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Prevalence of ESBL and Amp C producing Enterobacteriaceae in a tertiary care cancer hospital in South India with special reference to *E.coli* and *Klebsiellapneumoniae*

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Abstract:
Background and objectives*: The prevalence of ESBL and ampC producing strains among E.coli and Klebsiellapneumoniae was assessed among different samples received in Microbiology.*
Methods*: A total of 210 non-repeating clinical isolates of E.coli and Klebsiellapneumoniae were collected from various specimens of patients with hematological malignancy over a period of 3 months (July 2016 to September 2016) prospectively in a tertiary care cancer hospital in South India. This study assessed the prevalence of ESBL and ampC and also compared the sensitivity and specificity of different phenotypic methods of ESBL and ampC detection.*
Results*: The prevalence of ESBL and ampC β-lactamases among E.coli and Klebsiellapneumoniae was found to be 44.76% and 10.95% respectively. PCDDT (92.16%) was found to be more sensitive than DDST (83.33%) in detecting ESBL strains. The maximum ESBL production was seen in urine samples (59.18%), and that of ampC producers was seen in pus samples (20.90%). Both ESBL producers and AmpC producers had better sensitivity profile than ESBL non producers and AmpC non producers suggesting other mechanisms of resistance.*
Conclusion*: Other studies need to be conducted to understand the mechanism of resistance to carbapenems and to know the different carbapenemases prevalent here.*
Keywords:*AmpC, Enterobacteriaceae, ESBL, prevalence, resistance*

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I. Introduction

Beta-lactam agents are among the most common drugs used for treatment for bacterial infections and beta-lactamases continue to be the prominent cause of resistance to β-lactam antibiotics among Gram-negative bacteria worldwide[1]. Important among these enzymes are the Extended spectrum β-Lactamase (ESBLs) and ampC β-Lactamase (ampC). Treatment of these multiple drug resistant organisms is a deep scientific concern.

ESBLs are enzymes that hydrolyse oxyimino-cephalosporins conferring resistance to third generation cephalosporins such as cefotaxime, ceftazidime and ceftriaxone and to monobactams such as aztreonam. They are susceptible to β-lactamase inhibitors like clavulanic acid, tazobactam and sulbactam[2], whereas, ampC apart from being resistant to all generations of cephalosporins, cephamycins and monobactam except cefepime and cefpirome, are also not inhibited by clavulanic acid, tazobactam and sulbactam. They are not active against carbapenems and are inhibited by cloxacillin and boronic acid[3]. Antibiotic resistance due to these beta lactamases varies according to geographic locations and is directly proportional to the use and misuse of antibiotics. Failure to detect these enzymes has contributed to their uncontrolled spread, outbreaks and sometimes to avoidable therapeutic failures[3, 4, 5].Hence, their detection must be quick, for formulating an antibiotic policy and containment measures are needed to solve the issue of antibiotic resistance.

As no data was available on the prevalence of ESBL and ampC, this study was undertaken to determine the prevalence of the ESBL and ampC producing strains among *E.coli* and *Klebsiellapneumoniae* obtained from different samples received in the division of Microbiology and to compare the different phenotypic methods used to screen and confirm the presence of ESBL and ampC in these strains.

II. Methodology

1.1Study Setting And Design

The prospective study was conducted in a tertiary care cancer hospital, in south India. The study took place from July 2016 to September 2016. The present study was approved by Institutional Review Board, IRB No: 12/2015/03 and Human Ethics Committee, HEC No: 07/2016. A total of 210 clinical isolates of *E.coli* and *Klebsiellapneumoniae* were included in the study.

1.2. Microbiological methods

A total of 210 consecutive, non-repetitive clinical isolates of *E.coli* and *Klebsiellapneumoniae* obtained from processing blood, pus swab, pus aspirate, sputum, urine and CSF samples and identified by standard biochemical reactions was included in the study. All isolates other than *E.coli* and *Klebsiellapneumoniae* were excluded. Antimicrobial susceptibility testing was carried out by disc diffusion method on Mueller Hinton Agar (MHA) using current CLSI recommendations. The following methods were used for screening and confirmation of ampC and ESBL in these strains.

1.2.1. Screening for ESBL:

Isolates showing an inhibition zone size of ≤21 mm with ceftazidime (30 µg), ≤25 mm with ceftriaxone (30 µg) and ≤27 mm with cefotaxime (30 µg) were identified as potential ESBL producers and were short listed for confirmation of ESBL production[6, 7]

1.2.2. Screening for ampC:

Isolates showing an inhibition zone size of <18 mm with cefoxitin (30 µg) were identified as potential ampC producers and were short listed for confirmation of ampC production[8]

1.2.3. Confirmatory test for ESBL: 2 methods were used

1.2.3.1. Double Disc Synergy Test (DDST):

First, synergy was determined between a disc of amoxicillin-clavulanate (20 µg/10 µg) (augmentin) and a 30-µg disc of three third-generation cephalosporin antibiotics namely ceftriaxone, cefotaxime and ceftazidime placed at a distance of 20 mm from center to center on MHA swabbed with the test isolate. Clear extension of the edge of the inhibition zone of cephalosporin toward the augmentin disc resulting in a characteristically shaped zone referred to as 'keyhole' was interpreted as positive for ESBL production[6, 7].

1.2.3.2. Phenotypic Confirmatory Disc Diffusion test (PCDDT):

The test was done by using both cefotaxime (30µg) and ceftazidime (30µg) alone and in combination with clavulanic acid on a MHA plate inoculated with a bacterial suspension of 0.5 McFarland turbidity standards and incubated overnight at 37°C. A >5 mm increase in zone diameter for either antimicrobial agent tested in combination with clavulanic acid versus its zone when tested alone confirmed ESBL production as per Clinical and Laboratory Standards Institute (CLSI) 2016 guidelines[7].

1.2.4. Confirmatory test for ampC: 2 methods were used

1.2.4.1. Inhibitor based test with phenyl boronic acid:

The phenotypic detection of AmpC was evaluated with boronic acid disk tests. The stock solution was prepared by dissolving phenylboronic acid in dimethyl sulfoxide at a concentration of 20 mg/ml. From this solution, 20 µl (containing 400 µg of boronic acid) was dispensed onto cefoxitin (30 mcg) disks. The disks were then dried and used within 60 min. The test was performed by inoculating MHA with the test isolate and placing cefoxitin disks (30 mcg) with and without boronic acid onto the agar. The agar plates were incubated at 37°C overnight. The test was considered positive for the detection of ampC enzyme production when the diameter of the growth-inhibitory zone around a cefoxitin disk with boronic acid was 4 mm or larger than that around the disk containing cefoxitin disc alone[8, 9].

1.2.4.2. The cefoxitin-cloxacillin double disc synergy test (CC-DDS)

CC-DDS was performed using cefoxitin 30mcg and cefoxitin 30mcg plus cloxacillin 200mcg (HIMEDIA). The strains were inoculated onto MHA and placing cefoxitin disks (30 mcg) and cefoxitin (30 mcg) + cloxacillin (200mcg) disc onto the agar and then incubated at 37°C overnight. The test was considered positive for the detection of ampC enzyme production when the diameter of the growth-inhibitory zone around a cefoxitin with cloxacillin 200 mcg was ≥4 mm than that around the disk containing cefoxitin disc alone[8, 9].

β-lactamase negative *Escherichia coli* ATCC 25922 was used as the negative control and ESBL-producing*Klebsiellapneumoniae* ATCC 700603 was used as the positive control in this study.

III. Results

During the 3 month study period, 106 isolates of *E.coli* and 104 isolates of *Klebsiellapneumoniae* were obtained from various samples in the Division of Microbiology. Table I gives a detailed description of these samples.

Table I: Distribution of *E.coli*and *K.pneumoniae* in various samples

Specimens	Number of samples *N (%)	*E.coli* *N (%)	*K.pneumoniae* *N (%)
Pus swab	67(31.90%)	38(18.10%)	29(13.81%)
Urine	49(23.33%)	34(16.19%)	15(7.14%)
Throat swab	32(15.23%)	9(4.29%)	23(10.95%)
Sputum	27(12.85%)	7(3.33%)	20(9.52%)
Blood	26(12.38%)	12(5.71%)	14(6.67%)
Pus aspirate	8 (3.80%)	6(2.86%)	2(0.95%)
CSF	1 (0.47%)	0(0%)	1(0.47%)
Total	210	106(50.47%)	104(49.52%)

Screening for ESBL in these isolates was done with 3 oxyimino-cephalosporins namely ceftazidime, cefotaxime and ceftriaxone and the detailed description is given in Table II.

Table II: Screening of ESBL using 3 different cephalosporins

Bacterial species isolated	No of isolates screened	Ceftazidime Resistant N (%)	Cefotaxime Resistant N (%)	Ceftriaxone Resistant N (%)
E. coli	106	60 (56.60%)	54 (50.94%)	52 (49.06%)
Klebsiellapneumoniae	104	42 (40.38%)	40 (38.46%)	40 (38.46%)
Total	210	102 (48.57%)	94 (44.76%)	92 (43.81%)

Among these drugs the best screening was offered by Ceftazidime about 48.57%. In the screen test for ESBL production, 102(48.57%) were positive and these were subjected to 2 phenotypic confirmatory tests i.e; Double Disc Synergy Test (DDST) and the CLSI confirmatory method - Phenotypic Confirmatory Disc Diffusion Test (PCDDT).DDST detected 85(83.33%) of the ESBL producers and PCDDT detected 94 (92.16%) of them. The prevalence of ESBL was found to be 94/210 i.e., 44.76%. The detailed description is given in table III

Table III: Detection of ESBL producers by comparison of 2 different methods

Bacterial species isolated	Positive screen test for ESBL N(%)	No. of isolates confirmed by DDST N(%)	No. of isolates confirmed by PCDDT N(%)
E. coli	60	50 (83.33%)	54 (90%)
Klebsiellapneumoniae	42	35 (83.33%)	40 (95.24%)
Total	102 (48.57%)	85(83.33%)	94 (92.16%)

Of 90 (42.86%) screen-positive clinical isolates for ampC with cefoxitin disc (30µg), only 23 isolates (25.56%) were ampC positive using CC-DDS and 22 (24.44%) isolates were amp C positive using phenyl boronic acid method. The prevalence of ampC was found to be 23/210 i.e., 10.95%. The detailed description is given in table IV

Table IV: Detection of AmpC β-lactamases by comparison of 2 different methods

Bacterial species isolated	No of isolates screened	Positive screen test for ampCN(%)	Isolates confirmed by CC-DDS N(%)	Isolates confirmed with phenyl boronic acid N (%)
E coli	106	41 (38.68%)	16 (39.02%)	16(39.02%)
Klebsiellapneumoniae	104	49 (47.12%)	7 (14.29%)	6(12.24%)
Total	210	90 (42.86%)	23(25.56%)	22(24.44%)

The specimen and organism wise distribution of the ESBL producers and ampC producers is shown in table V. The maximum ESBL production was seen in urine samples (59.18%), and the maximum number of ampC producers was seen in pus samples (20.90%).

Table V: Specimen and organism wise distribution of ESBL and ampC producers

Isolates / Specimens	ESBL positive N (%)			ampC positive N (%)		
	E.coli	*Klebsiellapneumoniae*	Total ESBL	*E coli*	*Klebsiellapneumoniae*	Total ampC
Pus swab	18(48.65%)	9(30%)	27(40.30%)	9(24.32%)	5(16.67%)	14(20.90%)
Urine	22(64.71%)	7(46.67%)	29(59.18%)	5(14.71%)	0(0%)	5(10.20%)
Throat swab	4(44.44%)	9(39.13%)	13(40.63%)	0(0%)	1(4.35%)	1(3.13%)
Sputum	2(28.57%)	9(45%)	11(40.74%)	0(0%)	1(5%)	1(3.70%)
Blood	5(41.67%)	5(35.71%)	10(38.46%)	1(8.33%)	0(0%)	1(3.85%)
Pus aspirate	3(50%)	1(50%)	4(50%)	1(16.67%)	0(0%)	1(12.50%)
CSF	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Total	54(25.71%)	40 (19.05%)	94(44.76%)	16 (7.62%)	7 (3.33%)	23(10.95%)

The antibiotic sensitivity pattern revealed that the maximum sensitivity was noted for meropenem (81.43%) followed by imipenem (79.05%), tobramycin (72.38%), cefaperazone/sulbactam (71.43%), piperacillin/tazobactum (70%), amikacin and doxycycline (68.1%), gentamicin (63.33%), levofloxacin (58.57%), ciprofloxacin (38.57%). A high resistance rate was noted for ampicillin (95.24%), cefazolin (76.67%), cefuroxime (76.19%), cefotaxime (72.38%), cefipime (62.38%) and cotrimoxazole (62.38%).The detailed description is given in table VI

Table VI: Antibiotic susceptibility pattern of the isolates

Antibiotics	Sensitive N*(%)	Intermediate N(%)	Resistant N(%)
Meropenem	171(81.43%)	11(5.24%)	28(13.33%)
Imipenem	166(79.05%)	10(4.76%)	34(16.19%)
Tobramycin	152(72.38%)	5(2.38%)	53(25.23%)
Cefoperaone/Sulbactam	150(71.43%)	2(0.95%)	58(27.62%)
Piperacillin/Tazobactam	147(70%)	4(1.90%)	59(28.10%)
Amikacin	143(68.1%)	2(0.95%)	65(30.95%)
Doxycycline	143(68.1%)	18(8.57%)	49(23.33%)
Gentamicin	133(63.33%)	6(2.86%)	71(33.81%)
Levofloxacin	123(58.57%)	9(4.29%)	78(37.14%)
Ciprofloxacin	81(38.57%)	4(1.90%)	125(59.52%)
Cotrimoxazole	78(37.14%)	1(0.48%)	131(62.38%)
Cefipime	62(29.52%)	17(8.10%)	131(62.38%)
Cefotaxime	55(26.19%)	3(1.43%)	152(72.38%)
Amoxicillin/Clavulanic acid	47(22.38%)	20(9.52%)	143(68.1%)
Cefuroxime	42(20%)	8(3.81%)	160(76.19%)
Cefazolin	35(16.67%)	6(2.86%)	161(76.67%)
Ampicillin	7(3.33%)	3(1.43%)	200(95.24%)

The ESBL producers had more sensitive isolates for meropenem (93.62%), imipenem (93.62%), tobramycin (81.91%), cefaperazone/sulbactam (87.23%), piperacillin/tazobactum (85.11%), amikacin (79.79%), gentamicin (68.09%) and levofloxacin (61.70%) as compared to their non ESBL producing counterparts as is shown in table VII.

Table VII: Comparison of antibiotic susceptibility pattern of ESBL producers and ESBL non-producers

	ESBL+(S)	ESBL -(S)	ESBL +(I)	ESBL -(I)	ESBL+®	ESBL -(R)
Meropenem	88(93.62%)	83(71.55%)	1(1.06%)	8(6.90%)	5(5.32%)	25(21.55%)
Imipenem	88(93.62%)	78(67.24%)	1(1.06%)	9(7.76%)	5(5.32%)	29(25%)
Tobramycin	77(81.91%)	75(64.65%)	3(3.19%)	2(1.72%)	14(14.89%)	39(33.62%)
Cefoperaone/Sulbactam	82(87.23%)	68(58.62%)	0(0%)	0(0%)	12(12.77%)	48(41.38%)
Piperacillin/Tazobactam	80(85.11%)	67(57.76%)	4(4.26%)	0(0%)	10(10.64%)	49(42.24%)
Amikacin	75(79.79%)	68(58.62%)	1(1.06%)	1(0.86%)	18(19.15%)	47(40.52%)
Doxycycline	52(55.32%)	79(68.10%)	7(7.45%)	1(0.86%)	35(37.23%)	36(31.03%)
Gentamicin	64(68.09%)	69(59.48%)	2(2.13%)	1(0.86%)	28(29.79%)	46(39.66%)
Levofloxacin	58(61.70%)	65(56.03%)	6(6.38%)	3(2.59%)	30(31.91%)	48(41.38%)
Ciprofloxacin	31(32.98%)	50(43.10%)	3(3.19%)	1(0.86%)	60(63.83%)	65(56.03%)
Cotrimoxazole	27(28.72%)	51(43.97%)	0(0%)	1(0.86%)	67(71.28%)	64(55.17%)
Cefipime	8(8.51%)	54(46.55%)	15(15.96%)	2(1.72%)	71(75.53%)	60(51.72%)
Amoxicillin/Clavulanic acid	16(17.02%)	31(26.72%)	15(15.96%)	5(4.31%)	63(67.02%)	80(68.97%)

Footnotes: ESBL+ and ESBL- represents ESBL producers and non-producers respectively; S- Sensitive; I-Intermediate; R-Resistant.

The non ESBL producers probably had different mechanisms for their resistance pattern. For other antibiotics, the resistance pattern was found to be more in the ESBL producers as compared to their non-ESBL counterparts

The ampC producers also had more sensitive isolates for meropenem (100%), imipenem (95.65%), tobramycin (91.30%), cefaperazone/sulbactam (91.30%), piperacillin/tazobactum (86.96%), amikacin (82.61%), gentamicin (82.61%), levofloxacin (65.22%), ciprofloxacin (39.13%), cotrimoxazole (39.13%) and cefipime (47.83%) as compared to their non ampC producing counterparts as is shown in table VIII. The non ampC producers were found to be more resistant compared to ampC producers.

Table VIII: Comparison of antibiotic susceptibility pattern of ampC producers and ampCnon-producers

	ampC+(N)(S)	ampC -(N)(S)	ampC +(N)(I)	ampC-(N)(I)	ampC+(N)(R	ampC -(N)(R)
Meropenem	23(100%)	148(79.57%)		9(4.84%)		29(15.59%)
Imipenem	22(95.65%)	144(77.42%)		9(4.84%)	1(4.35%)	33(17.74%)
Tobramycin	21(91.30%)	131(70.43%)		5(2.69%)	2(8.70%)	50(26.88%)
Cefoperaone/Sulbactam	21(91.30%)	129(69.35%)			2(8.70%)	57(30.65%)
Piperacillin/Tazobactam	20(86.96%)	127(68.28%)		4(2.15%)	3(13.04%)	55(29.57%)
Amikacin	19(82.61%)	124(66.67%)		2(1.08%)	4(17.39%)	60(32.26%)
Doxycycline	14(60.87%)	117(62.90%)		8(4.30%)	9(39.13%)	61(32.80%)
Gentamicin	19(82.61%)	114(61.29%)		3(1.61%)	4(17.39%)	69(37.10%)
Levofloxacin	15(65.22%)	108(58.06%)	1(4.35%)	8(4.30%)	7(30.43%)	70(37.63%)
Ciprofloxacin	9(39.13%)	72(38.71%)		4(2.15%)	14(60.87%)	110(59.14%)
Cotrimoxazole	9(39.13%)	69(37.10%)		1(0.54%)	14(60.87%)	116(62.37%)
Cefipime	11(47.83%)	51(27.42%)	3(13.04%)	14(7.53%)	9(39.13%)	121(65.05%)
Amoxicillin/Clavulanic acid	1(4.35%)	46(24.73%)	2(8.70%)	18(9.68%)	20(86.96%)	122(65.59%)

N- Number of isolates; S- Sensitive; I- Intermediate; R- Resistant; ampC+ : ampC producers;
ampC -: ampCnonproducers

IV. Discussion

Infections by ESBL and ampC producing organisms have emerged as a major problem and the failure of therapy with broad spectrum antibiotics are creating serious problems. The prevalence of ESBL and ampC vary greatly worldwide and in different geographic areas and are rapidly changing over time. In our study, we found the prevalence of ESBL to be 44.76% and that of AmpC to be 10.95%. PCDDT was identified as the most sensitive and an inexpensive method for ESBL detection and was capable of detecting ESBL in 94 (44.76%) isolates; likewise, DDST, using amoxiclav as inhibitor of ESBL, showed positive result in only 85 (40.48%) isolates. So even in our study, PCDDT was found to be more sensitive than DDST in detecting ESBL strains. The performance of the confirmatory tests for AmpC varied from 24.44% in phenyl boronic acid method to 25.56% in CC-DDS. It has been seen in other studies that the specificity of inhibitor based assays is lower than Tris-EDTA method[8]. This could be the reason for reduced specificity of the ampC confirmatory tests in our study. Also, although the Clinical and Laboratory Standards Institute (CLSI) has issued recommendations for ESBL screening and for confirmation of ESBL for isolates of *Escherichia coli* and *Klebsiella spp*., no CLSI recommendations exists for detection of ampC.

Antibiogram patterns for the isolates analyzed showed that ESBL producing and ampC producing isolates possessed a higher degree of sensitivity towards most antibiotics including carbapenems compared to non-ESBL producers and non-ampCproducers(Table VII and VIII). Non ESBL producers and non ampC producers were more resistant to carbapenems and β-Lactam/β-lactamase inhibitor combinations. This could be due to the increased use of carbapenems as ours is a tertiary care cancer centre and also due to presence of other enzymes like KPC (Klebsiellapneumoniaecarbapenemases), metallo beta-lactamases which masks the detection of ESBL and ampC.

Also β-Lactam/β-lactamase inhibitor combinations like piperacillin/tazobactam and cefaperazone/sulbactam which are usually active against organisms possessing a single ESBL now have reduced efficacy probably due to the presence of multiple ESBLs which is also documented in other studies. In our study, we noticed in vitro 12.77% resistance to cefaperazone/sulbactam and 10.64% resistance to piperacillin/tazobactam among ESBL producers.

The carbapenems (imipenem, meropenem, ertapenem) are still the first option for treatment of serious infections with ESBL-producing *E. coli* and *K. pneumoniae*[10](Paterson et al., 2000). It has been reported that >98% of the ESBL-producing *E. coli* and *K. pneumoniae* are still susceptible to these drugs[10, 11].In our study, only 93.62% of the ESBL strains were sensitive to imipenem and meropenem. Carbapenem resistance has also been increasingly reported in many countries recently[11, 12]. In our study also, meropenem resistance was seen in 5.32% of ESBL producers, 21.55% of ESBL non-producers and in 15.59% of ampC non-producers. Imipenem resistance was seen in 5.32% of ESBL producers, 25% of ESBL non-producers, 4.35% of ampC producers and in 17.74% of ampC non-producers. Therefore, antibiotic therapy of different infections caused by these strains is challenging. The options of antibiotics are very limited, and require long term treatment with novel and costly antibiotics such as Tigecycline, Fosfomycin and Colistin.[11]

Furthermore, inappropriate use of antimicrobials has been shown to play a pivotal role in the emergence of multi drug resistant organisms. Selection of resistant forms can occur during or after such antimicrobial treatment[13, 14]. Therefore clinicians should ensure the use of appropriate antibiotics for recommended periods in adequate doses in order to prevent emergence of multidrug resistant organisms.

V. Conclusion

In conclusion, the screening of AmpC beta lactamases using Cefoxitin has excellent sensitivity but the performance of confirmatory tests differs widely. This study gives us an understanding to the current prevalence of ampC and ESBL among *E.coli* and *Klebsiellapneumoniae* isolates in our cancer centre. Sensitivity to carbapenems is decreasing and Tigecycline, Colistin and Fosfomycin may be needed to treat MDROs resistant to carbapenems. Other studies need to be conducted to understand the mechanism of resistance to carbapenems and to know the different carbapenemases prevalent here. Perhaps, preventive measures could go a long way in containing the menace of drug resistance in our settings.

VI. Limitations

Genotypic characterization of the enzymes has not been done which would have helped in characterization of the genomic pattern of the ESBL enzymes in the community.

Conflict of Interest:
The authors declare that they have no conflict of interest.

Acknowledgement: Nil

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