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Tigecycline antimicrobial activity tested against clinical bacteria from Latin American medical centres: results from SENTRY Antimicrobial Surveillance Program (2011–2014)

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ABSTRACT

Bacterial organisms (n = 13,494) were consecutively collected in 2011–2014 from 21 Latin American medical centres (11 nations). Antimicrobial susceptibility was determined by broth microdilution at a central laboratory. Tigecycline was very active against Gram-positive organisms, with $MIC_{50/90}$ values of 0.06/0.06 μg/mL for *Staphylococcus aureus* (n = 2878), 0.06/0.12 μg/mL for coagulase-negative staphylococci (n = 880), 0.06/0.06 μg/mL for enterococci (n = 708) and ≤0.03/≤0.03–0.06 μg/mL for streptococci (n = 1352). All Gram-positive species exhibited 100.0% susceptibility (FDA and/or EUCAST criteria), except for *Streptococcus pneumoniae* (99.8% susceptible). The *S. aureus* oxacillin resistance rate varied from 28.0% (Brazil) to 55.0% (Argentina), and the overall vancomycin resistance rate was 15.5% (*Enterococcus faecium*, 50.3%; and *Enterococcus faecalis*, 2.3%). The *E. faecium* vancomycin resistance rate varied from a low (26.3%) in Argentina to a high (71.7%) in Brazil. Against Enterobacteriaceae (n = 4543), tigecycline $MIC_{50/90}$ values were 0.25/1 μg/mL; 98.3% and 94.2% of strains were considered susceptible according to FDA and EUCAST breakpoints, respectively. Overall, 37.7% and 57.3% of *Escherichia coli* and *Klebsiella pneumoniae* exhibited the CLSI ESBL screening phenotype. The highest CLSI ESBL screening phenotype rates among *E. coli* and *Klebsiella* spp. strains were observed for isolates collected from Mexico (69.9%) and Chile (69.9%), respectively. Occurrence of carbapenem-resistant Enterobacteriaceae was substantially higher in Brazil (9.0%) and Argentina (6.3%) compared with Chile and Mexico (0.4–0.7%). Tigecycline was also active against *Acinetobacter* spp. ($MIC_{50/90}$, 1/2 μg/mL; 92.3/72.1% inhibited at ≤2/≤1 μg/mL) and *Stenotrophomonas maltophilia* ($MIC_{50/90}$, 0.5/2 μg/mL; 91.5/83.0% inhibited at ≤2/≤1 μg/mL).

1. Introduction

Tigecycline was the first of a class of antimicrobials named glycylcyclines and has been active in vitro against a variety of Gram-positive and Gram-negative organisms, including meticillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), Enterobacteriaceae strains that produce extended-spectrum β-lactamases (ESBLs) and carbapenemases, such as *Klebsiella pneumoniae* carbapenemases (KPC) and metallo-β-lactamases, and multidrug-resistant (MDR) *Acinetobacter* spp. [1]. Tigecycline was initially approved by the US Food and Drug Administration (FDA) in 2005 for the treatment of adults with complicated skin and skin-structure infections and complicated intra-abdominal infections [2]. In 2009, tigecycline also received FDA approval for the treatment of community-acquired bacterial pneumonia [1,2]. This minocycline derivative has provided clinicians with an alternative treatment option for infections caused by these 'difficult-to-treat' pathogens [3–7].

A limited number of Latin American countries possess a nationwide surveillance programme for monitoring antimicrobial resistance [8,9]. Data from monitoring surveillance programmes, such as the SENTRY Antimicrobial Surveillance Program, have provided information on the continuing activity of most clinically relevant antimicrobial agents against a wide spectrum of clinically important Gram-positive and Gram-negative pathogens from Latin America [10–12]. The objective of this investigation was to evaluate the in vitro activity of tigecycline tested against contemporary clinical isolates causing bacterial infections in Latin American medical centres. The prevalence of the most clinically important resistance phenotypes in the main Latin American countries was also evaluated.

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2. Methods

2.1. Bacterial strains

A total of 13,494 bacterial organisms, including 5818 (43.1%) Gram-positive cocci and 7676 (56.9%) Gram-negative bacilli, were collected between January 2011 and December 2014 from 21 Latin American medical centres located in 11 nations as part of the SENTRY Antimicrobial Surveillance Program. The number of isolates from each species/organism group collected from each country is listed in Table 1. Of note, Argentina, Brazil, Chile and Mexico contributed 78.9% of the isolates. The organisms were consecutively collected from various infection sites and only one isolate per patient episode was included in the study. The medical centres were guided by a common protocol. Species identification was performed by the participating centre and was confirmed at JMI Laboratories (North Liberty, IA) when necessary by VITEK®2 or matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) using a Bruker Daltonics MALDI Biotyper® (Bruker Corp., Billerica, MA) following the manufacturer's instructions.

2.2. Susceptibility testing

Isolates were tested for susceptibility to multiple antimicrobial agents at a central reference laboratory by reference broth microdilution methods as described by the Clinical and Laboratory Standards Institute (CLSI) [13] using validated broth microdilution panels produced by Thermo Fisher Scientific Inc. (Cleveland, OH). Minimum inhibitory concentration (MIC) results were interpreted according to CLSI criteria [14] as well as European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables [15]. Tigecycline MIC breakpoints were those found in the FDA approved package insert [2]. Vancomycin-resistant enterococci (VRE) were defined as isolates with a vancomycin MIC of ≥8 μg/mL (non-susceptible by CLSI criteria and resistant by EUCAST criteria) [14,15]. *Escherichia coli* and *Klebsiella* spp. isolates with decreased susceptibility (MIC ≥ 2 mg/L) to ceftazidime or ceftriaxone or aztreonam were grouped together and this group was defined as 'CLSI ESBL screening phenotype' based on the CLSI screening criteria for ESBL production [14]. Although an ESBL confirmation test was not performed and other β-lactamases, such as AmpC and KPC, may also produce a 'CLSI ESBL screening phenotype', these strains were grouped together because they usually demonstrate resistance to various broad-spectrum β-lactam compounds. Carbapenem-resistant Enterobacteriaceae (CRE) indicates an isolate non-susceptible (CLSI) to meropenem (≥2 μg/mL) or imipenem (≥2 μg/mL; except for *Proteus mirabilis* and indole-positive Proteae, which were categorised based on meropenem MIC only). Quality control was performed according to CLSI methods [14] using *E. coli* strains ATCC 25922 and 35218, *S. aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853 and *Enterococcus faecalis* ATCC 29212.

3. Results

The in vitro activity of tigecycline tested against clinical bacteria collected from Latin American countries during the 4-year period (2011–2014) of this investigation is summarised in the format of MIC distributions (Table 2). Tigecycline was active against Gram-positive organisms, with $MIC_{50/90}$ values of 0.06/0.06 μg/mL for *S. aureus* (2878 strains), 0.06/0.12 μg/mL for coagulase-negative staphylococci (CoNS) (880 strains), 0.06/0.06 μg/mL for enterococci (including 477 *E. faecalis*, 197 *Enterococcus faecium* and 34 other *Enterococcus* spp.), and ≤0.03/≤0.03–0.06 μg/mL for streptococci (639 *Streptococcus pneumoniae*, 449 β-haemolytic streptococci and 264 viridans group streptococci). All Gram-positive species exhibited a 100.0% susceptibility rate (FDA and/or EUCAST criteria), except for *S. pneumoniae* (99.8% susceptible). The highest tigecycline MIC value among Gram-positive organisms was only 0.5 μg/mL (one CoNS strain; Table 2). Furthermore, tigecycline MIC distributions for MRSA and VRE were very similar to those of their susceptible wild-type counterparts (Table 2).

Among the 4543 Enterobacteriaceae strains evaluated, tigecycline $MIC_{50/90}$ values were 0.25/1 μg/mL and 98.3% of strains were considered susceptible according the FDA breakpoint of ≤2 μg/mL [2] and 94.2% were inhibited at the EUCAST susceptible breakpoint of ≤1 μg/mL [15]. The most tigecycline-susceptible Enterobacteriaceae species were *E. coli* and *Klebsiella oxytoca* [$MIC_{50/90}$, 0.12/0.25 μg/mL; 100.0% susceptible (FDA)], followed by *Citrobacter* spp. ($MIC_{50/90}$, 0.25/0.5 μg/mL; 100.0% susceptible), *K. pneumoniae* and *Enterobacter* spp. ($MIC_{50/90}$ of 0.25/1 μg/mL; 98.5–98.8% susceptible) (Table 2). Tigecycline was particularly active against CLSI ESBL screening phenotype *E. coli* ($MIC_{50/90}$, 0.12/0.25 μg/mL; 100.0%

Table 1
Number of isolates for each species/group, stratified by country.

Organism	Number of isolates											
	ARG	BRA	CHI	COL	CR	ECU	GUA	MEX	PAN	PER	VEN	Total
Staphylococcus aureus	456	685	480	101	101	99	46	586	98	104	122	2878
CoNS	85	333	75	30	29	31	26	188	29	31	23	880
Enterococcus spp.	91	172	66	36	30	28	17	153	30	34	51	708
β-Haemolytic streptococci	130	118	57	14	8	10	5	74	10	3	20	449
Streptococcus pneumoniae	110	215	136	12	7	9	1	94	19	2	34	639
Viridans group streptococci	38	83	61	6	8	6	3	38	11	4	6	264
Enterobacteriaceae	543	1328	568	148	149	133	190	975	158	149	202	4543
Escherichia coli	142	380	204	65	65	59	97	425	60	65	66	1628
Klebsiella spp.	215	416	150	41	43	39	55	244	40	41	64	1348
Proteus mirabilis	32	66	42	3	9	4	12	28	12	7	8	223
Enterobacter spp.	68	195	88	22	20	18	9	174	19	21	47	681
Citrobacter spp.	17	51	18	1	0	0	6	31	3	2	0	129
Indole-positive Proteae	37	71	19	4	7	4	8	34	13	8	1	206
Serratia spp.	32	149	47	12	5	8	3	39	10	4	16	325
Pseudomonas aeruginosa	227	516	168	24	25	19	56	271	20	28	59	1413
Acinetobacter spp.	111	427	56	20	10	20	38	329	20	16	33	1080
Stenotrophomonas maltophilia	4	41	26	0	1	4	2	57	0	6	0	141
Haemophilus influenzae	94	142	95	16	2	0	0	15	0	0	1	365
Moraxella catarrhalis	41	36	55	1	1	0	0	0	0	0	0	134
Total	1930	4096	1843	408	371	359	384	2780	395	377	551	13,494

ARG, Argentina; BRA, Brazil; CHI, Chile; COL, Colombia; CR, Costa Rica; ECU, Ecuador; GUA, Guatemala; MEX, Mexico; PAN, Panama; PER, Peru; VEN, Venezuela; CoNS, coagulase-negative staphylococci.

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