

Study of Quinolone-Resistant *E. Coli* Isolated from Hospital-Acquired Urinary Tract Infection in Intensive Care Units

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ABSTRACT

Background: Catheter-associated urinary tract infection is the most common hospital-acquired infection which is treated empirically by quinolone antibiotics. Analysis of clinical characteristics, risk factors, and common pathogens has a major effect on the advancement of the prevention of CAUTI in medical settings.

Subjects and Methods: Urine samples were collected from Intensive Care Units at Mansoura University Main Hospital over two years. Samples were then transferred to the Microbiology lab, at Mansoura University Main Hospital for culture, identification, and sensitivity

Results: The most common pathogens were *E. coli* (27.4%) followed by *Candida* (21.2%) and *Staph aureus* (12.0 %). Females were slightly higher (52 %) than males (48 %). diabetes appeared to be the most common risk factor (31% of cases) followed by chronic kidney disease (23.5%) and cerebrovascular accidents (23%). Meropenem was the highest sensitive antibiotic (48.9%) followed by amikacin (47.4%), norfloxacin (46.2%), imipenem (41.8) while cefuroxime (100.0%), and cefaclor (100.0%) are the most resistant antibiotic followed by ceftriaxone (97.0%), doxycycline (96.0%).

Conclusion: cases in our study showed a high resistance rate to quinolone antibiotics which need infection control plans and antibiotic stewardship programs to reduce that rate.

Keywords: CAUTI, Quinolones, *E coli*.

Abbreviations: CAUTI (Catheter-associated urinary tract infection), HAI (hospital-acquired infections), FDA (Food and Drug Administration), CDC (Centers for Disease Control and Prevention), CLSI (Clinical & Laboratory Standards Institute: CLSI Guidelines).

INTRODUCTION

Catheter-associated urinary tract infection (CAUTI) is one of the most common hospital-acquired infections (HAI). These infections are most likely caused by bacteria entering the body during catheterization, as a result of prolonged or unnecessary use of urinary catheters, or due to disruption of the closed drainage system ⁽¹⁾.

For CAUTI, sex, physiologic score on admission, duration of catheterization, diabetes mellitus, immunocompromised patients, neurological disease, and high systemic antibiotic exposure on admission are all potential risk factors ⁽²⁾.

Escherichia coli is a Gram-negative bacterium of the Enterobacteriaceae family that can harmlessly colonize the human intestine or cause enteric or extra-intestinal infections, including serious invasive diseases such as bacteremia and sepsis, and is considered the most common pathogen causing UTI ⁽³⁾.

Quinolone antibiotics are a class of broad-spectrum antibiotics used to treat a variety of bacterial infections. The quinolones were active only against Gram-negative bacteria, and subsequent generations acquired activity against *Pseudomonas* species, Gram-positive and atypical bacterial strains. Ciprofloxacin is

FDA-accepted for the remedy of complex urinary tract infections ⁽⁴⁾.

In this study, we aim to Determine incidence, common pathogens, associated risk factors, and antibiotics susceptibility responsible for hospital-acquired urinary tract infection in Mansoura university hospital as well as to characterize the quinolone resistance phenotypes in *E. coli* isolated from UTI in ICU patients in Mansoura university hospital.

PATIENTS AND METHODS

Urine samples were collected from Intensive Care Units at Mansoura University Main Hospital over two years and transferred to the microbiology lab, for culture, identification, and sensitivity.

The study also included urine culture samples from patients who have CAUTI according to CDC, 2018 definition between January 2019 and January 2021 collected from ICU patients in Mansoura University Main Hospital.

Patients who have community-acquired UTI and Urine culture samples collected from patients other than ICU were excluded.

All cases were subjected to full clinical history taking and clinical examination. Also, 50 cases of *E. coli*

resistant to ciprofloxacin isolated from UTI in ICU patients in Mansoura University Main Hospital were chosen to undergo molecular characterization.

Bacterial identification and antimicrobial susceptibility:

Bacterial identification and antimicrobial susceptibility were done according to routine laboratory protocols using conventional biochemical tests and minimal inhibitory concentration following the **Clinical & Laboratory Standards Institute, (CLSI) 2018**.

Urine samples were cultured on MacConkey agar. A colony count of urine samples was done by culture of 1 µl of urine sample on nutrient agar. To diagnose UTI, the colony count should be at least $\geq 10^5$ CFU/ml.

Bacterial identification was done using manual biochemical reactions using citrate, urease, triple sugar, oxidase, and indole according to **CLSI 2018** guidelines. Antibiotic susceptibility was done using the disc diffusion technique according to CLSI guidelines. susceptibility to ciprofloxacin was done using minimal inhibitory concentration (MIC) according to **CLSI 2018 guidelines**

Ciprofloxacin susceptible: Isolates with minimum inhibitory concentration (MIC) ≤ 1 µg/mL
Intermediate: MIC 2 µg/mL
Resistant: MIC ≥ 4 µg/mL.

Ethical Approval

The ethics approval and written agreement to participate in the study have been signed by all patients and controls. The Institutional Review Board (IRB), Mansoura University MD.19.01.130, Faculty of Medicine, authorized the study. All participants have given their written approval and consent for the gathering of pertinent clinical data. All authors have read the author rules and gave their agreement for this work to be published. This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The data were analyzed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Number and percentage were used to express qualitative data, while quantitative data was tested for normalcy Kolmogorov-Smirnov test then expressed as range and median, regarding data comparison Chi-Square test or Fisher’s exact test was used for qualitative data. By using direct counting, genotypic and allelic frequencies were evaluated. Genetic models using allelic and dominant traits have been used.

At CI **95%**, a P-value of less than **0.05** was deemed statistically significant.

RESULTS

This study involved **744** CAUTI samples. *E. coli* was isolated in **204** samples (**27.4%**). This is illustrated in **Table (1)** and **Figure (1)**:

Table (1): Organisms isolated from the examined samples

Organism	N	%
<i>E. Coli</i>	204	27.4
<i>Staph. aureus</i>	89	12.0
<i>Staph. epidermidis</i>	66	8.9
<i>Klebsiella</i>	65	8.7
<i>Candida</i>	158	21.2
<i>Proteus</i>	14	1.9
<i>Pseudomonas</i>	74	9.9
<i>Citrobacter</i>	23	3.1
<i>Enterococcus</i>	51	6.9

This table shows that the most frequently isolated organisms are *E. coli* (27.4%) followed by *Candida* (21.2%).

Among the infected 204 patients with *E. coli*, **107** (52.5) were females, and **97** (47.5%) were males. Their mean age \pm SD was **49.5 \pm 14.7** years ranging from **16** to **84** years. **Table (2)** shows the clinical characteristics of these patients.

Cases were referred from ER (**40.2%**), outpatient clinics (**38.8%**), and inpatient departments (**24 %**). Regarding the surgical history of our cases, cases with hernia repair were the most commonest (**25%**), followed by appendectomy (**11.0%**).

Table (2): Clinical characteristics of the studied patients (N=204).

Clinical characteristic	Statistic	
	N	%
Sex		
Female	107	52.5%
Male	97	47.5%
Referral		
Outpatient Clinic	73	35.8%
Emergency Room (ER)	82	40.2%
Inpatient	49	24%
Readmission within the last 30-days	47	23%
History of surgery	23	11.3%
Appendectomy	4	16.7%
Anal fistulotomy	2	8.3%
Cholecystectomy	4	16.7%
Herniorrhaphy	6	25%
Cesarian section	4	16.7%
CABG	1	4.2%
surgery	1	4.2%
Hemorrhoidectomy	2	8.3%
Anal fissurectomy	2	8.3%
Quantitative	Mean ± SD	Median (Range)
Age (years)	49.5 ± 14.7	52 (16 – 84)
Number of days since hospital admission	8.9 ± 2.8	8 (4 – 25)
Number of days of ICU admission	7.7 ± 2.2	8 (3 – 22)
Number of days since catheter insertion	6.9 ± 2.1	7 (3 – 19)

The frequency of risk factors is shown in **Table (3)**. Diabetes was the most common (33.3%) followed by CKD (23.5%).

Table (3): Frequency of Risk factors for CAUTI.

Risk factors	N	%
Diabetes	68	33.3%
Chronic kidney disease (CKD)	48	23.5%
Hypertension	45	22.1%
Chronic liver disease (CLD)	32	15.7%
Cerebrovascular accident (stroke)	47	23%
Immunosuppressive therapy	7	3.4%
Previous UTI	24	11.8%

Concerning Symptoms and signs of CAUTI and their duration, **Table (4)** shows the frequency of symptoms and signs of CAUTI and duration (days) since their onset.

Table (4): Symptoms and signs of CAUTI and their duration

Finding	N (%)	Median duration (Range)
Fever	116 (56.9%)	2 (1 – 3)
Dysuria	54 (26.5%)	3 (2 – 3)
Urgency	48 (23.5%)	3 (1 – 3)
Frequent urination	22 (10.8%)	3 (1 – 3)
Pelvic pain	95 (46.6%)	2 (1 – 4)
Loin tenderness	113 (55.4)	2 (1 – 4)

Antibiotic susceptibility testing for isolated *E coli* was done by the disc diffusion method modified Kirby- Bauer-method. Fifty cases resistant to ciprofloxacin underwent susceptibility testing done by broth microdilution method. As shown in **Table (5)**, meropenem was the highest sensitive antibiotic (48.9%) followed by amikacin (47.4%) while cefuroxime (100.0%) and cefaclor (100.0%) are the most resistant antibiotic.

Table (5): Antibiotic resistance in the studied samples (N=204)

Antibiotic	No	Sensitive N (%)	Resistant N (%)
Ciprofloxacin	204	72 (35.3 %)	132 (64.7%)
Levofloxacin	128	30 (23.4%)	98 (76.6%)
Moxifloxacin	46	19 (41.3%)	27 (58.7)
Ofloxacin	28	7 (25.0%)	21 (75%)
Norfloxacin	13	6 (46.2%)	7 (53.8%)
Nitrofurantoin	38	10 (26.3%)	28 (73.7%)
Meropenem	88	43 (48.9%)	45 (51.1%)
Imipenem	91	38 (41.8%)	53 (58.2%)
Ertapenem	89	37 (41.6%)	52 (58.4%)
Aztreonam	60	8 (13.3%)	52 (86.7%)
Doxycycline	75	3 (4.0%)	72 (96.0%)
Trimethoprim/Sulfamethoxazole	91	5 (5.5%)	86 (94.5%)
Amikacin	78	37 (47.4%)	41 (52.6%)
Gentamicin	60	22 (36.7%)	38 (63.3%)
Cefepime	89	5 (5.6%)	84 (94.4%)
Cefotaxime	90	4 (4.4%)	86 (95.6%)
Cefoperazone	112	8 (7.1%)	104 (92.9%)
Ceftriaxone	134	4 (3.0%)	130 (97.0%)
Ceftazidime	100	13 (13%)	87 (87%)
Cefuroxime	17	0 (0%)	17 (100%)
Cefaclor	8	0 (0%)	8(100%)
Cefoxitin	54	14 (25.9%)	40 (74.1%)
Piperacillin / tazobactam	74	22 (29.7%)	52 (70.3%)
Cefoperazone /sulbactam	110	27 (24.5%)	83 (75.5%)
Amoxicillin / clavulanic acid	46	8 (17.4%)	38 (82.6%)

DISCUSSION

Urine samples were collected from Intensive care units at Mansoura University Main Hospital over two years between January 2019 and January 2021.

Samples were then transferred to the microbiology lab, at Mansoura University Main Hospital for culture, identification, and sensitivity. Also, 50 *E. coli* cultures resistant to ciprofloxacin isolated from ICU patients with CAUTI according to CDC 2018 definition were then chosen for DNA extraction and polymerase chain reaction in the Molecular Biology lab. in the Microbiology Unit, Clinical Pathology Department.

The most frequently isolated organisms from CAUTI samples were *E. coli* which was isolated in 204 samples (27.4%) followed by *Candida* (21.2%) and *Staph aureus* (12.0 %) which matches with **Mishra and Rao., 2019** who found *E. coli* to be the commonest microorganism causing CAUTI in their study.⁵

Clinical characteristics of patients in our study showed that females were slightly higher (52 %) than males (48 %) which may be attributable to the short urethra of females which eases bacterial colonization⁶.

The mean age of the studied cases was 49.5 ± 14.7 indicates that CAUTI occurs more frequently in elderly patients which could be explained by the fact that increased age is associated with decreased immunity with age as well as multiple comorbidities associated with aging^{7,8}.

Cases in our study were referred from the Emergency Room (40.2%), Outpatient Clinics (38.8%), and Inpatient Departments (24 %) with 23 % of them having a history of hospital admission in the past 30 days. Twenty-three (11.3%) patients had a history of surgery with appendectomy being the most frequent surgery.

Regarding the frequency of associated risk factors, diabetes appeared to be the most common risk factor (31% of cases) followed by chronic kidney disease (23.5%) and cerebrovascular accidents (23%). Diabetes, kidney disease, and cerebrovascular accidents are among the most common risk factors of CAUTI⁹. While the direct negative effect of diabetes and chronic kidney disease on the immune system can explain the increased risk of developing CAUTI¹⁰. Cerebrovascular accidents themselves don't increase risk directly but maybe through

prolongation of hospital stay and long duration of catheterization required for these cases¹¹.

Fever was the most frequent clinical symptom in cases enrolled in our study (56.9%) followed by loin tenderness (55.4%), pelvic pain (46.6%), and dysuria (26.5%) which convey in another study in which fever, flank pain, and dysuria are the most common symptoms in CAUTI patients¹².

In our study, antibiotic susceptibility testing for isolated *E coli* was done by the disc diffusion method and modified Kirby-Bauer method. Fifty cases resistant to ciprofloxacin underwent susceptibility testing done by broth microdilution method. Meropenem was the highest sensitive antibiotic (48.9%) followed by amikacin (47.4%), norfloxacin (46.2%), imipenem (41.8%), ertapenem (41.6%), and moxifloxacin (41.3%) while cefuroxime (100.0%) and cefaclor (100.0%) are the most resistant antibiotic followed by ceftriaxone (97.0%), doxycycline (96.0%), cefotaxime (95.6%) and cefepime (94.4%).

The high sensitivity of *E coli* isolated from CAUTI specimens to imipenem, Meropenem, and amikacin was also stated by other studies^{5,13,14}, while **Fahim, 2021** contrary to our study, reported high resistance of *E coli* samples to carbapenems and amikacin¹⁵.

We found a high resistance rate to cephalosporins despite their generation which matches with other studies¹⁶ as they claimed a high level of cephalosporins and ESBL resistance in *E coli* isolated in their study which was probably due to the inappropriate use of these drugs, especially in the community setting¹⁷.

Increased level of tetracycline resistance was also described by a meta-analysis study on data published between January 1st, 2000 to December 31, 2019, via PubMed/Medline and Science direct databases found that the highest resistant level was to tetracyclines (69.1%)¹⁸.

Isolates in our study showed a 64.7 % resistance rate to quinolones which is much higher when compared to the global rate which ranges between 35 % to 57 % and the European rate which ranges between 3 % in Norway to 50 % in North Macedonia, the Russian Federation and Turkey^{19, 20}.

These results could be explained by the extensive uncontrolled use of quinolones as an empirical remedy for UTI in Egypt.

CONCLUSION

We can conclude that *E coli* is the most common pathogen causing CAUTI. The use of empirical quinolones antibiotics for the treatment of CAUTI is inappropriate.

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- **Availability of data:** The paper itself contains the data sets that are used to support the findings.
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