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Plasmid Mediated Quinolone Resistance Determinants among Nosocomial Clinical *Pseudomonas aeruginosa* Isolates

Mohammed A. Saleh[1*] and Mohammed M. Balboula[2]

[1]Department of Microbiology and Immunology, Faculty of Medicine, Al-Azhar University, New Damietta, Egypt
[2]Department of General Surgery, Faculty of Medicine, Al-Azhar University, New Damietta, Egypt
**Corresponding author*

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A B S T R A C T

Quinolones are among the most commonly utilized antimicrobials for treatment of infections caused by *P. aeruginosa*. Plasmid mediated quinolone resistance (PMQR) is an expanding clinical concern worldwide with fluctuating prevalence rates. Spread of PMQR determinants along with other resistance mechanisms to *P. aeruginosa* clinical isolates would constrain the adequacy of quinolones in treatment of *Pseudomonas* infections. This study was designed to investigate the incidence of PMQR determinants among nosocomial *P. aeruginosa* isolates. A total of 110 clinical *P. aeruginosa* were collected over a period from January 2012 to October 2015frominpatients in Al-Azhar University Hospital, New Damietta, Egypt. Testing of isolates for resistance to four quinolones was performed using Kirby-Bauer disc diffusion method. Multiplex PCR was carried out for screening of the eight PMQR genes(*qnr*genes *(A,B,C,D,S), aac(6´)-Ib-cr, qepA and oqxAB*).Out of the 110 *P. aeruginosa* isolates tested, 47(42.7%)isolates were sensitive to the 4 tested quinolones while 63(57.3%) were resistant to one or more of them. Testing of isolates for PMQR genes showed that 5(4.5%) harbored *qnr* genes, 2(1.8%) were *qnr B* positive and 3(2.7%) were *qnr S* positive. Isolates were negative for the other tested PMQR genes. Generally, there is no statistically significant association between quinolone resistance and the presence of PMQR genes. This study highlighted diverse PMQR genes and their prevalence among *P. aeruginosa* isolates. The complex epidemiology of PMQR strains needs to be further studied in order to design measures to control their spread.

Introduction

Pseudomonas aeruginosa (P. aeruginosa) is a Gram-negative bacterium that inhabits a wide scope of environmental and pathogenic habitats. It has the capacity to cause extremely different acute and chronic infections (Hancock, 1998). It has been involved in diverse nosocomial infections including, pneumonia, blood stream infection, urinary tract infection, surgical site infection and burn wounds infection infection (Anuradha *et al.*, 2014). It is accountable for about 10 – 20 % of nosocomial infections (Carmeli *et al.*, 2002).

Quinolones are broad-spectrum antimicrobial agents that are widely utilized in both medical

and veterinary practice. They are the most effective antibiotics for oral treatment of *P. aeruginosa* infections in most countries (AL-Marjani, 2014).

However, the efficacy and resulting widespread use of quinolones have prompted a consistent worldwide increase in resistance (Guan *et al.,* 2013). Antibiotic resistance is a significant and mounting hurdle to the treatment and management of microbial disease (Wong and Kassen, 2011). The subsequent increase in quinolone resistance is currently undermining the clinical utility for various infections (Kim and Hooper, 2014).In particular, resistant *P. aeruginosa* infections are associated with adverse outcomes such as high mortality, morbidity, and expanded costs (Nathwani*et al.,* 2014).

Quinolones act by inhibiting the bacterial enzymes DNA gyrase and topoisomerase IV. Such formation of drug-enzyme-DNA complexes blocks DNA replication. Bacterial resistance to quinolones mainly is chromosomal-mediated including, mutations in the quinolone resistance determining regions (QRDRs) of DNA gyrase and topoisomerase IV, efflux pumps enhancement or decreased accumulation as a result of decreased permeability of bacterial cell wall (Azadpour *et al.,* 2014).

Multiple studies demonstrated that quinolone resistance can be also intervened by plasmid-carried genes. In 1998, plasmid mediated quinolone resistance (PMQR) was initially reported in a *Klebsiella pneumonia* in clinical isolates (Hooper, 1998). From that point forward, the causal mechanisms of resistance have been illustrated. Three mechanisms of PMQR were identified which are mediated by *qnr* genes (coding Qnr proteins*), aac(6´)-Ib-cr, qepA and oqxAB* genes (Kulková *et al.,* 2014).

Martínez-Martínez and colleagues reported the first PMQR mechanism which is mediated by *qnr* genes in 1998 (Martínez-Martínez *et al.,* 1998). So far, five *qnr* genes were recognized (*qnr A, B, S, C and D*) which encode Qnr proteins that inhibit quinolones binding to their bacterial targets (Kulková *et al.,* 2014, Azadpour *et al*., 2014, Alheib *et al.,* 2015). These *qnr* genes best owa low resistance level to quinolones, however, it supportsthe selection of chromosomal mutations resulting in resistance development in the host strain (Martinez *et al.,* 1998).

The second PMQR mechanism was distinguished in 2006, which is interceded by *aac(6´)-Ib-cr*gene that encodesamino glycoside acetyltransferase which acetylate aminoglycosides as well asciprofloxacin and norfloxacin (Robicsek *et al.,* 2006). Nevertheless, *aac(6´)-Ib-cr* contributes just to small increase in MIC levels (Poirel*et al.,* 2012).

The third PMQR mechanism, the active efflux, is intervened by two genes that encode quinolone transporters QepA and OqxAB which pump the drug out of the bacterial cell (Hansen *et al.,* 2007 and Yamane *et al.,* 2007).

Recently, a multiplex PCR assay for eight PMQR genes has been achieved (Ciesielczuk *et al.,* 2013).

PMQR determinants have been distinguished globally in many Gram-negative bacteria particularly Enterobacteriaceae family with variable frequency but they have not been examined in *P. aeruginosa* isolates except in small number of studies. As PMQR determinants are not taken into account in resistance screening by microbiological laboratories, this study was aimed to assess the prevalence of the eight genes (*qnr A, B, S, C, D,aac(6´)-Ib-cr , qepA and oqxAB*) that

confer PMQR among nosocomial *P. aeruginosa* isolates obtained from clinical samples collected from patients admitted to Al-Azhar University Hospital, New Damietta, Egypt.

Methods

Study design and participants

This prospective study was carried out over a period from January2012 to October 2015. It included 110 *P. aeruginosa* isolates recovered from 675 different clinical specimens collected from inpatients admitted to Al-Azhar University Hospital, New Damietta, Egypt and showing symptoms and signs of nosocomial infections in various body sites.

Collection of samples and microbiological examination

Different clinical samples were collected from nosocomially-infected patients and cultured on cetrimide and MacConky agar (Oxoid, England). Identification of *P. aeruginosa* isolates was carried out according to the standard microbiological methods including, colonial morphology, Gram stain, biochemical reactions and ability of growth at 42ºC (Koneman *et al.*, 2006).

Antibiotic susceptibility testing

To identify quinolone resistance among *P. aeruginosa* isolates, Kirby-Bauer disc diffusion technique was carried out on Muller-Hinton agar (Oxoid, England) according to Clinical Laboratory Standard Institute (CLSI) guidelines, 2012 using commercially available discs including, ciprofloxacin (5 µg), Ofloxacin (5 µg), norfloxacin (10 µg), and levofloxacin (5 µg) discs (Oxoid, England). Isolates which showed intermediate susceptibility were considered as resistant.

Multiplex PCR for PMQR determinants genes detection

DNA preparation was performed through a boiling technique. Freshly obtained *P. aeruginosa* colonies were transferred in 500 µl sterile distilled water and incubated at 100°C for 20 minutes. Then, the bacterial solution was centrifuged at 15000 g for 20 min in order to obtain a supernatant that was subsequently used as template DNA (Azadpour *et al.*, 2014). PCR for the eight PMQR genes was performed using the Multiplex PCR kit (Qiagen, Germany). PMQR primers and thermocycling conditions used were designed as described previously by Ciesielczuk *et al.*, 2013. Primers used are listed in Table 1. Thermocycling conditions were as follow: initial denaturation at 95 ºC for 15 minutes; 30 cycles of 94 ºC for 30 seconds, 63 ºC for 90 seconds and 72 ºC for 90 seconds; followed by a final extension at 72ºC for 10 min. Amplification products were detected by gel electrophoresison2 %, ethidium bromide stained agarose gels at 130 V for 2 h against 100 bp ladder DNA marker.

Statistical analysis

Ranges and percentages were used as descriptive statistics. Chi-square analysis was employed to validate correlation between PMQR determinants and resistance to quinolones. All statistical analyses were performed using Statistical Package for Social Science program (SPSS version 15.0 for windows, Chicago, IL). $P< 0.05$ was considered statistically significant.

Ethical approval

The study protocol was reviewed and approved by the local ethical committee of Faculty of Medicine, Al-Azhar University, New Damietta, Egypt.

Results and Discussion

This study included 110 *P. aeruginosa* isolates (16.2%) recovered from 675nosocomial clinical samples collected from various body sites. The distribution of *P. aeruginosa* isolates in relation to type of clinical sample are shown in Table 2. The highest rate of isolation was from endotracheal tube secretions (ETT)(24.3%) and the least from urine samples (13.4%). Out of the 110 *P. aeruginosa* isolates, 47 (42.7%) were sensitive to the four tested quinolones while 63 (57.2%) were resistant to one or more of them. Considering isolates which showed intermediate susceptibility as resistant, the results of quinolone susceptibility testing showed that the resistance rates against tested quinolones varied from16.3% to35.4% as demonstrated in Table3.

Screening of the tested *P. aeruginosa* isolates for PMQR genes revealed that 5(4.5%) were harboring *qnr* genes; 2(1.8%) were *qnrB* positive and 3(2.7 %) were *qnr S*positive (Table 4). One *qnrB* positive isolate (2.1%)was from the 47 quinolone- sensitive isolates while the other 4*qnr*positiveisolates (6.3%)were among the 63 quinolone-resistant isolates.

Interestingly, there is no statistically significant association between the presence of *qnr* genes and quinolone resistance (X^2 = 0.97, P value =0.32).Neither other *qnr* genes, *aac(6´)-Ib-cr* , *qepA nor oqxAB* gene was detected in our study isolates.

Currently, *P. aeruginosa* is not only one of the most frequent nosocomial pathogens and but also represent a challenge to treatment due to its antibiotic resistance (Daini and Charles-Onyeaghala, 2012). This study showed that nosocomial *P. aeruginosa* clinical isolates was recovered from tested clinical specimens at a rate of16.2 %. This is in agreement with Gad *et al.,* 2007 and Mahmoud *et al.,* 2013 who reported rate of 18% and 19% respectively.

The highest isolation rate of *P. aeruginosa* was encountered from ETT secretions (24.3%). Similarly, Khosravi *et al.,* 2012reported *P. aeruginosa* as the second most prevalent organism isolated from ETT secretions. However, other studies isolated the highest number of *P. aeruginosa* infection from pus samples (Anuradha *et al.,* 2014) and urine (Bashir *et al.,* 2011).

Evaluation of the efficacy of the quinolones used in this study against *P. aeruginosa* clinical isolates revealed that more than half of the isolates (57.2%) were resistant to one or more of the tested antibiotics. This signifies a real warning in light of the fact that widespread, irrational and inappropriate administration of antibioticis responsible for resistance.

In our investigation, the most effective drug against *P. Aeruginosa* was Levofloxacin followed by Ofloxacin then Ciprofloxacin and lastly Norfloxacin with resistance rates 18%, 25%, 28% and 40 % respectively. These data are coordinated with that that of Akingbade *et al.,* 2012 which indicated that Levofloxacin was the most potent quinolone used against *P. aeruginosa*. Ofloxacin, however, was the best quinolone, according to Nwanze *et al.,* 2007, while Idu and Odjiimogho, 2003 found that Ciprofloxacin is the most efficient one. These disparities in sensitivity pattern could be attributed to that provincial differences that possibly play a role in the resistance profile of bacteria and further supports the necessity to regularly perform antibiotic susceptibility testing on bacterial isolates from various locales. In spite of the fact that PMQR determinants have been investigated in many countries around the world, there is only a small number of reports on frequency of

PMQR determinants among *P. Aeruginosa* isolates. To our best knowledge, this is the first study to evaluate the eight PMQR genes together among nosocomial *P. aeruginosa* isolates obtained from different clinical samples.

Screening of the eight PMQR genes in this work, revealed that *qnr B and qnr S* genes were infrequently detected in only 2 (1.8%) and 3 (2.7%) of the tested isolates respectively.

Table.1 Primers for amplification of PMQR molecular determinants

PMQR gene	Primersequence 5′ to3′	size of amplicon (bp)
qnrA	F: 5′- CAGCAAGAGGATTTCTCACG-3′ R:5′- AATCCGGCAGCACTATTACTC-3′	630
qnrB (degenerate)	F:5-′ GGCTGTCAGTTCTATGATCG-3′ R:5′- GAGCAACGATGCCTGGTAG-3′	488
qnrS	F: 5′- GCAAGTTCATTGAACAGGGT-3′ R:5′- TCTAAACCGTCGAGTTCGGCG-3′	428
oqxAB	F: 5′- CCGCACCGATAAATTAGTCC-3′ R:5′- GGCGAGGTTTTGATAGTGGA-3′	313
aac(69)-Ib-cr	F: 5′- TTGGAAGCGGGGACGGAM-3′ R:5′- ACACGGCTGGACCATA-3′	260
qepA	F: 5′- GCAGGTCCAGCAGCGGGTAG-3′ R:5′- CTTCCTGCCCGAGTATCGTG-3′	218
qnrC	F: 5′- GCAGAATTCAGGGGTGTGAT-3′ R:5′- AACTGCTCCAAAAGCTGCTC-3′	118
qnr D	F: 5′- CGAGATCAATTTACGGGGAATA-3′ R:5′- AACAAGCTGAAGCGCCTG-3′	581

Abbreviations:bp: base-pairs;

Table.2 Distribution of *P.aeruginosa* isolates in relation to type of clinical sample

Clinical samples		***P. aeruginosa* isolates**	
Type	No.	No.	%
Wound swab	175	39	22.2
Urine	171	23	13.4
Blood	108	17	15.7
Sputum	107	21	14.6
Endotracheal tube secretions(ETT)	41	10	24.3
Pleural fluid	10	0	0
Stool	31	0	0
Ascitic fluid	32	0	0
Total	675	110	16.2

Table.3 Quinolone resistance among *P.aeruginosa* isolates

Quinolone	Resistant isolates		Intermediately susceptible isolates		Susceptible isolates	
	No	%	No	%	No	%
Norfloxacin	37	33.6	3	2.7	70	63.7
Ciprofloxacin	26	23.6	2	1.8	82	74.6
Ofloxacin	24	21.8	1	0.9	85	77.3
Levfloxacin	16	14.5	2	1.8	92	83.7

Table.4 Characteristics of PMQR genes positive *P.aeruginosa* isolates

Isolate No.	PMQR gene	Patient age (years)	Patient gender	Isolate source	Quinolone sensitivity			
					Norfloxacin	Ciprofloxacin	Ofloxacin	Levfloxacin
1	*qnr B*	45	Male	Wound	S	S	S	S
2	*qnr B*	33	Male	Wound	R	R	S	S
3	*qnrS*	51	Male	Wound	S	S	I	R
4	*qnrS*	30	Female	Urine	R	S	R	S
5	*qnrS*	61	Male	ETT	R	S	R	S

S: sensitive I: intermediate susceptibility R: resistant ETT: Endotracheal tube secretions

These findings were lower than the two previously conducted studies carried out by Michalska *et al.,* 2014 who reported the presence of *qnr B in 20%* of isolates recovered in Northeastern, Poland and Al-Marjani *et al.,* 2014 who detected *qnr S* in 21% of isolates in Bagdad, Iraq. Other studies failed to detect *qnr B or qnr S* genes among the examined isolates (Shin *et al.,* 2009, Xue-qing *et al.,* 2014, Cayci *et al.,* 2014).

Consequently, detection of *qnr* genes in our study might be potentially indicative of a rising pattern in the predominance rate of PMQR genes among isolates in Egypt.

Other *qnr* genes (A, C, D), *aac(6´)-Ib-cr* , *qepA and oqxAB*genes were not identified in our study, in concordance with the results verifiedin other literatures (Shin *et al.,* 2009, Jafari *et al.,* 2013, Xue-qing *et al.,* 2014, Michalska *et al.,* 2014, Cayci *et al.,* 2014, Wong *et al.,* 2015). Other investigators revealed the presence of *aac(6´)-Ib-cr* gene (Poole, 2011), *qnr A* gene (Al-Marjani, 2014) among their studied isolates.

In this analysis, quite there was no statistically significant correlation between presence of *qnr* determinants and quinolone resistance (P=0.32). Our finding concurs with other reports showing that *qnr* determinants alone does not grant resistance to quinolones, however its presence may accelerate selection of additional chromosomal mutations. Therefore, using quinolone resistance as marker for detection may under value the predominance of *qnr* determinants, which provokes concern for the undetected extent of these genes (Alheib *et al.,* 2015).

In conclusion, quinolone resistance is a public health issue, bearing in mind their widespread prevalence on one side and the extending resistance by plasmids on the other side. This investigation constitutes the first epidemiological survey of the eight PMQR determinants among *P. aeruginosa* isolates.

Emergence of *qnrB and S* genes in our study isolates may participate to development and spread of quinolone resistance, hence, judicious use of antibiotic and adjusted treatment protocols represent a necessity. These data highlight the obligation for screening of *P. aeruginosa* for PMQR determinants in hospital settings in further studies with larger number of isolates and broader geographic distribution to determine the widespread distribution of PMQR determinants and estimate the extent of the problem.

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