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REVIEW

Is Tigecycline a Good Choice in the Treatment of Multidrug-Resistant *Acinetobacter baumannii* Pneumonia?

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Summary

The aim of this study was to evaluate the efficacy of tigecycline in multidrug-resistant (MDR) *Acinetobacter baumannii* pneumonia. We retrospectively evaluated the outcome of adult patients with culture proven MDR *A. baumannii* pneumonia treated with tigecycline between January 2009 and March 2011. The study comprised a total of 72 MDR *A. baumannii* pneumonia cases (44 men, mean age 65.9±15.0). Tigecycline was used for a mean duration of 10.7±4.8 days. Microbiological eradication was observed in 47 cases (65.3%). Overall mortality was 55.5% and was lower in cases with microbiological eradication vs others (15/47 32% vs 25/25 100%, p<0.0001). Mortality and microbiological eradication rates were not different with monotherapy vs combination therapy (p>0.05). Patients who died had lower albumin levels, higher APACHE-II scores and CRP levels. The microbiological eradication rate of tigecycline in MDR *A. baumannii* was considerable. However, eradication of *A. baumannii* did not result in favorable clinical outcomes in those patients with low albumin, higher APACHE-II scores and CRP levels.

***Key words*: *A. baumannii*, multidrug resistant, pneumonia, tigecycline.**

INTRODUCTION

Nosocomial infections by multidrug-resistant (MDR) *Acinetobacter baumannii* is an increasingly important cause of mortality in intensive care units (ICU) in many countries around the world [1,2]. Efficacious treatment choices are very limited. Currently there is no universally effective antibiotic against MDR *A. baumannii*. Hence, treatment regimens are tailored according to local antibiotic resistance patterns and available antibiotics [3].

Tigecycline is a new glycylcycline antimicrobial active *in vitro* against a variety of Gram-positive and Gram-negative organisms including nosocomial MDR pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase producers and *A. baumannii*. The US Food and Drug Administration (FDA) has approved tigecycline for the treatment of complicated intra-abdominal infections, complicated skin and skin structure infections and community-acquired pneumonia [4]. However, although data regarding the efficacy of tigecycline in hospital-acquired (HAP) or ventilator-associated pneumonia (VAP) are very limited, its pharmacological and microbiological profiles encourage physicians' use of the drug in both indications caused by MDR tigecycline-sensitive pathogens featuring limited therapeutic options [5].

The aim of this study was to evaluate the microbiological and clinical efficacy of tigecycline in MDR *A. baumannii* pneumonia.

PATIENTS AND METHODS

Setting: Our setting is a tertiary-care educational hospital with >2000 beds. It is located in Izmir, which is Turkey's third largest city with a population of more than 3,700,000. The Respiratory Diseases clinic has 100 beds, eight of which are in the ICU.

Study design: This was a retrospective evaluation of clinical and microbiological outcomes in adult (>18 years old) patients with culture proven MDR *A. baumannii* pneumonia treated with tigecycline between January 2009 and March 2011 in the respiratory diseases clinic of our setting. Cases with any other concomitant nosocomial infection were excluded.

Demographic, clinical, radiological and laboratory data [complete blood count, C-reactive protein (CRP), liver and renal function tests], predisposing factors, history of hospitalization and antibiotic usage in the previous 90 days, "Acute Physiology and Chronic Health Evaluation" (APACHE) II scores, history of endotracheal intubation, re-intubation, tracheostomy, central venous catheter, fiberoptic bronchoscopy and corticosteroid consumption as well as information on length of hospital stay, concomitant antibiotic therapies, response to treatment and outcome data were obtained from each patient's hospital records.

Definitions: HAP and VAP were defined according to American Thoracic Society Guidelines 2005 [6]. Accordingly, HAP was defined as pneumonia that occured 48 hours or more after admission, which was not incubating at the time of admission. Pneumonia that occurred more than 48–72 hours after endotracheal intubation was considered as VAP. Cases who were not VAP were classified as non-VAP.

Microbiological analysis: Quantitative microbial cultures of endotracheal aspirate (Mucosafe®, Unoplast-Maersk Medical, Denmark) taken from patients with pneumonia were performed in the Clinical Bacteriology Laboratory. Concomitant blood culture was performed in all cases. In the quantitative analysis of endotracheal aspirate the cut-off value was 10^5 cfu/ml.

Identification of *A. baumannii* and determination of antimicrobial susceptibility were performed using the VITEK 2 automated system (BioMerieux Inc, Mercy L'etoil, France) and conventional methods. The following antimicrobials were tested: amikacin, netilmicin, ceftazidime, cefoperazone-sulbactam, piperacillin-tazobactam, imipenem, ciprofloxacin and tigecycline. For tigecycline susceptibility, the FDA clinical minimum

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inhibitory concentration (MIC) breakpoints for *Enterobacteriaceae* (2 mg/l--sensitive) were used. Cefoperazone/sulbactam susceptibility was analyzed via the disk diffusion test; CLSI criteria for susceptibility breakpoints for cefoperazone were used [7]. *A. baumannii* strains which were found as resistant to two or more antibiotic groups (penicillins, cephalosporins, carbapenems, aminoglycosides or quinolones) were considered as MDR.

Repeated lower respiratory system specimen analysis on days 3-7 after tigecycline therapy was performed to assess microbiological response in all patients. Microbiological response was defined as eradication of *A. baumannii* in repeated respiratory samples during or after the course of tigecycline therapy.

Clinical response: Clinical response was defined as partial or complete resolution of the symptoms and signs of infection with at least one month of *A. baumannii* pneumonia-free overall survival after the end of tigecycline treatment.

Treatment regimens: Tigecycline was administered with an initial loading dose of 100 mg, followed by 50 mg q12h. Imipenem/cilastatin, amikacin and netilmicin were intravenously given in standard dosage as 500 mg q6h, 1000 mg q24h and 300 mg q 24h, respectively. Cefoperazone/sulbactam was given as 2 g q8h, since most of the strains were intermediately-resistant. Daily hemogram and renal/liver function tests for adverse event follow-up were performed in all patients.

Patients with an *A. baumannii* strain resistant to all antibacterials but tigecycline received tigecycline as monotherapy. If there was intermediate or full susceptibility to any other antibacterial, it was combined with tigecycline.

Statistical analysis: Chi-square and Fisher's exact tests were used for categorical variables. Student's t-test was used for parametric variables. A $p < 0.05$ was considered significant.

RESULTS

A total of 72 cases (44 male, 28 female, mean age 65.9±15.0) fulfilled our inclusion criteria. The most frequent reason for hospitalization was chronic obstructive pulmonary disease (COPD), while the most frequent comorbidity was atherosclerotic heart disease (*Table 1*).

TABLE 1 - *Comorbidities and reasons of hospitalization in the study group (n=72).*

	n	%
Reasons of hospitalization		
Exacerbation of chronic obstructive lung disease	26	36.1
Hospital-acquired pneumonia	20	27.8
Community-acquired pneumonia	19	26.4
Healthcare-associated pneumonia	17	23.6
Asthma attack	3	4.2
Pulmonary embolism	3	4.2
Pulmonary tuberculosis	2	2.8
Bronchiectasis	2	2.8
Comorbidities*		
None	16	22.2
Atherosclerotic heart disease	19	26.4
Cerebrovascular disease	12	16.7
Diabetes mellitus	9	12.5
Solid tumor	8	11.1
Chronic renal failure	7	9.7
Hematologic malignity	5	6.9
Connective tissue diseases/vasculitis	3	4.2
Chronic liver disease	2	2.8

*56 cases (77.8 %) had comorbidities, 16 had two or more comorbidities

Forty-eight patients (66.7%) had a history of hospitalization, 60 (83.3%) had a history of antibiotic consumption in the previous 90 days and 13 (18.1%) had steroid consumption in the previous 30 days.

Clinical and microbiological diagnosis

Patients acquired MDR *A. baumannii* pneumonia a mean of 10.6±8.0 days after hospital admission. The mean duration of mechanical ventilation at the moment of the VAP diagnosis was 11.1±8.6 days. When *A. baumannii* was isolated from respiratory samples 47 were considered as VAP whereas 25 were considered as non-VAP.

In all cases *A. baumannii* was isolated from deep tracheal aspirate which included >25 granulocytes and <10 epithelial cells in the direct microscopy. Four cases had concomitant bacteremia.

All isolates were sensitive to tigecycline, resistant to piperacillin/tazobactam, ciprofloxacin and ceftazidime. The resistance rates for imipenem/cilastatin were 91.7%, cefoperazone/sulbactam 63.9%, amikacin 68.1% and netilmicin 54.2% (*Figure 1*).

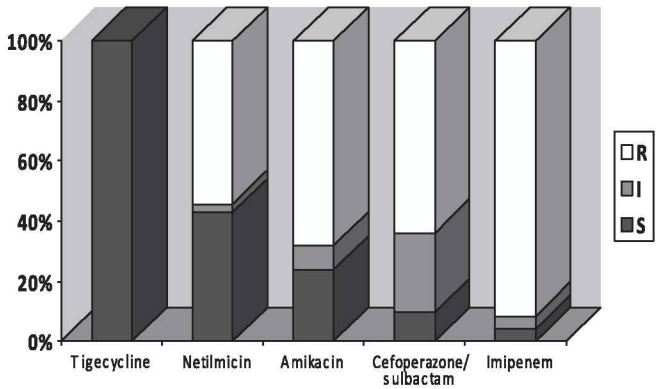

FIGURE 1 - Antibiotic susceptibility results of *A. baumannii*. All isolates were sensitive to tigecycline. The resistance rates for netilmicin, amikacin, cefoperazone and imipenem were 54.2%, 68.1%, 63.9% and 91.7% retrospectively.
Abbreviations: R= Resistant, I=Intermediate resistant, S=Sensitive

Treatment

The mean duration of tigecycline treatment was 10.7±4.8 days. Tigecycline was used as monotherapy in 23 cases. It was combined with cefoperazone/sulbactam, netilmicin and amikacin in 26, 13 and three cases, respectively. Combination arms included sensitive or intermediately-sensitive strains.

Microbiological success

Forty-seven cases (65.3%) had microbiological eradication in the control respiratory tract samples on days 3-7. There was no statistically significant difference between VAP and non-VAP cases in terms of microbiological eradication (28/47 vs 19/25, $p>0.05$).

When we analyzed monotherapy versus combination therapy there was no statistically significant difference in terms of microbiological eradication (14/23 vs 33/49, $p>0.05$). When we further analyzed combination treatment in terms of sensitivity of the combination antibiotic (sensitive vs intermediately-resistant), the microbiological eradication rate was similar in both arms. None of the patients developed tigecycline-resistant *A. baumannii* during treatment.

Clinical success and mortality

The overall one-month survival rate of our series was 46.1% (32/72). All 25 cases in whom there was no microbiological eradication died during the first month, while the mortality rate was 31.9% in patients whose germs were microbiologically eradicated (p<0.0001).

When we analyzed monotherapy versus combination therapy, there was no statistically significant difference in terms of mortality in the first month (12/23 vs 28/49, p>0.05) (*Table 2*). In addition, there was no significant difference in terms of mortality in the first month between monotherapy vs. any combination therapy group nor was there a difference between both combination arms which were sensitive vs the intermediately-sensitive combination group (p>0.05). All patients who survived were discharged from the hospital and survived at least one month after treatment.

Factors affecting microbiological eradication and mortality

Univariate analysis indicated that patients who experienced microbiological failure had lower albumin levels and hospital stay, higher mortality, CRP levels and APACHE-II scores (*Table 3*). Univariate analysis revealed that the mortality rate was higher in VAP cases vs non-VAP cases (30/47 vs 10/25, p=0.046). In addition, patients who died had lower albumin levels (2.7±0.4 vs 3.1±0.5, p=0.008), less microbiological eradication (37.5% vs 100%, p<0.0001) and less hospital stay (23.3±11.7 vs 34.2±25.0, p=0.029) and higher APACHE-II scores (21.4±4.9 vs 16.9±5.0, p<0.0001) and CRP levels (14.5±8.6 vs 10.3±7.3, p= 0.046).

Adverse effects

One patient had increased liver enzymes during tigecycline therapy which returned to normal after stopping the drug.

DISCUSSION

In this study we evaluated the outcomes of 72 MDR *A. baumannii* nosocomial pneumonia patients treated with tigecycline. The overall microbiological eradication rate was 65.3 % but one-month survival was relatively low (46.1%).

MDR *A. baumannii* is a global hospital-acquired infection problem involving pneumonia, bacteremia, urinary tract infection and meningitis--especially in patients with a history of prior antibiotic consumption or hospitalization within the past 90 days. Treatment options are limited and therapy must be tailored to the susceptibility pattern of the strain. Carbapenems, cefoperazone/sulbactam, netilmicin and colistin are among the possible treatment options. However, options are much more limited in strains resistant to cefoperazone/sulbactam, carbapenems and aminoglycosides. Colistin, which is the major treatment option in these strains, was not commercially available in Turkey during the study period. Hence, there is an obvious need for alternative treatment of MDR *A. baumannii* infections.

Tigecycline is a new and promising antimicrobial for the treatment of pneumonia. Its *in vitro* activity against MDR *A. baumannii* is favorable and its pharmacokinetics are suitable, achieving relatively high intrapulmonary concentrations [5,8]. Tigecycline has been found to have similar efficacy as levofloxacin in the treatment of community-acquired pneumonia requiring hospitalization [9]. Nevertheless, results of a phase 3 HAP or VAP study of tigecycline in which it was compared with imipenem were not sufficient for FDA approval [10]. Hence, data related to tigecycline efficacy in *Acinetobacter* HAP or VAP are limited.

The only parameter evaluated is clinical improvement in most of the studies related to MDR *A. baumannii* pneumonia. There are only a few studies which have assessed microbiological eradication rate. Schafer *et al.* evaluated the efficacy of tigecycline in 25 VAP or bacteremia cases and reported 84% clinical response [11]. They had microbiological outcome data of 15 cases and reported that 12 (80%) had microbiological response. In agreement with our results, none of the cases without microbiological response had good clinical response. Gordon *et al* reviewed 34 patients who received tigecycline for MDR *A. baumannii* or polymicrobial infection including MDR *A. baumannii* [12]. Twenty-three (68%) had a positive clinical outcome and microbiological clearance was demonstrated in 10 (30.3%) of these. Overall, the correlation between microbiological and clinical outcome was poor. They concluded that tigecycline retained excellent *in vitro* activity against MDR *A. baumannii*, but its clinical efficacy remained uncertain. In an-

TABLE 2 - *Comparison of cases received tigecycline monotherapy and combination therapy.*

	Tigecycline alone n=23	**Tigecycline and combination of any antibiotic n=49**	**p**
Age (mean ± SD)	63.2±16.0	67.2±14.4	NS
Leukocytes (/mm^3) (mean ± SD)	13154±6167	13654±7450	NS
Albumin (g/dl) (mean ± SD)	2.8±0.4	2.9±0.5	NS
C-reactive protein (CRP) (mg/dl) (mean ± SD)	12.73±7.81	12.64±8.60	NS
Re-intubation [n (%)]	3(13.0)	6(12.2)	NS
Systemic corticosteroid therapy [n (%)]	13(56.5)	21(42.9)	NS
Enteral feeding [n (%)]	13(56.5)	31(63.3)	NS
Comorbidity [n (%)]	18(78.3)	38(77.6)	NS
APACHE II (mean ± SD)	19.6±5.2	19.3±5.6	NS
Hospitalization, (days) (mean ± SD)			
ICU	21.1±16.3	17.8±21.1	NS
Hospital	29.3±16.4	27.6±20.9	NS
Microbiological eradication [n (%)]	14(60.9)	33(67.3)	NS
Mortality [n (%)]	12(52.1)	28(57.1)	NS

Abbreviations: APACHE=Acute physiology and chronic health evaluation, ICU=Intensive care unit.

TABLE 3 - *Comparison of cases with microbiological eradication and failure.*

	Microbiological eradication (n=47)	Microbiological failure (n=25)	p
Age (mean ± SD)	64.7±14.9	68.2±15.0	NS
Leukocytes (/mm^3) (mean ± SD)	13654±7772	13354±5706	NS
Albumin (g/dl)	3.0±0.5	2.7±0.4	0.036
C-reactive protein (CRP) (mg/dl) (mean ± SD)	10.49±6.79	16.84±9.37	0.003
Re-intubation [n (%)]	5(10.6)	4(16.0)	NS
Systemic corticosteroid consumption [n (%)]	22(46.8)	12(48.0)	NS
Enteral feeding [n (%)]	30(63.8)	14(56.0)	NS
Comorbidity [n (%)]	36(76.6)	22(88.0)	NS
APACHE II (mean ± SD)	18.0±5.4	22.1±4.5	0.001
VAP/HAP, (n)	28/19	19/6	NS
Tigecycline alone [n (%)]	14 (29.8)	9(36.0)	NS
Tigecycline and combination of any antibiotic [n (%)]	33(70.2)	16(64.0)	NS
Hospitalization (days) (mean ± SD)			
ICU	19.5±23.6	17.6±9.7	NS
Hospital	31.7±22.4	21.4±9.2	0.008
Mortality [n (%)]	15(31.9)	25(100)	<0.0001

Abbreviations: APACHE=Acute physiology and chronic health evaluation, VAP= Ventilator associated pneumonia, HAP= Hospital acquired pneumonia, ICU=Intensive care unit.

other study which evaluated tigecycline in 117 *A. baumannii* or multiresistant *S. aureus* (MRSA) VAP cases the overall clinical response rate was 63% [13]. In a recent study, Curcio *et al* evaluated the efficacy of tigecycline in 73 MDR *A. baumannii* VAP cases in seven Argentinian intensive care units and reported a clinical efficacy rate of 69.9% [14]. Their results suggest that tigecycline may be an acceptable alternative for therapy in patients with VAP caused by MDR-*Acinetobacter* spp. A systematic review by Karageorgopulos *et al* reports a cumulative clinical success rate of 76% in 42 MDR *A. baumannii* cases, 31 of which were VAP [15]. As stated above, the efficacy and safety of tigecycline was compared with imipenem/cilastatin in VAP and non-VAP cases [10] (including *A. baumannii*) in a phase 3 trial. Tigecycline treatment resulted in microbiological eradication in 9 of 10 non-VAP cases but in 12 of 21 VAP cases which resulted in disapproval by FDA.

In our series, there was no difference between VAP and non-VAP cases in terms of microbiological eradication (28/47 vs 19/25, p>0.05). Our microbiological success rate with tigecycline in MDR *A. baumannii* was comparable with previous studies [10,11,12]. Nevertheless, our clinical success rate was lower (46.1%). We may speculate that the lower clinical response despite positive microbiological response may have been due to high APACHE-II scores, low albumin levels and the high CRP levels of our cases. Another reason may be that none of our patients had received tigecycline empirically but only after antimicrobial susceptibility testing. This delay in administering appropriate antibiotic therapy might also have affected their clinical outcome.

There is insufficient data about the factors which effect microbiological and clinical success rate of tigecycline treatment in MDR *A. baumannii* infections. Curcio *et al* found that clinical response was lower and mortality was higher in cases with APACHE II scores of 15 or higher [13]. Similarly, in our study, APACHE II scores were inversely correlated with microbiological and clinical outcomes. In addition to these results, univariate analysis revealed that microbiological failure cases had lower albumin levels and length of hospital stay, higher mortality and CRP levels. Patients who died had lower albumin levels, microbiological eradication rate and length of hospital stay. Although relationships with APACHE II scores, CRP and albumin levels are to be expected, the decrease in the length of hospital stay is probably due to mortality which resulted in a shorter ICU stay.

In our study, tigecycline was used as monotherapy in 23 patients and was combined with an antibiotic in 49 patients. There was no significant difference in microbiological and clinical success between the two groups. In the study conducted by Schafer *et al*, tigecycline was found to be effective in most of 25 cases when used alone or in combination with other antimicrobials for VAP and/or bacteremia caused by MDR *A. baumannii* [11]. Poulakuo *et al* evaluated the efficacy of tigecycline alone and in combination with other antimicrobials in 18 cases of VAP, 15 of which were related to *A. baumannii* [16]. They reported that nine cases who received monotherapy had 77% clinical response and nine cases who had combination therapy had 100% clinical response. However, in this study the number of patients was so low that the clinical response rates were not statistically significant.

Our study is limited by its retrospective design, relatively small number of cases and the lack of any pharmacokinetic and pharmacodynamic data as we were unable to measure tigecycline levels. In addition since autopsy could not be performed, definite reasons for mortality could not be delineated. However, to our knowledge this is the largest single center series evaluating the microbiological and clinical efficacy of tigecycline in *A. baumannii* VAP and non-VAP and comparing tigecycline monotherapy with combination therapy.

In conclusion, our findings show that the microbiological eradication rate of tigecycline in MDR *A. baumannii* was considerable and seemed a prerequisite for a chance of cure. However, this microbiological success did not result in a favorable clinical outcome in those patients with low albumin levels, high

APACHE-II scores and CRP levels. Thus, physicians caring for patients with MDR *A. baumannii* pneumonia should pay attention to those factors. Finally, when compared with monotherapy, combination therapy did not achieve higher clinical and microbiological response.

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REFERENCES

[1] Perez F, Hujer AM, Hujer KM, Decker BK, Rather PN, Bonomo RA. Global challenge of multidrug-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother. 2007;51(10): 3471-84

[2] Alp E, Yerer M, Kocagoz S, Metan G, Esel D, Gurol Y, et al. The risk factors and spread of multidrug-resistant *Acinetobacter baumannii* in intubated patients in a medical intensive care unit. Turk J Med Sci 2009; 39: 761-769

[3] Tasbakan MS, Pullukcu H, Ekren PK, Oz AT, Midilli M, Aydemir S, et al. Colistin use in ventilator-associated pneumonia due to panresistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Mikrobiyol Bul. 2009;43(1):61-70

[4] Pankey G.A. Tigecycline. J Antimicrob Chemother. 2005; 56, 470-80.

[5] Curcio D, Fernández F, Cané A, Barcelona L, Stamboulian D. Indications of a new antibiotic in clinical practice: results of the tigecycline initial use registry. Braz J Infect Dis. 2008; 12, 198-201.

[6] American Thoracic Society: Hospital-acquired, Ventilator-associated and Healthcare- associated Pneumonia. Am J Respir Crit Care Med. 2005;171, 388-416.

[7] Clinical and Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing, 15th Information Supplement, Document M100-A15, CLSI, Wayne, Pa, 2005.

[8] Curcio D, Fernández F, Duret F. Initial use of tigecycline in Argentina. Rev. Chilena Infectol. 2007;24, 497-499.

[9] Falagas ME, Metaxas El. Tigecycline for the treatment of patients with community-acquired pneumonia requiring hospitalization. Expert Rev Anti Infect Ther. 2009;7(8):913-23.

[10] Freire AT, Melnyk V, Kim MJ, Datsenko O, Dzyublik O, Glumcher F, et al Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. Diagn Microbiol Infect Dis. 2010; 68(2): 140-51.

[11] Schafer JJ, Goff DA, Stevenson KB, Mangino JE. Early experience with tigecycline for ventilator-associated pneumonia and bacteremia caused by multidrugresistant *Acinetobacter baumannii*. Pharmacotherapy. 2007; 27, 980-987.

[12] Gordon NC, Wareham DW. A review of clinical and microbiological outcomes following treatment of infections involving multidrug-resistant *Acinetobacter baumannii* with tigecycline. J Antimicrob Chemother. 2009;63(4):775-80.

[13] Curcio D, Castagnino J, Vazquez W, Vergara G, Curiale A; Latin American Tigecycline Use Registry for Ventilator Associated Pneumonia (LatinVAP). Tigecycline in the treatment of ventilator-associated pneumonia: experience from the Latin American Tigecycline Use Registry. Infez Med. 2010;18(1):27-34

[14] Curcio D, Fernández F, Vergara J, Vazquez W, Luna CM. Late onset ventilator-associated pneumonia due to multidrug-resistant *Acinetobacter* spp.: experience with tigecycline. J Chemother 2009; 21: 58-62.

[15] Karageorgopoulos D, Kelesidis T, Kelesidis I, Falagas ME. Tigecycline for the treatment of multidrug-resistant (including carbapenem resistant) *Acinetobacter* infections: a review of the scientific evidence. J Antimicrob Chemother. 2008; 62: 45–55.

[16] Poulakou G, Kontopidou FV, Paramythiotou E. Tigecycline in the treatment of infections from multi-drug resistant gram-negative pathogens. J Infect 2009;58: 273 -284.