

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

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### 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 30<sup>th</sup> April 2014, the world is entering the "post-antibiotic" period when simple infections that were curable for years would threaten individuals' life. The

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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

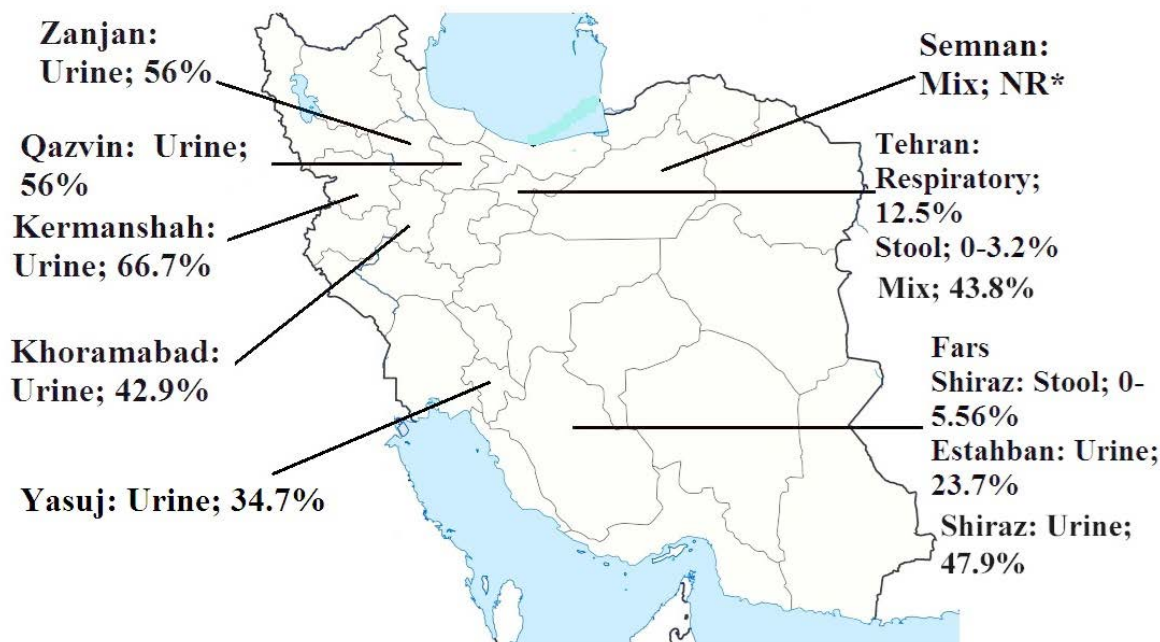


Fig. 1. Percentage of levofloxacin resistance *E. coli* in Iran

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.

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