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ORIGINAL ARTICLE

Distribution of Quinolone Plasmid Resistance Genes in ESBL and Carbapenemase Producing *Escherichia coli* Associated with Catheter Urinary Tract Infections

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ABSTRACT

Background: *Among hospitalized cases, urinary catheter-associated urinary tract infections (CAUTIs) are important problems.* ***Objective:*** *Finding plasmid-mediated quinolone resistance (PMQR) genes in Escherichia coli (E. coli) from CAUTI cases in intensive care units that exhibit high quinolone antibiotic resistance was the aim of this investigation. Additionally, the researchers aimed to speculate as to what connection these genes have with carbapenemase and Extended-spectrum beta-lactamase resistance (ESBL) resistances.* ***Methodology:*** *Adult cases with CAUTIs hospitalized to ICUs at Mansoura University Hospital in Egypt were included in the retrospective cross-sectional investigation. All isolated E. coli were added in the research, and the ciprofloxacin-resistant organisms were chosen for additional research using multiplex polymerase chain reaction (PCR) to detect the qnr A, qnr B, and qnr S genes. Additionally, we used phenotypic analysis to discover ESBL in these organisms.* ***Results:*** *204 (24.5%) E. coli isolates from CAUI cases were found during the study period. Using the MIC technique, fifty of these isolates showed ciprofloxacin resistance. In 26 isolates (52%), the double disc technique detected ESBL, whereas in 23 isolates (46%), CDT detected carbapenemase. Multiplex PCR revealed that qnrA was the most common gene (84%), followed by qnrB (46%), and qnrS (34%). A strong correlation (P = 0.001) was found between an increase in ciprofloxacin MIC and the presence of numerous qnr genes.The qnrA (88.5%), qnrB (50%) and qnrS (26.9%) genes are present in high ESBL E. coli. Additionally, the qnrA gene (78.2%), qnrB gene (60.9%), and qnrS gene (26.7%) are present in many E. coli carbapenemase producers.* ***Conclusions:*** *The study examines the frequency of QR genes mediated by ciprofloxacin-resistant plasmids in E. coli derived from hospital-acquired CAUTI. The qnr genes were often linked to carbapenem resistance, ESBL, and other forms of antibiotic resistance.*

INTRODUCTION

One of the commonest infections linked to healthcare is UTI [1]. One prominent risk factor for UTIs related to healthcare is the installation of a urinary catheter. Urinary catheters are thought to be responsible for over 70% of these infections, and in intensive care units, the correlation rises to 90% [2]. Urinary bladder stones and severe sepsis are just two of the side effects that can arise from CAUTIs [3].

CAUTIs can be brought on by many organisms, such as fungi, bacteria, and Gram-positive and Gram-negative bacteria. The uropathogenic *E. coli* is the most common bacteria that causes CAUTs [4].

Compared to non-CAUTI bacteria, CAUTI pathogens usually exhibit greater resistance to empirical antibiotics [5]. Resistance to quinolone in One kind of antibiotic resistance that is spreading around the world is *Escherichia coli* [6].

Quinolones are antibiotics that are widely used to treat urinary tract infections. Quinolone functions by converting gyrase and topoisomerase IV into toxic enzymes that divide bacterial chromosomes [7].

Genes encoding DNA gyrase or topoisome generate chromosomal alterations that occur in the quinolone resistance-determining region (QRDR). Other forms of QR arise as a result of having plasmid-mediated transfer of PMQR. QNRS, QNRA, and QNRB include these determinants. Moreover, resistance to other antibiotic classes may arise from the coexistence of mutations in the PMQR and other resistance genes [8].

According to a previous Egyptian research, uropathogenic *E. coli* had a high number of PMQR determinants and gyrA mutations[9]. They also

discovered a connection between PMQR and *E. coli* genes that are not destroyed by carbapenemase or ESBL in certain clinical samples. Nevertheless, there is insufficient information regarding the relationship between PMQR and carbapenemase resistance and ESBL in CAUTIs in intensive care units.

Thus, the aim of the study was to identify PMQR in *E. coli* resistant to quinolone antibiotics that were isolated from cases suffering from CAUTIs in ICUs and to forecast the correlation between PMQR and carbapenemase and ESBL resistances.

METHODOLOGY

The retrospective cross-sectional study included cases of CAUTIs who were admitted to ICUs at Mansoura University Hospital in Egypt between January 2019 and January 2021.

UTIs that occur when an indwelling urinary catheter is in place for more than two calendar days on the date of the event, with day 1 being the day of device placement, and that occurs on the day of the event, or the day prior are referred to as CAUTI. If you remove an indwelling urinary catheter after more than two calendar days, the catheter-associated UTI must occur on the day of discontinuation or the day after CDC.

According to the CDC the cases who were included had to be over the age of 18, admitted to intensive care units, and experiencing hospital-derived UTIs associated with the installation of a urinary tract catheter. The broth microdilution method revealed that 50 of the 744 cases showed ciprofloxacin resistance, and in 204 of those cases, the identified bacterial pathogen was *E. coli*. Cases without CAUTIs, those with CAUTIs caused by organisms other than *E. coli*, and those with community-acquired UTIs were not included in our analysis [10]. The study received ethical approval from the Mansoura Faculty of Medicine's ethical council (R. 23.05.2182), and we also got each patient's signed agreement.

Urine sample:

After washing our hands, putting on nonsterile gloves, looking for pee in the tubing, and assessing the tubing's placement on the bed, we took a urine sample. After extracting 10–15 mL of urine using a Luer-lock syringe that we had attached to the catheter's sample port, we took the syringe out and unclamped the tubing. To preserve sterility, we inverted the sterile container on the drape and opened the lid. Without touching it, we moved the urine to the sterile container, set the syringe on the drape, securely closed the lid, and used germicidal to clean the container's outside.

Urine samples collected from catheterized cases were promptly transported to the microbiological laboratory for colony counting, urine culture, and microscopic analysis of pus cells [11]. After identifying *E. coli* using Gram staining, we performed biochemical tests using urease, lysine, phenylalanine, methyl red, the Voges Proskauer test, the indole test, triple sugar iron agar, Simon citrate, urease, and subculturing on MacConkey agar [12]. By mixing the isolate with glycerol and brain-heart infusion broth, we created a pure suspension of *E. coli*, which we subsequently stored at -20 °C for multiplex polymerase chain reaction (PCR).

We used the disc diffusion method to perform the antibiotic sensitivity test. The antibiotic discs that were utilised were ciprofloxacin (5 µg), nitrofurantoin (30 µg), imipenem (10 µg), meropenem (10 µg), cefepime (30 µg), ceftriaxone (30 µg), gentamicin (10 µg), aztreonam (30 µg), cefotaxime (30 µg), ceftazidime (30 µg), and trimethoprim/sulfamethoxazole (25 µg) (Oxoid, United Kingdom). Per the CLSI criteria, we evaluated the inhibition zone width surrounding the antibiotic discs and classified the results as either sensitive or resistant [13]. Resistance to three or more antibiotic classes is known as multidrug resistance, or multidrug-resistant (MDR).

We detect ciprofloxacin-resistant *E. coli* using the Broth Microdilution Method.

Again, we checked the ciprofloxacin-resistant *E. coli* isolates and determined the MIC using the BMD technique and CLSI criteria. The tube with the highest dilution of ciprofloxacin yielded the MBC, but it did not produce bacterial growth [13]. We calculated ciprofloxacin's MBC [13] and utilized the following concentrations to determine if anything was susceptible, intermediate, or resistant to ciprofloxacin: susceptible at MIC≤1 µg/mL, intermediate at MIC 2 µg/mL, and resistant at MIC≥4 µg/mL.

Identification of *E. coli* ESBL

Cefotaxime and ceftazidime discs as well as ceftazidime + ceftazidime/clavulanic acid discs were applied. An increase of approximately 5 mm in the growth-inhibitory zone around the clavulanic acid-containing disc was interpreted as indicative of ESBL production. We employed *E. coli* ATCC 25922 as positive control and *Klebsiella pneumoniae* ATCC 700603 as a negative control. Carbapenemase activity is measured using the CDT.

To detect carbapenemase activity in *E. coli* isolates that were not imipenem-sensitive, we employed a disc that contained both imipenem and EDTA. Per CLSI's advice, we suspended the isolates in Muller-Hinton broth to prepare and adjust them to a concentration of 0.5 McFarland. We next subculture the isolates on a Mueller-Hinton agar plate [13]. One disc had 10 µg of imipenem, and the other contained 10 µl of EDTA at a concentration of 0.5 M. The discs were spaced 20 mm from one another. Overnight incubation was applied to the plate. When the inhibition diameter increased to ≥7 mm around the imipenem with the EDTA disc, it was assumed that carbapenemase was present.

We employed multiplex polymerase chain reaction amplification to identify the genes Qnr A, B, and S.

DNA extraction

DNA was prepared quickly using the Gene JET Genomic DNA Purification Kit, catalogue number K0721 (Thermo Scientific, USA).

We added the Proteinase K enzyme to aid in the digestion of the *E. coli* isolate. To get rid of the RNA, we added RNase A reagent. To bind DNA to the silica membrane, we put the product onto the purification column after mixing it with ethanol. After cleaning the columns with a prepared washing solution to get rid of any contaminants, we eluted DNA using an elution buffer with low ionic strength.

Multiplex PCR

For the three PMQR genes (qnrA, qnrB, and qnrS), we used multiplex PCR. We conducted the primers, thermal profile, and analysis in accordance with the earlier description [14].

The extracted DNA was added to the multiplex PCR reaction mixture, which included five microlitres of extracted DNA, 35 ul of the DreamTaq Green PCR Master Mix (2x) (Thermofisher Scientific, USA), and 20 pmol of each of the six primers (1 µl). The multiplex PCR sequences were as follows: Ten minutes of denaturation at 95°C, 35 cycles of amplification—one minute at 95°C, one minute at 54°C, and one minute at 72°C—and a final extension—ten minutes at 72°C. Primers used are shown in table 1.

Following gel electrophoresis, the PCR products were analysed using a 2% agarose gel to identify the amplified product, and a standard molecular weight marker DNA ladder of 50 bps was employed for comparison.

Table 1: Primers for qnr gene PCR

Gene	Primer sequence	Size of amplified product
Qnr A genes	F: AGAGGATTTCTCACGCCAGG R: TGCCAGGCACAGATCTTGAC	580
Qnr B genes	F: GGMATHGAAATTCGCCACTG R: TTTGCYGYYCGCCAGTCGAA	264
Qnr S genes	F: GCAAGTTCATTGAACAGGGT R: TCTAAACCGTCGAGTTCGGCG	428

Data is presented as numbers. PCR: Polymerase Chain Reaction.

Statistical methods

IBM SPPS 22.0 (Statistical Package for Social Science) was used to analyse the data that was gathered (SPSS, Inc., Chicago, IL). Frequency and percentage were used to display the qualitative data. Qualitative data were compared using the chi-square test, and P was deemed significant if it was less than 0.05. A nova test was used to compare quantitative data, and P was considered significant if it was less than 0.05.

RESULTS

The isolated organisms from cases with CAUTI were *Staphylococcus aureus* 89 isolates, *Staphylococcus epidermidis* 66 isolates, *Klebsiella* spp. 65 isolates, *Candida spp.*158 isolates, *Proteus* spp. 14 isolates, *Pseudomonas aeruginosa* 74 isolates, *Citrobacter spp.* 23 isolates, *Enterococcus* spp. 51 isolates, data not shown. 204 (24.5%) isolates of *E. coli* were obtained from individuals who had CAUTIs during the study period. According to the MIC technique, fifty of these isolates exhibited ciprofloxacin resistance. High levels of resistance to cephalosporins, cefepime (94%), ceftriaxone (94%), ceftazidime (78%), and cefotaxime (76%), were found in E. coli. **Table 2** shows that this E. coli had a significant prevalence of MDR pattern (82%).

Table 2: Antibiotics resistance of E. coli

	No. (%)
Cefotaxime	38 (76%)
Aztreonam	15 (30%)
Meropenem	26 (52%)
Imipenem	24 (48%)
trimethoprim/sulfamethoxazole	23 (46%)
Amikacin	22 (44%)
Garamicin	27 (54%)
Cefepime	47 (94%)
Ceftriaxone	47 (94%)
Ceftazidime	39 (78%)
Ciprofloxacin	50 (100%)
MDR	41 (82%)

Data is presented as frequency (%). MDR: multidrug-resistant.

Table 3 shows that 26 isolates (52%) had the ESBL identified by the double disc method, while 23 isolates (46%) had carbapenemase detected by CDT.

Table 3: ESBL and carbapenemase in E. coli

Type of resistance	No of cases (%)
ESBL	26 (52%)
Carbapenemase	23 (46%)

Data is presented as frequency (%). ESBL: beta-lactamase resistance.

Table 4: Frequency of PMQR genes by multiplex PCR

PMQR gene	No. (%)
qnrA	42 (84%)
qnrB	23 (46%)
qnrS	17 (34%)

Data is presented as frequency (%).PCR: Polymerase Chain Reaction

According to **table 4**, qnrA was the most often found gene by multiplex PCR (84%), followed by qnrB (46%), and qnrS (34%).

The presence of several QNR genes was significantly correlated with a rise in the MIC of ciprofloxacin resistance in the isolated *E. coli* (P=0.001), as shown in **table 5**.

Table 5: Association number of PMQR genes and MIC of ciprofloxacin

MIC concentration	PMQR genes			P value
	Single Positive (n=28) No. %	Double positive (n=12) No. %	Triple positive (n=10) No. %	
4	2 (7.1%)	0 (0%)	0 (0%)	**0.001***
8	14 (50%)	1 (8.3%)	0 (0%)	
16	12 (42.9%)	4 (33.3%)	0 (0%)	
32	0 (0%)	6 (50%)	0 (0%)	
64	0 (0%)	1 (8.3%)	7 (70%)	
128	0 (0%)	0 (0%)	3 (30%)	
Total	28 (100%)	12 (100%)	10 (100%)	

Data is presented as frequency (%). MIC: minimum inhibitory concentration, *: significant as P value ≤ 0.05.

The qnrA gene (88.5%), qnrB gene (50%), and qnrS gene (26.9%) are all present in high ESBL *E. coli*. Nevertheless, qnrA, qnrB, and qnrS genes did not significantly correlate with ESBL (p=0.37, P=0.56, and P=0.27, respectively). Additionally, a substantial percentage of *E. coli* carbapenemase producers carry the qnrA (78.2%), qnrB (60.9%), and qnrS (26.9%) genes. **Table 6** shows that carbapenemase and the presence of the qnrA, qnrB, and qnrS genes did not significantly correlate (P=0.31, P=0.052, and P=0.91, respectively).

Table 6: Association between PMQR genes, ESBL and Carbapenemase

	ESBL (n=26)	Carbapenemase (n=23)
qnrA	23 (88.5%)	18 (78.2%)
P	0.37	0.31
qnrB	13 (50%)	14 (60.9%)
P	0.56	0.052
qnrS	7 (26.9%)	8 (34.8%)
P	0.27	0.91

Data is presented as frequency (%). P: P value.

DISCUSSION

In addition to increasing the cost of hospital-derived infections, the use of antibiotics to treat UTIs also increases antibiotic resistance to first-line medicines [15].

The existence of biofilms leads to antibiotic resistance, which makes catheter-associated UTIs a serious problem. Urinary catheters become colonized by microorganisms over time, creating biofilms that make germs resistant to human defenses and antimicrobials, resulting in less-than-ideal antibiotic use.

The development of antibiotic-inactivating enzymes, such as plasmids that code for lactamases or efflux pumps, or chromosome changes that modify target enzymes and reduce drug concentration can result in antibiotic resistance in *E. coli* [16].

The current investigation found substantial rates of resistance to the various cephalosporin generations. This result was in line with earlier research [17, 18]. This result can be ascribed to the improper prescribing of these antibiotics, especially in a community context.

ESBL phenotypes were formed by 52% of the isolated *E. coli*, according to the double disc diffusion technique. According to earlier research, the ESBL activity of *E. coli* linked to UTIs ranged from 48% to 66.2% [19-21]. Additionally, the carbapenem resistance of the isolated E. coli was 46%, higher than that of previous report (34%) [19]. The MDR resistance of the isolated *E. coli* to the used antibiotics was 82%. These findings demonstrate the significance of stewardship programs by providing alarming evidence that uropathogenic *E. coli* inhealthcare settings accumulates genes that reduce the effectiveness of antibiotics [22-24].

One of the most often used antibiotics for *E. coli* treatment is quinolone. Some regions of the world attribute the increase in quinolone resistance to the transmission of plasmid-resistant genes (qnr) [25,26].

Through horizontal gene transfer, many bacteria can spread plasmids containing quinolone resistance genes, increasing quinolone resistance [27,28].

All of the *E. coli* isolates in this investigation that were resistant to ciprofloxacin had plasmid quinolone resistance genes identified using the MIC technique. Qnr A was the most found qnr gene (84%), followed by Qnr B (46%), and Qnr S (34%). Similar findings were reported in other studies [9, 29], suggesting that these genes were most common in ciprofloxacin-resistant E. coli. However, other research showed that isolates resistant to quinolone had a low incidence of PMQR [30,31]. This result implies that the variations in antibiotic use patterns across different geographic locations may result in a varied distribution of PMQR.

In this investigation, many QNR genes were detected in carbapenem-resistant *E. coli* and ESBL producers, although they were not statistically significant.

It is possible to have concurrent resistance to fluoroquinolones and beta-lactams. This could help explain how the same mobile genetic elements' qnr genes for quinolone resistance and extended beta-lactamase resistance are related [32]. Nevertheless, the study did not examine alterations in gyr genes or other genes that provide ciprofloxacin resistance in bacteria. This could help explain why isolated *E. coli* does not have a strong connection between the QNR genes, ESBL, and carbapenemase.

The uropathogenic *E. coli* is resistant to ciprofloxacin and carbapenem medicines. Since fluoroquinolone is still an option for E. coli that is resistant to carbapenem, this is a bad omen for the *E. coli* treatments that are currently accessible. According to a prior study conducted in Egypt, a population possessed genes that confer carbapenem resistance, and these genes contained several mutations in QRDR areas [33].

Multiple qnr genes were shown to be strongly associated (P = 0.001) with an increase in the lowest concentration of ciprofloxacin that was unable to kill the separated *E. coli*. Prior research has connected a higher degree of QR to the accumulation of numerous mutations in PMQR [9, 34].

CONCLUSIONS

Numerous *E. coli* strains are resistant to ciprofloxacin and hospital-acquired CAUTI due to PMQR determinants. The qnr genes were often linked to carbapenem resistance, ESBL, and other forms of antibiotic resistance. The importance of antibiotic surveillance systems, the requirement of antibiotic stewardship programs, and the necessity of strictly adhering to infection control guidelines for illnesses linked to urinary catheter use are all highlighted by this research.

Declarations

Consent for publication: Not applicable

Availability of data and material: Data are available upon request.

Competing interests: The author(s) declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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