Evaluation of Levofloxacin Prescription Pattern and Appropriateness Rate in the Outpatient Setting; A Cross-Sectional Study from Iran (2018-2019)

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Authors' contributions

*This work was carried out in collaboration among all authors. All authors read and approved the final
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ABSTRACT

Background: Levofloxacin is prescribed widely as a first-line or alternative treatment option for
different infectious diseases. The inappropriate use of this agent has increased the risk of antibiotic
resistance, which has convinced researchers to address this issue by designing antibiotic
prescription pattern studies.
Aim: This study aimed to evaluate levofloxacin's prescription pattern and appropriateness in the
outpatient setting in Iran.
Methodology: This cross-sectional study included all admitted prescriptions containing levofloxacin
from October 2018 to June 2019. Data regarding the demographics, clinical and laboratory
presentations, preexisting comorbidities, dose and duration of levofloxacin, and the prescribers

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medical specialty were collected by reviewing the patient's prescriptions or history taking. The pattern and appropriateness of prescriptions were evaluated according to the assessment tool based on accepted international guidelines.

Results: A total of 300 eligible patients (median age: 56.5 years; 56.7% male) were included in the study. Respiratory tract infections were the most common indication for levofloxacin prescription (55.6%); more than half of them were related to community-acquired pneumonia (29.6%). The inappropriateness rate for levofloxacin prescription was 55.3 %, of which 12.6% were related to community-acquired pneumonia, 9.6% skin infections, 8.4% rhinosinusitis, and 6.6% Urinary tract infection. Only 54 (18.0%) patients received levofloxacin with an appropriate indication, dose, and duration, indicating its rational use.

Conclusion: This study found that more than half of all levofloxacin prescriptions in the outpatient setting are inappropriate, contributed mainly to respiratory tract diseases. Interventions that target these health care providers are essential to improve prescribing of this valuable antibiotic.

1. INTRODUCTION

Antibiotics have a critical role in treating infectious diseases and increasing life expectancy [1]. Despite these beneficial roles, their inappropriate use and overuse might increase the risk of antibiotic resistance and adverse drug reactions and additional costs, ultimately leading to poor quality medical care and misallocation of resources [2].

It is estimated that about 80% of total antibiotic prescriptions are seen in outpatient settings according to the World Health Organization (WHO) statement [3], nearly half of which might be inappropriate due to incorrect antibiotic choice, dose, or duration of treatment [4]. A recent systematic review and meta-analysis showed that 45.25% of all antibiotic prescriptions are related to the outpatient setting, which this rate is higher than those seen in the other low- and middle-income countries [5]. One of the recommended strategies to combat the excessive use of antibiotics is to evaluate the appropriateness rate of their utilization [6]. This strategy can be performed through drug utilization evaluation (DUE), a systematically defined approach for assessing the pattern and appropriate use of antibiotics to achieve optimum and rational prescriptions [7].

Fluoroquinolones (FQs), despite their severe probable side effects, are still among the most widely used antibacterial agents [8]. Food and Drug Administration (FDA) released FQs boxed warnings several times due to increased risk of permanent and life-threatening adverse drug reactions [9-12]. The last version of boxed warnings has limited the fluoroquinolone prescription in several conditions such as acute bacterial rhinosinusitis, acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infection (UTI) to a medical situation that no other effective alternatives exist and the benefits outweighed the risks [13].

Levofloxacin, a third-generation FQ with broad-spectrum activity, is popularly prescribed for different infectious diseases. Although levofloxacin is mainly recommended as an alternative treatment option rather than a first-line option, the favorable pharmacokinetics, pharmacodynamics, and bactericidal effects are responsible for the growth in its prescription [14].

According to WHO's Access, Watch, Reserve (AWaRe) classification, levofloxacin is categorized as a "Watch Group Antibiotic," meaning that it should be prescribed cautiously in a limited number of conditions and considered as a target of local and national DUEs and Antibiotic Stewardship Programs (ASP) [15]. This issue is especially important for populations with high levofloxacin resistance, such as Iran, as reported by several studies [16,17].

To the best of our knowledge, this is the first DUE study of levofloxacin in the outpatient setting that aimed primarily at evaluating the prescription patterns and the inappropriateness rate of levofloxacin in outpatient settings. The secondary goals would be identifying the specific health conditions and specialties with the most inappropriate prescription in the outpatient setting. The result of this study might practically be used as a conceptual basis to design targeted interventions and ASP to reduce inappropriate levofloxacin utilization.

2. METHODS

2.1 Design and Site

This cross-sectional study was conducted in the 13 Aban Pharmacy, a referral community pharmacy affiliated with Tehran University of Medical Sciences, Tehran, Iran. The Institute of Pharmaceutical Sciences(TIPS) ethics committee, affiliated with Tehran University of Medical Sciences, approved the study protocol with this ethic code IR.TUMS.VCR.REC.163/1397. Data were collected during nine months between October 2018 and June 2019 in a 6-hour work shift (2 pm to 8 pm) on working days. Verbal and formal consent was obtained from participants.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria: adults, The patient's presence in the pharmacy, Oral levofloxacin in the patient prescription.

exclusion criteria: age< 18 years, hospitalized patients, intravenous levofloxacin, the patients were reluctant to participate in the study.

2.3 Data Collection

Data regarding the demographics, dose, and duration of levofloxacin, and the prescribers medical specialty were recorded from the patient's prescriptions. Some other data, including clinical and laboratory presentations, preexisting comorbidities, and drug history, were collected by an educated pharmacy student through face-to-face interviews. Finally, the collected data related to each patient were reviewed blindly by an infectious disease (ID) specialist . Based on the collected data and ID specialist diagnosis, the infectious disease of each patient was determined and classified. Then the ID specialist determined the appropriateness or inappropriateness of the prescriptions based on their compatibility with our assessment tool, which is based on the globally approved infectious disease guidelines. The dose and duration of treatment were evaluated by clinical pharmacist in cases where the levofloxacin indication was appropriate. At the end of the treatment period, the patients were followed up by telephone to know about any potential drug adverse effects during levofloxacin therapy. And if they experience any adverse effects, the Naranjo scores were calculated.

2.4 Development of Assessment Tool

As shown in the supplementary table, the assessment tool was developed under the supervision of an ID specialist and a clinical pharmacist via searching and reviewing the accepted global guidelines, systematic reviews, and randomized clinical trials [18-36]. All conditions that levofloxacin could be prescribed, place in therapy (first-line or alternative), dosing, and duration of treatment were included in this assessment tool.

2.5 Statical Analysis

Statistical analyses were performed using the IBM statistics SPSS25. First, the normality was checked with the Kolmogorov-Smirnov test for quantitative data, and mean ± standard deviation was used in normal data distribution. In the case of non-normal data distribution, median and interquartile range (IQR) were used. Frequency was used to analyze qualitative data.

3. RESULTS AND DISCUSSION

After reviewing the prescriptions of nearly two thousand patients, a total of 554 levofloxacin prescriptions were identified. Two hundred and fifty-four prescriptions were excluded based on the exclusion criteria. A total of 300 eligible patients were enrolled in the study. The demographic characteristics of the subjects are shown in Table 1. The median age was 56.5 years (IQR=19.5), and 170 (56.7%) were male. Nine (3.0%) patients reported a history of drug allergy (beta-lactams, macrolides, and fluoroquinolones). Two hundred and three out of 300 (66.7%) patients had a history of comorbidities (e.g., chronic heart failure, chronic kidney disease, chronic pulmonary disease, diabetes mellitus, autoimmune disease, and malignancy).

Table 2 represents the most appropriate and inappropriate prescriptions. Among all indications of levofloxacin, respiratory tract infections were the most common one (55.6%), followed by UTI (n=22, 7.3%), diabetic foot infections (DFI) (n=20, 6.6%), and skin infections (n=19, 6.3%).

According to the assessment tool, 166 (55.3%) had inappropriate indications; most of them were related to community-acquired pneumonia (CAP) (n=21, 12.6%), followed by skin infections (n=16, 9.6%), rhinosinusitis (n=14, 8.4%) and uncomplicated UTI (n=11, 6.6%). On the other hand, 134 (44.6%) of all prescriptions had

appropriate indications; most of them were related to CAP (n=68, 50.7%) followed by complicated UTI (n=11, 8.2%) and DFI (n=11, 8.2%). As illustrated in Fig. 1, among 300 included patients, 57 (19.0%) had a condition with no indication for levofloxacin prescription, of which 25 (8.3%) were related to common cold and influenza.

Levofloxacin has been prescribed in 38 (12.6%) patients with known chronic kidney disease and a GFR lower than 50ml/min with no dose adjustment. The dose and duration were correct in only 54 out of 134 (40.2%) appropriate indications. Therefore, only 54 out of 300 patients (18.0%) received levofloxacin for an appropriate indication with a correct dose and duration, indicating the rational levofloxacin prescription rate (Fig. 1).

In the present study, only in 46 out of 300 patients (15.33%), the diagnosis and prescribing were based on microbial cultures and susceptibility tests.

Fig. 3 presents the pattern of levofloxacin prescriptions based on the health care provider specialty. Pulmonologists (22.3%), ID specialists (21.6%), and oncologists (12.6%) were in charge of the most levofloxacin prescription. The most inappropriate prescriptions rate was related to general physicians (GPs) (86.6%), gastroenterologists (70.0%), and oncologists (57.8%). On the other hand, the least inappropriate prescription rate was related to internists, pulmonologists, and ID specialists.

The blue color indicates the percentage of appropriate prescriptions, and the red color indicates the percentage of inappropriate prescriptions. ID specialists= infectious disease specialists; GPs= general physicians.

Table 1. Patients demographic characteristics

No. of patients	300
Sex, N (%)	
Male	170(56.7)
Female	130 (43.3)
Age (years), Median (range)	56.5 (18-94)
Drug allergy, N (%)	
Penicillin	6(2.0)
Fluoroquinolone	2(0.6)
Macrolide	1(0.3)
Comorbidity, N (%)[*]	203(67.7)
Diabetes mellitus	67(22.3)
Chronic heart failure	43(14.3)
Chronic pulmonary disease	67(22.3)
Chronic kidney disease	38(12.6)
Others	69(23.0)

*some patient had more than one comorbidity

Table 2. Levofloxacin prescription pattern according to diagnosis

| Condition	Appropriate N (%)	Inappropriate N (%)	Total N (%)
Community-acquired pneumonia	68(50.7)	21(12.6)	89(29.6)
Urinary tract infection	11(8.2)	11(6.6)	22(7.3)
Rhinosinusitis	7(5.2)	14(8.4)	21(7.0)
Diabetic foot infection	11(8.2)	9(5.4)	20(6.6)
Skin and skin structure infection	3(2.2)	16(9.6)	19(6.3)
Chemotherapy-induced neutropenia Antibacterial prophylaxis	8(5.9)	8(4.8)	16(5.3)
Common cold	0	16(9.6)	16(5.3)
Surgery site infection	5(3.7)	9(5.4)	14(4.6)
Acute bacterial exacerbation of chronic bronchitis	7(5.2)	6(3.6)	13(4.3)
Influenza	0	9(5.4)	9(3.0)
Others	14(10.4)	42(25.3)	56(18.6)
Total	134(44.6)	166(55.3)	300(100.0)
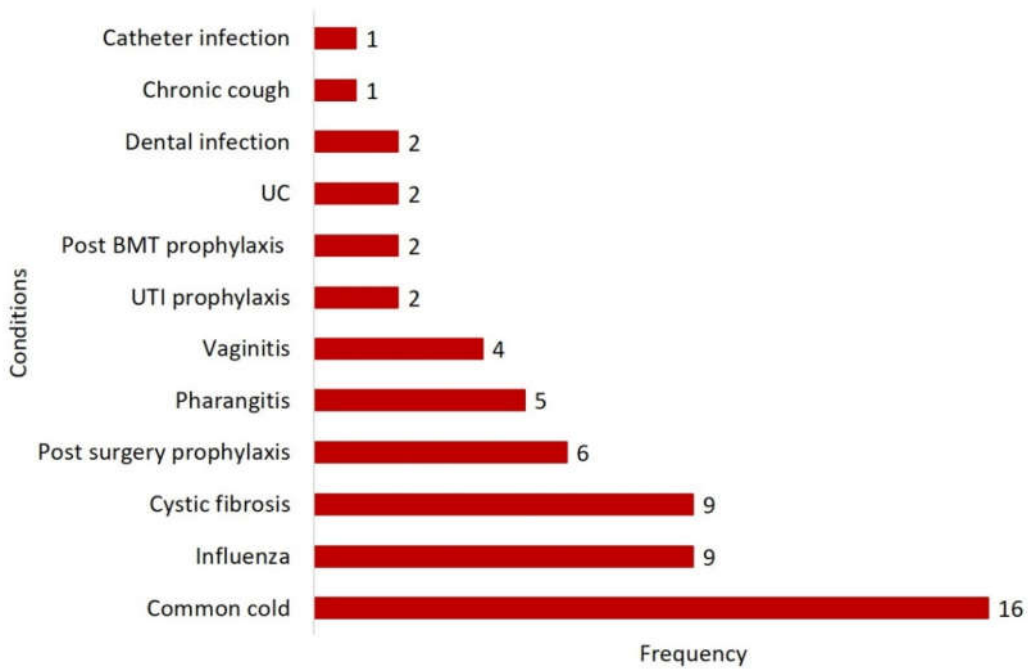
Fig. 1. Frequency of conditions in which levofloxacin has no therapeutic place. UTI= urinary tract infection; BMT=bone marrow transplantation; UC= ulcerative colitis
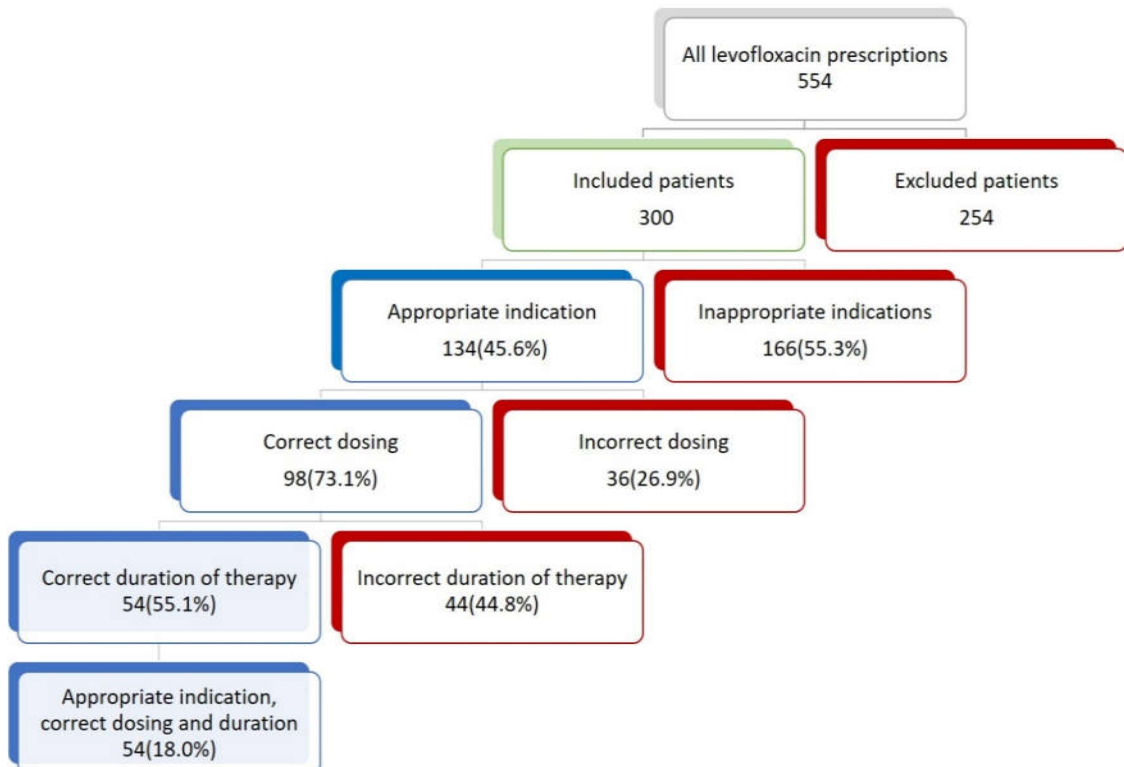

Fig. 2. Summary of levofloxacin administration in terms of appropriate indication, dose, and duration of treatment
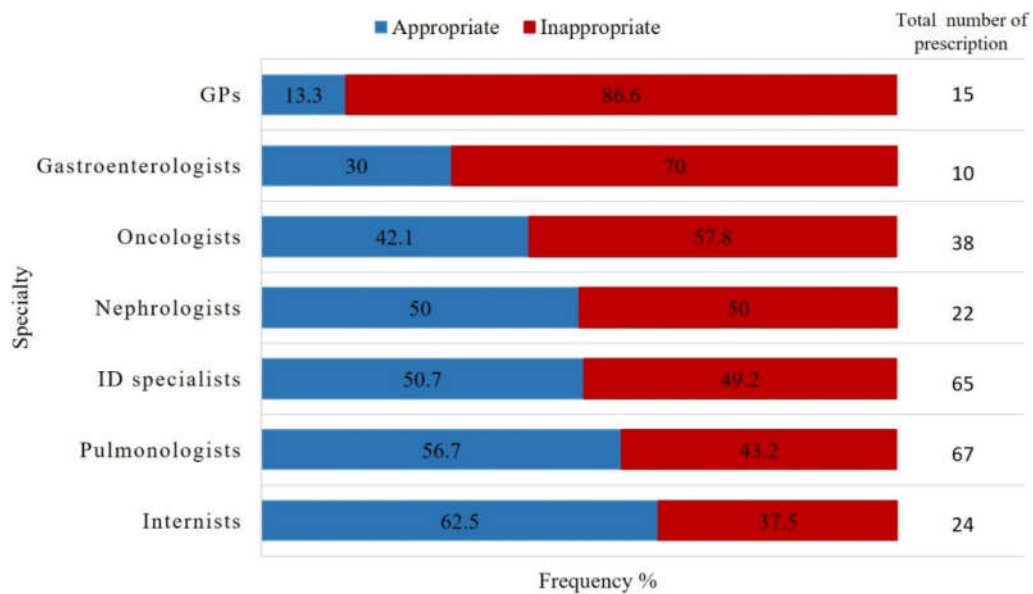
Fig. 3. Frequency of levofloxacin prescription and appropriateness based on physician's specialty

In the final follow-up of the patients, 12 out of 300 patients (4.0%) experienced adverse drug reactions associated with levofloxacin administration. Two patients experienced more than one side effect. In these patients, levofloxacin was prescribed inappropriately in 8 cases, indicating that it did not treat their infectious disease and caused them extra complications. In addition, In 4 patients with appropriate indications, the dose and duration were correct in only one patient. The Naranjo score in all ADRs was between 5 and 8, indicating the probability of adverse drug reactions associated with levofloxacin. Side effects observed in the order of frequency included joint pain (n=4, 1.2%), dizziness (n=2, 0.6%), diarrhea suspected to *Clostridium difficile* infection (n=2, 0.6%), skin rash (n=2, 0.6%), headache (n=1, 0.3%), phototoxicity (n=1, 0.3%), constipation (n=1, 0.3%), and dyspepsia (n=1, 0.3%). In 5 patients, adverse drug reactions led to the discontinuation of antibiotic therapy.

This study was conducted in an outpatient setting to evaluate the inappropriate rate and prescription pattern of levofloxacin. The results showed that levofloxacin was prescribed appropriately in less than half (45.6%) of the prescriptions based on the accurate indication. Even while an antibiotic's indication is appropriate, incorrect dose and duration lead to suboptimal treatment and irrational use [37]. Our

study found that the rate of levofloxacin rational use was 18% according to appropriate indication, dose, and duration.

Despite the latest FDA boxed warnings suggesting against the use of FQ in some diseases, including ABECB, acute rhinosinusitis, and uncomplicated UTI, our study found a high rate of inappropriate prescriptions for these conditions. Consistently, some recent evidence found no significant limitation in the inappropriate prescription of this class of antibiotics in these conditions [38].

Some studies have reported the FQs prescription in conditions with no indication for this practice.

In a survey by Kabani et al. [39], 25% of FQs prescriptions in outpatient settings were related to conditions in which antibiotics have no indication or have not been recommended as the first-line treatment option. Our study also found that 19% of levofloxacin prescriptions were contributed to conditions with no indication for this antibiotic, such as viral respiratory infections.

As mentioned above, our study, for the first time, evaluated the appropriateness rate of levofloxacin in an outpatient setting, estimating a rate of 45.6%. A similar survey in Vancouver General Hospital [40] evaluated moxifloxacin, another third-generation FQ, and found 67.4% of

cases with appropriate prescription based on their evidence-based assessment tool. The high appropriateness rate in this study is probably due to the priority of FQs prescription as a first-line for ABECB treatment at the time of the survey, which is in contrast to those recommended by present updated guidelines and FDA warnings. In addition, in this hospital, physicians had access to standard preprinted orders for CAP and ABECB, which may be another reason for the high appropriateness rate of FQs prescription compared to other studies.

Inappropriate use of antibiotics is associated with antimicrobial resistance and increased risk of serious adverse effects [2]. In this study, 14 probable ADRs associated with levofloxacin use were observed in 12 patients, of which only one had appropriate indication, dose, and duration. This means that these patients have been subjected to levofloxacin side effects without obtaining any benefit from that. To prevent ADRs and the emergence of antibiotic-resistant pathogens, the use of this class of antibiotics should be limited in conditions where the benefits outweigh the risks, and there are no other effective alternatives [13].

Studies suggest that physicians' knowledge is an essential factor for appropriate antibiotics prescribing [41]. In this study, as expected, GPs had the highest inappropriateness rate of levofloxacin prescription, which may be due to the lack of sufficient knowledge about the accurate indications. Of note, this result might be overestimated by the lower rate of levofloxacin prescription by them compared to other medical specialties. Moreover, in this study, the inappropriateness rate was found to be high among some specialists with high knowledge related to antibiotic use, indicating that some factors rather than physician's knowledge, such as patient satisfaction and pressure, and diagnostic uncertainty, could influence irrational antibiotic use [42].

Despite the high rate of outpatient antibiotic use in Iran, few interventional strategies were done to improve antibiotic prescription. Almost all of them were educational interventions that had no significant effect on the rate of antibiotic use [5]. Therefore, multifaceted strategies with a core educational intervention on medical health providers may be an efficient method for reducing inappropriate antibiotic use [43].

Electronic-based interventions, such as electronic registration of prescriptions and clinical decision support systems (CDSSs), are new approaches for improving health care quality and rational medication use [44]. Using CDSSs enhances adherence and commitment to guidelines and fills the gap between best and actual practice, reducing medical errors and inappropriate antibiotic prescription [45]. Additionally, in one study [46] that implemented a multimodal intervention with an educational core to decrease FQs use, FDA warnings have been added to electronic-based registration, where clinicians choose the oral FQs .Thus, as a result, a decrease in inappropriate prescriptions has been observed in this study. Recently, the electronic registration of prescriptions is widely used in Iran to be an excellent opportunity to implement electronic-based interventions.

The pharmacist-led intervention has shown promising effects leading to antibiotics' rational use. A collaboration between pharmacists and GPs in one study caused a reduction in inappropriate antibiotics use and improved the overall antibiotic prescribing by GPs [47].

Restriction on prescribing a specific class of antibiotics seems to be another effective strategy in reducing inappropriate antibiotic use and antibacterial resistance. Australia has a successful experience in a low rate of FQs resistant pathogens due to restriction on FQs use in humans through its national pharmaceutical subsidy scheme and banning the consumption of them in food-producing animals [48]. However, restrictions on a specific class of antibiotics may increase the use of other categories of antibiotics; therefore, these restriction interventions need a periodic evaluation of risks and benefits [49,50]

According to our result, the high inappropriateness rate of levofloxacin in the outpatient setting necessitates interventions on prescribing this antibiotic. Therefore, we recommend the following interventions for the future: (1) preparation of national protocols for prescribing broad-spectrum antibiotics, (2) designing multilevel educational interventions (health care providers and patients), (3) implementing a national policy by health policymakers to improve considering pharmacist-led interventions.

Center for Disease Control and Prevention (CDC) has suggested identifying the target group and high-priority conditions before any interventions in outpatient settings [51]. Based on the present study, the infections located in the respiratory tract, skin and soft tissue, and urinary tract have a high priority to be considered in antibiotic stewardship interventions. Also, some medical health providors, including GPs, gastroenterologists, and oncologists, should be primerly targeted in these interventional programs.

4. CONCLUSION

the present study revealed that levofloxacin was prescribed inappropriately in more than half of patients. Respiratory tract infections, skin and soft tissue infection,and UTI were the most inappropriate prescribed conditions. In addition to appropriate indications, dose and duration are two critical factors in antibacterial therapy, which were incorrect in more than half of patients. Also, irrational use of levofloxacin was associated with adverse drug reactions and compromising the safety of patients. Emergency interventions should be performed to save this life-saving antibiotic.

5. LIMITATION OF STUDY

This study was not a multi-center study; therefore, the results might not be applicable to other outpatient facilities. It is recommended that DUE studies be performed in a multi-center manner in different geographical areas with large sample sizes throughout the country to provides a valuable opportunity to study the prescription pattern and other factors affecting antibiotic prescription.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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