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Phenotypic prevalence of Extended Spectrum Beta-Lactamase (ESBL) producing Enterobacteriaceae and antibiotic coresistance in a tertiary care hospital

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Abstract

Introduction: The multidrug resistant Enterobacteriaceae isolates pose not only therapeutic problems but also serious concerns for infection control management. Early detection of lactamase producers is crucial to establish appropriate antimicrobial therapy and to prevent their interhospital and intrahospital dissemination.

Objective: To study the prevalence of ESBL producing bacteria among all the members of Enterobacteriaceae isolated from various clinical specimens collected from all wards across a tertiary care teaching hospital.

Methodology: ESBL production was detected among all the Enterobacteriaceae using, Phenotypic Combined Disk Diffusion Test (PCDDT), as recommended by the Clinical Laboratory Standards Institute (CLSI).

Results: There is a high prevalence (25.67%) of ESBL producers in our hospital and so, it is essential to report the ESBL production along with the routine sensitivity reports, which will help the clinician in prescribing proper antibiotics. Pediatric ward had the highest number of ESBL positive Blood cultures. The pus isolates culture sensitivity testing from Surgery ward, Orthopedics and Burn and Plastic Surgery ward showed maximum number of ESBL strains. ESBL isolates show coresistance to many other classes of antimicrobials. Carbapenems (Imipenem, Meropenem), BL/BLI combination viz. Cefoperazone-sulbactum and aminoglycoside (amikacin) came out to be effective against these.

Conclusion: A high degree of ESBL producers and carbapenem resistant Enterobacteriaceae is concerning; with emerging resistance to colistin, raising the fear of a return to the preantibiotic era. An urgent intervention including creating awareness and establishment of robust infection control and antibiotic stewardship program is the most important need of the hour.

Keywords: ESBL, Coresistance, Antimicrobial Susceptibility, Gram negative Bacilli, Nosocomial.

Introduction

ESBLs are plasmid mediated beta-lactamases capable of inactivating extended spectrum beta-lactams with an oxyimino side chain like cephalosporins (cefotaxime, ceftriaxone, and ceftazidime) and oxyimino-monobactam (aztreonam).[1] These plasmids also carry other antibiotic resistance genes, often rendering ESBL-producing strains multidrug-resistant.[2] Treatment of infections caused by ESBL-producing organisms with extended-spectrum cephalosporins or aztreonam may result in treatment failure even when the causative organisms appear to be susceptible to these antimicrobial agents using standard breakpoints. In addition, patients colonized or infected with ESBL-producing organisms should be placed under contact precautions to avoid cross transmission to other patients. These benefits warrant the detection of ESBL-producing organisms in clinical laboratories. They can be found in a variety of Enterobacteriaceae species; however, majority of the ESBL producing strains are *Klebsiella pneumoniae*, *Klebsiella oxytoca* and *Escherichia coli*. In India, the prevalence rate varies in different institutions from 28 to 84%.[3]

The choice of empirical antimicrobial requires knowledge of common pathogens in the given setting, which constantly changes, necessitating periodic review. Therefore, this study was conducted to know the prevalence of ESBL among members of the family Enterobacteriaceae isolated in various clinical specimens and to know associated co-resistance for other commonly used antimicrobial agents.

Material & Methods

The present prospective study was carried out from January to July 2016 in the Department of Microbiology of a tertiary care teaching hospital. The study protocol was approved by the Institutional Ethical Committee. A total of 7660 non-repetitive samples received from various OPDs, in -patient wards and Intensive Care Units. The samples were processed and isolates were identified by standard laboratory methods.[4,6] 1792 consecutive, non-repetitive clinical isolates of Enterobacteriaceae isolated from various clinical samples such as urine (327), pus/wound swabs (814), sputum (29), tracheal aspirate (11), blood (514), vaginal swab (21), CSF (44) and ascitic fluid (32) were included in the study.

Antimicrobial susceptibility was determined by the Kirby-Bauer disc diffusion method[6] and were interpreted according to the CLSI guidelines (Clinical and Laboratory Standards Institute).[7] ESBL production was detected by using the CLSI described phenotypic confirmatory combination disc diffusion test (PCDDT).[7]

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. *Escherichia coli* 25922 and a known in-house ESBL producer were used as negative and positive controls respectively.

Statistical analysis was performed using SPSS software. The association of study variables with ESBL and non-ESBL producing Enterobacteriaceae was tested by using Chi-square test for categorical data, for continuous data independent t test was used.

Results

Of the total 7660 samples received in the bacteriology section for culture and sensitivity over a period of six months, 1737 were urine, 2722 blood and 3201 were pus (pus swab, wound swab, vaginal swab, peritoneal fluid), CSF and respiratory specimens (sputum, throat swab, ET aspirate). Of these a total 1792 (Urine=327, Blood=514, Pus+ CSF+ Respiratory specimen=951) Enterobacteriaceae isolates were grown from non-repetitive samples. 460 (25.67%) (Urine=84, Blood=131, Pus+ CSF + Respiratory specimen=245) of the total Enterobacteriaceae isolated showed ESBL production while the rest 1332 (74.33%) (Urine=243, Blood=383, Pus+ CSF+ Respiratory specimen=706) were Non ESBL producers.

Age and sex distribution among ESBL and non ESBL isolates (Table 1) showed no significant difference between the groups. The hospitalized patients (In patients, ICU) had significantly ($p<0.005$) higher risk of acquisition of infection with ESBL organisms Upon analyzing ward and specimen wise prevalence of Multi-drug resistant (MDR) Enterobacteriaceae, Carbapenem resistant Enterobacteriaceae (CRE) and ESBLs (Table 2), it was found that the Pediatric ICU and Pediatric ward had the highest number (ESBL=10.65%, MDR= 10.55%, CRE= 11.15%) of antibiotic resistant Blood cultures. The pus isolates culture sensitivity testing from Surgery ward, Orthopedics and Burn & Plastic Surgery ward showed maximum number of ESBL, MDR and CRE strains. Though the prevalence of ESBL organism is less in Urinary isolates but the samples from Post-Operative Ward (3.1), Pediatric surgery (2.9), Obstetrics & Gynaecology (2.6) and Medical ICU (2.4) show relatively higher percentage. Even the urine samples collected from OPD patients showed ESBL prevalence (2.0%). Respiratory specimen from General Medicine ward, Medical ICU & PICU showed the max. Prevalence of ESBL, MDR and CRE isolates.

ESBL isolates show co-resistance to many other classes of antimicrobials. Table 3 shows Carbapenems (Imipenem, Meropenem), BL/BLI combination viz. Cefoperazone-sulbactum and aminoglycoside (amikacin) can be effective against these.

Table 1: Age & Sex Distribution among ESBL & NON ESBL Isolates

	ESBL (n=460)	Non ESBL (n=1332)	p value
Patient Age (in yrs.)			
<1	19(4.1)	53(4)	
1-20	207(45)	540(40.5)	
21-40	115(25)	418(31.4)	0.081
41-60	75(16.3)	222(16.7)	
>60	44(9.6)	99(7.4)	
Health Care Setting			
OPD	85(18.5)	170(12.8)	
IPD	238(51.7)	776(58.3)	0.005
ICU	137(29.8)	386(29)	
Patient Gender ratio			
M:F	264:195	757:566	0.911

Table 2: Specimen and ward wise distribution of Antibiotic Resistant Isolates

	GMW (% of total ESBL/MDR/CRE)	MICU	POP	Ortho	ENT	PICU	Gynae	Surg ward	Burns	Ped Sx	Ped Med	Optha	OPD	Total
Blood														
ESBL	8 (1.8%)	15(3.3%)	1(0.2)	0(0)	0(0)	60(13.2%)	2(0.4%)	1(0.2%)	0(0)	6(1.3%)	37(8.1%)	0(0)	0(0)	130(36.6)
MDR	14(1.4)	34(3.3)	6(0.6)	1(0.1)	1(0.1)	134(13.2)	7(0.7)	9(0.9)	2(0.2)	12(1.2)	80(7.9)	0(0)	0(0)	300(29.5)
CRE	8(1.3)	19(3.2)	4(0.7)	1(0.2)	0(0)	77(12.8)	3(0.5)	4(0.7)	2(0.3)	5(0.8)	57(9.5)	0(0)	0(0)	180(30)
Pus (Vag swab, Wound swab, Ear swab, pus swab)														
ESBL	11(2.4%)	19(4.1%)	21(4.6)	27(5.9)	9(2%)	5(1.1%)	24(5.2%)	52(11.4%)	35(7.37)	7(1.5%)	6(1.3%)	2(0.4 %)	7(1.5 %)	175(38.4)
MDR	16(1.6)	25(2.5)	78(7.7)	58(5.7)	9(0.9)	11(1.1)	22(2.2)	56(5.5)	166(16.3)	11(1.1)	12(1.2)	1(0.1)	1(0.6)	471(46.3)
CRE	5(0.8)	19(3.2)	45(7.5)	37(6.2)	4(0.7)	6(1)	18(3)	24(4)	94(15.7)	5(0.8)	11(1.8)	1(0.2)	2(0.3)	271(45.1)
3.Urine														
ESBL	4(0.9)	11(2.4)	14(3.1)	3(0.7)	0	5(1.1)	12(2.6)	4(0.9)	0	13(2.9)	9(2)	0	9(2%)	84(18.4)
MDR	14(1.4)	25(2.5)	18(1.8)	6(0.6)	0(0)	18(1.8)	16(1.6)	22(2.2)	9(0.9)	11(1.1)	17(1.7)	0(0)	6(0.6)	162(15.9)
CRE	6(1)	19(3.2)	14(2.3)	3(0.5)	0(0)	10(1.7)	11(1.8)	8(1.3)	5(0.8)	8(1.3)	10(1.7)	0	3(0.5)	97(16.2)
Respiratory Specimens (Throat swab, sputum, BAL, pleural fluid, drain)														
ESBL	6(1.3%)	8(1.7%)	2(0.4%)	0	8(1.7)	6(1.4)	0	0	0	0	4(1%)	0(0)	2(0.4)	36(7.9)
MDR	5(0.6)	11(1.4)	7(0.8)	1(0.1)	5(0.6)	4(0.5)	0(0)	2(0.2)	0(0)	0(0)	3(0.4)	0	2(0.2)	40(4.9)
CRE	2(0.4)	6(1.1)	4(0.6)	2(0.4)	0(0)	9(1.5)	0(0)	2(0.4)	0(0)	0(0)	1(0.2)	0(0)	1(0.2)	27(4.8)
Fluids (CSF, Peritoneal fluid)														
ESBL	2(0.4)	4(0.9)	3(0.7)	0	0	1(0.2)	0	0	0	1(0.2)	5(1.1)	0(0)	0(0)	16(3.5)
MDR	0(0)	0(0)	2(1.7)	0(0)	0(0)	19(1.9)	0(0)	1(0.1)	0(0)	2(0.2)	4(0.4)	6(0.6)	0	28(2.8)
CRE	0(0)	2(0.3)	4(0.7)	1(0.2)	0	8(1.3)	0(0)	0(0)	0	2(0.3)	3(0.5)	2(0.3)	0	22(3.6)

Table 3: Antimicrobial susceptibility among various ESBL isolates

	E.coli	*Klebsiella spp.*	*Proteus spp.*	*Providencia spp.*	*Citrobacter spp.*	*Enterobacter spp.*	*Morganella spp.*
Ceftriaxone	92(47.9)	75(38.7)	22(61.1)	17(58.6)	2(28.6)	2(100)	0(0)
Ceftazidime	111(57.8)	82(42.3)	16(44.4)	14(48.3)	3(42.9)	2(100)	0(0)
Cefepime	114(59.4)	104(53.6)	24(66.7)	17(58.6)	3(42.9)	2(100)	0(0)
Cefoperazone-sulbactum	172(89.6)	158(81.9)	33(91.7)	24(82.8)	6(85.8)	2(100)	0(0)
Imipenem	182(94.8)	162(83.5)	31(86.1)	25(86.2)	6(85.8)	2(100)	0(0)
Meropenem	181(94.3)	167(86.1)	32(88.9)	29(100)	5(71.4)	2(100)	0(0)
Ciprofloxacin	105(55.3)	107(55.2)	24(66.7)	17(58.6)	4(57.1)	2(100)	0(0)
Amikacin	173(90.6)	142(73.2)	23(63.9)	24(82.8)	5(71.4)	2(100)	0(0)

Discussion

The members of the family Enterobacteriaceae are one of the most important bacterial pathogens isolated from clinical samples.[6] In last few years, bacterial resistance has increased dramatically with plasmid mediated ESBL contributing to this increase worldwide. These plasmid also carry co-resistance genes for other non-β-lactam antibiotics; limiting the number of effective drugs. To make problems worse, plasmid-mediated ESBL enzymes spread fast among bacteria resulting into nosocomial outbreaks.[6] The prevalence of ESBL producers varies across continents and countries and also within hospitals.[7] In India, no countrywide study has been conducted so far for detection of the prevalence of ESBL production,[6] the prevalence rate varies in different institutions from 6-87%.[8] Since no data on ESBL prevalence in our institute was available, this study was conducted to look for ESBL prevalence and their antimicrobial susceptibility.

The occurrence of ESBL producers among the Enterobacteriaceae in the current study was 25.67 % which was similar to a study on urinary isolates from Dibrugarh[8] but higher than a similar study from Hyderabad (19.8%).[9] The prevalence was lower when compared with the studies from Valsad 48%,[10] Bhopal 48.27%,[6] Mumbai 53%,[11] Pondicherry (66.7%),[12] Amritsar 45.8%,[13] Sikkim 34.03%.[7] This clearly indicates that the prevalence of ESBLs varies greatly geographically and rapidly changing over time. This could be due to difference in the study design, population, associated risk factors, geographical distribution and probably due to differential clonal expansion and drug pressure in the community.[6]

The age wise distribution revealed the maximum number (45%) of ESBL producers in the age group 1-20 years as also seen in a similar study from north-west India.[14] Though the difference was not statistically significant among the ESBL and non ESBL isolates. In another study,[15] the age group most commonly affected was within 21 to 30 years. Shah et al[16] 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%). Similar findings were observed in the present study. Though the difference was found to be not statistically significant (p=0.911).

Exposure to hospital environment especially ICUs is a major risk factor for carriage of MDR bacteria especially in resource poor settings where hospitals can have high infection rates.[17] A multitude of factors including poor infrastructure of hospitals, low compliance with hand-hygiene, heavy workload with understaffing, overcrowding, lack of or poorly functioning infection control programme contribute to the problem.[17] In the present study, the occurrence of ESBL was higher in hospitalized patients (81.5%) as compared to outpatients (18.5%) which is statistically significant ($p<0.005$) and is in agreement with findings of other investigators.[14] The OPD isolates also have shown 18.5% ESBL resistance. The reason for which may be lack of hygiene, cross infection among the large populations, across the counter availability of antibiotics, lack of awareness and drug administration from quacks who frequently abuse antibiotics.[10]

The ESBL production was quite high among the pus samples (38.4%), followed by blood samples (36.6 %). On comparing with study by Kaur M et al, ESBL production in pus samples (51.37%), followed by urine samples (45.63%),[13] Umadevi S et al exudates (66.7%), urine (75%) was noted,[12] CRE (45.1%) rates are even higher than ESBL (38.4%) producers in pus samples, which has a potential to increase the morbidity and mortality, calling for an urgent review of institutional antibiotic usage, antibiotic stewardship, as well as infection control policy.[18] Similar, high degree of ESBL (24.0%) producers and CRE (26.9%) were noted in a study on blood stream infection in pediatric malignancy patients.[18]

Maximum ESBL producers were isolated from pediatric intensive care unit (PICU) patients 17%, followed by pediatric ward 13.5%, surgical ward 12.5% and medical ICU 12.1%. The burn and plastic surgery ward showed relatively higher number of CRE (16.8%) suggesting immediate need to review Carbapenem usage there. According to Segar L et al[15] most of the ESBL producers were from ICU (51.7%), Obstetrics and Gynaecology unit and general surgery. Also by Hooja S et al from Jaipur maximum ESBL producers were

isolated from intensive care unit (ICU) patients 70.0%, followed by pediatric ward 66.7% and surgical ward 63.6%.[14] The reason for high prevalence of ESBLs in ICU could be more debilitated patients, higher use of invasive devices, more ventilatory assistance and exposure to antimicrobial agents. The risk factors in surgery patients include catheterization and use of broad spectrum antibiotics preoperatively. Secondly in patients who have undergone surgery the duration of hospital stay may be a predisposing factor for colonization of ESBL producing organisms. Among the pediatric patient's risk factors include prior exposure to antibiotics, low birth weight, use of invasive devices, underlying illness and length of hospital stay.

Maximum ESBL production was seen among *Klebsiella spp.* (42.2%), followed by *E. coli* (41.7%), *Proteus spp.* (7.8%), *Providencia spp.* (6.3%), *Citrobacter spp.* (1.5%) and *Enterobacter spp.* (0.4%). More than 75% studies implicated *Klebsiella spp*. as the most common ESBL producing organism.[19] Kaur M et al showed maximum ESBL production among the isolates of *Klebsiella pneumoniae* (52.27%), followed by those of *E. coli* (46.43%).[13] *E. coli* (26.15%), *K. pneumoniae* (57.14%), *P. aeruginosa* (32.61%), *P. mirabilis* (42.86%), *M. morgani* (71.43%), *C. freundii* (50%) were found to be ESBL positive by DDST in a study from Sikkim.[7]

In our study, resistance to third generation cephalosporins was found to coexist with resistance to non β- lactam antibiotics as also reported by Tsering et al[7] indicating multidrug resistance pattern. One possible mechanism is the co-transmission of ESBL and resistance to other antimicrobials within the same conjugative plasmids.[17] Ciprofloxacin, in general had higher resistance rates (41.42 and 70.32 %) among both ESBL-producing and non-ESBL producing organisms, highlighting its extensive use. The 2008 SMART (Study for Monitoring Antimicrobial Trends) results have emphasized on the alarmingly high (80%) rates of *E. coli* isolates resistant to fluoroquinolones in India.[20] Martínez-Martínez and colleagues[21] 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. The susceptibility of the Gram-negative isolates tested for amikacin was high at 57.51%. Similar high sensitivity (76.6%) was noted by Thacker N et al.[18] Amikacin also fared better against ESBL bugs with 76.38 % sensitivity, making it good drug for combination antibiotic therapy. Good activity of Amikacin against ESBLs was noted by Segar L et al (55%)[15] and Nema S et al (83.92%).[6]

The other good options for treating these infections lies in the carbapenems, piperacillin-tazobactam, and cefoperazone-sulbactam. Cefoperazone-sulbactam was effective in 89.6% of the ESBL producers in the present study which was in unison with a recent study from India where 90% of the ESBL producers were sensitive to another BL/BLI, piperacillin-tazobactam.[22]

The ESBL were found to be quite sensitive to Imipenem (12.35% resistant) and Meropenem (7.67% resistant), with *Klebsiella spp.* (16.5 %) having the most and *E.coli* (5.2 %) having the least resistance. This good sensitivity profile of Imipenem is in harmony with the findings of Nema S et al[16] 100%, Dechen C Tsering et al[7] 97.53%, and Thacker et al, showed nearly half of the *Klebsiella* had carbapenem resistance.[18] A similar trend in *Klebsiella* has been reported from Delhi[18] which is explained by the high prevalence of carbapenemases, which are NDM-1 and easily transmissible. Carbapenem resistance is usually multifactorial: through β-lactamase enzymes or porin changes. The isolates resistant to carbapenem are sensitive only to two antibiotics i.e. tigecycline, and colistin. So, the resistance against carbapenem class of drugs has clinical as well as public health implications.

New technologies such as molecular techniques and modified mass spectrometry technique (matrix assisted light desorption ionization time-of-flight) are being suggested as quicker alternatives for routine laboratory diagnosis. However these are available only in research facilities and are still new in their development. Hence, routine detection of ESBLs by conventional methods should be done in every laboratory where molecular methods cannot be performed.[15]

Limitations: The information on ESBL infection-related mortality is unavailable. Molecular characterization of the identified ESBL isolates could not be done due to limited resources.

Conclusion

ESBLs were first identified in the 1980s and have gradually spread throughout the world by nosocomial routes. The phenotypic data generated in the current study indicates the high prevalence of ESBL producers in this region of central India. Longitudinal surveillance of the microbial flora and their antibiotic sensitivity pattern should be done in every hospital periodically. Good infection control practices and antibiotic management interventions are instrumental in preventing the emergence of outbreaks due to ESBL producing isolates, especially in high risk areas such as the medical ICU, pediatric wards and surgical wards.

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