

Resistance pattern of *Escherichia coli* to levofloxacin in Iran: a narrative review

Gholamhossein Hassanshahi¹, Ali Darehkordi², Mahmood Sheikh Fathollahi³, Soudeh Khanamani Falahati-Pour⁴, Ebrahim Rezazadeh Zarandi⁵, Shokrollah Assar^{1,5*}

¹Molecular Medicine Research Center, Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

²Department of Chemistry and Biophysics, School of Sciences, Vali-e-Asr University of Rafsanjan, Rafsanjan, Iran

³Department of Social Medicine, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

⁴Pistachio Safety Research Centre, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

⁵Department of Microbiology, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

Received: July 2019, Accepted: April 2020

ABSTRACT

Fluoroquinolones (FQs) are widely used in the treatment of infections caused by *Escherichia coli*. FQs are broad spectrum antibiotics with high tissue penetration, and ease of use. Therefore, given the concerns existing about drug resistance, we aim to review the latest findings about resistance patterns to levofloxacin (LVX) along with other FQs in *E. coli* infections in different parts of Iran. Evidence shows that quinolones have been used in Iran for nearly 50 years, and that 0-65% of *E. coli* isolates show resistance to FQs. In the western parts of Iran, the highest rate of resistance to LVX (66.7%) has been reported among patients having urinary tract infections with *E. coli* isolates. Few studies and information exist on the antimicrobial resistance of *E. coli* to LVX in different geographical locations of Iran. However, the findings of various studies on this subject show that *E. coli* resistance to LVX is more in the western part of Iran than in central and southern regions, but it is similar among inpatients and outpatients. Therefore, it is reasonable advisable to limit the overuse, inappropriate prescription, and self-medication of LVX to prevent the induction of FQ-resistant strains. Accordingly, in order to obtain a clearer image of resistance to FQs, especially LVX in *E. coli* in Iran, more extensive investigations in different geographical locations and periods of time are required. In addition, antimicrobial stewardship would be helpful in this regard.

Keywords: *Escherichia coli*; Fluoroquinolones; Levofloxacin; Iran; Antibiotic resistance

INTRODUCTION

Since the discovery and synthesis of antibiotics, life expectancy increased by 10 years; however, the World Health Organization (WHO) reported antibiotic resistance as a "major global threat" in 2014. According to a report by the UN-affiliated agency on 30th April 2014, the world is entering the "post-antibiotic" period when simple infections that were curable for years would threaten individuals' life. The

*Corresponding author: Shokrollah Assar, Ph.D, Molecular Medicine Research Center, Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran AND Department of Microbiology, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.
Tel: +98-9132929321
Fax: +98-3431315003
Email: assar_sh@rums.ac.ir

therapeutic effects of antibiotics are on the decline at an alarming and inevitable pace similar to the phenomenon of global warming (1, 2). Antimicrobial resistance is greatly increasing among bacteria, and governments are spending large amounts of budgets to control it. It is necessary to use appropriate drugs for the treatment of infections (3, 4). *Escherichia coli* is a bacterium in which antimicrobial resistance is increasingly high (5).

This microorganism is normally found in the gut microbiomes of mammals, birds, and fish (6, 7). It provides some benefits to the hosts and plays an important role in the production of vitamins K and B12 both in hosts and biotechnology (7, 8). However, *E. coli* is a major human pathogen that causes urinary tract infections (UTIs), enterocolitis, and septicemia in humans. Over 10 pathotypes of *E. coli* have been identified to date, and different pathotypes could cause similar diseases through various mechanisms (5, 9).

Nalidixic acid was the first quinolone synthesized in 1962 (10). Due to its low oral absorption, limited antibacterial spectrum, high ability to bind to proteins, and low tolerability, nalidixic acid was restricted in treating bacterial infections. Thus, many fluoroquinolone analogs have been produced since the last decades (11). For example, norfloxacin, ciprofloxacin, and LVX were patented in 1987, 1980, and 1965, respectively (12, 13).

LVX, the L-isomer of ofloxacin and one of the FQs, has been available since 1992 (14, 15). Following the introduction of LVX and due to its strong effects on a wide range of Gram-positive and Gram-negative bacteria, many studies have been conducted to determine its benefits. However, researchers have reported that LVX overuse gradually induces the expression of resistant genes and leads to the emergence of resistant strains. Therefore, standardized discs containing LVX have been introduced, with the susceptibility patterns of different bacteria evaluated (16-18). LVX interferes with the DNA replication of the bacterium by inhibiting the activity of the DNA gyrase enzyme, thereby inhibiting the DNA synthesis of the bacterium. This characteristic prevents bacterial replication and produces bactericidal effects (19).

LVX is frequently prescribed to treat *E. coli* infections (14, 20-22). Because LVX is an effective therapeutic agent, it is prescribed by Iranian physicians for treating infections. It has some properties, including daily administration, high effectiveness, low cost,

and minimum side effects (23). Several studies have been conducted on the antimicrobial resistance of *E. coli* to many antibiotics in Iran; however, few studies have been carried out to determine its resistance to LVX. Moreover, in a recent study on the limitation of the use of LVX, a reduction in the frequency of FQ-resistant *E. coli* species has been reported (24). Therefore, the present review aims to achieve a clearer image of the antimicrobial resistance of *E. coli* to LVX in Iran.

The mechanism of FQs' function. Quinolones with fluorine in their structure are called FQs, and LVX is a member of fluoroquinolone antibiotics. Fluorination enhances the effects of quinolones on both Gram-negative and Gram-positive bacteria and improves drug entry into the bacterial cells (25). According to the antimicrobial activity spectrum, quinolones are classified into four generations; the first generation includes cinoxacin, pefloxacin, and nalidixic acid; the second generation consists of ofloxacin, ciprofloxacin, enoxacin, lomefloxacin, and norfloxacin; the third generation is comprised of gemifloxacin, LVX, sparfloxacin, gatifloxacin, and moxifloxacin; and the fourth generation includes trovafloxacin and alatrofloxacin (10).

Quinolones have impacts on some facultative anaerobic Gram-negative bacilli, such as enterobacteriaceae. All compounds from the quinolone family have approximately a similar basic structure (4-aminoquinoline) and a mechanism of action (26). They inhibit DNA replication both selectively and reversibly, and stop sensitive bacteria by limiting the function of DNA gyrase and topoisomerase IV. DNA gyrase is a tetrameric enzyme with two subunits of A and B. These two subunits are encoded by *gyrA* and *gyrB* genes and play a central role in the unwinding and twisting processes of DNA. Similar to DNA gyrase, topoisomerase IV is a tetrameric enzyme with two subunits. These subunits are encoded by *parE* and *parC* genes and involved in separating two daughter chromosomes during the replication process. FQs commonly interfere with the GyrA subunit of DNA gyrase (27).

FQs serve as bactericidal drugs by inhibiting DNA replication and transcription. Both DNA strands are interconnected within the bacterial cell. For bacterial division, two strands of DNA should be separated from each other. To facilitate the separation of the strands, DNA gyrase helps strands get detached and

rejoined (28, 29). Thus, DNA gyrase is really essential for the survival and proliferation of bacteria. Most eukaryotic cells, especially in humans, lack this enzyme. Therefore, it could be considered an attractive target for antibacterial compounds, especially quinolones (30).

LVX's antimicrobial activity. LVX is most often used in treating patients suffering from several disorders, such as arthritis and skin infections, as well as disorders in the lungs, airways, sinuses, bones, urethra, kidneys, and prostate (31). It is reactive against a broad spectrum of bacteria and affects both Gram-positive and Gram-negative aerobic bacteria as well as some drug-resistant anaerobes. In addition, LVX is highly effective in treating unusual bacterial infections, such as non-gonococcal urethritis caused by *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *E. coli*-induced diarrhea, *Campylobacter jejuni* and *Shigella* spp. (32).

***E. coli* resistance to LVX in the world.** *E. coli* resistance to FQs was very low at approximately less than 2% in the 1990s; however, its resistance to LVX has significantly increased by more than 50% in 2000 (33). The resistance of some extended-spectrum beta-lactamase (ESBL)-producing microorganisms to LVX has reached 100%. In terms of geography, the reported prevalence rate of resistance to FQs varies among the European countries, from 7.9% in Sweden to 52% in Turkey. In the Asian countries, the prevalence rate of FQ-resistant *E. coli* in the samples of community-acquired UTI was reported to be about 25% in Korea (34) and 69% in India (35). In the United States, the frequency of LVX-resistant *E. coli* was 1% in 1994, but it varied from 2 to 27% among outpatients and inpatients with UTI in 2014 (36). It was reported that 23.4% of *E. coli* isolates in the Japanese population were resistant to LVX in 2012 (37).

It has been verified that *E. coli* resistance has been remarkably increasing to FQs, such as LVX, throughout the world. Within the 4-year period of 2005-2009, *E. coli* resistance to LVX increased from 29.49 to 43.20%. However, the resistance pattern of *E. coli* differed from one year (43.20% in 2008) to another (31.75% in 2009) (38). Studies conducted on the antimicrobial resistance of *E. coli* in North American countries in addition to the high resistance of *E. coli* to LVX suggest that at least it would be preferable not to choose LVX as the first line of treatment in

complicated UTIs (39).

***E. coli* resistance to FQs and LVX in Iran.** Many factors are involved in the induction of antibiotic resistance in *E. coli* (40), which are different in developed, developing, and underdeveloped countries (41). Most of the studies in this field have been carried out in developed countries, so the comparison of bacterial resistance patterns to other countries, such as Iran, is relatively difficult (40). Thus, the comparison of the LVX resistance pattern of *E. coli* inside different geographical regions of Iran to other countries could be useful.

FQs have been prescribed in Iran for about 50 years. Several studies have been conducted in recent years on the sensitivity and resistance patterns of *E. coli* to LVX and other FQs (Table 1). One of the first studies that investigated quinolone resistance in Iran was carried out by Gharegozlou et al. (1968). They studied 1,251 urine specimens and found that *E. coli* (131 samples) was the most frequent bacterium in urine cultures. In their studies, *E. coli* was shown to be sensitive to nalidixic acid in 16 out of 20 samples (80%) (42).

Iranian studies on the pattern of *E. coli* resistance to LVX have given inconsistent results. The report by Haeli et al. (2013) is the first available Iranian study to have investigated the LVX resistance pattern of *E. coli* in parallel with other FQs. They claimed *E. coli* resistance to LVX was 12.5% in Tehran population in the time period of 2009-2011 (43). The highest rate of resistance to LVX (64.3%) was reported by Akya et al. (2017) in patients with UTI caused by ESBL-producing isolates of *E. coli* in Kermanshah. However, the lowest rate of resistance to LVX was reported in non-ESBL isolates (21.3%). In their study, 66 out of 240 isolates (27.5%) produced ESBLs (44). In another Iranian report, the frequency of ESBL-producing *E. coli* isolates showed to be up to 89% (45). In other studies, resistance to LVX in UTI patients was 21.3-66.7% (44-50). Nonetheless, the proportion of ESBL-producing isolates was determined in these studies. LVX resistance in *E. coli* isolates from patients with diarrhea is surprisingly low. For instance, it was 0% and 5.6% in non-ESBL- and ESBL-producing isolates, respectively (51-53). Two studies used more than one organ specimen (specimens from different body sites), and the rate of resistance to LVX was 43.8% and 61.6% in the hospitalized patients (Fig. 1) (54, 55).

Table 1. Fluoroquinolones resistance pattern of *E. coli*

No.	Sample Type	In- or Out-Patient	City	Sample size	Type of Quinolone	Antibiogram Result (%)			Author	Study Year	Publish Year	Reference
						S	I	R				
1	Respiratory	In	Tehran	48 (ESBL*=10) (non ESBL=38)	Levofloxacin Ciprofloxacin	70.8 70.8	16.6 0	12.5 29.1	Haeili	2009-2011	2013	43
2	Stool	In	Shiraz	54 (ESBL=7) (non ESBL=47)	Levofloxacin Ciprofloxacin	NR NR	NR NR	5.56 8.33	Ghorbani-Dalini	2010	2015	52
3	Stool	Out	Shiraz	8 (DAEC)	Levofloxacin Ciprofloxacin	87.5 75	12.5 25	0 0	Abbasi	2012-2013	2016	51
4	Stool	Out	Tehran	31 (ESBL) 19 (non ESBL)	Levofloxacin Ciprofloxacin Levofloxacin Ciprofloxacin	NR NR NR NR	NR NR NR NR	3.2 29.3 0 3.2	Kazemian	2014-2015	2016	53
5	Urine	In	Khorramabad	140	Levofloxacin Ciprofloxacin Nalidixic acid Norfloxacin Ofloxacin	57.1 55 82.8 52.9 55	NR NR NR NR NR	42.9 45 17.2 47.1 45	Firoozeh	2012	2014	46
6	Urine	Out	Estahban	224	Levofloxacin Ciprofloxacin Nalidixic acid Norfloxacin Ofloxacin	70.5 56.3 44.6 67.4 68.3	5.8 4.5 6.7 4.9 2.7	23.7 39.2 48.7 27.7 29	Rashki	2012-2013	2015	48
7	Urine	In	Zanjan-Qazvin	200	Levofloxacin Ciprofloxacin Nalidixic acid Norfloxacin Gatifloxacin	42.5 44 32.5 44.5 42	1.5 0 1 0 0	56 56 66.5 55.5 58	Rezazadeh Akya	2014-2015	2016 2017	47 44
8	Urine	Out	Kermanshah	66 (ESBL) 174 (non ESBL)	Levofloxacin Ciprofloxacin Nalidixic acid Levofloxacin Ciprofloxacin Nalidixic acid	28.8 28.8 15.2 76.4 76.4 78.7	4.5 6 0 2.3 3.5 0	66.7 65.2 84.8 21.3 20.1 21.3				
9	Urine	Out	Yasuj	144	Levofloxacin Ciprofloxacin Nalidixic acid Gatifloxacin	34.7 36.1 60.4 35.4	NR NR NR NR	NR NR NR NR	Mirzaei	2014-2015	2018	56
10	Urine	In	Shiraz	121	Levofloxacin Ciprofloxacin Nalidixic acid Norfloxacin Ofloxacin	49.6 41.3 19 44.6 46.3	2.5 9.9 9.1 4.1 3.3	47.9 48.4 71.9 51.2 50.4	Malekzadegan	2016-2017	2019	50
11	Mix*	In	Semnan	216	Levofloxacin Ciprofloxacin	38.4 36.1	NR NR	NR NR	Pajand	2014	2017	54

Table 1. Continuing...

12	Mix	In	Tehran	16	Levofloxacin	56.2	NR	43.8	Azimi	2013-2018	2019	55
				49	Ciprofloxacin	53.1	NR	46.9				
				6	Nalidixicacid	83.3	NR	16.7				

Abbreviation: S: Sensitive, I: Intermediate, R: Resistant, ESBL: Extended Spectrum Beta-Lactamases, NR: Not Reported, DAEC: Diffuse-Adhering *Escherichia Coli*, Mix: Mixed clinical samples

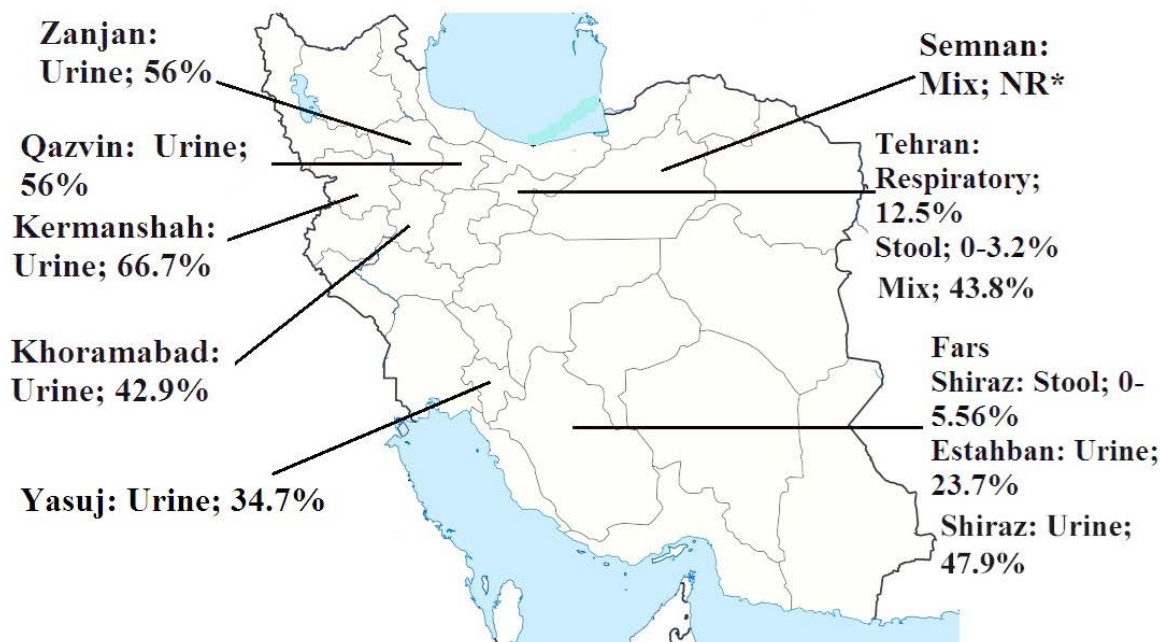


Fig. 1. Percentage of levofloxacin resistance *E. coli* in Iran

The antimicrobial susceptibility of *E. coli* to FQs, especially LVX, has been more or less examined in Iran. Such studies indicate that *E. coli* strains isolated from UTI exhibit the highest rate of resistance to LVX among other samples. However, LVX resistance was different in various geographic regions of Iran. The antimicrobial resistance of *E. coli* to LVX was higher in the western provinces of Iran, such as Lorestan (46), Qazvin, Zanjan (47), and Kermanshah (44) than in the central ones, such as Tehran, Alborz, and Semnan (54, 55), as well as in the southern province of Fars (51, 52). According to the study conducted in Yasuj, the center of Kohgiluyeh and Boyer-Ahmad Province, 50 (34.7%) of 144 urine samples showed *E. coli* resistance to LVX (56). Four different studies conducted in the southern regions of Iran, i.e. Shiraz and Estahban (48, 50-52), reported the antimicrobial resistance of *E. coli* isolates to LVX at 5.56

to 47.9%, while it was much higher (42.9-66.7%) in the western regions (44, 46, 47). One of the major points of present study was the significant difference in the resistance rate of *E. coli* isolated from inpatients and outpatients (Table 1). Therefore, one could conclude that the pattern of resistance to LVX in hospitalized and community-acquired patients did not significantly change from 2000 to 2015. The inappropriate administration, excessive prescription, and prescription of LVX without the antibiogram algorithm could be the reasons for not observing a difference between *E. coli* isolates from inpatients and outpatients in the Iranian health system. A study has been conducted in Tehran (the capital of Iran) in different periods of time, which have reported the pattern of *E. coli* resistance to LVX. According to this study, antimicrobial resistance to LVX has fluctuated between 33.3% and 100% during 2013 to 2018 (55).

In addition, data from other geographical regions of Iran indicate that LVX resistance has been following an ascendant pattern.

To sum it up, few studies have been conducted in Iran on *E. coli* resistance to FQs, especially LVX. Many studies have reported that the level of *E. coli* resistance to LVX in the western part of Iran has been increasing like many other countries in the world (44, 46, 47). The main reasons for the high prevalence of such resistance could be (a) the use of antibiotics in livestock, (b) the conditions of animal husbandry with livestock being common in the western region of Iran, (c) the local resistance pattern, (d) the duration of antibiotics consumption, (e) excessive prescription of antibiotics, (f) self-medication, (g) low health standards, (h) old age, (i) use of LVX for 48 hours during the last year (57). Indeed, to obtain a clearer view of the local pattern of *E. coli* resistance to LVX, further studies are required with different samples in different geographic regions of Iran to obtain comprehensive and accurate information about *E. coli* resistance to FQs, especially LVX.

CONCLUSION

It is worth saying that all aforementioned studies have been carried out on samples collected from out-patients and inpatients in different regions. Therefore, it is difficult to make a comparison among them. Most studies were conducted in a short period of time (one year) and in a limited geographical region. According to the literature, although LVX has not been used for a long time in Iran, the resistance of *E. coli*, as a nosocomial pathogen, has been increasingly high due to LVX overuse. Thus, more attention must be paid to employing stewardship antibiotics.

ACKNOWLEDGEMENTS

We thank faculty members of Rafsanjan University of Medical Sciences for their kind cooperation.

REFERENCES

1. Prasad K, Lekshmi G, Ostrikov K, Lussini V, Blinco J, Mohandas M, et al. Synergic bactericidal effects of reduced graphene oxide and silver nanoparticles against Gram-positive and Gram-negative bacteria. *Sci Rep* 2017;7: 1-11.
2. Burnham C-AD, Leeds J, Nordmann P, O'Grady J, Patel J. Diagnosing antimicrobial resistance. *Nat Rev Microbiol* 2017; 15: 697-703.
3. Paharik AE, Schreber HL, Spaulding CN, Dodson KW, Hultgren SJ. Narrowing the spectrum: the new frontier of precision antimicrobials. *Genome Med* 2017; 9: 110.
4. Eurosurveillance editorial team. European union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food 2012 published. *Euro Surveill* 2014; 19: 20748.
5. Allocati N, Masulli M, Alexeyev MF, Di Ilio C. *Escherichia coli* in Europe: an overview. *Int J Environ Res Public Health* 2013; 10: 6235-6254.
6. Leimbach A, Hacker J, Dobrindt U. *E. coli* as an all-rounder: the thin line between commensalism and pathogenicity. *Curr Top Microbiol Immunol* 2013; 358: 3-32.
7. Blount ZD. The unexhausted potential of *E. coli*. *eLife* 2015; 4: e05826.
8. Baeshen MN, Al-Hejin AM, Bora RS, Ahmed M, Ramadanass H, Saini KS, et al. Production of biopharmaceuticals in *E. coli*: current scenario and future perspectives. *J Microbiol Biotechnol* 2015; 25: 953-962.
9. Miri ST, Dashti A, Mostaan S, Kazemi F, Bouzari S. Identification of different *Escherichia coli* pathotypes in north and north-west provinces of Iran. *Iran J Microbiol* 2017; 9: 33-37.
10. Pham TD, Ziora ZM, Blaskovich MA. Quinolone antibiotics. *Medchemcomm* 2019; 10: 1719-1739.
11. Darehkordi A, Javanmiri M, Ghazi S, Assar S. Synthesis of N-aryl-2, 2, 2-trifluoroacetimidoyl piperazinylquinolone derivatives and their antibacterial evaluations. *J Fluor Chem* 2011; 132: 263-268.
12. Stone MRL, Masi M, Phetsang W, Pagès JM, Cooper MA, Blaskovich MAT. Fluoroquinolone-derived fluorescent probes for studies of bacterial penetration and efflux. *Medchemcomm* 2019; 10: 901-906.
13. Rehman A, Patrick WM, Lamont IL. Mechanisms of ciprofloxacin resistance in *Pseudomonas aeruginosa*: new approaches to an old problem. *J Med Microbiol* 2018; 68: 1-10.
14. Bernard J, Armand-Lefèvre L, Luce E, El Mniai A, Chau F, Casalino E, et al. Impact of a short exposure to levofloxacin on faecal densities and relative abundance of total and quinolone-resistant *Enterobacteriaceae*. *Clin Microbiol Infect* 2016; 22: 646.e1-646.e4.
15. Gill GK, Chhabra M, Chawla SP. Levofloxacin-induced desquamation: A possible and rare case report. *Curr Drug Saf* 2020; 15: 61-64.
16. Pan Z, Liu R, Zhang P, Zhou H, Fu Y, Zhou J. Com-

- ination of tigecycline and levofloxacin for successful treatment of nosocomial pneumonia caused by New Delhi Metallo- β -Lactamase-1-producing *Raoultella planticola*. *Microb Drug Resist* 2017; 23: 127-131.
17. Hsu PI, Tsai FW, Kao SS, Hsu WH, Cheng JS, Peng NJ, et al. Ten-day quadruple therapy comprising proton pump inhibitor, bismuth, tetracycline, and levofloxacin is more effective than standard levofloxacin triple therapy in the second-line treatment of *Helicobacter pylori* infection: A randomized controlled trial. *Am J Gastroenterol* 2017; 112: 1374-1381.
 18. Humphries RM, Hindler JA, Shaffer K, Campeau SA. Evaluation of ciprofloxacin and levofloxacin disk diffusion and Etest using the 2019 *Enterobacteriaceae* CLSI breakpoints. *J Clin Microbiol* 2019; 57: e01797-18.
 19. Ismail SJ, Mahmoud SS. First detection of New Delhi metallo- β -lactamases variants (NDM-1, NDM-2) among *Pseudomonas aeruginosa* isolated from Iraqi hospitals. *Iran J Microbiol* 2018; 10: 98-103.
 20. Asif M. Role of quinolones and quinoxaline derivatives in the advancement of treatment of tuberculosis. *Int J Sci World* 2015; 3: 18-36.
 21. Garoff L, Yadav K, Hughes D. Increased expression of Qnr is sufficient to confer clinical resistance to ciprofloxacin in *Escherichia coli*. *J Antimicrob Chemother* 2018; 73: 348-352.
 22. Kusachi S, Oe K, Okuda Y, Sasaki J, Maetani I, Watanabe M, et al. Clinical study on levofloxacin injection for surgical infection. *Japan J Chemother* 2017; 65: 445-455.
 23. Noel GJ. A review of levofloxacin for the treatment of bacterial infections. *Clin Med Ther* 2009; 1: 433-458.
 24. Wu H-H, Liu H-Y, Lin Y-C, Hsueh P-R, Lee Y-J. Correlation between levofloxacin consumption and the incidence of nosocomial infections due to fluoroquinolone-resistant *Escherichia coli*. *J Microbiol Immunol Infect* 2016; 49: 424-429.
 25. Bax BD, Chan PF, Eggleston DS, Fosberry A, Gentry DR, Gorrec F, et al. Type IIA topoisomerase inhibition by a new class of antibacterial agents. *Nature* 2010; 466: 935-940.
 26. Iredell J, Brown J, Tagg K. Antibiotic resistance in Enterobacteriaceae: mechanisms and clinical implications. *BMJ* 2016; 352:h6420.
 27. Aldred KJ, Kerns RJ, Osheroff N. Mechanism of quinolone action and resistance. *Biochemistry* 2014; 53: 1565-1574.
 28. Cormier R, Burda WN, Harrington L, Edlinger J, Kodigepalli KM, Thomas J, et al. Studies on the antimicrobial properties of N-acylated ciprofloxacin. *Bioorg Med Chem Lett* 2012; 22: 6513-6520.
 29. Collin F, Karkare S, Maxwell A. Exploiting bacterial DNA gyrase as a drug target: current state and perspectives. *Appl Microbiol Biotechnol* 2011; 92: 479-497.
 30. Ahmed A, Daneshtalab M. Nonclassical biological activities of quinolone derivatives. *J Pharm Pharm Sci* 2011; 15: 52-72.
 31. Wu H-H, Liu H-Y, Lin Y-C, Hsueh P-R, Lee Y-J. Correlation between levofloxacin consumption and the incidence of nosocomial infections due to fluoroquinolone-resistant *Escherichia coli*. *J Microbiol Immunol Infect* 2016; 49: 424-429.
 32. Zhanel GG, Hartel E, Adam H, Zelenitsky S, Zhanel MA, Golden A, et al. Solithromycin: a novel fluoroketolide for the treatment of community-acquired bacterial pneumonia. *Drugs* 2016; 76: 1737-1757.
 33. Dalhoff A. Global fluoroquinolone resistance epidemiology and implications for clinical use. *Interdiscip Perspect Infect Dis* 2012; 2012: 1-37.
 34. Lee S-J, Lee DS, Choe HS, Shim BS, Kim CS, Kim ME, et al. Antimicrobial resistance in community-acquired urinary tract infections: results from the Korean antimicrobial resistance monitoring system. *J Infect Chemother* 2011; 17: 440-446.
 35. Akram M, Shahid M, Khan AU. Etiology and antibiotic resistance patterns of community-acquired urinary tract infections in JNMC Hospital Aligarh, India. *Ann Clin Microbiol Antimicrob* 2007; 6: 1-7.
 36. Yassine I, Rafei R, Osman M, Mallat H, Dabboussi F, Hamze M. Plasmid-mediated quinolone resistance: Mechanisms, detection, and epidemiology in the Arab countries. *Infect Genet Evol* 2019; 76:104020.
 37. Yokota S-i, Sato T, Okubo T, Ohkoshi Y, Okabayashi T, Kuwahara O, et al. Prevalence of fluoroquinolone-resistant *Escherichia coli* O25: H4-ST131 (CTX-M-15-non-producing) strains isolated in Japan. *Chemotherapy* 2012; 58: 52-59.
 38. Jang WH, Yoo DH, Park SW. Prevalence of and risk factors for levofloxacin-resistant *E. coli* isolated from outpatients with urinary tract infection. *Korean J Urol* 2011; 52: 554-559.
 39. Hsueh P-R, Hoban DJ, Carmeli Y, Chen S-Y, Desikan S, Alejandria M, et al. Consensus review of the epidemiology and appropriate antimicrobial therapy of complicated urinary tract infections in Asia-Pacific region. *J Infect* 2011; 63: 114-123.
 40. Bengtsson-Palme J, Kristiansson E, Larsson DJ. Environmental factors influencing the development and spread of antibiotic resistance. *FEMS Microbiol Rev* 2018; 42: 68-80.
 41. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *Pharm Ther* 2015; 40: 277-283.
 42. Gharagozloo R, Ghavamian P. Bacteriological survey of urinary tract infection. *Acta Med Iran* 1968; 3-4: 105-119.
 43. Haeili MGA, Nomanpour B, Omrani M, Feizabadi MM. Drug resistance patterns of bacteria isolated from patients with nosocomial pneumonia at Tehran hospi-

- tals during 2009-2011. *J Infect Dev Countr* 2013; 7: 312-317.
44. Akya A, Chegenelorestani R, Elahi A, Hamzavi Y. Frequency of plasmid-mediated quinolone resistance genes in extended-spectrum β -lactamase-producing *Escherichia coli*. *J Mazandaran Univ Med Sci* 2017; 27: 41-51.
 45. Leylabadlo HEEH, Poulrak T, Aghazadeh M, Kafil HS, Samadi H. Extended-spectrum beta-lactamase producing Gram negative bacteria in Iran. *Afr J Infect Dis* 2017; 11: 39-53.
 46. Firoozeh F, Zibaei M, Soleimani-Asl Y. Detection of plasmid-mediated qnr genes among the quinolone-resistant *Escherichia coli* isolates in Iran. *J Infect Dev Ctries* 2014; 8: 818-822.
 47. Rezazadeh M, Baghchesaraei H, Peymani A. Plasmid-mediated quinolone-resistance (*qnr*) genes in clinical isolates of *Escherichia coli* collected from several hospitals of Qazvin and Zanjan provinces, Iran. *Osong Public Health Res Perspect* 2016; 7: 307-312.
 48. Rashki A, Rahdar M, Ghalehnoo ZR. Characterization of uropathogenic *Escherichia coli*: Distribution of adhesin-encoding genes and O-serotypes among ciprofloxacin susceptible and resistant isolates. *Jundishapur J Microbiol* 2019; 12(9):e89179.
 49. Iranpour D, Hassanpour M, Ansari H, Tajbakhsh S, Khamisipour G, Najafi A. Phylogenetic groups of *Escherichia coli* strains from patients with urinary tract infection in Iran based on the new Clermont phylotyping method. *Biomed Res Int* 2015; 2015: 846219.
 50. Malekzadegan Y, Rastegar E, Moradi M, Heidari H, Sedigh Ebrahim-Saraie H. Prevalence of quinolone-resistant uropathogenic *Escherichia coli* in a tertiary care hospital in south Iran. *Infect Drug Resist* 2019; 12: 1683-1689.
 51. Abbasi P, Kargar M, Doosti A, Mardaneh J, Ghorbani-Dalini S, Dehyadegari MA. Molecular detection of diffusely adherent *Escherichia coli* strains associated with diarrhea in Shiraz, Iran. *Arch Pediatr Infect Dis* 2017; 5 (2); e37629.
 52. Ghorbani-Dalini S, Kargar M, Doosti A, Abbasi P, Sarshar M. Molecular epidemiology of ESBL genes and multi-drug resistance in diarrheagenic *Escherichia coli* strains isolated from adults in Iran. *Iran J Pharm Res* 2015; 14: 1257-1262.
 53. Kazemian H, Heidari H, Ghanavati R, Mohebi R, Ghafourian S, Shavalipour A, et al. Characterization of antimicrobial resistance pattern and molecular analysis among extended spectrum β -Lactamase-producing *Escherichia coli*. *Pharm Sci* 2016; 22: 279-284.
 54. Pajand O, Ghassemi K, Kamali F, Taghavipoor S, Hojabri Z. Investigation of phylogenetic diversity among *Escherichia coli* isolates recovered from hospitalized patients. *Koomesh* 2017; 19: 207-212.
 55. Azimi T, Maham S, Fallah F, Azimi L, Gholinejad Z. Evaluating the antimicrobial resistance patterns among major bacterial pathogens isolated from clinical specimens taken from patients in Mofid Children's Hospital, Tehran, Iran: 2013-2018. *Infect Drug Resist* 2019; 12: 2089-2102.
 56. Mirzaii M, Jamshidi S, Zamanzadeh M, Marashifard M, Hosseini SAAM, Haeili M, et al. Determination of *gyrA* and *parC* mutations and prevalence of plasmid-mediated quinolone resistance genes in *Escherichia coli* and *Klebsiella pneumoniae* isolated from patients with urinary tract infection in Iran. *J Glob Antimicrob Resist* 2018;13:197-200.
 57. Manyi-Loh C, Mamphweli S, Meyer E, Okoh A. Antibiotic use in agriculture and its consequential resistance in environmental sources: potential public health implications. *Molecules* 2018; 23: 795.