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Tigecycline Resistant Pattern among Carbapenem Resistant Gram-negative Bacilli: Prospective Cross-sectional Study

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Authors' contributions

This work was carried out in collaboration among all authors. Authors Jyoti and AP developed the Protocol. Authors GV and Jyoti collected the data. Authors CS and RS supervised the study and reviewed and edited the manuscript. Authors Jyoti, GV and RS wrote the original draft. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Tigecycline is a unique tetracycline class of semi-synthetic, last-line broad spectrum antibiotic against multi-drug-resistant bacteria. However, recently, resistance to this antibiotic is on the rise.

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Aims: This study was conducted to determine the prevalence of tigecycline resistance amongst carbapenem-resistant Gram-negative bacilli (GNB) isolated from clinical samples (pus and sputum) as well as to evaluate their antimicrobial susceptibility pattern.
Study design: Prospective cross sectional
Place and Duration of Study: Department of Microbiology at Sanjay Gandhi Post Graduate Institute of Medical Sciences Lucknow, between January 2023 and December 2023.
Methodology: Identification of GNB grown on culture was done by conventional biochemical tests and later validated by MALDI-TOF MS. The antimicrobial sensitivity testing of isolates was done using the E-test, and disk diffusion method. Minimum inhibitory concentration determination was done by Broth micro-dilution (BMD) method.
Results: Amongst 8326 pus and respiratory samples, GNBs were recovered from 63.15% (5258/8326). Of 5258 GNB isolates, 50.74% (2668) were carbapenem-resistant, while 7.85% (413) demonstrated resistance to both tigecycline and carbapenem. Common isolates in this group were *Klebsiella pneumoniae* (37.04%), *Acinetobacter* spp. (25.18%), *Enterobacter spp.* (14.28%) and *Escherichia coli* (12.59%). BMD results demonstrated highest activity of tigecycline against carbapenem-resistant *E. coli*, followed by *Citrobacter* and *Enterobacter*. It works against resistant strains of *Acinetobacter baumannii* and *K. pneumoniae* as well, but in higher concentrations.
Conclusion: High tigecycline resistance (one of the last-resort drugs) among carbapenem resistant GNB isolates is a matter of clinical concern, leaving physicians with limited options for treatment of such infections. Proper adherence to the policies of antimicrobial stewardship programs can reduce the emergence of resistance.

Keywords: Antibiotic; bacteria; carbapenem-resistant; gram-negative; tigecycline.

1. INTRODUCTION

Antibiotics are widely used to fight bacterial infections. They have revolutionized medical treatment in the last century. Introduction of modern day Penicillin by Alexander Fleming in 1928 set up the paradigms for many new groups of antimicrobials. [1]. Antibiotics target either the metabolic functions or the growth process of bacteria. Drugs that target the bacterial enzymes, cell wall or cell membrane are bactericidal, while those affecting protein syntheses are bacteriostatic. [2,3]. Widespread use, easy access and evolutionary processes over a long period have led to rise in drug resistance. Resistant bugs are responsible for life-threatening infections and one of the main reasons for increased mortality among infected patients [4]. Tetracyclines, which are known for their broad spectrum of activity against a wide range of Gram-positive and Gram-negative pathogens are at times the only agent which demonstrate sensitivity to the causative organism. New derivatives of the antibiotics in this group are capable of thwarting majority of the resistance mechanisms present in bacteria [5]. Tigecycline, a glycylcycline, is a unique tetracycline class of semi-synthetic, broad-spectrum drug used as the last-line treatment option against multi-drug-resistant Gram-positive and Gram-negative bacteria [6]. It was approved by the Food and Drug Administration (FDA) in 2005 for all severe infections, but in 2010, the FDA issued an alert that it can be used only in the treatment of severe infections of complicated skin and skin structure infection (cSSTI), complicated intra-abdominal infection (cIAI), and community-acquired bacterial pneumonia (CAP) [7]. Being an intravenous and bacteriostatic antibiotic; it is always used in combination with drugs like carbapenems, cephalosporins or quinolones [8–9]. Physicians refrain from using this antibiotic for endovascular infections because of its high volume of distribution leading to poor serum concentration [10]. The mechanism of action of tigecycline is alike other tetracycline group of antibiotics. It acts as an inhibitor of bacterial protein elongation via reversible binding to a helical region of 16s rRNA in the 30s subunit of the bacterial ribosome and physically prevents the elongation factor Tu-GTP aminoacyl t-RNA complex from binding to the A-site and decoding mRNA. The binding of this antibiotic prevents the incorporation of amino acid residues into the elongation of the peptide chain and results in the loss of peptide formation and bacterial growth [11,12].

According to a review, tigecycline resistance rate in Africa from 2004 to 2016 was about 5.8%, which was much lower than that observed in Europe (37.4%) and North America (36.8%) [7]. High resistance rates against tigecycline among GNBs was reported from USA as well: 9.2% in *K. pneumonia*, 20.8% in *Enterobacter aerogenes*, 38.5% in *Klebsiella oxytoca*, 25.4% in *E. cloacae* and 20.0% in *Serratia marcescens* [7]. A study

conducted by *Sader et al*. in Europe documented reduced susceptibility to tigecycline among 11.4% of the carbapenem-resistant Enterobacteriaceae [13]. Between the years 2005 and 2007, seven medical centers in India, documented low susceptibility (70.6%) of *Acinetobacter spp*. to tigecycline. [14]. In 2019, another study from South India demonstrated low susceptibility to tigecycline among *Klebsiella spp.* (84%) when compared to *E. coli* (98%) and *Enterobacter spp*. (98%). [15]. Tigecycline is an effective antibiotic against multidrug resistant (MDR) - *E. coli* and *K. pneumoniae* having Minimum inhibitory concentration (MIC 90) levels of 0.5 µg/ml and 4 µg/ml, respectively [16].

This study was undertaken to determine the prevalence of tigecycline resistance in carbapenem-resistant gram-negative bacteria in clinical samples (pus and sputum) and also to evaluate their antimicrobial susceptibility patterns.

2. MATERIALS AND METHODS

The study was conducted in the Department of Microbiology at Sanjay Gandhi Post Graduate Institute of Medical Sciences Lucknow, a 1600-bed tertiary care hospital, between January 2023 and December 2023. Clinical samples received in the bacteriology lab during the study period were first subjected to direct Gram staining and microscopy, following which, culture on blood agar and MacConkey agar was done and the culture plates were incubated overnight at 37°C. Colonies observed on the culture plates after incubation were processed according to standard laboratory methods that involved Gram staining of the colonies to differentiate between Gram-positive and Gram-negative bacteria. Conventional biochemical tests were used to identify the isolates which were further validated by Matrix-assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (MALDI-TOF-MS) [17]. *Escherichia coli* ATCC strain (ATCC8739) was used as control in MALDI-TOF MS. All biochemical tests were done in our laboratory according to standard protocols [18]. GNBs that were isolated and identified from the non-duplicate pus and respiratory samples were included in our study. *Pseudomonas*, *Proteus*, and *Morganella* species were not considered, as these show intrinsic resistance to tigecycline due to efflux mechanism. Antimicrobial sensitivity testing of all the selected gram-negative isolates was done using the E-test method for tigecycline and colistin, while the Kirby-Bauer disk diffusion method was used for imipenem (10µg), meropenem (30µg), amikacin (30µg), ceftriaxone (30µg), ceftazidime (30µg), cefoperazone + sulbactam, and minocycline (30µg). Breakpoints for tigecycline were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [19]. Breakpoints of colistin and zone diameters of other antibiotics were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) 2022 M-100 [20]. The BMD tests were performed for imipenem, meropenem, and tigecycline and minimum inhibitory concentration (MIC) was determined.

2.1 Statistical Analyses

Data were recorded and analyzed by Microsoft Access, and Excel software version 25 of SPSS. Descriptive statistics such as percentage, frequency, and cross-tabulation were used in our study to represent the results in the form of figures and tables.

3. RESULTS

A total of 8,326 clinical samples (5344 pus/exudate and 2982 respiratory samples including sputum, tracheal aspirate, bronchoalveolar lavage) were received in our bacteriology laboratory at Department of Microbiology in SGPGIMS, Lucknow during the study period, out of which, 63.15% (n=5258/8326) were culture-positive for GNB. On performing the antimicrobial susceptibility testing for all positive cultures, 50.74% (n=2668/5258) were resistant to at least two antibiotics in the carbapenem group; 8.1% (n=426/5258) isolates were resistant to tigecycline; and 7.85% (n=413/5258) were resistant to both carbapenems and tigecycline [Fig. 1].

Among the tigecycline resistant (n=426) isolates, 45.77% (n=195/426) were resistant to colistin, 46% (n=196/426) to minocycline, 93.66% (n=399/426) to beta-lactamase inhibitors, 94.13% (n=401/426) to cephalosporin, 77.46% (n=330/426) to aminoglycosides and 91.78% (n=391/426) to fluoroquinolones [Table 1]. Out of all tigecycline resistant isolates only 13 isolates were carbapenem sensitive.

Out of the 413 tigecycline and carbapenem-resistant isolates, 37.04% (n=153/413) were identified as *Klebsiella pneumoniae,* 25.18% (n=104/413) as *Acinetobacter baumannii*, 14.28% (n=59/413) as *Enterobacter spp*., 12.59% (n=52/413) as *Escherichia coli*, 9.68% (n=40/413) as *Citrobacter species*, and 1.21% (n=5/413) as *Klebsiella oxytoca* [Fig. 2].

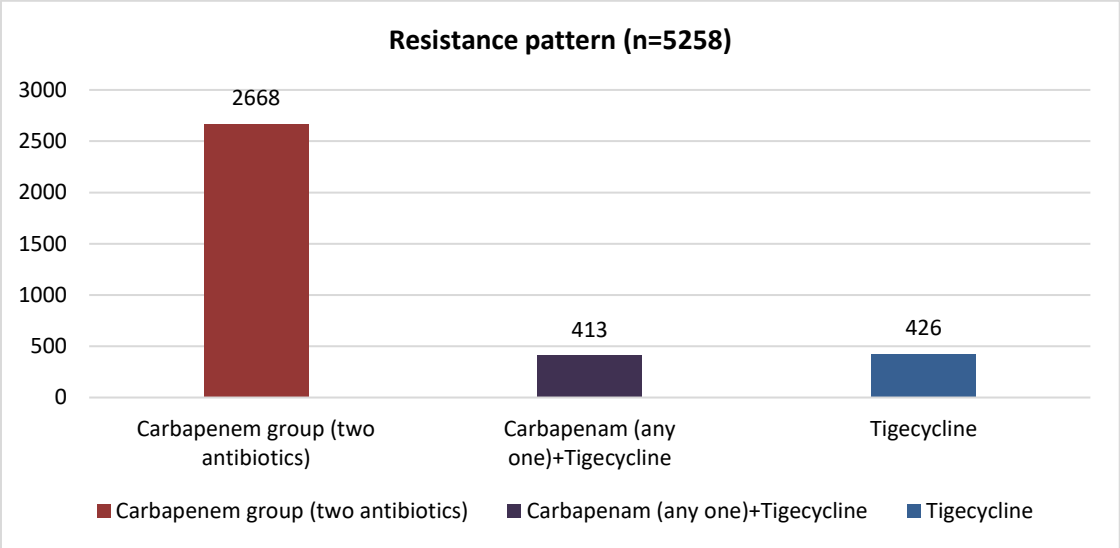

Fig. 1. Antibiogram of Gram-negative bacilli recovered in clinical samples

Table 1. Representation of other antibiotic resistance in isolates resistant to tigecycline (n=426)

Antibiotics	Resistant (%)	Sensitive (%)
Colistin	195 (45.77%)	232 (54.23%)
Minocycline	196 (46%)	230 (54%)
BL+BLI	399 (93.66%)	27 (6.34%)
Cephalosporin	401 (94.13%)	25 (5.87%)
Aminoglycosides	330 (77.46%)	343 (22.54%)
Fluoroquinolones	391 (91.78%)	35 (8.22%)

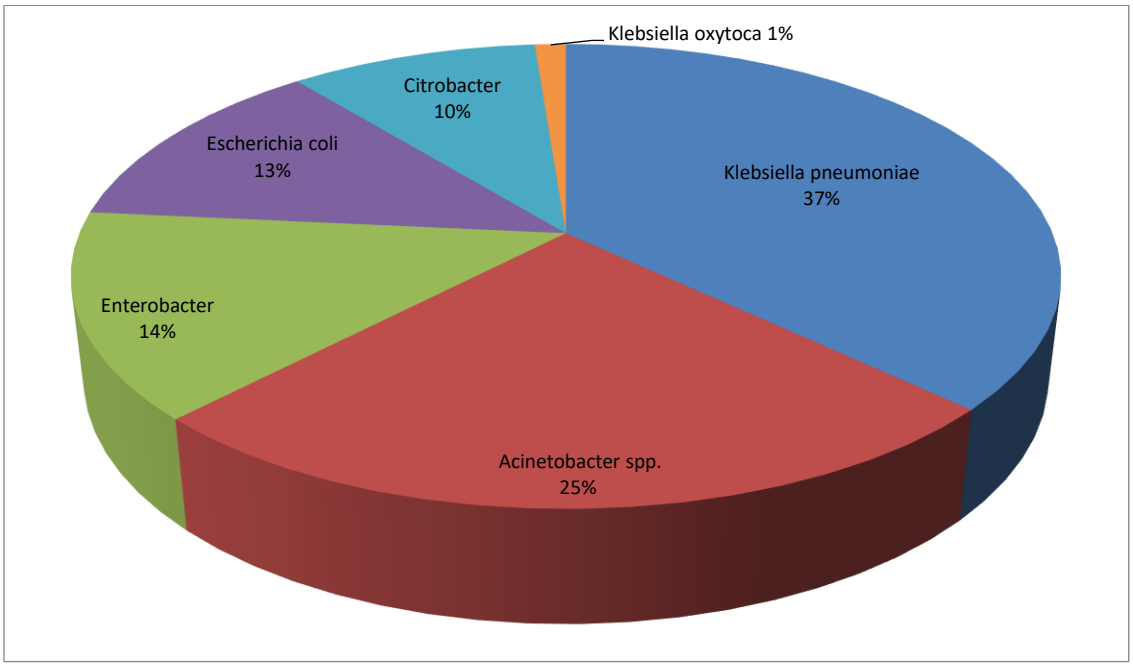

Fig. 2. Identification of bacterial isolates which were resistant to both tigecycline and carbapenem (n=413)

Table 2. MIC distributions for isolates for Imipenem, Meropenem and Tigecycline

Organism/ No. of Isolates	Antibiotics (range tested in µg/ml)	CLSI/ EUCAST breakpoint ≤S/≥R	Number of isolates with MIC (µg/ml)											% R
			≤1	≤2	4	8	16	32	64	128**	256	512	≥512	
Acinetobacter (50)	Imipenem (1-512)	≤1/≥4	-	-	-	-	6	1	4	4	14	14	7	100
	Meropenem (1-512)	≤1/≥4	-	-	2	1	3	2	2	17	6	8	9	96
	Tigecycline* (1-128)	≤1/≥2	-	-	8	7	3	7	13	(≥)12				100
K. pneumoniae (50)	Imipenem (1-512)	≤1/≥4	-	-	-	2	6	3	7	19	1	7	5	100
	Meropenem (1-512)	≤1/≥4	-	-	-	3	3	2	5	17	9	8	3	100
	Tigecycline* (1-128)	≤1/≥2	-	-	3	9	18	7	6	(≥)7				100
Enterobacter (50)	Imipenem (1-512)	≤1/≥4	-	-	-	4	3	7	11	8	9	3	5	100
	Meropenem (1-512)	≤1/≥4	-	-	1	3	5	9	12	7	6	3	4	98
	Tigecycline* (1-128)	≤1/≥2	-	3	9	17	10	6	3	(≥)2				94%
Citrobacter (40)	Imipenem (1-512)	≤1/≥4	-	-	-	2	6	7	6	4	9	2	4	100
	Meropenem (1-512)	≤1/≥4				3	6	4	11	9	4	2	1	100
	Tigecycline* (1-128)	≤1/≥2	-	2	8	13	4	5	7	(≥)1				95%
E. coli(50)	Imipenem (1-512)	≤1/≥4	-	-	-	3	2	-	3	18	17	5	2	100
	Meropenem (1-512)	≤1/≥4	-	-	2	3	4	4	13	16	5	2	1	96
	Tigecycline* (1-128)	≤1/≥2	-	3	9	17	8	1	6	(≥)6				94%

** EUCAST guidelines were followed to define breakpoints for Tigecycline, % R (Resistant)*

Among the isolates resistant to both carbapenem and tigecycline (n = 413), majority (70.9%, n=292/413) demonstrated simultaneous resistance towards aminoglycosides, first-generation cephalosporin, fluoroquinolones, and beta-lactamase inhibitors. Eighteen out of 413 (4.35%) isolates were found to be resistant to first-generation cephalosporin but susceptible to fluoroquinolones and aminoglycosides. However, 3.2% (n=13/413) resistant to aminoglycosides were found to be susceptible to first-generation cephalosporin and fluoroquinolones. The MIC of the clinical strains was determined by the BMD method. Fifty isolates of each strain and 40 isolates of *Citrobacter* spp. (due to less number) were included to determine the MIC value of imipenem, meropenem, and tigecycline [Table 2]. All isolates were resistant to imipenem, meropenem and tigecycline except 2 isolates of *Acinetobacter*, one isolate of *Enterobacter* and two isolates of *E. coli,* which were showing intermediate sensitivity to meropenem. Three isolates of Enterobacter, two of Citrobacter, three of *E. coli* were moderately sensitive to tigecycline [Table 2].

4. DISCUSSION

Antimicrobial resistance (AMR) with MDR strain has become a major global health issue [21]. The effectiveness of our current arsenal of antibiotics has been substantially hampered by AMR, and there are high chances that if a new drug is approved for clinical usage, it would eventually follow a similar pattern of development of resistance [22]. Tetracycline groups of antibiotics are widely used in the prevention and treatment of various types of bacterial infections (respiratory, skin, genital etc.) [23]. A new class of glycylcycline called tigecycline, has a broader spectrum of antibiotic activity that can inhibit both Gram-positive and Gram-negative bacteria as well as atypical, anaerobic, and antibiotic-resistant organisms [24]. In the current study on the clinical GNB isolates, we observed significantly high rate of resistance towards carbapenem and tigecycline. Amongst the isolates that were resistant to both tigecycline and carbapenems (n = 413), simultaneous resistance to beta-lactam-beta-lactamase inhibitors (BL-BLI) (93.66%), colistin (45.77%), minocycline (46%), cephalosporin (94.13%), aminoglycosides (77.46%), and fluoroquinolones (91.78%) was evident. The Tigecycline Evaluation and Surveillance Trial (TEST) study, which was undertaken globally between 2004 and 2014 to monitor the *in vitro* activities of tigecycline and a panel of antimicrobials against a range of clinically significant pathogens, described the effectiveness of tigecycline against MDR Gram-negative organisms like *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and members of the *Enterobacteriaceae* It was observed that 13% (n= 21,967/170,759) of isolates were MDR with maximum resistance observed among *Acinetobacter baumannii* isolates (44%). Low rates of tigecycline resistance among *Enterobacteriaceae* i.e. 15% (n=357/2402) for *Enterobacter* spp., 6% (n=235/4098) for *Klebsiella* spp. and 0.2% (n=8/3,222) for *E. coli* was observed in this global study, which was conducted more than a decade ago [25]. However, concurrent resistance to carbapenems, aminoglycosides, polymyxins and tigecycline (CAPT-resistant), are increasingly being reported worldwide (Pan-drug resistant GNBs in 25 countries in 5 continents) [26]. This indicates that we are slowly approaching the post-antibiotic era. A recent study from a tertiary care hospital in South Korea (2020) to evaluate tigecycline resistance in carbapenem-resistant *K pneumoniae* (CRKP) isolates showed resistance rate of 37.8% (17/45) [27] which was much higher than that reported in a multi-centric study done in the United States (18%) completed in 2013 [28]. In our study, an increased prevalence of tigecycline resistance (7.85%) among carbapenem-resistant clinical isolates was observed. It was worthy to note that only about 50% of tigecycline-resistant isolates were susceptible to colistin and/or minocycline. Reduced rate of colistin susceptibility in isolates might be due to its widespread use in healthcare sectors. Yan WJ, *et al* in his study from China on Carbapenem-resistant *Enterobacteriaceae* (CRE) showed an overall, 97% (295/305) susceptibility of his isolates to tigecycline and emphasized on improving strategies to monitor the resistant strains [29]. Mutations in *ramR*, *tetA,* and *rpsJ* genes were detected in tetracycline resistant isolates. Patients referred to tertiary care centres are uniquely threatened by MDR bugs as they have a history of being subjected to multiple antibiotic courses in the past. Despite being a single centre study, the prevalence data from our centre includes more than 5000 culture positive isolates representing a large region in Northern India. After extensive search of the literature, to the best of our knowledge, this is the first time that resistance to other antibiotics in tigecycline and carbapenem co-resistant isolates has been reported from India.

Often the antibiotics available to treat MDR GNB infections are tigecycline and colistin. Widespread use in clinical settings, either as a monotherapy or in combination with other antibiotics, resistance to tigecycline against *Klebsiella* spp. or other *Enterobacteriaceae* is on the rise [30]. The urgent need for developing more efficient antimicrobial treatments for CRKP infections is highlighted by the recent appearance of CRKP clinical isolates that are resistant to both tigecycline and colistin, as well as by the discovery of a plasmid-mediated colistin resistance gene called MCR-1 [31]. Similar to other studies from different geographical regions, the present study also confirms the emergence of pan-drug and multi-drug-resistant bacteria against last-resort antibiotics [32,33]. A study from Egypt detected a resistance rate of 16.8% of their enterobacterial isolates to both colistin and carbapenems [34]. The evolution of such multidrug-resistant isolates indicates a grim situation shortly where the treatment options for infectious diseases will either be limited or exhausted. Development of a new class of antibiotic takes almost two to three decades. With the development of resistance against the last retort antibiotics like colistin and tigecycline, physicians are left clueless in terms of treatment of infectious diseases in the future. It has been speculated that by 2050, antimicrobial drug resistance will kill more people than cancer [35]. There is a need for consolidated and rigorous efforts towards combating the menace of multi- or pan-drug resistance in bacteria to save mankind from infectious diseases.

Limitation of the study: This study is a single center study and hence may not be a true reflection of the community data. Moreover, our hospital being a tertiary care center, the patients referred to this place usually come after multiple prior admissions. This may be the reason for the high resistance pattern observed among GNBs in the present study. Correlation of microbial resistance with clinical outcome was not evaluated.

5. CONCLUSION

Carbapenems are considered one of the best antibiotics for treating infections caused by GNBs, but with the rapid emergence and dissemination of its resistance, physicians are left with limited options i.e. colistin and tigecycline. High tigecycline resistance among CR-GNBs is a matter of clinical concern. Knowledge of the local epidemiology and resistance patterns among clinical isolates are useful in planning treatment strategies. Tigecycline being a reserve drug, proper adherence to the policies of antimicrobial stewardship programs can prevent the emergence of its resistance. Further research can be done by genomic fingerprinting of the MDR isolates.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that no generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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