1)	6.3 (4)	64
	2007	52.9 (9)	-	-	-	5.9 (1)	-	-	41.2 (7)	-	-	-	17
	Overall	34.9 (37)	6.6 (7)	3.8 (4)	9.4 (10)	2.8 (3)	0.9 (1)	-	35.8 (38)	0.9 (1)	0.9 (1)	3.8 (4)	106
K. pneumoniae	2004	84.8 (56)	15.2 (10)	-	-	-	-	-	-	-	-	-	66
	2005	50.8 (101)	15.6 (31)	17.1 (34)	10.1 (20)	-	-	-	6.5 (13)	-	-	-	199

Pathogen	Year	Argentina	Brazil	Chile	Colombia	Guatemala	Honduras	Jamaica	Mexico	Panama	Puerto Rico	Venezuela	Latin America
	2006	19.8 (83)	5.2 (22)	7.9 (33)	8.6 (36)	7.4 (31)	2.9 (12)	5.5 (23)	27.1 (114)	6.0 (25)	5.2 (22)	4.5 (19)	420
	2007	26.9 (21)	2.6 (2)	-	-	-	-	-	70.5 (55)	-	-	-	78
	Overall	34.2 (261)	8.5 (65)	8.8 (67)	7.3 (56)	4.1 (31)	1.6 (12)	3.0 (23)	23.9 (182)	3.3 (25)	2.9 (22)	2.5 (19)	763
E. coli	2004	78.1 (57)	19.2 (14)	-	-	1.4 (1)	-	-	-	-	-	1.4 (1)	73
	2005	58.5 (124)	14.6 (31)	9.9 (21)	8.0 (17)	-	-	-	9.0 (19)	-	-	-	212
	2006	16.1 (90)	3.9 (22)	9.8 (55)	12.9 (72)	4.8 (27)	5.9 (33)	4.5 (25)	29.3 (164)	4.3 (24)	4.5 (25)	4.1 (23)	560
	2007	28.7 (25)	8.0 (7)	-	-	-	-	-	63.2 (55)	-	-	-	87
	Overall	31.8 (296)	7.9 (74)	8.2 (76)	9.5 (89)	3.0 (28)	3.5 (33)	2.7 (25)	25.5 (238)	2.6 (24)	2.7 (25)	2.6 (24)	932
Acinetobacter spp.	2004	81.5 (44)	16.7 (9)	-	-	1.9 (1)	-	-	-	-	-	-	54
	2005	57.6 (80)	7.9 (11)	19.4 (27)	7.9 (11)	-	-	-	7.2 (10)	-	-	-	139
	2006	15.4 (39)	9.9 (25)	7.5 (19)	11.1 (28)	6.3 (16)	5.9 (15)	5.9 (15)	24.1 (61)	5.9 (15)	3.6 (9)	4.3 (11)	253
	2007	37.5 (15)	-	-	-	2.5 (1)	-	-	60.0 (24)	-	-	-	40
	Overall	36.6 (178)	9.3 (45)	9.5 (46)	7.8 (38)	3.7 (18)	3.1 (15)	3.1 (15)	19.5 (95)	3.1 (15)	1.9 (9)	2.3 (11)	486

Total percentages are not always 100% per year due to rounding.

Table 3. Distribution [% (total number)] of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant (VR) *Enterococcus faecalis*, VR *Enterococcus faecium*, extended-spectrum β-lactamase positive (ESBL+) *Klebsiella pneumoniae*, ESBL+ *Escherichia coli* and imipenem-resistant *Acinetobacter* spp. in Latin America from 2004-2007.

Pathogen	Argentina	Brazil	Chile	Colombia	Guatemala	Honduras	Jamaica	Mexico	Panama	Puerto Rico	Venezuela	Latin America
MRSA	47.3	60.8	51.3	53.8	63.4	(4/9)	16.0	44.0	44.0	77.3	19.0	48.3
	(300)	(74)	(78)	(78)	(41)		(25)	(232)	(25)	(22)	(21)	(905)
VR *E. faecalis**	1.6	11.4	7.9	6.3	0.0	(0/5)	0.0	0.0	0.0	(0/5)	(0/8)	2.8
	(129)	(35)	(38)	(32)	(11)		(13)	(104)	(13)			(393)
VR *E. faecium**	62.2	(5/7)	(2/4)	10.0	(1/3)	(0/1)	-	31.6	(0/1)	(1/1)	(2/4)	44.3
	(37)			(10)				(38)				(106)
ESBL+ *K. pneumoniae**	35.6	52.3	52.2	32.1	64.5	58.3	26.1	21.4	48.0	50.0	26.3	36.7
	(261)	(65)	(67)	(56)	(31)	(12)	(23)	(182)	(25)	(22)	(19)	(763)
ESBL+ *E. coli**	8.4	20.3	36.8	20.2	28.6	33.3	8.0	34.0	16.7	0.0	8.3	20.8
	(296)	(74)	(76)	(89)	(28)	(33)	(25)	(238)	(24)	(25)	(24)	(932)
Imipenem-R *Acinetobacter**	39.3	31.1	6.5	30.8	0.0	0.0	0.0	1.1	0.0	(0/9)	36.4	21.4
	(178)	(45)	(46)	(39)	(18)	(15)	(15)	(95)	(15)		(11)	(486)

* % calculated when total n ≥10; numbers in parentheses represent the total number of isolates for each species; - indicates no isolates were submitted.

Gram-Positive Isolates

Staphylococcus aureus

All 905 *S. aureus* isolates collected between 2004 and 2007 were susceptible to tigecycline, linezolid and vancomycin ($MICs_{90}$ 0.25, 2 and 1 μg/mL, respectively), while 98.9% were susceptible to minocycline (MIC_{90} 1 μg/mL) (Table 4). Only 55.7% of isolates were susceptible to levofloxacin. Almost one-half of these *S. aureus* isolates (48.3%) were methicillin-resistant (MRSA) (Table 3).

Enterobacter faecalis and *E. faecium*

All *E. faecalis* isolates were susceptible to ampicillin, while most isolates were susceptible to penicillin (99.2%), linezolid (97.2%) and vancomycin (96.4%). Low $MICs_{90}$ were reported for tigecycline and amoxicillin-clavulanic acid (0.25 and 1 μg/mL, respectively; Table 4).

Against *E. faecium* the lowest MICs were reported for tigecycline (0.12 μg/mL), while 92.5% of isolates were susceptible to linezolid (MIC_{90} 2 μg/mL). Only 17.0% of isolates were susceptible to levofloxacin (MIC_{90} ≥64 μg/mL, Table 4). Nearly half (44.3%) of the *E. faecium* isolates observed in this study were vancomycin resistant (Table 3).

Gram-Negative Isolates

Non-Fermenters

Against the *Acinetobacter* spp. the lowest $MICs_{90}$ were reported for tigecycline and minocycline (2 μg/mL), with 94.9% of isolates susceptible to minocycline. Only 62.6% of isolates were susceptible to imipenem (MIC_{90} ≥32 μg/mL, Table 4).

Few agents were active against *P. aeruginosa*. Piperacillin-tazobactam was the most active agent reported against *P. aeruginosa* in this study, with 79.3% of isolates susceptible over the four study years (MIC_{90} 128 μg/mL, Table 4).

Enterobacteriaceae

Imipenem and tigecycline were the most active agents against *Enterobacter* spp., with 99.2 and 96.2% of isolates susceptible, respectively. Susceptibility to cephalosporins ranged from 58.0% to ceftazidime to 80.9% to cefepime (Table 4).

High susceptibilities were reported among isolates of *K. pneumoniae* against imipenem (99.6%; MIC_{90} 1 μg/mL) and tigecycline (95.7%; MIC_{90} 2 μg/mL) (Table 4).

Tigecycline was the most active agent against *E. coli*; all isolates were susceptible (MIC_{90} 0.5 μg/mL). Other active agents included imipenem (99.7% susceptible), amikacin (97.3% susceptible) and piperacillin-tazobactam (91.0% susceptible) (Table 4).

Among isolates of *S. marcescens*, 99.5% were susceptible to imipenem, while 97.3% were susceptible to tigecycline (Table 4).

Resistant Isolates

Tigecycline, vancomycin, linezolid and minocycline were effective against MRSA, with $MICs_{90}$ of 0.25, 1, 2 and 4 μg/mL, respectively. Susceptibilities to these agents were also

Table 4. *In vitro* activity of tigecycline and other antibiotics against Gram-positive and Gram-negative organisms collected in Latin America from 2004-2007.

	Overall (2004-2007)					
Antibacterial	**N**	**MIC_{50}**	**MIC_{90}**	**% S***	**% R***	**MIC range**
Gram positives						
S. aureus						
Tigecycline	905	0.12	0.25	100	N/A	0.03 - 0.5
Penicillin	905	≥16	≥16	6.5	93.5	≤0.06 - ≥16
Ampicillin	905	16	≥32	8.4	91.6	≤0.06 - ≥32
Amoxicillin-clavulanic acid	905	2	≥16	57.7	42.3	0.06 - ≥16
Piperacillin-tazobactam	905	2	≥32	59.4	40.6	≤0.25 - ≥32
Ceftriaxone	905	4	≥128	54.7	39.4	0.12 - ≥128
Imipenem†	538	0.25	≥32	59.5	36.8	≤0.12 - ≥32
Levofloxacin	905	0.25	16	55.7	41.2	≤0.06 -≥64
Minocycline	905	≤0.25	1	98.9	0.2	≤0.25 -≥16
Linezolid	905	2	2	100	N/A	≤0.5 - 4
Vancomycin	905	1	1	100	0.0	≤0.12 - 2
E. faecalis						
Tigecycline	393	0.12	0.25	N/A	N/A	≤0.008 - 1
Penicillin	393	2	4	99.2	0.8	≤0.06 - ≥16
Ampicillin	393	1	2	100	0.0	≤0.06 - 8
Amoxicillin-clavulanic acid	393	0.5	1	N/A	N/A	0.06 - 8
Piperacillin-tazobactam	393	2	8	N/A	N/A	≤0.25 - ≥32
Imipenem†	229	1	8	N/A	N/A	≤0.12 - ≥32
Levofloxacin	393	1	32	71.0	27.7	0.25 - ≥64
Minocycline	393	8	≥16	38.7	24.4	≤0.25 - ≥16
Linezolid	393	2	2	97.2	0.0	≤0.5 - 4
Vancomycin	393	1	2	96.4	2.8	≤0.12 - ≥64
E. faecium						
Tigecycline	106	0.06	0.12	100	0.0	≤0.008 - 0.25
Penicillin	106	≥16	≥16	22.6	77.4	≤0.06 - ≥16
Ampicillin	106	≥32	≥32	25.5	74.5	0.12 - ≥32
Amoxicillin-clavulanic acid	106	≥16	≥16	N/A	N/A	0.12 - ≥16
Piperacillin-tazobactam	106	≥32	≥32	N/A	N/A	≤0.25 - ≥32
Ceftriaxone	106	≥128	≥128	N/A	N/A	0.12 - ≥128
Imipenem†	54	≥32	≥32	N/A	N/A	0.5 - ≥32
Levofloxacin	106	≥64	≥64	17.0	78.3	0.5 -≥64
Minocycline	106	1	≥16	61.3	22.6	≤0.25 - ≥16
Linezolid	106	2	2	92.5	0.0	≤0.5 - 4
Vancomycin	106	2	≥64	53.8	44.3	≤0.12 - ≥64
Gram negatives						
***Acinetobacter* spp.**						
Tigecycline	486	0.5	2	N/A	N/A	≤0.008 - 8
Tigecycline (*Enterobacteriaceae* breakpoints¥)	486	0.5	2	96.7	0.4	≤0.008 - 8
Ampicillin	486	≥64	≥64	N/A	N/A	≤0.5 - ≥64
Amoxicillin-clavulanic acid	486	≥64	≥64	N/A	N/A	≤0.12 - ≥64
Piperacillin-tazobactam	486	128	≥256	19.1	62.3	≤0.06 - ≥256
Ceftazidime	486	≥64	≥64	18.1	75.1	≤8 - ≥64

Ceftriaxone	486	≥128	≥128	8.4	79.4	≤0.06 - ≥128
Cefepime	486	32	≥64	25.9	54.1	≤0.5 -≥64
Imipenem†	313	1	≥32	62.6	33.2	0.12 - ≥32
Levofloxacin	486	8	≥16	19.5	62.1	≤0.008 - ≥16
Amikacin	486	32	≥128	35.6	46.1	≤0.5 - ≥128
Minocycline	486	≤0.5	2	94.9	2.1	≤0.5 - ≥32
P. aeruginosa						
Tigecycline	715	8	≥32	N/A	N/A	0.12 - ≥32
Ampicillin	715	≥64	≥64	N/A	N/A	1- ≥64
Piperacillin-tazobactam	715	8	128	79.3	20.7	≤0.06 - ≥256
Ceftazidime	715	≤8	≥64	60.0	30.5	≤8 - ≥64
Cefepime	715	8	≥64	61.5	22.8	≤0.5 - ≥64
Imipenem†	446	1	16	66.1	18.8	0.12 - ≥32
Levofloxacin	715	2	≥16	50.5	45.0	0.03 - ≥16
Amikacin	715	4	64	72.2	18.5	≤0.5 - ≥128
Minocycline	715	≥32	≥32	5.2	79.6	≤0.5 - ≥32
***Enterobacter* spp.**						
Tigecycline	766	0.5	2	96.2	0.3	0.06 - 8
Ampicillin	766	≥64	≥64	0.4	93.5	4 - ≥64
Amoxicillin-clavulanic acid	766	≥64	≥64	3.3	94.6	1 - ≥64
Piperacillin-tazobactam	766	4	128	68.4	15.5	0.12 - ≥256
Ceftazidime	766	≤8	≥64	58.0	36.2	≤8 - ≥64
Ceftriaxone	766	1	≥128	61.6	28.5	≤0.06 -≥128
Cefepime	766	≤0.5	≥64	80.9	14.5	≤0.5 - ≥64
Imipenem†	484	0.5	1	99.2	0.6	≤0.06 - ≥32
Levofloxacin	766	0.06	≥16	76.6	19.6	≤0.008 - ≥16
Amikacin	766	2	32	89.4	5.4	≤0.5 - ≥128
Minocycline	766	4	≥32	72.5	17.6	≤0.5 - ≥32
K. pneumoniae						
Tigecycline	763	0.5	2	95.7	1.3	0.12 - 8
Ampicillin	763	≥64	≥64	0.3	90.4	1 - ≥64
Amoxicillin-clavulanic acid	763	16	≥64	49.1	35.0	0.5 - ≥64
Piperacillin-tazobactam	763	4	≥256	66.1	22.9	0.12 - ≥256
Ceftazidime	763	≤8	≥64	56.7	35.3	≤8 - ≥64
Ceftriaxone	763	1	≥128	56.7	35.6	≤0.06 - ≥128
Cefepime	763	1	≥64	67.6	26.5	≤0.5 -≥64
Imipenem†	459	0.5	1	99.6	0.4	≤0.06 - ≥32
Levofloxacin	763	0.25	≥16	63.4	32.2	≤0.008 -≥16
Amikacin	763	2	32	88.3	7.5	≤0.5 - ≥128
Minocycline	763	2	16	72.6	18.1	≤0.5 - ≥32
E. coli						
Tigecycline	932	0.25	0.5	100	0.0	≤0.008 - 2
Ampicillin	932	≥64	≥64	25.6	73.3	≤0.5 - ≥64
Amoxicillin-clavulanic acid	932	8	32	56.0	20.0	≤0.12 - ≥64
Piperacillin-tazobactam	932	1	16	91.0	4.1	≤0.06 - ≥256
Ceftazidime	932	≤8	32	77.9	12.4	≤8 - ≥64
Ceftriaxone	932	≤0.06	≥128	71.0	23.9	≤0.06 - ≥128
Cefepime	932	≤0.5	32	80.4	14.6	≤0.5 - ≥64
Imipenem†	583	0.25	0.5	99.7	0.2	≤0.06 - ≥32
Levofloxacin	932	0.5	≥16	53.8	41.2	≤0.008 - ≥16
Amikacin	932	2	8	97.3	1.3	≤0.5 - ≥128
Minocycline	932	2	16	68.3	18.7	≤0.5 - ≥32

S. marcescens						
Tigecycline	328	1	2	97.3	0.6	0.12 - 8
Ampicillin	328	≥64	≥64	0.3	94.5	4 -≥64
Amoxicillin-clavulanic acid	328	≥64	≥64	2.4	93.3	2 - ≥64
Piperacillin-tazobactam	328	2	128	80.2	11.0	≤0.06 - ≥256
Ceftazidime	328	≤8	32	79.0	12.5	≤8 - ≥64
Ceftriaxone	328	0.5	≥128	73.5	20.4	≤0.06 -≥128
Cefepime	328	≤0.5	≥64	81.7	14.6	≤0.5 - ≥64
Imipenem†	220	0.5	1	99.5	0.0	≤0.06 - 8
Levofloxacin	328	0.12	4	84.5	9.8	≤0.008 - ≥16
Amikacin	328	4	32	79.9	9.8	≤0.5 - ≥128
Minocycline	328	2	8	85.7	5.8	≤0.5 - ≥32

*Susceptibility and resistance were only determined when ≥10 isolates were available; †Imipenem numbers are lower due to some isolates being tested with meropenem (data not shown); ¥using Enterobacteriaceae breakpoints (S = 2, R = 8 µg/mL); N/A indicates breakpoint was not available.

Table 5. *In vitro* activity of tigecycline and other antibiotics against resistant Gram-positive and Gram-negative organisms collected in Latin America from 2004-2007.

Antibacterial	**N**	**MIC_{50}**	**MIC_{90}**	**% S***	**% R**	**MIC** range
Gram-positives						
MRSA						
Tigecycline	437	0.12	0.25	100	N/A	0.03 - 0.5
Levofloxacin	437	8	32	12.8	83.1	≤0.06 - ≥64
Minocycline	437	≤0.25	4	98.4	0.2	≤0.25 -≥16
Linezolid	437	2	2	100	N/A	≤0.5 - 4
Vancomycin	437	1	1	100	0.0	0.25 - 2
VR *E. faecium*						
Tigecycline	47	0.06	0.12	N/A	N/A	0.03 - 0.25
Penicillin	47	≥16	≥16	4.3	95.7	4 - ≥16
Ampicillin	47	≥32	≥32	4.3	95.7	2 - ≥32
Piperacillin-tazobactam	47	≥32	≥32	N/A	N/A	16 - ≥32
Imipenem§	22	≥32	≥32	N/A	N/A	8 - ≥32
Levofloxacin	47	≥64	≥64	0.0	100	16 - ≥64
Minocycline	47	≤0.25	≥16	74.5	17.0	≤0.25 - ≥16
Linezolid	47	2	2	97.9	0.0	1 - 4
Vancomycin	47	≥64	≥64	0.0	100	32 - ≥64
Gram-negatives						
Imipenem-R *Acinetobacter*						
Tigecycline	104	0.5	2	N/A	N/A	0.12 - 8
Tigecycline (*Enterobacteriaceae* breakpoint¥)	104	0.5	2	97.1	1.0	0.12 - 8
Ampicillin	104	≥64	≥64	N/A	N/A	32 - ≥64
Amoxicillin-clavulanic acid	104	≥64	≥64	N/A	N/A	16 -≥64
Piperacillin-tazobactam	104	≥256	≥256	1.9	95.2	4 - ≥256
Ceftazidime	104	≥64	≥64	6.7	89.4	≤8 - ≥64
Ceftriaxone	104	≥128	≥128	0.0	92.3	16 - ≥128
Cefepime	104	≥64	≥64	3.8	83.7	4 - ≥64
Imipenem§	104	≥32	≥32	0.0	100	16 - ≥32
Levofloxacin	104	8	≥16	4.8	68.3	0.25 -≥16
Amikacin	104	64	≥128	13.5	74.0	2 - ≥128
Minocycline	104	≤0.5	2	98.1	1.0	≤0.5 - 16

ESBL+ *K. pneumoniae*						
Tigecycline	280	0.5	2	93.6	1.8	0.12 - 8
Ampicillin	280	≥64	≥64	0.0	98.9	16 - ≥64
Amoxicillin-clavulanic acid	280	32	≥64	12.9	61.8	2 - ≥64
Piperacillin-tazobactam	280	64	≥256	35.0	42.9	0.25 - ≥256
Imipenem[§]	185	0.5	1	99.5	0.5	≤0.06 - 16
Levofloxacin	280	8	≥16	33.6	58.9	≤0.008 - ≥16
Amikacin	280	8	≥128	76.8	14.3	≤0.5 - ≥128
Minocycline	280	4	≥32	65.7	21.4	≤0.5 - ≥32
ESBL+ *E. coli*						
Tigecycline	194	0.25	0.5	100	0.0	0.06 - 2
Ampicillin	194	≥64	≥64	0.0	99.5	16 - ≥64
Amoxicillin-clavulanic acid	194	16	32	22.7	30.9	2 - ≥64
Piperacillin-tazobactam	194	8	32	86.1	3.6	0.25 - ≥256
Imipenem[§]	110	0.25	0.5	99.1	0.0	≤0.06 - 8
Levofloxacin	194	≥16	≥16	9.8	84.5	0.015 - ≥16
Amikacin	194	4	16	94.3	3.1	≤0.5 - ≥128
Minocycline	194	4	≥32	61.3	25.8	≤0.5 - ≥32

*Susceptibility was only determined when ≥10 isolates were available; [§]Imipenem numbers are lower due to some isolates being tested with meropenem; [ı]VR E. faecalis are not reported here as only four were reported during the four study years (2 in 2005, 2 in 2006); [¥]using Enterobacteriaceae breakpoints (S = 2, R = 8 μg/mL); N/A indicates breakpoint is not available.

high (100% for tigecycline, vancomycin and linezolid and 98.4% for minocycline) (Table 5).

Tigecycline was the most active agent against vancomycin-resistant (VR) *E. faecium*, with a MIC_{90} of 0.12 μg/mL over the four study years (Table 5). Linezolid was also active against VR *E. faecium*, with a MIC_{90} of 2 μg/mL and 97.9% of isolates susceptible (Table 5).

Imipenem-resistant *Acinetobacter* spp. had reduced susceptibility to most agents, with the exceptions of tigecycline (MIC_{90} 2 μg/mL) and minocycline (MIC_{90} 2 μg/mL) (Table 5).

Tigecycline and imipenem were the most active agents against ESBL-positive *K. pneumoniae*, with 93.6 and 99.5% of isolates susceptible, respectively (MIC_{90}s of 2 and 1 μg/mL, respectively). Similarly, tigecycline and imipenem were the most active agents against ESBL-positive *E. coli*, with susceptibilities of 100 and 99.1%, respectively, and MIC_{90}s of 0.5 μg/mL for each (Table 5).

Discussion

Several global surveillance studies are currently underway, including the SENTRY and SMART (Study for Monitoring Antimicrobial Resistance Trends) studies. These and other surveillance studies allow for the monitoring of global trends in resistance, as well as providing data on regional resistance and demographic trends. The T.E.S.T. study has been ongoing since 2004, collating global and local data on resistance trends among Gram-positive and Gram-negative organisms from nosocomial patients and community/outpatients. To date, 384 centers in 48 countries have contributed isolates to the T.E.S.T. global study.

Among the 33 centers contributing isolates in our study, 19 were located in Argentina and Mexico (11 and 8, respectively). Despite the fact that Brazil has the largest population of any country in Latin America, only two centers from Brazil provided isolates to this study. Thus, results for Latin America as a whole (44.3% vancomycin resistance among *E. faecium*) are biased towards results from those countries contributing the most isolates, in this case Argentina and Mexico. The WHONET Program [10,11] has previously shown high rates of vancomycin resistance among *E. faecium* isolates in Argentina (25%-33%) and Chile (41%-58.6%) from 2003 to 2004. The regional collection bias in this study therefore does not appear to exaggerate the prevalence of vancomycin-resistant *E. faecium* in Latin America.

The MRSA accounted for 48.3% of *S. aureus* isolates collected across Latin America during our study. This is a sizeable increase compared to previous studies, which report MRSA prevalences ranging from 26.5% to 38.6% (during the 1999-2000 winter season [9], from 1997-2001 [12], from 2000-2001 [13] or among clinical isolates in 2003 [14]). This disparity may be due in part to differences in countries contributing isolates to these studies: in Gales et al. [13], 11 centers in six countries contributed isolates (Argentina, Brazil, Chile, Colombia, Mexico and Venezuela); in Sader et al. [14], 10 centers in five undefined countries took part; and Mendes et al. [9] utilized isolates from 13 centers of three countries (Argentina, Brazil and Mexico). The study of Mendes et al. [9] focused on community-acquired respiratory tract organisms, which may account in part for the difference in susceptibility rates noted between that study and our current report.

MRSA rates varied widely between countries in this study, ranging from 16.0% in Jamaica to 77.3% in Puerto Rico. Similar results have previously been reported by Sader et al. [3], who found oxacillin resistance rates to vary significantly, even

between hospitals in the same country. Although MRSA are typically cross-resistant to several classes of antibacterial agents, all *S. aureus* isolates identified in our study were susceptible to tigecycline.

The results in our study suggest that susceptibility among isolates of *E. coli* has decreased in Latin American in recent years. Sader et al. [12] examined susceptibility rates among 457 *E. coli* isolates from nosocomial and community-acquired infections in Latin America from 1997-2001. Of the eight antibacterial agents used in both studies, susceptibility rates were lower for six in our study; susceptibility was reduced by as much as 39.8% in the case of ampicillin. Imipenem susceptibility was identical in these two studies, while levofloxacin susceptibility was 3.2% higher in our study.

Previous surveillance studies have shown reduced susceptibility rates in Latin America to commonly-used antibacterial agents. Gales et al. [15] reported that isolates of *P. aeruginosa* and *Acinetobacter* spp. from Latin America have reduced susceptibility rates to most antibacterial agents compared to isolates from other regions. These conclusions are supported by our study. Stelling et al. [16] examined susceptibility trends among *E. coli* isolates from 10 countries and found that isolation from Latin America was associated with increased nonsusceptibility for all six antimicrobial agents (cefepime, ceftazidime, ciprofloxacin, gentamicin, piperacillin-tazobactam and tobramycin).

As a result of the high frequencies of ESBLs reported in the SMART study from 2003-2004, Rossi et al. [17] have questioned the use of extended-spectrum cephalosporins as empirical therapy for intra-abdominal infections in some geographic areas. ESBL-positive *E. coli* have increased from 12.0% in the Rossi et al. study [17] to 20.8% in our study, while ESBL-positive *K. pneumoniae* increased from 27.6% to 36.7%. These increases in ESBL rates over such a short period reiterate Rossi's concerns about the use of inappropriate empirical therapy in the treatment of infections caused by resistant organisms, especially given that appropriate empirical therapy has been directly linked to clinical success (i.e., 18).

Tigecycline has been shown here to be highly active against most organisms collected from Latin America, such as *S. aureus* (including MRSA), *E. faecalis*, *E. faecium* (including VR isolates), *Acinetobacter* spp. (including MDR isolates), *Enterobacter* spp., *K. pneumoniae* (including ESBL-positive isolates), *E. coli* (including ESBL-positive isolates) and *S. marcescens*. Isolates of *S. aureus* (including oxacillin-resistant isolates) and *Enterococcus* spp. collected in Latin America from 2000 to 2002 have previously been shown to be highly susceptible to tigecycline, with $MIC_{s_{90}}$ of 0.5 μg/mL and 100% susceptibilities reported for both types of bacteria [19].

Tigecycline has previously been shown to be highly active against these same organisms on a global scale. Hoban et al. [20], in an early T.E.S.T. study report, presented data on 6,792 clinical isolates collected from 40 centers across Europe, North America and Asia in 2004. In this study, tigecycline was shown to be highly active against both Gram-positive isolates (including *E. faecalis*, *E. faecium* and *S. aureus*) and Gram-negative isolates (including *Acinetobacter baumannii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *E. coli* and *K. pneumoniae*), with susceptibilities ranging from 91.3% among ESBL-positive *K. pneumoniae* isolates to 100% among *E. coli* (ESBL-positive and -negative), VR *E. faecium* and VR *E. faecalis* isolates. As in our study, tigecycline had little activity against *P. aeruginosa*.

Bacterial resistance to many commonly-used antibacterial agents is increasing. This is particularly true in Latin America, where local antibacterial usage patterns and/or dissemination of resistant clones have led to increased resistance rates [4]. The resistance scenario in Latin America is further complicated by the recent appearance of metallo-β-lactamases among isolates of *A. baumannii*, *P. aeruginosa* and *K. pneumoniae* [21]. The development of new antibacterial agents that work through novel mechanisms, and are thus not affected by existing mechanisms of resistance, is critically needed. Tigecycline is one such agent that has been shown to be effective against most of the organisms identified in our study, even those resistant to other agents. Tigecycline may thus become an important tool in the treatment of infections caused by Gram-positive and Gram-negative organisms, including resistant strains.

Acknowledgements

The authors thank the many investigators who contributed isolates to this study. We also thank the staff of International Health Management Associated, Inc., Schaumburg, IL, USA for coordination of the T.E.S.T study.

This study was financially supported by Wyeth Pharmaceuticals. Medical writing support was provided by Micron Research Ltd; this collaboration was also supported by Wyeth Pharmaceuticals.

References

1. Deshpande L.M., Fritsche T.R., Moet G.J., et al. Antimicrobial resistance and molecular epidemiology of vancomycin-resistant enterococci from North America and Europe: a report from the SENTRY antimicrobial surveillance program. Diagn Microbiol Infect Dis **2007**;58(2):163-70.
2. Falagas M.E., Karveli E.A. The changing global epidemiology of *Acinetobacter baumannii* infections: a development with major public health implications. Clin Microbiol Infect **2007**;13:17-9.
3. Sader H.S., Jones R.N., Gales A.C., et al. SENTRY antimicrobial surveillance program report: Latin America and Brazilian results for 1997 through 2001. Braz J Infect Dis **2004**;8:25-79.
4. Andrade S.S., Sader H.S., Jones R.N., et al. Increased resistance to first-line agents among bacterial pathogens isolated from urinary tract infections in Latin America: time for local guidelines? Memórias de Instituto Oswaldo Cruz, Rio de Janeiro **2006**:101;741-8.
5. Felmingham D. The need for antimicrobial resistance surveillance. J Antimicrob Chemother **2002**;50(suppl. S1):1-7.
6. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, document M7-A6. NCCLS, **2003**.

7. Wyeth Pharmaceuticals Inc. Tygacil Product Insert. Philadelphia, PA, USA, **2007**. http://www.tygacil.com (last accessed 24 April 2007).
8. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing, 16th informational supplement, document M100-S16. CLSI, **2006**.
9. Mendes C., Marin M.E., Quiñones F., et al. Antibacterial resistance of community-acquired respiratory tract pathogens recovered from patients in Latin America : results from the PROTEKT Surveillance Study (1999-2000). Braz J Infect Dis **2003**;7:44-61.
10. Informe Anual de la Red de Monitoreo/Vigilancia de la Resistencia a los Antibióticos, 2003. Organización Panamericana de la Salud, Oficina Regional de la Organización Mundial de la Salud (OPS/DPC/CD/332/05).
11. Informe Anual de la Red de Monitoreo/Vigilancia de la Resistencia a los Antibióticos, 2004 (Brasilia, Brasil 27 al 29 de julio, 2005). Organización Panamericana de la Salud, Oficina Regional de la Organización Mundial de la Salud (OPS/HDM/CD/A/408/06).
12. Sader H.S., Jones R.N., Gales A.C., et al. SENTRY Antimicrobial Surveillance Program Report: Latin American and Brazilian Results for 1997 through 2001. Braz J Infect Dis **2004**;8:25-79.
13. Gales A.C., Andrade S.S., Sader H.S., Jones R.N. Activity of mupirocin and 14 additional antibiotics against staphylococci isolated from Latin American hospitals: report from the SENTRY antimicrobial surveillance program. J Chemother **2004**;16:323-8.
14. Sader H.S., Fritsche T.R., Streit J.M., Jones R.N. Daptomycin *in vitro* activity tested against Gram-positive strains collected from European and Latin American centers in 2003. J Chemother **2005**;17:477-83.
15. Gales A.C., Jones R.N. and Sader H.S. Global assessment of the antimicrobial activity of polymixin B against 54 731 isolates of Gram-negative bacilli: report from the SENTRY antimicrobial surveillance program 2001-2004. Clin Microbiol Infect **2006**;12:315-21.
16. Stelling J.M., Travers K., Jones R.N., et al. Integrating *Escherichia coli* antimicrobial susceptibility data from multiple surveillance programs. Emerg Infect Dis **2005**;11:873-82.
17. Rossi F., Baquero F., Hsueh P.-R., et al. *In vitro* susceptibilities of aerobic and facultative anaerobic Gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: 2004 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). J Antimicrob Chemother **2006**;58:205-10.
18. Krobot K., Yin D., Zhang Q., et al. Effect of inappropriate initial empiric antibiotic therapy on outcome of patients with community-acquired intra-abdominal infections requiring surgery. Eur J Clin Microbiol Infect Dis **2004**;23:682-7.
19. Gales A.C., Jones R.N., Andrade S.S., Pereira A.S., Sader H.S. *In vitro* activity of tigecycline, a new glycylcycline, tested against 1,326 clinical bacterial strains isolated from Latin America. Braz J Infect Dis **2005**:9;348-56.
20. Hoban D.J., Bouchillon S.K., Johnson B.M., et al. *In vitro* activity of tigecycline against 6792 Gram-negative and Gram-positive clinical isolates from the global Tigecycline Evaluation and Surveillance Trial (TEST Program, 2004). Diagn Microbiol Infect Dis **2005**:52;215-27.
21. Lincopan N., McCulloch JA, Reinert C., et al. First isolation of metallo-β-lactamase-producing multiresistant *Klebsiella pneumoniae* from a patient in Brazil. J Clin Microbiol **2005**;43:516-9.