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Original Article

Tigecycline therapy for multidrug-resistant bacteria: is it the right choice for pediatric patients

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Abstract

Introduction: The incidence of infections caused by multidrug-resistant pathogens is increasing worldwide, resulting in significant morbidity and mortality. Tigecycline has become a good option because it has a broad spectrum of antibacterial activity. This study aimed to reveal the clinical, microbiological, and laboratory outcomes of hospitalized children treated with tigecycline.

Methodology: We retrospectively collected the medical records of the hospitalized pediatric patients treated with tigecycline from April 1, 2018, to Apr 30, 2023, at Ege University Children's Hospital. Demographic features and clinical and laboratory findings were evaluated to determine the efficacy and safety of tigecycline therapy.

Results: Sixty-seven patients (65.7% male) with a median age of 6 years (2.5 months-17.5 years) were included. There was an underlying condition in 83.5% of the patients, and 55.2% were immunosuppressed. The most common infections were; lower respiratory tract infections (29.8%), intra-abdominal infections (20.9%), bloodstream infections (17.9%), and soft tissue infections (13.4%), respectively. *Acinetobacter* spp. (28.4%) was the most isolated microorganism, followed by *Klebsiella* spp. (19.4%) and *Enterococcus* spp. (14.9%). Tigecycline was used as a targeted treatment in 76.1% of the patients and was often used as a combination therapy (80.6%) with a median duration of 12 days (range, 2-60 days). Clinical response was achieved in 65.6% of patients, microbiologic response in 62.6%, and treatment failure in 34.3%. No major adverse events were noted during the therapy.

Conclusions: Tigecycline, which was mostly preferred in combination therapy, had high clinical response and microbiologic eradication rates, but these rates varied according to infection sites and microorganism species.

Key words: Tigecycline; multidrug-resistant; bacteremia; children.

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Introduction

Infections caused by multidrug-resistant (MDR) microorganisms have become a severe problem worldwide due to the difficulties in management [1]. MDR is defined as not susceptible to at least one agent in ≥ 3 antimicrobial categories and is responsible for more than 50% of healthcare-associated infections, causing mortality rates ranging from 30% to 70% [2-4]. Alternative antimicrobials are required to treat MDR infections.

Tigecycline, a semi-synthetic tetracycline, has broad-spectrum in vitro antimicrobial activity, including MDR Gram-positive and Gram-negative strains, except for *Pseudomonas* spp [5,6]. Tigecycline has antibacterial activity against Gram-positive (*Enterococcus* spp, vancomycin-resistant *Enterococci* (VRE), *Listeria, Streptococcus* spp, both methicillin-susceptible and -resistant *Staphylococcus aureus*, and *Staphylococcus epidermidis*), Gram-negative (*Acinetobacter baumannii, Klebsiella* spp, *Enterobacter* spp, *Escherichia coli*, *Citrobacter* spp, *Pasteurella multocida*, *Serratia marcescens*, and *Stenotrophomonas maltophilia*), anaerobic and atypical bacteria [7-9]. Tigecycline distributes well into the bile, CSF, and lung. It was approved by the US Food and Drug Administration (FDA) for complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial

pneumonia for patients 18 years of age and older [6,9,10]. However, it is not recommended in children younger than eight years of age due to possible discolouration of the teeth and in children younger than 18 years of age as safety and efficacy have not been established [11]. Tigecycline has been reported to be used in salvage therapy, but there is limited data evaluating tigecycline use in pediatric patients [11,12]. This study aimed to reveal the clinical and laboratory outcomes of children treated with tigecycline therapy and to determine the efficacy and safety of tigecycline therapy in pediatric practice patients.

Methodology

Study population and design

This single-center retrospective study was conducted at Ege University Children's Hospital, a tertiary-level university hospital. We retrospectively reviewed the medical records of the hospitalized children between Apr 1, 2018, and Apr 30, 2023, who were treated with tigecycline as a result of consultation with the pediatric infectious diseases department. The demographic data included age, gender, underlying disease, facilitating risk factors for infections, invasive procedure (central venous catheterization (CVC), mechanic ventilation (MV), gastrostomy and tracheostomy, etc.), surgical intervention, total parenteral nutrition (TPN), immunosuppression (primary/secondary)], length of hospital stay and medical data included the indication for treatment, infection site, antimicrobial agents before tigecycline therapy, information about the tigecycline therapy (dose, duration, single or combined, empirical or targeted, adverse reactions and outcome).

Laboratory test results: complete blood count, C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), biochemical tests including urea, creatinine, aspartate aminotransaminase (AST), alanine amino transaminase (ALT), amylase, total protein, total and direct bilirubin levels, glucose, electrolytes, fibrinogen, coagulation parameters (prothrombin time, activated partial thromboplastin time, international normalized ratio), culture and antibiogram results were retrieved from patients' medical records.

The duration of hospitalization, management, and outcomes were reported.

Microbiologic methods

Only the first or/and the single isolated bacteria considered to be the causative pathogens of infection from every pediatric patient were included in the study. All the strains were identified to the species level with MALDI-TOF MS (Matrix-assisted laser desorption ionization-time of flight mass spectrometry) (BioMérieux®). The antibiotic susceptibility testing of isolates was performed with the Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France), Kirby Bauer disc diffusion test, and the E-test. As the EUCAST breakpoints are not available for tigecycline and some of the bacteria, MIC values, and EUCAST tentative epidemiological cut-off values were used. (The European Committee on Antimicrobial Susceptibility Testing Breakpoint tables for interpretation of MICs and zone diameters. Version 11.0, 2021.) [13].

Tigecycline

Tigecycline has been used in two different ways, empirically or targeted. Empirical treatment with tigecycline was used in the following situations: in the absence of response to previously initiated antimicrobials, in line with local surveillance data, or without culture evidence in specific situations such as intra-abdominal infections. Targeted treatment means treatment initiated according to the culture antibiogram results.

Tigecycline was primarily administered based on culture results (targeted therapy). It was used as monotherapy for cases with culture-proven skin and soft tissue infections or intra-abdominal infections. In severely ill patients with bloodstream and/or VAP infections, it was administered in higher doses as part of combination therapy for salvage treatment.

The drug dosage was as follows [12,14-16]:

- Infants and Children < 8 years: 1 to 2 mg/kg/dose every 12 hours; maximum dose: 50 mg/dose
- Children ≥ 8 years and Adolescents:

8 to 11 years: IV: 1.2 to 2 mg/kg/dose every 12 hours; maximum dose: 50 mg/dose

≥ 12 years: IV: 50 mg every 12 hours

Serum concentrations of tigecycline could not be studied during the study period. Side effects and complications that developed in patients during treatment were also noted.

Definitions

Bacteria resistant to at least three antimicrobial agents of different antimicrobial categories were considered to be MDR [2].

Nosocomial (hospital-acquired) infections were defined according to the Centers for Disease Control's definition [17].

Clinical response was defined as the complete resolution of the clinical signs of infection. The microbiological response was defined as the eradication of the microorganism at the end of the treatment. Treatment failure was considered in patients who died or who did not achieve clinical and laboratory improvement.

Ethical Approval

The Research Ethics Committee of Ege University Faculty of Medicine and the Ministry of Health approved the study (Ethical decision No: 23-6T/16). This study was carried out following the Helsinki Declaration. The written consent of the children's parents was obtained.

Statistical analysis

The SPSS statistics software was used to perform the statistical analysis (version 25 for Windows). Mean SD or medians (interquartile range) were used for continuous data, and categorical variables and percentages were used. The Student's *t*-test was used for normally distributed and categorical data, and the 2 test was used. The Mann–Whitney U test is performed to examine differences in nonparametric data. A *p* of 0.05 was used to determine the statistical significance of differences and correlations. Correlation analyses have been performed using Pearson's r.

Results

Sixty-seven hospitalized children who had received intravenous tigecycline treatment for at least 48 hours were included in the study, and neonates were excluded. Of these, 65.7% (44/67) were male, with a median age of 6 years (2.5 months-17.5 years). There was an underlying condition in 83.5% (56/67) of the patients, and 55.2% (37/67) were immunosuppressed. Hemato-oncological malignancy (22.3%, 15/67), liver transplant recipient (14.9%, 10/67), bone marrow transplantation (13.4%, 9/67), primary immunodeficiency (4.5%, 3/67), gastrointestinal congenital malformations (17.9%, 12/67) and neurometabolic disease (5.9%, 4/67) were the most common comorbidities. Trauma was the reason for presentation in 9 of 11 previously healthy patients. The length of hospital stay-in median range was 65 days (6-388 days), and 76.1% (51/67) patients had pediatric intensive care unit (PICU) admission. The length of stay at the PICU was 22 days (1-240 days), and 59.7% (40/67) of the patients received invasive MV support. The infection was of nosocomial origin in 94% (63/67) of the patients. Among the predisposing factors, CVC was present in 86.5% (58/67), TPN in 59.7% (40/67) patients, and invasive surgical procedures (liver transplantation, surgery for congenital malformations of the Gİ tract or cardiovascular system, major trauma, etc.) in 50.7% (34/67) patients, and less invasive procedures such as urinary catheterization and nasogastric tube in 10.5%

Table 1. Characteristics of the hospitalized patients treated with tigecycline.

Characteristics	n (%)
Demographics of the patients (n = 67)	
Age (median, range)	6 years (2.5 months-17.5 years)
Sex, male	44 (65.7)
Comorbidities	56 (83.5)
Immunosuppression	37 (55.2)
- hematologic-oncological malignancy	15 (22.3)
- liver transplantation	10 (14.9)
- bone marrow transplantation	9 (13.4)
- primary immunodeficiency	3 (4.5)
Gİ tract malformations	12 (17.9)
Neurometabolic disorders	4(5.9)
Others	3 (4.5)
Length of hospital stay (day)-median(range)	65 (6-388)
Predisposing factors	
Central venous catheterization	58 (86.5)
PICU admission	51 (76.1)
Length of stay at PICU (day)- median(range)	22 (1-240)
Total parenteral nutrition	40 (59.7)
Invasive surgical procedures	34 (50.7)
Mechanical ventilation	40 (59.7)
Infection	
Origin	
- nosocomial	63 (94)
- community acquired	4 (6)
Site	
- Lower respiratory tract infection	20 (29.8)
VAP	17 (25.3)
HAP	2 (2.9)
CAP	1 (1.5)
- Intra-abdominal infections	14 (20.9)
- Bloodstream infections	12 (17.9)
- CLABSI	9 (13.4)
- Soft tissue infections	9 (13.4)
- Urinary tract	3 (4.5)
Microorganisms reported	
MDR bacteria	63 (90)
Acinetobacter baumannii	19 (28.4)
Klebsiella pneumoniae	13 (19.4)
Enterococcus spp.	10 (14.9)
Stenotrophomonas maltophilia	9 (13.4)
Pseudomonas spp.	8 (11.9)
Serratia spp.	5 (7.5)
Staphylococcus spp.	5 (7.5)
Escherichia coli	1 (1.5)
Laboratory parameters (mean ± SD)	
WBC (µL)	9994 ± 7432
ANC (µL)	6948 ± 6211
Platelet count (10^3/µL)	266 ± 213
CRP, mg/L	104 ± 150
Procalcitonin, µg/L	6.6 ± 14.6
Crude Mortality	23 (34.3)

ANC: absolute neutrophil count; CAP: community-acquired pneumonia; CLABSI: Central Line-associated Bloodstream Infection; CRP: C-reactive protein; HAP: hospital-acquired pneumonia; Gİ: gastrointestinal; MDR: multidrug-resistant; PCT: procalcitonin; PICU: pediatric intensive care unit; PLT: platelet count; VAP: ventilator-associated pneumonia; WBC: white blood cell.

(7/67) patients.

The most common infection was lower respiratory tract infection (29.8%, 20/67), followed by ventilator-associated pneumonia (VAP) (25.3%, 17/67), 2.9% (2/67) were hospital-acquired pneumonia (HAP) and 1.5% (1/67) was community-acquired pneumonia (CAP). The second most common indication was intra-abdominal infections (20.9%, 14/67), followed by bloodstream infections (17.9%, 12/67) and soft tissue infections (13.4%, 9/67). Characteristics of the hospitalized patients treated with tigecycline are shown in Table 1.

Microbiological results

The culture was most frequently performed from lower respiratory tract specimens (17 transtracheal aspirates (TTA), 1 bronchoalveolar lavage (BAL)), abdominal specimens (n = 12), and blood specimens (10 peripheral blood or 8 central venous catheters). Any microorganism was isolated from 70 culture materials of 85.1% (57/67) of the patients, and 90% (63/67) were MDR bacteria. *Acinetobacter* spp. (28.4%) was the most commonly isolated microorganism followed by *Klebsiella* spp. (19.4%) and *Enterococcus* spp. (14.9%). Tigecycline susceptibility could not be tested in 15 patients, and the rest were as follows; tigecycline susceptibility was detected in 40.3% (27/67), intermediate susceptibility in 17.9% (12/67), and resistance in 4.5% (3/67). Microorganism species are listed in Table 1.

Tigecycline therapy

Tigecycline was administered as targeted therapy in 76.1% of the patients (51/67). It was used as monotherapy in 19.4% (13/67) of cases, whereas the majority received tigecycline in combination with other antimicrobial agents (80.6%, 54/67). The most commonly co-administered antibiotics were meropenem (44.4%, 24/54), colistin (29.6%, 16/54), and aminoglycosides (22.2%, 12/54).

The median duration of tigecycline therapy was 12 days (range: 2–60 days). Prior to initiation of tigecycline, 95.5% of patients (64/67) had received broad-spectrum antibiotic treatment, with a median duration of 10 days (range: 2–26 days).

A detailed summary of tigecycline treatment modalities and microbiological characteristics is presented in Tables 2 and 3.

Adverse events

Adverse events related to tigecycline therapy were observed in 11.9% of patients (8/67) and were predominantly mild to moderate in severity. Mild prolongation of prothrombin time (PT) occurred in 4.5% (3/67), while elevated serum amylase and lipase levels were detected in 3% (2/67) of patients. A two-fold increase in serum creatine kinase and serum creatinine levels was noted in 1.5% (1/67) of patients, respectively. Additionally, one patient (1.5%) reported nausea.

Most adverse events occurred within the first week of therapy and resolved spontaneously without the need for intervention. No severe adverse reactions were documented, and no cases required dose adjustment or treatment discontinuation. Notably, no tooth discoloration was observed in any of the patients. A detailed overview of adverse events and treatment outcomes is provided in Table 4.

Treatment outcome

Clinical response was achieved in 65.6% (44/67) of the patients, microbiological response in 62.6% (42/67), and treatment failure in 34.3% (23/67) of the patients. When compared in terms of clinical response, no statistically significant difference was found between those receiving empirical (68%) or targeted (43%) therapy (p = 0.73). Also, there were no significant differences in clinical response between patients with single (53%) or combined (64%) therapy

Table 2. Summary of tigecycline treatment.

	Number of patients (%)
Duration of tigecycline treatment (day)-median (range)	12 (2-60)
Broad-spectrum antibiotics received prior to tigecycline	64 (95.5)
- Carbapenem	32 (47.7)
- Glycopeptide	24 (25.8)
- Colistin	15 (22.3)
- Linezolid	14 (20.8)
Duration of antibiotic prior to tigecycline (day)-median (range)	10 (2-26)
Tigecycline Usage	
-Targeted	51 (76.1)
- Empirical	16 (23.9)
Monotherapy	13 (19.4)
Combined treatment	54 (80.6)
- Combination with a single antibiotic	32 (47.7)
- Combinations with multiple antibiotics	35 (52.3)
Antibiotics combined	
- Meropenem	24 (44.4)
- Colistin	16 (29.6)
- Aminoglycosides	12 (22.2)
Tigecycline sensitivity	
MIC ≤ 2 μg/mL	27 (40.3)
MIC 4 μg/mL	12 (17.9)
MIC ≥ 8 μg/mL	3 (4.5)
Dosage	
2 × 1 mg/kg/dose i.v.	57 (85)
2 × 1.2 to 2 mg/kg/dose i.v.	10 (15)

MIC: minimum inhibitory concentration.

Table 3. Microorganisms isolated, treatment type, and clinical response of tigecycline therapy.

Infection Type	Microorganisms	MIC Values	Treatment Type	Clinical Response
Lower Respiratory Infections (20 patients)	*Acinetobacter baumannii* (n = 11, 55%)	MIC ≤ 2 µg/mL → n = 3 MIC = 4 µg/mL → n = 5	Monotherapy: 5 patients Combined treatment: 6 patients	8/11 patients responded clinically
	Enterococcus spp. (n = 1, 5%)	MIC = 4 µg/mL → n = 1	Combined treatment: 1 patient	1/1 patient responded clinically
	Pseudomonas spp. (n = 4, 20%)	MIC was not tested	Combined treatment: 4 patients	1/4 patient responded clinically
	Staphylococcus spp. (n = 1, 5%)	MIC = 0.5 µg/mL → n = 1	Combined treatment: 1 patient	1/1 patient responded clinically
	Klebsiella pneumoniae (n = 3, 15%)	MIC = 8 µg/mL → n = 1 MIC = 12 µg/mL → n = 1 MIC was not tested → n = 1	Combined treatment: 3 patients	3/3 patients responded clinically
	Stenotrophomonas maltophilia (n = 3, 15%)	MIC = 0.5 µg/mL → n = 1 MIC = 12 µg/mL → n = 1 MIC was not tested → n = 1	Combined treatment: 3 patients	1/3 patient responded clinically
Intra-abdominal Infections (14 patients)	*Acinetobacter baumannii* (n = 3, 21.4%)	MIC = 4 µg/mL → n = 2 MIC = 12 µg/mL → n = 1	Combined treatment: 3 patients	2/3 patients responded clinically
	Enterococcus spp. (n = 6, 42.9%)	MIC = 12 µg/mL → n = 6	Monotherapy: 3 patients Combined treatment: 3 patients	6/6 patients responded clinically
	Pseudomonas spp. (n = 2, 14.3%)	MIC = 12 µg/mL → n = 1 MIC was not tested → n = 1	Combined treatment: 2 patients	1/2 patient responded clinically
	Staphylococcus spp. (n = 1, 7.1%)	MIC = 12 µg/mL → n = 1	Combined treatment: 1 patient	1/1 patient responded clinically
	Klebsiella pneumoniae (n = 3, 21.4%)	MIC = 1 µg/mL → n = 2 MIC = 12 µg/mL → n = 1	Monotherapy: 1 patient Combined treatment: 2 patients	No patient responded clinically
	Serratia spp (n = 1, 7.1%)	MIC = 12 µg/mL → n = 1	Monotherapy: 1 patient	1/1 patient responded clinically
	Stenotrophomonas maltophilia (n = 2, 14.3%)	MIC = 12 µg/mL → n = 1 MIC was not tested → n = 1	Combined treatment: 2 patients	2/2 patients responded clinically
Bloodstream Infections (12 patients)	*Acinetobacter baumannii* (n = 1, 8.3%)	MIC = 2 µg/mL → n = 1	Monotherapy: 1 patient	1/1 patient responded clinically
	Staphylococcus spp. (n = 1, 8.3%)	MIC = 12 µg/mL → n = 1	Combined treatment: 1 patient	1/1 patient responded clinically
	Klebsiella pneumoniae (n = 1, 8.3%)	MIC = 12 µg/mL → n = 1	Combined treatment: 1 patient	1/1 patient responded clinically
	Serratia spp. (n = 3, 25%)	MIC = 1 µg/mL → n = 2 MIC = 12 µg/mL → n = 1	Combined treatment: 3 patients	3/3 patients responded clinically
	Stenotrophomonas maltophilia (n = 1, 8.3%)	MIC was not tested → n = 1	Monotherapy: 1 patient	No patient responded clinically
CLABSI (Central Line-Associated Bloodstream Infection) (9 patients)	*Acinetobacter baumannii* (n = 1, 11.1%)	MIC = 12 µg/mL → n = 1	Combined treatment: 1 patient	1/1 patient responded clinically
	Enterococcus spp. (n = 1, 11.1%)	MIC was not tested → n = 1	Combined treatment: 1 patient	1/1 patient responded clinically
	Staphylococcus spp. (n = 3,33.3%)	MIC = 0.5 µg/mL → n = 1 MIC = 12 µg/mL → n = 2	Combined treatment: 3 patients	3/3 patients responded clinically
	Klebsiella pneumoniae (n = 3, 33.3%)	MIC = 4 µg/mL → n = 1 MIC was not tested → n = 2	Combined treatment: 3 patients	3/3 patients responded clinically
	Serratia spp. (n = 1, 11.1%)	MIC = 4 µg/mL → n = 1	Combined treatment: 1 patient	1/1 patient responded clinically
	Stenotrophomonas maltophilia (n = 1, 11.1%)	MIC was not tested → n = 1	Combined treatment: 1 patient	No patient responded clinically
Soft Tissue Infections (9 patients)	*Acinetobacter baumannii* (n = 3, 33.3%)	MIC = 4 µg/mL → n = 3	Combined treatment: 3 patients	3/3 patients responded clinically
	Pseudomonas spp. (n = 2, 22.2%)	MIC = 4 µg/mL → n = 1 MIC = 0.5 µg/mL → n = 1	Combined treatment: 2 patients	2/2 patients responded clinically
	Klebsiella pneumoniae (n = 1, 11.1%)	MIC = 0.5 µg/mL → n = 1	Combined treatment: 1 patient	1/1 patient responded clinically
	Stenotrophomonas maltophilia (n = 2, 22.2%)	MIC was not tested → n = 2	Combined treatment: 2 patients	No patient responded clinically
	Escherichia coli (1, 11.1%)	MIC = 0.5 µg/mL → n = 3	Combined treatment: 1 patient	1/1 patient responded clinically
Urinary Tract Infections (3 patients)	*Klebsiella pneumoniae* (n = 2, 66.5%)	MIC = 12 µg/mL → n = 1 MIC was not tested → n = 1	Combined treatment: 2 patients	2/2 patients responded clinically
	Enterococcus spp. (n = 2, 66.7%)	MIC = 4 µg/mL → n = 1 MIC was not tested → n = 1	Monotherapy: 1 patient Combined treatment: 1 patient	1/2 patient responded clinically

(p = 0.46). A comparison of characteristics of the patients with clinical response and treatment failure is shown in Table 5.

While tigecycline treatment continued, 8 patients died. Microbiologically, culture eradication was achieved in 7 of them, and worsening of their underlying diseases (hemato-oncologic malignancy, cystic fibrosis) were considered the causes of death. The last patient was two months old and had a history of prematurity, operation due to complex congenital cardiopathy, and invasive MV. He was treated for nosocomial sepsis, and *Klebsiella pneumonia* and *Citrobacter freundii* grew in the peritoneal fluid sample. Tigecycline which was found to be sensitive (MIC: 1.0), was added to the combination therapy; however, the patient died on the sixth day of treatment without obtaining control culture material.

Table 4. Adverse events and outcome.

	n (%)
Total adverse events	8 (11.9)
- Elevated serum prothrombin time	3 (4.5)
- Elevated serum amylase-lipase	2 (3)
- Elevated serum creatine kinase	1 (1.5)
- Elevated serum creatinine	1 (1.5)
- Nausea	1 (1.5)
Outcome	
Clinical response	44 (65.6)
Microbiological response	42 (62.6)
Treatment failure	23 (34.4)
Clinical response depending on the infection site	
Lower respiratory tract infection	12/20 (60)
Intra-abdominal infections	8/14 (57.1)
Bloodstream infections	7/12 (58.3)
CLABSI	8/9 (88.8)
Soft tissue infections	5/9 (55.5)
Urinary tract	2/3 (66.6)
Microbiological response depending on the microorganism species	
Acinetobacter baumannii	15/19 (78.9)
Klebsiella pneumoniae	9/13 (69.2)
Enterococcus spp.	10/10 (100)
Stenotrophomonas maltophilia	3/9 (33.3)
Pseudomonas spp.	4/8 (50)
Serratia spp	4/5 (80)
Staphylococcus spp.	5/5 (100)
Escherichia coli	1/1 (100)

CLABSI: Central Line-associated Bloodstream Infection.

Discussion

The incidence of MDR bacterial infections has been increasing worldwide, and the lack of new antibiotics in managing these infections is challenging [18]. Therapeutic options for treating MDR bacteria in children are also limited. Tigecycline has broad-spectrum antimicrobial activity, including MDR Gram-positive and Gram-negative strains. It has a lower resistance potential because it is unaffected by the major mechanisms of tetracycline resistance (ribosomal protection proteins and efflux pumps) [8].

Tigecycline has been reported to be used in the management of severe infections in children, such as sepsis, pneumonia, intraabdominal infections, and meningitis [15,19,20]. Zhu *et al* [15] reported that pneumonia was the most common infection (71.4%) in hospitalized children treated with tigecycline. Limited data indicate that tigecycline is used as salvage therapy for patients with bacteremia and central line-associated bloodstream infections (CLABSIs) [19,20]. Lower respiratory tract infections, especially VAP, intraabdominal infections, and bloodstream infections were the most common infections in the present study.

Tigecycline is mostly used in children for infections caused by *A. baumannii, Klebsiella pneumoniae,* and

Table 5. Comparison of characteristics of the patients with clinical response and treatment failure.

	Clinical response (n = 44, 65.6%)	Treatment failure (n = 23, 34.4%)	p
Age, months [median (IQR)]	14.6 (210.7)	10.5 (134.2)	0.82
Length of hospital stay (days), [median (IQR)]	76.5 (102.2)	69 (71.2)	0.93
PICU admission, [n (%)]	34 (77.2)	17 (73.9)	0.49
Length of hospital stay at PICU (days), [median (IQR)]	20.5 (38.5)	34.5 (45.2)	0.62
Mechanical ventilation, n (%)	26 (59)	14 (60)	0.55
Duration of mechanical ventilation(days), [median (IQR)]	16.5 (52)	24.5 (32)	0.15
Duration of broad-spectrum antibiotherapy before tigecycline (days), [median (IQR)]	10 (8)	9 (4)	0.60
Duration of tigecycline treatment (days), [median (IQR)]	13 (15)	8 (18)	0.33
Previously healthy, n (%)	8 (18.1)	3 (13)	0.59
Comorbidities, n (%)	35 (79.5)	22 (95.6)	0.41
-Immunosuppression	21 (47.7)	16 (69.5)	0.08
Hematologic-oncological malignancy	8 (18.1)	7 (30.4)	0.24
Liver transplantation	7 (15.9)	3 (13)	0.59
Bone marrow transplantation	5 (11.3)	4 (17.3)	0.32
- GI tract malformations	8 (18.1)	4 (17.3)	0.93
- Others	4 (9)	3 (13)	0.61
invasive surgical procedure, n (%)	22 (50)	12 (52.1)	0.53
TPN, n (%)	27 (61.3)	13 (56.5)	0.45
Central venous catheterization, n (%)	26 (59)	15 (65.2)	0.41
Port Catheter, n (%)	8 (18.1)	3 (13)	0.43
External drainage catheter, n (%)	5 (11.3)	2 (8.6)	0.73

GI: gastrointestinal; PICU: pediatric intensive care unit; TPN: Total parenteral nutrition.

Escherichia coli [15,19]. Ye *et al.* [20] reviewed tigecycline therapy in children with severe infections, and *A. baumannii* and *Klebsiella pneumoniae* were the most common microorganisms. Similarly, *A. baumannii,* followed by *Klebsiella pneumoniae,* and *Enterococcus* spp*.,* were the most common isolated pathogens, and MDR bacteria consisted of 90% of the infections in the present study. The fact that 85% of our patients had comorbidities, (especially half of them were immunosuppressed, including patients referred for bone marrow, liver transplantation, and surgery for complex congenital malformations), long hospital stays, the high rate of invasive procedures, PICU admission and MV support may have led to increased exposure to broad-spectrum antibiotics resulting in high MDR rate. The microbiological response was highest in *Enterococcus* spp. (100%) and *Staphylococcus* spp. (100%) related infections; however, it was lowest in *Stenotrophomonas matlophilia* (33.3%). While it is known that tigecycline is ineffective against *P. aeruginosa*, it was administered to 8 patients with *P. aeruginosa* infection; 4 were patients diagnosed with VAP, 2 were diagnosed with intra-abdominal infections and the rest 2 were with skin-soft tissue infection. It was administered empirically to 4 patients with other than VAP and salvage therapy (combination with other broad-spectrum antimicrobials) to 4 patients who developed VAP. All patients received tigecycline in combination therapy, and the treatment continued due to clinical or microbiological response.

In this study, we determined clinical response in 65.6% of the patients, and microbiological eradication was 62.6%. The clinical response rate was highest in CLABSIs (88.8%), whereas low in soft tissue infections (55.5%). Clinical response was lower than expected in intraabdominal infections (57.1%) but higher than expected in lower respiratory tract infections (60%). Clinical response was 52.9% in VAP. Clinical improvement was reported in 50% and microbiological eradication was reported in 50.98% of the patients with tigecycline in a recent study which mostly included LRTIs [20]. Lin *et al.* [5] reported an overall improvement rate of 33% in VAP. Aslan *et al.* [11] reported a similar overall response rate (61.6%) to our study, but improvement was achieved in 80% of the patients with intraabdominal infections, which was higher than our study.

Several case reports on using tigecycline in salvage therapy for severe infections in children have been reported [21-25]. Tigecycline was mostly used in a targeted way (76.1%) based on the culture antibiogram results and was often preferred to be used in combination (80.6%) with other antibiotherapies in our study. Targeted tigecycline therapy was primarily administered to patients whose clinical status permitted waiting for microbiological culture results. In contrast, empirical use of tigecycline was preferred in patients with a history of prior colonization or those presenting with severe clinical deterioration. In a pediatric study with a high rate of clinical response and microbiological eradication, tigecycline was used as a combination therapy in all cases [26]. Differently, a recent study evaluating clinical and laboratory responses of children admitted to PICU revealed that tigecycline was primarily used as monotherapy (73.6%) and empirically (65.9%) [11]. We did not determine significant differences in clinical response between patients with single or combination therapy. Similarly, Song *et al.* [19] showed that clinical responses did not differ in patients who received tigecycline as monotherapy or combination therapy.

In our study, the median duration of tigecycline treatment was 10 days; prolonged or shorter durations have been reported in the literature [15,27]. There is no consensus yet on the duration of treatment in children, and more pharmacokinetic studies are required.

Gastrointestinal system side effects (nausea, vomiting, diarrhea) and prolonged PT time are the most frequently reported adverse reactions [11,27]. Discoloration of teeth is also among the expected long-term effects [20]. Adverse events were noted in 11.9% of the patients in our study, including biochemical alterations (increase in PT, amylase-lipase, creatine kinase, serum creatinine), and nausea. All the adverse events were mild and self-limiting, so there were no treatment disruptions. The most extended exposure to tigecycline was 60 days in our series, while we did not observe tooth discolouration.

The retrospective nature, reflecting a single-center experience, and including a small number of cases are the limitations of our study. The lack of serum tigecycline levels and its combination with other antimicrobials has made it difficult to understand the efficacy of tigecycline alone. However, the strengths of our study are that it included patients in whom tigecycline treatment was prescribed by a Pediatric Infectious Diseases specialist with appropriate indications and dosage, that it was used in a wide range of patient groups, not only in severe diseases, and that it included long-term follow-up results.

In conclusion, the clinical and microbiologic response was achieved in more than 60% of cases, and no major adverse drug reaction was observed with tigecycline therapy in our series. However, the fact that

it has primarily been given as a combination therapy overshadows its true efficacy. Hence, the efficacy and safety of tigecycline therapy in childhood can be elucidated by large-scale randomized controlled trials supported by pharmacokinetic investigations.

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Conflict of interests

No conflict of interests is declared.

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