

Original Research Article

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Prevalence of ESBL and MBL Producing Gram Negative Isolates from Various Clinical Samples in a Tertiary Care Hospital

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ABSTRACT

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Antimicrobial resistance is a growing threat worldwide. Increasing resistance to third generation cephalosporins has become a cause for concern. The prevalence of extended spectrum-lactamases (ESBLs) and metallo-beta-lactamases (MBL) among members of Enterobacteriaceae constitutes a serious threat to current -lactam therapy leading to treatment failure. A total of 276 Gram negative isolates were processed. ESBL was detected by phenotypic confirmatory disc diffusion test (PCDDT) using ceftazidime alone and in combination with clavulanic acid. MBL detection was done by Imipenem EDTA combined disc diffusion test and Modified Hodge test. Out of 276 isolates 69 (25%) were ESBL producers, 70 (25.3%) were MBL producers and 26 (9.42%) were both ESBL and MBL producers. Highest ESBL production was seen in *Escherichia coli* (46%) and maximum MBL production was seen in *Klebsiella pneumoniae* (34.8%). The study underlines problem of ESBL and MBL mediated resistance, which has created a therapeutic challenge for the clinicians and microbiologists. Simple disk method can be routinely employed to detect these common resistance mechanisms which will reduce the mortality and also spread of such resistant strains.

Introduction

Antibiotic resistance among Gram-negative bacilli (GNB) is a rapidly expanding problem due to the organisms' ability to mutate, and to acquire and transmit plasmids and other mobile genetic elements encoding resistance gene. Beta-lactamase antibiotics are among the most widely prescribed antibiotics worldwide and the emergence of resistance to these agents has resulted in a major clinical crisis (Siddiqui *et al.*, 2014). The β -lactam group of antibiotics is widely used to treat the infections caused by the pathogenic bacteria. Due to the extensive use of these antibiotics, β -lactamase mediated resistance has raised as major clinical crisis. The newer

β -lactamases, including extended-spectrum β -lactamases (ESBLs), ampC β -lactamases (AmpC), and metallo- β -lactamases (MBLs) have emerged worldwide as a cause of antimicrobial β -lactamase mediated resistance in gram negative bacteria (Kumar *et al.*, 2013). ESBLs are still considered as a threat since they are coded by plasmid and can be easily transmitted between species. ESBL producing organisms are highly effective in inactivating penicillins, most cephalosporins and aztreonam and are inhibited by β -lactamase inhibitors such as clavulanic acid (Fam *et al.*, 2006). ESBL producing isolates, in addition to being

resistant to β -lactam antibiotics, often exhibit resistance to other classes of drugs such as aminoglycosides, cotrimoxazole, tetracycline and fluoroquinolones. ESBLs are often located on plasmids that are transferable from strain to strain (Kamble, 2015). Carbapenems are used as drug of choice to treat infections caused by beta-lactam resistant bacteria. But extensive and sometimes unnecessary use of the carbapenems, poor sanitation and large population has facilitated the emergence of carbapenem resistant bacteria (Wadekar *et al.*, 2013).

Resistance to these antibiotics is due to decreased outer membrane permeability, increased efflux systems, alteration of penicillin binding proteins and carbapenem hydrolyzing enzymes carbapenemases (Kamalraj *et al.*, 2015). Resistance to carbapenem is predominantly mediated by metallo betalactamases, a class B type of betalactamases that recognize bivalent metal ions (Anil Rajput *et al.*, 2012). MBL can hydrolyze all metallo beta lactams except monobactams and are not inactivated by beta lactamase inhibitors like clavulanic acid, sulbactam and tazobactam (Chakraborty *et al.*, 2010). They may be chromosomally or plasmid mediated and therefore poses a threat of spread of resistance by gene transfer among gram negative bacteria (Kamalraj *et al.*, 2015).

The aim of the current study is to determine the percentage of ESBL and MBL producers among gram negative clinical isolates. Early detection of ESBL and MBL producing organisms is crucial to establish appropriate antimicrobial therapy and to prevent their inter hospital dissemination.

Materials and Methods

A total of 276 Gram negative organisms were isolated from various clinical samples (urine,

pus, blood, ET secretions, tracheal aspirates. They were identified by standard microbiological procedures (Collee *et al.*, 2007). The susceptibility of isolates to antibiotics was determined by Kirby- Bauer disc diffusion method using Clinical and Laboratory Standard Institute guidelines (CLSI, 2016). Antibiotics included were ceftazidime (30 μ g), aztreonam (30 μ g), cefipime (30 μ g), cefotaxime (30 μ g), cefoxitin (30 μ g), imipenem (10 μ g), meropenem (10 μ g), cefoperazone/ sulbactam (75/30 μ g), piperacillin/ tazobactam (100/10 μ g), gentamicin (10 μ g), amikacin (30 μ g), ciprofloxacin (5 μ g), cotrimoxazole (1.25/23.75 μ g), polymyxin B (300U) and colistin (10 μ g).

Isolates resistant to third generation cephalosporins were tested for ESBL production and isolates showing resistance to imipenem were tested for MBL production. Phenotypic detection of ESBL: The double disk diffusion method was used for detection of this enzyme as recommended by CLSI (CLSI, 2016). The suspension was streaked onto Mueller-Hinton agar plates (Hi Media, Mumbai, India). A disc of either ceftazidime (30 μ g) or cefotaxime alone (30 μ g) in combination with clavulanic acid (30 μ g/10 μ g) was placed at the distance of 20 mm (centre to centre). After incubation overnight at 35°C, a positive test result was considered as a 5 mm increase in inhibition zone compared with a disk without clavulanic acid. Phenotypic detection of MBL: Imipenem resistant isolates were screened for production of MBL by double disc diffusion test and modified Hodge test and strains showing positive results by both the methods are considered MBL producers.

Double disc diffusion test

Commercially available imipenem (10 μ g) and imipenem/EDTA (10+750 μ g) (Hi-media,

Mumbai) discs were placed on the Mueller Hinton agar at a distance of 20mm each other. After the incubation period of 16-18 hours at 37°C, the increase in inhibition zone size \geq 7mm around the IMP/EDTA disc than the IMP alone was considered as MBL positive (Yong *et al.*, 2002).

Modified Hodge test

An overnight culture of *E. coli* ATCC 25922 was adjusted to 0.5 McFarland standard and lawn culture was made on Muller Hinton agar (Hi-media, Mumbai). The 10 μ g of imipenem was placed on the centre of the plate and test culture was streaked from the edge of the disc to the periphery of the plate. After the incubation period of 16-18 hours at 37°C, the presence of a cloverleaf zone or distortion of inhibition around the imipenem disc was interpreted as positive for MBL production (CLSI, 2016).

Results and Discussion

The emergence of antibiotic resistance is a matter of great concern, particularly in hospitals. Antibiotic resistant bacteria appear to be biologically fit and capable of causing serious life threatening infections. The increase in antibiotic resistance among gram-negative bacilli, such as Enterobacteriaceae group, *Pseudomonas aeruginosa* and others, is a notable example and how bacteria can procure, maintain and express new genetic information that can confer resistance to one or several antibiotics. Resistance in gram-negative bacteria is a serious problem and calls for an effective infection control measures to curb their dissemination (Walsh *et al.*, 2005; Bradford, 2001). A total of 276 Gram negative organisms were isolated and further processed as study group. Out of 276 Gram negative isolates, *Escherichia coli* (41.6%) was the most common organism isolated followed by *Klebsiella*

pneumoniae(24%) and *Pseudomonas* spp (17.7%) (Table 1). Antibiotic resistance profile of various gram negative isolates is shown in table 2. Isolates resistant to third generation cephalosporins were tested for ESBL production and isolates showing resistance to imipenem were tested for MBL production.

Among 276 gram negative isolates 69(25%) were ESBL producers, 70(25.3%) were MBL producers and 26(9.42%) were both ESBL and MBL producers (Table 3).

In the present study 34(49.2%) ESBL producers were from IPD patients and 18(26%) were from OPD patients. Amongst the MBL producers 28(40%) were from IPD patients and 14(20%) were from OPD patients (Table 4). Our results showing high percentage of ESBL and MBL production in IPD patients were similar to findings of Oberoi *et al.*, (2013), Deshmukh *et al.*, (2011) and Prajapati *et al.*, (2013). These results corroborates the fact that a lot of risk factors associated with infections exist in indoor and ICU patients like environmental reservoir for multidrug resistant organisms, opportunities of cross transmission, sick and immunocompromised patients who are colonized, patients having multiple wounds and indwelling devices, heavy use of broad spectrum antibiotics and frequent contamination of the hands of health care workers while patient care. Highest ESBL production was seen in *Escherichia coli* (46%) followed by *Klebsiella pneumonia* (21.2%) (Table 5), which is comparable with studies by Kamble (2015), Agarwal *et al.*, (2008), Tsering *et al.*, (2008) and Shiju *et al.*, (2010). In our study highest MBL production was seen in *Klebsiella pneumoniae* (34.8%) and *Pseudomonas* spp (34.6%) (Table 5), which is comparable to studies conducted by Oberoi *et al.*, (2013), Kumar *et al.*, (2012) and Rao *et al.*, (2013).

Table.1 Distribution of various Gram negative isolates (N=276)

<i>Escherichia coli</i>	115(41.6%)
<i>Klebsiella pneumoniae</i>	66(24.0%)
<i>Pseudomonas spp</i>	49(17.7%)
<i>Acinetobacter spp</i>	25(9.1%)
<i>Citrobacter spp</i>	9(3.3%)
<i>Proteus spp</i>	7(2.5%)
<i>Enterobacter spp</i>	5(1.8%)

Table.2 Resistance pattern (% resistance) of various gram negative isolates (N=276)

<i>Antibiotic Tested</i>	<i>Escherichia coli</i> (115)	<i>Klebsiella pneumoniae</i> (66)	<i>Pseudomonas spp</i> (49)	<i>Acinetobacter spp</i> (25)	<i>Citrobacter spp</i> (9)	<i>Proteus spp</i> (7)	<i>Enterobacter spp</i> (5)
Ceftazidime	77(66.9%)	39(59%)	28(57.1%)	22(88%)	7(77.7%)	6(85.7%)	4(80%)
Ceftriaxone	75(65.2%)	38(57.5%)	NT	23(92%)	7(77.7%)	6(85.7%)	4(80%)
Cefefime	69(60%)	25(53.0%)	20(40.8%)	20(80%)	7(77.7%)	4(57.1%)	3(60%)
Cefoperazone-Sulbactam	69(60%)	36(54.5%)	13(26.5%)	18(72%)	5(55.5%)	4(57.1%)	3(60%)
Piperacillin-Tazobactam	69(60%)	32(48.4%)	19(38.7%)	19(76%)	6(66.6%)	3(42.8%)	2(40%)
Gentamicin	72(62.6%)	38(57.5%)	16(32.6%)	14(56%)	5(55.5%)	3(42.8%)	3(60%)
Amikacin	64(55.6%)	44(66.6%)	11(22.4%)	13(52%)	6(66.6%)	4(57.1%)	1(20%)
Ciprofloxacin	51(44.3%)	27(41%0	22(44.8%)	17(68%)	4(44.4%)	5(71.4%)	3(60%)
Imipenem	19(16.5%)	33(50%)	14(28.5%)	16(66%)	7(77.7%)	6(85.7%)	3(60%)
Meropenem	20(17.3%)	33(50%)	15(30.6%)	18(72%)	6(66.6%)	6(85.7%)	3(60%)
Cotrimoxazole	37(32.1%)	36(54.5%)	NT	20(80%)	8(88.8%)	7(100%)	4(80%)
Polymixin B	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	NT	0(0%)
Colistin	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	NT	0(0%)

Table.3 Percentage of ESBL and MBL producers among total Gram negative isolates

Total GNB isolates	276
ESBL producers	69(25%)
MBL producers	70(25.3%)
Both ESBL and MBL producer	26(9.42%)

Table.4 Area wise distribution of ESBL and MBL producers

	OPD	IPD	ICU
ESBL producers (N=69)	18(26%)	34(49.2%)	17(24.7%)
MBL producers (N=70)	14(20%)	28(40%)	28(40%)
Both ESBL and MBL producers (N=26)	4(15.4%)	12(46.2%)	10(38.4%)
Total (N=165)	36	74	55

Table.5 ESBL and MBL producers among various isolates

Organism	No. of isolates	ESBL producers No. (%)	MBL producers No. (%)	Both ESBL and MBL producers No.(%)
<i>Escherichia coli</i>	115	53(46.08%)	17(14.7%)	7(6.08%)
<i>Klebsiella pneumoniae</i>	66	14(21.2%)	23(34.8%)	5(7.57%)
<i>Pseudomonas spp</i>	49	1(2.04%)	17(34.6%)	6(12.2%)
<i>Acinetobacter spp</i>	25	1(4%)	7(28%)	5(20%)
<i>Citrobacter spp</i>	9	0(0%)	3(33.3%)	2(22.2%)
<i>Proteus spp</i>	7	0(0%)	2(28.5%)	1(25%)
<i>Enterobacter spp</i>	5	0(0%)	1(20%)	0 (0%)
Total	276	69(25%)	70(25.3%)	26(9.42%)

Table.6 Sample wise distribution of various ESBL positive isolates

ESBL producer	No. of isolates	Urine	Pus	High vaginal swabs	ET Secretions	Sputum
<i>Escherichia coli</i>	53	34(64.1%)	15(41.5%)	3(5.6%)	0(0%)	1(1.8%)
<i>Klebsiella pneumoniae</i>	14	6(42.8%)	6(42.8%)	0(0%)	1(7.14%)	1(7.1%)
<i>Pseudomonas spp</i>	1	0(0%)	0(0%)	0(0%)	1(100%)	0(0%)
<i>Acinetobacter spp</i>	1	0(0%)	1(100%)	0(0%)	0(0%)	0(0%)
Total	69	40(58%)	22(31.8%)	3(4.3%)	2(2.89%)	2(2.89%)

Table.7 Sample wise distribution of various MBL positive isolates (N=70)

MBL producer	No of isolates	Urine (17)	Pus (18)	Blood (4)	ET secretions (12)	Tracheal aspirate (11)	Sputum (4)	Central Line tip (4)
<i>Escherichia coli</i>	17	8(47.05%)	3(17.6%)	1(5.8%)	2(11.7%)	2(11.7%)	0(0%)	1(5.8%)
<i>Klebsiella pneumoniae</i>	23	2(8.7%)	7(30.4%)	0(0%)	3(13%)	6(26%)	2(8.7%)	3(13%)
<i>Pseudomonas spp</i>	17	6(35.3%)	4(23.5%)	2(11.7%)	3(17.6%)	2(11.7%)	0(0%)	0(0%)
<i>Acinetobacter spp</i>	7	0(0%)	1(14.2%)	1(14.2%)	2(28.4%)	2(28.4%)	1(14.2%)	0(0%)
<i>Citrobacter spp</i>	3	0(0%)	1(33.3%)	0(0%)	2(66.6%)	0(0%)	0(0%)	0(0%)
<i>Proteus spp</i>	2	1(50%)	1(50%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
<i>Enterobacter spp</i>	1	1(100%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
<i>Total</i>	70	18(25.7%)	17(24.2%)	4(5.7%)	12(17.1%)	12(17.1%)	3(4.2%)	4(5.7%)

Table.8 Sample wise distribution of both ESBL and MBL positive isolates

Name of the isolate	No of isolates	Urine	Pus	Sputum	Tracheal aspirate	ET secretions	Central line tip	Peritoneal fluid
<i>Escherichia coli</i>	7	1 (14.2%)	6(85.7%)	0(0%)	0(0%)	1(14.2%)	0(0%)	0(0%)
<i>Klebsiella pneumoniae</i>	5	1(20%)	1(20%)	0(0%)	0(0%)	1(20%)	0(0%)	2(40%)
<i>Pseudomonas spp</i>	6	2(33.3%)	1(16.6%)	0(0%)	1(16.6%)	1(16.6%)	1 (16.6%)	0(0%)
<i>Acinetobacter spp</i>	5	0(0%)	0(0%)	0(0%)	3(60%)	2(40%)	0(0%)	0(0%)
<i>Citrobacter spp</i>	2	1(50%)	0(0%)	0(0%)	0(0%)	1(50%)	0(0%)	0(0%)
<i>Proteus spp</i>	1	0(0%)	0(0%)	1(100%)	0(0%)	0(0%)	0(0%)	0(0%)
<i>Total</i>	26	5(19.2%)	8(30.7%)	1(3.8%)	4(15.3%)	5(19.2%)	1(3.8%)	2(7.7%)

In the present study highest percentage of ESBL and MBL production was seen in urine and pus isolates (Tables 5, 6, 7 and 8). Our results correlate with study of Grover *et al.*, (2013), Oberoi *et al.*, (2013) and Deshmukh *et al.*, (2011). Early detection of ESBL and MBL positive isolates is mandatory not only

for patient management but also for appropriate infection control measures to prevent the spread of the organisms (Uma devi *et al.*, 2011)

MBL are enzymes that can hydrolyse wide variety of beta lactams including penicillins,

cephems and carbapenems except aztreonam (Krishna, 2010). Production of MBL has vast therapeutic consequences since these organisms also carry multidrug resistance genes and the only viable option remains potentially toxic polymyxin B and colistin (Veenu gupta *et al.*, 2013).

In conclusion the early detection of beta lactamase producing isolates would be important for the reduction of mortality rates for patients and also to avoid the intra hospital dissemination of such strains. Simple phenotypic screening tests are proved to be rapid and convenient for their detection in the clinical laboratory. Monitoring and judicious usage of cephalosporins and imipenem, periodic surveillance of antibiotic resistance patterns and efforts to decrease empirical antibiotic therapy would go a long way in addressing some of the problems associated with ESBL an MBL producer. To overcome the problem of emergence and the spread of multidrug resistant organisms, a combined interaction between the microbiologist, clinicians and infection control team is needed.

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