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PREVALENCE OF MULTI-DRUG-RESISTANCE IN *PSEUDOMONAS AERUGINOSA*- A STUDY IN A TERTIARY CARE HOSPITAL PUNE, MAHARASHTRA, INDIA

Microbiology

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ABSTRACT

Background- This study was undertaken to know the multi drug resistance in isolates of Pseudomonas aeruginosa and exploring its relationship with type of specimen, age and gender.

Materials & Methods- 200 isolates of Pseudomonas aeruginosa were studied. The colonies were tested for biochemical tests. Identification was done and then put to Antibiotic susceptibility test by Kirby–Bauer method.

Results & Analysis-. In our study, 63 out of 200 isolates were found to be Multi drug Resistant (31.50 %). 6 MDR isolates out of 10 specimens (60%) detected from burn tissue. 24 out of 60 isolates (40%) were found in Urine,17 out of 75(22.66%)in pus, the lowest 2 out of 9 (22.22%) isolates from blood specimens. 50 out of 63(79.36%) MDR isolates were found in male and only 13out of 63(20.64%) were found in female patients. 21out of 62 (33.87%) MDR isolates were found from ICU followed by 16 out of 34(47.05%) from Surgery dept. The lowest 1 out of 11(9.09%) isolate was from OBG dept. The maximum 18 out of 50 (36%)MDR recorded in the patients between 41 to 60 years age, the lowest 5 out of 25 (20 %)in the age group up to 20 years detected. Highest resistance 36.5%was observed with ceftazidime and piperacillin antibiotics .Polymyxin B, recorded the lowest 3.5% resistance in the study.

Discussion- Pseudomonas aeruginosa are inherently resistant to many antimicrobial agents owing to various resistance mechanisms .63 out of 200 isolates(31.50%) were found to be resistant to three or more group of antibiotics and thus poses a serious threat to patients and clinicians in their management.

Conclusion-Multi drug resistance were found more prevalent in Male patients in comparison to female. The age between 41- 60 years were worst affected and age group between 0- 20 years were found least affected for MDR. ICU dept. recorded the highest number of MDR isolates where as Gynecology dept. shown least MDR in the study. Burn tissue had shown maximum percentage of MDR.

KEYWORDS

MDR, *Pseudomonas aeruginosa*

INTRODUCTION

Pseudomonas aeruginosa is one of the important bacterial pathogens causing various infections in hospitals.[1]Despite advances in medical and surgical care and introduction of wide variety of antimicrobial agents having anti-pseudomonal activities, *Pseudomonas aeruginosa* continues to cause complications in hospital acquired infections which become life threatening.[2] It is increasingly recognized as an emerging opportunistic pathogen of clinical relevance that causes infections in hospitalized patients particularly in burn patients, orthopedic related infections, respiratory disease, immunosuppressed and catheterized patients.[3]

Owing to the persistence of *Pseudomonas aeruginosa* in hospital environment, as a survival strategy an array of multidrug resistance mechanism are often seen in such strains Consequently treatment options are narrowed down to only few antibiotics.[4]

P.aeruginosa is a serious therapeutic challenge for treatment of both community and nosocomial infections and selection of the most appropriate antibiotic is complicated by the ability of *P.aeruginosa* to develop resistance to multiple classes of antibacterial agents even during the course of treatment.[5] Epidemiological studies have shown that infections caused by drug resistant *P.aeruginosa* are associated with significant increase in morbidity and mortality ,need for surgical intervention ,length of hospital stay and chronic care and overall cost of treating the infection.[5]Carbapenems are the antibiotics of choice for severe Pseudomonal infections.[6] However the resistance to this novel antibiotic is increasing worldwide.[7] Carbapenem resistance in *Pseudomonas aeruginosa* is most commonly due to production of metallo beta lactamase.[8]MBLs are broad spectrum enzymes that hydrolyze most beta lactam antibiotics except monobactums[9], Emergence of MBL producing *Pseudomonas aeruginosa* in the hospitals is alarming. Mortality rates are significantly higher in MBL producing *Pseudomonas aruginosa* compared to non MBL Pseudomonas aeruginosa.[10]

Infections caused by *P. aeruginosa* are frequently life threatening and often difficult to treat, due to the multiplicity of mechanisms of resistance. Its general resistance is due to a combination of factors .It is intrinsically resistant to antimicrobial agents, due to the low permeability of its cell wall. It has the genetic capacity to express a wide repertoire of resistance mechanisms. It can become resistant through mutations in the chromosomal genes which regulate the resistance genes. It can acquire additional resistance genes from other organisms via plasmids, transposons and bacteriophages and become resistant during a therapeutic course. In recent years, a considerable increase in the prevalence of multidrug resistance (MDR) in *P. aeruginosa* has been noticed; complicating decisions on treatment with antibiotics and its relation to high morbidity and mortality.[18,33]

Aim of the study- Prevalence of MDR in *Pseudomonas aeruginosa* in a tertiary care hoapital and also exploring its relationship with Type of specimen, the age and gender of patients for better equipping clinicians for line of treatment .(corrected)

Material & Methods-

Study design	-	Cross sectional
Study area	-	Microbiology laboratory of a tertiary care center where Clinical samples were processed.
Period of study	-	18 months
Sample size	-	Study was carried out on 200 isolates of *Pseudomonas aeruginosa* isolated from various clinical samples.

Processing of samples:

Method:
All the clinical samples including pus, respiratory samples, tissue, urine and blood received in the Microbiology laboratory for culture and sensitivity were processed. After initial Gram staining ,they were inoculated on blood agar and MacConkey's agar. The inoculated culture plates were incubated aerobically at 37 ^{0}C for 24 hours.[12]

Identification: Following the appearance of bacterial growth, only isolates of *Pseudomonas aeruginosa* were included in the study. The Standard Biochemical tests were applied for identification.

Details of the patient: Demographic details including age, sex, ward/critical unit were noted.

Antibiotic susceptibility test:
All *Pseudomonas aeruginosa* isolates were subjected to antimicrobial susceptibility test by Kirby Bauer's disc diffusion method as per CLSI guideline.[13,14]

Following antibiotic discs from HI MEDIA were used for antibiotic susceptibility test:

Piperacillin(10 µg), Piperacillin +Tazobactum(100/10 µg), Ceftazidime(30 µg), Cefepime (10 µg), Imipenem (10 µg), Meropenem (10 µg), Amikacin (30 µg), Gentamicin (10 µg) ,Ciprofloxacin(5 µg), Colistin (10 µg).

ATCC 27853 strain of *Pseudomonas aeruginosa* was used for quality control.

Observations-

Table 1-Distribution of Total isolates of MDR *Pseudomonas aeruginosa*

Sample	Total sample	Total MDR Sample	% MDR
Pus	75	17	22.66%
Urine	60	24	40.00%
sputum	24	08	33.33%
Burn Tissue	10	06	60.00%
ETT Asp.	11	03	27.27%
Blood	09	02	22.22%
Others	11	03	27.27%
Total	**200**	**63**	**31.50%**

Note- *Out of 200 isolates , 63 were found MDR (31.50%) and 137(68.50%)were non MDR*

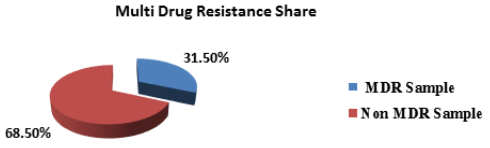


Table 2- sex wise distribution of MDR Pseudomonas aeruginosa

Gender	No. of samples	Percent share %
Male	50	79.36%
Female	13	20.64%

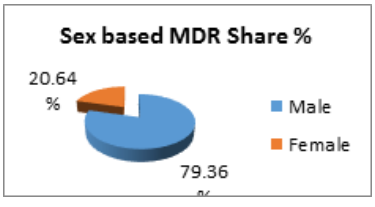


FIG -1 Out Of 200 isolates , 79.36% of MDR samples belong to Male. Only 20.64 % found from female patients.

Table 3-Age wise distribution of isolates of *Pseudomonas aeruginosa and MDR share*

Age in years	Total samples	MDR No.	MDR %
0-20	25	05	20%
21-40	44	11	25%
41-60	50	18	36%
> 60	81	29	35.80%
Total	200	63	31.50%

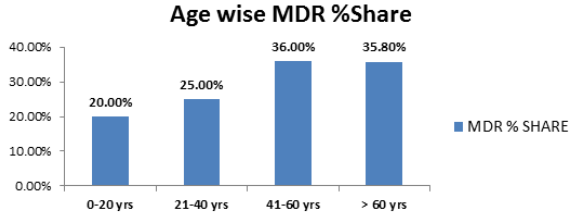


FIG -2

The detection of Multi drug resistant Pseudomonas aeruginosa found highest [36%] in the patients of age between 41-60 years and lowest [20%] in patients of age group less than 20 years.

Table 4- Department -wise distribution of samples and department wise MDR

Department	No. of Samples& % Share	MDR sample No. and % MDR
ICU	62 (31.00%)	21 (33.87%)
Medicine	33 (16.50 %)	09 (27.27%)
Surgery	34 (17.00 %)	16 (47.05%)
ENT	25 (12.50 %)	04 (16.00%)
Urology	11 (5.50 %)	05 (45.45%)
TB Chest	15 (7.50 %)	07(46.67%)
OBG	11 (5.50 %)	01 (9.09%)
OTHERS	09 (4.50 %)	00 (00%)
Total	**200 (100%)**	**63 (31.50%)**

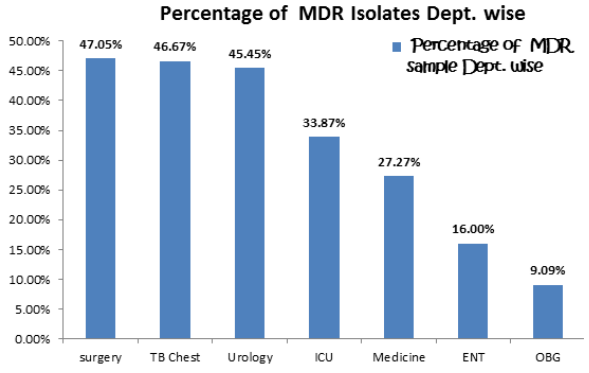


FIG -3

Maximum multi drug resistance was 47.05% from the samples collected from Surgery dept. TB Chest dept. recorded 46.67% .The lowest 9.09% were recorded from Gynecology department.

Table 5-Sample-wise distribution and multi drug resistance of *Pseudomonas aeruginosa*

Sample	NO. of sample & share %	No. of MDR isolates & MDR% out of total specimen wise isolates
Pus	75 (37.50%)	17 (22.66 %)
Urine	60 (30.00%)	24 (40.00 %)
Sputum	24 (12.00%)	08 (33.33 %)
Burn Tissue	10 (5.00%)	06 (60.00 %)
ETT aspirate	11 (5.50%)	03 (27.27 %)
Blood	09 (4.50%)	02 (22.22 %)
Others	11 (5.50%)	03 (27.27 %)
TOTAL	**200 (100.00 %)**	**63 (31.50%)**

M D R Percent- Share as per Type of Sample

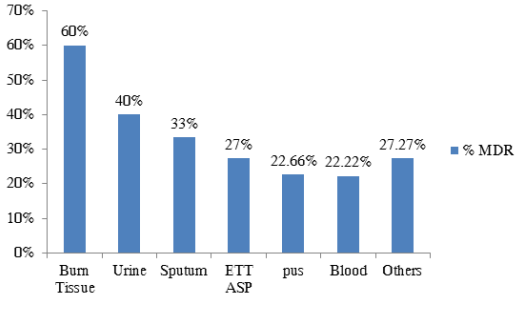


FIG -4

Burn tissue samples showed 60% highest MDR PA.22.22% was lowest MDR in blood specimens.

Table 6 :Antibiotic Susceptibility Pattern of *Pseudomonas aeruginosa*

SNO	Antibiotic	Total sample (No.)	Sensitive Sample (No)	Sensitive %	Resistant sample (No.)	Resistant %
1	Piperacillin	200	127	63.50 %	73	36.50%
2	Piptazo	200	154	77.00 %	46	23.00 %
3	Ceftazidime	200	127	63.50 %	73	36.50 %
4	Cefepime	200	141	70.50 %	59	29.50 %
5	Gentamycin	200	147	73.50 %	53	26.50 %
6	Tobramycin	200	141	70.50 %	59	29.50 %
7	Netilmycin	200	136	68.00 %	64	32.00 %
8	Amikacin	200	150	75.00%	50	25.00 %
9	Ciprofloxacin	200	146	73.00 %	54	27.00 %
10	Imepenem	200	180	90.00 %	20	10.00 %
11	Meropenem	200	180	90.00%	20	10.00 %
12	Colistin	200	191	95.50 %	09	04.50 %
13	Polymyxin	200	193	96.50 %	07	03.50 %

Note-The highest Resistance(36.50 %) was recorded by Ceftazidime and Piperacillin antibiotics while lowest (3.5%) resistance was shown by Polymxin B.

Antibiotics Resistance Pattern of *Pseudomonas aeruginosa*

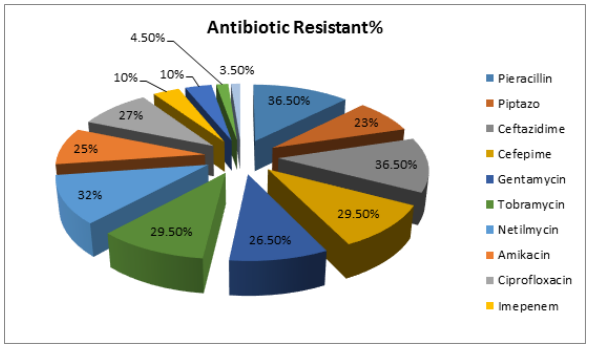


FIG-5

Results

We have studied 2100 clinical samples, out of which 200 samples were found positive for *Pseudomonas aeruginosa* which constitute 9.50 %. It is almost similar to previous study carried out in GMC Nanded, Maharashtra, India where 9.19% was the share of positive isolates of Pseudomonas aeruginosa.[27] Out of 200 isolates, 63 samples showed resistance to either three or more different group of antibiotics. The MDR ratio was 31.50 %. The gender share of MDR isolates was 79.36% in male and 20.64% in female.(Table 2)The highest 36% MDR isolates were found in the age group between 41-60 years where as the lowest(20%) were found in the age group of 0-20 year (Table 3).21 out of 62(33.87%) MDR isolates belong to ICU but maximum percent share of MDR was 16 out of 34(47.05 %) from Surgery dept. followed by 7 out of 15(46.67 %)from TB Chest dept.(Table 4). Though Pus samples were highest (75)isolates of *P. aeruginosa*but MDR isolated from pus were 17 (22.66%).The Burn tissue samples recorded highest 6 out of 10 (60%)MDR. (Table 5)

Discussion-

According to different studies, the term MDR *P. aeruginosa* has been described as resistance to at least three antibiotics from a variety of antibiotic classes, mainly aminoglycosides, penicillins, carbapenems, cephalosporins and quinolones.

Current study followed the definition of MDR *P. aeruginosa*as stated by European Center for Disease Prevention and Control (ECDC) and Centre for Disease Control and Prevention (CDC), where MDR *P. aeruginosa* was defined as the one that has acquired non susceptibility to at least one agent in three or more categories of antimicrobials.

In the present study Piperacillin- tazobactum showed greater anti-bacterial activity against *P. aeruginosa* compared to its mono therapy (i.e. piperacillin alone). Resistance rates of piperacillin-tazobactum combination were considerably lower (23%) in comparison to piperacillin alone (36.50%) as concurrent administration of a *B*lactamase inhibitor markedly expands the spectrum of activity. Bimla banjare et al (2015). [19]in their study noted less resistance to piperacillin and piperacillin tazobactam (17.45% and 7.94%),while a very high resistance to piperacillin was noted by Piyali Datta etal (2014).[20]They noted 73.2% Piperacillin resistance in their isolates of *Pseudomonas aeruginosa*. Asghar et al also noted a very high resistance (46.9%)) to piperacillin in their isolates of Pseudomonas aeruginosa.[21] While resistance to piperacillin , tazobactum was 30.4% and 41.2 % by Piyali Datta et al & Asghar et al respectively.

All these studies indicate increased resistance to the above antibiotics.

Increasing resistance to beta-lactams in *P. aeruginosa* has become a serious threat, particularly against third and fourth generation cephalosporins.

Ceftazidime and cefepime are the prescribed anti-pseudomonal third and fourth generation cephalosporins, respectively. The resistance to ceftazidime, in our study, was found to be 36.50% and the resistance to cefepime was found to be 29.50%. This is comparable to a study by Bimla Banjare et al .In their study the resistance to ceftazadime and cefipime was 29.28% & 25.10% respectively.[19] In the study of Shahid *et al.*[22]and Pitt *et al.* [23]ceftazidime resistance was 20% and 39.6% respectively .While low resistance was noted by Ayesha Ansari et al .In their study the resistance to ceftazadime and cefipime was found to be 22.03% and 16.01%.[18]In the study carried out by Wafa Ahmad at al (2015) noted 100% resistance to ceftazidime and 98% resistance to cefepime.[24]

The resistance to other antibiotics in our study was, Gentamycin 26.50%, Tobramycin 29.50%, Amikacin 25% and ciprofloxacin 27%. Banjare Bimla et al[19] have reported higher resistance in these antibiotics: gentamycin 46.86%, Tobramycin 25.20%, amikacin 39.33% and ciprofloxacin 28.40%. Ayesha Ansari et al. [18]and Rakesh M. Rajat et al. [25] also noted higher resistance for these drugs in their study.

In the present study 3.5% resistance was observed in Polymyxin – B & 4.5 % for colistin .While Piyali Datta et al[20] did not find any resistance to polymixin B and colistin in their strains. Bimla Banjare et al [19] also did not find any colistin resistant strain. However 3% of colistin resistance was noted in a study by Rakesh kumar et al (2014).[26]Awari Abhijit et al (2012). [27] have noted 25% colistin resistant strains in their study. 8.4%colistin resistant strains were found in the study carried out by S. Mohanty et al (2013).[28]

Polymixin B and colistin are the most effective antimicrobial agents against *Pseudomonas aeruginosa* .However they are very costly and nephrotoxicity limits their use and therefore should be used only as a last resort.

In the present study, Out of 200patients, 63 patients showed resistance to three or more different class of antibiotics. 31.50% of total clinical specimens were found multi drug resistant. In recent study in 2016 in Tertiary care center in India, Antibiotic resistance study revealed that 50% were MDR.[34]The other study carried out in the year 2014 in India on burn patients in teaching Institution recorded 36.2% (21/58) *P. aeruginosa* strains were MDR.[29]

Multidrug-resistant *P. aeruginosa* infection not only could increase mortality, but it may also be associated with increased patient morbidity. Aloush *et al.* demonstrated that isolation of MDR *P. aeruginosa* was associated with a higher incidence of surgery.[31]

Infections caused by *P.aeruginosa* are often severe and life threatening and are difficult to treat because of the limited susceptibility to antimicrobial agents and the high frequency of an emergence of antibiotic resistance during therapy, thus resulting in severe adverse outcomes.[31]

The problem of antibiotic resistance in *P. aeruginosa* is on the increase.[31] The heightened level of drug resistance is a result of the de novo emergence of resistance in a specific organism after exposure to antimicrobials as well as of patient-to-patient spread of resistant organisms.[31]Accumulation of resistance after exposure to various antibiotics and cross-resistance between agents may result in multidrug-resistant(MDR) *P. aeruginosa*. The most common site of isolation of MDR P. aeruginosa was wound (39%) followed by

Respiratory tract (22%), and then the Urinary tract (18%) .The multidrug resistance was observed in 74% cases in hospitalised patients.[31]The study carried out by Chander Anil et al , the MDR *Pseudomonas aeruginosa* was 20.69%.[35] Multidrug-resistant (MDR) *Pseudomonas aeruginosa* has been described mainly in patients who are immune compromised, or patients with cystic fibrosis or neoplastic diseases, or patients in Intensive Care units.[32]

Conclusion

It is established from the study that *Pseudomonas aeruginosa* pathogen is rapidly acquiring multi drug resistance in the area. The maximum MDR strains were detected from burn tissue. The multi-drug resistance was mainly nosocomial nature. The male were found affected more might be because of their habits, discontinued antimicrobial treatment and selection of antimicrobial agent without ABST. The patients in the age group of 41-60 years are found unfavourably affected with MDR strains, may be because of their continuous use of random selected antibiotics. Now it is the high time to decide that no antibiotic shall be consumed or prescribed without proper ABST to avoid MDR strains in *Pseudomonas aeruginosa*.

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