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Antimicrobial resistance and inducible beta-lactamase synthesis in *Pseudomonas aeruginosa* strains isolated from nosocomial infections of various localizations

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ABSTRACT: *Pseudomonas aeruginosa* (*P. aeruginosa*) is a major opportunistic pathogen associated with nosocomial infections. The intrinsic resistance of *P. aeruginosa* to many antibiotics and the ability of *P. aeruginosa* to rapidly acquire resistance make the management of infections difficult. This study aimed to evaluate the antibiotic resistance profiles and inducible beta-lactamase (ibl) synthesis in *P. aeruginosa* strains isolated from hospitalized patients at the Azerbaijan Medical Faculty Hospital. This study included 125 samples including 44 sputum samples from pneumonia patients, 44 urine samples from individuals with urinary tract infections, and 41 postoperative samples encompassing pus, drainage, and abscess contents derived from surgical site infections. *P. aeruginosa* was isolated by conventional culture methods and drug susceptibility and ibl synthesis were investigated by disc diffusion. Fisher's exact test compared the ibl synthesis of *P. aeruginosa* strains isolated from different infection sources. Statistical significance was accepted as 0.05 ($p \leq 0.05$). Of 26 *P. aeruginosa*, 19 (73.1%) were resistant to ceftazidime, 20 (76.9%) to cefepime, 20 (76.9%) to piperacillin and 23 (88.4%) to aztreonam, while 19 (73.1%) were susceptible to imipenem, 19 (73.1%) to amikacin, 23 (76.9%) to piperacillin and 23 (88.4%) to colistin. In addition, the ibl synthesis (+) *P. aeruginosa* strains isolated from pneumonia patients (77.8%) were marginally significantly higher than those isolated from urinary tract infections (25.0%) ($p=0.057$). Our results reveal high rates of antibiotic resistance among *P. aeruginosa* strains isolated from patients in our hospital, particularly against several key antibiotics. We recommend larger studies involving multiple centers and various sample types.

KEYWORDS: Antibiotic susceptibility testing; inducible beta-lactamase; nosocomial infections; *Pseudomonas aeruginosa*.

1. INTRODUCTION

Pseudomonas aeruginosa (P. aeruginosa) is a Gram-negative, obligate aerobic pathogen commonly found in healthy hosts, soil, and water microbiota. However, it poses a significant risk of opportunistic infections, particularly in scenarios involving invasive procedures, trauma, prolonged hospitalization, immunosuppression, and in geriatric populations [1-3]. In addition, it can cause contamination of solutions used in hospitals for injection or other purposes in improperly disinfected endoscopic equipment and is characterized by natural resistance to most antimicrobial agents. This versatile organism is responsible for a wide range of nosocomial and community-acquired infections, including but not limited to bacteremia, pneumonia, soft tissue, urinary tract, respiratory, wound, bone, and joint infections [4-6]. In high-risk patient cohorts, *P. aeruginosa* infections can lead to serious complications and significantly increase morbidity and mortality. Because of its clinical significance and treatment challenges, the World Health Organization has identified *P. aeruginosa* as one of six priority pathogens responsible for a significant burden of hospital-acquired infections and outbreaks [2]. The bacterium flourishes in environments characterized by a compromised epithelial barrier, reduced neutrophil activity, impaired mucociliary clearance, and the presence of medical implants [4].

There are several mechanisms by which *P. aeruginosa* develops resistance to antibiotics. One of these mechanisms is the synthesis of beta-lactamase enzymes, which inactivate the antibiotic by destroying the beta-lactam ring. Unlike other beta-lactamases, the inducible beta-lactamase (ibl) synthesis is only induced by specific antibiotics such as ceftazidime and imipenem [7-10]. The effect of the antibiotic on the cell wall leads to the production of beta-lactamase through a genetic cascade mechanism. This enzyme synthesis stops in the absence of these antibiotics. The enzyme in bacterial genes and plasmids is responsible for the ibl synthesis. The genes associated with ibl can be transferred to other bacterial strains through conjugation, spreading resistance within microbial populations. This is a major challenge as it can lead to the emergence of increasingly difficult-to-treat diseases [7-10].

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This study aimed to determine the antimicrobial resistance and ibl synthesis in *P. aeruginosa* strains isolated from patients with nosocomial infections at Azerbaijan Medical University Training and Surgical Clinic.

2. RESULTS

Our study focused on isolating *P. aeruginosa* from patients with nosocomial infections at the Azerbaijan Medical University Training and Surgical Clinic. We aimed to determine *P. aeruginosa*'s antimicrobial resistance profile. Among the 125 samples collected, *P. aeruginosa* was identified in 9 out of 41 patients (21.9%) with pneumonia, 9 out of 40 patients (22.5%) with surgical site infections, and 8 out of 44 patients (18.1%) with urinary tract infections. Of 26 *P. aeruginosa*, 19 (73.1%) were resistant to ceftazidime, 20 (76.9%) to cefepime, 20 (76.9%) to piperacillin and 23 (88.4%) to aztreonam, while 19 (73.1%) were susceptible to imipenem, 19 (73.1%) to amikacin, 23 (76.9%) to piperacillin and 23 (88.4%) to colistin. Of the 9 *P. aeruginosa* strains isolated especially from patients with pneumonia, 8 (88.9%) were resistant to ceftazidime, 7 (77.8%) to cefepime, 8 (88.9%) to piperacillin, 8 (88.9%) to aztreonam and 6 (66.7%) to gentamicin. Of the 9 *P. aeruginosa* strains isolated from patients with surgical site infections, 7 (77.8%) were resistant to ceftazidime, 8 (88.9%) to cefepime, 8 (88.9%) to piperacillin, 6 (66.7%) to meropenem and 9 (100%) to aztreonam. Of the 8 *P. aeruginosa* strains isolated from patients with urinary tract infections, 7 (87.5%) were resistant to meropenem, 6 (75.0%) to aztreonam, 6 (75.0%) to ciprofloxacin and 6 (75.0%) to levofloxacin (Table 1).

Table 1 . Susceptibility of *P. aeruginosa* strains to different antibiotics

Antibiotics	Strains that cause pneumonia (n:9)		Strains that cause surgical site infections (n:9)		Strains that cause urinary tract infections (n:8)	
	S (n, %)	R (n, %)	S (n, %)	R (n, %)	S (n, %)	R (n, %)
Ceftazidime (30µg)	1 (11.1%)	8 (88.9%)	2 (22.2%)	7 (77.8%)	4 (50.0%)	4 (50.0%)
Cefepime (30µg)	2 (22.2%)	7 (77.8%)	1 (11.1%)	8 (88.9%)	3 (37.5%)	5 (62.5%)
Piperacillin (100µg)	1 (11.1%)	8 (88.9%)	1 (11.1%)	8 (88.9%)	4 (50.0%)	4 (50.0%)
Piperacillin+Tazobactam (110µg)	5 (55.5%)	4 (44.4%)	4 (44.4%)	5 (55.6%)	6 (75.5%)	2 (25.0%)
Imipenem (10µg)	6 (66.7%)	3 (33.3%)	9 (100.0%)	0 (0.0%)	4 (50.0%)	4 (50.0%)
Meropenem (10µg)	6 (66.7%)	3 (33.3%)	3 (33.3%)	6 (66.7%)	1 (12.5%)	7 (87.5%)
Aztreonam (30µg)	1 (11.1%)	8 (88.9%)	0 (0.0%)	9 (100.0%)	2 (25.0%)	6 (75.5%)
Gentamicin (10µg)	3 (33.3%)	6 (66.7%)	6 (66.7%)	3 (33.3%)	6 (75.5%)	2 (25.0%)
Amikacin (30µg)	5 (55.6%)	4 (44.4%)	6 (66.7%)	3 (33.3%)	8 (100.0%)	0 (0.0%)
Netilmicin (30µg)	5 (55.6%)	4 (44.4%)	5 (55.6%)	4 (44.4%)	7 (87.5%)	1 (12.5%)
Ciprofloxacin (5µg)	5 (55.6%)	4 (44.4%)	6 (66.7%)	3 (33.3%)	2 (25.0%)	6 (75.5%)
Levofloxacin (5µg)	6 (66.7%)	3 (33.3%)	6 (66.7%)	3 (33.3%)	2 (25.0%)	6 (75.5%)
Colistin*	7 (77.8%)	2 (22.2%)	8 (88.9%)	1 (11.1%)	8 (100.0%)	0 (0.0%)

S: Susceptible, R: Resistant, *: The disc diffusion test is unreliable for colistin. Colistin susceptibility was determined using a minimum inhibitory concentration (MIC) method.

The study also investigated the characteristics of ibl synthesis in *P. aeruginosa* strains associated with nosocomial infections. Specifically, 7 out of 9 strains (77.8%) isolated from patients with pneumonia showed ibl positivity. In contrast, only 4 out of 9 strains (44.4%) from patients with surgical site infections and 2 out of 8 strains (25%) from patients with urinary tract infections showed ibl positivity (Table 2). The ibl synthesis of *P. aeruginosa* strains isolated from each infection source was analyzed in paired groups using Fisher's exact test. In the first comparison, we assessed the ibl synthesis between *P. aeruginosa* strains from surgical site infections and those isolated from patients with pneumonia. The results showed no significant difference between the two groups (p=0.335). Similarly, in the second comparison, we examined the ibl synthesis in strains isolated from surgical sites and those from urinary tract infections, also finding no significant difference (p=0.620). Finally, we evaluated the ibl synthesis between *P. aeruginosa* strains isolated from patients with pneumonia and urinary tract infections in the third comparison. Ibl synthesis of *P. aeruginosa* strains isolated from pneumonia patients were marginally significantly higher than those isolated from urinary tract infections (p=0.057) (Table 2).

Table 2. Comparison of the inducible beta-lactamase synthesis of *P. aeruginosa* strains isolated from different sources of infection

Comparison number	Infection source	Inducible beta-lactamase (+)	Inducible beta-lactamase (-)	Total(n)	(%)Proportion of Inducible beta-lactamase (+)	P value
1	Pneumonia	7	2	9	77,8	0.335
	Surgical cite	4	5	9	44,4	
2	Surgical cite	4	5	9	44,4	0.620
	Urinary tract	2	6	8	25,0	
3	Pneumonia	7	2	9	77,8	0.057
	Urinary tract	2	6	8	25,0	

3. DISCUSSION

Inappropriate use of antibiotics is known to cause antibiotic resistance and has become a global public health problem. According to the Global Risk Report, *P. aeruginosa* isolates, opportunistic pathogens isolated from clinical specimens, especially from immunocompromised patients, have been reported as one of the risk factors for microorganisms causing antimicrobial resistance [11]. According to the CDC, multidrug-resistant *P. aeruginosa* is in the category of serious threats [12]. The concurrent activation of multiple resistance mechanisms is a significant factor in the emergence of antibiotic resistance among *P. aeruginosa* isolates. Key contributors to this resistance profile include the inherent low permeability of the outer membrane, which is further influenced by the presence of porins that exhibit selective permeability. Additionally, the production of beta-lactamases and the upregulated activity of efflux pumps are critical mechanisms that facilitate the development of resistance [13].

The data presented in this study highlights significant resistance patterns of *P. aeruginosa* to beta-lactam antibiotics, aminoglycosides, and fluoroquinolones across infections such as pneumonia, surgical site infections, and urinary tract infections. These findings underscore the multifaceted challenge posed by *P. aeruginosa*, a pathogen notorious for its adaptive resistance mechanisms.

Resistance to ceftazidime, cefepime, piperacillin, and aztreonam was notably high in *P. aeruginosa* strains from pneumonia and surgical sites. Similar trends have been observed globally, with resistance rates exceeding 50% in certain regions, such as Asia and South America, where antibiotic misuse is prevalent [14]. The susceptibility of strains to imipenem and meropenem varied based on infection source. Requena-Cabello et al. [15] examined the antimicrobial resistance patterns of *P. aeruginosa* isolates between 2016 and 2021 and found that resistance rates for cefepime and ceftazidime ranged between 3.7% and 15.1%. Ceken et al. [2] found cefepime and ceftazidime resistance rates of 28.1% and 29.4%, while in the study by Kal-Cakmakliogullari et al. [16] these rates were 28% and 26%, respectively. In contrast, our study found significantly higher resistance rates for these agents. However, this may be due to the small number of *P. aeruginosa* isolates.

Broad-spectrum antibiotics, particularly carbapenems, selected cephalosporins and antipseudomonal penicillins, are the primary treatment regimen for *P. aeruginosa* infections. However, the widespread and increasing use of carbapenems in hospitalized patients has raised serious concerns about developing antimicrobial resistance [14]. Durmaz et al. [17] reported 37% resistance to both imipenem and meropenem. In a similar study, Gültepe et al. [18] found 33% resistance to imipenem and 29% to meropenem. Tümer et al. [19] found slightly lower resistance rates of 19% for imipenem and 25% for meropenem. In our study, imipenem resistance was 26.9% and meropenem resistance was 61.5%. The observed increase in meropenem resistance among *P. aeruginosa* strains isolated from our hospital underscores a concerning trend in our antibiotic stewardship practices, particularly with the management of carbapenems. This situation underscores the potential emergence of significant resistance challenges that we may face in the future.

Piperacillin-tazobactam (TZP) is a broad-spectrum antipseudomonal penicillin commonly used for the prophylaxis and treatment of *P. aeruginosa* infections [14]. A study by Uğur et al. [20] reported significant resistance rates among *P. aeruginosa* strains from intensive care unit samples, noting resistance levels of 19% in 2015, 42% in 2016, and peaking at 83% in 2017, with an overall rate of 53%. Tümer et al. [19] identified a resistance rate of 42%. Our investigation revealed a resistance rate of 42.1%, aligning closely with Tümer et al.'s findings, highlighting ongoing concerns regarding TZP efficacy against this pathogen.

Aminoglycosides are not used as monotherapy for Pseudomonas infections but are included in combination regimens [14]. Özyurt et al. [21] reported a resistance rate of 4% for amikacin and 25% for gentamicin, while Eyigör et al. [22] found these figures to be 1% for amikacin and 4% for gentamicin. A comprehensive analysis of 52,637 *P. aeruginosa* isolates showed that the resistance rate to amikacin was the lowest observed [23]. Kal Çakmaklıoğulları et al. [16] also found the lowest resistance to amikacin and gentamicin in *P. aeruginosa* strains in their study. We found resistance rates

of 26.9% to amikacin and 40.7% to gentamicin. This observation could be due to the limited number of *P. aeruginosa* isolates available for analysis.

Although ibl synthesis is accepted as a general feature in *P. aeruginosa* strains, it can be detected at different rates depending on the method used [18]. Our study detected ibl synthesis in 42.3% of *P. aeruginosa* strains using disc diffusion. In addition, ibl synthesis of *P. aeruginosa* strains isolated from pneumonia patients were marginally significantly higher than those isolated from urinary tract infections (p=0.057). Öztürk et al. [24] detected ibl in 31.9% of *P. aeruginosa* isolates using the same method.

4. CONCLUSION

In conclusion, our results reveal high rates of antibiotic resistance among *P. aeruginosa* strains isolated from patients in our hospital, particularly against several key antibiotics. We recommend larger studies involving multiple centers and various sample types to understand the resistance landscape better. It is essential to investigate the resistance mechanisms prevalent in the hospital environment to curb their spread and improve the effectiveness of therapeutic interventions. Comprehensive epidemiological studies will be critical in guiding empirical treatment strategies. Clinicians must recognize that antibiotic susceptibility profiles can vary over time across different geographical regions, hospitals, wards, and even within the same clinical unit. Therefore, vigilant monitoring of resistance development is crucial. Empirical treatment should be based on the antibiogram results, and susceptibility testing should be continually reassessed for any signs of resistance during therapy. By using antibiotics judiciously, informed by empirical data and infection control guidelines, we can significantly reduce the challenge of antimicrobial resistance.

5. MATERIALS AND METHODS

5.1 Bacterial isolates, identification and antibiotic susceptibility tests

The study was conducted with the approval of the Azerbaijan Medical University Local Ethics Committee (Date: 18.09.2019, Decision No.8). This study analyzed 125 samples, comprising 44 sputum specimens from pneumonia patients, 44 urine specimens from individuals with urinary tract infections, and 41 postoperative specimens, including pus, drainage, and abscess content from surgical site infections. All samples were collected from individuals hospitalized at the Azerbaijan Medical Faculty Hospital between 01.12.2019-30.11.2020. Clinical samples were inoculated into 5% sheep's blood agar (bioMérieux, France) MacConkey (bioMérieux, France), Nutrient (bioMérieux, France), Cetrimide (bioMérieux, France) and eosin methylene blue agar (bioMérieux, France) and incubated at 35 ˚C for 18-24 hours. *P. aeruginosa* isolates were identified by their typical colony morphology, Gram staining, oxidase and catalase tests, and conventional microbiological characteristics, such as sugar fermentation [25]. Antibiotic susceptibility testing was performed using the disc diffusion method according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) [26]. Susceptibility results to colistin only were evaluated using a minimum inhibitory concentration (MIC) [27]. In antibiotic disc diffusion tests: Imipenem 10µg (IP), Meropenem 10µg (MP), Aztreonam 30µg (ATM), Ceftazidime 30µg (CAZ), Cefepime 30µg (CEP), Gentamicin 10µg (GN), Amikacin 30µg (AK), Netilmicin 30µg (NET), Ciprofloxacin 5µg (CIP), Levofloxacin 5µg (LVX), Piperacillin 100µg (PRL) and Piperacillin/Tazobactam 110µg (TZP) antibiotic discs were used. Antibiotic discs were placed on Mueller-Hinton (MHA) agar plates (adjusted to 0.5 McFarland standards). The plates were incubated at 35 °C for 18-20 hours. The diameter of the zone of inhibition was recorded for each isolate and reported according to CLSI guidelines [26]. The synthesis of ibl in *P. aeruginosa* strains was assessed through a phenotypic assay utilizing two disks. This approach relies on the observation that the sensitivity of *P. aeruginosa* to beta-lactam antibiotics, specifically ceftazidime, diminishes in the presence of beta-lactamase-inducing agents such as cefoxitin or imipenem. In this procedure, a disk impregnated with either cefoxitin or imipenem is placed adjacent to a ceftazidime disk on a solid agar medium inoculated with the bacterial strain. Following a 24-hour incubation period, the results are analyzed. A visible reduction in the susceptibility zone around the ceftazidime disk, particularly on the side adjacent to the cefoxitin or imipenem disk, indicates the synthesis of ibl by the bacterial strain.

5.2 Statistical analysis

The ibl synthesis of *P. aeruginosa* strains isolated from each infection source was analyzed in paired groups using Fisher's exact test. P-value < 0.05 was considered statistically significant. Analyses were performed using IBM SPSS (Statistical Package for Social Science) Statistics 20.0.

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