Drugs & Therapy Perspectives (2020) 36:33–39
https://doi.org/10.1007/s40267-019-00688-8

ORIGINAL RESEARCH ARTICLE

Evaluation of levofloxacin utilization in intensive care units of tertiary care hospital: a retrospective observational study

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Published online: 14 November 2019

Abstract

Background The emergence of antibiotic-resistant bacteria is a major problem throughout the world, and rational use of antibiotics is, therefore, very important. Levofloxacin is one of the most commonly used antibiotics due to its wide spectrum antimicrobial activity and low potential for toxicity. Drug use evaluation (DUE) focuses on evaluation and improvement of drug prescribing patterns to achieve optimal patient outcomes.

Aim The study was designed to evaluate levofloxacin prescribing patterns, including appropriate indication, dose, dose adjustment in renal impairment, and duration of treatment, by conducting a DUE program in intensive care units (ICUs).

Methods A retrospective observational study was conducted over a 4-month period. A total of 222 patients receiving levofloxacin (a broad-spectrum fluoroquinolone) were identified. Patients were primarily recruited from ICUs.

Results The present study showed that levofloxacin was used empirically in most patients (78.4%). The most common indication for levofloxacin use was community-acquired pneumonia, observed in 75 patients (33.8%). Most commonly, the daily dose of levofloxacin was 500 mg or 750 mg, the frequency of administration was twice (27%) or once daily (73.0%), and the duration of treatment with levofloxacin was 7–10 days (67.6%). Inappropriate use of levofloxacin was observed in some patients (27.9%), the greatest proportion of which was attributed to absence of culture and sensitivity test (61.3%), followed by inappropriate indications (46.8%).

Conclusions Our study indicated that there is substantial scope for improvement in prescribing patterns at Damanhour Medical National Institute that could be achieved by adhering to standard guidelines of treatment and restriction policies to promote rationality of drug use.

Introduction

Infectious diseases are the most common causes of morbidity and mortality in developing countries. Antibiotics have been used globally over the last 50 years to control infectious diseases, and decrease morbidity and mortality [1]. Antibiotic use in hospitalized patients is common, with patients in intensive care units (ICUs) receiving antibiotics on 70% of their ICU days [2]. However, the control of infectious diseases is seriously threatened by the persistent increase of antibiotic resistance among bacteria, which is the inevitable consequence of the widespread use of antibiotics, extended duration of use, use of suboptimal doses, and longer stays in hospital [3]. Antibiotic resistance is a major factor contributing to delays in effective therapy, the length of hospitalization, and increases in patient morbidity and mortality, as well as the cost of medical care [4]. Therefore, rational prescribing of antibiotics is central to limiting the development and the spread of resistant bacteria in hospitals and communities [5, 6]. When considering this, the logical first step is to evaluate appropriateness of antibiotic usage [7]. This can be done by implementing a drug use evaluation (DUE), which has been defined by the American Society of Health System Pharmacists as a "criteria-based, ongoing, planning and systemic process for monitoring and evaluating the prophylactic, therapeutic and empiric use of drugs to help, assure that they were provided appropriately, safely and effectively" [5, 7].

The goal of a DUE is to promote optimal medication therapy to reduce the development of antibiotic resistance

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and lower overall health care costs by providing cost-effective treatments [8]. DUE is applied in various practice settings, including hospitals, targeting antibiotics that are prescribed frequently, to identify trends of overuse and inappropriate prescribing [4].

The total process of medication prescribing, administration, or dispensing can be assessed by DUE, which may be applied to a drug therapeutic class, disease state or condition, drug use process, or outcome. It conducts regular audits of patients' prescription and medication data before, during, and after dispensing in order to assess concordance with best practice in drug use [9]. It not only provides a means of identifying drug use problems, but also provides a means to correct the problem and thereby contribute to rational drug therapy [4].

Fluoroquinolones are one of the most commonly prescribed classes of antibiotics worldwide [10]. The development of newer generations of fluoroquinolones has expanded the traditional Gram-negative coverage to Gram-positive and anaerobic organisms [11]. Fluoroquinolones are mainly used in the treatment of pneumonia and urinary tract infections (UTIs) [12]. The inappropriate use of fluoroquinolones in both community and hospital settings is the major factor contributing to emergence of recent concerns about resistance [13]. Inappropriate use of fluoroquinolones is linked to indication, dose, and duration of therapy [14, 15].

Levofloxacin is a bactericidal fluoroquinolone antibiotic that displays broad-spectrum activity against Gram-negative, Gram-positive, and atypical bacteria [16]. It inhibits topoisomerase (DNA gyrase) enzymes in susceptible organisms, resulting in inhibition of supercoiled DNA relaxation, and promotes the breakage of double-stranded DNA [10]. Levofloxacin has been an appropriate choice for community-acquired pneumonia (CAP), acute bacterial sinusitis (ABS), UTI, and pyelonephritis [17]. Its adverse reactions include hyper- or hypoglycemia, photosensitivity, central nervous system (CNS) adverse reactions, such as convulsions, tendinitis, and tendon rupture, serious liver dysfunction with the possibility of hepatic failure, and prolonged QT interval leading to torsades de pointes [18, 19]. Via chelation, levofloxacin interacts with zinc-containing multivitamin metal cations (e.g. iron), antacids containing magnesium or aluminum, and sucralfate [20]. Blood glucose disturbances, including hyperglycemia and hypoglycemia, have been reported in patients treated concurrently with levofloxacin and antidiabetic drugs. Concomitant administration of levofloxacin with nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of seizures and CNS stimulation [16]. Levofloxacin is contraindicated in pregnancy, nursing mothers, children aged < 18 years, patients with hypersensitivity to the drug, and patients receiving drugs that prolong the QT interval [21].

The present study was planned to evaluate the use of levofloxacin, including indication, dose, and duration of treatment. The study also aimed to assess whether drug therapy met current standards, with a view to identifying medication-related problems, and improving prescriber awareness and practice regarding appropriate prescribing.

Methods

Design and site

Our observational, retrospective DUE study was conducted at Damanhour Medical National Institute, Damanhour, Egypt, over a 4-month period, from September 2018 to December 2018. Patients who received at least one dose of levofloxacin in ICUs were enrolled in the study.

Information about 222 patients who received levofloxacin for treatment of their infections was collected using a data collection form that included the following: demographic data, allergy history, past medical history, history of present illness, history of CNS diseases and/or seizure, site(s) of infection, dose, frequency of administration, bacterial culture(s) and sensitivity results, laboratory tests [fasting blood glucose and glycated hemoglobin (HbA_{1c}), when available], temperature, white blood cell count, neutrophil count, serum creatinine, and calculated creatinine clearance (CrCl) according to the Cockcroft–Gault equation in adults. Evidence-based assessment criteria were developed to evaluate the appropriateness of levofloxacin use.

Inclusion and exclusion criteria

The inclusion criteria included patients who received levofloxacin during their hospitalization in ICUs during the study periods. For those with repeated levofloxacin courses, an interval of < 15 days was considered as a single administration, while an interval of > 15 days was considered as multiple administrations. Patients aged < 18 years were excluded.

Data collection

Clinical pharmacists collected data retrospectively from a random sample of paper-based medical records. Data consisted of patient demographics (i.e. age, sex, admitting service, physician, and length of stay), medication use (i.e. dose, route of administration, and duration of therapy), antibiotic allergies, outcomes (i.e. success, indeterminate, or failure), comorbidities, concomitant use of medications, route of administration, levofloxacin adverse effects, therapeutic indications. Data were collected on an Excel sheet, which included patients' initials; study subject number;

antibiotic allergies; comorbidities; concomitant use of medications; significant adverse drug effects; therapeutic indications; and *drop-down lists*, which included the route of administration, type of therapy (directed, empirical, or prophylactic), and clinical outcomes achieved, which is complete resolution of bacterial infection signs and symptoms (improvement of all baseline parameters in the hospital or at discharge). The assessment was based on international guidelines for levofloxacin use [22, 23].

The DUE steps

In brief, the DUE consisted of the four steps shown in Fig. 1. According to the literature [24–27], the evaluation criteria for drug use include the following information: (1) diagnosis standards; (2) contraindications of the drug; (3) drug interaction standards; (4) drug administration standards; (5) treatment duration and drug dose; (6) drug dose per day; and (7) appropriate or inappropriate standards. Besides these standards, some other evaluation indices are needed to identify the accuracy of the collected data.

Data analysis

Descriptive statistical analyses were performed using Microsoft Office Excel 2016. Parameters of the studied patients were expressed as mean ± standard deviation, frequency, median, range, and percentage.

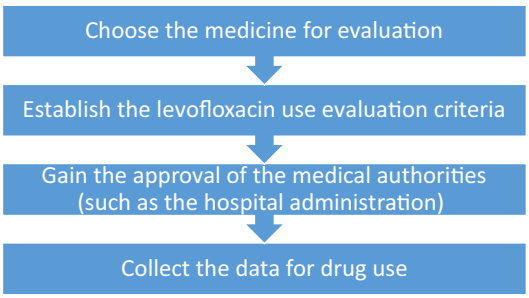

Fig. 1 Steps of levofloxacin use evaluation for our study

Results

A total of 222 patients during a 4-month period were identified according to the DUE criteria who received levofloxacin for the treatment of their infections. Basic patient characteristics are shown in Table 1. Mean patient age was 61.4 ± 15.2 years (median 65 years; range 18–80 years) [Fig. 2], and the mean length of hospital stay was 11.9 ± 4.9 days (median 10 days; range 1–30 days).

Our study revealed that 103 patients (46.4%) received levofloxacin as a first-line therapy. Seventy-five patients (33.8%) were treated with first-line levofloxacin for CAP; the remaining 28 patients (12.6%) were treated for acute bacterial exacerbations of chronic bronchitis (ABECB). Forty-one patients (18.5%) received levofloxacin as an alternative therapy for a post-operative indication for treatment of surgical-site infections occurring after surgery of the intestinal or genitourinary tract. Other indications for alternative therapy included severe sepsis, intra-abdominal infections (IAIs), burn, bone fracture, intracranial hemorrhage (ICH), and diabetic foot infection. Indications for levofloxacin are summarized in Table 2. The daily dose of levofloxacin was 500 mg or 750 mg, the frequency of administration was twice daily in 60 patients (27%) or once daily in 162 patients (73.0%), and the duration of

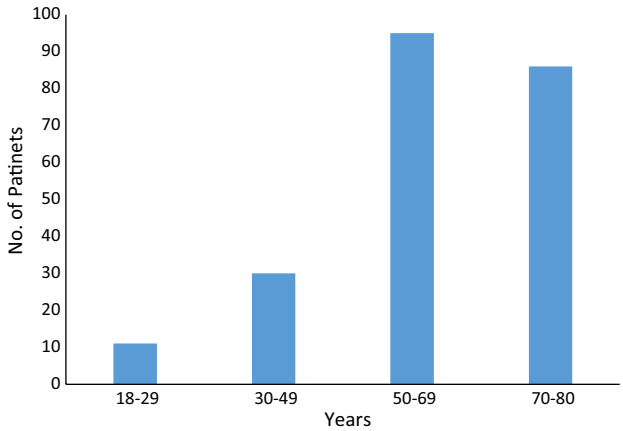

Fig. 2 Demographic age distribution of the study population ($n = 222$)

Table 1 Baseline characteristics of the study population ($n = 222$)

Age, years (median)	61.4 ± 15.2 (65)
No. of male/female patients (%)	119/103 (53.6/46.4)[a]
No. of diabetic/nondiabetic patients (%)	42/180 (18.9/81.1)[a]
Average length of stay in the hospital, days (median)	11.9 ± 4.9 (10)
No. of patients with renal impairment/no. of patients with dose adjustment (%)	32/10 (14.4/4.5)[a]

[a]The percentage of patients in the total study population

Table 2 Indications for treatment with levofloxacin ($n=222$)

Indications	No. of patients (%)[a]	No. of patients with appropriate use (%)[b]
Severe sepsis	15 (6.8)	8 (53.3)
Intra-abdominal infection	11 (5.0)	8 (72.7)
Post-operative	41 (18.5)	31 (75.6)
Burn	8 (3.6)	5 (62.5)
Acute bacterial exacerbations of chronic bronchitis	28 (12.6)	22 (78.6)
Bone fracture	7 (3.2)	5 (71.4)
Intracranial hemorrhage	12 (5.4)	8 (66.7)
Diabetic foot infection	25 (11.3)	16 (64)
Community-acquired pneumonia	75 (33.8)	57 (76)

[a]The percentage of patients in the total study population

[b]The percentage of patients with appropriate use for each indication

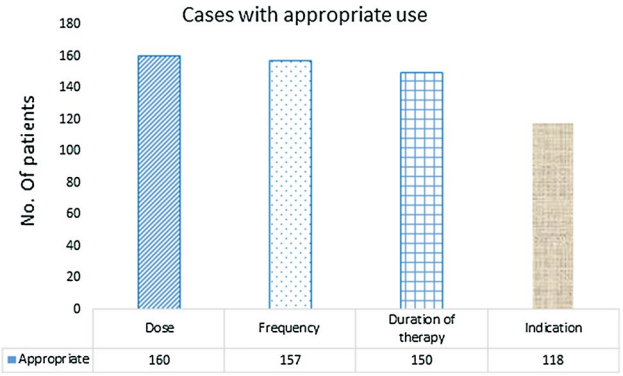

Fig. 3 Criteria referenced appropriate use of levofloxacin ($n=222$)

treatment with levofloxacin was 7–10 days in 150 patients (67.6%). In patients with CAP treated with levofloxacin 500 mg every 24 h, the duration of therapy ranged from 7 days to 14 days; for those treated with levofloxacin 750 mg every 24 h, the duration was 5 days. Of the 28 patients with ABECB, six patients (21.4%) received levofloxacin 500 mg orally every 24 h for 7 days. Of the 41 patients with surgical-site infections, ten patients (24.4%) received 750 mg levofloxacin intravenously every 24 h in combination with metronidazole.

In our study, levofloxacin was empirically prescribed in 174 patients (78.4%), and in 48 patients (21.6%), it was prescribed as prophylaxis. Most of the appropriate use of levofloxacin was for ABECB (78.6%), the most common first-line indication, while most of the inappropriate use of levofloxacin was for sepsis (46.7%), as shown in Table 2. Levofloxacin utilization was appropriate regarding dose in 160 patients (72.1%). Levofloxacin was indicated appropriately in 118 patients (53.2%), 150 patients (67.6%) received the appropriate duration of therapy, and dose frequency was appropriate in 157 patients (70.7%) [Fig. 3].

Of the 222 patients, 32 (14.4%) had renal impairment. Of these patients, ten (31.3%) did not receive the correct dose adjustment according to their level of renal impairment: stage 3 (CrCl 30–60 ml/min), stage 4 (CrCl 15–29 ml/min), or stage 5 (CrCl < 15 ml/min). Prior to starting antibiotic therapy, cultures were taken in 86 patients (38.7%) from different sites of infection: blood, urine, sputum, pus, bone, cerebrospinal fluid, and deep tracheal aspirate. Among the drugs co-administered with levofloxacin, the mostly used therapeutic class of drug was diuretics (58 patients), followed by antihypertensive agents (50 patients), antidiabetic drugs (48 patients), and NSAIDs (42 patients). A total of 58 patients (26.1%) were taking additional medications that can affect blood glucose levels concomitantly with their levofloxacin therapy: of these, 10 (4.5%) received corticosteroids, and 48 (21.6%) received oral hypoglycemic agents and/or insulin regimens (Table 3).

Baseline blood glucose levels before the administration of levofloxacin were checked only in 24 patients (10.8%), and hyperglycemia (blood glucose > 150 mg/dL) was reported in 18 patients (8.1%).

Nine patients (4.1%) experienced adverse drug events; six patients (2.7%) experienced QT prolongation resulting in the replacement of levofloxacin with a therapeutic alternative. Two patients (0.9%) experienced severe diarrhea, which was associated with the initiation of levofloxacin. One patient

Table 3 Therapeutic class of drugs co-administered with levofloxacin ($n=222$)

Therapeutic class of drugs	No. of patients	Percentage
Antimicrobials	24	10.8
Antihistamines	8	3.6
NSAIDs	42	18.9
Antidiarrheals	18	8.1
Antacids	7	3.2
Antiemetics	22	9.9
Diuretics	58	26.1
Antihypertensives	50	22.5
Antispasmodics	20	9.0
Oral hypoglycemic agents/insulin	20/28	41.7/58.3
Anticoagulants	30	13.5
Antidyslipidemics	18	8.1
Tricyclic antidepressants	14	6.3
Antiarrhythmics	28	12.6
Multivitamins	4	1.8
Antifungals	30	13.5
Laxatives	10	4.5
Corticosteroids	10	4.5

NSAID nonsteroidal anti-inflammatory drug

(0.5%) who was taking NSAIDs concurrently with levofloxacin experienced seizures.

Discussion

Levofloxacin is a third-generation fluoroquinolone with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and atypical respiratory pathogens [21]. It is approved for a wide range of indications, including ABS, ABECB, nosocomial and community acquired pneumonia, UTIs, acute pyelonephritis, chronic bacterial prostatitis, skin and soft tissue infections, and inhalational anthrax (post-exposure) [28].

The development of antibiotic resistance by microorganisms is of global concern. Emergence of antibiotics resistance is a result of the use, over use, and misuse of antibiotics [29]. Irrational drug use, polypharmacy, incorrect drug choices, incorrect doses, and drug interactions are factors contributing to increased morbidity and mortality, increased costs for patients, and the use of drugs of low efficacy [30]. Medicine utilization review is the most common and systematic criteria-based approach used to evaluate patterns of drug use and to determine levels of appropriateness in prescribing to deliver better healthcare services.

In this study, the most common indication for levofloxacin use was for CAP (33.8%). This is consistent with a study conducted at a teaching hospital in Lebanon, wherein the most common indication (86%) for this drug was CAP [13], and in a secondary care center at Hyderabad, India, the most common indication was lower respiratory tract infections (bronchitis, pneumonitis), in 41.9% of patients [28].

Of the 222 patients, 118 (53.2%) met the established criteria for the use of levofloxacin and 104 (46.8%) did not, as per standard treatment guidelines (STGs). In all the indications studied, 160 patients (72.1%) met the benchmark requirement, and of 32 patients with renal impairment, ten patients (31.3%) did not receive the correct dose adjustment based on their level of renal impairment. The duration of therapy was mostly appropriate for all the justified indications studied (67.6%). According to STGs for CAP, the duration of therapy ranged from 7 days to 14 days if the levofloxacin dose was 500 mg every 24 h and was 5 days if the levofloxacin dose was 750 mg every 24 h; the results appropriately meet the STGs (100%). In 28 patients with ABECB, the dose of levofloxacin deviated from STGs in six patients (21.4%). In 41 patients with surgical-site infections, the dose of levofloxacin deviated from STGs in ten patients (24.4%).

Before the initiation of antibiotic treatment, cultures should be taken in all patients whenever possible. In our study, cultures were only taken from 86 (38.7%) of the patients. Clinical pharmacists can play a tremendous role in de-escalating treatment when indicated and in sparing the use of levofloxacin.

In only 18 patients (8.1%), blood glucose was > 150 mg/dL. A number of studies indicate that fluoroquinolones have varying effects on glucose metabolism [31, 32]. Kabbara et al. [13] showed that levofloxacin was associated with a higher risk of hyperglycemia than ciprofloxacin and moxifloxacin. Several confounding factors may have contributed to these findings. For example, the presence of stress factors and other disease state interactions may have increased blood glucose levels. In addition, 4.5% of the patients were taking corticosteroids concomitantly with levofloxacin, which can cause hyperglycemia due to a decrease in both insulin secretion and insulin sensitivity. Careful monitoring of blood glucose is recommended especially when levofloxacin is administered in diabetic patients due to the increased risk of developing detachment of the retina.

In only seven patients (3.2%), levofloxacin was co-administered with antacids that might decrease its absorption by chelation; therefore, antacids were administered at least 2 h before or 2 h after orally administered levofloxacin to decrease the potential for interaction with multivalent cations.

Our study observed seizures in one patient who was taking NSAIDs concurrently with levofloxacin. Liu stated that all quinolones may cause CNS stimulation by blocking the binding of GABA to $GABA_A$ receptors [21]. Co-administration with NSAIDs increase the risk of seizures [33]. Therefore, caution is advised when administering levofloxacin in patients with risk factors for seizures, such as convulsive diseases like epilepsy, and concomitant use of NSAIDs.

The present study revealed that concomitant use of levofloxacin with azithromycin caused some serious adverse effects, such as QT prolongation in six patients. This may be explained by other accompanying risk factors, such as coexisting conditions, concomitant medication use, or the limitation of the study design. However, there is evidence of azithromycin-induced QT prolongation observed in patients with hypokalemia or a previous history of cardiac abnormalities, and in those concomitantly taking other QT-prolonging drugs, such as trazodone and methadone. Hence, it is difficult to isolate azithromycin as a sole factor resulting in QT prolongation [34]. Therefore, the use of levofloxacin should be limited in patients with other conditions that may increase the risk of QT prolongation, including congenital long QT syndrome, myocardial infarction, hypertension, coronary artery disease, and hypocalcemia, and in patients receiving medications known to cause electrolyte imbalances or QT-prolonging agents, such as clarithromycin and azithromycin.

This study has shown that none of the patients has received levofloxacin against the contraindications of pregnancy or hypersensitivity to the drug; this result is very encouraging.

Overall, our findings have important implications for clinical practice. Hence, we recommend the following clinical interventions for the future:

- Close monitoring for drug–drug interactions, and immediate discontinuations of levofloxacin sometimes may be needed.
- Adjustment of the dose and duration of levofloxacin therapy to obtain maximum efficacy with least adverse effects.
- Careful monitoring of blood glucose is recommended in diabetic and nondiabetic patients.
- Use of levofloxacin should be monitored to prevent the development of resistant strains.
- Prescribers should direct therapy with culture and sensitivity test results whenever possible.
- Clinical pharmacists can have a valuable effect on decreasing the widespread resistance by auditing and promoting rational antibiotic therapy. Thus, pharmacists with other health care professionals can contribute to optimize patient care and appropriate drug use.

The study has several limitations. Our study was retrospective in nature, the survival rate was not followed up, and the pharmacists were not in direct contact with the patients.

The present study focused only on ICUs. However, a more representative result would be obtained if other departments (for example, surgical and orthopedic) were included. The study period was limited and hence seasonal variations in prescribing patterns were not revealed.

Conclusion

The present study has revealed better use of levofloxacin pertaining to indications and contraindications, and the most appropriate levofloxacin utilization was for ABECB and CAP treatment.

In 27.9% of patients, levofloxacin irrational use was detected. This means that levofloxacin use deviated from STGs. Such use facilitates the emergence of resistant strains to levofloxacin and will subsequently limit its use in the near future. The inappropriate utilization of levofloxacin may also compromise patient safety as well as affect the patient economically.

Frequent prescription review followed by continuous drug utilization studies must be carried out in order to tailor hospital antibiotic usage guidelines so as to promote rational antibiotic usage.

Acknowledgements The authors thank the clinical pharmacists at Damanhour Medical National Institute for their assistance and participation in collecting the patient data for this study.

Compliance with ethical standards

All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Funding The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest The authors, R.H. Werida, A.M. El-Okaby, and N.M. El-Khodary, declare that they have no conflicts of interest.

Ethical approval and informed consent Ethics and research approvals were granted by Damanhour Medical National Institute Research Ethics Committee. The need for informed consent for this study was waived by the ethics committee.

References

1. World Health Organization. Interventions and strategies to improve the use of antimicrobials in developing countries: a review. Geneva: WHO; 2001.
2. Camins BC, King MD, Wells JB, et al. Impact of an antimicrobial utilization program on antimicrobial use at a large teaching hospital a randomized controlled trial. Infect Control Hosp Epidemiol. 2009;30(10):931–8.
3. Sileshi A, Tenna A, Feyissa M, et al. Evaluation of ceftriaxone utilization in medical and emergency wards of Tikur Anbessa specialized hospital: a prospective cross-sectional study. BMC Pharmacol Toxicol. 2016;17(1):7.
4. Lee H, Jung D, Yeom JS, et al. Evaluation of ceftriaxone utilization at multicenter study. Korean J Intern Med. 2009;24(4):374.
5. Goudanavar P, Panavila L, Ninan N, et al. Drug use evaluation of third generation cephalosporins in a tertiary care teaching hospital. Int J Ther Appl. 2016;32:81–5.
6. Ibrahim M, Bilal N, Hamid M. Increased multi-drug resistant *Escherichia coli* from hospitals in Khartoum state, Sudan. Afr Health Sci. 2012;12(3):368–75.
7. Yinnon AM, Skorohod Y, Schlesinger Y, et al. Cefuroxime utilization evaluation: impact of physician education on prescribing patterns. Isr Med Assoc J. 2000;2(3):187–91.
8. Samilski JA, Lau TT, Elbe DH, et al. Drug use evaluation of moxifloxacin (Avelox) using a hand-held electronic device at a Canadian teaching hospital. P T. 2012;37(5):291.
9. Doherty P, Kirsa S, Chao S, et al. SHPA standards of practice for drug use evaluation in Australian hospitals: SHPA Committee of Specialty Practice in Drug Use Evaluation. J Pharm Pract Res. 2004;34(3):220–3.
10. Aldred KJ, Kerns RJ, Osheroff N. Mechanism of quinolone action and resistance. Biochemistry. 2014;53(10):1565–74.
11. King DE, Malone R, Lilley SH. New classification and update on the quinolone antibiotics. Am Fam Physician. 2000;61(9):2741–8.
12. Oliphant CM, Green GM. Quinolones: a comprehensive review. Am Fam Physician. 2002;65(3):455–64.
13. Kabbara WK, Ramadan WH, Rahbany P, et al. Evaluation of the appropriate use of commonly prescribed fluoroquinolones and the risk of dysglycemia. Ther Clin Risk Manag. 2015;11:639.
14. Frothingham R. Glucose homeostasis abnormalities associated with use of gatifloxacin. Clin Infect Dis. 2005;41(9):1269–76.
15. Shafran SD. Glucose homeostasis abnormalities and fluoroquinolones: a Canadian thought-leader perspective from Stephen D.

Shafran, MD, FRCPC. Medscape. 2005;11(1). https://www.medscape.org/viewarticle/498397.
16. Anderson VR, Perry CM. Levofloxacin. Drugs. 2008;68(4):535–65.
17. Riahifard N, Tavakoli K, Yamaki J, et al. Synthesis and evaluation of antimicrobial activity of [R4W4K]-levofloxacin and [R4W4K]-levofloxacin-Q conjugates. Molecules. 2017;22(6):957.
18. Tanne JH. FDA adds "black box" warning label to fluoroquinolone antibiotics. BMJ. 2008;337:a816.
19. Yamaguchi H, Kawai H, Matsumoto T, et al. Post-marketing surveillance of the safety of levofloxacin in Japan. Chemotherapy. 2007;53(2):85–103.
20. Pitman SK, Hoang UT, Wi CH, et al. Revisiting oral fluoroquinolone and multivalent cation drug-drug interactions: are they still relevant? Antibiotics. 2019;8(3):108.
21. Liu HH. Safety profile of the fluoroquinolones. Drug Saf. 2010;33(5):353–69.
22. Levofloxacin L-D. Lexicomp: Wolters Kluwer Health, Inc., Hudson. http://online.lexi.com. Accessed 2019.
23. Schaeffer A. Levofloxacin: an updated review of its use in the treatment of bacterial infections. J Urol. 2003;170(1):337.
24. Bae JP. Project Officer Health Care Financing Administration Office of Research and Demonstrations. In Evaluation of Drug Review Demonstration Projects, Project Officer Health Care Financing Administration Office of Research and Demonstrations. HCFA Evaluation of Drug Review Projects-Final Report. 1998:1–376. http://www.abtassociates.com/reports/19986221703451.pdf.
25. Qingping S, Feng D, Ran S, et al. Drug use evaluation of cefepime in the first affiliated hospital of Bengbu medical college: a retrospective and prospective analysis. BMC Infect Dis. 2013;13(1):160.
26. Raveh D, Muallem-Zilcha E, Greenberg A, et al. Prospective drug utilization evaluation of three broad-spectrum antimicrobials: cefepime, piperacillin-tazobactam and meropenem. QJM. 2006;99(6):397–406.
27. World Health Organization. Introduction to drug utilization research: WHO; 2003. Available at: http://apps.who.int/medicinedocs/pdf/s4876e/s4876e.
28. Jagarlamudi A, Pasha A, Rettala M, et al. Drug utilization evaluation of levofloxacin at a secondary care center in Hyderabad, India. Indian J Pharm Pract. 2018;11(1):25.
29. Gyawali S, Upadhyay N, Gautam S, et al. A study on drug use of ceftriaxone in a private hospital in Nepal. World J Pharm Sci. 2015;3(1):111–9.
30. Ayinalem GA, Gelaw BK, Belay AZ, et al. Drug use evaluation of ceftriaxone in medical ward of Dessie Referral Hospital, North East Ethiopia. Int J Basic Clin Pharmacol. 2013;2:711–7.
31. Lewis RJ, Mohr JF. Dysglycaemias and fluoroquinolones. Drug Saf. 2008;31(4):283–92.
32. Lodise T, Graves J, Miller C, et al. Effects of gatifloxacin and levofloxacin on rates of hypoglycemia and hyperglycemia among elderly hospitalized patients. Pharmacotherapy. 2007;27(11):1498–505.
33. Bellon A, Perez-Garcia G, Coverdale JH, et al. Seizures associated with levofloxacin: case presentation and literature review. Eur J Clin Pharmacol. 2009;65(10):959.
34. Lu ZK, Yuan J, Li M, et al. Cardiac risks associated with antibiotics: azithromycin and levofloxacin. Expert Opin Drug Saf. 2015;14(2):295–303.