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Dissemination Multi-Drug and Carbapenems Resistant *Pseudomonas aeruginosa* among Clinical Isolates in Najaf Hospitals

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Abstract

Background: *Pseudomonas aeruginosa* is one of the most common Gram negative pathogens associated with nosocomial infections. Carbapenems, specially imipenem and meropenem have the widest activity ranges of any β-lactam antibiotics and are often the most appropriate agents for use in the treatment of infections caused by multi-drug resistant *P. aeruginosa.* Resistance to carbapenems is emerging, and it is a great problem to therapeutic the serious infections caused by this bacteria.

Aim of the study: Investigations the occurrence of multi-drug resistant and detection of carbapenems antibiotic resistant among susceptibility profile in *P. aeruginosa* which isolated from various locations in Najaf hospitals.

Methods: A total of 996 clinical samples were obtained from patients visited/or admitted to three main hospitals in the Najaf city and identification was done with the automated VITEK-2 compact system. All were screened for the antibiotic susceptibility patterns of isolates were determined by automated VITEK-2 compact system.

Results: 52 (5.2%) isolates of *P. aeruginosa* were identified. Antibiotic susceptibility pattern revealed that 33 (63.5%) of the isolates were multi-drug resistance, (28.8%) of isolates were (MDR) and (34.6%) extensive drug resistance (XDR). Based on the results from susceptibility testing, 13 (25%) of *P. aeruginosa* isolates were found to be resistant to at least one of carbapenems and all these isolates were detected as multi-drug resistance.

Conclusions: Increase resistant to carbapenems, this just confirms the importance of this problem during the treatment of serious infections with multidrug-resistant *P. aeruginosa.*

Recommendations: Use of carbapenems should be restricted and not the appropriate of antibiotics without laboratory tests in order to avoid the emergence of extremely drug resistance isolates.

Keywords: *Pseudomonas aeruginosa*, Antibiotic, Resistance, carbapenems.

INTRODUCTION

Pseudomonas aeruginosa a commensal bacterium of normal human microflora, which is found on skin surfaces, in nostril, in upper respiratory tract. It colonizes the intestine of up to 40% of healthy people(1). This percentage increases among hospitalized patients proportionally with increasing duration of hospitalization(2).Therefore the *P. aeruginosa* is one of the most common microorganisms, obtained from clinical research material and causing hospital-acquired infections (HAI)(3). Treatment of serious infections requires an empirical strategy providing broad-spectrum coverage to a wide range of suspected pathogens in an intensive care unit, such as *P. aeruginosa* (4). Emergence and spread of *this bacteria* by

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resistant to most of the available antimicrobial agents, and now being frequently related with healthcare associated infections(5). The currently available carbapenems (imipenem and meropenem) represent a realistic option for initial empirical therapy in many serious nosocomial infections because of their broad spectrum of activity and the continued susceptibility of difficult to treat and antibiotic resistant pathogens to these agents(6,7). The assistances of different mechanisms of resistance to carbapenems among a collection of imipenem- and meropenem-nonsusceptible *P. aeruginosa* isolates were development. Increasing resistance to carbapenems mediated by metallo-*β*-lactamase (MBL) is a cause for concern because MBL-producing *P. aeruginosa* strains have been reported to be important causes of nosocomial infections, and other mechanisms of the resistance to carbapenems, such as the production of AmpC, extended-spectrum *β*-lactamases, or reduced outer membrane porin OprD loss and overexpression of the MexAB-OprM efflux system can be involved as well, but the overall rates of morbidity and mortality among infected patients(8,9). However, resistance to carbapenem is being observed more frequently among Gram-negative bacteria, such as *P. aeruginosa* and *Acinetobacter* spp. Data from many European centers show an increasing resistance of *P. aeruginosa* strains to carbapenems, conditioned by beta-lactamase synthesis(10). During the last years, the prevalence of carbapenem-resistant *P. aeruginosa* isolates in Najaf hospitals has increased. Such a high rate prompted us to study the characteristics of carbapenem-resistant *P. aeruginosa* isolates and changes in resistance at our hospitals and to present the guidelines in the future in order to decrease such a resistance. The study is carried out to achieve the following objectives:

1. Evaluate the current incidence and antibiotic susceptibility profiles of *P. aeruginosa* isolates.

2. Investigations the occurrence of multi-drug resistant, especially in carbapenems resistance isolates.

METHODOLOGY:

The study was performed at within the three of the biggest hospitals in Najaf city / Iraq, between August till the end of October, 2013.The clinical samples were only considered in the present study. Additionally, only one positive culture per a patient was included, while infections caused by more than one organism, isolates of *P.aeruginosa* was discriminate by use selective media. preliminary identification of *P. aeruginosa* using colony structure and colony morphology, gram stain, oxidase positive reaction, typical smell, and development of pyocyanin pigments. All bacterial isolates were cultured selectively using cetrimide medium. Isolate confirmations were conducted using conventional biochemical tests. Then confirmed by Automated Microbiology System VITEK-2 compact system, which is designed for the rapid identification (ID) by GN-ID cards, and then the isolates were stored at –20°C in glycerol nutrient broth.

Antibiogram testing was performed with the automated VITEK-2 compact system based on Minimum Inhibitory Concentration (MIC) technique purpose using AST-N222 cards, according to Clinical and Laboratory Standards Institute (CLSI) guidelines[(11)],susceptibility of the bacterial isolates were performed against 16 different antibiotics belonged to nine classes (antipseudomonal penicillins, β-lactam/β-lactamase inhibitors, cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, lipopeptides, tetracyclines and folate pathway inhibitors). *E. coli* ATCC 25922 was used as a quality control to ensure the accuracy of the antimicrobial susceptibility results.

RESULTS: A total of 996 clinical samples were obtained during the study period. According to source of infection , The samples were isolated from 496(49.8%) patients with urinary tract

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infection, 107(10.7%) burn wound infection, 43(4.3%) ear infection, 21(2.1%) respiratory tract infections, 60(6%) genital tract infection, 157(15.8%) septicemia , 21(2.1%) patients with gastrointestinal tract infection and 91(9.1%) patients with other body fluids infection(Figure 1).

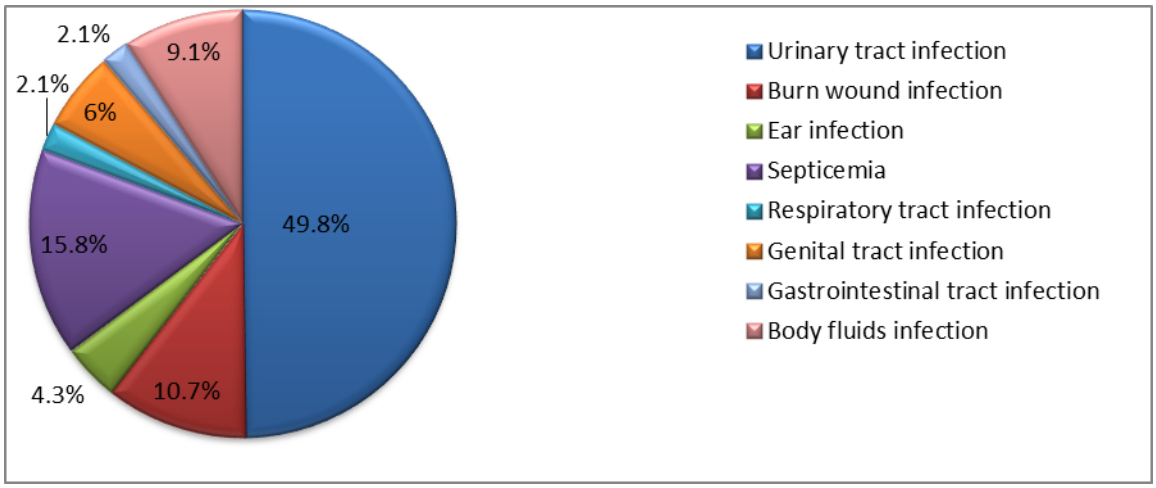

Figure (1): Distribution of clinical samples (n=996).

Table (1): Percentage of *P. aeruginosa* isolates according to source of isolation and gender

Source of sample	No. (%) of *P. aeruginosa* isolates	Gender	
		Male	Female
Urine n=496	10 (2.0)	3	7
Burn wound n=107	20 (18.7)	16	4
Ear n=43	17 (39.5)	9	8
Sputum n=21	0 (0)	0	0
Genital tract n=60	1 (1.7)	0	1
Blood n=157	2 (1.3)	2	0
Stool n=21	0 (0)	0	0
Body fluids n=91	2 (2.2)	0	2
Total n=996	52 (5.2)	30	22

This table shows, out of 479 samples contained Gram-negative aerobic rods. The result showed that 52 isolates were identified as *P. aeruginosa* at percentage (5.2%). Out of the total 52 isolates were identified as *P. aeruginosa* from patients suffering from different infections, 30(57.7%) were males and 22 (42.3%) were females.

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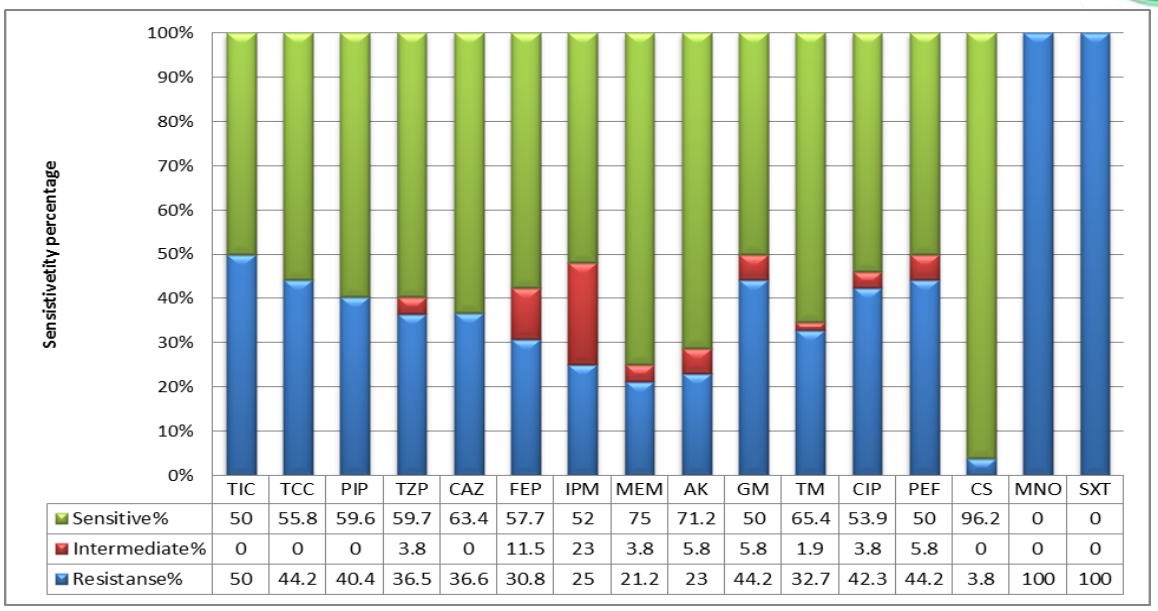

	TIC	TCC	PIP	TZP	CAZ	FEP	IPM	MEM	AK	GM	TM	CIP	PEF	CS	MNO	SXT
Sensitive%	50	55.8	59.6	59.7	63.4	57.7	52	75	71.2	50	65.4	53.9	50	96.2	0	0
Intermediate%	0	0	0	3.8	0	11.5	23	3.8	5.8	5.8	1.9	3.8	5.8	0	0	0
Resistanse%	50	44.2	40.4	36.5	36.6	30.8	25	21.2	23	44.2	32.7	42.3	44.2	3.8	100	100

Figure (2): Antibiogram testing of *P. aeruginosa* isolates with the automated VITEK-2 compact system by using AST-N222 cards(n=16). TIC, Ticarcillin; TCC, Ticarcillin-clavulanic acid; PIP, Piperacillin; TZP, Piperacillin-tazobactam; CAZ, Ceftazidime FEP, Cefepime; IPM, Imipenem; MEM, Meropenem; AN, Amikacin; GN, Gentamicin; TM, Tobramycin; CIP, Ciprofloxacin; PEF, Pefloxacin; CS, Colistin; MNO, Minocycline and SXT, Trimethoprim/sulfamethoxazole.

The interpretations results as shown in this figure revealed that varied in their resistance and sensitivity to the antibiotics. It was recorded that 50% and 40.4% resistant of isolates to ticarcillin and piperacillin (penicillins) respectively. The resistance to β-lactam/β-lactamase inhibitor combinations was appeared in 44.2% resistant to ticarcillin-clavulanic acid and 36.5% isolates were resistant to piperacillin-tazobactam. The rates of resistance to the third generation cephalosporins were found that 36.6% resistant to ceftazidime. Additionally, 30.8% of the isolates exhibited resistance to the fourth generation cephalosporin, cefepime. It was found that 23%, 44.2% and 32.7 % of the isolates were resistant to amikacin, gentamicin and tobramycin, respectively. According to the results of the fluoroquinolones susceptibility testing, 42.3% and 44.2% of the isolates were resistant to ciprofloxacin and pefloxacin, respectively. Relatively, the rate of resistance will initiated lowest to carbapenems group which represented by imipenem and meropenem (were the most effective β-lactam antibiotics); the resistance was appeared 25% to imipenem and 21.2% isolates were resistant to meropenem. The lowest rate of resistance was appeared for colistin 3.8%.While the highest resistance rate was found 100% against minocycline and trimethoprim/sulfamethoxazole.

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Table (2): The incidence of MDR, XDR and PDR among *P. aeruginosa* isolates

Type of resistance	No. of isolates	No. of resistance to antibiotic classes (n=9)	Isolate code No.
MDR (n=15, 28.8%)	**4**	**3**	**5, 11, 30, 48**
	3	**4**	**8, 15, 42**
	6	**5**	**3, 6, 20, 31, 38, 51**
	2	**6**	**2, 32**
XDR (n=18, 34.6%)	**11**	**7**	**1, 13, 14, 17, 19, 37, 40, 46, 47, 50, 52**
	7	**8**	**10, 12, 24, 18, 23, 29, 49**
PDR (n=0, 0%)	0	0	ND*

*ND=Not Detected

This table shows the prevalence of multi-drug resistance (MDR), extensive drug resistance (XDR) and pan-drug resistant (PDR) was examined among 52 *P. aeruginosa* of isolates. MDR isolates were explained as developed non-susceptibility to at least one agent in three or more antimicrobial classes, XDR was described as non-susceptibility to at least one agent in all but two or fewer antimicrobial classes (i.e. bacterial isolates remain susceptible to only one or two classes) and PDR when isolates non-susceptible to all agents in all antimicrobial classes tested. The results of the study revealed that *P. aeruginosa* isolates were resistant to most antibiotics and considered to be multi-drug resistance (33/52, 63.5%) , (15/52, 28.8%) isolates were (MDR) is resisting to antimicrobial from at least three of the nine-antipseudomonal classes tested in this study, (18/52, 34.6%) were found to be (XDR) these isolates remain susceptible to only one or two classes and (PDR) was not detected among isolates tested.

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Table (3): Percentage rates of resistance to antibiotics of *P.aeruginosa* isolates according to the site of infection

Antibiotic	Site of infection		
	Burn wound swab (n=20)	Ear swab (n=17)	Urine (n=10)
Ticarcillin	18(90%)	4(23.5%)	4(40%)
Pipracillin	18(90%)	2(11.7%)	1(10%)
Ticarcillin+ Clavulanic Acid	17(85%)	2(11.7%)	4(40%)
Pipracillin+ Tazobactam	16(80%)	2(11.7%)	1(10%)
Ceftazidim	15(75%)	3(17.6%)	1(10%)
Cefepime	14(70%)	1(5.8%)	1(10%)
Imipenem	13(65%)	0(0%)	0(0%)
Meropenem	11(55%)	0(0%)	0(0%)
Amikacin	11(55%)	1(5.8%)	0(0%)
Gentamicin	17(85%)	5(29.4%)	1(10%)
Tobramycin	15(75%)	2(11.7%)	0(0%)
Ciprofloxacin	12(60%)	8(47%)	2(20%)
Pefloxacin	12(60%)	9(52.9%)	2(20%)
colistin	0(0%)	1(5.8%)	1(10%)
monocyclin	20(100%)	20(100%)	20(100%)
trimethoprim+ sulfamthoxazole	20(100%)	20(100%)	20(100%)

This table revealed that the 95% burn wound isolates of *P. aeruginosa* high resistance rates and were measured Multi Drug Resistant *Pseudomonas aeruginosa* (MDRPa) if they showed resistance to the three or more categories of antipseudomonal agents except one isolate resistance only to two categories of antipseudomonal agents. Consequently 20 burns wound isolates were found the pattern of resistance revealed that the highest resistance was 100% for minocycline and trimethoprim/sulfamethoxazole, 90% ticarcillin and pipracillin, 85% ticarcillin+clavulanic acid and gentamicin, 80% pipracillin+tazobactam, 75% ceftazidime and tobramycin, 70% cefepime, 65% imipenem, 60% ciprofloxacin and pefloxacin, 55% amikacin, but all burn wound isolates sensitive to colistin.

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Table (4): Incidence of MDR, XDR and PDR among *P. aeruginosa* Carbapenem-resistant isolates

	Carbapenem-resistant isolates of *P. aeruginosa* (n=13)		
Type of resistance	**MDR (n=1)**	**XDR (n=12)**	
resistant classes	**5**	**7**	**8**
Isolate code No.	51	37, 40, 46, 47, 50	10, 12, 24, 18, 23, 29, 49
%	7.7	92.3	

All 13 carbapenem-resistant *P. aeruginosa* isolates were detected as multi-drug resistance 13/52(25%), the incidence of (MDR), (XDR) and (PDR) was examined among isolates of 13 carbapenem-resistant *P. aeruginosa* showed the most common isolates are (XDR) 92.3%, (5/13) involved resistant to 7 agents while (3/13) were resist to 8 agents and only 7.7% (1/13) carbapenem-resistant *P. aeruginosa* showed (MDR). While PDR pattern was not detected among isolates tested.

DISCUSSION:

During the study period, the incidence rate of *P. aeruginosa* among the examined samples was accounted 5.2%.This incidence is moderate compared with other data from around the world disclosed by the SENTRY antimicrobial resistance surveillance program such as United States, 10.1%, Brazil 14.6%, Canada 8.6%, Europe 9.3% [12] and Taiwan 11.4% [13]. In reports of national surveys of dissemination of nosocomial infections, *P. aeruginosa* implications were 30.5% [14], 26.1% [15], 18.8% [16] in Najaf, 28.2% in Al-Diwaniya [17], 13.2% in Hilla [18] and 18.3% in Al-Nsseryia [19]. This variation could be related to the type of samples, infection control practices, and intensive use of antibiotics.

In the present study highest rate 39.5% of isolates were recovered from patients with ear infections. This finding is similar to several other national studies [20, 21]. Additionally, this organism is one of the most important causes of infection in burn patients worldwide. The second highest isolation rate from patient samples in this investigation was from burn exudate 18.7%. Previous studies performed in hospitals in various cities of Iraq, demonstrated high rates of *P. aeruginosa* isolated from burn infections [22, 23]. This may be attributed to inappropriate infection control measures to burn patients in Iraqi hospitals.

Beta-lactam antibiotics are the largest and most common used group of antimicrobial agents world-wide. Present study showed that the moderate resistant 36.5%-50% to piperacillin-tazobactam, piperacillin, ticarcillin-clavulanic acid and ticarcillin. Resistance to β-lactams and β-lactam inhibitor antibiotics may be due to excessive β-lactamase production and/or active efflux mechanism [24]. Another interesting finding is the moderate resistance rates with ceftazidime 36.6% and cefepime 30.8%. This trend has also been reported in Al-Nasseryia

hospitals [19]. Carbepenems (Imipenem, Meropenem) are useful in treatment of some cases of multi-drug resistant strains of *P. aeruginosa* [25]. In this study, notable resistance to *P. aeruginosa* was observed against imipenem 25% and meropenem 21.2%. Previously, resistance to imipenem has been reported in Najaf varied from 7.4% to 16.9% [14, 16]. Numerous reports on the carbapenem resistance Gram-negative isolates in Najaf hospitals, which have been related with aspects such as the presence of MBL, KPC, and class D carbapenemases [26], probably due to differences in intrinsic activity (efficiency of binding to the essential penicillin binding proteins (PBPs))[27] and/or susceptibility to intrinsic and mutational resistance mechanisms [28] .Therefore, use of carbapenems should be restricted in order to avoid the emergence of extremely drug resistance isolates. The highest sensitivity of *P. aeruginosa* was found to Colistin, this might be due to the less frequent use of this drug in the general practice because of the un sustained availability in hospitals and local markets[29, 30]. In this study, antibiotic susceptibility pattern revealed that 63.5% of the isolates were resistant to ≥1 agent in ≥3 antimicrobial classes. Though, the incidence of MDR and XDR *P. aeruginosa* isolates were 28.8% and 34.6%, respectively, which is was correlated well with the previous study which was performed in Najaf hospitals[16] who found that the incidence of multi-drug resistant 64.2% in *P. aeruginosa* isolates.

CONCLUSIONS:

the currently available carbapenems in Najaf (imipenem and meropenem) are still the first line agents for combating infections due to antibiotic-resistant *P. aeruginosa*. As our study showed, *P. aeruginosa* isolates were increase resistant to carbapenems, this just confirms the importance of this problem during the treatment of serious infections with multidrug-resistant *P. aeruginosa.*

RECOMMENDATIONS:

we need a deep understanding of the ever-changing epidemiology and impact of *P. aeruginosa* carbapenem resistance mechanisms is crucial, along with pharmacokinetic/pharmacodynamic (PK/PD) modelling, to optimize antimicrobial therapy in order to prevent and combat infections by multidrug-resistant (MDR) *P. aeruginosa.*

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