Antimicrobial activity of tigecycline against bacterial isolates from intensive care units in a teaching hospital in Central Saudi Arabia

Ali M. Somily, MD, FRCPC, *Abdulaziz S. Al-Khattaf,* MSC Bact, PhD, *Abdelmageed M. Kambal,* MD, FRC Path.

ABSTRACT

الأهداف: اختبار فعالية التايجساكلين على البكتريا المعزولة من المرضى في وحدات العناية المركزة بما فيها البكتريا السالبة لصبغة غرام ذات المقاومة العالية للمضادات الحيوية (MDR)، و كذلك البكتريا الموجبة لصبغة غرام في مستشفى الملك خالد الجامعي.

الطريقة: تم اختيار حساسية البكتريا الموجبة لصبغة غرام و كذلك السالبة لصبغة غرام ذات الحساسية العالية للمضادات الحيوية ذات الأهمية السريرية و المعزولة من المرضى في وحدات العناية المركزة – مستشفى الملك خالد الجامعي KKUH – الرياض – المملكة العربية السعودية لعقار التايجساكلين خلال الفترة من 1 نوفمبر 2006 حتى 31 ديسمبر 2008م، و قد اختبرت هذه الحساسية بطريقتي انتشار المضاد الحيوي (DD) من الأقراص أو طريقة اختبار E في بعض البكتريا المعزولة أو بالطريقتين معا في عزلات أخرى. كما تمت الموافقة على الدراسة من اللجنة الطبية في المستشفى.

النتائج: تم اختبار جميع عزلات البكتيريا الموجبة الصبغة والتي تم اختيارها عن طريق انتشار المضاد الحيوي (DD) و اختبار E للحساسية لعقار التايجساكلين. كما تم اختبار عدد 254 بكتيريا سالبة الصبغة للمقاومة لعقار التايجساكلين. ومن ضمن 176 عزلة تم اختبارها بطريقة انتشار المضاد الحيوي (DD)، ظهرت 159 (90%) حساسية، و 6 (3.4%) كانت مقاومة، و 11 (6.2%) كانت متوسطة الحساسية. ومن بين 188 عزلة تم اختبارها بطريقة اختبار E، كانت 140 (74.4%) حساسية، و 35 (18.6%) مقاومة، و 13 (6.9%) متوسطة الحساسية. للمقارنة بين الطريقتين، تم اختبار 109 عزلة من البكتيريا السالبة عن طريق انتشار المضاد الحيوي DD و اختبار E. أن التباين بين الطريقتين لم يكن إحصائيا.

خاتمة: أظهر عقار التايجساكلين فعالية عالية ضد كل البكتيريا السالبة الصبغة MDR و لبكتيريا الموجبة الصبغة من مرضى وحدات العناية المركزة في المستشفى و الجراحة في مستشفى الملك خالد الجامعي KKUH. كما أنه لا يوجد أي دلالة إحصائية بين استعمال طريقة اختبار E و انتشار المضاد الحيوي (DD) لكشف حساسية التايجساكلين تجاه هذه المعزولات.

Objectives: To test the activity of tigecycline against bacterial isolates including multi-drug resistant (MDR) gram negative and gram positive organisms from intensive care patients.

Methods: Clinically significant gram positive and MDR gram negative isolates from specimens of patients in the intensive care units of King Khalid University Hospital (KKUH), Riyadh, Kingdom of Saudi Arbia between November 1, 2006 and December 31, 2008 were tested against tigecycline by disc diffusion (DD) method. In some isolates, the minimal inhibitory concentration was carried out by E-test method. Some of the gram negative isolates, and gram positive isolates were tested using both methods. The study was approved by the hospital ethics committee.

Results: All the 83 gram positive organisms tested by both DD and E-test were susceptible to tigecycline. Two hundred and fifty-four MDR gram negative isolates were tested for susceptibility to tigecycline. Of these 176 tested by DD, 159 (90%) were susceptible, 6 (3.4%) were resistant, and 11 (6.2%) were intermediately susceptible (data are not the same in table 3). From the 188 isolates tested by E-test, 140 (74.4%) were susceptible, 35 (18.6%) were resistant, and 13 (6.9%) showed intermediate susceptibility. For comparison between the methods, 109 isolates of the MDR gram negative organisms were tested by both E test and DD. The difference between the 2 methods was not significant.

Conclusion: Tigecycline was active against gram positive and most MDR gram negative isolates from patients in medical and surgical intensive cases in KKUH. There was no significant difference between the DD and E-test methods for susceptibility testing of tigecycline against these isolates.

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From the Department of Pathology/Microbiology, College of Medicine & King Saud University, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Ali M. Somily, Assistant Professor & Consultant Microbiologist, Department of Pathology/ Microbiology (32), College of Medicine & King Saud University, King Khalid University Hospital, PO Box 2925, Riyadh 11461, Kingdom of Saudi Arabia. Tel. +966 (1) 4672640. Fax. +966 (1) 4679162. E-mail: ali.somily@gmail.com/somily@ksu.edu.sa

Tigecycline is a noval glycycline derivative of minocyclic with bacteriostatic broad-spectrum activity against gram positive and gram negative bacteria.[1] It is the first of a new class of antibiotics called glycylcyclines.[2] It is active against many otherwise multi-resistant bacteria including *Methicillin resistant Staphylococci* (MRSA), *Vancomycin resistant enterococci* (VRE)[3,4] and anaerobes.[5] Tigecycline is also active against gram negative bacteria that produce extended spectrum beta lactamases,[6] and microorganisms that developed resistance to tetracyclines as well as intracellular bacteria,[7,8] and non-tuberculosis mycobacteria.[1] However, the drug is not significantly active against *Proteus species, Morganella species, Providencia species,*[9,10] and Pseudomonas group of organisms.[9,11] Tigecycline inhibits bacterial protein synthesis by blocking the attachment of aminoacyl tRNA to the A site of the ribosome preventing the elongation of the peptide chain.[12] It evades the 2 bacterial resistance mechanisms to tetracyclines, namely, ribosomal protection and drug efflux.[13] This is because its activity is not affected by the acquired ribosomal protection tet (M), efflux (A-E), and tet (K) genes.[13,14] The drug was approved for use by the Food and Drug Administration (FDA) in June 2005[15] and by the European Medicine Agency in April 2006[4] for empiric monotherapy of nosocomial and community-acquired skin, soft tissue, and intra-abdominal infections.[4] It has also been used to treat infections including complicated appendicitis, intra-abdominal and perforated abscesses, deep soft tissue infections, infected burns, ulcers and surgical wound infections with suspected or confirmed resistant microorganisms.[4] Tigecycline is administered intravenously in an approved FDA dose of 100 mg loading dose followed by 50 mg maintenance dose every 12 hours.[1] The side effects of tigecycline include mild gastrointestinal disturbances such as vomiting and abdominal pain.[1] The objective of this study was to measure and study the *in vitro* activity of tigecycline against gram positive and multi-drug resistant (MDR) gram negative bacterial isolates from different clinical specimens of patients in the intensive care units of King Khalid University Hospital (KKUH) in Riyadh, Saudi Arabia.

Methods. Clinically, significant gram positive organisms and MDR gram negative organisms were included in this study. All these organisms originated from patients in different Intensive Care Units of KKUH during the period of 1 November 2006 to 31 December 2008. King Khalid University Hospital is the main teaching hospital in Riyadh with 850 bed capacity. It contains 5 adult and pediatric intensive care units. The study was approved by the hospital ethics committee and patient consent was obtained. The authors declare that they have no conflicting interest, support, or fund from any drug company.

A total of 83 gram positive organisms and 254 MDR gram negative organisms were studied. The organisms were identified by conventional bacteriological methods and/or the micro scan automated identification machine (Dade Bering, Siemens Company, Deerfield, IL, USA). All gram negative isolates were MDR such as resistant to at least 3 groups of antibiotic usually used for treatment of infections caused by these organisms. Most of the *Enterobacteriaceae* in this study were extended spectrum beta lactamases producers.

The anti-microbial susceptibility of the bacterial isolates was performed by the disc-diffusion (DD) comparative Kirby Bauer method following the Clinical Laboratory Standard Institute (CLSI) recommendations.[16] The medium used was Mueller Hinton Agar (Oxoid, Bashingstoke Hmsphire, UK) incubated at 35°C for 24-48 hours. The minimum inhibitory concentration (MIC) was carried out by E-test method (AB Bio Disk, 16956 Solna, Sweden). The interpretation of the susceptibility results was carried out following the CLSI recommendations for all antimicrobial agents except tigecycline where the results were interpreted according to the FDA recommendations.[1] The following were used as control organisms: *Pseudomonas aeruginosa (P. aeruginosa)* (ATCC No. 27853), *Escherichia coli (E. coli)* (ATCC No. 25922), *Enterococcus faecalis (E. faecalis)* (ATCC No. 29212), *Staphylococcus* (ATCC No. 29213), and *Klebsiella pneumoniae (K. pneumoniae)* (ATCC No. 700603).

Data were analyzed using SPSS version 12.0 (SPSS Inc. Wacker Drive, Chicago, USA) to calculate the correlation of susceptibility pattern and the type of errors of isolates tested by MIC method (E-test) and DD method. *Pseudomonas* isolates results were excluded from the analysis since these organisms are intrinsically resistant to tigecycline. Categorical agreement was defined if these results were within the same susceptibility category, and determined by method in NCCLS M23-A2 and ranked as follows: very major error, false-susceptible result by the DD test; major error, false-resistant result produced by the DD test; and minor error, intermediate result by the DD method, and a resistant or susceptible category for the E-test.

Results. The sources and identity of the gram positive organisms are shown in **Table 1**. Of the 83 gram positive isolates, the highest number (n=24) were *Methicillin sensitive staphylococcus aureus* (MSSA), 21 were *E. faecalis*, while 10 isolates were Methicillin Resistant *Staphylococcus aureus* (MRSA). Group A and Group B *Streptococci* represented 10 and 8 isolates. The major source of origin of the isolates was urine followed

by wound isolates. All these gram positive organisms were found to be susceptible to tigecycline as tested by both DD and E test method. The sources and identity of the MDR gram negative isolates are shown in **Table 2**. The majority of isolates in descending frequency were *E. coli* (n=87), *Acinetobacter species* (n=85), *P. aeruginosa* (n=34) and *Klebsiella pneumonia* (n=24). These isolates were mainly from deep respiratory sites of patients representing (n=94) isolates, followed by urine (n=84) isolates.

Table 3 decipates the activity of tigecycline in 176 MDR gram negative organisms tested by the DD method. Tigecycline was 100% active against isolates of *E. coli, K. pneumoniae, Stenotrophomonas maltiphilia* and *Enterobacter aerogenes*. It was also active against 91% of *Acinetobacter species*, 50% of *Enterobacter cloacae* and as expected only 31% of *P. aeruginosa* isolates tested were inhibited by tigecycline. As this agent is known to have less activity against these isolates.

Table 4 shows the susceptibility of the MDR gram negative isolates carried out by DD method. This is presented as diameter ranges of inhibition zones of tigecycline for 50% and 90% of isolates shown in **Table 3**. Isolates of *Serratia marcescens, chryeobacterum stenotrophomonas maltophilia* and *Proteus species* used were omitted due to the small number of these isolates encountered. The difference between the 2 ranges of diameters of 50% and 90% of isolates was obvious for the *P. aeruginosa* (14-16 mm versus 0-8 mm), *K. pneumoniae* isolates (25-26 mm versus 20-21 mm) and *Enterobacter species* isolates (20-21 mm versus 13-14 mm).

Table 5 shows the activity of tigecycline against 188 isolates of MDR gram negative organisms tested by E test method. Tigecycline was found to be 100% active against isolates of *K. pneumoniae*, *Stenotrophomonas maltophilia* and *Enterobacter cloacae*. It was also active against 98% of *E. coli* isolates and 83% active against *Acinetobacter* isolates. As expected, tigecycline was active only against 14% of the *P. aeruginosa* isolates. Of the 188 MDR isolates tested, 140 (74%) were susceptible to tigecycline, 13 (6.9%) showed intermediate susceptibility while 35 (18.6%) were resistant.

Table 6 shows the MIC 50 and MIC 90 of the MDR gram negative isolates tested by E test method as shown in **Table 5** (n=184). Isolates of *Serratia*,

Table 1 - Sources and identity of the gram positive organisms tested for tigecycline susceptibility (N=83).

Site / source	Organisms					Total
	MSSA	MRSA	GAS	GBS	*E. faecalis*	
Tissue	1	-	-	-	-	1
Blood	1	-	-	-	-	1
Abscess	5	-	2	-	-	7
Wound	7	4	-	-	2	13
Throat	1	1	6	-	-	8
Respiratory	3	2	-	-	-	5
Catheter Tip	-	1	-	-	-	1
Urine	-	-	-	16	19	35
Genital	-	-	-	4	-	4
Skin / Nose	6	2	-	-	-	8
Total	**24**	**10**	**8**	**20**	**21**	**83**

MSSA - *Methicillin Susceptible Staphylococcus aureus,* MRSA - *Methicillin Resistant Staphylococcus aureus*, GAS - *Group A B Haemolytic Streptococcus*, GBS - Group B B *Haemolytic Streptococcus*, *E. feacalis - Enterococcus feacalis*

Table 2 - The sources and identity of multidrug resistant (MDR) gram negative isolates tested for tigecycline susceptibility (N=254).

Site/ Source	*Stenotro-phomonas maltophilia*	*Escherichia coli*	*Acineto - bacter species*	*Pseudomonas aeruginosa*	*Chryseo-bacterium species*	*Klebsiella pneumoniae*	*Enterobacter species*	*Serratia*	*Proteus species*	Total
Blood	-	3	1	-	-	1	-	-	-	5
Body Fluids	2	1	2	-	-	-	-	-	-	5
Catheter site	-	2	3	-	-	-	-	-	-	5
Catheter tip	-	1	2	-	-	-	-	-	-	3
Deep resp. site	4	10	52	18	1	7	1	1	-	94
Super sw.	-	4	4	2	1	4	4	-	-	19
Tissue	1	-	-	-	-	-	-	-	-	1
Trach. site	-	-	1	1	-	-	-	-	-	2
Urine	1	56	12	4	-	8	-	2	1	84
Wound	-	10	8	9	-	4	5	-	-	36
Total	**8**	**87**	**85**	**34**	**2**	**24**	**10**	**3**	**1**	**254**

Deep resp. site - deep respiratory sites, Trach - tracheal site

Chryseobacterium and *Proteus* were excluded due to their small numbers. The difference between MIC 50 and MIC 90 was clear in *Pseudomonas* and *Acinetobacter* isolates.

Table 7 shows the comparison of results of testing of tigecycline in 109 strains carried out by both E-test and DD methods. As shown in **Table** 7, 109 isolates of the 188 tested by E-test were also tested by DD methods. The discrepancy between the 2 methods was as follows: 4 isolates which were susceptible by DD method were resistant by E-test method showing a major error of 4%. A minor error of DD intermediate susceptibility E-test resistance or susceptibility, DD susceptibility or resistant, but E-test intermediately susceptible was shown in 18 (17%) of the isolates. Therefore, there were no significant differences between the 2 methods in detecting resistance to tigecycline in MDR gram negative bacteria.

Table 3 - Activity of tigecycline against multi-drug resistant gram negative isolates tested by disc-diffusion method (N=176).

Organisms	E - test				Susceptible %
	Susceptible	Intermediate resistance	Resistant	Total	
Stenotrophomonas	37			37	100
Escherichia coli	86			86	100
Acinetobacter Species	30		3	33	91
Pseudomonas aeruginosa	5	10	1	16	31
Klebsiella pneumonia	24			24	100
Enterobacter cloacae	3	1	2	6	50
Enterobacter aerogenes	4			4	100
Total	**159**	**11**	**6**	**176**	**90**

Table 4 - Ranges of zone diameter of inhibition of tigecycline against multi-drug resistant gram negative organism in mm (N=168).

Organisms	Range zone diameter 50%	Range zone diameter 90%	Total number of isolates
Escherichia coli	25 - 26	23 - 24	86
Acinetobacter spp	21 - 22	18 - 19	32
Pseudomonas spp	14 - 16	0.0 - 8	16
Klebsiella pneumonia	25 - 26	20 - 21	24
Enterobacter species	20 - 21	13 - 14	10

Table 5 - Activity of tigecycline against multi-drug resistant gram negative isolates determined by E-test (N=188).

Isolates	Susceptible	Intermediate Resistance	Resistant	Total	Susceptibility %
Acinetobacter spp	59	10	2	71	83
Escherichia coli	52	0	1	53	98
Pseudomonas aeruginosa	4	2	28	34	14
Klebsiella pneumonia	11	0	0	11	100
Stenotrophomonas	07	0	0	07	100
Enterobacter cloacae	1	0	3	4	25
Enterobacter aerogenes	4	0	0	4	100
Chryseobacterium	0	0	1	1	-
Serratia marcescens	2	0	0	2	-
Proteus species	0	1	0	1	-
Total	**140**	**13**	**35**	**188**	

Discussion. The rapid and continuing increase of antimicrobial resistance in bacteria during the last 3 decades has become a major concern.[3] In some parts of the world, incidence of MRSA became more than 55%, that of VRE more than 27%[17] studies also showed similar increase in gram negative organisms resistance.[18] These facts necessitate testing new antimicrobial agents such as tigecycline against the widest possible range of these MDR organisms worldwide.[19] Our study similar to others,[6,20-22] aimed to test the activity of this agent against organisms isolated from hospitalized patient, which is resistant to the usually conventional used antimicrobial agents. This study has the following limitations: the susceptibility of the MDR gram negative to colistin, an important reappearing anti-microbial agent for these organisms was outdone. Similarly, susceptibility to the general used tetracycline was not carried out to compare with susceptibility of tigecycline. There was no clinical follow-up of the patients from whom these organisms were isolated. Some organisms tested, such as *Acinetobacter species* was not large enough to obtain satisfactory statistical analysis. The groups of gram positive organisms we tested included different bacterial species; namely MRSA, streptococci, enterococci are similar to other studies.[4,23,24] Likewise, in our study, the range of the gram negative organisms is also similar to other studies.[25-26] Most of gram negative and gram positive isolates were from respiratory, urine, and wound specimens. This is similar to other studies whose isolates were originated from such specimens from hospitalized patients.[28] All gram positive organisms tested were susceptible to tigecycline showing a 100% activity of tigecycline against these isolates. Results similar to these were previously reported[29] all the gram positive isolate tested in that study have MIC 90 µg/ml within the susceptibility range.[28] Our susceptibility results of *Staphylococcus aureus* both methicillin susceptible and methicillin resistant as well as *Streptococcus agalactiae* to tigecycline resembles those reported in another study were 100% of *Streptococcus agalactiae* and 94% of *Staphylococci* were susceptible to tigecycline.[4] Similar to our results, all MRSA tested in other studies were 100% susceptible to this agent.[3,20,21] The zone diameter interpretation of susceptibility used in our study for the *Enterobacteriae* was similar to that used in a previous study.[22] According to the percentage of susceptibility of isolates of *E. coli* and *K. pneumoniae*, our study was similar to other study noticed before.[21] The range of MIC 50% and 90% of the gram negative isolates tested in our study compared to previous studies MIC 50 µg/ml and 90 µg/ml,[2,6,30] showed similar results in some studies[6] for *K. pneumoniae* isolate and slightly higher results for these isolates and *E. coli* isolate in other studies.[2,30] However, the overall susceptibility in these

Table 6 - Ranges of mic 50 and mic 90 of tigecycline against multi-drug resistant gram negative organisms (N=184).

Organism	MIC 50 µg/ml	MIC 90 µg/ml	Number of isolates
Acinetobacter spp	1.0 - 1.5	3.0 - 4.0	71
Escherichia coli	0.32 - 0.38	0.75 - 1.00	53
Pseudomonas aeruginosa I	16 - 32	65 - 128	34
Klebsiella pneumonia	0.5 - 0.75	1.5 - 2.0	11
Enterobacter spp	0.75 - 1.00	4.0 - 8.4	8
Stenotrophomonas maltophilia	0.19 - 0.25	0.5 - 0.75	7

MIC - minimum inhibitory concentration

Table 7 - Comparison between result of susceptibility to tigecycline carried out by DD and E-test method on 109 MDR gram negative isolates.

Tests	Organisms										Total
	Stenotro-phomonas	*E. coli*	*Acineto-bacter spp.*	*Pseudo-monas aerug.*	*Chryseo-bacterium*	*K. pneu.*	*Enterobacter cloacae*	*Serratia marcescens*	*Proteus*	*Enterobacter aerogenes*	
Sensitivity											
Sensitive	2	51	13	1		11	1	1		4	84
Resistant											
Sensitive	-	1	1	2	-	-	-	-	-	-	4
Intermediate				10	-	-	1	-	-	-	11
Resistant				1	-	-	2	-	-	-	3
Intermediate											
Sensitive			1	1	1	-	-	-	1	-	4
Resistant											
Total	2	52	18	15	1	11	4	1	1	4	109

E. coli - Escherichia coli, K. pneu - Klebsiella pneumonia,

studies[2,6,30] was similar to our findings. *Acinetobacter species* MIC in our study was higher than that reported previously.[2,6,30-32] The susceptibility percentage in our study of these isolates was higher than that reported in these studies. For *P. aeruginosa* isolate, the MIC in our study was high indicating lower percentage of susceptibility of these isolate to tigecycline as reported in previous studies.[26,33] This findings showed beyond doubt the inactivity of tigecyline against these isolates. The MIC of *Stenotrophomonas maltophilia* in this was lower compared to those of *P. aeruginosa* isolate showing a 100% susceptibility to this agent. Similar results of such MIC were shown in previous reports.[34,35] Our results on *Acinetobacter species*,[30,32] a common hospital acquired organism in the intensive care units resembles other study.[30,32] In this study, the in-vitro activity of tigecycline was carried out by DD as in other studies[29] and MIC by E test as in others.[4] Unlike our study, none of the previous reports compared the role of both methods in detecting susceptibility to tigecycline. However, our results showed no significant difference between the 2 methods in this respect despite of the few major mistakes shown.

In conclusion, tigecycline showed 100% activity against all gram positive isolates and high activity against the most common gram negative isolates. A significant findings in this study are: all our isolates were from the intensive care units. This means that all of these isolates are from severely ill patients in whom infection and disease is expected, it is mandatory to use as empirical therapy, a drug which can cover, most of the suspected organisms. This makes tigecycline a suitable agent for this purpose. Another important result is the non-significant difference in testing for tigecycline susceptibility by either DD or E test for MIC meaning that either test can be used for this purpose. However, both methods have advantages and disadvantages, while the DD (Kirby Bauer method is well standardized, highly reproducible, simple to perform and inexpensive, it does not produce MIC results and it is not suitable for rapidly growing organisms. However, E-test method has the advantages of easiness to perform compared to the agar and dilution, MIC methodscan test fastidious bacteria and can be used with variety of test media. But, it has the disadvantage of being costly.[36]

References

1. Stein GE, Craig WA. Tigecycline: a critical analysis. ***Clin Infect*** Dis 2006; 43: 518-524.
2. Rose WE, Rybak MJ. Tigecycline: first of a new class of antimicrobial agents. ***Pharmacotherapy*** 2006; 26: 1099-110.
3. Bradford PA. Tigecycline: a first in class glycylcycline. ***Clinical Microbiology Newsletter*** 2004; 26: 21.
4. Sorlozano A, Gutierrez J, Roman E, de Dios Luna J, Roman J, Liebana J, et al. A comparison of the activity of tigecycline against multiresistant clinical isolates of Staphylococcus aureus and Streptococcus agalactiae. ***Diagn Microbiol Infect Dis*** 2007; 58: 487-489.
5. Grisold AJ, Wendelin I, Presterl E, Raggam RB, Masoud L, Badura A, et al. In vitro activity of ten antibiotics, including tigecycline, against Bacteroides species in Austria. ***Eur J Clin Microbiol Infect Dis*** 2007; 26: 525-527.
6. Souli M, Kontopidou FV, Koratzanis E, Antoniadou A, Giannitsioti E, Evangelopoulou P, et al. In vitro activity of tigecycline against multiple-drug-resistant, including pan-resistant, gram-negative and gram-positive clinical isolates from Greek hospitals. ***Antimicrob Agents Chemother*** 2006; 50: 3166-3169.
7. Wyeth Pharmaceuticals. Tygacil (tigecycline). Philadelphia (PA): Wyeth Pharmaceuticals; 2005.
8. Roblin PM, Hammerschlag MR. In vitro activity of GAR-936 against *Chlamydia pneumoniae* and *Chlamydia trachomatis*. ***Int J Antimicrob Agents*** 2000; 16: 61-63.
9. Noskin GA. Tigecycline: a new glycylcycline for treatment of serious infections. Tigecycline: a new glycylcycline for treatment of serious infections. ***Clin Infect Dis*** 2005; 41 Suppl 5: S303-S314.
10. Fritsche TR, Strabala PA, Sader HS, Dowzicky MJ, Jones RN. Activity of tigecycline tested against a global collection of Enterobacteriaceae, including tetracycline-resistant isolates. ***Diagn Microbiol Infect Dis*** 2005; 52: 209-213.
11. Sader HS, Jones RN, Stilwell MG, Dowzicky MJ, Fritsche TR. Tigecycline activity tested against 26,474 bloodstream infection isolates: a collection from 6 continents. ***Diagn Microbiol Infect Dis*** 2005; 52: 181-186.
12. Bauer G, Berens C, Projan SJ, Hillen W. Comparison of tetracycline and tigecycline binding to ribosomes mapped by dimethylsulphate and drug-directed Fe2+ cleavage of 16S rRNA. ***J Antimicrob Chemother*** 2004; 53: 592-599.
13. Fluit AC, Florijn A, Verhoef J, Milatovic D. Presence of tetracycline resistance determinants and susceptibility to tigecycline and minocycline. ***Antimicrob Agents Chemother*** 2005; 49: 1636-1638.
14. Hirata T, Saito A, Nishino K, Tamura N, Yamaguchi A. Effects of efflux transporter genes on susceptibility of *Escherichia coli* to tigecycline (GAR-936). ***Antimicrob Agents Chemother*** 2004; 48: 2179-2184.
15. Livermore DM. Tigecycline: what is it, and where should it be used? ***J Antimicrob Chemother*** 2005; 56: 611-614.
16. Clinical and Laboratory Standard Institute. Performance standards for antimicrobial suscetibility testing. Eighteenth Informations Supplement,. 9th Ed. Approved standard M100-S18. Wayned (PA): CLSI; 2008.
17. Postier RG, Green SL, Klein SR, Ellis-Grosse EJ, Loh E; Tigecycline 200 Study Group. Results of a multicenter, randomized, open-label efficacy and safety study of two doses of tigecycline for complicated skin and skin-structure infections in hospitalized patients. ***Clin Ther*** 2004; 26: 704-714.
18. Murry J, Wilson S, Klein S, Yellin A, Loe E. The clinical response to tigecycline in the treatment of complicated intra-abdominal infections in hospitalized patients, a phase 2 clinical trial abstract (L-739). Proceedings of the 3rd Inter-Science Conference on antimicrobial agents and Chemotherapy; 2003 September 14-17, Chicago, IL, USA. Washington (DC): American Society for Microbiology, 2003. p. 416.

19. Reinert RR, Low DE, Rossi F, Zhang X, Wattal C, Dowzicky MJ. Antimicrobial susceptibility among organisms from the Asia/Pacific Rim, Europe and Latin and North America collected as part of TEST and the in vitro activity of tigecycline. ***J Antimicrob Chemother*** 2007; 60: 1018-1029.
20. Denys GA, Koch KM, Dowzicky MJ. Distribution of resistant gram-positive organisms across the census regions of the United States and in vitro activity of tigecycline, a new glycylcycline antimicrobial. ***Am J Infect Control*** 2007; 35: 521-526.
21. Denis O, Deplano A, Nonhoff C, Hallin M, De Ryck R, Vanhoof R, et al. In vitro activities of ceftobiprole, tigecycline, daptomycin, and 19 other antimicrobials against methicillin-resistant Staphylococcus aureus strains from a national survey of Belgian hospitals. ***Antimicrob Agents Chemother*** 2006; 50: 2680-1685.
22. Ratnam I, Franklin C, Spelman DW. In vitro activities of 'new' and 'conventional' antibiotics against multi-drug resistant Gram negative bacteria from patients in the intensive care unit. ***Pathology*** 2007; 39: 586-588.
23. Bouchillon S, Hackel M, Johnson J, Hoban D, Johnson B, Badal R, et al. Tigecycline antibacterial activity in current (2004-2006) global population - A Gender Population Analysis - T.E.S.T. Program 2006. 17th European Congress of Clinical Microbiology and Infectious Diseases. 2007 Mar 31 04 Apr 2007; ICC, Munich, Germany. Germany: European Congress of Clinical Microbiology and Infectious Diseases; 2007.
24. Vouillamoz J, Moreillon P, Giddey M, Entenza JM. In vitro activities of tigecycline combined with other antimicrobials against multiresistant gram-positive and gram-negative pathogens. ***J Antimicrob Chemother*** 2008; 61: 371-374.
25. Morosini MI, García-Castillo M, Coque TM, Valverde V, Novais A, Loza E, et al. Antibiotic co resistance in Extended-Spectrum-B Lactamase-producing Enterobacteriaceae and in vitro activity of tigecycline. ***Antimicrob Agents Chemother*** 2006: 50: 2695-2699.
26. Kelesidis T, Karageorgopoulos DE, Kelesidis I, Falagas ME. Tigecycline for the treatment of multidrug-resistant Enterobacteriaceae: a systematic review of the evidence from microbiological and clinical studies. ***J Antimicrob Chemother*** 2008; 62: 895-904.
27. Waites KB, Duffy, LB, Dowzicky MJ. Antimicrobial susceptibility among pathogens collected from hospitalized patients in the United States and in vitro activity of tigecycline, a new glycylcycline antimicrobial. ***Antimicrob Agents Chemother*** 2006; 50: 3479-3484.
28. Anthony KB, Fishman NO, Linkin DR, Gasink LB, Edelstein PH, Lautenbach E. Clinical and microbiological outcomes of serious infections with multidrug-resistant gram-negative organisms treated with tigecycline. ***Clin Infect Dis*** 2008; 46: 567-570.
29. Brown SD, Traczewski MM. Comparative in vitro antimicrobial activity of tigecycline, a new glycylcycline compound, in freshly prepared medium and quality control. ***J Clin Microbiol*** 2007; 45: 2173-2179.
30. Fraise AP. Tigecycline: the answer to beta-lactam and fluoroquinolone resistance? ***J Infect*** 2006; 53: 293-300.
31. Hoban DJ, Bouchillon SK, Dowzicky MJ. Antimicrobial susceptibility of extended-spectrum beta-lactamase producers and multidrug-resistant Acinetobacter baumannii throughout the United States and comparative in vitro activity of tigecycline, a new glycylcycline antimicrobial. ***Diagn Microbiol Infect Dis*** 2007; 57: 423-428.
32. Pachón-Ibáñez ME, Jiménez-Mejías ME, Pichardo C, Llanos AC, Pachón J. Activity of tigecycline (GAR-936) against Acinetobacter baumannii strains, including those resistant to imipenem. ***Antimicrob Agents Chemother*** 2004; 48: 4479-4481.
33. Sader HS, Mallick R, Kuznik A, Fritsche TR, Jones RN. Use of in vitro susceptibility and pathogen prevalence data to model the expected clinical success rates of tigecycline and other commonly used antimicrobials for empirical treatment of complicated skin and skin-structure infections. ***Int J Antimicrob Agents*** 2007; 30: 514-520.
34. Betriu C, Rodríguez-Avial I, Sánchez BA, Gómez M, Picazo JJ. Comparative in vitro activities of tigecycline (GAR-936) and other antimicrobial agents against Stenotrophomonas maltophilia. ***J Antimicrob Chemother*** 2002; 50: 758-759.
35. Milatovic D, Schmitz FJ, Verhoef J, Fluit AC. Activities of the tigecyclcycline tigecycline (GAR 936) against 1,924 recent European Clinical Bacterial Isolates. ***Antimicro Agents Chemother*** 2002; 46: 400-404.
36. Murray PR, Bazon EJ, Jorgensen JH, Landry ML, Pfaller MA. Manual of Clinical Microbiology. 9th ed. USA: American Society of Microbiology; 2007.

Ethical Consent

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.