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ORIGINAL ARTICLE

The Relation between Antibiotic Resistance pattern and the Risk Factors Associated with Urinary Tract Infections Caused by *E. coli.*

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ABSTRACT

Background: *Urinary tract infections (UTIs) are one of the most common bacterial infections which affect more than 150 million individuals each year worldwide.* ***Objective****: this study was conducted to assess the risk factors associated with urinary tract infections (UTIs) caused by resistant Escherichia coli.* ***Methodology*** *Four hundred and thirty urine samples were collected from outpatients who had urinary tract symptoms, ages ranging from 10 to 75 years in Beni-Suef Egypt, during a period extended from January 2021 to the end January 2022 and processed by standard microbiological methods.* ***Results*** *A total of 430 patients were included in this study: 210 (48.82%) uncomplicated and 220 (51.15%) complicated UTIs. Of 430 UTIs patients 287(66.8%) were females (77(36.6%) were complicated and 210(100%) were uncomplicated), while 143 male UTIs patients were classified as complicated (65%). The prevalence of pathogenic microbes reveals bacterial species predominate in UTIs with 376 (87.42%) E. coli high-frequency bacterial strains 85 (19.9%), followed by Klebsiella sp. 70 (16.3), Pseudomonas aeruginosa 58 (13.5%) and Enterococcus sp. 58 (13.5%). Proteus mirabilis 46(10.9%). Among 85 E coli isolates 46 from complicated and 39 isolates from uncomplicated UTIs patients showed the highest resistance to piperacillin/tazobactam 35(41.2%), sulfamethoxazole /trimethoprim 35 (41.2%), amoxicillin-clavulanic acid 34 (40%) and cefepime 34 (40%) and the least resistant antibiotics in the present study were colistin (3.5%), imipenem (5%), quinolones (5%) and nitrofurantoin (5%).* ***Conclusion****, nitrofurantoin, and quinoline remain still the best choice for treating complicated and uncomplicated UTI. Risk increases with the number of patients hospitalizations.*

INTRODUCTION

Urinary tract infections (UTIs) are a common community-acquired bacterial disease which frequently affects female outpatients. UTIs are recurrent infections caused by *Escherichia coli*, the most common member of the family *Enterobacteriaceae*, which accounts for 75-90% of all UTIs in both inpatients and outpatients. The annual incidence of UTIs diagnosed rates were greater than 10% for females and 3% for males[1,2]. UTIs are controlled by individuals risk factors, including sex, age, family history, sexual activity, chronic comorbidities[3]. Recurrent urinary tract infections (rUTIs) are defined as repeated infections three times or more annually[4]. UTIs are becoming growingly hard to treat owing to the fast spread of drug resistance among Gram-negative bacteria, including *Klebsiella* sp. and *E. coli* [1,5]. UTIs occur by *E. coli* enters the urinary tract through the urinary meatus prior to climbing up the urethra and into the bladder lumen. Infections of the lower urinary tract and bladder without symptoms or systemic infection are called uncomplicated cystitis. Also, acute cystitis in a premenopausal woman without functional urinary tract abnormalities or non-pregnant is classified as uncomplicated[6]. Cystitis in immunocompromised or pregnant woman and patients with functional urinary tract abnormalities, an indwelling catheter, or a history of renal transplantation were classified as 'complicated cystitis[7]. In about 0.34% of cases, microbes cause cystitis to ascend further through the ureters into the kidney, where they cause an infection of the calices, renal pelvis, and cortex that leads to the clinical features of pyelonephritis[8]. When untreated UTIs, the pathogenic bacteria may reach into

the bloodstream (bacteremia) from the kidney, and if a synchronous systemic inflammatory response is present, this may lead to septicemia[9]. About 27% of all cases of septicemia occur due to previous UTIs and are called urosepsis[10]. Trimethoprim/sulfamethoxazole, cephalosporins, ciprofloxacin, penicillins fosfomycin, and nitrofurantoin are common antibiotics employed in the treatment UTIs. *E. coli* and other pathogenic bacteria are becoming rapidly resistant to these antibiotics, leading to reduced efficacy of criterion regimens[1]. The curing of UTIs with trimethoprim/ sulfamethoxazole is the bespoke antibiotic in tuning where the prevalence of resistance is more than 20% as maintained by the Infectious Diseases Society of America (IDSA) protocol. Quinolones are the drug of choice if the trimethoprim/sulfamethoxazole resistance rate is over 20%[11]. Quinolones are potent antibacterial, have been employed for the latter two decades, and it has been widely used for treatment community acquired UTIs. The linkage between the increase in bacterial resistance to quinolones and wide prescription has been recorded in several countries. Factors linked with ciprofloxacin resistance in *E. coli* have been recorded as abnormalities of the UTI, age > 65 years, urinary catheterization, and past treatment with quinolones [1. 12,13]. Interpolation of a urinary catheter into the urethra and bladder led to the release of host factors such as fibrinogen, which covered the catheter. These factors allow diverse microbes, including members of the genera *Enterococcus, Klebsiella,* and *Staphylococcus*, to bind and assemble biofilms on the catheter surface. The genomes of these microbes encode fibrinogen-binding adhesins that are vital to biofilm formation on the catheter and lead to raised mortality rates if the infections advance to pyelonephritis and urosepsis [14]. There is a pressing need to develop new approaches or antibiotic regimens to combat and break the vicious cycle of rUTI antibiotic resistance bacteria. Therefore, this study aims to assess the risk factors associated with resistant *E. coli* through urinary tract infections (UTIs).

METHODOLOGY

Patients:

This study was conducted over a period extended from January 2021 to January 2022. A total of 430 outpatients with urinary tract infections from special laboratories (Alfa Dar-ELFoad laboratory, Dar Elkhebra laboratory) Beni-Suef Egypt, aged ranging from 10 to 75 years and included the following cases: community acquired UTIs who has upper UTI, pregnant women, individual with urinary tract abnormalities, patients with a urinary catheter, patients with urological operation, or those who have urolithiasis were interpreted as having complicated or uncomplicated UTI. All urine samples and the data were collected from mid-stream clean-catch by Prof Dr. Iman Mohamed Gaddoue; Prof. Consultant – MD Microbiology - NHI- GOTHI. Epidemiological data were prospectively collected, and samples were immediately taken to the microbiological laboratory and processed. Individuals who had *E. coli* in their samples were interviewed. The questionnaire collected data relating to demographic properties which including (address, age, sex) symptoms (urgency, dysuria, blood in urine, pelvic pain or frequent urge to urinate but incomplete voiding), criteria signalize the presence of complicated UTI underlying disease, whether there had been recurrent hospitalization, and antibiotics that have been used in the last year. A consent was obtained from each patient about the questionnaire.

Isolation and purification of bacterial species

A loopfull of undiluted urine samples was spread on appropriate culture media (Eosin Methylene Blue (EMB) and MacConkey) agar *(*Himedia India*), and* the cultivated plates were incubated at 37◦C for 24h. Well-isolated single colonies were subcultured on the same media to check for the purity of the isolated bacteria. Purified isolates were identified using microscopical, morphological *(*macroscopic morphology and color in the specific agar media) physiological, and biochemical tests according to microbiological methods 8th ed[15] Bergey's manual of systematic bacteriology [16].

Antibiotics susceptibility of *E. coli* isolates

The antibiotics susceptibility pattern of 85 *E. coli* isolates and *E. coli* ATCC 8739 was assessed by using the disc diffusion method on Mueller-Hinton (HM) medium according to Clinical and Laboratory Standards Institute guidelines (CLSI) [17]. The antibiotics discs (Oxoid, England) included nitrofurantoin 300µg/ml, colistin 10µg/ml, imipenem 10µg/ml, amoxicillin-clavulanic acid 20/10µg/ml, ceftazidime 30µg/ml, ciprofloxacin 5µg/ml, levofloxacin 5µg/ml, chloramphenicol 30µg/ml, sulfamethoxazole/ trimethoprim 25µg/ml, norfloxacin 10µg/ml, aztreonam 30µg/ml, doxycycline 30µg/ml, ampicillin/sulbactam 20µg/ml, cefepime 30µg/ml, piperacillin/ tazobactam 75/10µg/ml, amikacin 30 µg/ml and cefoperazone/sulbactam 105µg/ml. Fresh cultures grown on Mueller-Hinton (MH) broth (Himedia India) were inoculated with a swab (Citos swab, China) to provide semi-confluent growth on (MH) agar plates (Himedia India) and loaded with the above antibiotics discs on plates and incubated for 24h at 37^{o}C. The diameters of inhibition zones were measured, and the experiment was performed in three triplicates.

Statistical analysis

Data were analyzed using the statistical package for the social sciences (SPSS), version 20 to compare the ages of patients in the two groups and analyses categorical data. It was considered significant at $p \leq 0.05$. A multivariate analysis was performed with all significant variables, and the odd ratio was calculated with a confidence interval of 95%.

RESULTS

A total of 430 urine samples from outpatients who have urinary tract symptoms aged between 10 and 75 years with a median of 41.5 were submitted to the microbiology laboratory during the 13 months. Of 430 cases 210 (48.82%) were uncomplicated UTI cases and 220 (51.51%) were complicated. The complicated cases were 77(36.6%) from female patients while 143(65%) were obtained from males. All male cases were classified as complicated UTI patients. The median age was 36 with a range from 10 to75 for uncomplicated UTIs, while 47(10 to 75) for complicated UTI patients. Also, 76.7% of 210 uncomplicated UTIs patients and 56% of 220 complicated UTIs patients were from rural villages**.** Of the 220 patients with complicated UTIs, 80(36.3%) had urinary catheters, 53(11.6%) presented with kidney and ureters stones, 35(15.9%) with nephritis, 38(17.2%) suffered from diabetes mellitus type 2, 17(7.7%) with cystitis, 9(4%) with renal failure and 68(14.9%) had old urological operations, As that uncomplicated UTIs female patients were 210, including 88 (41.89%) were pregnant, 98 (46.65%) had acute cystitis and 61 (29%) had acute nephritis. In the Univariate analysis of demographic, clinical signs, and symptoms of patients**,** the median age of all patients with UTIs was 41.5 and the isolates from a rural village were 66 %. Also, all samples were collected from health care centers 105 (24.4%), nursing homes 43 (10%), and private practices 282 (65.6%). As for the clinical status; signs, and symptoms were patients with urinary catheters 80 (18.6%), patients with kidney and ureters calculus 53 (12.3%), patients with renal failure 9 (2%), patients with nephritis 86 (20%), pregnancy patients 88 (20.4%), patients with cystitis 115 (26.7%), patients with urological operations 68(15.8%) and patients with Diabetes mellitus type 2; 82(19%).The result as shown in (table 1). The prevalence of microorganisms isolated from UTIs urine samples revealed that bacterial strains predominate in patients under study. The most frequent isolates were *E. coli* with a percentage of 85(19.9%), followed by *Klebsiella* sp. 70 (16.3%), *Pseudomonas aeruginosa* 58 (13.5%), *Enterococcus* sp. 58 (13.5), *Proteus mirabilis* 46(10.9%), *Enterobacter* sp. 39(9.1%) and *S. aureus* 19(4.4%) as shown in (table 2). Among the 85 *E. coli* isolates, 39 *E. coli* were isolated from uncomplicated UTI and 46 from complicated UTI.

Table 1. Univariate analysis: demographic and clinical signs and symptoms of the cases.

	Total, n = 430	**Complicated UTI n = 220 (%)**	**Uncomplicated UTI n = 210 (%)**	**P value**
Demographic parameters:				
Age in years median (%):	41.5(10-75)	47 (10-75)	36 (10-75)	0.000
Gender				
Male	143(33.2%)	143(65%)	---	0.001
Female	287(66.8%)	77(35%)	210(100%)	0.001
Residence in rural villages	284 (66%)	123(56%)	161 (76.7%)	0.003
Health care provider n (%):				
Health care centers	105(24.4%)	70(31.8%)	35(16.7%)	0.003
Nursing homes	43(10%)	43(19.5%)	---	0.001
Private practices	282(65.6%)	107(28.7%)	175(83.3%)	0.002
Clinical status, signs, and symptoms: n (%):				
Urinary catheter	80(18.6%)	80(36.3%)	---	0.002
kidney and ureters stones	53(12.3%)	53(24)	---	0.000
Renal failure	9(2%)	9(4%)	---	0.000
Nephritis	86(20%)	35(15.9%)	51(24.3%)	0.002
Pregnancy	88(20.4%)	---	88(41.9%)	0.000
Cystitis	115(26.7%)	17(7.7%)	98(46.7%)	0.004
Urological operations	68(15.8%)	68(30.9%)	---	0.001
Diabetes mellitus type 2	82(19%)	38(17.3%)	44(20.9%)	0.001

Table 2. Prevalence of uropathogenic microbes

Uropathogenic	Frequency (%)
E. coli	85 (19.8)
Klebsiella spp.	70 (16.3)
Enterococcus spp.	58 (13.5)
Pseudomonas aeruginosa	58 (13.5)
Proteus mirabilis	47 (10.9)
Enterobacter spp.	39 (9.1)
S. aureus	19 (4.4)
Candida spp.	35(8.1)
Others	19 (4.4)
Total	430 (100%)

Tables (3) showed that *E. coli* isolates were highly resistant to piperacillin/tazobactam 35(41.2%), sulfamethoxazole/trimethoprim 35(41.2%), amoxicillin-clavulanic acid 34(40%) and cefepime 34 (40%), respectively. *E. coli* isolates exhibited high sensitivity rates to nitrofurantoin and amikacin from complicated and uncomplicated UTIs. The significant differences in resistance rates for colistin, ciprofloxacin, levofloxacin, and imipenem, but no statistically significant differences were observed in resistance patterns between isolates from complicated UTIs and uncomplicated UTIs.

Table 3. Resistance pattern of 85 *E. coli* isolates

N	Antibiotics	Total n (%)	*E. coli* un-complicated cases n = 39 (%)	*E. coli* complicated cases n = 46 (%)	P value
1	Colistin 10µg	3(3.5%)	1 (2.5%)	2 (4.3%)	0.000
2	Imipenem 10µg	5 (5.8%)	3 (7.7%)	2 (4.3%)	0.000
3	Amoxicillin-clavulanic acid 20/10µg	34(40%)	18(46.1%)	16 (34.7%)	0.009
4	Ceftazidime 30µg	21 (24.7%)	8(20.5%)	13 (28.2%)	0.002
5	Ciprofloxacin 5µg	5 (5.8%)	3 (7.7%)	2 (4.3%)	0.000
6	Levofloxacin 5µg	5 (5.8%)	3 (7.7%)	2 (4.3%)	0.000
7	Chloramphenicol 30µg	22 (25.9%)	10 (25.6%)	12 (26%)	0.001
8	Sulfamethoxazole/trimethoprim 25µg	35 (41.2%)	17(43.5%)	18 (39.1%)	0.021
9	Norfloxacin 10µg	10 (11.7%)	5 (12.8%)	5(10.8%)	0.000
10	Aztreonam 30µg	31(36.4%)	15 (38.4%)	16 (34.7%)	0.009
11	Doxycycline 30µg	21 (24.7%)	13 (33.3%)	8 (17.3%)	0.002
12	Ampicillin/Sulbactam 20µg	19 (22.9%)	17(43.5%)	12 (26%)	0.001
13	Cefepime 30µg	34 (40%)	18 (46.1%)	16 (34.7%)	0.009
14	Piperacillin/tazobactam 75/10µg	35 (41.2%)	16 (41%)	19 (38.7%)	0.029
15	Amikacin 30µg	14 (16.4%)	8 (20.5%)	6 (13%)	0.001
16	Cefoperazone/sulbactam 105µg	28 (32.9%)	19(48.7%)	9(19.5%)	0.008
17	Nitrofurantoin 30µg	3 (3.5%)	1 (2.5%)	2 (4.3%)	0.000

Table (4) showed that in the multivariate analysis, age more than 50 [odds ratio (OR): 1.23; confidence interval (CI): 1.14–1.4; P = 0.000], Quinolones use over than once in the last year (OR: 1.5; CI: 1.18–1.96; P = 0.001), Recurrent UTI (OR: 4.8; CI: 2.98–7.86; P < 0.003) and previous hospitalization (OR: 3.5; CI: 2.41–5.06; P < 0.006) were found to be linked with antibiotic resistance among the *E. coli* strains. Both backward and forward a selection method recorded the same significant variables. So, previous use of quinolones, recurrent UTIs, age over 50, and previous hospitalization were identified as independent risk factors when a multivariate regression was performed on all significant variables.

Table 4. Multivariate regression: independent risk factors for *E. coli* community-acquired infection:

	Odds ratio (OR)	95% Confidence Interval (CI)		P value (P)
		Lower	Upper	
Age more than 50	1.23	1.143	1.400	0.000
Quinolones use.	1.51	1.187	1.963	0.001
Recurrent UTIs	4.84	2.986	7.865	0.003
Previous hospitalization	3.50	2.417	5.069	0.002

DISCUSSION

Our study included 430 urine samples from outpatients with signs and symptoms of UTIs, 287(66.72%) cases of females were categorized of 210 (48.82%) uncomplicated and 77(17.90%) complicated UTI, while 143 (33.24%) males are classified as complicated cases. We noticed the high complicated UTI cases in males143(100%), while in females 77(17.90%). This finding is compatible with another study one by Arslan et al.,[1] who recorded 611 Gram-negative bacterial isolates 290; were isolated from complicated and 321 were isolated from uncomplicated UTIs. All male patients were classified as complicated UTIs.

The discrimination between complicated and uncomplicated UTIs is based on the presence of risk factors or gender, and it is used to guide the choice and duration of antibiotic treatment. Pyelonephritis and acute cystitis in healthy premenopausal non-pregnant women without urinary tract abnormality are categorized as uncomplicated. Otherwise, are considered complicated UTI. *E. coli* remains dominated pathogenicity bacteria responsible for UTI uncomplicated and complicated but with various prevalence according to characteristics of the host and epidemiology [18, 19].

Consistent with previous reports, urinary tract infections are major cause of morbidity in females with uropathogenic *E. coli* persistence as the primary causative agent. The strongest risk factor for UTI is a history of prior UTIs but the biological grounds and risk factors for long-term recurrence remain obscure in contrast to healthy women [20, 21].

Moreover, *E. coli* is the most frequent bacterial strain in both complicated (~ 50%) and uncomplicated (75–95%) UTI[22]. The empirical treatment of complicated and uncomplicated UTI is becoming more challenging due to the rapid emergence of resistance to different classes of antibiotics (beta-lactams quinolones, sulfa-drug,). Antibiotic susceptibility analysis of urinary tract infection isolates should be recognized in order to prescribe suitable drugs[1]. We found overall high resistance rates *E coli* isolates for the commonly used oral antibiotics, such as piperacillin/tazobactam 35(41.2%), sulfamethoxazole/trimethoprim 35(41.2%), amoxicillin-clavulanic acid 34(40%) and cefepime 34 (40%), respectively. A previous study by Kareem and Hassan [23] showed that *E. coli* isolated from UTIs has high resistance to most common antibiotics used in the treatment of UTIs. They found the highest resistance rates to levofloxacin, ciprofloxacin, 60/80(75%) followed by norfloxacin 57/80 (71.25%) trimethoprim /sulfamethoxazole 55/80 (68.75%). Resistance patterns of uncomplicated UTI in symptomatic patients were found as cotrimoxazole 15.8%, ciprofloxacin 10.5%, amoxicillin/clavulanic acid 5.3%, nitrofurantoin 0% [24].

Other studies, from developing countries, reported a high incidence of multidrug-resistant phenotype among uropathogenic *E. coli* with frequency rates of 78%, 32.2%, and 92.9%, isolated from UTI in Iran, Libya, and Bangladesh, respectively [25-27].

Furthermore**,** the high resistance rates recorded by *E, coli* isolated from UTI for commonly used antibiotics were amoxicillin (43.2%), cotrimoxazole (24.5%), ciprofloxacin (17.4%), and amoxicillin-clavulanic acid (15.5%), whereas resistance low for fosfomycin and nitrofurantoin (≤1.5%).[28]. In multivariable analysis, the risk for developing infections due to age of more than 50 [odds ratio (OR): 1.23; confidence interval (CI): 1.14–1.4; P = 0.000]. Quinolones used more than once in the last year (OR: 1.5; CI: 1.18–1.96; P = 0.001), Recurrent UTI (OR: 4.8; CI: 2.98–7.86; P < 0.003) and previous hospitalization (OR: 3.5; CI: 2.41–5.06; P < 0.006) were found to be linked with antibiotic resistance among the *E. coli* strains**.**

Another study by Killgore *et al***.,** [29] found that not only previous use of quinolone (during the 4 prior to UTI) to be awaken independent risk factor for UTI due to ciprofloxacin-resistant *E. coli*, but also recurrent UTI (OR 8.13, 95% CI 2.95–22.37, p < 0.0001). In our study, many variables were significantly more frequent in the community acquired UTIs with *E. coli*. In addition, we also found a strong relationship between medical invasive procedures (like urine catheters) and quinolone resistance. These findings strongly propose that the main source of quinolone resistance may be the hospital setting. According to these guidelines and recommendations of the Infectious Diseases Society of America (IDSA) that when the percentage of resistant trimethoprim/ sulfamethoxazole isolates exceeds the 20% threshold for effective empirical treatment, the clinician should use alternative therapy with fluoroquinolone or nitrofurantoin[30].

In our society, nitrofurantoin is advised for the empirical management of uncomplicated cystitis. Because nitrofurantoin is 90% renal eliminated and has a very high urine concentration, it is an effective urinary anti-infective drug for the majority of Gram-positive and Gram-negative uropathogens[31] Urologists should recommended the use of parenteral amikacin to treat complex infections or pyelonephritis. The multivariable analysis, foreteller for *E. coli* resistance to cotrimoxazole and ciprofloxacin were treated in the urological unit (odds ratio [OR] 2.04, 95% confidence interval [CI] 1.63-2.54; p <0.001 and OR 1.33, 95% CI 1.07-1.64; p = 0.010, respectively, male sex (OR 1.93, 95% CI 1.630-2.29; p <0.001 and OR 1.22, 95% CI 1.22-1.04; p = 0.015), and only to a lesser extent urine sample from indwelling catheters (OR 1.30, 95% CI 1.05-1.61; p = 0.014 and OR 1.26, 95% CI 1.04-1.53; p = 0.020). Age ≥65 years related to higher resistance to ciprofloxacin (OR 1.42, 95% CI 1.21-1.67; p <0.001),

but lower resistance to cotrimoxazole (OR 0.76, 95% CI 0.67-0.86; p <0.001[27].

CONCLUSION

Nitrofurantoin, ciprofloxacin, and levofloxacin continue to be appropriate empiric treatment in most patients with complicated and uncomplicated UTI. Besides, there is a strong indicator that patients with UTI in the past months were infected with bacterial strains resistant to piperacillin/tazobactam sulfamethoxazole/trimethoprim, amoxicillin/ clavulanic acid, and cefepime. Another risk factor that possibly helps guide empirical therapy is renal transplantation. Patients with age more than 50, quinolones use more than once in the last year, recurrent UTI, and previous hospitalization were identified by us as independent risk factors for antibiotic resistance for community acquired UTIs by *E. coli*. The risk increases with the number of hospitalizations. In patients with one or more of the risks identified here, the empiric use of quinolones should be reconsidered, and it is necessary to consider the type of UTI (uncomplicated VS. complicated), as well as the sex and age of each patient.

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Authors contribution statement:

A.G.M.: Conceptualization, formal analysis, methodology, writing – review, and editing. **G.M.E.**: conceptualization, formal analysis supervision, writing - review & editing. **A.O.E.**: methodology, investigation. **M.S.A.**: methodology, data curation writing - review & editing. **H. M.E.**: methodology, resources, visualization, data curation.

Availability of data and materials:

All data generated or analyzed during this study are included in this published article.

Consent for publication: Not applicable

Competing interests:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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