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Coproduction of Extended Spectrum, AmpC and Metallo β- Lactamases in *Pseudomonas aeruginosa* Isolates from a Super Speciality Center

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A B S T R A C T

Pseudomonas aeruginosa (*P. aeruginosa*) is one of the leading causes of hospital as well as community acquired infections. They're strenuous to treat as most of isolates exhibit various degrees of beta- lactamase mediated resistance to majority of the beta-lactam antibiotics. Single isolate can express multiple β- lactamase enzymes, further limiting the treatment options. Therefore, this study was outlined to research the coexistence of various beta-lactamase enzymes in clinical isolates of *P. aeruginosa*. The aim of the study was to detect the co-prevalence of Extended Spectrum Beta lactmases (ESBL), AmpC and Metallo β-Lactamases (MBL) in *Pseudomonas aeruginosa* isolates from a superspeciality center. Fifty clinical isolates of *P. aeruginosa* were tested for the presence of AmpC beta-lactamase, extended spectrum beta- lactamase (ESBL) and metallo beta-lactamase (MBL) enzyme. Discernment of AmpC beta-lactamase was performed by disk antagonism while ESBL detection was done by the combined disk diffusion method as per Clinical and Laboratory Standards Institute (CLSI) guidelines and MBL were detected by the Imipenem EDTA disk potentiation test. Eleven of 50 (22%) isolates were confirmed to be positive for AmpC and Extended spectrum beta lactamases. Co-production of AmpC along side ESBL and MBL was reported in 12 % isolates. The study shows the high prevalence of multidrug resistant *P. aeruginosa* producing beta-lactamase enzymes of diverse mechanisms. Consequently, formulation of a correct antibiotic policy and taking measures to restrict the indiscriminative use of cephalosporins and carbapenems should be taken to mitigate the emergence of this multiple beta-lactamase producing

Introduction

The rise in antibiotic resistance among gram-negative bacteria may be a classic example of how a bacteria can procure, maintain, and express new genetic information which will confer resistance to at least one or several other antibiotics. A consensus appears to prevail that quinolones and broad-spectrum β-lactam resistance are increasing in members of the Enterobacteriaceae which is the reason why treatment regimes for the eradication of

Pseudomonas aeruginosa (*P. aeruginosa*) infections are getting increasingly limited (Balan, *et al.,* 2013). The advent of carbapenems within the 1980s heralded a replacement treatment option for serious bacterial infections.

But now Carbapenem resistance is observed in Enterobacteriaceae and is becoming common also in *P. aeruginosa. P. aeruginosa* is one of the main etiological agents of nosocomial infection. They're extremely difficult to treat as most of them exhibit varying degrees of innate resistance. Acquired resistance is mediated by the assembly of chromosomal and plasmid-mediated AmpC beta-lactamases, extended-spectrum beta-lactamases (ESBLs), and Metallo-beta-lactamases (MBLs).

AmpC beta-lactamases play a crucial role in the resistance of Gram-negative bacilli. AmpC enzymes are grouped into Ambler Class C classification (Balan K *et al.,* 2013). These enzymes confer a high level of resistance to several beta-lactam antibiotics including the third-generation cephalosporins and cephamycins. With the gradual increase in the occurrence of those multiple beta-lactamase enzymes, early detection is crucial for the initiation of proper antibiotic therapy and infection control policy.

The aim of this study to detect the co-prevalence of ESBL, AmpC, and Metallo β-Lactamases in *Pseudomonas aeruginosa* isolates from a super-specialty center

Materials and Methods

The study was conducted at the Department of Microbiology of a teaching Superspeciality hospital.

Bacterial isolates and characterization

A total of fifty random sequenced isolates of *P. aeruginosa* were isolated from varied clinical samples received for routine laboratory investigations from patients getting to the hospital from December 2018 to June 2019. These isolates were identified as *P. aeruginosa* by standard conventional methods.

Antimicrobial susceptibility testing

The antimicrobial susceptibility of those isolates was performed on Mueller-Hinton agar (MHA) using commercial antibiotic discs (Hi-Media Laboratories Ltd, Mumbai) by the standard quality Kirby-Bauer disc diffusion technique and interpreted as per CLSI recommendation.[2] The antibiotics used were gentamicin (10µg), amikacin (30µg), tobramycin (10µg), ciprofloxacin (5µg), ceftazidime (30µg), levofloxacin (5µg), piperacillin/tazobactam (100/10µg), meropenem (10µg), imipenem (10µg), colistin (10µg), cefepime (30µg), netilimicin (30µg), ticarcillin clavulanic acid (75/10µg). *P. aeruginosa* ATCC 27853 was used as control.

ESBL detection

Isolate that showed immune to a minimum of one among the third generation cephalosporins were tested for ESBL production by phenotypic confirmation test suggested by CLSI.

CLSI phenotypic confirmation test

A McFarland 0.5 standard suspension of the *P. aeruginosa* isolate was inoculated onto the MHA plate. Ceftazidime (30µg) and ceftazidime/clavulanic acid (30/10µg), discs were placed on inoculated MHA plate at a distance of 30mm aside from center to center. The culture was incubated at 37°C overnight. The observation of a ≥5mm increase in zone diameter of ceftazidime/clavulanic acid disc than ceftazidime disc alone was considered ESBL producer (CLSI 2018).

AmpC β-lactamase detection

Cefoxitin-resistant isolates were screened for AmpC β-lactamase production.

Inducible AmpC detection

Disc antagonism test

A McFarland 0.5 standard suspension of the isolate was inoculated onto the MHA plate. Cefotaxime (30µg) and cefoxitin (30µg) discs were placed 20mm aside from center to center. The culture was incubated at 37°C nightlong. Isolates showing blunting of the cefotaxime zone of inhibition adjacent to the cefoxitin disc indicate inducible AmpC production (Padiyath, *et al.,* 2013).

MBL detection

Screening for MBLs

Isolates immune to meropenem or imipenem were screened for MBL production. All audition positive isolates were subjected to corroboratory check (Padiyath, *et al.*, 2013).

Disc potentiation test

The standard suspension of the check isolate was inoculated onto the MHA plate. A 0.5M resolution of EDTA was prepared by dissolving 186.1gm of disodium EDTA $2H_2O$ in 1000mL of distilled water and pH was adjusted to eight by victimization NaOH. The mixture was sterilized by autoclaving. Two 10µg imipenem disc was placed 20mm aside from center to center onto the MHA plate. To at least one disc of imipenem, 5µl of 0.5M EDTA was added. The zone of inhibition of imipenem and imipenem/EDTA discs were compared once 16-18 hours of incubation at 35°C. A rise within the zone of inhibition by a minimum of 7 mm with imipenem/EDTA disc than imipenem alone was thought about as MBL positive (Padiyath, *et al.*, 2013).

Results and Discussion

Bacterial Isolates

A total of 50 non-repetitive and non redundant clinical isolates of *P. aeruginosa* (bile 20, mucous trap 13, pus 7, blood 6, tissue 2, cerebrospinal fluid 2, and bronchoalveolar lavage 1) from the inpatient department (IPD) and the outpatient department (OPD) were included in this study. Out of which, 29 (58%) strains were isolated from male patients and 21(42%) from female patients. The majority of the isolates (96%) were from the inpatient department (IPD), while 4% of isolates were from the outpatient department (OPD) of the hospital. Thirty-three (66%) isolates were from patients admitted to intensive care units.

Associated risk factors for the development of *P. aeruginosa* were studied in all the patients. Eighteen (36%) patients were found to be immunocompromised or having comorbid conditions like diabetes mellitus, hypertension, tuberculosis, etc. Apart from this, the patients were also studied for other most common risk factors commonly seen in *P. aeruginosa* shown in table 1.Except for 6 patients, all other patients were already on multiple antibiotics.

Antibacterial Susceptibility Profile

Among tested antibiotics, Seventy-six percent of isolates were resistant to fluoroquinolone (ciprofloxacin and levofloxacin). The beta lactams were found to be less effective in *P. aeruginosa* with 70% resistance mediated towards piperacillin and tazobactam, whereas more than half of the isolates were resistant to other beta-lactam antibiotics. Amino-glycosides (gentamicin, netilmicin, and tobramycin) also showed a resistance rate up to 51.4%, whereas amikacin showed a higher

resistance rate of 58%. Colistin was found to be the best drug for the treatment of infections caused by *P. aeruginosa*, as its resistance was not seen in this study (Figure 1).

Coproduction of ESBL/AmpC/MBL was presented in (Table 3). Eleven isolates (22%) were positive for both ESBL and AmpC while six isolates (12%) were positive for AmpC and MBL. Coproduction of ESBL and MBL was detected in 9 (18%) of the isolates. All three enzyme production were seen in 6(12%) isolates.

Many patients infected with *P. aeruginosa* having coproduction of various β- lactamases developed serious complications. Six patients (12%) developed bloodstream infections, five patients (10%) developed pneumonia/VAP and urinary Tract infection (UTI) each and one developed (2%)surgical site infection. However, ten patients(20%) eventually succumbed to this infection.

Pseudomonas aeruginosa is the commonest pathogen causing nosocomial infection mostly in immunocompromised patients. These infections include bacteremia, endocarditis, meningitis, otitis, osteomyelitis, burn, wound infection, etc. It's mostly present in the hospital environment (sinks, drains, respirators, humidifiers, and disinfectant solutions, etc.). Most of the hospital isolates are multi-drug resistant organisms (MDROs). Carbapenems are the drug of choice for MDR strains of *P. aeruginosa*. Nowadays, Carbapenem resistance has been observed in *P. aeruginosa* putting more pressure on reserved class drugs like Colistin for the treatment of such infections.

In the present study, we took 50 non repeated isolates of *P. aeruginosa*. Maximum number of *P. aeruginosa* was isolated from bile samples (40%) followed by mucous trap(26%), pus(14%), blood(12%), Tissue(4%), cerebrospinal fluid (2%) and bronchoalveolar lavage (2%). However, Chander A *et al.,* Senthamarai S *et al.,* and Padiyath S *et al.,* reported *P. aeruginosa* mostly in wound infections followed by respiratory tract infections in their studies. The probable reason for this might be that our place of study may be a super-specialty center and here general samples are less common. *P. aeruginosa* was more commonly isolated from male patients (58%, 29/50) than female patients (42%, 21/50) within the present study. Similar observations were made by Pal *et al.,* Senthamarai S *et al.,* & Ranjan S *et al.,* Adults starting from age bracket 55-65 years were most ordinarily affected age bracket which is analogous to other studies conducted in our institute (Ranjan *et al.,* 2014) (Chander *et al.,* 2013) (Senthamarai *et al.,*2014).

The majority of the patients were from the inpatient departments (96%) while outpatients constituted only 4% of the cases. Out of the inpatients, 66% of patients belonged to medical care units. The majority of the patients belonged to gastroenterology and gastro surgery departments. Thirty-six percent of patients were immunocompromised or were having other comorbid conditions like DM, hypertension, tuberculosis, etc. The patients were also studied for other commonest risk factors related to *P. aeruginosa*, presence of an indwelling catheter (40%) and prolonged ICU stay / bed ridden patients (46%) constituted the main risk factor. The majority of the patients (88%) were on multiple antibiotics.

Colistin was found to be the most beneficial drug for the treatment of infections caused by *P. aeruginosa*, as its resistance wasn't seen during this study. Similar findings were seen by Padiyath *et al.,* and Choudhary V *et al.,* (Padiyath, *et al.,* 2013) (Choudhary, *et al.,* 2018). Varaiya *et al.,* depicted very low (57.5%) colistin susceptibility. This difference

might be thanks to the study environment under which the study was performed. Colistin remains the mainstay of treatment for multidrug-resistant *P. aeruginosa* (Kumar, *et al.,* 2018). Imipenem, Meropenem which were initially very active against P. aeruginosa, showed marked resistance (74%), results of which are in concordance with previous other studies (Kumar, *et al.,* 2018). High resistance to Ceftazidime (72%) was observed in our study, but similarly, 70% and 78% strains immune to Ceftazidime are reported by Behare *et al.,* and Kumar *et al.,* (Behra, *et al.,* 2008) (Kumar, *et al.,* 2014). Among tested antibiotics, seventy-six percent isolates were immune to fluoroquinolone (ciprofloxacin and levofloxacin). The beta-lactams were found to possess limited efficacy in *P. aeruginosa* with 70% resistance mediated towards piperacillin and tazobactam, whereas quite half the isolates were immune to other beta-lactam antibiotics. Aminoglycosides (gentamicin, netilmicin, and tobramycin) also showed a resistance rate up to 51.4%, whereas amikacin showed a higher resistance rate of 58%. Similar finding were seen in a study done by Gupta R *et al.,* (Gupta, *et al.,* 2016). Resistance to ceftazidime is especially mediated by the assembly of β-lactamases like extended-spectrum β- lactamase, Metallo- β-lactamase and infrequently AmpC β-lactamases. The high resistance to cephalosporins exhibited by *P. aeruginosa* during this study might be thanks to the selective pressure of cephalosporin usage (Padiyath, *et al.,* 2013).

ESBLs are Class A β- lactamases, which hydrolyze all cephalosporins, penicillins, and monobactams but not cephamycins or carbapenems. They're inhibited in vitro by clavulanate. ESBL production was seen in 42% isolates. Variable incidence of ESBL production has been seen in our country starting from as low as 13 you must as high as 80 %. A Lower prevalence of 20-25% ESBL producing isolates have been reported from different parts of India like Nagpur (Tankhiwale, *et al.,* 2016) and Lucknow (Shaikh, *et al.,* 2015) and an even higher rate of 59.45% has been reported from Uttar Pradesh (Haider, *et al.,* 2014) and 57.75% from Bangalore (Easwaran, *et al.,* 2016). The high frequency of ESBLs in *P. aeruginosa* is thanks to the horizontal spread of genes. This varied ESBL production might be thanks to the nonjudicial use of antibiotics or thanks to environmental influence.

AmpC β lactamases are cephalosporinases that aren't inhibited by clavulanic acid. Within the current study, the AmpC production was seen in 16% isolates. Compared to those findings other studies have reported a better prevalence of AmpC producers while some have reported lower prevalence. Studies from Pudduchery, Gujarat, and Himachal Pradesh reported a prevalence of 20-35%, whereas Upadhyay S *et al.,* reported 59.40% and Gupta, *et al.,* reported 51.4% AmpC producing *P. aeruginosa*. This wide selection of prevalence of the AmpC producers in various studies might be thanks to the differences within the geographical distribution, which can have cause variations within the prevalence of the β- lactamases present within the different organisms (Choudhary, *et al.,*2018).

The only β- lactams active against co- AmpC and ESBL producers are carbapenems. Lately, carbapenem resistance is increasing in *P. aeruginosa*. This has been attributed to decreased outer membrane permeability which is thanks to the loss of Opr D porin, upregulation of active efflux pump system, alteration of penicillin-binding protein, or by the production of carbapenemases (Padiyath, *et al.,* 2013).

Table.1 Risk factors associated

Chronic obstructive pulmonary disease	**1**
Burn	0
Cystic fibrosis	0
Length of hospital stay(ICU/ bedridden)	23
Mechanical ventilation	16
Malignant disease	3
Long term care facilities	
Age>86 yrs	2
Antibiotic treatment for previous 3 months	7
Indwelling devices	20
Physical disabilities	6

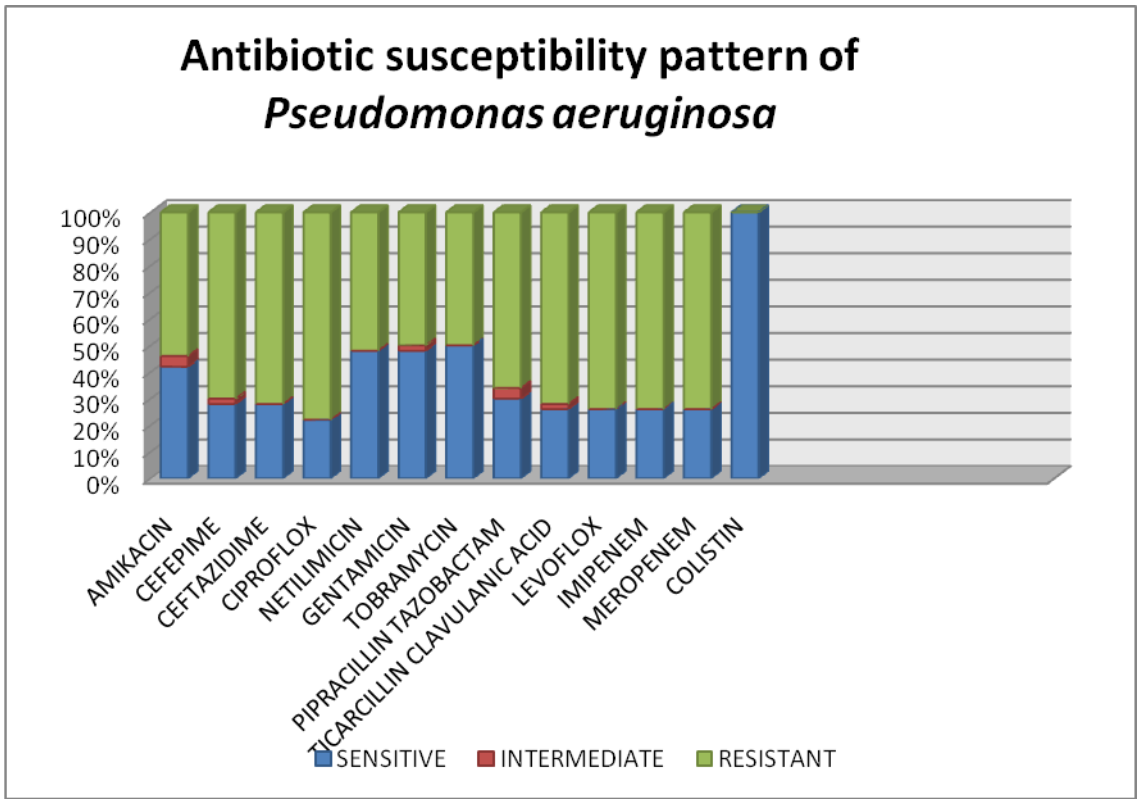
Table.2 Proportion of ESBL, AmpC and MBL production in P.aeruginosa isolates.

Enzyme	Number of Isolates of *Pseudomonas aeruginosa* showing the presence of enzyme (N=50)	Number of Isolates of *Pseudomonas aeruginosa* showing the presence of enzyme(N=50)
AmpC	8	16%
ESBL	21	42%
MBL	21	42%

Table.3 Coproduction of various β- lactamases

Enzyme	Number of Isolates of *Pseudomonas aeruginosa* showing the presence of enzyme (N=50)	Number of Isolates of *Pseudomonas aeruginosa* showing the presence of enzyme (N=50)
AmpC + ESBL	11	22%
AmpC + MBL	6	12%
ESBL+MBL	9	18%
AmpC +ESBL+MBL	6	12%
No resistance/other resistance	18	36%

Fig.1 Antibiotic susceptibility pattern of *Pseudomonas aeruginosa*



Metallo β- lactamases are carbapenemases, which require zinc divalent cation, as a cofactor for enzyme activity. They're ready to hydrolyze all β- lactams except monobactam and are universally inhibited by ethylenediamine tetra ethanoic acid (EDTA) also as other chelating divalent cations. The incidence of MBL producers within the present study was 42% which correlated well with other studies as 33.3%, 41% respectively (Anuradha *et al.,* 2014) (Chate *et al.,* 2014). Although, few studies reported a quite high incidence of MBL producing *P. aeruginosa* strains as 61.5% and 69.5% (Behra B *et al.,* 2008) (Sharma *et al.*, 2010)

Coproduction of ESBL/AmpC/MBL was also observed in our study. Eleven isolates (22%) were positive for both ESBL and AmpC while six isolates (12%) were positive for AmpC and MBL. Coproduction of ESBL and MBL was detected in 9 (18%) of the isolates. All the three enzymes were seen in 6(12%) isolates while 36% showed the presence of no resistance. Studies from various parts of India have reported prevalence rates of MBL and ESBL/AmpC co-existence between 4-27% (4% by Padiyath *et al.*, 7.77% by Minhas, *et al.*, 10.12% by Tankhiwale *et al.*, 18.8% by Rawat *et al.*, 27.72% by Upadhyay *et al.*,) (Choudhary *et al.*, 2018).

Many patients affected by *P. aeruginosa* having coproduction of varied β- lactamases developed serious complications. Six patients (12%) developed blood-stream infection, five patients (10%) developed pneumonia/VAP and tract infection (UTI) each and one developed (2%) surgical site infection. However, ten patients (20%) eventually succumbed to the present infection. Multiple β-lactamase producing *P. aeruginosa* may cause major therapeutic failure and pose a big clinical challenge if they continue to be

undetected. Since these organisms might carry other drug-resistant genes, the sole available treatment option remains is that the administration of colistin which is potentially toxic. The potential limitation of this study is that molecular analysis and characterization of ESBL, AmpC, and MBL types weren't administered. Though Polymerase Chain Reaction (PCR) is taken into account as the gold standard for detection of newer β-lactamases however it's very costly and requires expertise and is beyond the scope of routine Clinical Microbiology Laboratories in India. Considering the existence of numerous sorts of newer β-lactamases, the most disadvantage of PCR is that it requires tailor-made DNA primers, cannot differentiate between variants, and should not detect new variants. Similarly, E tests for ESBL, Amp C, and MBL are often used but they're also very costly and can't be used routinely. Hence, detection of resistance using simple disc methods described within the present study should be encouraged.

In the present study deduce that *Pseudomonas aeruginosa* being a stubborn multidrug-resistant pathogen leaves colistin as the last resort for treatment of life-threatening infections in the hospital.

Increasing occurrence of multiple β-lactamases in clinical isolates of *P. aeruginosa* could lead to therapeutic failure. In routine circumstances, routine culture, and susceptibility tests should be performed to detect the emergence of resistance to *Pseudomonas aeruginosa* as early as possible. Attention by the hospital infection control team is essential to implement stringent preventive measures to contain the spread of the infection and promote the judicious use of antimicrobial agents.

Antibiotic resistance is increasing at an alarming rate, leading to increased morbidity, mortality, and treatment costs. A key factor in the development of antibiotic resistance is the inappropriate use of antibiotics. The medical fraternity needs to understand that antibiotics constitute a precious and finite resource. Until and unless responsive efforts are made to contain the peril of drug resistance, multi-drug resistant organisms, uncurable by every known antibiotic, may emerge victorious, reversing the medical progress made by mankind and throwing us back to the pre-antibiotic era.

Hence, early detection of β-lactamase production can benefit the implementation of proper antibiotic therapy and infection control policies.

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