History of Medicine, 2024, 10(2): 1062-1073
DOI: https://doi.org/10.17720/d6q6m940

***Title**: Clinical experience of Tigecycline in pediatric and neonatal patients in a tertiary care hospital in Pakistan".*

Falak Abro[1], Syeda Anum Fatima[2], Nazia Bibi[3], Fozia Baloch[4], Sehrish Muzaffar[5]

1. *Assistant professor, department of Pediatrics Dow Medical university of Health sciences Karachi drfalakabro@gmail.com*
2. *Clinical pharmacist , Aga khan university hospital Karachi s.anumrizvi@gmail.com*
3. *Assistant Professor ,Department of Pediatrics , Lady reading hospital Peshawar, mnazia264@gmail.com*
4. *Assistant professor, Department of Pediatrics, Bilawal medical college for boys LUMHS Jamshoro balochfozia94@gmail.com*
5. *Sehrish Muzaffar Registrar, Department of Pediatrics Liaquat university of LUMHS Jamshoro sehrish.muzafar@yahoo.com*

Conflict of interest: All authors declare no conflict of interests.
Funding: no any outsider funding taken for this study.

Corresponding author:
Fozia Baloch,
Balochfozia94@gmail.com

Abstract:
Background:

The rise of Multi-Drug Resistant (MDR) and Extensively Drug Resistant (XDR) infections has led to fewer choices of antimicrobials in the pediatric population. Since tigecycline has in vitro activity against gram-positive and gram-negative infections, it can be used as a combination therapy in pediatric and neonatal populations.

Objective:

To study tigecycline use for MDR and XDR infections, and microbiological and clinical outcomes in pediatrics and neonates.

Methods:

Retrospective chart review was performed for twenty-eight pediatric and neonatal patients who received tigecycline at least 48 hours after a report of antimicrobial susceptibility at different culture sites. The outcomes observed were microbial eradication, clinical improvement, mortality, and adverse effects in the described patients.

Results:

The median duration of therapy was 11 days, and median length of stay in the hospital was 30 days. Twenty-two (78.6%) children were in the intensive care unit with median length of stay of 13 days. Microbiological eradication was checked in only twenty patients, achieved in

15 (75%) children with a median duration of 2.5 (2-3) days. The mortality rate of patients was 11 (39.3%), among which three (11%) had multidrug-resistant, seven (25%) had extensive drug-resistant, and one patient had a pan-sensitive pathogen. The highest rate of mortality was associated with bloodstream infections, although there was no statistical significance associated.

Conclusion:

Tigecycline is an option for children mainly due to infections caused by MDR and XDR pathogens. More prospective and controlled trials are needed to determine the relationship between dosing and pharmacokinetic parameters for this population set.

Introduction:

The emergence of drug-resistant *Enterobacteriaceae* for the last two decades has increased the worldwide threat to health care and risk of treatment failure in nosocomial and community-acquired infections, leaving limited options of antibiotics for treatment. (1) Plasmid-mediated changes or chromosomal overproduction of mutant AmpC enzymes are considered the primary reason for spreading antibiotic resistance. (2) Carbapenem-resistant *Enterobacteriaceae* can cause significant serious infections like urinary tract infections, intra-abdominal infections, pneumonia, and device-associated infections leading to prolonged hospitalization and poor patient outcomes resulting in increased morbidity and mortality. [(3)]

Tigecycline is an antimicrobial group of glycylcyclines with a broad-spectrum bacteriostatic property against Gram-positive and Gram-negative organisms. It is the last-line therapeutic choice used concomitantly with other antibiotics against multidrug-resistant (MDR) and extensively drug-resistant (XDR) pathogens, especially carbapenem-resistant *Enterobacteriaceae* in critically ill patients. (4) It was approved by the American Food drugs and administration (FDA) for complicated skin, soft tissues, intra-abdominal infections, and community-acquired pneumonia in adults in 2005. It is also widely used off-label in the treatment of Ventilator-associated pneumonia (VAP), hospital-acquired pneumonia (HAP), bloodstream infections (BSI), catheter-related infections, osteomyelitis, and urinary tract infection caused by MDR and XDR microorganisms. (5, 6) According to the Food and Drug Administration (FDA), the use of tigecycline in the pediatric population less than 18 years should not be considered until no other antibacterial choices are available against gram-negative pathogens. (7)

However, limited clinical data is available on the safety and efficacy of tigecycline when used with a combination of other antimicrobial drugs in the pediatric population. It has been reported to treat life-threatening infections (like sepsis, bacteremia, urinary tract infections, peritonitis, nosocomial pneumonia, skin, and soft tissue infections, or meningitis) in the pediatric age group, including neonates. (8, 9) The recommended loading dose is 1.5 or 2.0 mg/kg of intravenous tigecycline followed by a maintenance dose of 1mg/kg every 12 hours (maximum dose of 50 mg every 12 h). (10, 11) Since the experience of tigecycline use in children against MDR and XDR pathogens is never reported in Pakistan, we retrospectively identified and analyzed cases who had been treated with tigecycline over the past five years in a tertiary hospital.

Methodology:

The retrospective files review from January 2016 to December 2020 was conducted in the Pediatrics and Child Health Department at the Aga Khan University Hospital (AKUH), Karachi. Data of children aged from 0 months to 18 years were admitted and administered intravenous tigecycline during the hospital stay. Targeted treatment was defined as children who received tigecycline for at least 48 hours, after a report of antimicrobial susceptibility of the isolated pathogens with a loading dose of 2 mg/kg, followed by 1 mg/kg q12 h. Empiric treatment was defined as starting tigecycline therapy when no response to sepsis with other antimicrobials. Children who received less than four doses of intravenous tigecycline were excluded from the study. Data was collected on a predesigned structured questionnaire on demographics, clinical characteristics, laboratory investigation, combination antibiotic treatment is given, duration of tigecycline therapy, adverse effects of tigecycline after 48 hours of its administration (i.e., diarrhea, nausea, vomiting, liver function tests, blood urea nitrogen/creatinine, platelets count, prothrombin time/international normalized ratio), length of hospital stay (days), site of infection, type of isolated pathogens and their susceptibility pattern of antibiotics, mortality, microbial eradication (defined as eradication of multidrug or extensive drug-resistant gram-negative bacteria achieved, at least after 48 hours of treatment of tigecycline by repeating cultures). Multidrug resistance gram-negative bacteria (MDR) are defined as resistance to at least three antimicrobial agents against the gram-negative pathogen. Extensively drug-resistant gram-negative bacteria (XDR) are defined as resistant to almost all classes of antibiotics except one or two classes of antibiotics (mainly polymyxin and tigecycline).

The Ethical Review Committee of AKUH exempted the study. Statistical analysis was performed using SPSS version 22 software. For categorical variables such as gender, antibiotic used for treatment, antimicrobial susceptibility pattern, and mortality, the frequency with percentages is reported, and for quantitative variables such as length of hospital stay (days), duration of tigecycline treatment, Mean±SD /median ± interquartile range (IQR) are reported depending upon data distribution. Fisher's exact test was used to compare the mortality of bloodstream infections to that of non-bacteremia infections. A p-value < 0.05 was considered significant.

Results:

During the study period, of 28 participant files reviewed, twenty-five (89%) patients received targeted tigecycline treatment with combination antibiotics against culture-proven gram-negative organisms, and three (10.7%) received empiric tigecycline treatment because of progressive sepsis and no response to broad-spectrum antibiotics. Male predominance was observed in 19 (68%) cases. Antibiotics used in these patients before tigecycline therapy were, meropenem 28 (100%), colistin 19 (68%), Fosfomycin 13 (46.4%) and vancomycin 20 (71.4%). Bacteremia 15 (53.6%) was the most common indication for tigecycline use, followed by pneumonia 6 (21.4%) and intra- abdominal sepsis 6 (21.4%), as shown in table 1.

Table 1 Demographics and clinical characteristics of Tigecycline use in children in hospital.	
Variables	N= 28 (%)
Age	
Neonates	9 (32)
<1year	5 (17.9)
1-5 years	3 (10.7)
>5 years	11 (39.3)
Gender	
Female	9 (32)
Male	19 (68)
Positive culture	25 (89)
-From one site	16 (57.1)
-From more than one site	9 (32.1)
Site of infection	
Bacteremia	15 (53.6)
Urinary tract infection	2 (7.1)
Pneumonia	6 (21.4)
Skin and Soft Tissue Infection	3 (10.7)
Meningitis/Ventriculitis	2 (7.1)
Intra-abdominal sepsis	6 (21.4)

Central line-associated infection	2 (7.1)
Pre-existing condition	21 (75)
Intensive care	22 (78.6)
Mechanical Ventilation	16 (57.1)
Length of hospital stay in days; Median (IQR)	30 (11-40)
Sterility achieved (Microbiological eradication) n=20	15 (75.0)
Antibiotic susceptibility pattern of isolated pathogens Multidrug-resistant Extensive drug-resistant	25 (89.2) 7 (25.0) 18 (64.3)
Duration of Tigecycline treatment in days; (Median (IQR))	11 (10-17)
Mortality	11 (39.3)

The most frequent isolated pathogens were E-coli 8 (28.6%), Acinetobacter 3 (10.7%), Serratia 7 (25%), Klebsiella 8 (28.6%), Raoultella 2 (7.1%), and all of them were carbapenem-resistant. Of the three patients who received empiric therapy with tigecycline for at least five days, one had Candida, one had Aspergillus Flavus, and one had pan-sensitive Enterobacter. The median duration of tigecycline therapy was 11 (10-17) days, and the median length of stay in the hospital was 30 (11-40) days. Twenty-two (78.6%) children were in the intensive care unit at the time of their infection with a median length of stay of 13 (6-19) days. The median duration of mechanical ventilation was 7.5 (4-14) days. Multi-organ involvement was seen in 10 (35.7%) cases. Tigecycline combination therapy was used with meropenem in 3 (10.7%) children, with meropenem, and colistin 13 (46.4%), with meropenem and Fosfomycin 9 (32%), with meropenem, Fosfomycin, and colistin in 3 (10.7%) children. Survival of Tigecycline targeted therapy with combination antibiotics is shown in table 2.

History of Medicine, 2024, 10(2): 1062-1073
DOI: https://doi.org/10.17720/d6q6m940

Table 2 Survival of Tigecycline targeted therapy with combination antibiotics.		
Combination therapy	Survival XDR n=11 (%)	Survival MDR n=4 (%)
Tigecycline + Meropenem	1 (7)	1 (7)
Tigecycline + Meropenem + Colistin	4 (27)	3 (20)
Tigecycline+ Meropenem + Fosfomycin	5 (33)	-
Tigecycline+ Meropenem + Fosfomycin+ Colistin	1 (7)	-

Microbiological eradication was checked in only twenty patients, achieved in 15 (75%) children with a median duration of 2.5 (2-3) days. The mortality rate of patients was 11 (39.3%), among which three (11%) had multidrug-resistant pathogens, seven (25%) had extensive drug-resistant pathogens, and one (3.6%) who had pan sensitive Enterobacter died due to respiratory failure secondary to comorbid (thalassemia major and hepatitis C). Data on the clinical adverse effects of tigecycline therapy after 48 hours of administration were not available in records. However, deranged liver function test in 6 (21.4%) cases, raised prothrombin time/international normalized ratio 2 (7.1%), raised blood urea nitrogen/creatinine 2 (7.1%) and thrombocytopenia in 20 (71.4%) children were identified, which may also have an alternative explanation of overwhelming sepsis. By comparing the mortalities of bacteremia and non-bacteremia infection through Fischer's exact test, they were insignificant. The mortality of all cases is summarized in table 3.

Table 3 Clinical presentation of children who expired with MDR and XDR gram negative infections.

Case #	Age	Gender	Pre-existing Condition	Multi-organ involvement (yes/no)	Site of culture	Isolated organism (MDR or XDR)	Combination therapy with tigecycline	Tigecycline therapy (days)	Length of stay (days)	Microbial eradication (yes/no)
1	Neonate	Female	Congenital heart disease/Meconium aspiration syndrome	Yes	Blood	Serratia (XDR)	Meropenem Fosfomycin Colistin	3	5	Yes
2	Neonate	Male	d-TGA status post arterial switch, pneumoperitoneum, laparotomy with wound dehiscence	Yes	Blood Trachea Peritoneum	Serratia (XDR)	Meropenem Fosfomycin	11	40	Yes
3	13 years	Male	B-cell ALL with Febrile neutropenia	Yes	Blood	E. coli (XDR)	Meropenem Colistin	4	25	Yes
4	4 years	Male	Intestinal Burkitt lymphoma, Status post laparotomy, Acute respiratory distress syndrome.	Yes	Blood	E. coli (XDR)	Meropenem	17	40	Yes
5	11 months	Male	Hemophagocytic lymph histiocytosis	Yes	Blood	Klebsiella pneumonia (MDR)	Meropenem Colistin	2	10	Not checked
6	3 months	Male	Pneumoperitoneum	Yes	Peritoneum	Raoultella (XDR)	Meropenem Colistin	10	16	Not checked
7	6 years	Female	B-cell ALL relapse with Febrile neutropenia	No	Blood	E. coli (MDR)	Meropenem Fosfomycin	14	39	No

8	13 years	Female	Status post left lower limb amputation due to degloving injury	Yes	CSF Skin and Soft Tissue	Raoultella (XDR)	Meropenem Fosfomycin	10	33	Yes
9	11 years	Male	-	Yes	Pleura Trachea	Serratia Klebsiella pneumonia (XDR)	Meropenem Fosfomycin Colistin	17	40	No
10	7 years	Male	B-cell ALL with Febrile neutropenia	Yes	Blood Central line	E. coli (MDR)	Meropenem Fosfomycin	10	12	No

d-TGA= Dextro-Transposition of the Great Arteries, ALL= Acute lymphoblastic leukemia, CSF=cerebral spinal fluid, MDR=multi drug resistant, XDR= Extensive drug resistant.

DISCUSSION

Data regarding the tigecycline in pediatrics and neonates is scarce. The use of tigecycline in the pediatric population has been reserved for the last resort for infection caused by MDR and XDR organisms though the drug is not FDA approved in the age group less than eight years (12). Among the 20 patients checked for microbial eradication, only 15 cultures became sterile; cultures were taken from various sites. Mortality related to bacteremia was eight out of eleven, among which five patients had microbial eradication (4 blood and 1 Cerebrospinal Fluid culture). The reason for these mortalities might have been septic shock and multi-organ failure secondary to sepsis. Three patients could not achieve a sterile profile (2 of them had bacteremia), and the rest of the three patients' sterility was not checked. One study report that sustained bacteremia might contribute to hemodynamic changes to extracellular fluid, decreasing the Area under the curve (AUC) of tigecycline and resulting in suboptimal dosing (9). Meropenem was used in all cases with tigecycline for synergism even though all patients reported carbapenem resistance. Except for one, all the mortalities had multi-organ involvement. Studies by Mastrolia et al. and E. Roilides et al. also note increased mortality with patients who received tigecycline therapy for bloodstream infections than non-bacteremia (8, 13).

Among the neonatal population, one study reported tigecycline's use in seven patients (14), while a 5-year experience has reported its use in only four neonates (9). Our study has reported use in nine neonates. Two of them had bacteremia. We used a dose of 2 mg per kg as loading and then 1 mg per kg per dose as maintenance therapy. A case series reported

maintenance dosages ranging from 1 – 3.2 mg/ kg per dose in children, while other similar studies have reported dosages with wide variability (7, 11, 13, 15).

In our study, MDR E. Coli and Klebsiella was the most common causative agent for infections. In a study reported by Mian-Lian Wu et al., Acinetobacter was the most common microorganism indicated for tigecycline use (10). The use of tigecycline in MDR and XDR cases targets two resistance mechanisms, namely efflux pump mechanism and ribosomal activation (16, 17).

Clinical adverse effects were difficult to distinguish from the disease course; however, in previously published literature, thrombocytopenia was the most reported adverse effect with tigecycline use (9, 18, 19). Twenty patients developed thrombocytopenia 48-hours post tigecycline initiation, though the exact cause is still unknown and can be due to infection, parenteral nutrition or hypoxic insult. The other adverse effects found in our study with tigecycline use were deranged LFTs, increased INR and increased creatinine. Elevated LFTs and coagulation profiles have also been reported previously (13, 20). A recent study also reported a 34.6% elevation in INR with tigecycline use (21). Moreover, children's adverse effects reported with tigecycline use included diarrhea, vomiting, acute pancreatitis, and delayed neutrophil engraftment (11, 22, 23).

The strength of our study is the inclusion of neonatal and pediatric patients presenting with MDR and XDR organisms with different cultural sites. Though this was a single-center retrospective study, it reports the safe and effective use of tigecycline in the absence of a sufficient amount of clinical data. As the studies reported for tigecycline use in pediatric patients less than eight years of age are primarily single-center and retrospective with a variation in the dose, use reported in this review warrants the need for a trial to determine the appropriate dose and duration of tigecycline in children as salvage therapy. Our study was a retrospective chart review of hospital records, and data on all variables for the severity scoring for the complicated cases were not available.

Conclusion:

In the era of multidrug-resistant organisms, much attention is being given to old antibiotics. The use of tigecycline in pediatrics and specifical neonates is not much studied previously. Hence, we report clinical outcomes from the use of tigecycline in pediatric and neonatal patient populations as salvage therapy, where in most cases, it has been successful in eradicating the disease-causing pathogen. However, there is a need for randomized control trials and pharmacokinetic-pharmacodynamics analysis of tigecycline in pediatrics and neonates to optimize dose and therapeutic outcomes.

References:

1. Elshamy AA, Aboshanab KM. A review on bacterial resistance to carbapenems: epidemiology, detection and treatment options. Future science OA. 2020;6(3):FSO438.
2. Livermore DM, Woodford N. The β-lactamase threat in Enterobacteriaceae, Pseudomonas and Acinetobacter. Trends in microbiology. 2006;14(9):413-20.

3. Morrill HJ, Pogue JM, Kaye KS, LaPlante KL, editors. Treatment options for carbapenem-resistant Enterobacteriaceae infections. Open forum infectious diseases; 2015: Oxford University Press.
4. Yaghoubi S, Zekiy AO, Krutova M, Gholami M, Kouhsari E, Sholeh M, et al. Tigecycline antibacterial activity, clinical effectiveness, and mechanisms and epidemiology of resistance: narrative review. European Journal of Clinical Microbiology & Infectious Diseases. 2021:1-20.
5. Zha L, Pan L, Guo J, French N, Villanueva EV, Tefsen B. Effectiveness and safety of high dose tigecycline for the treatment of severe infections: a systematic review and meta-analysis. Advances in therapy. 2020;37(3):1049-64.
6. Kuo S-C, Wang F-D, Fung C-P, Chen L-Y, Chen S-J, Chiang M-C, et al. Clinical experience with tigecycline as treatment for serious infections in elderly and critically ill patients. Journal of Microbiology, Immunology and Infection. 2011;44(1):45-51.
7. Sharland M, Rodvold KA, Tucker HR, Baillon-Plot N, Tawadrous M, Hickman MA, et al. Safety and efficacy of tigecycline to treat multidrug-resistant infections in pediatrics: an evidence synthesis. The Pediatric infectious disease journal. 2019;38(7):710-5.
8. Mastrolia MV, Galli L, De Martino M, Chiappini E. Use of tigecycline in pediatric clinical practice. Expert review of anti-infective therapy. 2017;15(6):605-12.
9. İpek MS, Gunel ME, Ozbek E. Tigecycline Use in Neonates: 5-Year Experience of a Tertiary Center. Journal of Pediatric Infectious Diseases. 2019;14(03):103-7.
10. Zhu ZY, Yang JF, Ni YH, Ye WF, Wang J, Wu ML. Retrospective analysis of tigecycline shows that it may be an option for children with severe infections. Acta Paediatrica. 2016;105(10):e480-e4.
11. Purdy J, Jouve S, Yan JL, Balter I, Dartois N, Cooper CA, et al. Pharmacokinetics and safety profile of tigecycline in children aged 8 to 11 years with selected serious infections: a multicenter, open-label, ascending-dose study. Clinical therapeutics. 2012;34(2):496-507. e1.
12. Slover CM, Rodvold KA, Danziger LH. Tigecycline: a novel broad-spectrum antimicrobial. Annals of Pharmacotherapy. 2007;41(6):965-72.
13. Iosifidis E, Violaki A, Michalopoulou E, Volakli E, Diamanti E, Koliouskas D, et al. Use of tigecycline in pediatric patients with infections predominantly due to extensively drug-resistant gram-negative bacteria. Journal of the Pediatric Infectious Diseases Society. 2017;6(2):123-8.
14. Ozkaya-Parlakay A, Gulhan B, Kanik-Yuksek S, Guney D, Gonulal D, Demirtas G, et al. Tigecycline therapy in pediatric patients with multidrug resistant bacteremia. Enfermedades infecciosas y microbiologia clinica (English ed). 2020;38(10):471-3.
15. Chen F, Shen C, Pang X, Zhang Z, Deng Y, Han L, et al. Effectiveness of tigecycline in the treatment of infections caused by carbapenem-resistant gram-negative bacteria in pediatric liver transplant recipients: A retrospective study. Transplant Infectious Disease. 2020;22(1):e13199.
16. Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiology and molecular biology reviews. 2001;65(2):232-60.
17. Peterson LR. A review of tigecycline—the first glycylcycline. International journal of antimicrobial agents. 2008;32:S215-S22.
18. Eckmann C, Heizmann W, Bodmann K-F, von Eiff C, Petrik C, Loeschmann P-A. Tigecycline in the treatment of patients with necrotizing skin and soft tissue infections due to multiresistant bacteria. Surgical infections. 2015;16(5):618-25.
19. Kenney B, Stack G. Drug-induced thrombocytopenia. Archives of pathology & laboratory medicine. 2009;133(2):309-14.
20. Hurtado IC, Trujillo M, Restrepo A, Garcés C, Tamayo C, Mesa JG. Experience with tigecycline compassionate use in pediatric patients infected with carbapenem resistant Klebsiella pneumoniae. Revista chilena de infectologia: organo oficial de la Sociedad Chilena de Infectologia. 2012;29(3):317-21.

21. Akdağ D, Işıkgöz-Taşbakan M, Pullukcu H, Sipahi H, Sipahi OuRa. Tigecycline versus INR increase; more than expected? Expert opinion on drug safety. 2020;19(3):335-7.
22. Maximova N, Zanon D, Verzegnassi F, Granzotto M. Neutrophils Engraftment Delay During Tigecycline Treatment in 2 Bone Marrow–transplanted Patients. Journal of pediatric hematology/oncology. 2013;35(1):e33-e7.
23. Prot-Labarthe S, Youdaren R, Benkerrou M, Basmaci R, Lorrot M. Pediatric acute pancreatitis related to tigecycline. The pediatric infectious disease Journal. 2010;29(9):890-1.