



# Five-Years Tigecycline Experience an Analysis of Real-Life Data

## Beş Yıllık Tigesiklin Deneyimi Gerçek Yaşam Verilerinin Bir Analizi

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### Abstract

**Aim:** Tigecycline has been approved by the Food and Drug Administration for the treatment of complicated intra-abdominal infections, skin and soft tissue infections and community-acquired pneumonia. In our study, we examined the efficacy of tigecycline in clinical practice and reported real life data from our hospital over a period of five years.

**Methods:** The study was conducted between 2008 and 2013 on patients who received tigecycline for longer than 48 hours in Ankara Training and Research Hospital. Clinical success was defined as clinical recovery and microbiological cure in patients who used tigecycline. Any reason for discontinuation of tigecycline treatment was considered a clinical failure.

**Results:** In our hospital, 320 patients were administered tigecycline between 2008 and 2013. Tigecycline was mainly used for pneumonia and skin and soft tissue infections. Tigecycline was used as monotherapy in 174 patients (54.1%). The most frequently isolated agent in tigecycline-treated patients was *Acinetobacter baumannii* (43.4%) followed by *Enterococcus* (6.9%). A change in treatment was not considered necessary in 243 (75.9%) patients who received tigecycline, while it was changed in 77 patients (24.1%).

**Conclusion:** In conclusion, the use of tigecycline can be an effective treatment choice, either as monotherapy or as a combination antibiotic therapy.

**Keywords:** Tigecycline, real life data, minocycline

### Öz

**Amaç:** Komplike intraabdominal enfeksiyonlar, deri ve yumuşak doku enfeksiyonları ve toplum kökenli pnömoni tedavisi için Tigesiklin kullanımına Gıda ve İlaç Dairesi tarafından onay verilmiştir. Çalışmamızda; beş yıllık süreçte hastanemiz bünyesinde tigesiklin kullanımının klinik pratikteki yeri irdelenmiş ve gerçek yaşam verileri sunulmuştur.

**Yöntemler:** Çalışma, 2008 ve 2013 yılları arasında, Ankara Eğitim ve Araştırma Hastanesi'nde, 48 saatten daha uzun süre ile tigesiklin kullanılan hastaların verileri retrospektif olarak değerlendirilmiştir. Klinik başarı, tigesiklini tek başına veya kombinasyonda kullanan hastaların tümünde klinik iyileşme ve mikrobiyolojik kür sağlanması olarak tanımlanmıştır. Herhangi bir nedenle tigesiklin tedavisinin kesilmesi klinik başarısızlık olarak tanımlanmıştır.

**Bulgular:** Hastanemizde, 2008-2013 tarihleri arasında 320 hastaya tigesiklin kullanılmıştır. Tigesiklin en sık pnömoni ve deri-yumuşak doku enfeksiyonlarının tedavisinde kullanılmıştır. Hastaların 173'ünde (%54,1) monoterapi olarak kullanılmıştır. Hastalarda en sık izole edilen etken *Acinetobacter baumannii* olup (%43,4), ikinci sıklıkta *Enterococcus* izole edilmiştir (%6,9). Tedavi alan hastaların 243'ünde (%75,9) tedavi değişikliğine gerek görülmemiş olup 77 hastada (%24,1) tedavi değiştirilmiştir.

**Sonuç:** Sonuç olarak, çoğul dirençli bakteri enfeksiyonlarının tedavisinde, monoterapi ya da kombinasyon olarak kullanıldığında tigesiklin bir seçenek olarak düşünülmelidir.

**Anahtar Sözcükler:** Tigesiklin, gerçek yaşam verisi, minosiklin

### Introduction

Tigecycline, a derivative of minocycline, is the first glycylicline antibiotic approved by the US Food and

Drug Administration (FDA). It shows structural similarities to tetracycline. Tigecycline reversibly binds to the 30S ribosomal subunit and thereby inhibits protein synthesis

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(1,2). This drug can bypass the two significant resistance mechanisms of tetracycline. The first one is the tetracycline-specific efflux pump mechanism, for which tigecycline serves as a poor substrate. The second resistance mechanism is the Tet(M) protein-mediated modification that inhibits binding of tetracycline, but allows binding of tigecycline to the bacterial ribosomes (3).

Tigecycline is bacteriostatic in nature; however, reports of bactericidal activity have been demonstrated against certain microorganisms (4,5). It has a broad clinical spectrum of activity against many gram-negative bacteria such as those of *Enterobacteriaceae* family, including extended-spectrum-beta-lactamase-producing *Enterobacteriaceae*, and against many multi-drug resistant strains of Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis*, penicillin-resistant *Streptococcus pneumoniae* and vancomycin-resistant *Enterococcus*. Also, tigecycline has an improved activity *in vitro* against *Enterobacter*, *Acinetobacter* and *Stenotrophomonas maltophilia* strains. However, it has no *in vitro* efficiency against *Proteus* spp., *Providencia* spp. and non-fermentative *Pseudomonas*

*aeruginosa*. Tigecycline is very effective against anaerobic bacteria such as *Bacteroides* spp., including *B. fragilis*, *B. Thetaiotaomicron* and *B. Uniformis*, with some exceptions like *Clostridium perfringens* and *Clostridium difficile* (6-10).

Tigecycline has been approved by the FDA for the treatment of complicated intra-abdominal infections, skin and soft tissue infections and community-acquired pneumonia (11,12). However, information concerning the role of tigecycline in community-acquired pneumonia, ventilator-associated pneumonia, urinary infections, central nervous system infections, and bone infections is limited.

In our study, we examined the efficacy of tigecycline in clinical practice and reported real life data from our hospital over a period of five years.

### Methods

A retrospective study was conducted by the department of infectious diseases and clinical microbiology at a 650-bed training and research hospital in Ankara, located in the capital city of Turkey. The study was conducted between

**Table 1. Patient demographics, comorbidities and clinical characteristics at baseline**

Patient demographics	Total population	Patients with treatment on ICU	Patients with treatment outside ICU
	320	163	157
<b>Demographic characteristics</b>			
Male, % (n)	47.5% (152)	46.0% (75)	49.0% (77)
Age, mean years ± SD (range)	59.5±19.2 (17-97)	62.9±19.8 (18-97)	56.1±18 (17-95)
<b>Clinical characteristics</b>			
Duration of tigecycline therapy	10.6±6.6 days (range, 2-35).	10.87±7 days (range, 2-35)	10.5±6.5 days (range, 2-30)
Empiric use % (n)	35.6% (114)	25.8% (42)	45.9% (72)
Combination of antibiotics, % (n)	45.9% (147)	59.5% (97)	31.8% (50)
<b>Type of infections</b>			
Community-acquired pneumonia	4.6% (15)	6.1% (10)	3.1% (5)
Hospital-acquired pneumonia	25% (80)	47.8% (78)	1.2% (2)
Complicated skin and soft tissue infection	25% (80)	8.6% (14)	42.0% (66)
Intraabdominal infection	14.7% (47)	11.0% (18)	18.5% (29)
Surgical site infections	10.0% (32)	5.5% (9)	14.6% (23)
Urinary tract infection	9.4% (30)	9.8% (16)	8.9% (14)
Intravascular catheter-related infections	4.4% (14)	6.1% (10)	2.5% (4)
Osteomyelitis	3.8% (12)	0.0% (0)	7.6% (12)
Blood stream infection	1.6% (5)	2.5% (4)	0.6% (1)
Meningitis	0.9% (3)	1.2% (2)	0.6% (1)
Prosthetic joint infections	0.6% (2)	0.0% (0)	1.3% (2)
SD: Standard deviation, ICU: Intensive care unit			

2008 and 2013 on patients who received tigecycline for longer than 48 hours in the hospital. All patients in the study received tigecycline doses recommended by the FDA (an initial loading dose of 100 mg, followed by 50 mg administered intravenously every 12 hours). All data were acquired by scanning the hospital database and patient files. Patients' age, gender, ward type (clinic or intensive care), indication for tigecycline use, microbiological diagnosis, treatment modifications, combination antibiotic therapy, and clinical responses were recorded.

Clinical success was defined as clinical recovery and microbiological cure in patients who used tigecycline, alone or in combination. Any reason for discontinuation of tigecycline treatment was considered a clinical failure.

### Statistical Analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) version 23 software program.

### Results

In our hospital, 320 patients were administered tigecycline for more than 48 hours, between 2008 and 2013. Of these, 168 patients were female (52.5%) and 152 patients were male (47.5%). The average age of the patients was 59.6±19.22 (19-97) years. The average duration of tigecycline treatment was 10.6±6.6 days (2-35). The demographic and clinical characteristics of the patients and treatment indications are listed in Table 1.

Although tigecycline was mainly used for pneumonia indication, the other most common indications included complicated skin and soft tissue infections, and also intra-abdominal infections (Table 2).

Indications for tigecycline use, duration of treatment and clinical response rates are given in the ratio of tigecycline use and clinical effectiveness, in intensive care and non-intensive care units, are given in Table 3.

Tigecycline was used as monotherapy in 174 patients (54.1%), while it was used in combination with another antibiotic in 147 patients (45.9%). The most preferred combination agents were aminoglycosides, and the most common indication for combination therapy was pneumonia. A list of preferred agents for combination therapy is shown in Table 4.

The most frequently isolated agent in tigecycline-treated patients was *Acinetobacter baumannii* (43.4%) followed by *Enterococcus* (6.9%). In many cases, some form of the empirical treatments (36.6%) was already started before the tigecycline treatment. The distribution of the isolated agents is shown in Table 5.

A change in treatment was not considered necessary in 243 (75.9%) patients who received tigecycline, while the treatment was changed in 77 patients (24.1%). This treatment change was due to unresponsiveness and side effects in 85.7% (66/77 and 20.6% of the total population) and 14.3% of the treated patients, respectively. Side effects that required treatment change were nausea/vomiting in 10 patients and an allergic reaction in one patient.

**Table 2. Type of infections, duration of treatment and clinical efficacy of tigecycline**

Type of infections	n (%)	Duration of treatment days mean	Clinical efficacy n (%)	Clinical failure n (%)
Hospital-acquired pneumonia	80 (25)	11.6±7.0	13 (16.2)	67 (83.7)
Community-acquired pneumonia	15 (4.6)	7.1±5.7	7 (46.7)	8 (53.3)
Complicated skin and soft tissue infections	80 (25)	11±7.9	50 (62.5)	30 (37.5)
Intraabdominal infections	47 (14.7)	10.1±6.6	28 (59.5)	19 (40.5)
Surgical site infections	32 (10)	10.3±6.2	23 (71.8)	9 (28.2)
Urinary tract infection	30 (9.4)	9.3±5.7	15 (50)	15 (50)
Catheter infections	14 (4.4)	9.2±7.3	5 (35.7)	9 (64.3)
Osteomyelitis	12 (3.8)	13.5±9.7	9 (75)	3 (25)
Bloodstream infections	5 (1.6)	17.6±3.7	0	5 (100)
Meningitis	3 (0.9)	7±2	1 (33.3)	2 (66.6)
Prosthetic joint infections	2 (0.6)	15.5±2.1	2 (100)	0
Total	320 (100)	10.6±6.6	153 (47.8)	167 (52.2)

**Table 3. Duration of treatment and clinical efficacy of tigecycline according to type of unit**

Type of unit	n (%)	Duration of treatment, days mean	Clinical efficacy n (%)	Clinical failure n (%)
Intensive care unit	163 (50.9)	10.8±6.9	34 (20.9)	129 (79.1)
Non- intensive care unit	157 (49.1)	10.4±6.4	119 (75.8)	38 (24.2)

## Discussion

In this analysis, we presented real life data of 320 patients who received tigecycline over a five-year period. Tigecycline is used for many indications other than those approved by the FDA. The rate of tigecycline use was 54.3% for the FDA approved indications, namely complicated skin and soft tissue infections (including surgical site infection), complicated intra-abdominal infections, and community-acquired pneumonia. Skin and soft tissue infections were the most common among these indications. The FDA and European Medicines Agency have reported a high mortality rate among patients treated with tigecycline in clinical trials

(13,14). Due to its benefits and effectiveness, one must consider the risk-benefit ratio for tigecycline use, especially in resistant bacteria. Tigecycline has been used for many indications besides the FDA approved one. Although real life data about its use are limited, some studies involving intensive care patients have suggested promising results with tigecycline treatment (15,16). In this study, ventilator-associated pneumonia in intensive care patients was one of the most common causes of tigecycline use. The main reason behind this was identification of possibly resistant bacteria, and therefore tigecycline was combined with other antibiotics.

Clinical effectiveness of tigecycline treatment was analyzed with respect to the infection sites. High success rates were found in osteomyelitis, surgical site infections, complicated skin and soft tissue infections, and intra-abdominal infections. Even though tigecycline has no approved indication for osteomyelitis, it has demonstrated good bone penetration in previous studies, and has a broad-spectrum activity against nosocomial pathogens, which are a frequent cause of osteomyelitis (17-19). In our study, the success rate of tigecycline treatment was also high in prosthetic joint infections, even though the number of patients of this cause was low. Treatment failure with tigecycline was mostly observed in bloodstream infections, catheter-associated infections, *Acinetobacter* meningitis and ventilator-associated pneumonia. These findings are also in line with FDA warnings (20).

Tigecycline was generally preferred as monotherapy for skin and soft tissue infections and intra-abdominal infections, and it is mostly initiated as empirical therapy. It was used for targeted treatment and as a part of

**Table 4. Antibiotics used in combination with tigecycline**

Antibiotic agent	Patients, % (n)
All agents	45.9% (147)
Aminoglycosides (Amikacin, Gentamicin, Netilmicin)	39.4% (58)
Carbapenem (Meropenem, Imipenem)	22.4% (33)
Fluoroquinolone (Ciprofloxacin, Levofloxacin, Moxifloxacin)	5.4% (8)
Piperacillin tazobactam	2.7% (4)
Glycopeptide (Vancomycin, Teicoplanin)	6.1% (9)
Colistin	10.8% (16)
Cefoperazone sulbactam	0.6% (1)
Linezolid	3.4% (5)
Metronidazole	2.7% (4)
Others*	6.1% (9)

\*: Cephalosporins (Cefixime, Ceftriaxone), Sulbactam

**Table 5. Microorganisms isolated from patients treated with tigecycline according to the infection site**

	Total	Empiric	<i>A. baumannii</i>	<i>Enterococcus</i> spp.	ESBL*	MSS*	MRS*
Community-acquired pneumonia	4.6% (15)	100% (15)	0	0	0	0	0
Hospital-acquired pneumonia	25% (80)	10% (8)	86.25% (69)	0	2.5% (2)	0	1.2% (1)
Complicated Skin and soft tissue infection	25% (80)	58.8% (39)	26.3% (21)	3.8% (3)	8.8% (7)	7.5% (6)	5.1% (4)
Intraabdominal infection	14.7% (47)	59.6% (28)	10.6% (5)	12.8% (6)	8.5% (4)	0	0
Surgical site infection	10.0% (32)	34.4% (11)	31.3% (10)	9.4% (3)	21.9% (7)	0	3.1% (1)
Urinary tract infection	9.4% (30)	13.3% (4)	53.3% (16)	16.7% (5)	13.3% (4)	0	3.3% (1)
Intravascular catheter-related infection	4.4% (14)	14.3% (2)	535.7% (5)	21.4% (3)	14.2% (2)	14.2% (2)	0
Osteomyelitis	3.8% (12)	50.0% (6)	41.7% (5)	8.3% (1)	0	0	0
Blood stream infection	1.6% (5)	0	80.0% (4)	20.0% (1)	0	0	0
Meningitis	0.9% (3)	0	100.0% (3)	0	0	0	0
Prosthetic joint infection	0.6% (2)	50.0% (1)	50.0% (1)	0	0	0	0
Total	100% (100)	35.6% (114)	43.4% (139)	6.9% (22)	9.4% (30)	2.5% (8)	2.3% (7)

\*ESBL: Extended spectrum beta-lactamase, MRS: Methicillin resistant *Staphylococcus* spp., MSS: Methicillin sensitive *Staphylococcus* spp.

a combination antibiotic therapy in the remaining unidentified infections. The most common cause of targeted tigecycline use was *A. baumannii* infections.

Tigecycline was usually preferred in combination therapies of *A. baumannii* infections with multi-drug resistance. *A. baumannii* is a rapidly emerging pathogen that causes nosocomial infections, especially in intensive care units; and multi-drug resistant *Acinetobacter* infections face treatment difficulties. The rise of carbapenem-resistant *A. baumannii* presents a serious treatment control challenge. Colistin, a relatively old polymyxin drug, and the newer tigecycline, are being used in various antimicrobial combinations for the treatment of this infection (21). In this study, aminoglycosides were the most preferred antibiotics with tigecycline combination, followed by carbapenems.

Treatment change was required in one fourth of patients, 3% of which were due to unwanted side effects.

The retrospective nature of our study, presenting real life data, is important because there was no intervention in selection of patients. However, the key limitations of this study include absence of any other agent for comparative analysis, and lack of evaluation of any underlying causes that might have affected the treatment failure.

## Conclusion

In the light of the increasing threat to multi-drug resistant infections, with limited treatment options, the use of tigecycline can be concluded to be an effective treatment choice, either as monotherapy or as a combination antibiotic therapy. Its low side effect profile also serves an added advantage. However, one must consider the risk of possible treatment failure in case of severe bacteremia infections.

## Authorship Contributions

Surgical and Medical Practices: F.T., N.E.T., Ş.H., T.I., C.B. Concept: F.T., N.E.T., Ş.H., T.I., C.B. Design: F.T., N.E.T., Ş.H., T.I., C.B., F.Ş.E., G.T.E., Ç.A.H., S.K., Data Collection or Processing: F.T., N.E.T., Ş.H., T.I., C.B., F.Ş.E., G.T.E. Analysis or Interpretation: F.T., N.E.T., Ş.H., T.I., C.B., Ç.A.H., S.K. Literature Search: F.T., N.E.T., Ş.H., T.I., C.B., F.Ş.E., G.T.E. Writing: F.T., N.E.T.s

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