

1-1-2008

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ESRAGÜL AKINCI

İPEK MUMCUOĞLU

PINAR ÖNGÜRÜ

F. NURHAYAT BAYAZIT

SEVİNÇ ERSOY ŞEN

*See next page for additional authors*

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### Recommended Citation

AKINCI, ESRAGÜL; MUMCUOĞLU, İPEK; ÖNGÜRÜ, PINAR; BAYAZIT, F. NURHAYAT; ŞEN, SEVİNÇ ERSOY; ERBAY, AYŞE; BALABAN, NERİMAN; and BODUR, HÜRREM (2008) "In Vitro Activity of Tigecycline Against *Acinetobacter baumannii* Strains Isolated From Nosocomial Infections," *Turkish Journal of Medical Sciences*: Vol. 38: No. 6, Article 13. Available at: <https://journals.tubitak.gov.tr/medical/vol38/iss6/13>

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### Authors

ESRAGÜL AKINCI, İPEK MUMCUOĞLU, PINAR ÖNGÜRÜ, F. NURHAYAT BAYAZIT, SEVİNÇ ERSOY ŞEN, AYŞE ERBAY, NERİMAN BALABAN, and HÜRREM BODUR

## In Vitro Activity of Tigecycline Against *Acinetobacter baumannii* Strains Isolated From Nosocomial Infections

Esragül AKINCI<sup>1</sup>  
İpek MUMCUOĞLU<sup>2</sup>  
Pınar ÖNGÜRÜ<sup>1</sup>  
F. Nurhayat BAYAZIT<sup>1</sup>  
Sevinç ERSOY ŞEN<sup>1</sup>  
Ayşe ERBAY<sup>1</sup>  
Neriman BALABAN<sup>2</sup>  
Hürrem BODUR<sup>1</sup>

**Aims:** *Acinetobacter* species usually affect hospitalized patients and are involved in many infections associated with a high mortality rate. Management of infections caused by these strains is very difficult, as the strains often display multiple drug resistance, including carbapenem resistance. Tigecycline is the most recently developed semi-synthetic broad spectrum glycylyccline antibiotic. The present study was conducted to evaluate the in vitro susceptibility of *Acinetobacter baumannii* strains isolated from the hospitalized patients to tigecycline.

**Materials and Methods:** *Acinetobacter* isolates were collected from hospitalized patients with documented nosocomial infections between June 2005 and October 2006. Only one isolate per patient was accepted. Minimum inhibitory concentrations (MICs) were determined by E-test against tigecycline and other frequently used antibiotics.

**Results:** Overall, 98 *A. baumannii* isolates were collected from the cultures of nosocomially infected patients. Tigecycline was the most active agent against *A. baumannii* isolates among those tested, followed by netilmicin. MIC values of tigecycline were  $\leq 2$   $\mu\text{g/ml}$  for 79 (80.6%) of the strains.

**Conclusions:** Tigecycline may have an important role in the treatment of nosocomial infections with multidrug-resistant *Acinetobacter* isolates, for which there are limited choices available for treatment.

**Key Words:** Tigecycline, *Acinetobacter*, antibiotic, resistance

<sup>1</sup> Department of Clinic of Infectious Diseases and Clinical Microbiology, Ankara Numune Education and Research Hospital, Ankara - TURKEY

<sup>2</sup> Department of Microbiology and Clinical Microbiology, Ankara Numune Education and Research Hospital, Ankara - TURKEY

### Nozokomiyal İnfeksiyonlardan İzole Edilen *Acinetobacter baumannii* İzolatlarında Tigesiklinin İn Vitro Duyarlılığı

**Problem:** *Acinetobacter* suşları sıklıkla hastanede yatan hastalarda yüksek mortalite oranı ile seyreden infeksiyonlara neden olur. Bu suşların meydana getirdiği infeksiyonların tedavisi çok güçtür ve bu suşlar sıklıkla karbapenem direnci de dahil olmak üzere çoklu dirençlidirler. Tigesiklin son yıllarda geliştirilen, geniş spektrumlu, semisentetik bir glisiklin antibiyotiktir. Bu çalışma, hastanede yatan hastalardan izole edilen *Acinetobacter baumannii* suşlarında in vitro tigesiklin duyarlılığını değerlendirmek için yapılmıştır.

**Materyal ve Metod:** Çalışmada Haziran 2005 - Ekim 2006 tarihleri arasında hastane infeksiyonu dokümanite edilen hastalardan izole edilen *Acinetobacter* suşları toplandı. Her bir hasta için sadece tek bir suş alındı. E-test ile tigesiklin ve diğer sık kullanılan antibiyotiklere karşı minimum inhibitör konsantrasyonları (MİK) belirlendi.

**Bulgular:** Hastane infeksiyonu olan hastaların kültürlerinden toplam 98 *A. baumannii* izolatu toplandı. *A. baumannii* suşlarına karşı tigesiklin en etkili antibiyotik idi. Bunu netilmisin izledi. Tigesiklin MİK değeri 79 (% 80.6) izolat için  $\leq 2$   $\mu\text{g/mL}$  olarak bulundu.

**Sonuç:** Sınırlı tedavi seçeneği olan çoklu dirençli *Acinetobacter* izolatlarının neden olduğu infeksiyonların tedavisinde tigesiklin önemli bir rol oynayabilir.

**Anahtar Sözcükler:** Tigesiklin, *Acinetobacter*, antibiyotik, direnç

Received: September 21, 2007  
Accepted: September 03, 2008

#### Correspondence

Esragül AKINCI  
Department of Clinic of Infectious Diseases and Clinical Microbiology  
Ankara Numune Education and Research Hospital,  
Ankara - TURKEY

esragulakinci@yahoo.com

#### Introduction

*Acinetobacter* species usually affect hospitalized patients and are involved in many infections associated with a high mortality rate. Management of these infections is complicated by the emergence of strains resistant to most available antimicrobial agents, including carbapenems.

Tigecycline is the most recently developed semi-synthetic broad spectrum glycylyccline antibiotic. It has activity against a wide range of Gram-negative, Gram-positive and anaerobic bacteria, including strains with well-defined resistance

mechanisms. Tigecycline possesses activity against clinical isolates resistant to tetracyclines and multidrug-resistant pathogens. It has a different mechanism of interaction with the bacterial ribosome, which differentiates tigecycline from the structurally related tetracyclines and contributes to the enhanced clinical effectiveness of this agent (1,2).

The present study was conducted to evaluate the *in vitro* susceptibility of *Acinetobacter baumannii* strains isolated from hospitalized patients to tigecycline and compare with the susceptibility to the other most commonly used antimicrobial agents.

## Materials and Methods

*Acinetobacter* isolates were collected from hospitalized patients with documented nosocomial infections between June 2005 and October 2006. Only one isolate per patient was accepted. Identification of *A. baumannii* strains was made by Gram stain, oxidase test and Vitek 2 GN (bioMerieux/France) system.

Minimum inhibitory concentrations (MICs) were determined by E-test (AB Biodisk, Sweden) according to the manufacturer's recommendations. Mueller-Hinton medium was used for antimicrobial susceptibility tests and the plates were incubated at 5% CO<sub>2</sub> for 24 hours. Antimicrobial agents tested were ampicillin-sulbactam, amikacin, netilmicin, imipenem, ciprofloxacin, cefepime, trimethoprim-sulfamethoxazole, and tigecycline. Evaluation of MIC values was made according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (3). Susceptible break points of  $\leq 2$   $\mu\text{g/ml}$  for tigecycline were applied as approved by the United States Food and Drug Administration (FDA) (Tygacil, 2005) and as published in previous studies (4,5). Quality control was performed using *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* 27853 strains.

## Results

Overall, 98 *A. baumannii* isolates were collected from the cultures of nosocomially infected patients (Table 1). All of the strains were resistant to more than three antibiotics (multidrug-resistant) and 56 (57.1%) were resistant to imipenem (MIC  $>32$   $\mu\text{g/ml}$ ). Forty-four (78.6%) of the imipenem-resistant strains were susceptible to tigecycline (MIC  $\leq 2$   $\mu\text{g/ml}$ ). Tigecycline was

Table 1. Isolation sites of *Acinetobacter baumannii* strains.

Site of isolation	Number
Wound	34
Blood	33
Deep endotracheal aspirate	15
Urine	12
Sterile body fluids	4

the most active agent tested against *A. baumannii* isolates, followed by netilmicin (Table 2). MIC values of tigecycline were  $\leq 2$   $\mu\text{g/ml}$  for 79 (80.6%) of the strains (Table 3).

## Discussion

Resistance rates are high among the *Acinetobacter* species isolated from nosocomially infected patients. Recent surveillance studies have shown that the isolates of *A. baumannii* complex are increasingly resistant to cephalosporins, aminoglycosides, fluoroquinolones and carbapenems (6-8). During the past five years, the incidence of nosocomial *A. baumannii* infections appears to have increased, and surveillance studies suggest that highly resistant strains of *A. baumannii* are particularly prevalent among intensive care unit (ICU) patients (1). Management of infections caused by these strains is very difficult, as the strains often display multiple-drug resistance, including carbapenem resistance. In our hospital, most of the *Acinetobacter* strains are multidrug-resistant and carbapenem resistance rate is high (9,10). Infections with these multidrug-resistant pathogens adversely affect the clinical outcomes and treatment of infections. Thus, new agents to treat these infections are needed.

Tigecycline is a broad-spectrum glycylycine antimicrobial agent, which acts by binding to the 30S ribosomal subunit. Many other antimicrobial classes, such as aminoglycosides, macrolides, streptogramins and oxazolidinones, act in similar way. Tigecycline, however, overcomes the main types of genetic mechanisms primarily responsible for clinical resistance to these compounds. The glycylycines inhibit protein synthesis in wild-type ribosomes, as well as TetM-protected and tet-R ribosomes, and bind five-fold more strongly to the ribosomes than tetracycline and minocycline. It is likely that this enhanced binding is responsible for overcoming

Table 2. Antimicrobial susceptibility to tigecycline and other antibiotics of 98 *Acinetobacter baumannii* strains isolated from nosocomially infected patients.

Antimicrobial agents	Range	MIC ( $\mu\text{g/ml}$ )		Susceptibility n (%)
		MIC <sub>50</sub>	MIC <sub>90</sub>	
Tigecycline	0.016 - 50	1	4	79 (80.6)
Imipenem	0.016 - >32	>32	>32	42 (42.9)
Ciprofloxacin	0.0125 - >32	>32	>32	14 (14.3)
Netilmicin	0.023 - 64	4	16	77 (78.6)
Amikacin	0.094 - >256	>256	>256	29 (29.6)
Cefepime	1 - >256	24	>256	18 (18.4)
TMP/SMZ	0.016 - >32	>32	>32	25 (25.5)
Ampicillin/sulbactam	0.125 - >256	16	>256	38 (38.8)

TMP/SMZ: Trimethoprim sulfamethoxazole.

Table 3. MIC ( $\mu\text{g/ml}$ ) values of tigecycline against 98 *Acinetobacter baumannii* strains.

MIC ( $\mu\text{g/ml}$ )	Number of isolates (%)
$\leq 2$	79 (80.6)
3	7 (7.2)
4	9 (9.2)
16	1 (1)
32	1 (1)
50	1 (1)

the ribosomal protection mechanism of tetracycline resistance (1,8). The most significant characteristic of tigecycline is its activity against resistant Gram-positive bacteria such as penicillin-resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* and many species of multidrug-resistant Gram-negative bacteria, including *Acinetobacter* species (2).

In the present study, tigecycline was the most active agent against multidrug-resistant *A. baumannii* strains. MIC<sub>50</sub> and MIC<sub>90</sub> values were 1 and 4  $\mu\text{g/ml}$ , respectively. Several studies have tested the *in vitro* activity of tigecycline against *Acinetobacter* species and reported good antimicrobial activity (4,8,11). In a multicenter trial, tigecycline was detected as 8- to 128-fold more active than other agents against *Acinetobacter* species,

and tigecycline MIC<sub>50</sub> and MIC<sub>90</sub> results of 0.5 and 1.0  $\mu\text{g/ml}$  were obtained for *A. baumannii* isolates (11). In another study, activity of tigecycline was tested against nosocomial *Acinetobacter* species from patients hospitalized in the ICU, and it was detected as the most active (MIC<sub>50</sub>: 1  $\mu\text{g/ml}$ , MIC<sub>90</sub>: 2  $\mu\text{g/ml}$ , MIC range: 0.06-8  $\mu\text{g/ml}$ ) compound (8).

Carbapenem-resistant *A. baumannii* was first reported in 1991. Since that time, several carbapenem-resistant isolates have been reported worldwide (7,12). In 1998, Pandrug-resistant *A. baumannii* was recorded in Taiwan (13). Over the past few years, many of the agents currently used to treat nosocomial infections have failed in the treatment of these resistant strains (14). In the present study, 78.6% of imipenem-resistant isolates were susceptible to tigecycline. In another study, tigecycline exhibited good *in vitro* activity (MIC  $\leq 2$   $\mu\text{g/ml}$ ) in 42% of imipenem-resistant *A. baumannii* strains (4).

There are some clinical studies showing good efficacy and safety of tigecycline (2,15,16). In one case report, a patient with septic shock due to pan-drug-resistant *A. baumannii* was successfully treated with a combination of antibiotics including tigecycline (17).

In conclusion, tigecycline may have an important role in the treatment of nosocomial infections with multidrug-resistant *Acinetobacter* isolates, for which there are limited treatment choices available.

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