Tigecycline: Role in the Management of cIAI and cSSTI in the Indian Context

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Abstract
The current millennium has witnessed an increased antimicrobial resistance which poses a mammoth challenge for public health management. This has resulted in an increase in morbidity and mortality, resulting in an increase in financial burden to the patients. A recent analysis from 10 hospitals in India reported that mortality rate increases by 1.57 times in patients suffering from multidrug resistance (MDR) bacterial infections as compared to patients infected with similar but susceptible infections. Due to the emergence of MDR and extensively drug-resistant (XDR) bacteria, most of the broad-spectrum antibiotics have been rendered ineffective. The mortality rate with Gram-negative strains is higher than with Gram-positive strains. Tigecycline is the first in class glycyclycline antibiotic with an expanded broad-spectrum activity. Tigecycline enters bacterial cells through energy-dependent pathways or via passive diffusion, to reversibly bind to the 30S ribosomal subunit. It has potent in vitro activity against Gram-negative carbapenemase producers, except Pseudomonas aeruginosa and Proteus spp. It also has good in vitro activity against Carbapenem-resistant Klebsiella pneumoniae strains. Hence, it is considered as a therapeutic option in XDR isolates. Recent meta-analyses have shown tigecycline to be as effective as its comparators with reducing mortality rates. Due to increased resistance reported in carbapenem-resistant isolates in Indian health-care settings, a colistin/polymyxin B-based combination therapy as a treatment option is being sought. A lower mortality rate has been reported with colistin-based combination therapy in Carbapenem-resistant Enterobacteriaceae-associated infections. Combinations with tigecycline, Fosfomycin, and chloramphenicol have shown to improve treatment outcomes. Tigecycline can be a good alternative in MDR and XDR complicated intra-abdominal and complicated skin and soft tissue infections. Appropriately designed clinical trials in Indian health-care setups will reinforce clinician’s confidence in using tigecycline in complex clinical situations.

Keywords
Multidrug resistance, extensively drug resistance, tigecycline, carbapenem-resistant Enterobacteriaceae, combination therapy

Antibiotic Resistance in India
The threat of antimicrobial resistance has been a major challenge faced by the public health in the current millennium, with increased rates of morbidity, mortality, along with increased financial burden. The emergence and spread of multidrug resistance (MDR) have rendered most broad-spectrum antibiotics ineffective. Multidrug resistant pathogens such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), extended spectrum β-lactamase (ESBL), and metallo-β-lactamase (MBL) producing Gram-negative bacilli, all exhibit potent resistance mechanisms and are considered clinically important.

Results from the 2008 SMART (Study for Monitoring Antimicrobial Resistance Trends) trial revealed very low susceptibility rates to ampicillin sulbactam (28.8%) as well as high rates of ESBL-producing Escherichia coli and Klebsiella pneumonia (61.2% and 46.8%, respectively) in India.¹ A recent analysis of 10 Indian hospitals revealed a significant relationship between MDR and mortality; patients who acquired MDR bacterial infections were 1.57 times more likely to die compared to patients with similar susceptible infections.² In particular, in-hospital mortality was significantly higher among patients infected with MDR/extensively drug-resistant (XDR) pathogens such as Staphylococcus aureus, E. coli, Klebsiella pneumoniae, and Acinetobacter baumannii.² Among MDR infections, those caused by Gram-negative

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bacteria were associated with higher mortality rates vs. those caused by Gram-positive bacteria (17.7% vs. 10.8%).

Factors affecting the choice of antibiotics in these patients include the antimicrobial susceptibility, the site of infection, host factors like age, severity of illness, immune status, and comorbidities like renal failure, hepatic dysfunction, and the choice of antimicrobial combination therapy with optimal dosing. The emergence of these multidrug-resistant organisms is a matter of concern, particularly in patients with serious, complicated, and nosocomial infections as virtually all common infectious bacteria have developed resistance to at least 1 class of antibiotics. Tigecycline has been found to be active against multidrug-resistant Gram-positive and Gram-negative pathogens. The objective of this review is to reiterate the continued susceptibility of tigecycline against MDR pathogens based on recent evidence generated from India.

**Tigecycline—Spectrum of Activity**

Tigecycline is an expanded broad-spectrum, first in class glycyclcline antibiotic designed to overcome the major mechanisms of tetracycline resistance: drug efflux and ribosomal protection. It contains a central 4-ring carbocyclic skeleton, with a substitution of an N-alkyl-glycylamido group on the D-9 position which enables this. Tigecycline enters bacterial cells through energy-dependent pathways or via passive diffusion, to reversibly bind to the 30S ribosomal subunit. As such, it blocks the incorporation of aminoacyl-transfer RNA into the acceptor ribosomal A site, inhibiting protein synthesis. Due to its greater affinity to the corresponding ribosomal sites in comparison with tetracyclines, antibacterial activity against tetracycline-resistant organisms with Tet(M) protected ribosomes as well as organisms that display efflux-based resistance, tigecycline overcomes the problems with earlier tetracyclines. In addition, other common antibiotic resistance mechanisms such as target site modification, enzymatic degradation of the drug, and DNA gyrase mutations, which confer resistance to β-lactam antibiotics and fluoroquinolones do not affect tigecycline. Accordingly, tigecycline has demonstrated *in vitro* and *in vivo* activity against a broad spectrum of bacterial pathogens. In particular, tigecycline is active against difficult to treat pathogens such as MRSA, VRE, ESBL, and carbapenem-producing *Enterobacteriaceae* and as well as MDR strains of *Acinetobacter* spp. and *Stenotrophomonas maltophilia*. Conversely, tigecycline shows reduced activity against *Pseudomonas* spp., *Proteus* spp., *Providencia* spp., and *Morganella* spp. It follows that its primary role is to treat MDR Gram-negative infections caused by *Klebsiella* spp., *E. coli*, and *Acinetobacter* spp.

European Committee on Antimicrobial Susceptibility Testing (EUCAST) has issued the clinical breakpoints for tigecycline toward various organisms (see Table 1).

EUCAST and Clinical and Laboratory Standards Institute breakpoints are not issued for *A. baumannii*. British Society of Antimicrobial Chemotherapy recommends a minimum inhibitory concentration (MIC) method based on EUCAST nonspecies-related PK/PD breakpoints where MIC of ≤0.5 µg/mL is taken as sensitive (S) and >0.5 µg/mL as resistant (see Table 2).

As a part of Tigecycline Evaluation and Surveillance Trial (TEST), an on-going global surveillance study, World Health Organization “priority pathogens,” (including all priority 1 pathogens [carbapenem-resistant *A. baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, and third-generation cephalosporin-resistant and carbapenem-resistant *Enterobacteriaceae*), two priority 2 pathogens [vancomycin-resistant *Enterococcus faecium* and MRSA], and two priority 3 pathogens [penicillin-nonsusceptible *Streptococcus pneumoniae* and ampicillin-resistant *Haemophilus influenzae*) isolates collected between 2014 and 2016, from 5 regions (Africa [5 centers]; Asia [21 centers]; Europe [105 centers]; North America [33 centers]; and South America [15 centers]) were tested for their susceptibility and resistance. The MIC90 for tigecycline is depicted in Table 3.

### Table 1. Tigecycline Eucast Clinical Breakpoints

| Organism                                      | MIC Breakpoint (mg/L) | Zone Diameter (mm) |
|-----------------------------------------------|-----------------------|--------------------|
|                                               | Sensitivity ≤         | Resistant >        | Sensitive ≥       | Resistant <       |
| *Enterobacteriaceae*                         |                       |                    | 18c                | 18c                |
| Acinetobacter spp.                           | 0.5a                  | 0.5a               | IEe                | IEe                |
| Staphylococcus spp.                          | 0.5a                  | 0.5a               | 18                 | 18                 |
| Enterococcus spp.                            | 0.25a                 | 0.25a              | 18                 | 18                 |
| Streptococcus groups A                       | 0.125a                | 0.125a             | 19                 | 19                 |
| B C G                                        |                       |                    |                    |                    |

**Source:** eucast.org.

**Notes:**
- For tigecycline broth microdilution MIC determination, the medium must be prepared fresh on the day of use.
- IE insufficient evidence that the organism or group is a good target for therapy with the agent.
- Zone diameter breakpoints validated for *E. coli* only. For *C. koseri*, use an MIC method.
Susceptibility of common pathogens to tigecycline and comparator antibiotics was evaluated as a part of TEST study on clinical samples collected from 2 tertiary care centers in India (CMC, Vellore and Breach Candy Hospital Trust, Mumbai). A total of 989 isolates were collected between January 2015 and September 2017. The MIC for tigecycline and the comparator antibiotics was determined using broth microdilution method.

The results of the study were in-line with the globally reported values (Table 4). The authors concluded that tigecycline is a potential reserved drug owing to the growing drug resistance.19

Tigecycline has been approved in the United States and Europe for the treatment of complicated skin and soft-tissue infections (cSSTI) and complicated intra-abdominal infections (cIAI) and additionally for community acquired bacteria pneumonia (CAP) in the United States. In India, tigecycline was approved for the same indications by the CDSCO in August 2006.

### Concerns With Tigecycline Use

The effectiveness of tigecycline against MDR organisms against comparators has been studied in multiple studies with conflicting results. Cai et al20 reported no difference in all-cause mortality and drug-related mortality in the approved indications of cIAI, cSSTI, and CAP between tigecycline and other regimens in their meta-analysis. Subsequently, Tasina et al21 concluded that tigecycline is no better than standard antimicrobial agents for the treatment of serious infections and is associated with increased adverse events. While other meta-analyses have suggested that there is an increase in mortality with tigecycline treatment,22-24 these findings are reflected in the black box warning issued by the FDA which states: “An increase in all-cause mortality has been observed in a meta-analysis of Phase 3 and 4 clinical trials in TYGACIL-treated patients versus comparator. The cause of this mortality risk difference of 0.6% (95% CI 0.1, 1.2) has not been established. TYGACIL should be reserved for use in situations when alternative treatments are not suitable.”25 Nevertheless, it is important for clinicians to bear in mind that meta-analyses are subject to their own limitations including bias and heterogeneity.26

### Table 2. Tigecycline Antimicrobial Susceptibility—FDA.16

| Pathogen                          | Minimum Inhibitory Concentration (µg/mL) | Disk Diffusion (Zone Diameters in mm) |
|----------------------------------|----------------------------------------|---------------------------------------|
|                                  | S | I | R | S I R |                      |
| Staphylococcus aureus (including methicillin resistant isolates) | ≤0.5 | - | - | ≥19 | - | - |
| Streptococcus spp. other than S. pneumoniae | ≤0.25 | - | - | ≥19 | - | - |
| Enterococcus faecalis (vancomycin-susceptible isolates only) | ≤0.25 | - | - | ≥19 | - | - |
| Enterobacteriaceaeb | ≤2 | 4 | ≥8 | ≥19 | 15-18 | ≤14 |
| Haemophilus influenzae | ≤0.25 | - | - | ≥19 | - | - |
| Anaerobesc | ≤4 | 8 | ≥16 | NA | NA | NA |

Source: US Food & Drug.16

Notes: For disk diffusion, use paper disks impregnated with 15-mcg tigecycline.

Abbreviations: I, Intermediate; R, resistant; S, susceptible.

The current absence of resistant isolates precludes defining any results other than “susceptible.” Isolates yielding MIC results suggestive of “nonsusceptible” category should be submitted to reference laboratory for further testing.

Tigecycline has decreased in vitro activity against Morganella spp., Proteus spp., and Providencia spp.

Agar dilution.

### Table 3. The MIC90 of Tigecycline Against WHO Priority Pathogens.18

| Organism                  | Sample Size (n) | MIC90 (mg/L) |
|---------------------------|-----------------|--------------|
| Acinetobacter baumannii   | 2,720           | 2            |
| Klebsiella pneumoniae     | 6,561           | 1-2          |
| Escherichia coli          | 8,484           | 0.25         |
| Enterobacter spp.         | 7,725           | 1-2          |
| Serratia marcescens       | 2,957           | 2            |
| Pseudomonas aeruginosa    | 6,508           | 16           |
| Methicillin Resistant S. aureus | 2,820          | 0.12-0.5     |

Source: Seifert et al.18

Tigecycline resistance was found in Enterobacteriaceae (0.0%-0.3% using either FDA or EUCAST breakpoints), K. pneumoniae (0.0%-1.3% using FDA breakpoints and 3.4%-6.7% using EUCAST breakpoints), Enterobacter spp. (0.5%-1.1% using FDA breakpoints and 3.1%-4.8% using EUCAST breakpoints), and Serratia marcescens (0.0%-1.3% using FDA breakpoints and 2.7%-7.6% using EUCAST breakpoints).18

The statistical validity of some of the aforementioned studies have thus been questioned previously.27,28 Furthermore, a recent meta-analysis also showed that tigecycline was not associated with higher mortality vs. comparators and was observed to be as effective as comparators for its approved indication (5,268 patients, 11 trials, 2.5% tigecycline vs. 1.8% comparator; odds ratio [OR], 1.38; 95% confidence interval [CI], 0.95-2.00; P = .09).29 It remains that while the causality of excess mortality observed in clinical trials is unclear, it may relate to the underlying disease severity and activity of tigecycline against particularly virulent microorganisms.26
the illness and severity of the adverse events. However, the real-world evidence reflects the consistency of severely ill patients was not captured in phase-III studies. The apprehensions regarding the safety of tigecycline are associated with the fact that data evidence on tigecycline’s safety. The analysis was conducted as a part of picturizing real-world trends (SMART) 2009 program, 66 (28%) of the 235 isolates from India carried ≥1 carbapenemase gene of which 50% of these contained the blaNDM-1 gene. 37 In addition, the Indian subcontinent is also known to possess pathogens with the Class D OXA-181 carbapenem-hydrolyzing β-lactamases producing clones. 38 In 2008, the epidemic of MBL-producing Enterobacteriaceae (a Class B carbapenemase) increased dramatically with the isolation of an ST14 K. pneumoniae with a new MBL gene, blaNDM-1, from a patient who received treatment in New Delhi. 39 Carbapenem-resistant K. pneumoniae (CRKP) infections have also emerged as a pressing problem in the Indian ICU setting, and linked with increased mortality especially in solid organ transplant patients. 40-42 The imminent danger of CRE strains being disseminated in large hospitals can increase the burden of nosocomial infections, thereby limiting treatment options.

**Clinical Efficacy and Safety of Tigecycline**

Several randomized controlled trials have evaluated the efficacy of tigecycline and found it to be noninferior to comparators for the treatment of complicated skin and skin structure infections (cSSSIs) and cIAIs. 31 In an Indian study to evaluate the *in vitro* activity of tigecycline against carbapenemase-producing Gram-negative clinical isolates, potent *in vitro* activity against Gram-negative carbapenemase producers (using FDA breakpoint, sensitivity rates of tigecycline varied from 68% to 92%), except *P. aeruginosa* and *Proteus* spp., was demonstrated. 32 Retrospective analysis of data from 2 international, randomized, double blind studies assessing the safety and efficacy of tigecycline monotherapy in Indian (n = 86) and Taiwanese patients (n = 41) hospitalized with cSSSIs revealed comparable cure rates at the test-of-cure-assessment between tigecycline and vancomycin-aztreonam in the clinically evaluable populations in India (83.3% vs. 75.8%) and the clinical modified intent-to-treat populations (78.6% vs. 66.7%). 33 Nausea and vomiting occurred significantly more frequently with tigecycline in comparison to vancomycin-aztreonam; however, the authors concluded that these adverse events were mild to moderate and controlled with appropriate therapy. 33 Furthermore, serious adverse events (19/86 patients) were comparable between the 2 groups; even though 4 fatalities occurred in the Indian cohort, 3 in the tigecycline group, these were considered probably not or definitely not related to the study drugs. 33

**Table 4. Tigecycline Susceptibility (TEST Data From Two Indian Tertiary Care Hospitals).** 19

| Organism                     | Sample Size (n) | Susceptibility (%) |
|------------------------------|----------------|-------------------|
| *Klebsiella spp.*            | 140            | 84                |
| *Escherichia coli*           | 142            | 98                |
| *Enterobacter spp.*          | 106            | 95                |
| *Serratia spp.*              | 42             | 98                |
| *Haemophilus influenzae*     | 55             | 100               |
| ESBL-producing *Enterobacteriaceae* | 99          | 100               |
| *Meropenem-resistant Enterobacteriaceae* | 101       | 84                |
| *Staphylococcus aureus*      | 150            | 99                |
| *Enterococcus spp.*          | 89             | 98                |
| *Methicillin-resistant S. aureus* | 68          | 97                |
| *Vancomycin-resistant Enterococcus faecalis* | 7         | 100               |

Source: Veeraraghavan et al. 19

Safety data of tigecycline was pooled from 5 observational European studies. The patients included in these studies were hospitalized for cSSTIs (n = 254) or cIAIs (n = 785) and were prescribed tigecycline alone or in combination. Out of 254 patients with cSSTI, 190 experienced adverse events and 590 from 785 patients with cIAI experienced adverse events. Severe adverse events (SAEs) were recorded in 29 (14.6%) and 151 (25.6%) patients, respectively. The percentage of patients dying due to adverse events were 9.6% in cSSTI patients and 18.3% in cIAI patients. The most common SAEs leading to death were multigain failure (occurring in 8 [4.0%] cSSTI and 59 [10.0%] cIAI patients) and sepsis (occurring in 8 [4.0%] cSSTI and 36 [6.1%] cIAI patients). The analysis was conducted as a part of picturizing real-world evidence on tigecycline’s safety. The apprehensions regarding the safety of tigecycline are associated with the fact that data of severely ill patients was not captured in phase-III studies. However, the real-world evidence reflects the consistency of the illness and severity of the adverse events. 30

**CREs: A Growing Menace**

The growing worldwide problem of carbapenem resistance in *Enterobacteriaceae* is limiting treatment options for invasive Carbapenem-resistance *Enterobacteriaceae* (CRE)-associated infections such as bloodstream infections, urinary tract infections, wound infections, and pneumonia. The Centers for Disease Control and Prevention reports that every 1 in 7 catheters and surgery-related infections can be caused by a resistant pathogen including CREs. 34 As carbapenem resistance has been increasingly reported in Indian intensive care units (ICUs), the Indian Council of Medical Research advised 20 tertiary care hospitals in southern India to restrict the use of carbapenems and polymyxins. 35 Carbapenem overuse, especially in ICUs, contributes to increasing comorbidities leading to sepsis and fatality. 36

In the Study for Monitoring Antimicrobial Resistance Trends (SMART) 2009 program, 66 (28%) of the 235 isolates from India carried ≥1 carbapenemase gene of which 50% of these contained the blaNDM-1 gene. 37 In addition, the Indian subcontinent is also known to possess pathogens with the Class D OXA-181 carbapenem-hydrolyzing β-lactamases producing clones. 38 In 2008, the epidemic of MBL-producing Enterobacteriaceae (a Class B carbapenemase) increased dramatically with the isolation of an ST14 K. pneumoniae with a new MBL gene, blaNDM-1, from a patient who received treatment in New Delhi. 39 Carbapenem-resistant K. pneumoniae (CRKP) infections have also emerged as a pressing problem in the Indian ICU setting, and linked with increased mortality especially in solid organ transplant patients. 40-42 The imminent danger of CRE strains being disseminated in large hospitals can increase the burden of nosocomial infections, thereby limiting treatment options.
Managing CREs With Tigecycline

A prospective study by Kusuma et al43 at JSS Hospital, Karnataka found tigecycline to be effective in MRSA, MDR E. coli, and Acinetobacter isolates. In the case of CRKP infections, a recent 3-year prospective study by Mouloudi et al44 evaluated the use of tigecycline in patients after liver transplantation with infections caused by CRKP (n = 18). Overall, tigecycline showed good safety and tolerance in this patient cohort, suggesting that it may have a role even in compromised hosts. In addition, a systematic review by Ni et al45 revealed that the effectiveness of tigecycline in treating CRE-associated infections may be improved in a combination treatment. Subgroup analyses showed that 30-day mortality was significantly lower in patients who received tigecycline combination therapy than in those who received monotherapy (OR = 1.83 [95% CI = 1.07-3.12; P = .03]) and other antibiotic regimens (OR = 0.59 [95% CI = 0.39-0.88; P = .01]), respectively.

In recent years, emergence of tigecycline resistance has been due to subinhibitory concentrations of the drug being achieved for treating certain strains of MDR K. pneumoniae and E. coli, and expression of efflux pump genes associated decreased susceptibility.46 Therefore, judicious use and close monitoring is essential to preserve the efficacy of this drug in critical illnesses.

Role of Combination Therapy

Although accurate clinical management of CRE infections is yet to be established, with increasing reports of carbapenem-resistant isolates in Indian health-care settings, combination therapy over monotherapy is being explored as a treatment option.40,47 The most active in vitro agents against CRE pathogens are considered to be colistin (polymyxin E) and polymyxin B.48 In fact, colistin and tigecycline have good in vitro activity against CRKP strains and are one of the therapeutic options in CRKP isolates.44,49 However, observations of colistin resistance in India are also being reported.50,51 A treatment outcome of 50 Indian patients with CRE-associated infections in a tertiary care hospital showed a comparatively lower mortality rate with colistin-based combination therapy (44.8%) than colistin monotherapy (66.6%).40 Combination therapy with agents such as tigecycline, fosfomycin, and chloramphenicol has been shown to improve treatment outcomes.47,52-53

Expert Opinion

In an era of drug resistance, and given the scarcity of new antibiotics, tigecycline has a place in therapy as a go to antibiotic.14,29 An in vitro study conducted between 2006 and 2012 to assess activity of tigecycline against bacterial isolate confirmed the continued potency against MDR Gram-positive organisms.12 The same study also reported an increase in MDR (from 4.4% in 2006 to 8.5% in 2012) and XDR (from 0.5% in 2006 to 1.5% in 2012) Enterobacteriaceae. The broad-spectrum activity of tigecycline puts it in a unique position in antibiotic therapy.54 Tigecycline has been found to be effective even against colistin-resistant strains of K. pneumoniae.47 There is apprehension in the minds of clinicians as there have been reports from trials showing increased mortality in the tigecycline arm. However, the real-world evidence reflects the severity of the adverse events to be related to the critical nature of the illnesses.30 Published data have shown that tigecycline in the approved dose and indications do not skew the mortality in the negative direction. The dearth of pan Indian clinical data needs to be addressed. Clinical studies in Indian health-care setups will help in generating robust data to support the in vitro evidence.

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The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr S Swaminathan has been a speaker at Pfizer forums and has received advisory board and consultant honoraria from Pfizer Ltd. Dr P Kundu is a full-time employee of Pfizer Ltd, India.

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