Vol. 29, No. 2, 2025, Pages 44-51

Thi-Qar Medical Journal (TQMJ)

Thi-Qar Medical Journal was established in 2006 and is published by the College of Medicine, University of Thi-Qar, Iraq

ISSN (PRINT): 1992-9218 | ISSN (ONLINE): 3006-4791

www.jmed.utq.edu.iq utjmed@utq.edu.iq

Prevalence of the Carbapenem and Fluoroquinolone Resistance Gene among K. pneumoniae Isolated from Genitourinary Tract Infections in Infertile Males.

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Received: 4.4.2025
Revised: 23.5.2025
Accepted: 1.6.2025
DOI:
10.32792/jmed.2025.29.22

Keywords:
Carbapenem Resistance
fluoroquinolone resistance
MDR K. pneumoniae
genitourinary tract infections

How to cite

Rasha Mohsen AL-Hussaini[1], Ibtisam Habeeb Al-Azawi[2]. Prevalence of the Carbapenem and Fluoroquinolone Resistance Gene among K. pneumoniae Isolated from Genitourinary Tract Infections in Infertile Males. *Thi-Qar Medical Journal (TQMJ)*. 2025;Volume(29):44-51.

Abstract

One of the most significant opportunistic Gram-negative bacteria that frequently linked to catheter associated and urinary tract infection is *Klebsiella pneumoniae*. Their ability to produce biofilms and antibiotic resistance are the two main factors that contribute to the persistent infections. The dissemination of carbapenems and fluoroquinolones resistance offers a significant confrontation to the treatment of life-threatening infections produced by *K. pneumoniae*. The study aimed to investigation the prevalence of the carbapenems and fluoroquinolones resistance genes (bla_{OXA-48}, and *qnrS*) in *K. pneumoniae*. From December 2023 until July 2024, a total of 200 samples were collected in this study including urine (n=100, 50%), and semen (n=100, 50%) from admitted patients to Fertility Center and outpatient from Private Labs in Al-Najaf, Al-Diwaniyah and Karbala governorates. Semen culture and urine culture were done for all the patients. Using Vitek2 compact system to identification and susceptibility to antibiotic profiling of K. pneumoniae. PCR experiment were performed on the isolates with specific primers to bla_{OXA-48}, and *qnrS*. The results showed the recovery rate of K. *pneumoniae* isolates was (n= 17, 8.5%) from the clinical samples, divided as follow 13 isolates from urine and four isolates from semen, The prevalence of carbapenem resistance gene among *K. pneumoniae* isolates was to bla_{OXA-48} gene (64.7%), While fluroquinolones resistance gene *qnrS* was (94%). The study concluded increased carbapenem and fluoroquinolone resistance gene in Al-Najaf, Al-Diwaniyah and Karbala governorates highlights the importance of this problem while managing life-threatening multidrug-resistant *K. pneumoniae* infections.

1.1. Introduction

Carbapenems resistance may be attributed to carbapenemase synthesis, porin loss, and efflux pump overexpression. *Klebsiella pneumoniae* has acquired the genes that encode for carbapenemase, an enzyme that can be degrade most B-lactam antibiotics, including carbapenems, and in this way confers resistance to these antibiotics resulting in failure of treatment (1). Carbapenemase are divided into three Ambler classes: A, B and D. The most well-known class A carbapenemase is *K. pneumoniae* carbapenemase (*KPC*), class B carbapenemase is most often found as New Delhi metalo B-lactamase (*NDM*), and the most widely recognized class D carbapenemase is Oxacillinase-48 (*OXA-48*), which is seen in *K. pneumoniae* (2). As a result, the intense use of carbapenems has been joined by the emergence and dissemination of carbapenem-resistant *K. pneumoniae* (3).

Quinolones block DNA topoisomerase II and IV, which are crucial for the replication of bacteria. The A subunit of DNA topoisomerase II is the primary target of quinolones in Gram-negative bacteria, but DNA topoisomerase IV is inhibited in Gram-positive bacteria (4). One common fluoroquinolone used to treat bacterial infections is ciprofloxacin (5). Because fluoroquinolones have a broad spectrum of activity and are therefore often used to treat infectious diseases, the establishment of resistance to these drugs is occur very quickly (6).

The most significant human microbe in the genus *Klebsiella* is *K. pneumoniae*, which causes variety of infections in hospitals, long-term care facilities, and communities around the globe. These infections include urinary tract infection, abdomen, lungs, soft tissues, surgical sites, and even bacteremia (7). *Klebsiella pneumoniae* exhibit antibacterial agent resistance by at least one of the subsequent mechanisms: development of specific enzymes "such as β-lactamases or aminoglycoside modifying enzymes" (8), decreased cell permeability du*e to loss of outer membrane proteins (OMPs) (9), efflux pump overexpression "which are transmembrane proteins, with the antimicrobial agent being usually excreted out of the bacterial cell through an energy-consuming process". For instance, an efflux pump called KpnGH contribute to antimicrobial resistance in *K. pneumoniae* (10) and finally modification or change the antimicrobial agent's target (11).

The sensitivity and resistance patterns to antibiotics differ between communities and hospitals. Patterns of antibiotic sensitivity and resistance at the community and hospital levels differ significantly. There are two potential reasons for the observed variation in drug resistance patterns: the emergence of microorganism resistant to antibiotics and the misuse of antimicrobials (12).

Infertility, a condition being not quite the same as different existing wellbeing associated issues, in including social and psychological aspects, influences 10-15% of couplers in the reproductive age group (13). Moreover, 15% of male factor infertility is contributed to infectious etiologies involving bacteria, virus, fungi and protozoa (14). *K. pneumoniae* enhanced cell necrosis, decreased progressive sperm motility, and reduced the DNA fragmentation rate in an *in vitro* investigation (15).

Adhesive fimbriae, lipopolysaccharide (LPS), capsule, and siderophores comprise the fundamental virulence factors that facilitate *K. pneumoniae* pathogenicity. Additionally, they have the ability to hydrolyze a variety of antibiotics, particularly carbapenems, which are so-called *K. pneumoniae* carbapenemase- producers. This puts weak patients at risk because of their resistance to multiple antibiotics (16) and result in an impressive medical services cost (17). This study aimed to investigation the prevalence of the carbapenems and fluoroquinolones resistance genes (*bla*$_{OXA-48}$, and *qnrS*) in *K. pneumoniae*.

1.2. Methodology and Approaches

1.2.1. Sample collection

A total, 200 clinical samples were obtained from patients distributed as 100 urine, and 100 seminal fluids. The patients were hospitalized at Fertilization Centers and outpatient from Private Labs in Al-Najaf, Al-Hamza in Al- Diwaniyah and Karbala governorates during period from December 2023 until July 2024.

1.2.2. Isolation of *K. pneumoniae*

Under safety handling conditions, the urine samples were obtained from patients from the middle of the stream and placed in sterile screw-cap containers and seminal fluid was collected in a sterile plastic vial Then the sample was transferred directly to the laboratory and incubated at 37°C for 30 min to allow normal liquefaction (seminal fluid). All samples were streaked based on standard procedures by using differential and selective media (MacConkey, blood agar) for detection of *K. pneumoniae* and incubated at 37°C for 24 hours aerobically (18). Confirmative diagnosis of isolates was achieved using conventional biochemical tests and confirmed by the Viteck2 compact system (Biomerieux, France).

1.2.3. Antibiotic susceptibility test

Klebsiella pneumoniae isolates were subjected to antibiotics susceptibility test by Vitek2 compact system (Biomerieux, France). All isolates were examined against 16 antibiotic agents related to 8 antibiotic classes. All data were evaluated in accordance with the guidelines provided by Clinical and Laboratory Standards Institute 2021 (19), all results were interpreted and all *K. pneumoniae* isolates were classed as resistant, intermediate, or susceptible to each tested antibiotics agent.

1.2.4 Molecular study

According to the manufacturer's instructions, genomic DNA was extracted from *K. pneumoniae* isolates using the Genomic DNA Extraction Kit (FavorPrep, Austria). The Nanodrop instrument (THERMO, USA) was used to measure the concentration and purity of DNA for each isolate.

Polymerase chain reaction (PCR) was employed for screening the carbapenem and fluroquinolone resistance genes *bla*$_{OXA-48}$, and *qnrS*. In this study, all primers were provided by the Promega company, USA. Primers details are tabulated in Table 1.

Table 1: Carbapenem and fluroquinolone resistance genes of *K. pneumoniae*

N	Gene	Primer Sequence		Amplicon size (bp)	Annealing Temp./time	Reference
1	*OXA-48*	F	CTTGATCGCCCTCGATT	281	56 ºC/30 sec.	20
		R	GATTTGCTCCGTGGCCGAAA			
2	*qnrS*	F	GCAAGTTCATTGAACAGGGT	428	60 ºC/30 sec.	21
		R	GCAAGTTCATTGAACAGGGT			

1.3. Results and Conclusions

Out of 200 collected samples only 99 (49.5%) samples gave positive results for culturing, and out of 99 positive culturing samples, only 17 isolates (8.5%) were identified to be *K. pneumoniae* depending on culture characteristics and biochemical tests as in Table (2).

Table 2: *K. pneumoniae* isolates distribution based on the source of samples

Sample source	Total number	Bacterial culture results No. (%)			P-value (P ≤0.05)
		No growth	Bacterial growth		
			K. pneumoniae	Other bacteria	
Urine	100	24 (24%)	13 (13%)	63 (63%)	< 0.0001*
Seminal fluid	100	77 (77%)	4 (4%)	19 (19%)	< 0.0001*
Total	200	101 (50.5%)	17 (8.5%)	82 (41%)	< 0.0001*
P-value (P ≤0.05)		< 0.0001*	0.0872NS	< 0.0001*	
*Significant differences at (P ≤0.05) by chi Squair test. NS: non-significant					

All data were evaluated in accordance with the guidelines provided by the CLSI 2021 (19), all results were interpreted and all *K. pneumoniae* isolates were recognized as resistant, intermediate, or sensitive to each tested antibiotics agent Table (3). Among 17 *K. pnumoniae* isolates, 100% (17/17) were found to be resistant to ampicillin, followed by Cefuroxime (76.4%; 13/17), Cefuroxime Axetil (76.4%; 13/17), Ceftriaxone (64.7%; 11/17), Cefixime (64.7%; 11/17) and Ceftazidime (58.8%; 10/17).

Table 3: Antibiotics susceptibility patterns of *K. pneumoniae* isolates

Antibiotics classes	Antibiotics	Resistant (R)		Intermediate (I)		Sensitive (S)		P-value (P ≤0.05)
		Isolate No.	%	Isolate No.	%	Isolate No.	%	
B-lactam	Ampicillin	17	100%	0	0%	0	0%	------
Cephalosporins	Cefuroxime (2rd G)	13	76.4 %	0	0%	4	23.5 %	< 0.0001*
	Cefuroxime Axetil (2rd G)	13	76.4 %	0	0%	4	23.5 %	< 0.0001*
	Cefoxitin (2rd G)	7	41%	0	0%	10	58.8%	< 0.0001*
	Ceftazidime (3rd G)	10	58.8 %	1	5.8 %	6	35.2 %	< 0.0001*
	Cefixime (3rd G)	11	64.7%	0	0%	6	35.2%	< 0.0001*
	Ceftriaxone (3rd G)	11	64.7%	0	0%	6	35.2%	< 0.0001*
	Cefepime (4th G)	7	41 %	3	17.6%	7	41 %	0.0030*
Carbapenem	Ertapenem	2	11.7 %	2	11.7 %	13	76.4 %	< 0.0001*
	Meropenem	3	17.6 %	0	0 %	14	83.9 %	< 0.0001*
Quinolone	Ciprofloxacin	6	35.2 %	3	17.6 %	8	47 %	0.0010*
Aminoglycoside	Gentamicin	3	17.6 %	0	0 %	14	83.9 %	< 0.0001*
	Amikacin	2	11.7 %	0	0 %	15	88.2 %	< 0.0001*
Combination	Piperacillin/ Tazobactam	5	29.4 %	0	0 %	12	70.5 %	< 0.0001*

Folate pathway inhibitors	**Trimethoprim/ Sulfamethoxazole**	7	41 %	0	0 %	10	58.8 %	< 0.0001*
Macrolides	**Nitrofurantoin**	4	23.5%	11	64.7%	2	11.7%	< 0.0001*
P-value (P ≤0.05)		< 0.0001*		< 0.0001*		< 0.0001*		
***Significant differences under (P ≤0.05) by chi Squair test**								

According to a study, the multi-drug resistance (MDR) among *K. pneumoniae* isolates was 64.7% (n = 11/17). Furthermore, two of 17 (11.8%) isolates were recognized as XDR. Moreover, four of 17 (23.5%) of them were sensitive to most antibiotics belonging to eight categories tested in the current study (Table 4).

Table 4: The distribution of antibiotics susceptibility patterns of *K. pneumoniae* isolates from urine and seminal fluid samples.

Clinical sample	Isolate No.	Antibiotics Susceptibility Patterns			P-value (P ≤0.05)
		Sensitive	MDR	XDR	
Urine	13	3 (23 %)	8 (61.5%)	2 (15.4%)	< 0.0001*
Seminal fluid	4	1 (25 %)	3 (75 %)	0 (0%)	< 0.0001*
Total	17	4 (23.5%)	11 (64.7%)	2 (11.8%)	< 0.0001*
P-value (P ≤0.05)		0.9452NS	0.4426NS	0.0009NS	
***Significant differences at (P ≤0.05) by chi Squair test. NS: non-significant**					

Carbapenem resistance gene bla_{OXA-48} gene were evaluated in all 17 *K. pneumoniae* isolates. The results revealed that 11/17 (64.7%) were positive to bla_{OXA-48} gene of *K. pneumoniae* isolates were found as shown in Figure 1 and Table 5.

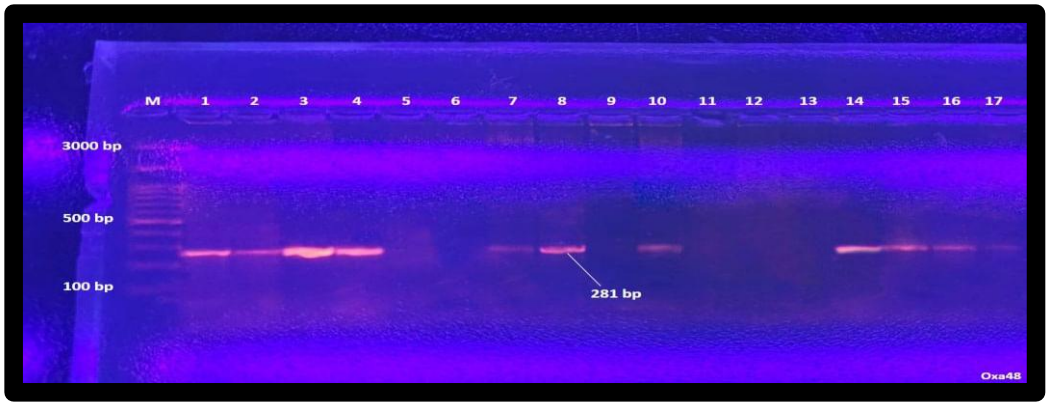

Fig.1: Agarose gel electrophoresis (1.5%) of PCR amplified of bla_{OXA-48} gene (281bp) of *Klebsiella pneumonia* for (55) minutes at (70 volt). M: ladder) DNA marker). The number of positive *K. pneumoniae* isolates were (1,2,3,4,7,8,10,14,15,16,17), whereas the number of negative isolates were (5,6,9,11,12,13).

All recovered *Klebsiella pneumoniae* were assessed for fluroquinolone resistance gene *qnrS* by PCR. The finding indicated that 16/17 (94%) were positive to *qnrS* gene of *K. pneumoniae* isolates were found as shown in Figure 2 and Table 5.

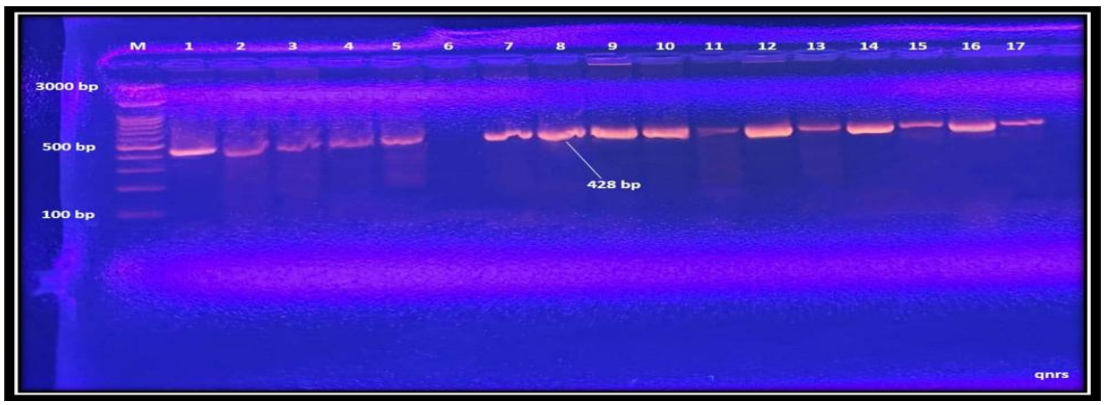

Fig. 2: Agarose gel electrophoresis (1.5%) of PCR amplified of *qnrS* gene (428bp) of *Klebsiella pneumonia* for (55) minutes at (70 volt) M: ladder (DNA marker). Number of positive *K. pneumoniae* isolates were (1,2,3,4,5,7,8,9,10,11,12,13,14,15,16,17) and only number (6) was negative.

Table 5: Distribution of carbapenem and fluroquinolone resistance genes among *K. pneumoniae* isolates

Isolate (n=17)	Antibiotic resistance genes	
	***bla*$_{OXA-48}$**	***qnrS***
Positive	11 (64.7%)	16 (94.1%)
Negative	6 (35.3%)	1 (5.9%)
P-value (P ≤0.05)	0.0036*	< 0.0001*
***Significant differences at (P ≤0.05) by chi Squair test.**		

Discussion

The current study demonstrated that all *K. pneumoniae* isolates were resistant to ampicillin (100%), and these results agreed with study by Al-Azawi (22) in Al-Diwaniya city.

A probable explanation for the increased resistance of *K. pneumoniae* isolates to ampicillin, second and third generation of cephalosporins is through the production of extended-spectrum B-lactamase (ESBL) (23).

Antibiotic-resistant bacteria disseminate both within and between hospitals, as well as elevated levels of bacterial resistance, are frequently associated with each other (24). Moreover, a rise in the prevalence of carbapenem-resistant *Klebsiella spp.* may result from increased B-lactam/B-lactamase inhibitor consumption (25, 26).

A screening for the antibiotic susceptibility of *K. pneumoniae* isolates against sixteen widely used antibiotics revealed that 11 (64.7%) of *K. pneumoniae* isolates were multi-drug resistance (MDR), while 2 (11.8%) were extensive-drug resistance (XDR) and these finding similar to results of Al-Kamoosi and AL-Azawi (27) in Al-Najaf city.

Carbapenems, an efficient B-lactam antibiotic, are typically used as a last option to treat severe infections resulting from MDR Gram-negative bacteria, such as *K. pneumoniae* (28). The increased usage of carbapenems has led to the appearance of carbapenem-hydrolyzing B-lactamases, or carbapenemases as a prevalent mechanism of resistance (29).

The current study found a rate of carbapenem resistance in *K. pneumoniae* (Ertapenem 11.7% and Meropenem 17.6%). Similar outcomes were observed from researches done in the Model Hospital, Kathmandu (30), North India (31), and Chitwan Medical College, Chitwan (32).

In the present study, Carbapenem resistance gene *bla*$_{OXA-48}$ gene were 64.7%. The previous study, in Egypt (33) were record similar results, presence of *bla*$_{OXA-48}$ gene in *Klebsiella pneumoniae* (58.8%).

According to Moodley and Perovic's 2018 research (34) on *Enterobacteriaceae*, around 75.2% of the isolates carried one or more carbapenem-producing genes. The most common carbapenemase type was *bla*$_{OXA-48}$ and its variants (36.5%), with *K. pneumoniae* accounting for a high percentage of carbapenemase-producing isolates (52.8%).

The release of ESBL enzyme carbapenemase has led to a significant increase in bacterial resistance to antibiotics in the B-lactam group (35). Moreover, the accumulation and expression of many genes (each coding for resistance to particular drug) on resistance plasmid

(R) or elevated expression of genes encoding multidrug efflux pumps result in resistance to multiple antibiotics (36). Furthermore, the genes that encode the B-lactamase enzymes are frequently linked to drugs that are not B-lactams, such as aminoglycosides and fluoroquinolones. Thus, complicated multi-drug resistant phenotypes and even pan-resistance are caused by bacterial resistance determinants (37).

According to the current investigation, 94% of *K. pneumoniae* exhibited *qnrS* prevalence. Comparable results (38) showed a higher rate (78%). Conversely, other studies show a low *qnrS* rate, as in 16% in Japan (39) and 2% in Kenya (40).

In another study by Sani *et al.,* (41) were found among fluoroquinolones resistance genes of *K. pneumoniae*, *qnrS* gene (41.67%) was the most prevalent.

The *Enterobacteriaceae* family, which includes *K. pneumoniae*, has plasmids that resulting in widespread fluoroquinolone resistance (42). These genes include the *qnr* gene family, which physically protects DNA gyrase and topoisomerase IV from fluroquinolones inhibitory effect (43).

Conclusion

Increased carbapenem and fluoroquinolone resistance genes in Al-Najaf, Al-Diwaniyah and Karbala governorates highlights the importance of this problem while managing life-threatening multidrug-resistant *K. pneumoniae* infections.

Acknowledgments

The authors thank the microbiology laboratories of Al-Najaf, Al-Diwaniyah and Karbala for their support in sample collection and processing during the study.

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