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EVALUATION OF *IN VITRO* TIGECYCLINE ACTIVITY AGAINST MULTIDRUG-RESISTANT *ACINETOBACTER BAUMANNII* CLINICAL ISOLATES FROM POLAND

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Abstract: *Acinetobacter baumannii* is a major cause of nosocomial infections worldwide. Therapeutic options in management of this bacteria are limited. Tigecycline is considered as an alternative treatment of infections caused by multidrug-resistant *A. baumannii* strains, however this resistance has emerged recently. Another growing problem is a lack of international consensus between U.S. FDA and EUCAST recommendations, regarding tigecycline breakpoints for *Acinetobacter* spp., and frequently off-label use. The aim of the present study was to assess the *in vitro* susceptibility to tigecycline and other antimicrobials, routinely used in the treatment of infections, among 155 *A. baumannii* isolates, collected between 2008-2013 from a hospital in Poland. The most active agent against the tested MDR strains was colistin (99.3% susceptible isolates). Our study has shown a low efficiency of tigecycline, with 74.2% of non-susceptible strains (according to the U.S. FDA guidelines). Tigecycline MIC values ranged from 0.125 to 48 mg/L. The MIC_{50} and MIC_{90} were 3 and 8 mg/L, respectively, and 25.8% (40) of the isolates displayed MIC = 2 mg/L. The highest percentage of tigecycline-resistant strains were noted in 2010 (56.3%). Our study revealed remarkably high tigecycline non-susceptibility rates among MDR *A. baumannii* isolates, therefore this antimicrobial should be administered with caution.

Keywords: multidrug-resistant, *A. baumannii*, tigecycline, Etest

Acinetobacter (*A.*) *baumannii* is a Gram-negative, aerobic, non-fastidious, oxidase-negative opportunistic bacterial pathogen, which has emerged as a major cause of nosocomial infections, such as pneumonia (most often ventilator-associated pneumonia, VAP), infections of the bloodstream, urinary tract, surgical sites or others occurring especially in intensive care units, critically ill or immunocompromised patients (1, 2).

Recently, an increasing number of clinically significant *A. baumannii* infections has been observed worldwide. The most important features of the bacterium are: the ability to prolonged survival in the hospital environment, a high degree of genome plasticity and, as a result, ability to rapidly acquire resistance determinants. During the last decades, *A. baumannii* resistance to most or all antimicrobial agents available for therapeutic use, has been observed. The percentage of strains non-susceptible to carbapenems, that until recently were considered as antibiotics of last-resort, increased. The carbapenem resistance phenotype has become increasingly prevalent or even (in some regions) dominant (3, 4).

Due to the increasing resistance, a group of international experts, through an initiative of the European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention, introduced terminology clearly defining multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) phenotypes of clinically relevant bacterial species. MDR was defined as acquired non-susceptibility to at least one antimicrobial agent in three or more antimicrobial categories, described by Magiorakos et al. (5). This definition covers different bacterial species, including *Acinetobacter*, of epidemiological significance, increasing antimicrobial resistance and importance within the healthcare system.

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Isolation of strains resistant to all antimicrobial agents available for the treatment, limits therapeutic options and causes high mortality of patients with *Acinetobacter* infections (6). Colistin remains active against the MDR strains of *A. baumannii*, although resistance to this agent has also been reported (7, 8). Tigecycline, belonging to a new class of antimicrobials, known as glycylcyclines, is an alternative antimicrobial to treat infections caused by the MDR *A. baumannii*, however resistance to this drug in *A. baumannii* is a rising problem (9). This agent possesses bacteriostatic activity against Gram-negative bacilli, nevertheless the susceptibility breakpoint for *Acinetobacter* spp. has not been adequately determined.

The mechanism of action of this derivative of minocycline is based on reversible binding to the 30S subunit of the bacterial ribosome, which inhibits the synthesis of amino acids. Tigecycline shows broad-spectrum activity against Gram-positive and Gram-negative bacteria, anaerobes and atypical bacteria as well as difficult-to-treat pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp., penicillin-resistant *Streptococcus pneumoniae*, MDR *Acinetobacter baumannii*, and Gram-negative bacterial strains that produce extended-spectrum β-lactamases (ESBL) (9). Minimal organ toxicity and lack of dosage adjustment in most patients are important considerations for use of this compound in infection therapy (10).

Tigecycline was initially approved by the U.S. Food and Drug Administration (FDA) in 2005, and by the European Medicines Agency in 2006 for the treatment of adults with complicated intra-abdominal infections and complicated skin and skin structure infections. In 2008, tigecycline also received FDA approval for the treatment of adult patients with community-acquired bacterial pneumonia (11). The clearest applications of tigecycline are for on-label indications, but it could be also used to treat other infections caused by multidrug-resistant pathogens. Other clinical applications for tigecycline, not currently approved by the FDA, include: hospital-acquired or ventilator-associated pneumonia, diabetic foot infections, nosocomial urinary tract infections, and bloodstream infections (10, 12, 13).

The level of resistance of *A. baumannii* to tigecycline in various regions of the world differs with the highest rates of non-susceptibility noted in MDR strains (9). In case report studies many investigators underline evolution and acquiring of resistance to tigecycline by strains recovered from patients during long-term tigecycline monotherapy (4, 14, 15).

The increasing number of serious infections caused by MDR *A. baumannii* prompted the search of a new class of antimicrobial agents as an alternative to medication with carbapenems and colistin, and as a drug of last-resort, because in the nearest future no treatment options may exist (10, 16).

The mechanism of rapid development of tigecycline resistance among MDR *A. baumannii* strains is poorly understood. Tigecycline non-susceptibility observed in *Acinetobacter* spp. clinical isolates has been associated with up-regulation of chromosomally encoded multidrug efflux system, AdeABC, belonging to the resistance-nodulation-cell division (RND) family of transporters (15, 17). The expression of the pump is regulated by two-component system, containing a sensor kinase (AdeS) and a response regulator (AdeR), encoded by the adeRS operon. Overexpression may be responsible for reducing accumulation of many antimicrobials, including aminoglycosides, fluoroquinolones, β-lactams, macrolides, chloramphenicol, tetracycline, trimethoprim, and tigecycline. Overexpression of the AdeABC efflux system can be caused by the therapeutic use of tigecycline or other antibiotics. Molecular mechanism of overexpression may be related to the ISAba-1 insertion upstream of the adeABC operon, or by point mutations in adeR and adeS genes (10, 18).

Due to the growing tigecycline resistance, monitoring of its activity against *A. baumannii* is crucial. Both global and local level surveillance, using reference and commercial methods (e.g., disk diffusion, Etest), may provide important insights into the activity of tigecycline (19).

The aim of the study was to assess the *in vitro* susceptibility of *A. baumannii* clinical isolates to tigecycline (Etest method) and to other antimicrobials (automated method), routinely used in the treatment of infections. *A. baumannii* strains were isolated from patients hospitalized in Krakow's hospital, Poland between 2008 and 2013.

MATERIALS AND METHODS

Patients and bacterial strains

The study was conducted at the Ludwik Rydygier Memorial Specialized Hospital, 700-bed, tertiary care medical center in Krakow, Poland. A total of 155 MDR *A. baumannii* clinical strains were collected from patients hospitalized in different wards of this medical center between 2008 and 2013. In particular years, various numbers of isolates were recovered: in 2008 – 15 strains, i.e. 9.7%

of the total number (155) of the examined *A. baumannii* isolates, in 2009 – 74 (47.7%), 2010 – 16 (10.3%), 2011 – 17 (11.0%), 2012 – 10 (6.5%) and in 2013 – 23 (14.8%) strains, respectively. Each strain was isolated from another patient. Multi-susceptible *A. baumannii* strains were not included to the study.

The patients enrolled in this study were treated in the following hospital units: intensive care (86; 55.5%), burn therapy (39; 25.1%), orthopedic (11; 7.1%), surgical (6; 3.9%), and others, comprising: neurology (3; 2.0%), plastic surgery (3; 2.0%), urology (2; 1.4%), hematology (1; 0.6%), cardiology (1; 0.6%), toxicology (1; 0.6%), oncology (1; 0.6%) and nephrology (1; 0.6%). Data recorded for each patient included age, sex, and type of clinical specimen. The mean patient age was 56.6 years (from 15 to 100) and 117 (75.5%) of patients were male, while 38 (24.5%) were female. Endotracheal aspirates (ETAs) (74; 47.7%;), wound swabs (31; 20.0%), blood samples (27; 17.4%), urine (17; 11.0%) and catheters (6; 3.9%) were the source of isolates. Quantitative cultures were performed for ETA and urine. Growth > 10^5 CFU/mL was taken as the threshold for microbiological diagnosis of VAP, while growth > 10^4 CFU/mL was taken as the cut-off for urine. The information concerning clinical data (e.g., antimicrobial treatment) of patients was unavailable.

Susceptibility testing methods

All the isolates were identified using Vitek 2 Compact system (bioMérieux, France). Identification was confirmed by the species-specific PCR for the $bla_{\text{OXA-51-like}}$ gene (20).

Antimicrobial susceptibility testing with determination of minimal inhibitory concentration (MIC) values for imipenem, meropenem, amikacin, gentamicin, tobramycin, ciprofloxacin and colistin was performed by using Vitek 2 Compact semiquantitative automatic system (susceptibility cards used in the study do not contain tigecycline) and interpreted according to CLSI breakpoints (21).

The susceptibility of *A. baumannii* isolates to tigecycline was determined by using the quantitative Etest method (bioMérieux, France), which measured the MIC value of the antimicrobial agent. For this purpose, the colonies from a 18-hour culture of *A. baumannii* on solid medium were suspended in 0.85% NaCl solution in order to obtain an equivalent of 0.5 McFarland units. The bacterial suspension was inoculated onto Mueller-Hinton 2 agar (bioMérieux, France). Etest® TGC (TGC – tigecycline) gradient stripes (0.016 to 256 mg/L) were placed on the agar and incubated in aerobic conditions in accordance with the manufacturer's recommendations.

Quality control was performed using *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 reference strains.

Tigecycline interpretative breakpoints for *A. baumannii*

The U.S. FDA did not approve the interpretative criteria of tigecycline for *A. baumannii in vitro* susceptibility testing, therefore the FDA recommendations of tigecycline breakpoints used for *Enterobacteriaceae* (susceptible, MIC = 2 mg/L; intermediate, MIC > 2 or < 8 mg/L; resistant, MIC = 8 mg/L) were applied as MIC interpretation criteria for *A. baumannii* (22-24).

According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) expert rules the evidence that *A. baumannii* is a good

Table 1. Antimicrobial susceptibility of 155 Acinetobacter baumannii isolates with MIC50 and MIC90 values.

Antimicrobial agent	No. (%) of isolates			MIC [mg/L]	
	R	I	S	50%	90%
Imipenem	141 (91.0)	2 (1.3)	12 (7.7)	≥ 16	≥ 16
Meropenem	144 (92.9)	1 (0.6)	10 (6.5)	≥ 16	≥ 16
Amikacin	62 (40.0)	32 (20.6)	61 (39.4)	16	≥ 64
Gentamicin	138 (89.0)	4 (2.6)	13 (8.4)	≥ 16	≥ 16
Tobramicin	62 (40.0)	60 (38.7)	33 (21.3)	8	≥ 16
Ciprofloxacin	155 (100.0)	0 (0)	0 (0)	≥ 4	≥ 4
Colistin	1 (0.6)	0 (0)	154 (99.4)	≤ 0.5	≤ 0.5

R - resistant; I - intermediate susceptible; S - susceptible

target for therapy with tigecycline is insufficient (25). The results of susceptibility testing should be reported as MIC values with a comment, but without an accompanying S, I or R category (10). According to some authors, the tigecycline MIC of *A. baumannii* were also interpreted using EUCAST categories for *Enterobacteriaceae* (susceptible, MIC = 1 mg/L; resistant, MIC > 2 mg/L) (23, 25, 26).

Due to the lack of an international consensus regarding tigecycline breakpoints for *Acinetobacter* spp., the interpretation of results obtained in our study was conducted using susceptibility breakpoints for *Enterobacteriaceae* established by the U.S. FDA and EUCAST recommendations, for comparison purpose only.

Statistical analysis

Statistical analysis was performed to determine the differences between the level of resistance to tigecycline in the years 2008-2010 and 2011-2013 and between the criteria of FDA and EUCAST. Statistical methods were also applied to compare the resistance to tigecycline of the tested organisms isolated from different clinical specimens. The Chi-square test of Independence (χ^2) alone or with Yates' correction (when expected values were less than five), or Fisher's Exact test (two-sided) were used to compare discrete variables. A p value less than 0.05 was considered statistically significant. All analyses were performed with StatsDirect, version 2.7.9 (StatsDirect Ltd., Cheshire, UK).

Ethics statement

The present study does not require an approval from the ethics committee.

RESULTS

A total of 155 *A. baumannii* strains, in accordance with expert rules described by Magiorakos et al. (5) were multidrug-resistant. Data detailing the susceptibility to all tested antimicrobial agents (except tigecycline) and the values of MIC_{50} and MIC_{90} for *A. baumannii* strains isolated between 2008 and 2013, are shown in Table 1.

Colistin was the agent which displayed a good activity (99.4% susceptible isolates) against tested MDR strains, with MIC_{90} less than 0.5 mg/L, followed by amikacin (39.4% susceptible isolates). Notably, in our study the only isolate resistant to colistin was susceptible to tigecycline with MIC 2 mg/L. A high level of carbapenem non-susceptibility was observed, with 92.9% and 91.0% of isolates resistant to meropenem and imipenem, respectively. Ciprofloxacin and gentamicin also should not be taken into account when selecting the most appropriate antimicrobial therapy, due to a high percentage of resistant strains, 100% and 89%, respectively (Table 1).

The distribution of tigecycline MIC values of *A. baumannii* is shown in Figure 1. The MIC_{50} and MIC_{90} values were 3 and 8 mg/L, respectively, with a wide MIC range of tigecycline, from 0.125 to 48 mg/L. Forty (25.8%) of the isolates displayed MIC = 2 mg/L and the MIC value most frequently observed among the tested strains, was 3 mg/L (23.2%).

MIC values for tigecycline were interpreted according to breakpoints for *Enterobacteriaceae* set by the FDA and EUCAST recommendations, for comparison purposes only (Table 2). Using FDA breakpoints it was found that 40 *A. baumannii* isolates (25.8%) were susceptible to tigecycline, while according to EUCAST interpretative criteria, only 17 strains (11.0%) were susceptible to this antimicrobial agent. On the basis of EUCAST breakpoints, a high tigecycline resistance rate of 74.2% was observed, when only 24.5% of isolates were resistant according FDA interpretation-based category. The percentage of non-susceptibility (resistant or intermediate susceptible strains) was 74.2% and 89.0% with American and European recommendations, respectively.

Table 2. Evaluation of *Acinetobacter baumannii* susceptibility to tigecycline according to EUCAST and FDA breakpoints.

Interpretation of tigecycline MIC value	Recommendation	
	EUCAST	FDA
	No. (%) of isolates	No. (%) of isolates
Resistant	115 (74.2)	38 (24.5)
Intermediate susceptible	23 (14.8)	77 (49.7)
Susceptible	17 (11.0)	40 (25.8)
Total	155 (100.0)	155 (100.0)

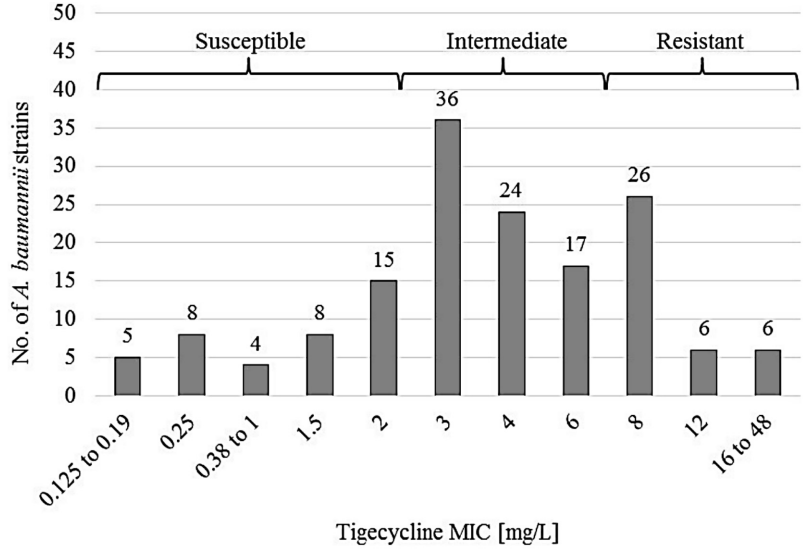

Figure 1. Distribution of tigecycline MIC values of *Acinetobacter baumannii* isolates (interpretation by FDA)

According to FDA interpretation, compared to EUCAST rules, tigecycline-resistant strains of *A. baumannii* occurred significantly less frequently in the years 2008-2010 ($p < 0.001$; statistically significant, Chi-square test of Independence) and 2011-2013 ($p < 0.001$; statistically significant, Chi-square test of Independence).

The FDA criteria were used to further analyse the occurrence of tigecycline resistance among isolates. The level of resistance to tigecycline has changed over the years covered by the study. The highest percentage of resistance among *A. baumannii* strains was noted in 2010 (56.3%), followed by 2012 (50.0%) and 2013 (30.4%). Twenty-zero eight was the year without confirmed resistant isolates and in the years 2009 and 2011 we observed resistance in 20.3% and 11.8% isolates, respectively.

The investigated period of time was divided into the years 2008-2010 and 2011-2013, when 105 and 50 strains of *A. baumannii* were isolated. Tigecycline resistance of *A. baumannii* strains in the selected years was compared with the use of the χ^2 test and an increase of resistance was demonstrated from 22.8% in the years 2008-2010 to 28.0% in the years 2011-2013, although statistically this relationship was not significant ($p = 0.487$) (Table 3).

Chi-square test or Fisher's Exact test (two-sided) were applied to compare the tigecycline resistance levels of strains isolated from wound swabs and other specimens. No statistically significant difference ($p = 0.05$) in the tigecycline resistance between isolates recovered from wound swabs and strains cultured from other clinical materials (ETA, $p = 0.714$; blood samples, $p = 0.991$; urine, $p = 0.523$; catheter, $p = 0.335$) was observed.

DISCUSSION

Non-fastidious bacilli of the species *A. baumannii* were the main cause of infections occurring in patients of the Rydygier Memorial Specialized Hospital in Krakow, Poland. Eighty six (55.5%) patients of our studied group were admitted to the intensive care unit, and endotracheal aspirates were the specimens most often taken from those subjects. It may have been associated with the development of hospital-acquired pneumonia (data not available). When a MDR *A. baumannii* strain was isolated and other treatment options were limited or unavailable, tigecycline may have been used off-label as a last-resort medication (27). Several authors have also reported the use of tigecycline in *A. baumannii* infections of respiratory tract (VAP), blood (bacteremia) and other, in which this drug was not recommended (28-31).

For the first time, tigecycline was approved in 2005, and since then, the proposed scope of its application has been extended. Moreover, it is a relatively new antibacterial agent so future modifications or other changes in the recommendations for its use may be necessary due to a growing body of experience, results of new clinical trials, evolving

epidemiological situation, and the increasing resistance of clinically relevant pathogens.

Etest was considered as a reliable method of tigecycline susceptibility testing (23, 32), although some investigators revealed that MICs obtained by this method were generally two- to fourfold higher than broth microdilution MICs among selected bacterial species (*A. baumannii*, *Serratia marcescens*, *Streptococcus pneumoniae*) (19). It is difficult to pinpoint the factors that may be affecting susceptibility testing performance against *Acinetobacter* spp., however some researchers observed that a variable concentration of manganese in Mueller Hinton 2 agar medium, used in Etest and disk diffusion method, had an impact on the tigecycline MICs against *A. baumannii* (10, 19).

Since the clinical breakpoints of tigecycline for *A. baumannii* are not available, recommendations for the use of this antibacterial agent are problematic. The lack of an international consensus and reports of increasing resistance among *A. baumannii* isolates are of growing concern (16, 33). Non-susceptibility to this glycylcycline was observed most frequently in MDR *A. baumannii* and certain species of the family *Enterobacteriaceae* (especially *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp.) (34).

Our study was restricted to the strains isolated from patients of a single tertiary hospital, therefore generalization to other clinical settings was limited. Another drawback of this study was the absence of molecular identification of isolates. Without isolate genotyping, it was difficult to determine if regional changes in MIC values were caused by local outbreaks or widespread increases in resistance in the general bacterial population (35).

Interpretation of MICs for tigecycline according to the European and American guidelines has shown a higher percentage of resistant strains with the EUCAST criteria, due to the more stringent breakpoints. Zarkotou et al. (23), who had tested tigecycline against 56 *A. baumannii* isolates by Etest, also noted the higher rates of resistant strains (17; 30.4% *versus* 6; 10.7%) and lower rates of susceptible isolates (16; 28.6% *versus* 39; 69.6%), when the EUCAST rules were applied and compared with FDA. In this Greek study, the MIC_{50} and MIC_{90} of tigecycline for MDR *A. baumannii* were reported to be 2 and 4 mg/L, respectively. Chen et al. (36) in the "Tigecycline *In Vitro* Surveillance" in Taiwan, reported higher tigecycline resistance when the EUCAST breakpoints were applied (31.9% resistant strains for EUCAST criteria compared to 8.8% for FDA criteria). Liu et al. (26) obtained similar results (39.4% compared to 9.9%, respectively). Our conclusions were comparable to both groups. Many authors based their interpretations of tigecycline MICs for *A. baumannii* on the FDA *Enterobacteriaceae* breakpoints (9, 30, 37, 38). The comparison of our results with results of other investigators was also conducted on the basis of the FDA criteria.

High rates of non-susceptibility to most antimicrobial agents of the first-line treatment options for *Acinetobacter* infections were reported for the analyzed *A. baumannii* isolates. Tigecycline and colistin, antimicrobials commonly used in therapy, still presented good activity against this microorganism (11, 35). Our study revealed that colistin could be the most appropriate regimen for the treatment of *Acinetobacter* infections. Remarkably high tigecycline non-susceptibility rates (74.2% according to FDA criteria) of *A. baumannii* clinical isolates, demonstrated in our study, suggest that tigecycline may not be an option to treat *A. baumannii* infections. Ku and coworkers (34), who compared the efficacy of colistin to tigecycline for the treatment of *A. baumannii* infections, revealed that 82% of the tested *A. baumannii* clinical isolates were non-susceptible to tigecycline. They pointed out that tigecycline monotherapy should be limited to patients without severe sepsis and that it was more commonly used for wound infections, than colistin (34). In contrast, Eser et al. (29) observed potent tigecycline *in vitro* activity (MIC_{90} 1.5 mg/L) among 32 MDR *A. baumannii* strains and its utility as a therapeutic

Table 3. Resistance to tigecycline among *Acinetobacter baumannii* strains.

Interpretative criteria	No. (%) of tigecycline-resistant *A. baumannii* strains		p value [a]
	2008-2010	2011-2013	
	n = 105	n = 50	
FDA	24 (22.8%)	14 (28%)	0.487 NS

[a] p value Chi-square test of Independence (χ^2); $p \leq 0.05$ was deemed statistically significant; NS - non significant.

option in patients with respiratory infections. Moreover, the study conducted by Anthony et al. (14) revealed, that in the group of patients with tigecycline resistant strains the mortality rate was higher than in the group from whom susceptible isolates were cultured. These data suggest that clinical outcome can be predicted by the tigecycline MIC values for *A. baumannii* determined pretherapeutically. There are many studies evaluating tigecycline susceptibility for *A. baumannii* strains. Our observations were different from those reported by other investigators, who observed tigecycline non-susceptibility in 50% of the MDR *A. baumannii* isolates in Italy (30), 45.5% in Taiwan (39), and 44% in Turkey (31). The studies on MDR *A. baumannii* conducted in Italy and Egypt reported even lower non-susceptibility rate to tigecycline of 27.5% and 26.8% isolates, respectively (37, 38).

Concerning the activity of tigecycline against MDR *A. baumannii* isolates, our results (25.8%) were similar to those reported by Navon-Venezia et al. (28), who obtained 22.0% susceptibility and Sun et al. (22), who noted 17.7% susceptibility, against the tested isolates.

In addition, the MIC_{50} and MIC_{90} for tigecycline (3 and 8 mg/L, respectively) were higher than that previously reported by other authors (11, 18, 19, 40-42), lower than those reported by Navon-Venezia et al (28) and similar to those obtained by Mohamed and Youssef (38).

The high MICs of tigecycline observed in our study differed from the previous reports in which *Acinetobacter* isolates were almost uniformly susceptible to tigecycline. It is worth noting that a Latin American global surveillance study called T.E.S.T (The Tigecycline Evaluation and Surveillance Trial) revealed good activity of this agent against *A. baumannii*, where 95.8% of the isolates displayed a MIC ≤ 2 mg/L (MIC_{50} 0.5 mg/L and MIC_{90} 2 mg/L) (43). Another study concerning *Acinetobacter* spp. strains from 32 countries showed a high activity of tigecycline which inhibited 97.0% of isolates at ≤ 2 mg/L ($MIC_{50/90}$, 0.5/2 mg/L). Over 140 strains from Poland, included in this investigation, demonstrated $MIC_{50/90}$, values as 1 and 2 mg/L, respectively (44). In a recent study (global surveillance program SENTRY), Sader and coworkers (2013) observed good activity of tigecycline among meropenem-non-susceptible *A. baumannii* isolates (89.8% and 65.2% of susceptible strains according FDA and EUCAST criteria, respectively).

The distribution of tigecycline MICs varied according to the geographic region and even within the regions (44). Discrepancies between the results of various studies may be attributed to the use of different methods of antimicrobial susceptibility assessment in either case, discordance between the methods or to variations within the analyzed population of isolates (e.g., a high percentage of clonal strains reflecting local outbreaks in institutions or cities).

The effectiveness of this glycylcycline alone or in combination with other antimicrobials for the treatment of MDR *A. baumannii* infections in critically ill patients is still uncertain, due to the lack of large, well-controlled clinical trials and extended clinical experience. The results of the present study, along with reports of decreasing susceptibility to tigecycline among *Acinetobacter* strains, suggest that antimicrobial resistance should be monitored through surveillance programs in order to detect the local, regional, and national variations in resistance patterns and to guide appropriate empirical antimicrobial therapy (6, 11).

To conclude, our results suggest that tigecycline may be of limited clinical utility for the treatment of infections involving the MDR *Acinetobacter* non-fermentative bacilli. Further investigations of *A. baumannii* isolates are required to assess the efficiency of tigecycline in the management of nosocomial infections caused by this significant pathogen. Tigecycline should be used with caution, together with monitoring of susceptibility patterns in order to delay the emergence of increased resistance in this bacteria (4, 23, 29, 43).

Conflict of interest

Conflicts of interest (financial or personal): none.

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