Medical Laboratory Journal
Online ISSN: 2538-4449
Golestan University of Medical Sciences

Comparative evaluation of in vitro activity of tigecycline using the disc diffusion method and the VITEK-2 COMPACT in clinical isolates at a tertiary care cancer center

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Abstract

Background: Tigecycline susceptibility testing and reporting remain enigmatic due to the lack of established guidelines. Disc diffusion, as a method of performing susceptibility testing, is more widely accepted worldwide due to its ease of use. Limited published literature is available from India on the utility of this method, especially in a cancer care setting. Hence, this study was conducted to evaluate the performance characteristics of disc diffusion by comparing its results with those of the VITEK-2 COMPACT, considering the latter as the standard.

Methods: Disc diffusion was performed using Kirby-Bauer's method on Mueller-Hinton agar with a HiMedia 15 mcg TGC disc, following FDA and EUCAST breakpoints. According to CLSI criteria, disc diffusion breakpoints can be considered acceptable when categorical agreement is ≥ 90%, the very major error is ≤ 1.5%, and the major error is ≤ 3%.

Results: Using Cohen's kappa coefficient, the kappa value was 0.328, with a p-value of <0.05. The agreement percentage observed was 60.84%. Two strains reported as resistant by VITEK-2 COMPACT were misclassified as sensitive by disc diffusion, resulting in a very major error rate of 0.76%. A major error rate of 9.5% and a minor error rate of 27.7% were noted, as 25 strains reported as susceptible were identified as resistant.

Conclusion: Since poor agreement was observed, exceeding the acceptable performance rate, the disc diffusion method was unacceptable according to CLSI criteria. There is a gap in uniformity and a lack of streamlined, harmonized TST, which might become an alarming cause for concern.

Article History

Received: 30 January 2024
Received in revised form: 16 June 2024
Accepted: 17 July 2024
Published online: 21 August 2024
DOI: 10.29252/mlj.18.4.17

Keywords

Tigecycline
Disk diffusion antimicrobial tests
Microbial drug resistance
Multiple drug resistance
Klebsiella pneumoniae
Broth microdilution test

Article Type: Original Article

Introduction

With the apparent rise in multidrug-resistant organisms, tigecycline (TGC) and colistin are often considered last-resort antibiotics in the pipeline. TGC, a minocycline derivative, overcomes major tetracycline resistance mechanisms (1). Tigecycline susceptibility testing (TST) and reporting remain enigmatic due to the lack of established guidelines by either the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST). EUCAST provides interpretive breakpoints for *Escherichia coli* and *Citrobacter koseri*, whereas CLSI mentions TGC only as part of quality control. According to CLSI 2023, rare cases may arise where an agent is appropriate for an isolate but lacks CLSI breakpoints (e.g., TGC) (2,3). In such cases, the FDA Susceptibility Test Interpretive Criteria (FDA STIC) should be consulted. The Food and Drug Administration (FDA) has provided interpretive criteria for TGC against Enterobacteriaceae for both disk diffusion and MIC testing (4). The outcomes of in vitro TST-classified as Susceptible (S), Intermediate (I), or Resistant (R)-depend on the testing method used. Disk diffusion, as a method of susceptibility testing, remains widely accepted worldwide due to its ease of use. However, limited published literature is available from India on the utility of this method for tigecycline susceptibility testing, particularly in a cancer care setting. Therefore, the study aimed to detect TST of gram-negative isolates from blood and stool cultures and evaluate the performance characteristics of disk diffusion by comparing its results with those from VITEK-2 COMPACT, considering the latter as the standard. The agreement between the interpretations of disk diffusion breakpoints and MIC results from VITEK-2 COMPACT, using FDA breakpoints for Enterobacterales isolates, was assessed. In addition, the study sought to analyze the changing trends in TST among these clinical isolates.

Methods

After obtaining Ethics Committee approval (IEC-3/900967), the study was conducted over six months, from May 2023 to October 2023, in the Department of Microbiology, ACTREC, TATA Memorial Centre, Navi Mumbai, I ndia. A retrospective analysis of a prospectively maintained laboratory database, including electronic systems and manual registers of TST results, was performed for a period of two years and two months (31.01.2021 to 31.03.2023). Isolates for which TST had been conducted concurrently by disc diffusion (DD) and VITEK-2 COMPACT-either as part of routine antibiotic susceptibility testing per lab protocol or upon request by clinicians-were included. Interpretations from DD were compared with MIC results obtained from VITEK-2 COMPACT.

Bacterial isolates were retrieved from routine bacteriology cultures of clinical specimens, such as blood, stool, urine, tissue, pus, and pus swabs. They were identified using standard microbiological techniques, including Gram's stain, colony morphology, biochemical tests, and, in some cases, VITEK-2 COMPACT when the results could not be reached manually. The isolates were obtained from carcinoma patients across various Disease Management Groups and Hematopoietic Stem Cell Transplant recipients, encompassing both admitted and outpatient statuses. Isolates for which only one method was performed were excluded from the study.

Disc diffusion was performed using Kirby Bauer's method on Mueller-Hinton agar and a Hi-media 15 mcg TGC disc, following CLSI guidelines and the manufacturer's instructions.

The VITEK-2 AST-N406 (Biomerieux, Inc., Durham, NC, USA) testing was performed using software version 5.04. The susceptibility card contained tigecycline at concentrations of 1.5.4 and 8 µg/ml, used according to the manufacturer's recommendations. It employs a miniaturized, abbreviated, and automated version of the doubling dilution technique for determining Minimum Inhibitory Concentrations (MICs) through the microdilution method.

FDA breakpoints were applied, where disc diffusion diameters of ≥19 mm were considered sensitive, 15-18 mm intermediate, and ≤14 mm resistant. MIC recommendations were as follows: ≤2 µg/ml as sensitive, 4 µg/ml as intermediate, and ≥8 µg/ml as resistant (3). For comparing results in case of *E. coli*, the EUCAST guidelines were used: a zone diameter of ≥18 mm was considered sensitive, and <18 mm was considered resistant. MIC values of ≤0.5 µg/ml were classified as susceptible, while values >0.5 µg/ml were resistant (4).

The misclassification of a resistant strain as susceptible by DD was considered a very major error (VME), whereas the reporting of a susceptible strain as resistant was classified as a major error (ME). The interpretive categories of either susceptible or resistant reported as intermediate, or vice versa, were considered minor errors (mEs). Categorical agreement (CA) was evaluated as the percentage of isolate characterizations produced by the disc diffusion method that were consistent with the results (R, S, or I) reported by the VITEK-2 COMPACT method. According to CLSI criteria, when CA is ≥90%, VME is ≤1.5%, and ME is ≤3%, the disc diffusion breakpoints can be considered acceptable (5).

Descriptive statistics were used to summarize the data. Categorical data were described using counts and percentages. Concordance between the interpretations from FDA disc breakpoints and FDA MIC interpretations of VITEK-2 COMPACT was assessed using Cohen's Kappa statistic, and its 95% confidence interval was reported. Concordance between interpretations was visualized using

a River Plot. A Kappa value of less than 0.4 was considered poor, between 0.4 and 0.75 was considered good, and greater than 0.75 represented excellent agreement. A negative Kappa value indicated agreement worse than expected, or disagreement. Trends in tigecycline susceptibility were assessed using proportions. A p-value of less than 0.05 was considered statistically significant. All data analysis was performed using SPSS software (Version 25.0).

Results

A total of 263 isolates were enrolled in the study. Isolates from stool specimens received for weekly surveillance reporting comprised the majority, 180 (68.44%), followed by blood cultures, 50 (19.01%). Other specimens included CSF, 7 (2.67%); wound swabs, 5 (1.90%); sterile body fluid, 5 (1.90%); sputum, 5 (1.90%); NDBAL, 3 (1.14%); urine, 2 (0.76%); abdominal suture site swabs, 2 (0.76%); drain fluid, 1 (0.38%); liver tissue, 1 (0.38%); pleural fluid, 1 (0.38%); and ventriculoperitoneal shunt fluid, 1 (0.38%).

Table 1 shows the distribution of Gram-negative isolates in the study. *Escherichia coli* was the most commonly isolated organism, 142 (54%), followed by *Klebsiella spp*, 102 (38.78%). *Acinetobacter* spp and Gram-negative non-fermenters were interpreted with Enterobacterales breakpoints, but no comparisons could be made due to the small number of isolates.

Table 1 also shows the mean diameter of inhibition and median MIC along with respective ranges for *E. coli*, *Klebsiella spp*, and non-fermenter Gram-negative bacilli. Since these bacilli were few in number, not much statistical correlation could be carried out by considering them as a group.

Table 2 shows the overall distribution of susceptibility and the comparison profile between both methods. Major discordance was observed in the results, as 76.0% of isolates were reported as susceptible by VITEK-2 COMPACT compared to 47.14% by disc diffusion. A significant discordance was noted in the intermediate category, with only six (2.28%) isolates reported as intermediate by VITEK-2 COMPACT, while disc diffusion showed 76 (28.89%). The resistant category did not show much variation between the two methods: 57 (21.67%) vs. 63 (23.9%) by VITEK-2 COMPACT and disc diffusion, respectively. VITEK-2 MIC showed 76% overall susceptibility, which included 50.95% (134/263) *E. coli* and 18.63% (49/263) *Klebsiella pneumoniae*. In contrast, disc diffusion testing showed 47.14% (124/263) susceptibility, comprising 36.50% *E. coli* and 5.70% *Klebsiella pneumoniae*. Tigecycline susceptibility among *E. coli* isolates using the FDA breakpoint on VITEK MIC was 94.36% (134/142), while using the EUCAST breakpoint it was 86.61% (123/142).

Table 3 and Figure 1 show the comparison of interpretations of disc diameters and MICs for 263 isolates. Using Cohen's kappa coefficient, the kappa value was 0.328, with a p-value of <0.05. The agreement percentage was 60.84%. Two strains reported as resistant were misclassified as sensitive by disc diffusion, resulting in a VME rate of 0.76%. MEs were noted at 9.5%, and mEs at 27.7%, as 25 strains reported as susceptible were identified as resistant. Lesser CA was observed in blood culture isolates (58%) compared to stool samples (63.89%), although this trend was not observed in the agreement values for *E. coli* in blood (77%) and stool (68.75%) or for *Klebsiella* in blood (60.41%) and stool (57.14%). No comparison showed good agreement, except between EUCAST MIC and FDA MIC, but with a p-value of 0.477, this was not statistically significant. On comparing disc diffusion and VITEK interpretations using EUCAST and FDA breakpoints for *E. coli*, poor agreement was noted. Since poor agreement was observed and disc diffusion diameters exceeded the acceptable performance rate, they were not deemed acceptable according to CLSI criteria.

Table 1. Distribution of mean, median and ranges for disc diameter and mic of gram-negative isolates

Organism		No	Percentage	Median MIC	Range of MIC	Mean diameter	Range of diameter
Acinetobacter Baumanii		6	2.28%	NA	NA	NA	NA
Enterobacterales	*Enterobacter aerogenes*	1	0.38%	NA	NA	NA	NA
	Enterobacter cloacae	6	2.28%	NA	NA	NA	NA
	Escherichia. coli	142	54%	1.5	0.5-8	22	10-30
	Klebsiella spp.	102	38.78%	3.7	0.5-8	15	4-25
Other Gram-negative non-fermenters		6	2.28%	0.5	0.5-6	23	10-26

MIC=Minimum Inhibitory Concentration; Spp=Species; NA=Not Applicable

Table 2. Overall susceptibility profile of TGC by two methods as per FDA interpretation

FDA interpretation of MIC	FDA interpretation of disc diameter			
	I	R	S	Total
I	3	1	2	6 (2.28%)
R	18	37	2	57 (21.67%)
S	55	25	120	200 (76%)
Total	76 (28.89%)	63 (23.9%)	124 (47.14%)	263

FDA=Food and drug administration; I=Intermediate; R=Resistant; S=Sensitive

Table 3. Profile of comparison of study isolates under various statistical headings

No	Comparison heading	Number of isolate (n)	Kappa	P-value	Very major error	Major error	Minor error	Categorical agreement	Interpretation
1	Overall isolates	263	0.328	0.00	0.76%	9.5%	1.14%	60.84%	Poor agreement
2	Stool specimen isolates	129	0.397	0.00	1.5%	9.3	38.7%	63.89%	Poor agreement
3	Blood culture isolates	50	0.2063	0.012	0%	14%	26%	58%	Poor agreement
4	*Escherichia coli*	142	0.194	0.00	0%	3.5%	25.3%	78.17%	Poor agreement
5	*E. coli* in blood	26	0.048	0.233	0%	3.84%	4%	77%	Poor agreement
6	*E. coli* in stool	112	0.213	0.00	0%	3.51%	27.67%	68.75%	Poor agreement
7	*Klebsiella* spp.	99	0.192	0.001	1.01%	18.18%	33.3%	44.45%	Poor agreement
8	*Klebsiella* spp. in blood	48	0.2437	0.2113	0%	10.41%	2.08%	60.41%	Poor agreement
9	*Klebsiella* spp. in stool	63	0.308	< 0.001	1.01%	0.08%	20.20%	57.14%	Poor agreement
10	EUCAST disc and MIC in *E. coli*	142	0.11	0.147	0.70%	19.01%	NA	69.72%	Poor agreement
11	EUCAST MIC and FDA MIC in *E. coli*	142	0.477	< 0.0001	0.70%	0.70%	NA	90.85%	Good agreement
12	EUCAST and FDA disc in *E coli*	142	0.473	< 0.0001	0.70%	0.70%	NA	73.9%	Poor agreement

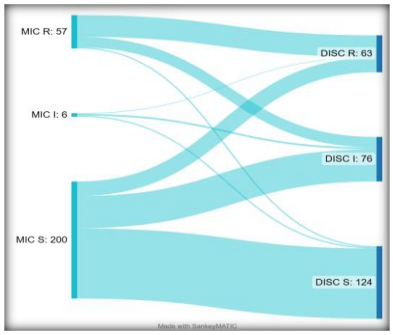

Figure 1. River plot showing the comparison between the two methods.
S=Sensitive, I=Intermediate, R=Resistant, MIC=Minimum Inhibitory Concentration.
Susceptibility results on the left side are given by VITEK-2 COMPACT, while the interpretations of disc diffusion are shown on the right side.

Upon analyzing the yearly trend of tigecycline susceptibility from 2021 to 2023, it was observed that the number of susceptible isolates increased from 96 (70%) in 2021 and 17 (18.68%) in 2022 to 30 (85.7%) in 2023. However, the total isolates collected in 2023 were only up to March, which may account for the smaller sample size. Tigecycline-resistant strains varied from 34 (24.8%) in 2021 to 17 (18.68%) in 2022 and 5 (14.28%) in 2023.

Discussion

TGC has emerged as a salvage drug as it overcomes resistance mechanisms applicable to tetracycline by evading tetracycline-specific efflux pump mechanisms and providing ribosomal protection (6). Although currently approved by the FDA (2005) for the treatment of complicated skin and intra-abdominal infections, there is a rising surge in clinical data supporting its use as monotherapy for empirical coverage of various MDRs (7). However, the fear of developing resistance is not far behind, as the detection of high-level TIG resistance has been observed due to mobile plasmid-mediated transmissible *tet*(X) and resistance-nodulation-division efflux pump *tmexCD-toprJ* genes (8).

In our study, disc diffusion exhibited poor performance compared with VITEK-2 COMPACT, showing a CA of 60.84%, VME of 0.76%, and ME of 9.5% when using FDA cutoffs (Table 3). Even when analyzed individually for *E. coli* (CA 78.17%, VME 0%, ME 3.5%), *Klebsiella spp*. (CA 33.3%, VME 1.01%, ME 18.18%), stool culture isolates (CA 63.89%, VME 1.5%, ME 9.3%), and blood culture isolates (CA 58%, VME 0%, ME 14%), the disc diffusion breakpoints did not perform well. Furthermore, there was no specimen-specific variation observed when comparing disc diameter performance for *E. coli* in blood (CA 77%, VME 0%, ME 3.84%), *E. coli* in stool (CA 68.75%, VME 0%, ME 3.51%), *Klebsiella spp*. in blood (CA 60.41%, VME 0%, ME 10.41%), and *Klebsiella spp*. in stool (CA 57.14%, VME 1.01%, ME 1.01%), as poor agreement was noted across all groups. Due to its high volume of distribution, tigecycline achieves very low serum concentrations (0.6 mg/L) with standard dosing, and it is therefore not reported as a drug of choice for bacteremia. However, it is used in centers catering to immunocompromised populations, where last-resort antibiotics may be critically required as lifesaving drugs under compassionate use protocols and cascade reporting protocols (9). In addition, weekly stool sample surveillance for admitted patients from hematolymphoid wards (Both adult and pediatric), as well as pre- and post-bone marrow transplant patients, is conducted at our center to evaluate gut microbiota changes and guide empirical drug selection in cases of gut translocation leading to sepsis (10). While some of the comparisons were statistically significant ($p < 0.05$), they did not show any significant agreement.

Disc diffusion reported lower susceptibility rates compared to VITEK-2 COMPACT (Table 2). This could be attributed to the higher manganese content in the media used for disc diffusion testing. J. Veenemans et al. have suggested that manganese concentrations in the test medium above 8 mg/L can affect in vitro TST results, whereas tigecycline's activity remains unaffected in human serum, which contains lower manganese concentrations (11). In addition, variations in divalent cation concentrations have been reported to affect the results of antibiotics such as piperacillin, gentamicin, amikacin, tobramycin, and tetracycline in Mueller-Hinton broth or agar from different manufacturers, with manganese concentrations above 500 mg/L being particularly notable (12-15). Various studies have investigated differences in inhibition zone diameters and E test results based on manganese content, with smaller zones observed at higher manganese concentrations (16-18). The Mueller-Hinton agar used in our study from HiMedia contained 210 µg/L of manganese, which is significantly higher than the normal range reported in human serum (0.8-1.2 µg/L). This elevated manganese content contributed to the lower susceptibility rates reported by disc diffusion (19,20).

A major discrepancy noted in our study pertains to the reporting of the Intermediate category. The "Intermediate" category indicates an equivocal result and should be reported if the organism is not susceptible to other alternative drugs. This category also serves as a buffer zone, accommodating technical variations. VITEK-2 COMPACT reported six strains as intermediate, compared to 76 reported by disc diffusion diameter. Among the 76 intermediate strains, only three were concordantly intermediate by both methods. Fifty-five of the 76 intermediate strains were reported as sensitive by VITEK-2 COMPACT. This contrasts with the phenomenon of false resistance reported by Lat et al. (21). The VITEK-2 COMPACT AST card N-406 contains tigecycline concentrations of 1.5, 4, and 8 µg/mL, with a calling range of ≤0.5 to ≥8. Whether VITEK-2 COMPACT falsely reported these strains as sensitive cannot be conclusively determined without comparison to the reference Broth Microdilution test. Nonetheless, the influence of high manganese content on the reporting of these strains as intermediate also cannot be overlooked. In summary, MIC values of 1.5-2 from VITEK-2 COMPACT require careful assessment with BMD before reporting. Overlapping MICs in this range should be meticulously evaluated through clinical trials in the future to establish appropriate in vivo correlations.

Susceptibility to tigecycline varies from 97-98% in *E. coli* and 82-90% in *Klebsiella pneumoniae* as reported by various studies (22-30). Recent studies from India have shown a decrease in susceptibility rates compared to previous years (25). In our study, no such trend was observed, as 70.58% of strains were reported as sensitive in 2021, while 79.2% were reported in 2022. However, a larger number of isolates followed over a longer time period is needed to generate more data for evaluating susceptibility rate trends over years.

There was also discordance in the susceptibility pattern of *E. coli* reported by the FDA and EUCAST guidelines, but a good agreement was observed between them (Table 3). Since 2019, a grey zone has emerged for isolates with MICs of 0.5-8 µg/ml. These may be termed resistant according to EUCAST but susceptible or intermediate according to the FDA, as EUCAST considers an isolate with an MIC > 0.5 mg/L resistant. Despite the sixteen-fold difference in MIC cutoffs for reporting resistance between the two methods, no major discrepancies were noted in our study. This could be attributed to the mean MIC of *E. coli* isolates in our study, which was 1.07. This value might explain the lack of significant discrepancies, as no extreme values were observed in the data that could influence interpretation according to EUCAST (31).

Table 4 highlights different studies conducted in various locations to compare interpretations of different methods for TST. No single method demonstrates complete agreement with BMD, and the studies do not unanimously endorse a specific method. This aligns with the findings of our study.

We could not perform a comparison with the broth microdilution test, which could have served as the gold standard for both tests. We will continue to collect isolates and perform TST using various other methods to gain a panoramic view of this subject.

To summarize, center-specific protocols can be developed by making appropriate comparisons with various methods to combat this enigma. Furthermore, microbiologists should abstain from unscientific and irrational reporting of TST. If such reporting is necessary on a compassionate basis, it should always be accompanied by microbiology-specific remarks stating the mode of reporting in your lab and the extent of its relevance.

Table 4. Various studies highlighting the comparison done between different methods of tigecycline reporting

No	Year	Place	Author	Methodology	Number of isolates	Result
1	2021	China	Hongling Li et al. (32)	Disc diffusion and VITEK-2 compact compared against BMD	100	VITEK-2 compact yielded major errors greater than 3%.
2	2021	Benha	Saleh (33)	Disc diffusion and VITEK-2 compact compared with BMD	35	Categorical agreement VITEK=78% Dis diffusion=74%
3	2018	Croatia	Branka Bednic et al. (34)	E test compared against BMD	154	94.7% essential agreement
4	2014	Italy	Grandesso et al. (35)	E test and VITEK-2 compared against BMD sensititre	85	Better agreement with VITEK-2
5	2012	Greece	Olympia Zarkotou et al. (36)	VITEK-2, E test, MIC testing strip compared against BMD	241	VITEK-2 produced 9.1/21.2% major errors.
6	2010	South East Michigan	Dror Marchaim et al. (37)	BMD, VITEK-2, MicroScan	4427	E test gave more resistant results.
8	2011	New York	Lat et al. (21)	VITEK-2, E test compared with BMD	48	VITEK-2 compact gave comparable results.
9	2015	Beijing, China	Zhang et al. (38)	MTS, Agar dilution, VITEK-2, disc diffusion compared against BMD	319	Major error rates by both VITEK-2 and disc diffusion
10	2018	Germany	Idelevich et al. (39)	VITEK-2 , BD Phoenix, MicroScanWalkaway and gradient diffusion assays E test and MIC Test Strip were compared against BMD	150	BD Phoenix and MIC Test Strip were better.
11	2018	Turkey	Simsek and Demir et al. (40)	E test compared with BMD	1265	Poor performance noted
12	2012	Belgium	Huang et al. (41)	VITEK compared with BMD	501	VITEK better for only E. *coli* isolates.

Conclusion

The disc diffusion method did not perform well compared to VITEK-2 COMPACT. Clinicians and laboratory personnel should be made aware of the discrepancies in reporting this drug. In the absence of appropriate breakpoints or standardized international guidelines from CLSI/EUCAST, AST guidelines for TST should be formulated at the national level to maintain uniformity in reporting.

Acknowledgement

We acknowledge Neha Jewrak for her contribution in collecting data for the manuscript and the technical staff of the microbiology department.

Funding sources

No funding was taken for this study.

Ethical statement

Institutional Ethics Committee permission was obtained (IEC-3/900967). A waiver of patient consent was granted as the study did not involve any direct contact with the patients, and no personal details of the patients were used in the analysis.

Conflicts of interest

There are no conflicts of interests to declare by any of the authors.

Author contributions

SL: conceptualized the study, supervised test performance, examined results, performed data analysis, and wrote the manuscript. VB: supervised test performance, examined results, supervised the literature search, and reviewed the manuscript writing. SB: reviewed the manuscript writing process. NK: encouraged SL and VB to investigate the clinical aspect of reporting Tigecycline in their patient population and conceived this original idea.

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How to Cite:

Lall S, Bhat V, Biswas S, Khattry N. Comparative evaluation of in vitro activity of tigecycline using the disc diffusion method and the VITEK-2 COMPACT in clinical isolates at a tertiary care cancer center. *Med Lab J.* 2024;18(4):17-21.