



# Salvage Use of Tigecycline for Severely Ill Children

## Ciddi Hastalığı Olan Çocuklarda Tigesiklin Kurtarma Tedavisi

Manolya Kara<sup>1</sup>, Murat Sütçü<sup>1</sup>, Hacer Aktürk<sup>1</sup>, Özden Türel<sup>2</sup>, Selda Hançerli Törün<sup>1</sup>, Bahar Akgün Karapınar<sup>3</sup>, Gürkan Atay<sup>4</sup>, Nezahat Gürler<sup>3</sup>, Nuran Salman<sup>1</sup>, Ayper Somer<sup>1</sup>

<sup>1</sup> Department of Pediatric Infectious Diseases, Istanbul University School of Istanbul Medicine, Istanbul, Turkey

<sup>2</sup> Department of Pediatric Infectious Diseases, Bezm-i Alem Vakıf University School of Medicine, Istanbul, Turkey

<sup>3</sup> Department of Microbiology and Clinical Microbiology, Istanbul University School of Istanbul Medicine, Istanbul, Turkey

<sup>4</sup> Department of Pediatric Intensive Care, Istanbul University School of Istanbul Medicine, Istanbul, Turkey

### Abstract

**Objective:** Tigecycline has a wide spectrum antimicrobial activity including multi-drug resistant and extended drug resistant nosocomial Gram-negative bacteria. Although its pediatric use has not been approved, clinicians are sometimes obligated to choose tigecycline as salvage therapy. In this study, we present our clinical experience regarding tigecycline use in children.

**Material and Methods:** This was a retrospective study of children who had been given tigecycline therapy at least 48 consecutive hours of duration in the pediatric departments of two tertiary-centers from January 2011 to March 2016.

**Results:** Twenty four patients (13 female, 54.2%) with median age of 96 months (1-192) were enrolled. Tigecycline was started for ventilator associated pneumonia (n= 10, 41.7%), blood stream infection (n= 7, 29.2%), catheter related infection (n= 1, 4.2%), complicated skin soft tissue infection (n= 1, 4.2%) and empirically (n= 5, 20.8%). The most common isolated pathogen was *Acinetobacter baumannii* (n= 13, 54.2%). Other pathogens were *Klebsiella* spp. (n= 4, 16.6%), methicilline resistant *Staphylococcus aureus*, (n=1, 4.2%) and *Leptospira* spp. (n= 1, 4.2%). All of the patients had tigecycline combination therapy. The most common combination was tigecycline + colistin (n= 10, 41.7%). Two patients (8.3%) had mild adverse events. The mortality rate was 45.8%. There was negative correlation between the age of patients and mortality rate (p= 0.006).

**Conclusion:** Tigecycline may be used in critically ill children as salvage therapy with considerably mild side effects.

**Keywords:** Children, salvage therapy, tigecycline

### Özet

**Giriş:** Tigesiklin çok ilaca dirençli ve genişletilmiş ilaç direnci olan gram-negatif bakterilere karşı geniş antimikrobiyal etki spektrumu göstermektedir. Çocuklarda kullanımı onaylanmamış olmakla birlikte hekimler zorunlu hallerde kurtarma tedavisi olarak tigesiklin kullanmaktadır.

**Gereç ve Yöntemler:** Bu çalışmada Ocak 2011-Mart 2016 tarihleri arasında iki üniversite hastanesinin pediatri kliniklerinde en az 48 saat süre ile tigesiklin tedavisi verilmiş çocuk hastalar geriye dönük incelenmiştir.

**Bulgular:** Çalışmaya yaş ortancası 96 ay (1-192) olan 24 (13 kız, %54.2) hasta dahil edildi. Tigesiklin tedavisi; ventilatör ilişkili pnömoni (n= 10, %41.7), kan akımı enfeksiyonu (n= 7, %29.2), kateter ilişkili kan akımı enfeksiyonu (n= 1, %4.2), komplike cilt yumuşak doku enfeksiyonu (n= 1, %4.2) nedeni ile ve empirik (n= 5, %20.8) olarak başlanmıştır. En sık izole edilen mikroorganizma *Acinetobacter baumannii* (n= 13, %54.2) idi. Diğer etkenler sırası ile *Klebsiella* spp. (n= 4, %16.6), metisiline dirençli *Staphylococcus aureus* (n= 1, 4.2%) ve *Leptospira* spp. (n= 1, 4.2%) olarak saptandı. Hastaların tamamına tigesiklin kombinasyon tedavisi verildi; en sık tercih edilen kombinasyon tigesiklin + kolistin (n= 10, %41.7) idi. Birer (%4.2) hastada tedavi sırasında transaminaz yükselmesi ve kolestatik sarılık gelişti. Mortalite oranı %45.8 idi. Hasta yaşı ile mortalite arasında negatif korelasyon saptandı (p= 0.006).

**Sonuç:** Tigesiklin, ciddi hastalığı olan çocukların kurtarma tedavisinde tolere edilebilir yan etki profili ile tercih edilebilir

**Anahtar Kelimeler:** Çocuk, kurtarma tedavisi, tigesiklin

### Correspondence Address / Yazışma Adresi

**Manolya Kara**  
İstanbul Üniversitesi İstanbul Tıp Fakültesi,  
Çocuk Enfeksiyon Hastalıkları Bilim Dalı,  
İstanbul-Türkiye

**E-mail:** manolya\_kara@yahoo.com

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## Introduction

Tigecycline, a bacteriostatic glycylcyline, is a derivative of minocycline. It binds to the 30s subunit on the ribosome and interferes with bacterial synthesis (1). Tigecycline has a wide spectrum of in vitro activity against many gram-positive and gram-negative microorganisms, including the multiresistant strains other than *Pseudomonas* spp. which it displayed modest activity with minimal inhibitory concentration (MIC) 90% of 16 µg/mL (2,3). It also has fairly well anaerobic coverage other than *Morganella*, *Proteus* and *Providencia* species. It is a very powerful chemotherapeutic agent since it is not effected from most of the resistance mechanisms of the pathogens. Although it has been approved for complicated skin-soft tissue infections (cSSI), complicated intra-abdominal infections (cIAI) and community-acquired pneumonia (CAP) in adults, use of tigecycline is not recommended in patients younger than 18 years, as safety and effectiveness has not been established (1,4-7). However, the use of tigecycline can be obligatory for selected patients, especially for those with multidrug-resistant (MDR) and extensive-drug resistant (XDR) nosocomial gram negative bacteria related infections (7,8). Quite a few data, mainly from isolated case reports, is available in literature regarding tigecycline use in pediatric patients (8-13). In order to asses and contribute our experience to current literature, we performed a retrospective analysis of our patients who had been treated with tigecycline from two different tertiary centers in our country.

## Materials and Methods

### Demographic and Clinical Data

This was a retrospective study of children who had been given tigecycline therapy between January 2011 and March 2016 in the pediatric departments of two tertiary-centers.

Patients between 0-18 years of age who had been given tigecycline treatment at least 48 consecutive hours of duration were enrolled. Infections were mainly ventilator associated pneumonia (VAP), catheter related infections (CRI), bloodstream infections (BSI), complicated skin-soft tissue infections and sepsis. Tigecycline therapy was started empirically for selective cases who had already been given broad spectrum antimicrobial treatment without clinical improvement.

Patients' charts were reviewed and data regarding demographics, medical condition and tigecycline administration regimen were recorded. Detailed survey included underlying chronic disorders, type of the infection requiring tigecycline use, time difference between hospitalization and start of tigecycline therapy, responsible pathogen, culture positive specimen, antibiotic susceptibility results, types and duration of

antibiotics priorly used, reason for tigecycline use (persistent infection/relapse/clinical failure), dose and duration of tigecycline therapy, other antibiotics combined with tigecycline, adverse effects (nausea, vomiting, diarrhea, headache, abdominal pain, hypertension, acute pancreatitis, anemia, rash, somnolence, insomnia, elevated liver enzymes, renal failure and others), microbiologic and clinical outcomes.

### Laboratory Evaluation

Laboratory evaluation included complete blood count, liver transaminases, renal function tests, serum amylase and lipase levels, prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT) that have been ordered throughout the therapy. Microbiological culture reports of peripheral and catheter drawn blood samples, tracheal aspirate material or other body fluids together with antimicrobial susceptibility test results were recorded.

Between January 2011 and January 2016, tracheal aspirate specimens and blood samples of the patients were analysed in Microbiology Department of Istanbul University, Medical Faculty. Gram preparations of lower respiratory tract specimens were evaluated microscopically and then cultured into blood agar, chocolate agar and Mac Conkey agar medias. Blood and chocolate agars were incubated in 5% CO<sub>2</sub> media and Mc Conkey agar was incubated in 37°C normal atmosphere for 24-48 hours. Blood cultures were analysed by BACTEC 9120 (Becton Dickinson, USA) system. They were cultured in 5% sheep blood agar or chocolate agar if positive signals were obtained. Antimicrobial susceptibility test was performed and interpreted according to Clinical Laboratory Standarts Institute (CLSI) recommendations (14). Cefoxitin disc diffusion test (30 µg, Becton Dickinson, USA) was used to determine methicilline resistance for *Staphylococcus aureus*. Minimal inhibitory concentration (MIC) analysis of tigecycline was performed by E test (BioMeriëux, France) and results were evaluated according to CLSI limit values. Tigecycline susceptibility was defined as susceptible between 0.5-4 µg/mL), intermediate susceptibility (MIC value between 4-8 µg/mL) and resistance (MIC value >16 µg/mL).

### Definition

The term multi-drug resistance was used for acquired non-susceptibility to at least one agent in three or more antimicrobial categories, whereas extended-drug resistance was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories) (15). Microbiologic outcome was defined as the time of therapy required for the specified culture to become negative. Clinical outcome was the status of the patient at the end of tigecycline therapy which was generally accepted as either survival or death.

## Statistics

Statistical analysis of data was performed with statistical package for social science (SPSS) for Windows version 21.0 (SPSS 21.0, SPSS Inc. USA).

## Results

Twenty four patients (13 female, 54.2%) with median age of 96 months (range, 1-192 months) were enrolled in the study. Detailed analysis of patients was summarized in Table 1. Median time of hospitalization before start of tigecycline therapy was 27 days (range, 7-162 days). Tigecycline was chosen for MDR or XDR pathogen related infections. Among those, 10 patients (41.7%) suffered from VAP, 7 patients (29.2%) had BSI, one patient (4.2%) had catheter related infection and one patient (4.2%) had cSSI. It was started empirically in 5 patients (20.8%).

Patients were hospitalized due to several disorders before tigecycline use. Seven patients (29.2%) had malignancy [operated brain tumor (n= 3, 12.5%), acute myelocytic leukemia (n= 2, 8.3%), Ewing sarcoma (n= 1, 4.2%) and lymphoma (n= 1, 4.2%)]. Three patients (12.5%) were under immune suppressive therapy secondary to transplantation history [liver transplantation (n= 2, 8.3%) and severe combined immune deficiency and bone marrow transplantation (n= 1, 4.2%)]. Congenital heart disease (n= 1, 4.2%), diabetes mellitus type 1 (n= 1, 4.2%), trauma (n= 2, 8.3%), glycogen storage disease (n= 1, 4.2%), chronic neurological disorder [myopathy (n= 1, 4.2%), cerebral palsy (n= 1, 4.2%) and perinatal asphyxia (n= 1, 4.2%)], encephalitis (n= 2, 8.3%), leptospirosis (n= 1, 4.2%), prematurity (n= 1, 4.2%) and prolonged fever (n= 1, 4.8%) were other reasons of hospitalization.

In 79.1% of the cases, the responsible microorganism was either MDR or XDR nosocomial gram-negative bacteria. The most common isolated pathogen was *Acinetobacter baumannii* that was encountered in 13 patients (54.2%). XDR *A. baumannii* rate was 92.3% (n= 12) (MIC values were specified in Table 1). Other pathogens were *Klebsiella* spp. [*Klebsiella oxytoca* and *Klebsiella pneumoniae*, (n= 4, 16.6%), all of them were XDR], Methicilline resistant *Staphylococcus aureus* [MRSA, n= 1, 4.2%] and *Leptospira* spp. (n= 1, 4.2%). No underlying pathogen could be identified in 5 patients (20.8%) whom tigecycline therapy had been started empirically. MIC values were gathered from 13 patients. Among those, 5 (38.4%) of the *A. baumannii* isolates presented intermediate susceptibility to tigecycline.

The mortality rate among patients with documented *A. baumannii* infections was 54.5% (n= 6). No significant difference was obtained in terms of isolated pathogen on mortality. Median duration of therapy was 9 days (range, 2-25 days). Patients were given either 1 mg/kg/dose (n= 8, 33.3%) or 1.2 mg/

kg/dose (n= 16.66.7%); maximum 50 mg dose of tigecycline 2 times a day. None of the patients had loading dose of therapy. Several broad spectrum antibiotics including carbapenems (n= 14, 70.8%), anti-pseudomonal penicillins (n= 5, 20.8%), fluoroquinolones (n= 5, 20.8%) and colistin (n= 4, 16.6%) had been given prior to tigecycline.

All of the patients had different regimens of combination therapy. Sixteen patients (66.6%) had dual combination, whereas 8 patients (33.3%) had multiple-drug combination. The most preferred combination was tigecycline + colistin (n= 10, 41.7%). Three patients (12.5%) were given tigecycline + colistin + ampicillin sulbactam while 2 patients (8.3%) had tigecycline + ciprofloxacin. Other combination regimens were tigecycline + ceftriaxone (n= 1, 4.2%); tigecycline + colistin + rifampisin (n= 1, 4.2%); tigecycline + meropenem + colistin (n= 3, 12.5%); tigecycline + colistin + meropenem + amikacin (n= 1, 4.2%); tigecycline + colistin + meropenem + amikacin (n= 1, 4.2%); tigecycline + ciprofloxacin + linezolid (n= 1, 4.2%). One patient (4.2%) had tigecycline + colistin + rifampicin + cefoperazone sulbactam combination therapy. No statistical difference was observed when dual combination therapy is compared with multi-drug combination regimen.

Median time of microbiologic outcome was 10 days (range, 5-20 days). Two patients (8.3%) had mild adverse events as they did not require the taper of the therapy. One patient (4.2%) had elevated liver transaminases and 1 patient (4.2%) had cholestatic jaundice. In both cases, these side effects resolved after cessation of therapy and both of them survived. In terms of clinical outcome, 13 patients (54.2%) survived at the end of tigecycline treatment. Median age of mortality patients was 86 months (range, 9-164 months). There was negative correlation between the age of patients and mortality rate (p= 0.006). Of the mortalities (n= 11, 45.8%), 4 patients (16.6%) had suffered from VAP, 4 patients from BSI (16.6%) and 3 patients (12.5%) from sepsis. No statistical significance was determined in terms of types of infections on mortality.

## Discussion

Since the discovery of penicillin by Sir Alexander Fleming in 1929, scientists and bacteria have been in competition. As new drugs have been launched, newer resistance mechanisms were attained by microorganisms. Unfortunately, only a few new group of antibiotics have been discovered in the last decades as most of them are the derivatives of the existing ones. Tigecycline is such an antibiotic which has been created as a semisynthetic derivative of tetracycline (11). Although tetracyclines have been used widely since 1948, their clinical importance has been diminished in time due to acquisition of bacterial resistance. The capability of tigecycline comes from its structural property which enables it to be unaffected by

Table 1. Summary of patients' data

	Age (m)/gender	Primary disease	Infection	Isolate	Dose (bid)	DT (day)	Antibiotics before TGCY	CT	MIC-TGCY	MO (day)	CO
1	190 /F	Trauma	BSI	<i>A. baumannii</i>	1 mg/kg	14	C-S, MER, AMK	CST	4	10	Survival
2	182/F	Ewing sarcoma	cSSI	<i>A. baumannii</i>	1.2 mg/kg	12	CST, IPM, AMK	CST, RIF	1	30	Survival
3	81/F	Lymphoma	BSI	<i>A. baumannii</i>	1.2 mg/kg	2	MER	CST	0.5	-	Exitus
4	62/M	Myopathy	VAP	<i>A. baumannii</i>	1.2 mg/kg	14	C-S, AMK	CST	4	5	Survival
5	118/F	Medulloblastoma	VAP	<i>A. baumannii</i>	1.2 mg/kg	14	P-T, AMK	CST	4	-	Exitus
6	13/F	Encephalitis	Sepsis	Empirical	1 mg/kg	5	MER	CST	-	5	Survival
7	37/M	Juvenile polipozis	VAP	<i>A. baumannii</i>	1.2 mg/kg	7	VAN, MER, CIP	CST	1	-	Exitus
8	192/M	Perinatal asphyxia	VAP	<i>A. baumannii</i>	1.2 mg/kg	10	A-S	CST, A-S	-	7	Survival
9	122/M	Encephalitis	BSI	<i>A. baumannii</i>	1.2 mg/kg	9	A-S, MER	CST, A-S	4	-	Exitus
10	164/M	Leptospirosis	BSI	<i>Leptospira</i>	1 mg/kg	3	CEFTX, DOX	CEFTX	-	-	Exitus
11	106/M	Medulloblastoma	VAP	<i>A. baumannii</i>	1.2 mg/kg	8	P-T, AMK	CST, A-S	1	-	Exitus
12	86/F	SCID + BMT	Sepsis	Empirical	1 mg/kg	5	VN, MER, CIP, CST	CST	-	-	Exitus
13	15/F	Prolonged fever	Sepsis	Empirical	1.2 mg/kg	4	VAN, CIP, AMK	CST	-	-	Exitus
14	129/F	AML	Sepsis	Empirical	1.2 mg/kg	3	CST, MER, LZD	CST, MER	-	-	Exitus
15	9/F	CHD	CrBSI	<i>A. baumannii</i>	1 mg/kg	21	VAN, MER, CST, AMK	CST, AMK	1	10	Survival*
16	158/F	Type 1 DM	VAP	MRSA	1 mg/kg	16	CIP, VAN, MER, LZD	LZD, CIP	-	7	Survival**
17	146/F	Brain tumor	VAP	<i>K. pneumoniae</i>	1 mg/kg	18	MER, AMK	CST, AMK	-	10	Survival
18	125/F	Trauma	VAP	<i>A. baumannii</i>	1 mg/kg	25	CIP	CIP	-	14	Survival
19	46/M	Cerebral palsy	VAP	<i>A. baumannii</i>	1.2 mg/kg	7	MER, AMK	CIP	-	5	Survival
20	61/M	GSD	VAP	<i>A. baumannii</i>	1.2 mg/kg	14	MER, LZD, CIP	CST, RIF, C-S	8	-	Exitus
21	7/F	Liver transplant	BSI	<i>K. oxytoca</i>	1.2 mg/kg	20	C-S, MER, AMK	COL	1	10	Survival
22	9/M	Liver transplant	BSI	<i>K. pneumoniae</i>	1.2 mg/kg	3	P-T	CST, MER	2	-	Exitus
23	181/M	AML	Sepsis	Empirical	1.2 mg/kg	14	C-S, MER, AMK	CST, MER	-	-	Survival
24	1/M	Prematurity	BSI	<i>K. pneumoniae</i>	1.2 mg/kg	19	VAN, MER, CIP	CST, MER, AMK	1	12	Survival*

\* Elevated liver enzymes, \*\* Cholestasis, A-S: Ampicillin sulbactam, AMK: Amikacin, BSI: Blood stream infection, CEFTX: Ceftriaxone, CIP: Ciprofloxacin, CO: Clinical outcome, CrBSI: Catheter related BSI, C-S: Cefoperazone-sulbactam, cSSI: Complicated skin-soft tissue infection, CST: Colistin, CT: Combination therapy, DOX: Doksiziklin, DT: Duration of therapy, GSD: Glycogen storage disease, IPM: imipenem, LZD: Linezolid, MER: Meropenem, MO: Microbiologic outcome, MRSA: Methicillin resistant *Staphylococcus aureus*, P-T: Piperacillin/tazobactam, RIF: Rifampin, SCID-BMT: Severe combined immune deficiency, TEC: Telicoplanine, TGCY: Tigecycline, VAN: Vancomycine.

bacterial resistant mechanisms such as ribosomal protection and active efflux proteins (11,16).

Although Food and Drug Administration (FDA) approved the clinical use of tigecycline for cSSI, cIAI and CAP only in adults, it is emphasized that it can be preferred under 18 years of age only if there is no alternative option (1,4). Unfortunately, clinicians are sometimes obligated to use tigecycline in children and the indication spectrum is usually wider than recommended (1). In our study, tigecycline was preferred mainly for off-label use such as VAP, BSI and sepsis. Similarly, Iosifidis et al reported the clinical use of tigecycline for unapproved indications as BSI, lower respiratory tract infections and septic thrombophlebitis (12). In addition, miscellaneous indications with considerably favourable outcome such as meningitis, urinary tract infections and febrile neutropenia have been reported in case series (17-19).

MDR or XDR gram-negative bacteria are major threats for hospitalized patients especially in high risk wards like intensive care units and oncology departments. In recent years, resistant *A. baumannii* strains have been isolated as emerging cause of nosocomial infections throughout the world. It is also same for our country (20,21). In our study 92.3% of *A. baumannii* were XDR. It can cause life-threatening nosocomial infections like VAP, BSI, CSSI, meningitis, endocarditis and urinary tract infections (22). Several risk factors such as prolonged hospital stay, presence of chronic conditions, artificial respiration, surgical intervention, invasive procedures, inadequate and inappropriate antibiotic use have been described (23). Similarly, majority of our patients had underlying chronic disorders meeting the most of the risk factors mentioned above.

Although carbapenems are the most common preferred antibiotics for resistant *Acinetobacter* infections, insusceptibility against carbapenems has been rising in many parts of the world. For our country, Kurtoglu et al reported that the incidence of carbapenem resistant *A. baumannii* rate may reach up to 80% (24). Tigecycline and colistin may be satisfactory alternatives in that situation. But unfortunately, resistance against these antibiotics has also been increasing. Colistin and tigecycline resistant rates were reported as 5% and 16%, respectively in a study from our country (25). Although, we could not be able to achieve all of the MIC values, among the determined isolates, 45.4% of the *A. baumannii* presented intermediate susceptibility to tigecycline.

Since pediatric tigecycline use hasn't been approved, appropriate dosage is still undetermined. For adults, a loading dose of 100 mg intravenously followed by 50 mg twice daily is recommended (1). A Phase II, multi-center open label clinical trial, the only pediatric study, proposes a tigecycline dosage of approximately 1.2 mg/kg q12h for children aged 8-11 years (13). In the same study, no loading dose was evaluated. In con-

sistent with this study and previously reported case series, our patients received a tigecycline dosage of 1-1.2 mg/kg q12h (8,12,13,26). In literature; gastrointestinal symptoms such as nausea, vomiting and diarrhea are the most common reported side effects. In addition, acute pancreatitis, hypertension and neutrophile engraftment delay have been associated with tigecycline use in isolated case series (16,18,27). As Iosifidis et al mentioned in their report, since most of our patients were intubated and sedated we could not detect the real incidence of gastrointestinal symptoms (12). Although the number of patients in our study were limited, the only observed adverse effects such as elevated liver transaminases and cholestasis were mild and did not require cessation of therapy. For these reason, we can claim that the dose of 1.2 mg/kg; (maximum 50 mg dose) twice a day has been generally well tolerated. On the other hand, previous studies indicate that tigecycline is not such an innocent drug. FDA warns clinicians that they should use tigecycline in the case when other alternatives are not suitable (1,4). In a metaanalysis of different clinical trials in which tigecycline was used in the treatment of cSSSI, cIAI and CAP in adults, mortality was significantly higher in tigecycline group than comparator (4). Mc Govern et al. reported the increased mortality rate with tigecycline therapy, in 12 of 13 phase 3 and 4 comparative clinical trials. In the same study, they specified that, particularly patients with VAP and baseline bacteremia had greater risk of clinical failure and mortality (28). Forty percent of the patients with VAP died during our follow-up. Unlike previously reported, there was no significant difference regarding mortality rate among different types of infections. But, it would be appropriate to emphasize that the number of our patients is inadequate to draw a substantial conclusion. When overall mortality risk was considered, we found a negative correlation between the mortality rate and the age of the patient. This was an expected finding since these underlying serious infections cause increased mortality in younger population.

Another important issue is whether treatment failure and increased mortality is related with inadequate dosage of tigecycline. It would be relevant to think that way since tigecycline resistance has been increasing. To combat this situation, either increased doses of tigecycline or combination therapies should be evaluated as suggested (29). On the other hand, adverse drug reactions will be more encountered in the case of high dosage use. So, combination therapy can be an important option to treat MDR infections with several advantages including synergistic effect, broad coverage and prevention of drug resistance development. In a recent review article, colistin-tigecycline combination was referred as the most studied combination that showed promising results. In vitro and animal studies together with limited clinical reports demonstrate

the tigecycline-colistin combination showed synergistic or bactericidal effects against carbapenem resistant *A. baumannii* (30-32). For these reasons, authors suggest the initiation of colistin in the first place, when a MDR infection is identified (32). In consistent with the recommended, all of our patients were given combination therapy, with most of them (47.6%) being as tigecycline + colistin. In literature data, tigecycline plus sulbactam, carbapenem or rifampicin combination have also been suggested (33-35). Although we have experienced with different dual and multidrug combination therapies, no significant difference were observed between them in terms of clinical outcome.

Tigecycline may be a savior for clinicians for treatment of MDR/XDR nosocomial infections. Although it's use has not been approved for children, it is sometimes obligatory to choose tigecycline as a rescue antibiotic. Clinical experience regarding pediatric tigecycline use is very scarce in literature. Therefore, it is crucial for clinicians to report the outcome of pediatric tigecycline use.

**Ethics Committee Approval:** This study was performed with the permission of Local Clinical Research Ethical Committee.

**Informed Consent:** Since it was a retrospective case-control study, no informed consent was taken.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - MK, MS, HA; Design - MK, MS; Data Collection and Processing - MS, ÖT, HA, SHT, GA, BAK; Analysis and Interpretation - NG, NS, AS; Writting - MK; Confirmation - AS, NS.

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