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Antibiotic resistance pattern of enterobacteriaceae isolated from clinical samples with special reference to tigecycline sensitivity

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Abstract
Background & Objectives: Majority of the Gram negative pathogens causing Nosocomial infections belong to the family Enterobacteriaceae. They are normal flora in the intestine of the patients and develop antimicrobial resistance easily if antimicrobial is administered in appropriate dose. The emergence of the antimicrobial resistance in them is a therapeutic challenge. Various enzymes like ESBL, MBL etc. produced by them, make them resistant to beta lactums, the main group of antibiotic used. At present, only few drugs are available for the treatment of nosocomial infections caused by these multidrug resistant Enterobacteriaceae. Tigecycline has good therapeutic coverage against these pathogens. Thus, the study was undertaken to determine the in vitro susceptibility of the pathogens belonging to the family Enterobacteriaceae to tigecycline, especially to ESBL producers.
Methods: This was a prospective study conducted at the Department of Microbiology, Father Muller Medical College Hospital during the period from January to April 2016. The clinical isolates belonging to the family Enterobacteriaceae, isolated from various samples were included in the study. The antimicrobial susceptibility pattern of the pathogen was compared with susceptibility to tigecycline.
Results: A total of 271 samples were analyzed during the study period and a total of 294 pathogens were isolated belonging to enterobacteriaeceae family. The most common isolate was Escherichia coli (35.3%), followed by Klebsiella pneumoniae (24.8%). The production of ESBL was seen in 61(21%) isolates. Among the total 294 isolates included in the study, tigecycline resistance was observed in only 55 isolates (185). Among the ESBL producers, highest resistance to tigecycline was seen in Klebsiella pneumoniae followed by E.coli, 6(37.5%) and 4 (9.3%).
Interpretation & Conclusions: Historically, tigecycline had a good activity against most ESBLs producing isolates. However, nowadays some ESBLs (*K pneumoniae, E coli*) are also shown to develop resistance against tigecycline. Hence, tigecycline cannot be used as empirical drug for the treatment of nosocomial infection. The susceptibility test for the tigecycline needs to be carried out before started it for therapeutic purpose.

Keywords: enterobacteriaeceae, ESBL, tigecycline

Introduction
Globally, antimicrobial resistance of bacteria belonging to the Enterobacteriaceae family is an emerging problem [1-3]. From a clinical perspective, identifying the resistance pattern is the key success in the appropriate treatment of patients [1]. Enterobacteriaceae are the common isolates among clinical samples of any hospital and empiric antibiotic treatment is not effective in elimination of these pathogens many a time in clinical practice [2]. Resistance forms of Enterobacteriaceae pose a therapeutic challenge in healthcare settings [3]. Empirically antibiotics fail to eliminate pathogens in many cases. The knowledge of resistance pattern of different clinical isolates of hospital has been the global necessity for control of emergence of resistance to antimicrobial agents [1-3]. Extended spectrum beta-lactamase (ESBL) has emerged as the most worrisome mechanisms of resistance among Enterobacteriaceae which pose a therapeutic challenge in healthcare settings [1].
Enterobacteriaceae belong to the normal enteric flora in humans and may cause infections [1]. *E coli* are the leading urinary tract pathogens with septicemia potential, whereas *K pneumonia* causes opportunistic infections and often outbreaks in hospital settings [4-7].

Beta lactam are the first choice for treatment of infections caused by the Enterobacteriaceae and might be destroyed by extended spectrum of β-lactamases. ESBL producing Enterobacteriaceae are a challenge to clinical microbiology laboratory and infection control teams [5, 6]. Multi drug resistance has significantly increased in recent years [1, 2]. The organisms producing enzymes of extended spectrum β-lactamases are resistant to virtually all β-lactam antibiotics [1-4]. ESBLs are plasmid mediated class A enzymes commonly found in the family Enterobacteriaceae mainly *K pneumoniae* and *E coli Infections* caused by ESBLs-producing bacteria often involve immunocompromised patients, making it difficult to eradicate the organisms in high risk wards, such as intensive care units [1-3].

The emergence and spread of resistance in Enterobacteriaceae are complicating the treatment of serious nosocomial infections and threatening to create species resistant to all currently available agents [1-7]. The present increase in resistance to second and third generation cephalosporin observed in medical institutions as a result of the acquisition and expression of extended spectrum β-lactam enzymes among Enterobacteriaceae has posed a serious public health problem [1-3]. The clinical implications are extremely serious and lack of sensitive diagnostic method needed to guide therapy, monitor resistance developments and implementing intervention strategies have complicating the problem [1-3].

The ESBL producing bacteria are increasingly causing urinary tract infections both in hospitalized and outpatients [4-7]. The increase of drug resistance among these organisms has made therapy difficult and has led greater use of expensive broad spectrum antibiotics such as third generation of cephalosporin [5-7]. The vast majority of Enterobacteriaceae, including ESBL producers, remains susceptible to carbapenems and these agents are considered preferred empiric therapy for serious Enterobacteriaceae infections, carbapenem resistance is also increasing at alarming rate [7]. Better antibiotic stewardship and infection control are needed to prevent further spread of ESBLs and other forms of resistance in Enterobacteriaceae throughout the world [1-3]. Area specific monitoring studies aimed to gain knowledge about the type of pathogens responsible for specific infections and their resistance patterns may help the clinicians to choose the correct empirical treatment [4-6].

Tigecycline is the first drug in the glycylcycline class of antibiotics [3]. Although it is structurally related to minocycline, alterations to the molecule resulted in its expanded spectrum of activity and decreased susceptibility to the development of resistance when compared with other tetracycline antibiotics [2]. Randomized trials have shown tigecycline to be efficacious for the treatment of complicated intra-abdominal infections and complicated skin and skin structure infections [1-3]. The dose of tigecycline is 50 mg intravenously every 12 hours after a 100-mg loading dose [3]. Nausea, vomiting, and diarrhea were the most common adverse events reported with tigecycline therapy and may result in discontinuation of therapy [1-3].

Tigecycline has excellent in vitro activity against gram negative bacilli. In one laboratory study of multi drug resistant gram negative bacilli, tigecycline maintained a low MIC against all of the organisms [1-3]. Older options might include intravenous administration of polymyxin B or colistin, drug that are rarely used, even in large medical centers, and for which standard susceptibility criteria are not available [1-4]. A study of 89 carbapenem non-susceptible Enterobacteriaceae isolates from China showed that polymyxin B was much more active than tigecycline [6]. The aim of this study was to: 1To find the antibiotic resistance pattern of enterobacteriaceae; 2 find the prevalence of extended spectrum beta lactamases producing enterobacteriaceae from blood, body fluid, pus and urine; 3 find proportion of tigecycline resistance in ESBLs producing enterobacteriaceae by disc diffusion; 4 determine high level and low level of tigecycline resistance in ESBLs producing enterobacteriaceae by disc diffusion method.

Materials and Method

This was a prospective study conducted at the Father Muller Medical College Hospital. The study was conducted after the approval of the protocol by the Institutional Ethics Committee from January to April 2016The clinical isolates which were ESBL producing Enterobacteriaceae, isolated from various samples received in Microbiology section was included in the study. Depending on the clinical suspicion laboratory samples collected from the patients, processed and cultured in specific culture media in accordance to the standard microbiological methods.

The primary identification of bacterial isolates were made based on colony morphology, pigmentation, lactose fermentation of Mac Conkey Media, Gram's staining reaction, motility, catalase and oxidase tests. The species identification were made based on indole test, H2S production, urease test, citrate test, reactions on Triple Sugar Iron agar. The antibiogram was conducted with an array of standard antibiotics: ampicillin (10 µg), amoxycillin/clavulanicacid (20/10µg), cefazolin (30µg), cefuroxime (30 µg), ceftriaxone (30µg), Ceftazidime (30µg), cotrimoxazole (25µg), gentamycin (10µg), amikacin (30µg), Nitrofurantoin (300µg), ciprofloxcian (5µg), levofloxacin (5µg), chloramphenicol (30µg), piperacillin/tazobactam (100/10 µg), imipenem (10 µg), meropenem (10 µg), colistin (10 µg), ceftazime/clavulunate (30/10µg), tigecycline (15 µg). The zone of diameter was measured and interpreted as per the Clinical and Laboratory Standard Institute guidelines. The ESBL producers were identified when the difference between the zone size between Ceftazidime-Clavulanicacid (30µg) and ceftazidime (30µg) was > 5mm. Other information regarding the patient including age, gender, date of admission, was also collected from the case records of the patients.

Results

A total of 271 samples were analyzed during the study period and a total of 294 pathogens were isolated belonging to enterobacteriaceae family. Of the 271 samples 23 were multibacterial. The most common sample was urine 121 (44.6%), pus 55 (20.2%), wound swab 55(20.2%) as shown in Table1. The most frequent pathogen isolated were *E coli 104* (35.3%) followed by *Klebsiellapneumoniae*73 (24.8%), *Citrobacter koseri* 29 (9.8%), *Proteus mirabilis* 11 (3.7%), *Proteus vulgaris* 9 (3.0%), Enterobacter spp. 4 (1.3%), *Citrobacter freundii*3 (1.0%) as shown in table 2. ESBL Production was demonstrated in 21% isolates. ESBL producers they are *E coli 43* (14.6%), *Klebsiella pneumoniae*16 (5.4%), *Citrobacter koseri* 1 (0.3%), *Citrobacter freundii*1 (0.3%).

Table 1: Enterobacteriaceae growth sample distribution

Sample	Frequency (Percentage)
Urine	121 (44.65)
Pus	55 (20.295)
Wound Swab	55 (20.295)
Perianal Abscess	4 (1.476)
Bone Tissue	2 (0.738)
Tracheal discharge	1 (0.369)
Eye Discharge	1 (0.369)
Ear Swab	1 (0.369)
Pseudocyst Aspirate	1 (0.369)
Blood	23 (8.487)
CVC tip	3 (1.107)
Peritoneal Fluid	2 (0.738)
Ascitic Fluid	2 (0.738)
Total	271 (100)

Table 2: Pattern of Enterobacteriaceae isolated from clinical samples

Bacteria	Frequency of isolates Sample percentage
Ecoli	104 (35.37)
Ecoli(ESBL)	43 (14.625)
Klebsiellapneumoniae	73 (24.829)
K pneumonia (ESBL)	16 (5.442)
Citrobacterkoseri	29 (9.863)
Citrobacter koseri (ESBL)	1 (0.340)
Citrobacterfreundii	3 (1.020)
Citrobacterfreundii(ESBL)	1 (0.340)
Proteus vulgaris	9 (3.061)
Proteus mirabilis	11 (3.741)
Enterobacter spp.	4 (1.360)
Total	294 (100)

The antimicrobial susceptibility spectrum revealed that of the 294 isolates, 270 (93.1%) were resistant to ampicillin, 261 (88.7%) to amoxyclav, 239 (81.2%) to cefazolin, 220 (87.6%) to cefuroxime, 206 (70.06%) to ceftriaxone, 203 (69.04%) to ceftazidime, 162 (55.10%) to co-trimoxazole, 99 (33.67%) to gentamicin, 69 (23.46%) to amikacin, 154 (52.38%) to ciprofloxacin, 131 (44.55%) to levofloxacin, 89 (30.27%) to piperacillin/tazobactum, 80 (27.21%) to cefoperazone/sublacam, 53 (17.96%) to imipenem, 48 (16.32%) to meropenem, 55 (18.70%) to tigecycline, nitrofurantoin is the drug only used in urine sample it showed 27% resistance among all Enterobacteriaceae in urine samples.

Resistance among various species of the Enterobacteriaceae isolates to some commonly used antibiotics is presented in table 3. Among 294 isolates, 61 are ESBL producers including 43 (70.49%) *E coli*, 16 (26.22%) *K pneumoniae*, 1 (1.63%) *C koseri*and 1 (1.63%) *C freundii*. The ESBL producing *E coli* shows maximum resistance to ciprofloxacin 28 (65.1%) followed by co-trimoxazole 27 (62.8%), levofloxacin 25 (58.1%), gentamicin 13 (30.2%), cefoperazone/sublactum 30 (28.8%), amikacin 8 (18.6%), imipenem 19 (18.2%), meropenem 17 (16.3%), tigecycline 4 (9.3%), piperacillin/tazobactum 2 (4.6%) as shown in table 4.

In the case of ESBL producers *K pneumoniae* 6 (37.5%) shows maximum resistance to tigecycline followed by *E coli* 4 (9.30%), *C koseri* and *C freundii* does not show resistance, it is 100% sensitive. In the case of Enterobacteriaceae *P vulgaris* 5 (55.55%) show maximum resistance to tigecycline followed by *P mirabilis* 6 (54.54%), *K pneumoniae* 20 (27.39%), *E coli* 10 (9.61%), *C freundii* 1 (33.33%) shown in table5.The *E coli* show maximum sensitive zone (32mm), the low zone size is 17mm. In ESBL producers *K pneumoniae* show minimum zone size, and maximum size occurring in *E coli* Compare to ESBL producers and non-ESBL producers the high tigecycline resistance present in ESBL producers.

Table 3: Antibiotic resistance pattern of Enterobacteriaceae

Antibiotics	GEN	AK	CIP	LE	PIT	CPZ	IPM	MRP
E coli (104)	38 (36.53)	70 (67.3)	70 (67.3)	60 (67.3)	33 (31.73)	30 (28.84)	19 (18.26)	17 (16.34)
E coli (ESBL) (43)	13 (30.23)	28 (65.11)	28 (65.11)	25 (58.13)	2 (4.65)	2 (4.65)	1 (2.32)	1 (2.32)
Kpneumoniae (73)	28 (38.35)	32 (43.83)	32 (43.83)	29 (39.72)	35 (47.94)	32 (43.83)	21 (28.76)	18 (24.65)
Kpneumoniae (ESBL) (16)	10 (62.5)	7 (43.75)	7 (43.75)	5 (31.25)	7 (43.75)	5 (31.25)	3 (18.75)	2 (12.5)
P vulgaris (9)	0	0	0	0	0	0	2(22.22)	4 (44.44)
P mirabilis (11)	1 (9.09)	3 (27.27)	3 (27.27)	1 (9.09)	0	0	1 (9.09)	0
C koseri (29)	8 (27.58)	10 (34.48)	10 (34.48)	9 (31.03)	11 (37.93)	11 (37.93)	6 (20.68)	6 (20.68)
C koseri (ESBL) (1)	1 (100)	1 (100)	1 (100)	0	0	0	0	0
C freundii (3)	0	1 (33.33)	1 (33.33)	0	1 (33.33)	0	0	0
C freundii (ESBL) (1)	0	1 (100)	1 (100)	1 (100)	0	0	0	0
Enterobacter Spp(4)	1 (25)	0	0	0	0	0	0	0

Table 4: Antibiotic resistance pattern of ESBL producers

Antibiotics	E.coli (ESBL) (43)	K.pneumoniae (ESBL) (16)	C.koseri (ESBL) (1)	C.freundii (ESBL) (1)
Cotrimoxazole	27(62.79)	13(81.25)	1(100)	0(0.0)
Gentamicin	13(30.23)	10(62.5)	1(100)	0(0.0)
Amikacin	8(18.60)	5(31.25)	1(100)	0(0.0)
Ciprofloxacin	28(65.11)	7(43.75)	1(100)	1(100)
Levofloxacin	25(58.13)	5(31.25)	0(0.0)	1(100)
Piperacillin/tazobactum	2(4.65)	7(43.75)	0(0.0)	0(0.0)
Cefoperazone/ sublactum	30(28.84)	5(31.25)	0(0.0)	0(0.0)
Imipenem	19(18.26)	3(18.75)	0(0.0)	0(0.0)
Meropenem	17(16.34)	2(12.5)	0(0.0)	0(0.0)
Tigecycline	4(9.30)	6(37.5)	0(0.0)	0(0.0)

Table 5: Resistance spectrum of enterobacteriaceae to tigecycline

Bacteria (n)	Tigecycline
Ecoli(104)	10(9.61)
Ecoli(ESBL) (43)	4(9.30)
Klebsiella pneumonia(73)	20(27.39)
Klebsiella pneumonia(ESBL) (16)	6(37.5)
Proteus vulgaris(9)	5(55.55)
Proteus mirabilis(11)	6(54.54)
Citrobacterkoseri(29)	2(6.89)
Citrobacterkoseri(ESBL) (1)	0(0.0)
Citrobacterfreundii(3)	1(33.33)
Citrobacterfreundii(ESBL) (1)	0(0.0)
Enterobacter spp.(4)	1(25)

Discussion

Studies revealed that Enterobacteriaceae isolates are more common in males. In our study, the predominant source of the isolates was urine (45%) which is in contrast to the study conducted in Europe where the predominant source was respiratory samples. This proves the fact that UTI are the most common among the infectious diseases occurring in our community and health care settings. *E coli* followed by *Klebsiella pneumoniae* were the predominant Enterobacteriaceae isolated.

When the antibiotic sensitivity of Enterobacteriaceae isolates was analyzed, maximum sensitivity was seen to imipenem, meropenem and tigecycline. Similar results were observed in other studies [7, 8]. Nitrofurantoin can therefore be used effectively for most non-life threatening urinary tract infections with little regard to the antibiotic resistance mechanisms at play among ESBL producing isolates. From our experience many clinicians prefer to prescribe other drugs yet nitrofurantoin remains effective in most cases where there are multiple resistances also evident in other studies [8-10].

The predominant isolates observed in the study were *E coli* 104 (35.374%) was the predominant isolate followed by *Klebsiella pneumoniae*73 (24.829%), *Citrobacter koseri* 29 (9.865), *Proteus mirabilis* 11 (3.741), *Proteus vulgaris* 9 (3.061%), *Enterobacter* spp. 4 (1.360%), *Citrobacterfreundii*3 (1.020%). Recently, several hospital settings across the globe have reported increase in the isolation of *Citrobacter* species [11]. High percentage of resistance to ampicillin, amoxyclav, ciprofloxacin and the third generation cephalosporin was observed in the present study. In other studies it is observed that penicillin group combinations like ampicillin + sulbactam and amoxicillin + clavulanic acid are not much effective against Enterobacteriaceae. Similar pattern was observed in other studies [12, 13].

Organisms like *E coli* and *Klebsiella* sp are intrinsically resistant to these antibiotics because of production of ESBL in them [14]. Resistance in *Enterobacter* may be because of production of AmpC beta lactamase. ESBL producer organisms are usually resistant to many antibiotics. In a study done by Shahid *et al*. [15] for prevalence of ESBL-producing bacteria in an Indian hospital, it was reported that 14.4% of *E coli* and 24.6% of Klebsiella are ESBL producers [16]. Resistance to these groups of antibiotics is associated with the overuse of these antibiotics in various infections, particularly urinary tract infection and easy availability of these antibiotics [15, 17].

In this study, it was observed that sensitivity for ciprofloxacin was less. One of the important reasons is overuse of these antibiotics for minor infections like urinary tract infections, etc. Similar observations were shown by other studies also [17]. As an exception in a similar study, most *E coli* and *Klebsiella* were found to be sensitive to ciprofloxacin [18]. It is observed in some other studies that resistance to fluoroquinolone antibiotics are also escalating. Resistanceto gentamicin are observed in this study and were in higher proportions when compared to previous studies [19-22].

One of the important findings of the study is the decreased sensitivity to meropenem, while the overall meropenem resistance was about 16.32%. It was observed that *E coli* was more sensitive than *Klebsiella*. The resistance to carbapenem group of drug, i.e., meropenem, in this study is much more as compared with other studies. In a study done by Wood *et al*. two surveillance databases were searched for imipenem or ertapenem resistance in Enterobacteriaceae [22]. In a similar study done in an Indian hospital, it was observed that most of the Enterobacteriaceae were sensitive to carbapenems [15]. *E coli* was 99% sensitive and *Klebsiella* was 100% sensitive to carbapenems. Carbapenems are considered as drug of choice for multidrug-resistant Enterobacteriaceae; hence, resistance toward these should be a matter of serious concern [3]. Various reasons for resistance to Enterobacteriaceae are considered, like productions of ESBLs like AmpC, metallo- betalactamases, etc., and losing of outer membrane [3, 7]. These resistance genes are located on plasmid and can easily be moved from one organism to another through conjugation. These genes are associated with other drug resistance genes and move together [23].

ESBL producers were isolated from all the sites of the body from which samples were obtained namely, urine, pus, blood and aspirates. In our study, urine section shows high number of ESBL producers. Among 294 isolates, 61 are ESBL producers in this study including 43 (70.49%) in *E coli*, 16 (26.22%) in *K pneumoniae*, 1 (1.63%) in *C koseri*, 1 (1.63%) *C freundii*. The ESBL producing *E coli shows* maximum resistance to ciprofloxacin 28 (65.11%) followed by co-trimoxazole 27 (62.79%), levofloxacin 25 (58.13%), gentamicin 13 (30.23%), amikacin 8 (18.60%), imipenem 19 (18.26%), meropenem 17 (16.34%), tigecycline 4 (9.30%), pipeacillin/tazobactum 2 (4.65%).

In the case of ESBL producers *K pneumoniae* 6 (37.5%) shows maximum resistance to tigecycline followed by *E coli 4* (9.30%). *C koseri* and *C freundii* does not show resistance, it is 100% sensitive. The *E coli show* maximum sensitive zone (32mm), the low zone size is 17mm. In ESBL producers *K.pneumoniae* show minimum zone size, and maximum size occurring in *E coli* compared to ESBL producers and non-ESBL producers the high tigecycline resistance maximum present in ESBL producers. Pavani *et al*. [24] studies has proven that tigecycline is 100% sensitive but in this study tigecycline show resistance pattern, it mainly seen in ESBL isolates and it leads to the therapeutic problem in health care settings.

Conclusion

Enterobacteriaceae remain the most frequently encountered bacterial isolates recovered from clinical specimens. Worldwide, antimicrobial resistance of an Enterobacteriaceae is an emerging problem and extended spectrum beta-lactamase (ESBL) has emerged as the most worrisome mechanisms of resistance. Historically, tigecycline had a good activity against most ESBLs

producing isolates. However, nowadays some ESBLs (*E coli, K pneumoniae*) are also shown to develop resistance against tigecycline. When compared to previous studies in this study *E coli* and *K pneumoniae* showed large zone size variation. However the most worrisome observations were that *E coli* show high resistance pattern to tigecycline. The possible explanation for this is that in the recent past tigecycline has been the cornerstone in treating infections and their rampant prescription without having an antibiogram results by the professionals and non-adherence to the dose and schedule, and over the counter prescription must have lead to the resistant strains. Efforts needs to be initiated towards remedial measures and on adherence to the good practice guidelines and antibiotic policy to minimize the evolution of drug resistant strains.

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