

## Original Research Article

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## AmpC and Extended Spectrum Beta Lactamase Producing Isolates of *E. coli*, *Klebsiella spp.* and *P. mirabilis* in a Tertiary Care Center and their Sensitivity to Other Antibiotics

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### ABSTRACT

*Enterobacteriaceae* cause protean infections and are the common Gram negative isolates in a microbiology laboratory. Spectrum of multi-drug resistance includes AmpC, Extended spectrum beta lactamase and carbapenemase production with others. This was a cross sectional study to determine susceptibility pattern of AmpC and extended spectrum beta lactamase producing isolates against different antimicrobials. There was significant difference between the pure AmpC producing, pure ESBL producing, AmpC ESBL co-producing and AmpC ESBL non-producing isolates of *E. coli*, *Klebsiella spp.* and *P. mirabilis* regarding the resistance pattern against amoxicillin-clavulanate, piperacillin-tazobactam and co-trimoxazole for which the higher number of pure AmpC producers or AmpC ESBL co-producers were found to be resistant as compared to pure ESBL producers. In addition, there was significant difference in the resistance pattern against imipenem and chloramphenicol among pure AmpC producing, pure ESBL producing, AmpC ESBL co-producing and AmpC ESBL non-producing isolates of *E. coli*, sulfonamide in case of *Klebsiella spp.* and imipenem in case of *P. mirabilis* isolates. The difference can be justified by the fact that the AmpC producers are not inhibited by the beta lactamase inhibitors like clavulanic acid.

#### Keywords

AmpC and  
Extended Spectrum  
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#### Article Info

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### Introduction

*Enterobacteriaceae* cause protean infections in both community and the hospital setting (Mackowiak *et al.*, 1978; Johanson *et al.*, 1969). They comprise the most common Gram-negative isolates in microbiology laboratories, including the vast majority of urinary isolates and a large proportion of isolates from the blood, the peritoneal cavity, and the respiratory tract and isolated from other sites too (Donnenberg, 2012). The spectrum of multidrug-resistant Gram-negative organisms (MDRGN) including AmpC, extended spectrum  $\beta$ -lactamases

(ESBLs) and carbapenemase producer continues to evolve. Beginning in the 1980s and with increasing speed over the past decade, the *Enterobacteriaceae* have become more resistant and, hence, a major concern (Savard and Perl, 2012).

Beta-lactam antibiotics are commonest antibiotics used in treatment of infections due to Gram negative organisms. The prevalence of multidrug resistant Gram negative bacteria (including  $\beta$ -lactam antibiotics) is on a rise in the recent past and the AmpC  $\beta$ -lactamases

and/or ESBL production has been a matter of concern (Peter-Getzlaff *et al.*, 2011). AmpC producing isolates have been obtained from intensive care units, long term care facilities, rehabilitation centers and OPDs (Peter-Getzlaff *et al.*, 2011). This study was undertaken to study the prevalence of AmpC  $\beta$ -lactamase and ESBL producers at a tertiary care center and to study the susceptibility pattern of these isolates against different antimicrobials.

### **Materials and Methods**

The study was carried out at a tertiary care center from Nov 2012 to Oct 2014. Two hundred clinical isolates which included *E. coli*, *Klebsiella spp* and *P. mirabilis* were collected and tested. The organisms were identified on the basis of colony morphology and biochemical reactions as per conventional isolation and identification procedure (Chirchton, 1996). All isolates were subjected for antibiotic susceptibility testing using Kirby Bauer Disk diffusion method as per CLSI 2012 guidelines (CLSI, 2012).

### **Screening tests for $\beta$ lactamase production**

Isolates were screened for AmpC  $\beta$ -lactamase production using 30  $\mu$ g cefoxitin disc (CX) by disc diffusion method as per CLSI guidelines (CLSI 2012). Isolates showing zone of inhibition  $\leq 18$  mm were considered as non-susceptible to cefoxitin (CX) i.e. potential  $\beta$ -lactamase producer. These isolates were subjected to confirmatory tests for AmpC  $\beta$ -lactamase production.

Screening for ESBL production was done using 30  $\mu$ g ceftazidime disc (CAZ) by disc diffusion method as per CLSI guidelines (CLSI 2012). Isolates showing zone of inhibition  $\leq 22$  mm were considered as non-susceptible to ceftazidime (CAZ) i.e. potential ESBL producer. These isolates were

subjected to confirmatory test for ESBL production.

### **Confirmatory Tests**

#### **Disc Potentiation Test (using cefoxitin and cefoxitin/boronic acid) (Pitout *et al.*, 2010)**

The isolate to be tested was inoculated on MHA using standard method (CLSI, 2012). CX (30 $\mu$ g) and CX+BA (30 $\mu$ g + 400 $\mu$ g) are placed on inoculated MHA and incubated overnight at 37°C. The difference in diameters of zone of inhibition noted. An organism showing difference in the diameters of zone of inhibition  $\geq 5$ mm was considered AmpC  $\beta$  lactamase producer (Image 1). Boronic acid is reversible inhibitor of AmpC  $\beta$  lactamase enzyme. It binds tightly to AmpC and brings about a structure based mechanism of inhibition.

#### **Double Disc Diffusion Test (DDDT) (Grover *et al.*, 2013)**

A disc of ceftazidime (CAZ) (30  $\mu$ g) alone and a disc of ceftazidime in combination with clavulanic acid (CAC) (30/10  $\mu$ g) were used for each isolates. Both the discs were placed on a lawn culture of the test isolate on MHA plate and incubated overnight at 37°C. A  $\geq 5$  mm increase in zone diameter for either antimicrobial agent tested in combination with clavulanic acid versus its zone when tested alone was designated as ESBL positive (Image 2). Clavulanic acid inhibits the extended spectrum  $\beta$ - lactamase enzyme and there is enhanced zone of inhibition around disc containing clavulanic acid as compared to the disc without clavulanic acid.

### **Results and Discussion**

A Total of 217 isolates were collected during the study period. One hundred and three (47.47%) were *Klebsiella spp.* (88 K.

*pneumoniae*, 15 *K. oxytoca*), 90 (41.48%) were *E. coli* and 24 (11.06%) were *P. mirabilis*. Out of 217 isolates, 67 (30.88%) were isolated from urine, 58 (26.73%) from pus, 24 (11.06%) from tracheal aspirates, 20 (9.22%) from blood and 48 (22.12%) were isolated from miscellaneous samples. One hundred and fifty nine (73.27%) isolates were from males while 58 (26.73%) were from females. Location-wise, 81(37.33%) patients were from ICU while 136 (62.67%) were from other wards.

Out of 217 isolates, 173 (79.72%) were positive for cefoxitin screen i.e., resistant to 30µg cefoxitin with diameter of zone of inhibition ≤18mm while 44 (20.28%) were negative for cefoxitin screen i.e., diameter of zone of inhibition >18mm. Out of 90 *E. coli* isolates, 72 (80.00%) were positive for cefoxitin screen while 18 (20.00%) were negative. Out of 88 *K. pneumoniae* isolates, 69 (78.41%) were positive for cefoxitin screen while 19 (21.59%) were negative. All *K. oxytoca* isolates were positive for cefoxitin screen. Out of 24 *P. mirabilis* isolates, 17 (70.83%) were positive for cefoxitin screen while 7 (29.17%) were negative. A total of 136 (62.67%) isolates were found to be AmpC β-Lactamase producers by disc potentiation test with difference in the diameters of zones of inhibition ≥5mm considered to be positive. Out of 90 *E. coli* isolates, 59 (65.56%) were AmpC producers while 31(34.44%) were non-AmpC producers.

Out of 88 *K. pneumoniae* isolates, 51 (57.96%) were AmpC producers while 37(42.04%) were non-AmpC producers. Out of 15 *K. oxytoca* isolates, 14 (93.33%) were AmpC producers while 1(6.67%) was non-AmpC producers. Out of 24 *P. mirabilis* isolates, 12 (50.00%) were AmpC producers while 12(50.00%) were non-AmpC producers.

There were 159/217 (73.27%) isolates resistant for ceftazidime which included 62 (68.89%) *E. coli* (n=90), 80 (77.67%) *Klebsiella spp.* (103) and 17 (70.83%) *P. mirabilis* (24). 82/159 (51.57%) ceftazidime resistant isolates were found to be ESBL producers by double disc diffusion test using clavulanic acid as inhibitor. The total ESBL production according to double disc diffusion test was found to be 92/217 (42.40%) of which 45 (20.74%) were pure ESBL producers while 47 (21.66%) were ESBL+ AmpC co-producers.

The susceptibility pattern of the AmpC and ESBL producers against other antibiotics tested and the comparison between the two groups was as mentioned in the tables 1, 2 and 3.

By definition, the AmpC β-lactamase producers are resistant to oxyimino-cephalosporins and cephamycins and also not inhibited by β-lactamase inhibitors in the form of clavulanic acid and tazobactam but inhibited by chemicals like boronic acid and cloxacillin. Extended spectrum β-lactamase (ESBL) on the other hand confer resistance against fourth generation cephalosporins (cefepime, ceftazidime) in addition to oxyimino-cephalosporins and are inhibited by clavulanic acid. Despite this fact, co-production of AmpC and ESBLs has been documented in many studies (Grover *et al.*, 2013; Doi and Paterson, 2007; Bakthavatchalu *et al.*, 2013; Mohanty *et al.*, 2010). Prevalence of AmpC producers have been reported to be from 8% to as high as 41.3% in various studies from India and from 1.15% to as high as 46.7% in various studies from other countries (Peter-Getzlaff *et al.*, 2011; Grover *et al.*, 2013; Bakthavatchalu *et al.*, 2013; Polsfuss *et al.*, 2011; Li *et al.*, 2003; Singhal *et al.*, 2005; Manoharan *et al.*, 2012; Maraskolhr *et al.*, 2014; Rudresh and Nagarathnamma, 2011; Tan *et al.*, 2009;

Helmy and Wasfi, 2014; Ingram *et al.*, 2011; Yilmaz *et al.*, 2013; Coudron, 2005).

In the present study found that 62.67% isolates to be AmpC  $\beta$ -Lactamase producers by disc potentiation test which included *E. coli* 65.56%, *K. pneumoniae* 57.96%, *K. oxytoca* 93.33% and *P. mirabilis* 50.00%. Yilmaz *et al.*, reported 39.56% isolates to be positive by disc potentiation test including 48.69% and 18.29% *E. coli* and *K. pneumoniae* respectively (Yilmaz *et al.*, 2013). Manoharan *et al* reported 12.5% isolates to be AmpC producers by disc potentiation test (Manoharan *et al.*, 2012). Maraskolhe *et al.*, reported 35.76% isolates to be positive by disc potentiation test which included 30%, 85.71% and 55.56% AmpC producers amongst *E. coli*, *K. pneumoniae* and *K. oxytoca* respectively (Maraskolhe *et al.*, 2014). In a study by Rudresh, 41.25% isolates were positive by disc potentiation test which included 41.30% positive isolates of *E. coli*, 45.45% *Klebsiella spp.* and 25% positive isolates of *P. mirabilis* (Rudresh and Nagarathnamma, 2011). Bakthavatchalu *et al.*, reported 25.87% isolates positive by disc potentiation test including 18.26%, 42.37% and 24.14% isolates amongst *E. coli*, *K. pneumoniae* and *P. mirabilis* respectively (Bakthavatchalu *et al.*, 2013). We found higher number of AmpC producers by disc potentiation test as compared to the other studies.

In our study, we found 41.48% isolates to be pure AmpC producers, 21.20% to be pure ESBL producers and 21.20% were AmpC+ ESBL co-producers. Shoorashetty *et al.*, reported 6% and 41% isolates to be pure AmpC and pure ESBL producers respectively while 27.5% isolates to be AmpC and ESBL co-producers (Shoorashetty *et al.*, 2011). Bakthavatchalu *et al.*, reported 5.4% and 26.25% pure AmpC and pure ESBL producers respectively with 20.46% AmpC

and ESBL co-producers (Bakthavatchalu *et al.*, 2013). Mohanty *et al.*, reported 20.35% and 3.54% pure AmpC and pure ESBL producers respectively with 58.41% isolates to be AmpC ESBL co-producers (Mohanty *et al.*, 2010). Grover *et al* reported 4.96 and 30.15% isolates to be pure AmpC and pure ESBL producers respectively with 9.92% isolates to be AmpC ESBL co-producers (Grover *et al.*, 2013).

There was significant difference between the pure AmpC producing, pure ESBL producing, AmpC ESBL co-producing and AmpC ESBL non-producing isolates of *E. coli*, *Klebsiella spp.* and *P. mirabilis* regarding the resistance pattern against amoxycillin-clavulanate, piperacillin-tazobactam and co-trimoxazole for which the higher number of pure AmpC producers or AmpC ESBL co-producers were found to be resistant as compared to pure ESBL producers.

In addition, there was significant difference in the resistance pattern against imipenem and chloramphenicol among pure AmpC producing, pure ESBL producing, AmpC ESBL co-producing and AmpC ESBL non-producing isolates of *E. coli*, sulfonamide in case of *Klebsiella spp* and imipenem in case of *P. mirabilis* isolates. The difference can be justified by the fact that the AmpC producers are not inhibited by the beta lactamase inhibitors like clavulanic acid.

Yilmaz *et al.*, reported significant resistance against ceftazidime, cefotaxime and amoxycillin+ clavulanic acid in case of AmpC producers, (Yilmaz *et al.*, 2013). Grover *et al.*, reported a significant resistance against gentamicin, third generation cephalosporins, cefepime and fluoroquinolones by  $\beta$ -lactamase producers (Grover *et al.*, 2013).

**Table.1** Antimicrobial susceptibility of *E. coli* isolates

Antimicrobial	<i>E. coli</i> (90)				p Value
	Pure AmpC Producer (34)	Pure ESBL Producer (17)	AmpC ESBL Co-producer (25)	Non-AmpC Non-ESBL (14)	
<b>Ampicillin</b>	23(67.65%)	10(58.82%)	20(80%)	6(42.86%)	0.1160
<b>Ceftazidime</b>	25(73.53%)	*	*	1(7.14%)	NA
<b>Ceftazidime+ Clavulanate</b>	34(100%)	*	*	1(7.14%)	NA
<b>Ceftriaxone</b>	19(55.88%)	*	*	4(28.57%)	NA
<b>Cefepime</b>	9(26.47%)	*	*	2(14.29%)	NA
<b>Aminoglycosides</b>	18(52.94%)	6(35.29%)	17(68%)	8(57.14%)	0.2179
<b>Amoxicillin+ Clavulanate</b>	32(94.12%)	6(35.29%)	1(4%)	6(42.86%)	<b>&lt;0.0001</b>
<b>Piperacillin+ Tazobactam</b>	19(55.88%)	6(35.29%)	24(96%)	5(35.71%)	<b>0.0001</b>
<b>Quinolones</b>	21(61.76%)	7(41.18%)	13(52%)	5(35.71%)	0.3141
<b>Imipenem</b>	17(50%)	4(23.53%)	15(60%)	4(28.57%)	0.0625
<b>Co-trimoxazole</b>	23(67.65%)	7(41.18%)	20(80%)	6(42.86%)	<b>0.0265</b>
<b>Sulfonamides</b>	19(55.88%)	6(35.29%)	14(56%)	7(50%)	0.5206
<b>Aztreonam</b>	24(70.59%)	*	*	4(28.57%)	NA
<b>Tetracycline</b>	18(52.94%)	9(52.94%)	15(60%)	7(50%)	0.9256
<b>Chloramphenicol</b>	20(58.82%)	6(35.29%)	10(40%)	1(7.14%)	<b>0.0101</b>
<b>Nitrofurantoin</b>	3/11(27.27%)	6/10(60%)	7/11(63.64%)	1/8(12.5%)	0.0642

\*ESBL producing isolates are resistant to other cephalosporins, and aztreonam

**Table.2** Antimicrobial susceptibility of *Klebsiella Spp.* Isolates

Antimicrobial	<i>Klebsiella spp. (103)</i>				<i>p</i> Value
	Pure AmpC Producer (48)	Pure ESBL Producer (22)	AmpC ESBL Co-producer (17)	Non-AmpC Non-ESBL(16)	
<b>Ampicillin</b>	**	**	**	**	NA
<b>Ceftazidime</b>	39(81.25%)	*	*	5(31.25%)	NA
<b>Ceftazidime+ Clavulanate</b>	48(100%)	*	*	5(31.25%)	NA
<b>Ceftriaxone</b>	28(58.33%)	*	*	4(25%)	NA
<b>Cefepime</b>	15(31.25%)	*	*	3(18.75%)	NA
<b>Aminoglycosides</b>	30(62.5%)	8(36.36%)	11(64.71%)	8(50%)	0.1726
<b>Amoxicillin+ Clavulanate</b>	46(95.83%)	11(50%)	3(17.65%)	8(50%)	<b>&lt;0.0001</b>
<b>Piperacillin+ Tazobactam</b>	25(52.08%)	9(40.91%)	15(88.24%)	6(37.5%)	<b>0.0101</b>
<b>Quinolones</b>	26(54.17%)	6(27.27%)	11(64.71%)	6(37.5%)	0.0681
<b>Imipenem</b>	26(54.17%)	9(40.91%)	12(70.59%)	8(50%)	0.3229
<b>Co-trimoxazole</b>	28(58.33%)	7(31.82%)	9(52.94%)	9(56.25%)	0.2152
<b>Sulfonamides</b>	32(66.67%)	11(50%)	11(64.71%)	4(25%)	<b>0.0254</b>
<b>Aztreonam</b>	28(58.33%)	*	*	9(56.25%)	NA
<b>Tetracycline</b>	29(60.42%)	9(40.91%)	7(41.18%)	7(43.75%)	0.3105
<b>Chloramphenicol</b>	23(47.92%)	6(27.27%)	8(47.06%)	5(31.25%)	0.3139
<b>Nitrofurantoin</b>	5/8(62.5%)	1/8(12.5%)	2/5(40%)	2/3(66.67%)	0.1714

\*ESBL producing isolates are resistant to other cephalosporins, and aztreonam

\*\*Intrinsic resistance

**Table.3** Antimicrobial susceptibility of *P. mirabilis* isolates

Antimicrobial	<i>P. mirabilis</i> (24)				p Value
	Pure AmpC Producer (8)	Pure ESBL Producer (7)	AmpC ESBL Co-producer (4)	Non-AmpC Non-ESBL(5)	
<b>Ampicillin</b>	3(37.5%)	1(14.29%)	4(100%)	2(40%)	<b>0.0498</b>
<b>Ceftazidime</b>	5(62.5%)	*	*	2(40%)	NA
<b>Ceftazidime+ Clavulanate</b>	7(87.5%)	*	*	2(40%)	NA
<b>Ceftriaxone</b>	4(50%)	*	*	4(80%)	NA
<b>Cefepime</b>	2(25%)	*	*	2(40%)	NA
<b>Aminoglycosides</b>	3(37.5%)	1(14.29%)	3(75%)	3(60%)	0.1922
<b>Amoxicillin+ Clavulanate</b>	7(87.5%)	1(14.29%)	0	2(40%)	<b>0.0076</b>
<b>Piperacillin+ Tazobactam</b>	3(37.5%)	1(14.29%)	4(100%)	1(20%)	<b>0.0302</b>
<b>Quinolones</b>	5(62.5%)	3(42.86%)	3(75%)	2(40%)	0.6396
<b>Imipenem</b>	5(62.5%)	0	3(75%)	2(40%)	<b>0.0401</b>
<b>Co-trimoxazole</b>	7(87.5%)	2(28.57%)	4(100%)	2(40%)	<b>0.0286</b>
<b>Sulfonamides</b>	4(50%)	5(71.43%)	2(50%)	3(60%)	0.8393
<b>Aztreonam</b>	5(62.5%)	*	*	4(80%)	NA
<b>Tetracycline</b>	***	***	***	***	NA
<b>Chloramphenicol</b>	3(37.5%)	1(14.29%)	2(50%)	1(20%)	0.5595
<b>Nitrofurantoin</b>	***	***	***	***	NA

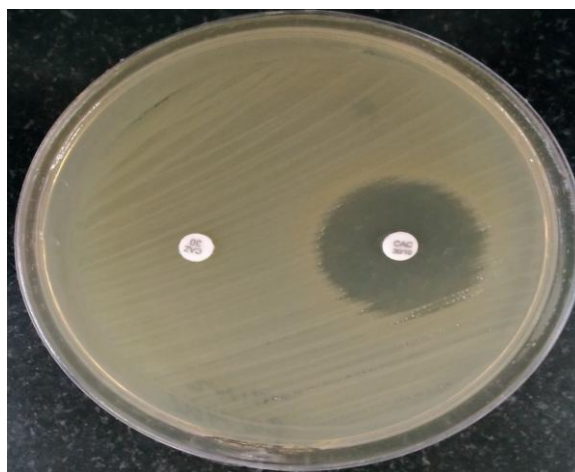
\*ESBL producing isolates are resistant to other cephalosporins, and aztreonam

\*\*\*Intrinsic resistance

**Image 1** Disc Potentiation Test [CX: Cefoxitin; CX+BA: Cefoxitin plus boronic acid]. Difference in the diameters of zones of inhibition >5 mm indicates positive test (AmpC  $\beta$ - lactamase producer)



**Image 2** Double Disc Diffusion Test [CAZ: Ceftazidime; CAC: Ceftazidime plus clavulanic acid]. Difference in the diameters of zones of inhibition >5 mm indicates positive test (Extended Spectrum  $\beta$ - lactamase producer)



Bakthavatchalu *et al.*, reported 97%, >80%, 63%,  $\approx$ 70%, and >50% resistance against ampicillin, third generation cephalosporins, cefepime, aminoglycosides and fluoroquinolones respectively (Bakthavatchalu *et al.*, 2013). Vandana *et al.*, reported 67%, 92%, 90%, 82%, 48%, and 97% resistance against amikacin, cefepime, co-trimoxazole, gentamicin, piperacillin+tazobactam and aztreonam respectively (Vandana and Hannavar, 2009).

The above quoted studies reported imipenem resistance to be nil as against in our study we found 54.24%, 58.46% and 66.67% resistance against imipenem amongst AmpC producing *E. coli*, *Klebsiella spp.* and *P. mirabilis* isolates respectively while 45.24% and 53.85% resistance against imipenem amongst ESBL producing *E. coli* and *Klebsiella spp.* isolates respectively. The higher resistance against cefepime in the studies by Vandana *et al.*, and Bakthavatchalu *et al.*, as compared to



our study may be because the former has studied the AmpC production among ESBL producers and the later has quoted the resistance pattern of AmpC and ESBL producers together and the ESBL producers by definition are resistant to fourth generation cephalosporins (cefepime).

The higher resistance against imipenem in AmpC and ESBL producing isolates could be because of the beta lactamase producing isolates producing carbapenemase or the additional mechanism in the form of efflux.

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