International Journal of Research and Review
Vol.7; Issue: 1; January 2020
Website: www.ijrrjournal.com
Original Research Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Antimicrobial Susceptibility Pattern of *Pseudomonas aeruginosa* with Special Reference to ESBL Producers from Various Clinical Samples at a Tertiary Care Center in Bihar

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ABSTRACT

Background: *P. aeruginosa* is a Gram negative non-fermentative bacillus which is an opportunistic pathogen responsible for various nosocomial infections like UTI, wound infections or severe sepsis. *P. aeruginosa* is extensively found in hospital environment and is resistant to many antimicrobials due to acquired and intrinsic resistance factors. Production of Extended Spectrum β- Lactamases (ESBLs) is a major cause of antimicrobial resistance in *P. aeruginosa* which is now seen throughout the world. ESBL production offers resistance to most of the β-lactam antibiotics including 3rd generation cephalosporins and these strains also acquire resistance to other classes of antibiotics resulting in MDR strains. Because of the extensive distribution of the ESBL producing isolates throughout the world we aim this study to know the prevalence of ESBL producing *P. aeruginosa* isolates and their antimicrobial susceptibility pattern to guide the clinicians to formulate proper antimicrobial therapy in such infections.

Methods: This prospective analytical study was conducted in the department of microbiology of Indira Gandhi Institute of Medical Sciences, Patna during the period of October 2014 to March 2015 to evaluate ESBL production and antimicrobial susceptibility of *P. aeruginosa* isolates from various clinical samples.

Results: A total of 102 strains of *P. aeruginosa* was isolated from 1000 various clinical samples. 27 isolates (26.5%) of *P. aeruginosa* isolates were ESBL producers. All the isolates were sensitive to Colistin and Polymyxin B and Imipenem has the highest sensitivity among ESBL producing isolates and Ampicillin along with most the Cephalosporins showed very low sensitivity.

Conclusion: We conclude that there is a significant prevalence of ESBL producing *P. aeruginosa* strains in our hospital which are mostly multi drug resistant(MDR) and constant monitoring of their changing antibiogram along with nosocomial infections caused by such strains is important to guide the proper antimicrobial therapy and reinforce infection control practices.

Keywords: *P. aeruginosa*, ESBL, Nosocomial infections, MDR, Imipenem.

INTRODUCTION

P. aeruginosa belongs to the family *Pseudomonadaceae,* is a Gram negative, non-fermentative, non-sporing and oxidase positive bacilli. [1] *P. aeruginosa* is one of the most common opportunistic pathogen and well established pathogen for nosocomial infections which includes common urinary tract infections to severe sepsis. [2,3] *P. aeruginosa* is widely distributed in nature including hospital environment and is intrinsically resistant to many antimicrobials and antiseptics because of the low permeability of its efflux pumps and naturally occurring chromosomal

AmpC β lactamase and also through acquired plasmid mediated β lactamase resistance. [4] Extended Spectrum β-Lactamases (ESBLs) have emerged worldwide as an important cause of antimicrobial resistance in Gram negative bacteria including *P. aeruginosa* that has resulted into emergence of multi drug resistant (MDR) strains which are resistant to 3rd generation cephalosporins, the most commonly used empirical antimicrobials for Gram negative bacterial infections. ESBL producing strains also shows resistance to other classes of antibiotics. [5, 6] Because of the indiscriminate use of 3rd generation cephalosporins there is a rise in ESBL producing strains which are mostly multi drug resistant and limits the therapeutic options thus making a challenge for treating physicians in both hospital and community settings. [7, 8]

Because of the widespread distribution of such *P. aeruginosa* isolates the study was undertaken to know prevalence of ESBL producing and non ESBL producing *P. aeruginosa* isolates and antimicrobial susceptibility pattern to guide the clinicians to formulate appropriate empirical antimicrobial therapy.

MATERIALS AND METHODS

Study design-

This was a laboratory based prospective study conducted for a period of 6 months, from October 2014 to March 2015 in the department of Microbiology at I.G.I.M.S, Patna after taking Ethical clearance. Demographic and clinical details of the patients will be collected from hospital records after taking consent from the patient or their guardians. Various clinical samples like pus, urine, blood, sputum, ear swabs, high vaginal swabs, endotracheal secretions and different body fluids were collected from different ICUs, wards and OPD patients as per standard microbiological guidelines. [9]

Laboratory Methods-

Different clinical samples collected in the microbiology laboratory were inoculated in Blood Agar (BA) and MacConkey Agar (MA) plates maintaining strict aseptic conditions. Plates were incubated at 37^0C for 24-48 hours under aerobic conditions. Provisional identification of *P. aeruginosa* was done by examining the Gram staining morphology and colony characteristics on Blood Agar and MacConkey agar media. Different biochemical tests were performed for identification of the isolates as per standard microbiological guidelines. [10]

Antimicrobial Susceptibility Testing-

Antimicrobial susceptibility testing of the isolates was done by Kirby-Bauer disc diffusion method on Mueller-Hinton agar plates. [11] The following antibiotic discs from HiMedia, Mumbai were tested: Amoxicillin (10 μg), Ampicillin-clavulanate(30 μg), Cefotaxime (30 μg), Cefazolin(30 μg), Ceftriaxone(30 μg), Ceftazidime (30μg), Cefepime (30 μg), Piperacillin-tazobactam (100μg/10 μg), Imipenem (10 μg), Meropenem (10 μg), Gentamicin (10 μg), Amikacin (30 μg), Cefoperazone-sulbactam (50/50μg), Aztreonam (30 μg), Ciprofloxacin (5 μg), Levofloxacin (5μg), Nitrofurantoin (200μg) (for urinary isolates), Tigecycline (15μg), Tobramycin(10 μg) and Polymyxin B(300 units). Sensitivity to Colistin and Netilmicin was tested using E strips from HiMedia, Mumbai. Zone sizes obtained were measured and interpretation was made according to CLSI 2014 guidelines. [12] *Pseudomonas aeruginosa* ATCC 27853 was used as the control organism for antibiotic sensitivity.

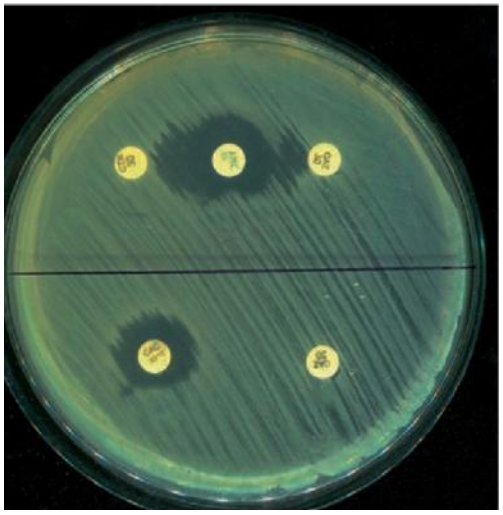
Phenotypic Detection of ESBL Positive Isolates-

Strains resistant to ceftazidime and/or cefepime were first screened for ESBL production by Nitrocefin disc test (using commercially available discs from Sigma Aldrich) as per manufactures directions and then confirmed by disc potentiation test. A disc of ceftazidime (30μg) and ceftazidime + clavulanic acid (30μg/10 μg) was placed 20mm apart, centre to centre on Mueller Hinton agar plate, and was incubated overnight at 37^0C. A zone difference greater

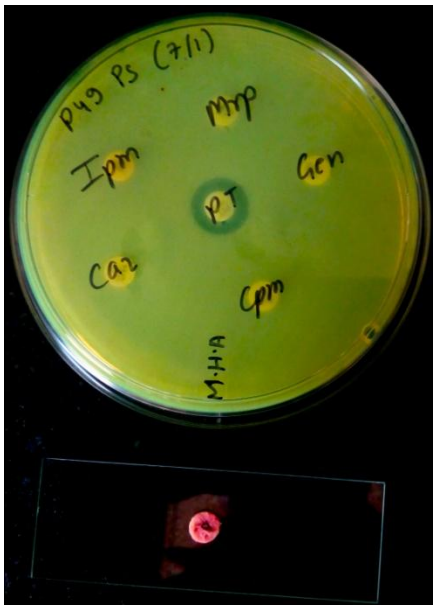
than or equal to 5mm around ceftazidime and ceftazidime + clavulanic acid was interpreted as ESBL positive isolate.

Statistical Analysis-

Statistical analysis like percentage or ratio for different qualitative variable was done using Microsoft Excel sheet (2007) and was represented by Bar or Pie charts. Chi square test was used to look for statistical significance ($p < .05$)



Disc Potentiation Test for ESBL detection



ESBL detection using Nitrocefin Disc (Sigma Aldrich)

MIC detection of Colistin detected by E-strip (HiMedia, Mumbai)

RESULTS

102 strains of *P. aeruginosa* were isolated and identified by standard microbiological procedures out of 1000 clinical samples investigated with an isolation rate of 10.2 %. The age and sex distribution of the patients is shown in Table-1 and Fig: 1. Most of the patient was from age group of 20-40 years (53 in number) and then of older age group (>60 years) i.e. 23 patients. The male: female ratio was (42: 58) i.e. 1: 1.4. The sample distribution from different ward and ICUs is shown in Table-2 and Fig: 2. Majority of the samples (70, 68.6%) was from admitted patients. Most common sample from OPD and Indoor patients with isolation of *P. aeruginosa* was Urine (27, 84%) and Ascitic fluid (16, 33.3%) respectively.

Out of the 102 isolates, 82 isolates (80.4%) showed resistance to Ceftazidime which were screened and tested for ESBL production and 27 among them was ESBL producers' i.e., 26.5% of *P. aeruginosa* isolates were ESBL producers. Most of the ESBL producing strains were isolated from clinical samples from admitted patients from different wards and ICUs (23, 85%) and most of them are from Urine, Pus and

Blood samples (18, 78%). (Table-3 & Fig: 3).

All of the isolates were sensitive to Polymyxin B and Colistin. *P. aeruginosa* isolates were highly resistant to antibiotics like Amoxicillin (81.8%), Ampicillin (92.8%), Nalidixic Acid (85.5%), and Cefazolin (72.3%). Moderate resistance was seen for Levofloxacin (60%), Cefotaxime (66.7%), Gentamicin (66.7%) and Ciprofloxacin (66.7%). Isolates showed good sensitivity against antibiotics like Amikacin (67.7%), Imipenem (71%), Piperacillin-Tazobactam (64%), Tobramycin (60%) and Meropenem (55%). ESBL producing isolates are most sensitive to Imipenem and resistant to Ampicillin and most of the cephalosporins (Table- 4 & Fig: 4).

Table-1: Age and sex distribution of the patients

Age(in years)	<20	20-40	41-60	>60
Male	3	21	7	13
Female	7	32	9	10
Total	10	53	16	23

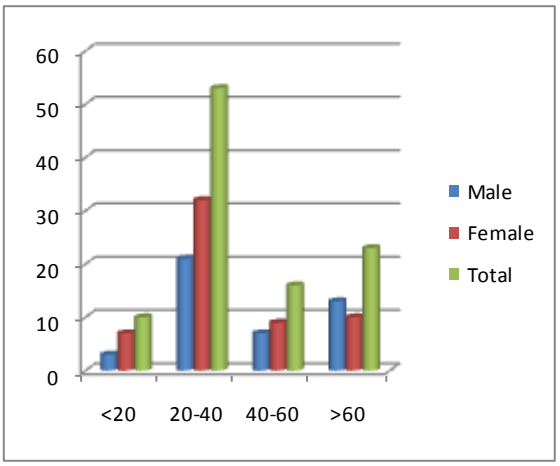


Fig: 1- Age and sex distribution of the patients

Table-2: Sample distribution from OPD and Indoor patients (n=102)

Sample	OPD	Ward	ICUs
Urine	27	11	10
Ascitic fluid	0	16	3
Blood	0	4	3
Pus	1	6	3
Bile	0	8	2
Sputum	3	2	0
Pleural fluid	0	1	0
Endotracheal aspirate	0	0	1
Contact lens	1	0	0
Total	32	48	22

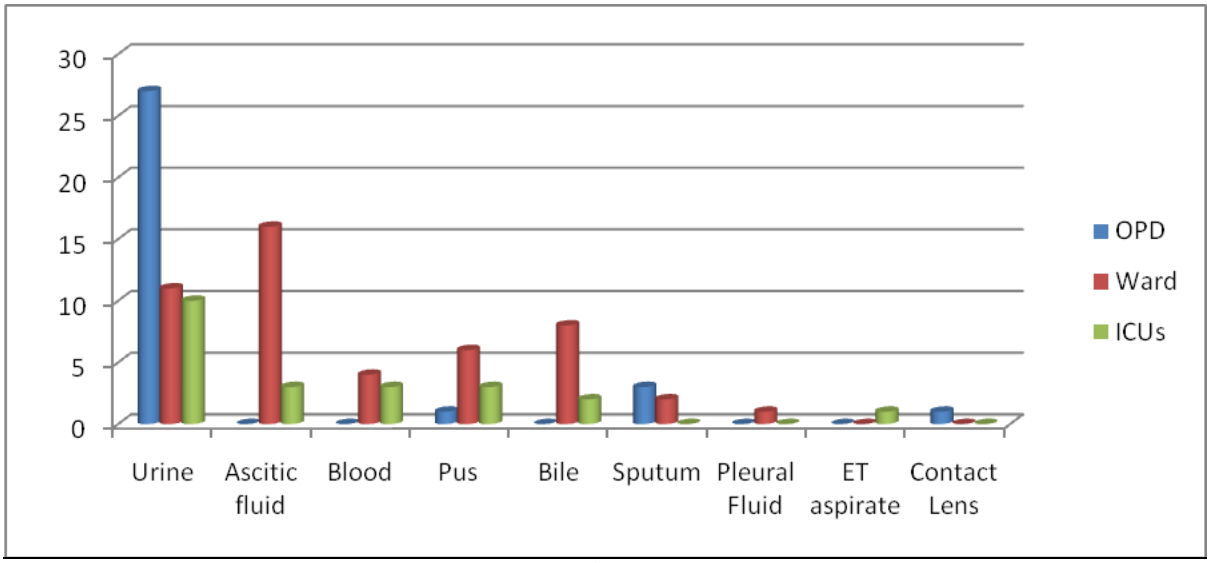


Fig: 2- Sample distribution from OPD and Indoor patients

Table-3 Sample and ward distribution of ESBL producing isolates (n=27) -

Ward	Pus	Blood	Urine	Ascitic fluid	Bile	Sputum
Medicine	1	2	1	2	0	3
Surgery	2	0	1	0	1	0
NICU	0	2	0	0	0	0
Orthopedics	2	0	1	0	0	0
Trauma	1	1	0	0	0	0
GI surgery	0	0	0	1	2	0
OPD			4			
Total	6	5	7	3	3	3

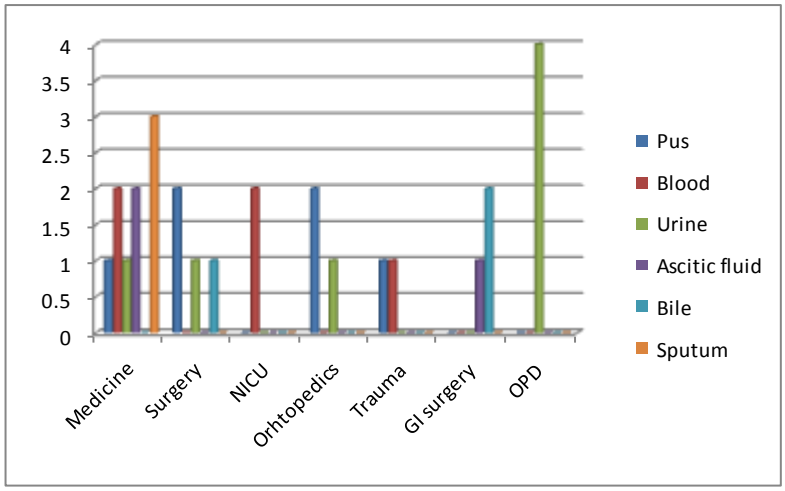


Fig: 3- Sample and ward distribution of ESBL producing isolates

Table-4- Antimicrobial Resistance of ESBL and non-ESBL producing *P. aeruginosa* strains

Antibiotic	ESBL strains (%)	Non-ESNL strains (%)	Overall (%)	p- value
Amoxicillin	96.3 (26/27)	93.3 (70/75)	94.1	.57
Ampicillin Clavulanic acid	92.6(25/27)	85.6 (64/75)	87.3	.33
Aztreonam	85.2 (23/27)	53.3 (40/75)	69.3	.003
Cefotaxime	77.8 (21/27)	59.7(45/75)	68.8	.097
Ceftazidime	96.3 (26/27)	74.7 (56/75)	80.4	.02
Cefazolin	81.5 (22/27)	72 (54/75)	74.1	.33
Cefepime	85.2 (23/27)	60 (45/75)	66.7	.02
Cefoperazone-sulbactam	70.4 (19/27)	50.3 (40/75)	57.8	.12
Ceftriaxone	92.6 (25/27)	78.7 (59/75)	82.4	.104
Amikacin	63 (17/27)	21.3 (16/75)	32.4	.0001
Gentamicin	88.9 (24/27)	68 (51/75)	72.5	.03
Tigecycline	77.8 (21/27)	69.3 (52/75)	71.6	.40
Tobramycin	51.9 (14/27)	36 (27/75)	40.2	.15
Netilmicin	40.7 (11/27)	9.3 (7/75)	17.6	.0002
Piperacillin-tazobactam	40.7 (11/27)	21.3 (16/75)	26.5	.05
Imipenem	7.4 (2/27)	9.33 (7/75)	8.8	.76
Meropenem	3.7 (1/27)	10.7 (8/75)	8.8	.27
Ciprofloxacin	88.9 (24/27)	58.7 (44/75)	66.7	.004
Levofloxacin	77.8 (21/27)	50.3 (40/75)	59.8	.03
Nitrofurantoin	11.1 (3/27)	9.3 (7/75)	9.8	.79
Polymyxin B	0 (27/27)	0 (75/75)	0	
Colistin	0 (27/27)	0 (75/75)	0	

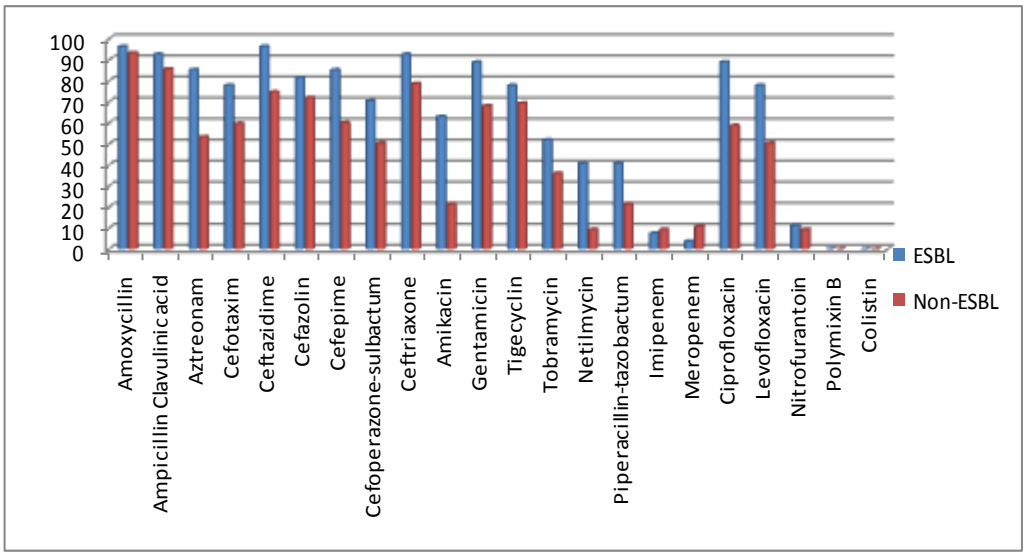


Fig: 4- Antimicrobial Resistance of ESBL and non-ESBL producing *P. aeruginosa* strains

Table-5: Distribution of MDR isolates among different samples

Sample	OPD	Ward	ICUs	Total
Urine	1	6	5	12
Ascitic fluid	0	3	2	5
Blood	0	3	3	6
Pus	1	4	3	8
Bile	0	2	1	3
Sputum	2	2	0	4
Endotracheal aspirate	0	0	1	1
Total	4	20	15	39

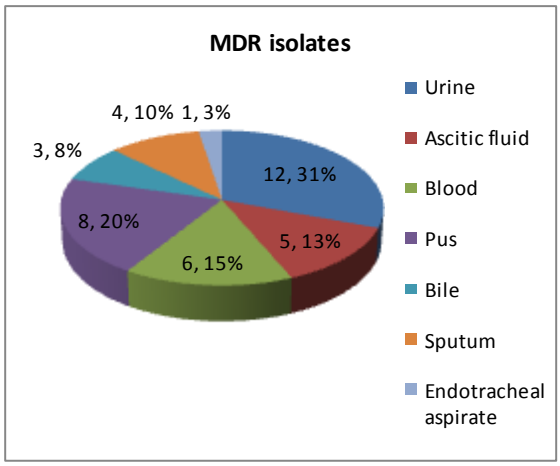


Fig: 5- Distribution of MDR isolates among different samples

DISCUSSION

In the present study we observed that the male: female ratio of the patients was 1: 1.4(42 and 58 isolates respectively) and the most of them was from age group 20-40 years (53, 52%). The results go with harmony with study done by Senthamarai S et al. where they found a Male: female ratio of 1.5: 1 and 45.1% of patients were from age group of 21-40 years. The isolation rate of *P. aeruginosa* from various clinical samples were 10.2 % which again similar to findings by Senthamarai S et al. where the isolation rate was 12.5%. [13]

Most of the samples were from patients admitted in different wards and ICU patients (70, 68.6%) and similar finding was seen in studies done by J.K. Jeyabharathi et al. where all isolates were from different wards. [14]

In our study we found that 26.5 % (27 out of 102) isolates were ESBL producers and this was in harmony with findings by other researchers like J.K. Jeyabharathi et al. (28%), Senthamarai S et al. (35.4%), Shaikh S et al. (25.13%). [13-15]

Most of the ESBL producing isolates were from pus and blood samples (11, 40.7%) followed by urine samples which are on par with studies done by J.K. Jeyabharathi et al. (63%) and Shaikh S et al. (42.15% and 20.45%). [14, 15]

Antimicrobial susceptibility of all the isolates showed that they were highly resistant to most of the β- lactam antibiotics and Cephalosporins with overall resistance percentages ranging from 60 to 94 and ESBL producing strains showing even higher resistance as shown in Table & Fig: 4. The sensitivity pattern is similar to works done by other authors like Shaikh S et al. where they found 100% resistance to Ampicillin, 59.6% resistance to Aztreonam, 78.7% resistance to Cefotaxim, 91.5% resistance to Ceftazidime and 65.96% resistance to Cefepime in ESBL producing isolates. [15] Study conducted by Kaur A et al. showed sensitivity of *P. aeruginosa* isolates were 39.1% to Ceftazidime, 42.2% to Cefepime and 44.8% to Aztreonam which again corresponds to our study findings. [16]

Fluoroquinolones like Ciprofloxacin and Levofloxacin showed lesser overall resistance, 66.7 and 59.8 % respectively which are in harmony with study done by Kaur A et al. where the overall resistance was up to 75.9%. [16]

P. aeruginosa isolates showed much lesser resistance to aminoglycoside antibiotics like Amikacin, Netilmicin and Tobramycin (32.4, 17.6 and 40.2% respectively) with the exception of Gentamicin (72.5%) which makes them better choice than β- Lactams or Cephalosporins for *P. aeruginosa* infections. Study conducted by different authors also showed similar results with resistance of *P. aeruginosa* isolates to Amikacin were 39.1 % (Kaur A et al.) and 52% (J.K. Jeyabharathi et al.).

Resistance to Gentamicin among ESBL producing isolates were 94.74% and 94.1 % respectively in studies by Shaikh S et al. and Senthamarai S et al. that

corresponds to our results (72.5% resistance). [13, 15]

Piperacillin-tazobactam and Nitrofurantoin especially for urinary isolates showed high sensitivity (26.5 and 8.8% resistance respectively) which makes them good choice for empirical therapy. Studies done by Senthamarai S et al. found resistance to piperacillin-tazobactam is 35.2% and no resistance to Nitrofurantoin which is similar to our study results. [13]

Carbapenems like Imipenem and Meropenem showed best sensitivity to *P. aeruginosa* isolates including the ESBL producing isolates (Resistance 8.8%) which makes them best choice to treat ESBL producing isolates. Studies done by other authors showed resistance to Imipenem in ESBL producing isolates is 0-30 % which again goes with our results and makes it one of the best choices for those isolates. [13-16]

ESBL producing isolates were found to be more resistant to most of the antibiotics and most of them were multidrug resistant (showing resistance to more than 3 classes of antibiotics) also. We found statistically significant difference ($p< 0.05$) in resistance among ESBL producing and non-ESBL strains in some antibiotics like Aztreonam, Ceftazidime, Cefepime, Amikacin, Gentamicin, Netilmicin, Piperacillin-tazobactam, Ciprofloxacin and Levofloxacin. The results show that ESBL production not only effect sensitivity to β-Lactam antibiotics but these strains are simultaneously resistant to many other classes of antimicrobials which are commonly used as empirical treatment in Gram negative bacterial infections. In a study conducted on MBL (Metallo-β-lactamase) isolates by Choudhary V et al. similar statistically significant difference in antimicrobial sensitivity pattern was found among MBL producing and non-MBL isolates of *P. Aeruginosa.* [17-20]

In our study Colistin and Polymyxin B showed 100% sensitivity among all ESBL producing and non-ESBL isolates which is also seen in study conducted by Kaur A et al. [16]

A total of 39 isolates (38.2%) were found to be MDR and majority of them were from ESBL producing isolates. Urine, Pus and Blood samples contributes to most of the MDR isolates which are also major contributors of ESBL producing isolates (Table & Fig. 5). The prevalence of MDR isolates was much higher in wards and ICUs (35, 89.7%) which were also seen in study done by Dou Yi et al. where they found 89.87% of *P. aeruginosa* isolates were MDR in studies of burn wards. [21] Another study conducted by H A Noha et al. also showed 56% MDR *P. aeruginosa* strains from burn ward of children. [22]

Our study showed a significant percentage of isolates are ESBL producing and MDR which have a direct impact on selecting proper antibiotics especially for empirical therapy and improper selection of antibiotics is common as shown in study done by Pinheiro et al. where they found 37.3% of cases were treated with inappropriate antibiotics. Their study also showed that combination therapy didn't improve mortality in severe *P. aeruginosa* infections when compared with monotherapy. [23]

In a study conducted by Kim et al. it was seen that patients with *P. aeruginosa* bacteremia has a high mortality and most of them died just after the onset day. Inappropriate empirical therapy before the onset of the bacteremia may be a significant contributor to the mortality. In neutropenic patients adequate empirical or targeted combination therapy was seen to be associated with significantly lower mortality rates. [24]

Detection of ESBL production is necessary in selecting proper antimicrobials for empirical therapy especially in severe sepsis as inappropriate therapy have significantly rises the mortality rate and it has been shown in a study by Frakking et al. [25]

CONCLUSION

ESBL producing strains of *P. aeruginosa* are on rise and are found

globally which are difficult to treat due to their multi drug resistance and inappropriate empirical therapy is commonly seen due to high resistance to commonly used antibiotics. This results in higher mortality in patients with severe infections like septicemia. Detection of ESBL activity by rapid tests like Nitrocefin discs and proper selection of antibiotics for empirical therapy guided by current antibiogram and risk profile of the patient may decrease the morality significantly. This policy also helps in judicious use of 3rd generation Cephalosporins along with Carbapenems like Imipenem which are still the best options to treat severe infections with ESBL producing strains.

Funding: Self
Conflict of Interest: None declared
Ethical approval: Taken

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How to cite this article: Das S, Azad M, Bimal K et.al. Antimicrobial susceptibility pattern of *pseudomonas aeruginosa* with special reference to ESBL producers from various clinical samples at a tertiary care center in Bihar. International Journal of Research and Review. 2020; 7(1): 557-565.

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