

In vitro susceptibility pattern of Tigecycline against MRSA, ESBL producing Escherichia coli, Klebsiella species and Acinetobacter isolates in a rural tertiary care hospital

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ABSTRACT

Background: Tigecycline is the first commercially available glycylglycine, derivatives of the tetracycline antibiotics, having enhanced activity against various pathogens. In vitro activity has been demonstrated against multi drug resistant Gram positive and Gram negative pathogens like MRSA, ESBL producing Esch.coli and Klebsiella spp. and Acinetobacter. **Objective:** To determine Tigecycline in vitro susceptibility pattern in MRSA, ESBL producing Esch.coli and Klebsiella spp. and Acinetobacter spp.

Material and Methods: Investigations were carried out from August 2012-January 2014 to detect MRSA,ESBL producing Escherichia coli and Klebsiella spp. as well as Acinetobacter spp. by using a standard protocols and Tigecycline in-vitro susceptibility testing was done by Kirby Bauer Disc diffusion method and it's MIC value against resistant isolates was evaluated.Statistical analysis was done by Fishers exact method.

Result: Out of 107 Staphylococcus aureus isolates 52(48.59%) were MRSA, none of them showed resistance to Tigecycline. Out of 82 Esch.coli isolates 14 (i.e 17.07%) were ESBL producers, none of them showed resistance to Tigecycline.Out of 67 Klebsiella isolates 21 (i.e 31.34%) were ESBL producers out of which only 1 (i.e 4.76%) was resistant to Tigecycline.Out of 19 Acinetobacter spp.isolated 3 (i.e 15.78%) were resistant to Tigecycline. The MIC range for ESBL producing Eschcoli, Klebsiella spp., MRSA and acinetobacter spp were 0.14-0.45 µg/ml,0.25-2.4 µg/ml,0.12-0.26 µg/ml, 1-3.2 µg/ml respectively.

Conclusion: The results of the study confirm the excellent in vitro activity of Tigecycline against Gram positive and Gram negative multidrug resistant pathogens.

Key words: Tigecycline, susceptibility, MRSA, ESBL producing Klebsiella spp, acinetobacter

Introduction

Due to gradual emergence and spread of multidrug resistant (MDR) pathogens in health care settings clinicians are facing an acute shortage of antibiotics with broad spectrum activity that can be suitably used in initial empirical therapy. [1] Pathogens like methicillin resistant Staphylococcus aureus (MRSA), vancomycin resistant enterococci (VRE) and extended spectrum β lactamase

(ESBL) producing Gram-negative bacilli harbour genetic determinants, which render them resistant to most of the available antimicrobials. Carbapenems were considered to be antibiotic of choice in the treatment of life threatening infections caused by MDR Enterobacteriaceae and non-fermenters such as Pseudomonas aeruginosa and Acinetobacter spp. However in recent years due to the emergence and spread of

Carbapenem resistant MBL producing non-fermenters, the only treatment option is the potentially toxic Colistin / Polymyxin B group of antibiotics. [2] Due to the alarming spread of these MDR bacteria both in the hospital and community settings there is a need for the development and evaluation of new broad spectrum antimicrobial agents.

In this scenario, the development of a new class of antimicrobial agents, glycylicyclines, represented by tigecycline, a 9-t-butylglyclamide derivative of minocycline is a significant advancement. Of the glycylicyclines, tigecycline is the most studied and appears to hold promise as a new antimicrobial agent that can be administered as monotherapy to patients with many types of serious bacterial infections. Tigecycline is the first commercially available member of the glycylicyclines. The glycylicyclines are derivatives of the tetracycline antibiotics, with structural modifications that allow for potent gram-positive, gram-negative, and anaerobic activity, including certain multidrug-resistant strains. [3-6]

The enhanced activity can be attributed to stronger binding affinity and enhanced protection against several mechanisms of resistance that affect other antibiotic classes such as tetracyclines. Tigecycline exhibits generally bacteriostatic action by reversibly binding to the 30S ribosomal subunit and inhibiting protein translation. Tigecycline has a spectrum of activity unparalleled by any other broad spectrum agent and includes Methicillin resistant *Staphylococcus aureus* (MRSA), Vancomycin resistant Enterococci (VRE), Penicillin resistant *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, Extended spectrum β Lactamase (ESBL) producing Gram-

negative bacteria, Multidrug resistant (MDR) *Acinetobacter* spp., anaerobes and rapid growing Mycobacterial species. [3,5,7] Moreover, tigecycline is not affected by most of the known mechanisms of resistance to tetracycline encountered in bacteria. However it has limited activity against *Pseudomonas aeruginosa* and reduced activity against *Proteus mirabilis*. Because of the promising microbiological, pharmacodynamic and pharmacokinetic profile against clinically important bacteria, tigecycline is being evaluated for empirical therapy of seriously ill patients. [5,8]

Its currently approved indications include complicated skin and skin structure infections and complicated intra-abdominal infections. It has also been found to be effective for the treatment of community- as well as hospital-acquired and ventilator-associated pneumonia and bacteremia, sepsis with shock and urinary tract infections. Tigecycline appears to be a valuable treatment option for the management of superbugs, especially where conventional therapy has failed.

Tigecycline has an excellent activity against various drug resistant pathogens, but there are variations in its susceptibility pattern in different parts of the world due to either genetic changes in the bacteria or indiscriminate use of antibiotics. Also there is dearth of data regarding Tigecycline susceptibility to multidrug resistant pathogens in this area. Therefore, in this context, the present study was undertaken to detect the in vitro susceptibility pattern of Tigecycline in terms of their MIC values against MRSA, ESBL producing gram negative bacteria as well as *Acinetobacter* strain isolated from various clinical samples in a tertiary care hospital. The knowledge of susceptibility pattern of Tigecycline thus obtained will

enable the clinicians to use the drug rationally for the treatment of multidrug resistant pathogens in this area.

Material and methods

This hospital based cross sectional prospective study was conducted in the department of Microbiology, Burdwan Medical College, Barhaman, West Bengal, within a study period of 18 months (August 2012-January 2014).

A total of 412 different samples of urine, blood, pus and respiratory secretions including sputum were processed during this period to isolate Staphylococcus aureus, Escherichia coli, Klebsiella spp., and Acinetobacter strains using conventional isolation and identification procedure based on Gram staining, colony morphology and biochemical reactions.^[9]

Acinetobacter isolates were identified by Gram stain followed by biochemical reactions including positive catalase and negative oxidase test, oxidative utilization of glucose, citrate utilization as the sole source sole carbon; and negative indole, methyl red, voges proskauer and urease test.^[10]

All the isolates identified were subjected to antimicrobial susceptibility testing by Kirby Bauer Disc diffusion method using antibiotic discs procured from Hi-Media Laboratories Pvt Ltd, India. The results were interpreted as per Clinical Laboratory Standards Institute (CLSI 2012).^[11]

Escherichia coli and Klebsiella spp. isolates which showed < 22 mm zone of inhibition with ceftazidime were subjected to ESBL confirmation test by Double Disk Synergy Test. An increase in zone diameter of ≥ 5 mm for ceftazidime tested in combination with Clavulanic acid vs. its zone when tested alone, was taken confirmatory for ESBL production by the strain.^[11] E.coli ATCC 25922 was used as quality control.

All Staphylococcus aureus isolates were tested for methicillin resistance by modified Kirby- Bauer disk diffusion technique using 30 microgram Cefoxitin disk. Plates were incubated on Muller Hilton agar at 33-35° C for 24 hrs, Susceptibility to Cefoxitin was interpreted as per CLSI guidelines.^[11] A zone diameter of > 22 mm was taken as susceptible, at < 21 mm as resistant. Quality control strain of MRSA ATCC 33591 was used along with test organism. Bacterial suspensions of isolates of ESBL producing Esch.coli and Klebsiella spp., all MRSA and Acinetobacter isolates were plated on Mueller Hinton Agar (MHA) and then Tigecycline E-strips (Hi-Media, India) were applied on inoculated media. The plates were incubated aerobically at 35-37°C for 16-20 hrs. The results of MIC and disk diffusion for Tigecycline were interpreted according to United States, Food and Drug Administration (FDA) approved guidelines.^[12]

FDA approved criteria for disc diffusion and MIC of Tigecycline

	MIC (µg/ml)	Zone diameter (mm)		
	S	S	I	R
MRSA	<0.5	> 19	15-18	<14
Gram-negative organisms	<2	> 19	15-18	<14

Statistical analysis was done by Fishers exact test using Epi info7 software and the findings were tabulated.

Results

A total of 275 samples were isolated from total 412 samples and the isolates were distributed in 83 (71.55%) of pus, 57(67.85%)of blood,44 (59.45%)of respiratory secretions including sputum and 91(65.94%) of urine samples (table1). Out of this 275 samples 82(29.81%) Esch.coli, 67(24.37%) Klebsiella spp. 107(38.90%) Staphylococcus aureus and 19(6.90%) Acinetobacter were isolated. (Table 2)

52 out of 107 Staphylococcus aureus isolates (48.59%) showed resistance to Cefoxitin and labelled as MRSA. Again among 82 isolated Escherichia coli, 14 (17.07%) and 21(31.34%) out of 67 isolated Klebsiella spp. were found to be ESBL producers. (Table 3)

Antibiogram of Staphylococcus aureus isolates revealed 104 (97.19%) were sensitive to vancomycin, 102(95.32%) to linezolid and 107 (100%) to Tigecycline. (Table 4a)

Antimicrobial susceptibility pattern of three gram negative bacteria (Esch. coli, Klebsiella spp., Acinetobacter) against 8 different antimicrobials showed variable range of sensitivity pattern as shown in (Table 4b).

Amongst the ESBL producing isolates, all Esch.coli (14/14,100%) were found to be Tigecycline sensitive whereas only one Klebsiella spp. i.e. 4.76% (1/21) was found to be resistant to it. The MIC range of ESBL Esch.coli was 0.14-0.45µg/ml and ESBL Klebsiella was 0.25-2.4µg/ml respectively. MIC value of all 52 MRSA isolates to Tigecycline were also within sensitivity range i.e. 0.1-0.26 µg/ml. Out of 19 Acinetobacter isolates only three (15.78%) were Tigecycline resistant and the MIC range was 1-3.2µg/ml. (Table 5)

Fishers exact test was done to difference in sensitivity on applying Ceftazidime and Tigecycline for Esch.coli, Klebsiella spp., and Acinetobacter spp. and Cefoxitin and Tigecycline for Staph aureus and was found to be highly significant P<0.05 as shown in table no6.

Table1: Total number of isolates obtained from various samples

Samples	Total no of samples cultured	Total no of isolate obtained
Pus	116	83(71.55%)
Blood	84	57(67.85%)
Respiratory secretions including sputum	74	44(59.45%)
Urine	138	91(65.94%)
Total	412	275(66.74%)

Table 2: Sample wise distribution of various isolates

SAMPLES	Esch.coli	Klebsiella spp.	Staph.aureus	Acinetobacter
Pus (n=83)	14 (16.86 %)	8(9.63%)	53(63.85%)	8(9.63%)
Blood (n=57)	14(24.56%)	18(31.57%)	23(40.35%)	2(3.5%)
Respiratory secretions including sputum (n=44)	9(20.45%)	14(31.81%)	16(36.36%)	5(11.36%)
Urine (n=91)	45(49.45%)	27(29.67%)	15(16.48%)	4(4.39%)
Total (n=275)	82(29.81%)	67(24.36%)	107(38.90%)	19(6.90%)

Table: 3 Percentage distribution of ESBL producing Esch.coli and Klebsiella spp. as well as MRSA isolates

Total number of microorganisms	ESBL producers	MRSA
Esch.coli (n=82)	14(17.07%)	-----
Klebsiella spp. (n=67)	21(31.34%)	-----
Staph.aureus (n=107)	-----	52 (48.59%)

Table 4a: Antibiotic sensitivity pattern of Staphylococcus aureus

Antibiotics	Staph aureus (n=107)
Cefoxitin(30µg)	55 (51.4%)
Linezolid(30µg)	102 (95.32%)
Cotrimoxazole(25µg)	78 (72.8%)
Vancomycin(30µg)	104 (97.19%)
Levofloxacin(5µg)	88 (82.24%)
Gentamicin(10µg)	82 (76.63%)
Tigecycline(15µg)	107 (100%)

Table 4b: Antibiotic sensitivity pattern of various isolates

ANTIBIOTIC	Esch.coli (n=82)	Klebsiella spp. (n=67)	Acinetobacter spp. (n=19)
Gentamicin (10µg)	41 (50%)	32 (47.7%)	3 (15.8)
Cefotaxime(30µg)	52 (63.4%)	38 (56.7%)	2 (10.5%)
Ciprofloxacin (5µg)	58 (70.7%)	42 (62.6%)	2 (10.5%)
Ceftriaxone(30µg)	51 (62.2%)	43 (64.2%)	5 (26.3%)
Amikacin (30µg)	68 (82.9%)	50 (74.6%)	5 (26.3%)
Cotrimoxazole (25µg)	38 (46.3%)	33 (49.3%)	4 (21%)
Ceftazidime(30µg)	68 (82.9%)	46 (68.6%)	5 (26.3%)
Tigecycline (15µg)	82 (100%)	66 (98.5%)	16 (84.2%)

Table 5: Interpretation of susceptibility of drug resistant isolates to Tigecycline in terms of their MIC values

Isolates	Total no	MIC range (µg/ml)	Sensitive	Intermediate	Resistant
ESBL E.coli	14	0.14-0.45	14(100%)	—	0 (0%)
ESBL Klebsiella	21	0.25-2.4	20 (95.20%)	—	1 (4.76%)
MRSA	52	0.12-0.26	52 (100%)	—	0 (0%)
Acinetobacter	19	1-3.2	16 (84.22%)	—	3 (15.78%)

Table 6: Statistical analysis as done by Fishers exact test

Isolates	Antibiotics	Sensitive	Resistant	P value
Esch.coli	Ceftazidime	68	14	<0.001
	Tigecycline	82	0	
Klebsiella spp.	Ceftazidime	46	21	<0.001
	Tigecycline	66	1	
Acinetobacter spp.	Ceftazidime	5	14	<0.001
	Tigecycline	16	3	
Staph.aureus	Cefoxitin	55	52	<0.001
	Tigecycline	107	0	

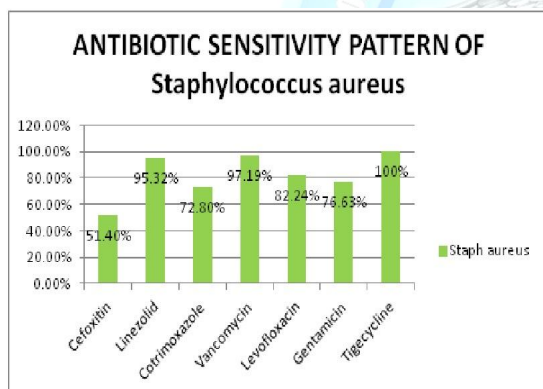


Fig. 1 Antibiotic sensitivity pattern

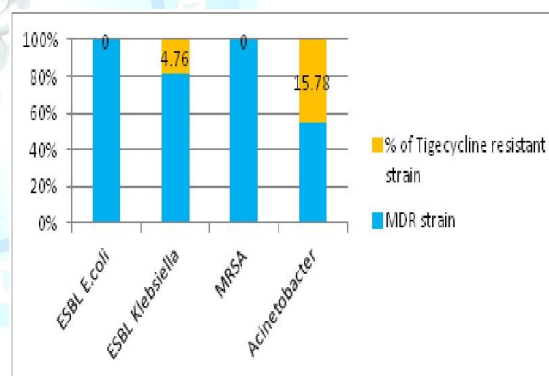


Fig. 3 Interpretation of susceptibility of drug resistant isolates to Tigecycline in terms of their MIC values

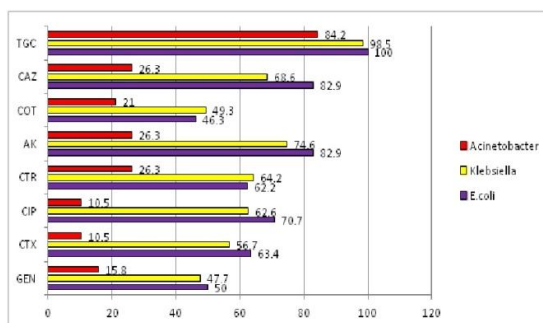


Fig. 2 Antibiotic sensitivity pattern of various isolates

(GEN=gentamicin, CTX=Cefotaxime, CIP=Ciprofloxacin, CTR=Ceftriaxone, AK=Amikacin, COT=Cotrimoxazole, CAZ=Ceftazidime, TGC=Tigecycline)

Discussion

The growing bacterial resistance against different antimicrobials has become an impending threat to the successful treatment of both communities as well as hospital acquired infections caused by multidrug resistant organisms. Moreover, formal antibiotic policies as well as lack of proper infection control measures in health institutions have further made the

situation more deteriorating in developing countries. In this context, the present study may help to throw a light on Tigecycline to come up as a potent antimicrobial agent against ESBL producing enterobacteriaceae, MRSA as well as notoriously drug resistant Acinetobacter strains.

In our study, we detected 17.07% of Esch. Coli (14/82), 13.34% (21/67) of Klebsiella spp. as ESBL producing and 48.59% (52/107) of Staph aureus as MRSA, (Table 3) almost similar results were found in a study conducted by Rossi F et al^[13] on the isolates collected from 33 centres in Latin America where 48.30% Staphylococcus aureus isolates were methicillin resistant and ESBL production were reported in 20.80% of E.coli and 36.70% of klebsiella and isolates.

In another study conducted on the isolates from Argentina by Fernandez et al^[14] also reported ESBL producing E.coli as 17.70% and those of Klebsiella as 50.50% among the total no of E.coli and Klebsiella isolates respectively. A bit decreased percentage values were reported from Denmark by Norskov-Lauritsen N et al^[15] on antimicrobial susceptibility of Tigecycline as comparators against bacterial isolates collected as part of the TEST study in Europe (2004-2007), where ESBL producing E.coli and Klebsiella pneumonia were 8.50% and 13.60% among all the E.coli and Klebsiella isolates and percentage of MRSA were 26.5% of all Staph.aureus isolates.

However in all the above three studies percentage values of ESBL producing Klebsiella spp. were greater than that of Esch.coli indicating that ESBL production is more among Klebsiella spp than Esch.coli.

Regarding Tigecycline sensitivity pattern, we observed no resistance among ESBL Esch coli but only one (4.76%)

isolate of ESBL Klebsiella was resistant to Tigecycline (MIC 2.4µg/ml). (Table 5)

In a study conducted by Anand Manoharan et al^[16] in Tamil Nadu on evaluation of Tigecycline activity in clinical isolates among Indian medical centers, also revealed that majority (90.90%) of the Enterobacteriaceae were found to be ESBL producers and Tigecycline was uniformly active against all Esch.coli and Klebsiella spp with MIC₉₀ =0.19 µg/ml and 1 µg /ml respectively.

Similar results were shown in a study conducted in Lebanon by Araj GF et al^[17] on Tigecycline in vitro activity against commonly encountered multidrug resistant gram negative pathogens in Middle East countries which showed no resistance to tigecycline in ESBL producing strains of E.coli and K. pneumonia. Jamal WY et al^[18] in their study in Kuwait on in vitro activity of Tigecycline against gram negative bacterial isolates including ESBL producing strains, reported ESBL production as 62% and 82.10% (higher percentage value than our study finding) among Esch.coli and Klebsiella pneumonia isolates respectively and tigecycline had excellent in vitro activity against ESBL-Enterobacteriaceae with MIC range 0.25-2 µgm/ml.

In our study all MRSA isolates showed 100% sensitivity to Tigecycline. Similar results were seen in a study conducted by Reinert et al^[19] on the isolates collected from Asia, Pacific rim, Europe, Latin and North America. Their results revealed 100% sensitivity of MRSA isolates to tigecycline by microdilution method. Anand Manoharan et al also reported excellent potency of Tigecycline against MRSA. (n=119, MIC₉₀= 0.19µg/ml) Souli et al^[20] showed 99% of MRSA isolates to be inhibited by Tigecycline at a concentration of <0.5 µ/ml.This was consistent well with our study finding where 100% of MRSA isolates were

inhibited by Tigecycline at a concentration of $\leq 0.26 \mu\text{g/ml}$.

Study conducted in Rawalpindi, Pakistan by Abdul Sattar^[21] observed that all MRSA isolates were sensitive to tigecycline with zone diameters ranging from 21-31mm by modified Kirby-Bauer disc diffusion method. Mean zone diameter was 25.48mm. The MICs of tigecycline against MRSA isolates revealed that all 100% isolates were in susceptible range with MICs from 0.047 to $0.32 \mu\text{g/ml}$, mean $0.097 \mu\text{g/ml}$.

In present study only 15.78% (i.e 3 out of 19) Acinetobacter isolates were found to be resistant to Tigecycline i.e 84.22% showed sensitivity to the drug which was somewhat more than value (i.e 61.40%) observed by Shareek P.S, D.Suresh Kumar et al^[22] in Apollo hospital, Chennai, India. However, Manoharan et al^[16] reported that among 17 MDR Acinetobacter spp. strain susceptibility to tigecycline was only 70.6%. Reported by Bijayini Behera et al,^[12] 42% isolates of Acinetobacter baumannii were found to be susceptible to Tigecycline, in their study from All India Institute of Medical Sciences, New Delhi, India. In another study conducted in Spain by R. Insa et al^[23] on in vitro activity of Tigecycline against clinical isolates of Acinetobacter baumannii, 88% of isolates were susceptible to Tigecycline and the range of MIC was 0.012-8 $\mu\text{g/ml}$ with MIC_{50} and MIC_{90} values 0.5 and 3 $\mu\text{g/ml}$ respectively which corresponded well with the present study finding. Study by Rouchelle Tellis et al^[24] in Mangalore showed all MRSA isolates were sensitive to Tigecycline by E-test method. The MIC_{90} and MIC_{50} for MRSA strains in the study was 0.25 and 0.12 $\mu\text{g/ml}$ respectively. All the ESBL producing members of family Enterobacteriaceae were sensitive to Tigecycline by E-test and disc diffusion method. MIC_{90} of E.coli and Klebsiella was

0.19 $\mu\text{g/ml}$ and $1 \mu\text{g/ml}$ respectively. Out of 14 MDR Acinetobacter spp., 11 were sensitive to Tigecycline by disc diffusion test but only 9 (64.28%) were sensitive by E-test. In another study conducted in USA by Pankey GA et al^[25] on In vitro antibacterial activity of tigecycline against resistant Gram-negative bacilli and enterococci by time-kill assay, Tigecycline MICs ($\mu\text{g/ml}$) were ≤ 1 for E. coli and K. pneumoniae, regardless of the isolates' ESBL production and for Acinetobacter baumannii MIC range was 0.06 to 4 $\mu\text{g/ml}$.

In our study statistical analysis also supported that sensitivity to Tigecycline against these pathogens was highly significant ($p < 0.05$) in comparison to other two discriminating drugs. (Table-6)

Tigecycline shows high potency against Gram-negative bacilli belonging to the family Enterobacteriaceae in whom multi-drug resistant strains have emerged as important nosocomial pathogens. In the present study we found that tigecycline had good activity against Esch.coli and Klebsiella spp.

Tigecycline also has good activity against other non-fermentative GNB, which includes Acinetobacter spp. Prevalence of tigecycline resistance amongst Acinetobacter spp. is worrisome. Combination regimen with Tigecycline needs further evaluation. The activity of tigecycline against staphylococci is completely unaltered by the presence of methicillin or glycopeptide resistance. It is the most potent antimicrobial when tested against glycopeptides resistant Staph.aureus. The potency of tigecycline was evident against both methicillin susceptible and resistant strain of Staphylococcus aureus.

Tigecycline does not require dose adjustment in patients with impaired renal function and is conveniently administered every 12 hourly. It appears

to have low potential for organ toxicity and drug-drug interactions. These properties, along with twice daily dosing parentally and the lack of need to monitor renal function, make the use of this antibiotic relatively uncomplicated. One concern will be for patients who develop moderate-to-severe nausea and vomiting during tigecycline therapy. Since it has proven activity against highly resistant organisms, it should be reserved only for life-threatening situations and/or when resistant pathogens are suspected. However its lack of activity against *P. aeruginosa* and low serum concentrations limits its use in some patient populations, such as those with neutropenic fever. The present study shows that tigecycline is a potent antimicrobial against ESBL producing Enterobacteriaceae, MRSA as well as drug resistant *Acinetobacter* spp..

In summary, tigecycline could be valuable therapeutic option for the treatment of infections caused by Multi drug resistant pathogens. Continued surveillance is necessary to generate local and epidemiological data on resistance profile of clinically important pathogens. This could also help in evaluating newer antimicrobial agents and guide rational antibiotic therapy.

Our study is limited by the fact that number of samples tested here were not much enough to be a representative one. Broad scale study in different geographical area should be needed further. Moreover, to test in vivo efficacy of Tigecycline was beyond the scope of our study.

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