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Authors’ contributions

This work was carried out in collaboration between all authors. Author SEA designed the study, wrote the protocol and interpreted the data. Author BA anchored the field study, gathered the initial data and performed preliminary data analysis. While authors OA and LEI managed the literature searches and produced the initial draft. All authors read and approved the final manuscript.

Article Information

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ABSTRACT

Aims: Urinary tract infection (UTI) is one the most common bacterial infection and Escherichia coli (E. coli) has been isolated from the majority of UTI cases. On the other hand, the rate of UTIs caused by quinolones resistant E. coli is increasing worldwide. We aimed to perform a systematic review of quinolones resistance of E. coli isolated from urinary tract infections in Iran over last ten years.

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1. INTRODUCTION

In medical references, *E. coli* is the most common agent of urinary tract infections (UTIs) in all parts of the world [1,2]. According to a study it is estimated that 130–175 million human UTIs occur every year in the world, with about 80% being caused by uropathogenic *E. coli* (EUPEC) strains [2]. Using new antibiotics for the treatment of bacterial infections, resistance to the drugs has emerged. Resistance to the new generations of antibiotics and subsequently the development of resistant strains has become prevalent not only among the hospital-acquired infections but also among community-acquired infections [3]. Consequently, the choice of empiric treatments for UTIs has now become challenging, since 20–50% of *E. coli* isolates are now resistant to the first-line of antibiotics [4]. Following the increased resistance to co-trimoxazole and ampicillin as the first line therapy, quinolones have been widely prescribed as an alternative for the treatment of UTIs [6-10]. These antibiotics have become some of the most frequently prescribed antimicrobial agents worldwide and have widely been used in the clinical treatment of various bacterial infections, including the UTIs caused by *E. coli*. However, many studies have reported the isolation of quinolone resistant strains of *E. coli* [3,4].

Resistant to quinolones may occurred as a consequence of point mutations in the genes encoding the targets gyrase (gyrA and gyrB) and topoisomerase IV (parC and parE), or increased the levels of the multidrug efflux pump AcrAB (11-13), and the presence of plasmid-borne mechanisms including QnrA, QnrB, QnrS, and Aac(6)-Ib-cr [14-16].

Given this emerging problem, determining the resistant rate of isolates for quinolones is essential for the better treatment of UTIs.

In different parts of Iran, researchers have reported the prevalence of quinolone resistance for *E. coli* isolated from urinary tract infections [6-10]. However, a systematic review of comprehensive information of these studies has not been performed and subsequently the picture of emerging resistance of *E. coli* in Iran is not available. This study was conducted to determine a national picture of in vitro susceptibilities for ciprofloxacin, nalidixic acid, norfloxacin and ofloxacin among urine isolates of *E. coli*. Since studies used different methods of susceptibility testing with various antibiotics, samples and the isolates (community acquired and nosocomial origin), we systematically reviewed and did meta-analysis of the collected data of these studies.

2. METHODS

2.1 Literature Search

The literature search was performed during the period from 2001 until 2011. For the review process we followed the PRISMA recommendations (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Searched keywords were the MeSH (Medical Subject Headings) terms "Escherichia coli" OR "E. coli" AND "quinolone resistance" AND "antibiotic susceptibility pattern" AND "Iran" in several electronic databases and publishers. These included: PubMed, ScienceDirect, Scopus, Embase, Springer Link Contemporary,
Web of Knowledge (ISI), BioMed Central, BMJ Journals, Cochrane Library, Directory of Open Access Journals (DOAJ), Ebscohost, Emerald Journals, Google Scholar, MD Consult, Ovid SP, Oxford Journals, ProQuest, and Wiley Inter Science Journals. Moreover, Iranian databases of literatures including Iranian Database of Publication (Magiran), Scientific Information Database (SID), Iranian Research Institute for Information Science and Technology (IranDoc), Iranian Database of Medical Sciences Papers (IranMedex), Global Medical Articles Library (Medlib) and Regional Information Centre for Science and Technology (RICeST) were investigated. Additionally, abstract books of microbiology, bacteriology, antibiotic resistance and infectious diseases of Iranian Congresses during the period from 2001 until 2011 were also explored. Iranian medical universities’ websites were searched for relevant reports of congresses, research projects and theses as well.

2.2 Inclusion Criteria

Among all articles or abstracts found, those with the following features were included in the study:

1. *E. coli* samples were collected from Iranian inpatient and outpatient.
2. *E. coli* samples were isolated from urine specimens.
3. Antibiotic susceptibility pattern of *E. coli* isolates was determined by standards methods such as Disk Agar Diffusion (DAD), Minimum Inhibitory Concentration (MIC) and E-test.

2.3 Exclusion Criteria

Studies with at least one of the below criteria were excluded:

1. Case report studies.
2. Studies with low sample size (less than 20 cases).
3. Methods for determination of antibiotic susceptibility testing could not be found from study.
4. The origin of samples was not clear.
5. Duplicate publications both in English and Persian languages (the article published later and/or with more detailed results was chosen for analysis.)
6. Duplicate publications and congress abstracts.

2.4 Critical Appraisal and Selection of Studies

Eighty resources both English and Persian languages were reviewed by three groups namely microbiologists, epidemiologists and specialist of infectious diseases. From 96 studies, 43 were excluded because of one of the above mentioned reasons and 53 studies [6-10,17-64] were selected for data extraction and analysis (Fig. 1). The relevant data including urine sampling methods (mid-stream urinary, catheter and suprapubic aspiration), year and location of sampling, type of patients (inpatient and outpatient), methods for antibiotic susceptibility testing (DAD, MIC and E-test), types of antibiotics, the gender and age (average age) of patients was also recorded. All data were collected and were inserted into an Excel file.

2.5 Statistical Analysis

Statistical analysis of all data was performed using STATA11 software. For the purpose of this study we weighted each study using inverse of variance. In addition, random effect model was used to calculate pooled summary estimate of resistance. Heterogeneity among studies was tested using chi-squared. In order to find the reason for heterogeneity, the result of each antibiotic was pooled according to different variables such as urine sampling methods (mid-stream urinary, catheter and suprapubic aspiration), year and location of sampling, type of patients (inpatient and outpatient), methods for antibiotic susceptibility testing (DAD, MIC and E-test), types of antibiotics, the gender and age (average age) of patients using meta-regression. Antibiotic susceptibility pattern of *E. coli* isolates from UTIs in Iran was pooled by forest plot using the Meta-Analyst software. Statistical heterogeneity of the results was checked using Cochrane Q-test with significance set at $P<0.05$. 

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3. RESULTS

In this study, the data of 53 cross-sectional studies (15304 urine samples) from 2001 to 2011 on quinolones resistance of *E. coli* isolated from UTIs in 22 cities of Iran was collected. Of 53 studies, 44, 41, 8 and 6 of them tested ciprofloxacin, nalidixic acid, norfloxacin and ofloxacin, respectively. Moreover, 31, 12 and 10 of studies were done on out-patients, hospitalized patients and both, respectively. For testing the susceptibility of isolates, 49 and 4 of studies used disk diffusion and E test, respectively. The majority of studies (48 studies) were done on both men and women, while 3 and 2 studies tested only urine samples of women and men, respectively.

Most studies (75.4%) used patients with a wide range of age. But 11 (20.7%) and 2(3.8%) studies used patients under 18 year and adult, respectively. Forty six of studies (86.8%) used midstream sampling method, while the rest used varies methods for sampling including catheter, suprapubic and urine bag. Out of 53 studies, 42(79.2%) were original research, 9 were data collections and 2 were theses or abstract.
First, the data were analyzed for antibiotic resistance to find out resistance to quinolone (Figs. 2–5). Each graph shows the estimated vertical size of resistance in the study. Overall resistance for nalidixic acid, ciprofloxacin, norfloxacin and ofloxacin were 42.3%, 28.2%, 48.5% and 24.1%, respectively. For each antibiotic, the pooled percentage of resistance using random effect has been presented. The results of most studies were significantly heterogenic (P<0.001) (Table 1).

4. DISCUSSION

Urinary tract infections are the most common bacterial infections in human and account for significant morbidity and health care costs [1,2,65-67]. Among both outpatients and inpatients, E. coli is the principal pathogen in urinary tract infections, accounting for 75 to 90% of uncomplicated UTIs [65,67]. Therefore, physicians need to obtain information on local resistance rates by ongoing surveillance performed to monitor changes in the susceptibility of uropathogenic E. coli [68]. On the other hand, the increased prevalence of infections caused by quinolone resistant E. coli makes the empirical treatment of UTIs more difficult.

Our results showed resistance to quinolone drugs are significantly heterogenic among studies performed in Iran which indicated the data of susceptibility testing might be affected by factors such as the method of susceptibility testing, number of samples, age and gender of patients, inpatients or outpatients and so on. However given the large number of samples tested, in particular for nalidixic acid and ciprofloxacin, the results reflect the increased resistance to this group of antibiotics in Iran. A few studies have tested the resistance to norfloxacin and ofloxacin in Iran, however; the resistant rate to these antibiotics is quite considerable. The resistance rate to ciprofloxacin in E. coli isolates vary over the years and between countries, ranging from, 1% to 38% [69]. For example, Of 1,858 E. coli isolates from outpatient midstream urine specimens at 40 North American clinical laboratories in 2004 to 2005, 10.8% of isolates were resistant to ciprofloxacin [70]. This rate of resistance is much lower than the rate in Iran.

![Fig. 2. Meta-analysis of data for resistance to nalidixic acid](image-url)
Fig. 3. Meta-analysis of data for resistance to ciprofloxacin

Fig. 4. Meta-analysis of data for resistance to ofloxacin
This study also found quinolone resistant isolates of *E. coli* from urine were frequently multidrug resistant. The latter results are consistent with our results that point out the higher resistance rate of *E. coli* to quinolones in developing countries. One of the important factors contributing to these high resistance rates might be the high antibiotic use. Studies have also reported the risk factors for emerging of quinolone resistant *E. coli*. For instance, in patients with previous urinary tract infection, urinary catheterization and prior quinolone exposure are associated with a high risk of ciprofloxacin resistant *E. coli* which may cause treatment failure [71]. Moreover, a multivariate analysis also indicated that age over 50 was found to be associated with ciprofloxacin resistance [72]. This is consistent with our results for both ciprofloxacin and nalidixic acid which showed significantly higher resistant rate among older patients (P<0.05). This increased prevalence of resistance requires susceptibility testing of drugs used for treatment of UTIs. Research showed the ciprofloxacin resistant *E. coli* may arise *de novo* in poultry from susceptible progenitors and transmitted to humans via the food supply to cause potentially life-threatening infections [69]. Therefore the use of antibiotics should be supervised not only for humans but also for animal treatments.

### 5. CONCLUSION

In conclusion given the fact that resistance to quinolones has been increased in our country, rational use of this group of antibiotics is required. Given the lower resistant rate of ofloxacin, it is more effective for empirical therapy in Iran. Furthermore, the urine culture and antimicrobial susceptibility testing are essential in successful treatment of UTIs. Finally, the increasing pattern of resistance to quinolones requires ongoing surveillance to
identify further changes of resistance among uropathogenic E. coli.

**COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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