Original Article

Study of extended spectrum β-lactamase producing Enterobacteriaceae and antibiotic coresistance in a tertiary care teaching hospital

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Abstract

Aims: To study the prevalence of extended spectrum β-lactamase (ESBL) producing Enterobacteriaceae and coresistance to other commonly used antibiotics from the Bhopal region of Central India. **Settings and Design:** A prospective study was conducted from September 2011 to August 2012 in Microbiology Department of our tertiary health care center. **Materials and Methods:** A total of 1044 Enterobacteriaceae isolates were recovered from various specimens. ESBL production was detected by using Clinical Laboratory Standard Institute (CLSI) that described the phenotypic confirmatory test along with routine antibiotic susceptibility testing. **Statistical Analysis:** Two-tailed *Z*-test. **Results:** *Escherichia coli* was the most common isolate (65.32%). ESBL production was confirmed in 504 (48.27%) isolates. The isolates of *E. coli* (50.14%) were the most common ESBL producers. Maximum ESBL isolates were obtained from urine samples (52.28%) and male patients (52.54%). Sensitivity to imipenem was 100% followed by piperacillin–tazobactam (89.28%), meropenem (87.5%), and amikacin (83.92%). Significant resistance was detected against trimethoprim–sulfomethoxazole, fluoroquinolones, and gentamicin. **Conclusion:** This is the only study conducted from Central India and shows high prevalence of ESBL production among Enterobacteriaceae. Imipenem seems to be more sensitive than meropenem. Piperacillin–tazobactam combination was found to be the best among the β-lactam–β-lactamase inhibitor combinations. Prevalence of ESBL producers were more in males than females.

Key words: Antibiotic coresistance, Enterobacteriaceae, extended spectrum β-lactamase

INTRODUCTION

Beta-lactam antimicrobial agents are the most commonly used treatment of bacterial infections.[1] Productions of β-lactamases are reported to be the leading cause of resistance to these antimicrobial agents, especially by gram-negative bacteria.[1,2] These enzymes are numerous and they mutate continuously in response to heavy pressure of antibiotic use and have lead to the development of extended spectrum β-lactamases (ESBL).[3] In recent years, there has been an increased incidence and prevalence of ESBLs among family Enterobacteriaceae.[3]

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ESBL are placed under Bush's functional class 2be.[4] They are plasmid-mediated enzymes and are derived from point mutation of TEM on SHV β-lactamases that are widely distributed among the Enterobacteriaceae.[3,5] In recent years, several new ESBLs of the non-TEM and the non-SHV types emerged, such as the enzymes of the CTX-M, PER, VEB, and the GES lineages.[6] ESBL inactivate β-lactam antibiotics containing the oxyimino group such as oxyimino-cephalosporin and oxyimino-monobactam.[5] They have no effect on cephamycins and carbapenems and are commonly inhibited by β-lactamase inhibitors such as clavulinic acid, sulbactam, and Tazobactam.[7,8]

Plasmid coding for ESBL enzymes may carry coresistance genes for other non-β-lactam antibiotics.[9] Therefore, it is common for organisms expressing an ESBL to express

coresistance to other antibiotics, such as aminoglycosides, trimethoprim, sulfomethoxazole, and tetracycline, leading to treatment failure. Being plasmid mediated, these enzymes spread fast among various bacteria. Hence, reliable detection of ESBL production by the clinical microbiology laboratory is essential.

Although various studies have been conducted on the ESBL-producing strains of Enterobacteriaceae in different regions of India like Dibrugarh,[10] Bangalore,[11] Pondicherry,[12] Bijapur,[13] New Delhi,[14] Hyderabad,[15] Mumbai,[16] no published data are available on the prevalence of ESBL production in the Bhopal region of Madhya Pradesh in Central India.

Therefore, the study was conducted at a tertiary care hospital, Bhopal, to know the prevalence of ESBL among members of the family Enterobacteriaceae isolated in various clinical specimens and to know associated coresistance for other commonly used antimicrobial agents.

MATERIALS AND METHODS

A prospective study was conducted over a period of 1 year (September 2011 to August 2012) at a tertiary care teaching hospital.

Bacterial isolates

A total of 1044 consecutive, nonrepetitive clinical isolates of Enterobacteriaceae isolated from various clinical samples such as urine (656), pus/wound swabs (231), sputum (49), tracheal aspirate (39), blood (40), vaginal swab (19), and ascitic fluid (10) were included in the study. Samples were processed and isolates were identified by standard laboratory methods.[17]

Antimicrobial agents susceptibility testing

Antimicrobial susceptibility was determined by the Kirby-Bauer disc diffusion method[18] according to Clinical Laboratory Standard Institute (CLSI) guidelines.[19] Antibiotic discs were obtained from HiMedia, Mumbai.

The antibiotics used for antibiogram determination of collected strains were ampicillin (10 μg), cefuroxime (30 μg), ceftriaxone (30 μg), cefotaxime (30 μg), ceftazidime (30 μg), cefepime (30 μg), cefoxitin (30 μg), aztreonam (30 μg), amoxicillin–clavulinic acid (20/10 μg), ampicillin–sulbactam (10/10 μg), piperacillin–tazobactam (100/10 μg), gentamicin (10 μg), amikacin (30 μg), ciprofloxacin (5 μg), imipenem (10 μg), meropenem (10 μg), trimethoprim–sulfamethoxazole (1.25/23.75 μg). Norfloxacin (10 μg) and nitrofurantoin (300 μg) were tested against isolates from urine samples only.

Detection of ESBL

ESBL production was detected by using the CLSI described phenotypic confirmatory test along with routine antibiotic susceptibility testing. Cefotaxime and ceftazidime discs alone and in combination with clavulinic acid were used. A >5 mm increase in zone was considered as confirmation of ESBL production.[19]

Although CLSI described phenotypic confirmatory test is applicable for *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*, an attempt was made to look for ESBL production among the other members of Enterobacteriaceae.

ESBL-producing Enterobacteriaceae isolates which were found to be resistant to cefoxitin (zone diameter < 18 mm)[19] were not considered for the study. This is to exclude associated Amp-C type of β-lactamases.[20,21]

Throughout the study, *K. pneumoniae* ATCC 700603 and *E. coli* ATCC 25922 (HiMedia Laboratories, Mumbai) were used as positive and negative controls, respectively, for ESBL production.

RESULTS

In 1 year study period, a total of 1044 Enterobacteriaceae isolates were obtained. Table 1 shows different isolates of family Enterobacteriaceae isolated from clinical samples. *E. coli* was the most common (65.32%) isolate followed by *K. pneumoniae* (24.9%) and others.

A total of 504 of these isolates produced ESBL. The detection rate of ESBL in our study was 48.27%. *E. coli* was the most common ESBL producing Enterobacteriaceae (50.14%) followed by *K. pneumoniae* (48.27%) and others [Table 2].

ESBL producing strains were obtained from various specimens as shown in Table 3. The majority of ESBL isolates were from urine samples (52.28%).

Sex wise distribution of ESBL producers as shown in Table 4 revealed that the prevalence was more among the males as compared to females.

The antibiotic susceptibility pattern of ESBL isolates to other antibiotics is shown in Figure 1. All the isolates were sensitive to imipenem. The majority of ESBL producers (>80%) were sensitive to meropenem, piperacillin-tazobactam, and amikacin. Only 50% of ESBL isolates were sensitive to gentamicin. Occurrence of coresistance among ESBL isolates was observed. Poor sensitivity (<15%) was found against trimethoprim–sulfamethoxazole, amoxicillin–clavulinic acid, ampicillin–sulbactam, and ciprofloxacin. The susceptibility of

Table 1: Isolates of family Enterobacteriaceae from clinical samples

Organism	Number of isolates	Percentage
E. coli	682	65.32
K. pneumoniae	260	24.9
Proteus spp.	53	5.07
Enterobacter spp.	18	1.72
Citrobacter spp.	11	1.05
Providentia spp.	08	0.76
Morganella morganii	08	0.76
Salmonella spp.	04	0.38
Total	1044	100

Table 2: ESBL producers among different isolates of family Enterobacteriaceae

Organism	ESBL producers	Percentage
E. coli	343	50.14
K. pneumoniae	126	48.27
Proteus spp.	23	42.59
Enterobacter spp.	6	33.33
Citrobacter spp.	2	18.18
Providentia spp.	3	37.5
Morganella morganii	1	12.5
Salmonella spp.	0	0
Total	504	48.27

ESBL: Extended spectrum β-lactamase

Table 3: Specimen wise distribution of ESBL producers

Specimen	Number of isolates	ESBL producers	Percentage
Urine	656	343	52.28
Pus/wound swab	231	104	45.02
Sputum	49	18	36.73
Tracheal aspirate	39	17	43.58
Blood	40	15	37.05
High vaginal swab	19	05	26.03
Ascitic fluid	10	02	20
Total	1044	504	48.27

ESBL: Extended spectrum β-lactamase

Table 4: Sex wise distribution of ESBL producers

Sex	Number of isolates (*n*=1044)	ESBL producers (*n*=504)	Percentage
Male	531	279	52.54
Female	513	225	43.86

Using the two-tailed Z-test with 95% CI, $P<0.01$, ESBL: Extended spectrum β-lactamase

ESBL-producing urinary isolates to nitrofurantoin and nalidixic acid was 82.5% and 15.16%, respectively.

DISCUSSION

The members of the family Enterobacteriaceae are among the most important bacterial human pathogens accounting for the majority of bacteria isolated from clinical samples.[22] The β-lactam group of drugs including extended spectrum cephalosporins are commonly used for treatment of such infections. In recent years, bacterial resistance to these drugs has increased dramatically with ESBL contributing to this increase.[3,5] These enzymes are plasmid coded which may also carry coresistance genes for other commonly used non-β-lactam antibiotics and thus limiting the number of useful drugs against these bacteria.[9] To make problems worse, plasmid-mediated ESBL enzymes spread fast among various bacteria resulting into a number of nosocomial outbreaks.[23-25] Hence, reliable and accurate detection of ESBL in a microbiology laboratory is a must. In a recent study conducted by Gavin *et al.*,[26] it was found that the majority of physicians changed therapy after a report of an ESBL-producing pathogen from microbiology laboratory highlighting the importance of ESBL detection. Since no data on ESBL prevalence in our area were available, a study was conducted in our institute to look for prevalence of ESBL among members of the family Enterobacteriaceae and antimicrobial susceptibility pattern of such isolates.

In one-year study period, a total of 1044 Enterobacteriaceae isolates were analysed. The majority were *E. coli* (65.82%) followed by *K. pneumoniae* (24.9%), *Proteus* spp. (5.07%), and others [Table 1]. Metri *et al.*[13] from Bijapur have also reported *E. coli* and *K. pneumoniae* as the most common Enterobacteriaceae which were prevalent in their clinical samples, and this was well comparable to the reports from our study. Rudresh *et al.*[11] from Bangalore too reported the prevalence of 40.2% *E. coli* and 33.1% *Klebsiella* spp.

No countrywide study has been conducted so far for detection of the prevalence of ESBL production in India. Individual studies were done in different parts of the country, which showed various prevalence rates.

The prevalence of ESBL-producing organisms in this study was found to be 48.27% which was higher than that which was reported by other studies done in Hyderabad (19.8%),[15] Dibrugarh (24.56%),[10] and Bijapur (32.1%).[13] The prevalence was lower when compared with the studies which were done in Mumbai (53%),[16] Bangalore (62.3%),[11] and Pondicherry (66.7%).[12] The wide variation in the prevalence is probably due to the variation in the risk factors and in the extent of antibiotic use.

A report from Pondicherry, India, showed that ESBL production was 81% in *E. coli* and 74% in *K. pneumonia*.[12] In a similar study by Rudresh *et al.*,[11] 40.2% of the *E. coli* and 33.1% of *K. pneumoniae* isolates were reported to be ESBL producers. This study also reveals similar findings with *E. coli* as the major ESBL producer (50.14%) followed by *K. pneumoniae* (48.27%) [Table 2]. Although *Salmonella* spp. is known to produce ESBLs,[15,27] none of the *Salmonella* spp. in our study showed ESBL production.

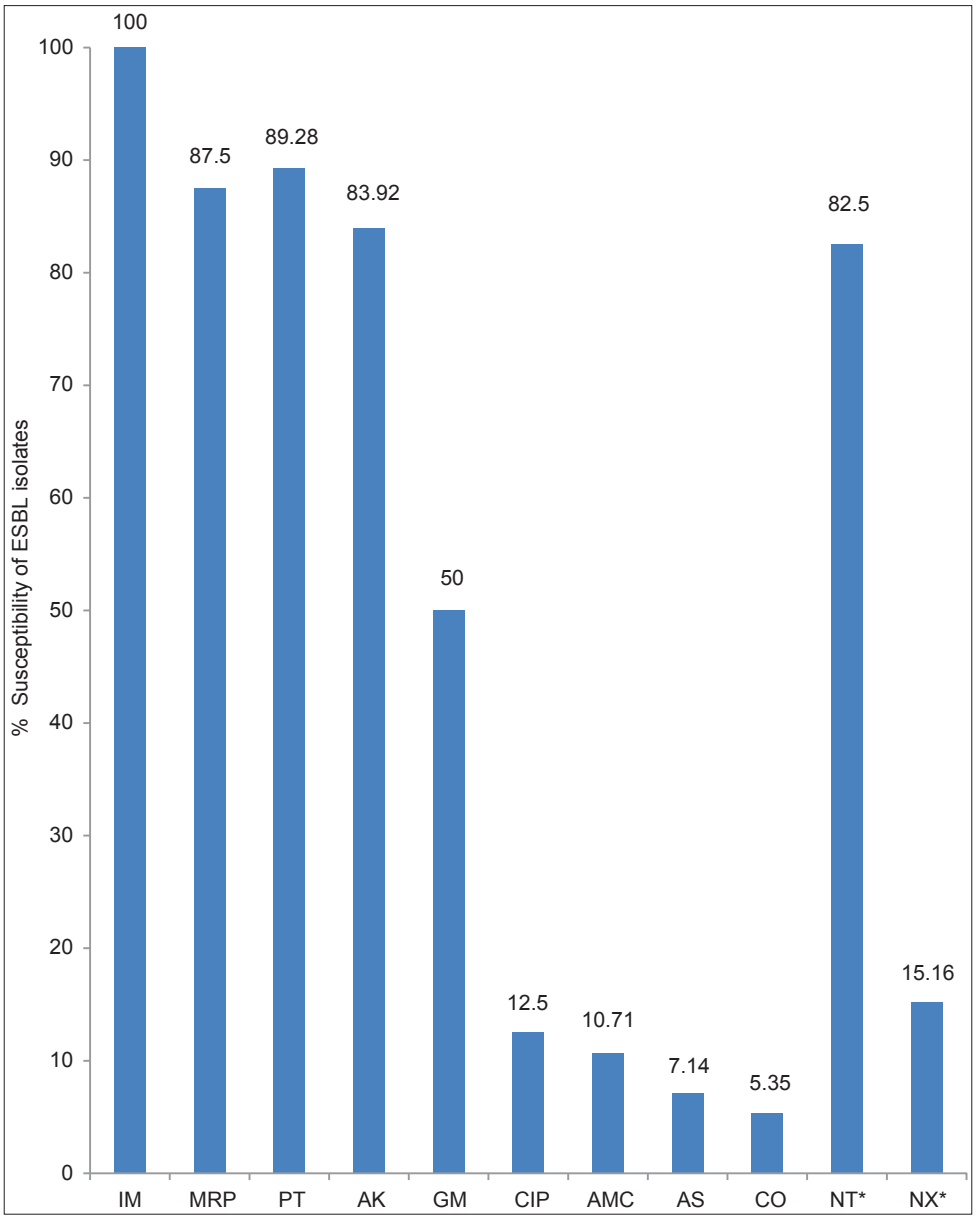

Figure 1: Susceptibility of the ESBL isolates to various antibiotics. IM: imipenem, MRP: meropenem, PT: piperacillin–tazobactam, AK: amikacin, GM: gentamicin, CIP: ciprofloxacin, AMC: amoxicillin–clavulinic acid, AS: ampicillin–sulbactam, CO: trimethoprim–sulfamethoxazole, NT: nitrofurantoin, NX: norfloxacin. Asterisk indicates antibiotics tested against urinary isolates only

This could be due to the few isolates (4) obtained during the study period.

In our study, ESBL isolates were obtained from different clinical specimens [Table 3]. The majority of ESBL isolates were from urine samples. A study from North Karnataka, India, revealed similar findings.[13] Umadevi *et al.*[12] also found a maximum number of ESBL-producing isolates from the urine sample of patients.

Shah *et al.*[28] studied the relation of ESBL-producing Enterobacteriaceae with respect to age and gender and reported more ESBL-positive isolates in males (65.33%) than females (34.67%). Nibedita Das *et al.*[10] also found a slight male preponderance for ESBL production among the study subjects. Similar findings were observed in the present study. 52.54% of ESBL isolates were obtained from males while 43.46% from females [Table 4]. After applying the two-tailed *Z*-test with 95% CI, this difference was found to be statistically significant ($P < 0.01$).

In this study, all ESBL isolates were found to be sensitive to imipenem and more than 80% were susceptible to piperacillin–tazobactam (89.28%), meropenem (87.5%), and amikacin (83.92%) [Figure 1].

Although belonging to the same carbapenem group, imipenem showed better *in vitro* activity against

ESBL-producing isolates than meropenem in our study. This result correlates well with the findings in other studies.[29,30] This is likely to be due to overuse of meropenem in our health care setting leading to heavy selection pressure and development of resistance among Enterobacteriaceae isolates. Hence we need to keep in mind that carbapenems are antimicrobials that should be kept in reserve.[29] They should be used only in life-threatening infections and in outbreak situations. This approach intends to preserve the therapeutic value of these precious drugs.

In our study, when sensitivity of the β-lactam–β-lactamase inhibitor combination was compared, it was observed that sensitivity of piperacillin–tazobactam was far better than amoxicillin–clavulinic acid and ampicillin–sulbactum [Figure 1]. Wong-Beringer[31] and al Zahrani *et al*.[32] have also reported good sensitivity of piperacillin–tazobactam against ESBL isolates. Bano *et al*.[33] conducted a study in patients with bacteremia due to ESBL-producing *E. coli* and suggested that piperacillin–tazobactam and amoxicillin–clavulinic acid are suitable alternatives to carbapenems for treating such patients if active *in vitro* and would be particularly useful as definitive therapy. According to Peterson,[34] piperacillin–tazobactam is clinically reliable for the treatment of serious infections caused by susceptible strains of ESBL-producing *E. coli* and *Klebsiella* spp. Our study also highlights the same results.

Antibiotic coresistance among ESBL isolates have been noted as a serious problem even at our tertiary health center. In our study, only 50% ESBL-producing organisms were sensitive to gentamicin, 12.5% to ciprofloxacin, and 5.35% to trimethoprim–sulfamethoxazole. Norfloxacin and nitrofurantoin were tested only for urinary isolates. ESBL isolated from urine samples showed good *in vitro* activity against nitrofurantoin (82.5% sensitive), but only 15.16% were sensitive to norfloxacin. Thus, low sensitivity of ESBL-producing Enterobacteriaceae has been observed for gentamicin, fluoroquinolones, and trimethoprim–sulfamethoxazole. Rudresh *et al*.[11] reported a similar susceptibility pattern for ESBL isolates with 46.9% isolates sensitive to gentamicin followed by ciprofloxacin (29.5%) and trimethoprim–sulfomethoxazole (23.4%). Nibebita Das *et al*.[10] in their study have showed 30.96% sensitivity toward fluoroquinolones and 2.39% toward trimethoprim–sulfamethoxazole. Ullah *et al*.[35] have also observed coresistance of ESBL isolated to different antibiotics. This may be due to occurrence of genes encoding resistance to aminoglycoside, trimethoprim–Sulfomethoxazole, and quinolones on the same plasmid that encodes for ESBL production.[5,9] Martínez-Martínez and colleagues[36] have performed an analysis of mechanism of quinolone resistance in *K. pneumoniae* isolates of clinical origin and found that porin loss was observed only in those *K. pneumoniae* strains producing an ESBL. A significant number of these porin deficient strains also showed active efflux of quinolones.

CONCLUSIONS

High prevalence of ESBL production among the members of Enterobacteriaceae is a matter of concern. This study showed that the phenotypic confirmatory test can reliably detect ESBL production. Instead of screening and confirming ESBL production, direct phenotypic confirmatory test along with routine antibiotic susceptibility testing can help to report ESBL production within 48 hours. This protocol can be followed on a routine basis and for all Enterobacteriaceae isolates to save time. This will help clinicians in selecting and prescribing proper antibiotics for treatment of such infections. Carbapenems still remains most effective drug against ESBL-producing organisms. Imipenem seems to be superior to meropenem. There is a need to "reserve" these precious drugs and should be used only in life-threatening infections. Their overuse or misuse can pose great problem.[29] If piperacillin–tazobactam or amikacin is found to be sensitive *in vitro*, either of these drugs can be used as alternatives to carbapenems. The situation may vary from region to region, so institutional antibiograms or local patterns of susceptibility are necessary and this helps for preparation of antibiotic policy of individual institute. An appropriate and judicious antibiotic use may lead to withdrawal of the selective pressure and there is possibility that the resistance bacteria will no longer have survival advantages.

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