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ANALYSIS OF ANTIBIOGRAM OF *PSEUDOMONAS AERUGINOSA* FROM VARIOUS CLINICAL SPECIMENS WITH SPECIAL REFERENCE TO MDR – CAUSE FOR CONCERN

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ABSTRACT

Development of antimicrobial resistance by Pseudomonas has been progressive and relentless that renders existing antibiotics obsolete. A great challenge exists if there is an emergence of MDR pseudomonas as clinicians are left with limited therapeutic options; we aimed to investigate the susceptibility pattern of P. *aeruginosa* isolates in our settings and to do analysis of antibiogram from various clinical samples with special reference to MDR P. areuginosa isolates. This study was designed to conduct in a tertiary care teaching hospital in Chennai over a period of one year. Different types of clinical specimens such as Sputum, Urine, Pus, Throat swab, Eye swab, Ear swab, High vaginal swab (HVS). etc received were analyzed. All isolates of *Pseudomaons aeruginosa* were identified by standard microbiological procedure and subjected for antipseudomonal antibiotic susceptibility by Kirby bauer disc diffusion method as recommended by CLSI guidelines. Results obtained showed the isolation rate of *Pseudomaons aeruginosa* was 6.7% (142/2119). The maximum isolates (63/142) were obtained from pus/wound swab which accounts for 44.36% of total. We observed 99.29% of isolates were sensitive to Imipenam followed by combination drug, Piperacillin and Tazobactam (90.84%). And Amikacin (72.53%).A total of 21 isolates were resistant to three or more of the antibiotics, thus MDR

(Multi Drug Resistamt) rate was found to be 14.78%. All MDR isolates were sensitive to Imipenam except one obtained from pus. This study emphasizes the need for continuous monitoring of Pseudomonas antibiogram to provide the clinicians the up to date knowledge about the emergence of resistance, if any.

KEYWORDS: *Pseudomaons aeruginosa,* Tazobactam and Amikacin.

INTRODUCTION

Pseudomonas aeurginosa is considered as the most challenging bacteria to treat as it is inherently resistant to variety of antibiotics. Development of antimicrobial resistance by Pseudomonas has been progressive and relentless that renders existing antibiotics obsolete. In the recent past, advances in the field of drug development have been observed to combat ever evolving mechanism of resistance by this pathogen.

Among the six famous ESCAPE pathogens *(Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter species, Pseudomonas aeruginosa and Enterobacter species)***,** Pseudomonas is recognized as an epitome of opportunistic pathogen.[1]

Its role as an effective opportunistic pathogen can be attributed to the following facts

1. Minimal nutritional requirements
2. Tolerance to wide variety of physical condition
3. Extreme adaptability to adverse conditions.[2] It typically causes infections in burns, bedsores and wounds. It is also implicated in late meningitis following lumbar puncture and post tracheostomy pulmonary infections. Septicaemia and Endocarditis may occur in patients who are debilitated due to immunosuppressive therapy or malignancy.

Pseudomonas is primarily a nosocomial pathogen, as reports of National Nosocomial surveillance data from 1986 -2003 states that *Pseudomonas aeruginosa* as the second most common cause of Pneumonia accounting for 18.1% and third most common cause of UTI (16.3%). Another study reported alarming increase in the proportion of resistant strains in 2003 compared with 1998, though the infection rate caused by *Pseudomonas aeruginosa* has remained stable during this period.[3]

Being a versatile pathogen with the ability to resist variety of antimicrobials inherently, it is well recognized as public health threat. Several mechanisms may contribute to the bacterium's notable resistance, but lower outer membrane permeability in combination with

multi drug efflux systems account for its intrinsic resistance. For example, overexpression of Mex AB- Opr M efflux system contributes to resistance to many β lactams, fluoroquinolones, sulfonamides, aminoglycosides and macrolides.

In addition, expression of aminoglycoside modifying enzymes, production of biofilm and wide variety of β lactamases (recently ESBL have been described), over expression of chromosomally encoded cephalosporinase - Amp C is prevalent in *Pseudomonas aeruginosa.* Production of metallo-β-lactamases mediates resistance to broad spectrum betalactams including carbapenems. Finally, mutations in DNA gyrase and topoisomerase IV attributes to fluoroquinolones resistance. This is further complicated by coexistence of several resistant mechanism in the same strain.[4,5]

A great challenge exists if there is an emergence of Multi Drug Resistant (MDR) pseudomonas as clinicians are left with limited therapeutic options. Prior knowledge about the antibiogram profile against commonly prescribed drugs would help the clinicians to select appropriate antimicrobial agents against these resistant strains in any health care settings. The present study therefore was carried out to identify the susceptibility pattern of P. *aeruginosa* isolates in our settings and to do analysis of antibiogram from various clinical samples with special reference to MDR *P. aeruginosa* isolates.

MATERIALS AND METHODS

This study was conducted in the Department of Microbiology in a tertiary care teaching hospital in Chennai over a period of one year. Different types of clinical specimens such as Sputum, Urine, Pus, Throat swab, Eye swab, Ear swab, High Vaginal swab (HVS). etc received from both outpatients and inpatients during the study period were analyzed. Only one isolate from each patient was included in this study.

Laboratory identification of Pseudomonas aeruginosa

For the primary isolation, specimens were inoculated on routine culture media including Macconkey agar, Nutrient agar, Blood agar and Chocolate agar. Pigment production was interpreted on the basis of growth on Nutrient agar. All the plates were incubated at 37^{o}c for 24 hrs. All gram negative, catalase and oxidase positive colonies were identified up to species level by standard microbiological procedure. All consecutive, non duplicate strains of *Pseudomonas aeruginosa* isolated during the study period were considered.

Antimicrobial susceptibility test

Antimicrobial susceptibility test was performed by Kirby – Bauer disc diffusion method as per Clinical Laboratory Standard Institute (CLSI 2010) guidelines. All the isolates were tested against the following panel of Antipseudomonal antibiotics of standard strengths. Amikacin (30µg), Gentamicin (10µg), Ciprofloxacin (5µg), Ceftazidime (30µg), Piperacillin (100 µg), Aztreonam (30µg), Piperacillin and Tazobactam (100/10µg), Cefepime (30µg), Tobramycin (10µg) and Imipenam (10µg). all the antibiotic discs used in the study were purchased from Hi Media Pvt.Ltd.,Mumbai. Results were interpreted according to the CLSI guidelines.[6,7]

Isolates were considered MDR pseudomonas if they are non susceptible to atleast one agent in atleast three antimicrobial categories of the following classes: Cephalosporins, betalactam and betalactamase inhibitor, Carbapenems, Fluoroquinolones and Aminoglycosides.[8]

RESULTS

During the study period, 142 strains of *Pseudomonas aeruginosa* were isolated among 2119 clinical samples received from various departments of our hospital. Thus, the isolation rate of *Pseudomonas aeruginosa* was found to be 6.7%.

Out of 142 clinical isolates, 94(66.19%) were from male patients and 48 (33.8%) from female patients. Male to female ratio was 2:1. It showed that male patients were more vulnerable to pseudomonas infection than females.

Comprehensive analysis of clinical isolates according to gender and different age groups, revealed that both male (46.8%) and female patients (47.8%) were found to have high prevalence on age group 21-40 yrs, though the percentage slightly differs. The next common age group being 41-60 yrs, followed by >61 yrs and <20 yrs in both gender. (Fig:1).

Pseudomonas aeruginosa has been increasingly associated with wound infections. Even in our study the maximum isolates (63) were obtained from pus/wound swab which accounts for 44.36% of total.(Fig- 2).

Urinary Tract Infection (UTI) was the next common infection followed by respiratory infections as 42(29.57%) and 27(19.01%) isolates were identified from Urine and Sputum respectively. Another interesting observation was that all the blood samples received during the study period was found to be negative for Pseudomonas aeruginosa.

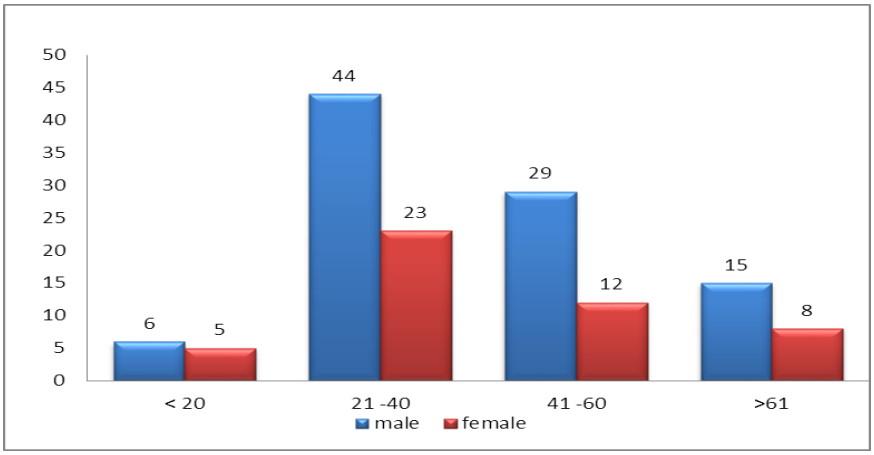

Fig 1: Age and Genderwise distribution of clinical isolates of Pseudomonas aeurginosa.

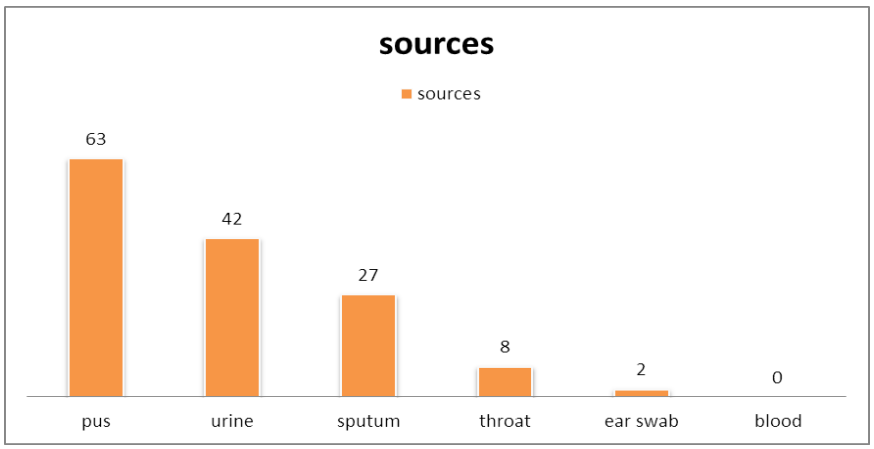

Fig- 2: Distribution of various sources of Pseudomonas aeurginosa isolated.

Out of 63 Pseudomonas from pus specimen, one isolate was found to be resistant to Imipenam, thus accounting for the sensitivity 98.41%. Piperacillin & Tazobactam combination was also effective in 88.8% of pus specimen. Piperacillin, Gentamicin and Aztreonam observed to have 42.8% each.

In urine, isolates had shown 100% sensitivity to Imipenam followed by Piperacillin & Tazobactam (90.47%). Surprisingly, Fluroquinolones, the common class of antibiotic recommended for UTI, was found to have only 69.04%.Among them, ciprofloxacin showed high level of resistance, this is a remarkable finding as it is commonly prescribed for UTI in outpatient clinics. Both the injectable antibiotics Amikacin and Gentamicin had shown to have high level of susceptibility for urinary isolates than other specimens. On the otherhand, Aztreonam (33.3%) found to have lower susceptibility rate where urinary isolates are concerned.

Respiratory samples such as sputum and throat swab from LRI &URI in our study, revealed Imipenam and Piperacillin & Tazobactam, can be the appropriate choice of antibiotics with 92 – 100% sensitivity. Gentamicin appeared to be more sensitive to LRI isolates than URI isolates as sputum & Throat swab showed 59.2% and 37.5% respectively. Similarly, Aztreonam was more effective for sputum (51.85%) isolates than throat swab (37.5%). Irrespective of various categories of clinical specimens, Cephalosporins had not shown promising susceptibility (25% -50%). (Table 1).

Among the antipseudomonal antibiotics tested against the isolates, highest sensitivity was observed for Imipenam (99.29%) followed by Piperacillin and Tazobactam (90.84%). In contrast, piperacillin alone reported to have sensitivity of 47.18%.Least sensitivity was observed to ciprofloxacin and ceftriaxone exhibiting 31.69% each. Among the aminoglycosides tested Amikacin (72.53%) showed high sensitivity than Gentamicin (54.22%). Analysis of sensitivity pattern according to the antimicrobial class revealed low sensitivity to Cephalosporins (31% to 38%). **(**Table 2**).**

Table 1: Comparison of Antimicrobial susceptibility pattern of Pseudomonas aeurginosa from various clinical samples.

Antibiotics	Pus n=63(%)	Urine n=42(%)	Sputum n=27(%)	Throat swab n=8(%)	Ear swab n=2(%)
Penicillins					
Piperacillin	27(42.8%)	20(47.6%)	16(59.25%)	3(37.5%)	1(50%)
Fluroquinolones					
Ciprofloxacin	22(34.92%)	14(33.3%)	7(25.92%)	2(25%)	0(0%)
Ofloxacin	32(50.79%)	23(54.76%)	14(51.85%)	6(75%)	1(50%)
Levofloxacin	45(71.4%)	29(69.04%)	19(70.37%)	6(75%)	2(100%)
Aminoglycosides					
Gentamicin	27 (42.85%)	30(71.42%)	16(59.25%)	3(37.5%)	1(50%)
Amikacin	47(74.6%)	33(78.57%)	17(62.96%)	5(62.5%)	1(50%)
Cephalosporins					
Ceftazidime	20 (31.7%)	14(33.3%)	10(37.03%)	2(25%)	1(50%)
Ceftriaxone	21(33.33%)	12(28.57%)	8(29.62%)	3(37.5%)	1(50%)
Cefepime	24(38.09%)	16(38.09%)	10(37.03%)	3(37.5%)	1(50%)
Monobactams					
Aztreonam	27(42.85%)	14(33.3%)	14(51.85%)	3(37.5%)	1(50%)
β lactam & β lactamase inhibitor					
Piperacillin & Tazaobactam	56(88.8%)	38(90.47%)	25(92.59%)	8(100%)	2(100%)
Nitrofuran					
Nitrofurantoin	----	19(45.23%)	------	------	------
Carbapenems					
Imipenem	**62(**98.41%**)**	**42(100%)**	**27(100%)**	**8(100%)**	**2(100%)**

Table 2: Overall Antimicrobial susceptibility pattern of Pseudomonas aeurginosa.

S .No	Antipseudomonal antibiotics tested	No. Of Sensitive isolates n=142 (%)
1	Imipenam	141(99.29%)
2	Piperacillin &Tazobactam	129(90.84%)
3	Amikacin	103(72.53%)
4	Levofloxacin	101(71.12%)
5	Gentamicin	77(54.22%)
6	Ofloxacin	76(53.52%)
7	Piperacillin	67(47.18%)
8	Cefepime	54(38.02%)
9	Ceftazidime	47(33.09%)
10	Ciprofloxacin	45(31.69%)
11	Ceftriaxone	45(31.69%)

Out of 142 isolates, 21 were found to be resistant to more than 3 antimicrobial categories which accounts for 14.78%. (Fig 3).

Maximum MDR isolates were obtained from pus 12(57.14%) followed by urine and sputum. All strains had shown 100% resistance to 3rd and 4th generation Cephalosporins tested in our study. Quite interestingly, all strains were sensitive to Imipenam except one which was found to be susceptible to polymyxin B and Colistin when tested. (Fig 4).

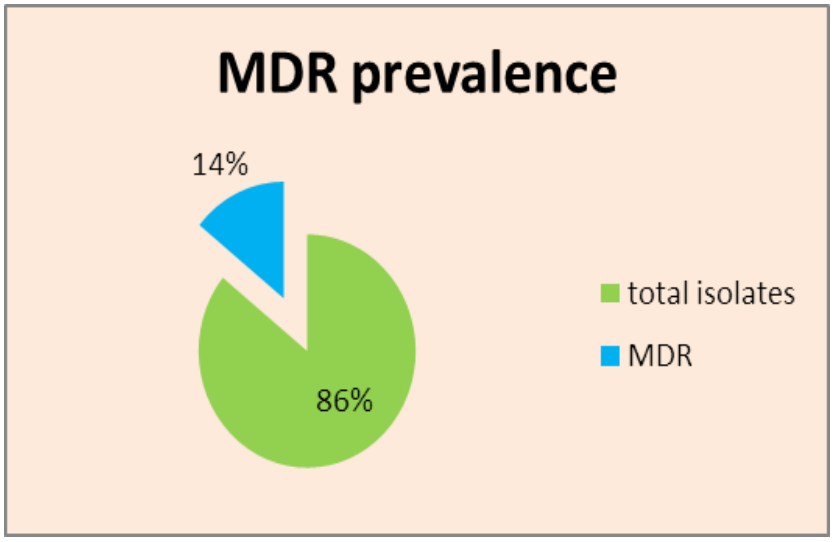

Fig 3: Prevalence of MDR isolates of Pseudomonas aeurginosa from various clinical samples.

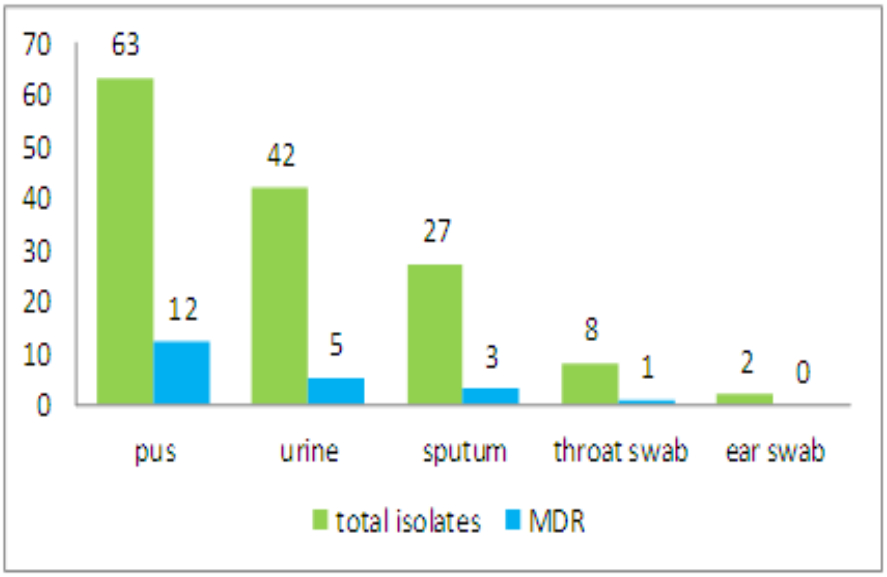

Fig 4: Distribution of MDR Pseudomonas aeurginosa from various clinical samples.

DISCUSSION

This study at tertiary care hospital, Chennai revealed the prevalence rate of Pseudomonas aeruginosa was 6.7%. This rate is comparable to a similar study conducted in Andhrapradesh which had shown 9.28%.[9] Another study conducted in Medical Internal ICU and Coronary ICU from Turkey had shown similar observation where the isolation rate was 9.4% and 9.1% respectively.[10] In contrast, high prevalence rate of 32% was obtained by an Indian author,Anupurba et al., in his research.[11] Similar studies conducted across the globe have also reported highly variable rates such as 18% (Pakistan), 50% (Africa) & 27% (America) respectively.[12,13,14] All these studies depict that occurrence rate of Pseudomonas aeruginosa varies with geographical difference.

Sexwise correlation of pseudomonas prevalence data in our study revealed that male patients had high prevalence than females. Similar preponderance was noticed from other researchers, Ahmed et al.,[15] & Jamshaid et al.,[16] in India in their studies. In contrast, a recent study from Nepal had reported female preponderance[17] than male patients. This might be explained by the fact that gender prevalence may also differ with geographical variation and study period. On the whole, male are more susceptible than female.

As consistent with our finding that, patients in the age group of 21-30 yrs had high occurrence of pseudomonal infections, Chander Anil et al.,[17] had also demonstrated the same. However, high occurrence in elderly age group (> 60 yrs) has been shown by another similar study.[9]

As the distribution of clinical samples in each Hospital is determined by the surrounding environment associated with it, we found that maximum isolates were obtained from pus/wound (63), therefore, among other infections, wound infection observed to be the most prevalent in our region followed by UTI. This is in accordance with the findings observed in several similar studies tabulated below.

Place	Author	year	% of Pseudomonas from Pus
Noida .U.P(18)	Tarana sarwat et al	2015	33.33%
Maharashtra (19)	Sathyajeet et al	2014	44.76%
Davangree (20)	Mohan et al	2013	45.56%
Bhubaneshwar (21)	Pathi et al	2013	29.15%
Nepal (17)	Chander anil et al.,	2013	27.60%
Kashmir (22)	Arshi et al.,	2007	57.64%
A.P (9)	Srinivas et al	2012	55.35%

On the other hand, similar study reports from Pakistan[23] & Gujarat[24] was found to differ from our findings as they had shown higher isolation rate from urine (UTI). This findings reveal variation of sample distribution with place of study emphasizing the need to conduct local study to monitor bacterial profile.

On comparing the antibiogram profile of strains with various categories of sample, it was observed that sputum isolates showed higher sensitivity to Piperacillin (59.25%) among the isolates from other clinical samples to Piperacillin. Although fluoroquinolones sensitivity was in the wide range (25%-70%), sputum isolates are more suceptible than others. As far as, Aminoglycosides are concerned whether it is Gentamicin (70%) or Amikacin (78%) they are quite effective against urinary isolates. Nitrofurantoin for urinary isolates revealed 45.23% sensitivity. Cephalosporins are less sensitive to all isolates, however isolates from Ear swab and Sputum showed good sensitivity than other samples.

Synergism tested using Piperacillin & Tazobactam was found to be very effective as isolates had shown higher sensitivy in all sample categories (88%-100%) when compared to Piperacillin alone (37%-59%) which is in corroboration with an earlier study reported in India.[17]

All isolates were susceptible to Imipenam except the one from pus. Hence pus isolates are likely to be suspected for MDR strains compared to other specimens.

Drug susceptibility pattern of Pseudomonas aeruginosa was found to be highly variable. Worldwide, there has been an alarming increase in IRPS (Imipenam Resistance Pseudomonas aeruginosa).[25] One striking feature in this study was that only one strain from pus sample was found to be resistant to the Carbapenam, Imipenam. This high sensitivity (99.29%) to Imipenam, might be due to rational use of antibiotics by our clinicians who restrict their inappropriate usage by following antibiotic policy.

However, studies from different places in recent times have reported varying degrees of sensitivity. 94.3% from Davangree[20], 95.2% from AP[9] and 68% from Karnataka.[26]

Piperacillin & Tazobactam (PIT) (90.84%), Amikacin (72.53%) and Levofloxacin (71.12%) are found to be the most effective drugs against Pseudomonas aeruginosa isolated in this study.

Piperacillin & Tazobactam (PIT) (90.84%) sensitivity is consistent with the findings of an earlier studies from ICU of National heart centre at Nepal[17] and Kerala[15] which had reported higher sensitivity for combination drug 84.8%and 89%.

In our study ceftazidime sensitivity was 33.09%, thus exhibited high rate of resistance to the third generation cephalosporins (77.91%). similar high rate of 69.64%, 86%, 93.9% had been reported from an earlier studies done.[9,17] In contrast, similar studies conducted during 2001 had reported ceftazidime as highly efficacious drug[27,28], this clearly indicates that resistance to ceftazidime is on the rise over the last decade. This may be due to excessive use of this drug in clinical practice.

In the present study, we identified 21out of 142 isolates were resistant to more than 3 antibiotic categories, thus MDR rate was found to be 14.78%.Rates of our study are comparable to the studies done in North India and Nepal which reported 31.3%[29] and 20.69%.[17] In contrast, study from Pune had shown high rate of MDR as 57%.[30] In our study, 57.14% of MDR isolates were from pus .this is in harmony with the findings of an earlier study[9] which had shown 56.85% from pus suggesting MDR isolates was high in wound infections.

Though, the study results revealed mild difference in susceptibility pattern from other recent reports, consistent pattern of antibiogram for samples couldn't made out as it was found to be exhibit distinct pattern from specimen to specimen. As there is no international surveillance

system that can keep a track of emergence of MDR organisms specifically, establishing true prevalence of MDR pseudomonas was quite difficult. However in the recent past, several researchers have reported that there has been alarming increase in MDR pseudomonas.[22,26,29] Occurrence rate of MDR isolates in our study emphasizes the need for continuous monitoring of Pseudomonas susceptibility to know the emergence of resistant isolate, if any.

Conclusion: As clinicians are left with limited therapeutic options and selection of inappropriate antibiotics for empirical treatment can predispose to increased mortality rate, knowledge about the antibiogram pattern is essential for the clinicians to choose the most appropriate drug. Hence this study emphasize the need for continuous antimicrobial surveillance for early detection of emergence of MDR pseudomonas aeruginosa.

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