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In vitro activity of tigecycline against isolates collected from complicated skin and skin structure infections and intra-abdominal infections in Africa and Middle East countries: TEST 2007–2012☆,☆☆

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ABSTRACT

Complicated skin and skin structure infections (cSSSIs) and intra-abdominal infections (IAIs) are problematic due to decreasing therapeutic options available against multidrug-resistant pathogens common among these types of infections. A total of 2245 isolates from African and the Middle Eastern (AfME) countries were collected to determine *in vitro* activity for tigecycline and comparators during 2007–2012 as part of the Tigecycline Evaluation Surveillance Trial program. Tigecycline was launched in the AfME in 2007 and remains active against a wide range of targeted pathogens worldwide. Isolates were recovered from cSSSI (1990) and IAI (255) from 38 sites in 11 AfME countries. *Staphylococcus aureus* was the most common species from cSSSI (27.9%), and the methicillin-resistant *S. aureus* rate was 25%. *Enterococcus* spp. (7.1%) and *Streptococcus agalactiae* (2.9%) were other common Gram-positive pathogens represented. *Enterobacter* spp. (14.5%), *Pseudomonas aeruginosa* (13.9%), *Escherichia coli* (11.4%), *Klebsiella* spp. (10.9%), and *Acinetobacter* spp. (7.2 %) were the most common Gram-negative species collected. Tigecycline MIC_{90} values were 0.25 μg/mL against *S. aureus*. *E. coli* and *Enterobacter* spp. had tigecycline MIC_{90} values of 1 and 2 μg/mL, respectively. *E. coli* was the most frequently collected species from IAI (28.3%), followed by *Klebsiella* spp. (20.8%), *Enterococcus* spp. (11.8%), and *Stenotrophomonas maltophilia* (6.3%). Isolates collected from IAI had the following tigecycline MIC_{90} values: *E. coli* (1 μg/mL), *Klebsiella* spp. and other Enterobacteriaceae (2 μg/mL), *Enterococcus* spp. (0.25 μg/mL), and *S. maltophilia* (1 μg/mL). Tigecycline *in vitro* activity was observed against a broad spectrum of bacterial species, including strains resistant to other antimicrobial classes.

1. Introduction

Resistance trends have changed over the last decade with an initial rise of methicillin-resistant *Staphylococcus aureus* (MRSA) and a more recent decline due to diligent infection control practices (Livermore, 2012). The convergence of community-associated and hospital-associated MRSA clones into both environments has complicated the ability to determine appropriate empiric therapy against this particular Gram-positive pathogen (Otter and French, 2011). In addition, drug-resistant mechanisms among Gram-negative pathogens are continually emerging, which are often regionally or even institutionally specific and can be globally disseminated (Menichetti and Tagliaferri, 2012). The recent environment of evolving antimicrobial susceptibility patterns and diverse range of bacterial resistance mechanisms has made empiric broad spectrum coverage for complicated infections necessary. Directed therapeutic approaches can only be determined when offending pathogen(s) are isolated and documented as a true pathogen by the microbiology laboratory. Unfortunately, antimicrobial development has slowed during the last decade, and clinicians are facing a challenge in the availability of therapeutic options to the evolving bacterial resistance problem throughout the world (Bassetti et al., 2011). With multidrug resistance (MDR) increasing on a global scale, the need for novel therapeutic agents is becoming an essential health care issue.

Tigecycline is a glycylcycline class antibacterial agent that inhibits protein translation in bacteria by binding to the 30 S ribosomal unit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome, sometimes bactericidal but with a predominately bacteriostatic mode of action (Rose and Rybak, 2006). Tigecycline has demonstrated activity against Gram-positive and many Gram-negative pathogens, including MDR strains (Dunn, 2006).

Complicated skin and skin structure infections (cSSSIs) produce different clinical presentations depending on the causative bacterial pathogen and the site of infection. They can be classified as complicated or uncomplicated according to the term coined in 1998 by the

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Food and Drug Administration (FDA) (Giordano et al., 2007). Tigecycline has been approved by the FDA for the treatment of cSSSI and has been used successfully in the treatment of these infections (Sader et al., 2007; Tygacil®, 2010).

Intra-abdominal infections (IAIs) represent a particular clinical challenge, as they differ from other types of infections in a number of aspects. The clinical spectrum of IAI is very broad, ranging from uncomplicated acute appendicitis to generalized peritonitis caused by a perforated ischemic bowel. The etiology includes Gram-negative, Gram-positive, anaerobic, and fungal species. The treatment is complex, and since approval in 2005, tigecycline has been added to the antimicrobial armamentarium (Blot et al., 2012).

This study collected isolates from the Tigecycline Evaluation Surveillance Trial (TEST) program in hospitals located in African and the Middle Eastern (AfME) countries and reports the susceptibility of tigecycline and comparator agents against both Gram-positive and Gram-negative pathogens from cSSSI and IAI. While designed clinical trials of novel therapeutic approaches are necessary, the most important factor to guide clinicians in their choice of therapy should be knowledge of the susceptibility patterns of strains present in their own geographical area (Michalopoulos and Falagas, 2010).

2. Methods

A total of 2245 Gram-positive and Gram-negative isolates were included in this study. All isolates were derived from skin, wound, burn, and other integumentary locations for cSSSI (1990) and from bodily fluids, stomach, large and small colon, rectum, liver, gall bladder, pancreas, and other intra-abdominal organs for IAI (255). Each center was requested to submit a quota of Gram-negative and Gram-positive isolates including: *Acinetobacter* spp. (15 isolates), *Escherichia coli* (25), *Enterobacter* spp. (25), *Pseudomonas aeruginosa* (20), *Serratia* spp. (10), *Klebsiella* spp. (25), *S. aureus* (25), *Enterococcus* spp. (15), and *Streptococcus agalactiae* (10). Only 1e isolate per patient was accepted into this study.

Isolate inclusion was independent of medical history, antimicrobial use, age or gender, and specific numbers of isolates, and species were requested from each medical center (non–prevalence-based study). Isolates were collected between January 2007 and June 2012 from 38 sites in 11 countries including Egypt (1 center), Morocco (2 centers), Mauritius (1 center), Namibia (1 center), South Africa (13 centers), Tunisia (1 center), Israel (12 centers), Jordan (2 centers), Lebanon (1 center), Oman (1 center), and Saudi Arabia (3 centers). Isolates were identified to the species level and tested at each site by the participating laboratory.

MICs were determined at individual centers using broth microdilution testing methodology (CLSI, 2012a) with MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) or Sensititre (TREK Diagnostic Systems, Cleveland, OH, USA) panels. MIC interpretive criteria followed published guidelines established by the CLSI (CLSI, 2012b), where available, and the FDA for tigecycline (FDA, 2010).

Quality control (QC) testing was performed by each site on each day of testing using the following ATCC control strains: *P. aeruginosa* ATCC 27853, *E. coli* ATCC 25922, *E. coli* ATCC 35218, *S. aureus* ATCC 29213, *Streptococcus pneumoniae* ATCC 49619, and *Enterococcus faecalis* ATCC 29212, following CLSI and manufacturer's guidelines (CLSI, 2012b). Results were included in the analysis only when corresponding QC results were within the acceptable ranges. Statistical significance was determined using Fisher's exact test, 2 tailed, and Cochran-Armitage trend test (Asymptotic *P*-value)/2-tailed test.

3. Results

The *in vitro* activity of tigecycline and comparators versus selected Gram-negative and Gram-positive species from cSSSI is shown in Tables 1 and 2, respectively. The collection from cSSSI includes 555 *S. aureus* (27.9%), 288 *Enterobacter* spp. (14.5%), and 276 *P. aeruginosa* (13.9%). Among the collection of *S. aureus*, the prevalence of MRSA

Table 1
In vitro activity of tigecycline and comparators versus selected Gram-negative isolates from cSSSIs.

Organism, drug, number	MIC_{50}	MIC_{90}	%S	%I	%R
Enterobacter spp. (288)					
Amikacin	2	4	96.9	1.4	1.7
Amox-clav	>32	>32	3.1	1.7	95.1
Ampicillin	>32	>32	2.45	7.0	90.6
Cefepime	≤0.5	16	88.5	2.8	8.7
Ceftriaxone	0.5	64	61.8	2.8	35.4
Levofloxacin	0.06	4	88.5	3.1	8.3
Meropenem	≤0.06	0.25	97.2	0.7	2.1
Minocycline	4	16	63.5	21.2	15.3
Pip-tazo	2	128	78.5	10.1	11.5
Tigecycline	0.5	2	97.6	1.7	0.7
E. coli (227)					
Amikacin	2	8	98.7	0.4	0.9
Amox-clav	8	32	53.7	22.0	24.2
Ampicillin	>32	>32	15.9	0	84.1
Cefepime	≤0.5	>32	81.5	5.3	13.2
Ceftriaxone	0.12	>64	63.9	0.4	35.7
Levofloxacin	0.5	>8	55.1	1.8	43.2
Meropenem	≤0.06	0.12	95.6	2.6	1.8
Minocycline	4	>16	59.0	14.5	26.4
Pip-tazo	2	64	85.9	8.8	5.3
Tigecycline	0.25	1	99.6	0	0.4
Klebsiella spp. (216)					
Amikacin	2	16	90.7	6.0	3.2
Amox-clav	8	>32	54.2	19	26.9
Ampicillin	>32	>32	0.5	9.3	90.3
Cefepime	≤0.5	>32	65.3	6.9	27.8
Ceftriaxone	0.25	>64	52.8	0.5	46.8
Levofloxacin	0.25	>8	66.7	5.1	28.2
Meropenem	≤0.06	2	89.8	0.5	9.7
Minocycline	4	>16	60.2	14.4	25.5
Pipe-tazo	4	>128	68.5	11.1	20.4
Tigecycline	0.5	2	92.6	6.5	0.9
Serratia spp. (86)					
Amikacin	2	4	100	0	0
Amox-clav	>32	>32	7	2.3	90.7
Ampicillin	>32	>32	5.9	10.6	83.5
Cefepime	≤0.5	2	96.5	0	3.5
Ceftriaxone	0.25	4	81.4	3.5	15.1
Levofloxacin	0.12	1	96.5	1.2	2.3
Meropenem	≤0.06	0.25	96.5	2.3	1.2
Minocycline	4	8	60.5	30.2	9.3
Pip-tazo	2	8	98.8	1.2	0
Tigecycline	1	2	94.2	4.7	1.2
P. aeruginosa (276)					
Amikacin	4	32	87.0	6.2	6.9
Cefepime	4	32	79.0	9.1	12.0
Levofloxacin	1	>8	65.9	7.3	26.8
Meropenem	1	16	75.7	5.8	18.5
Minocycline	16	>16	na	na	na
Pip-tazo	8	128	75.0	11.6	13.4
Tigecycline	8	16	na	na	na
Acinetobacter spp. (143)					
Amikacin	64	>64	35.7	12.6	51.8
Cefepime	32	>32	29.4	16.8	53.9
Ceftriaxone	>64	>64	7.0	16.8	76.2
Levofloxacin	8	>8	29.4	15.4	55.2
Meropenem	>16	>16	33.6	0.7	65.7
Minocycline	4	16	66.4	21.7	11.9
Pip-tazo	>128	>128	21.0	4.9	74.1
Tigecycline	0.5	2	na	na	na

Enterobacter spp. include *E. aerogenes* (33), *E. amnigenus* (1), *E. asburiae* (2), *E. cloacae* (244), *E. agglomerans* (4), *E. gergoviae* (1), *E. sakazakii* (1), *Enterobacter*, non-speciated (2). *Klebsiella* spp. includes *K. oxytoca* (26), *K. ozaenae* (1), and *K. pneumoniae* (189). *Serratia* spp. include *S. liquefaciens* (2), *S. marcescens* (83), *S. rubidaea* (1). *Acinetobacter* spp. include *A. baumannii* (138), *A. lwoffii* (1), and *Acinetobacter*, non-speciated (4).
S = susceptible; I = intermediate; R = resistance; na = not applicable

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