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Patterns of fluoroquinolone utilization and resistance in a tertiary care hospital: a retrospective cross-sectional analysis study from a developing country

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Abstract

Background Fluoroquinolones are the most commonly prescribed antibiotics. Because of their known tendency to drive antimicrobial resistance, their prescribing patterns need to be more restricted. This study aimed to describe the clinical practice of fluoroquinolone prescription, dose adjustments for renal impairment patients and bacterial resistance profiles, eventually providing evidence-based recommendations to optimize antibiotic prescribing practices in the local population.

Methods This retrospective, cross-sectional study was conducted at An-Najah National University Hospital in Palestine. The data were collected from admitted patients who were given ciprofloxacin or levofloxacin from July 2021 to June 2023. Data from 692 inpatients across various hospital departments were examined (409 for levofloxacin and 283 for ciprofloxacin). Statistical analysis was performed via IBM SPSS version 23.0 to summarize the demographic, clinical, and epidemiological data.

Results The sociodemographic profile revealed diverse age distributions, with 25.4% and 39% older than 50 years for ciprofloxacin and levofloxacin, respectively. Ciprofloxacin was predominantly used in the oncology department (28.2%), with surgical prophylaxis (22.6%) and febrile or afebrile neutropenia (21.1%) being the most common indications. Levofloxacin was predominantly used in the medical ward (45.7%), mainly for lower respiratory tract infection (58.8%) and prophylaxis for bone marrow transplantation (16.5%). *Enterococcus* and methicillin-resistant *Staphylococcus aureus* were the most commonly isolated pathogens, with 62.5% of the isolates demonstrating resistance to ciprofloxacin. Moreover, extended-spectrum beta-lactamase-producing *Enterobacterales* were the most common pathogen isolated, with 33.3% being resistant to levofloxacin. Statistical analysis revealed a significant association between the choice of antibiotic and the approach to therapy. Levofloxacin was significantly more likely

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than ciprofloxacin to be used as empiric therapy ($p < 0.001$), whereas ciprofloxacin was more likely to be used as targeted therapy ($p < 0.001$).

Conclusions This study investigated prescribing practices and resistance to levofloxacin and ciprofloxacin in a large hospital in a developing country. According to the bacterial resistance profiles, we conclude that there is a need for hospital departments to exercise greater restraint on the use of these antibiotics. To this end, further studies addressing the clinical efficacy of fluoroquinolones against the current treatment guidelines to evaluate their appropriateness should be carried out.

Keywords Fluoroquinolone, Ciprofloxacin, Levofloxacin, Pneumonia, Antibiotic resistance, Indication, Dose, Duration

Background

Among topoisomerase inhibitors, quinolone antibiotics are considered the most successful class, and they have great significance as antimicrobial options since their discovery in the 1960s [1, 2]. In 1962, nalidixic acid, a prototype of quinolones, was discovered as a byproduct of the synthesis of the antimalarial chloroquine and is used clinically for the treatment of gram-negative bacterial infections, especially urinary tract infections [1, 3]. Other fluoroquinolones were released to the market in the late 1980s with remarkable entry of antibacterial options due to their broad-spectrum coverage, good oral bioavailability, excellent tissue penetration and efficacy in treating many infections [4, 5]. Ciprofloxacin and levofloxacin have been reported as the most commonly prescribed antibiotics in recent years [6–8]. Unlike any other class of antibiotics, fluoroquinolones have a unique mechanism of action [7].

Although the exact antibacterial activity is not fully understood [9], the current data focus on targeting bacterial topoisomerase II (DNA gyrase) in gram-negative bacteria and topoisomerase IV primarily in gram-positive bacteria, resulting in the inhibition of bacterial DNA synthesis [5, 7, 10]. The pharmacodynamic profile of these bactericidal agents is generally concentration dependent [4, 5], and all the agents except moxifloxacin are excreted by the renal system and require dose adjustment in selected patients [4]. Mutations in these target enzymes can lead to fluoroquinolone resistance [5, 11].

The Food and Drug Administration (FDA) has approved many indications for fluoroquinolones, including but not limited to urinary tract infections; skin, bone, and joint infections; gastrointestinal infections; salmonellosis; nosocomial and community-acquired pneumonia; certain intra-abdominal infections in cases of beta-lactam allergy; acute bacterial exacerbation of chronic bronchitis; acute pyelonephritis; prophylaxis in patients with hematological malignancies; hematopoietic stem cell transplantation; and high-risk prolonged neutropenia [1, 7, 12–14].

The widespread and inappropriate consumption of antibiotics is a significant factor contributing to antimicrobial resistance, leading to treatment failure, elevated health care costs and increased risk of mortality [15, 16]. This issue has significantly aggravated since the COVID-19 pandemic as a result of the unreasonable increase in antibiotic utilization due to the lack of efficient treatment options for SARS-CoV-2 [17, 18]. Estimates suggest that hundreds of thousands of deaths occur annually as a result of antibiotic resistance, which is considered a leading cause of death worldwide, and that number is expected to increase to many million annually by several years in the future [6, 19].

Therefore, as we lack studies in Palestine to describe fluoroquinolone prescribing practices in the inpatient setting, our study is the first, to the best of our knowledge, to retrospectively describe the clinical practice of fluoroquinolone use, including indications, dose, treatment duration, dose adjustment in renal impairment patients and bacterial resistance profiles over a 2-year study at an academic tertiary care hospital. The significance of this study can be multifactorial and critical for various reasons. In addition to those mentioned previously, it may help us delay the emergence of the postantibiotic era, supporting antibiotic stewardship programs and educational resources that can be used in continuing medical education credits.

Methods

Study design and setting

A retrospective observational study was conducted at An-Najah National University Hospital (NNUH), which is mainly an academic tertiary center with a 135-bed capacity. We studied data collected from patients who were admitted to this hospital and given ciprofloxacin or levofloxacin from July 1st, 2021, to June 30th, 2023. We reviewed patients' medical records to collect the required variables, including patient sociodemographic characteristics, history and disease comorbidities and patients' current admission situation. NNUH is located in Nablus, in the northern part of the West Bank, Palestine. NNUH was established as the first medical educational facility in Palestine and includes approximately 2,000 students from various medical specialties, along with 70 specialists and 100 resident physicians. This hospital has various departments, including nephrology, oncology, bone marrow

transplantation, cardiology, cardiac surgery, internal medicine, pediatrics, general and specialized surgery, intensive care units (medical, surgical, pediatric and cardiac) and emergency departments.

Study population and sample size

The study's sample size was determined using a predefined analysis that ensured adequate statistical power and representativeness. We used the Raosoft sample size calculator with a 50% response distribution, a 0.05 margin of error, and a 95% confidence level to recommend a minimum sample size of 377 patients. To increase the reliability and statistical power, we enrolled a sample of 692 patients (283 patients given ciprofloxacin and 409 given levofloxacin). The study population included all hospitalized patients in all impatient departments based on predefined inclusion and exclusion criteria. We excluded hemodialysis center, records with missing information, and patients given only one dose. This methodological approach stands in contrast to convenience sampling methodologies, ensuring a robust and representative sample.

Data collection instrument

By using Google Sheets, the required variables were collected and extracted from previously published studies [5–8, 20–22].

The tool that was used for gathering information consisted of three main sections:

1. Patient sociodemographic characteristics: file number, sex, and age.
2. History and disease comorbidities: cardiovascular diseases, diabetes mellitus, chronic kidney disease, acute kidney injury, hematological malignancy, solid malignancy, liver disease, respiratory disease, thyroid disorders, immune disorders other than autoimmune hepatitis, neurology and psychology, and blood disorders other than malignancy.
3. Patients' current admission situation:

- Admission ward.
- The indications for fluoroquinolone agents included soft tissue infection, intra-abdominal infections, afebrile neutropenia prophylaxis or treatment, sepsis/septic shock, fever of unknown source, postchemotherapy vomiting or diarrhea, gastroenteritis, upper respiratory tract infections, lower respiratory tract infections (mainly pneumonia), surgical prophylaxis, urinary tract infection, joint/bone infections, pleural/pericardial effusion, and prophylaxis via bone marrow transplantation.
- Combination with another antibiotic or not, and if combined with which agents.
- Treatment regimens (dose, frequency, duration).
- The need for dose adjustment in cases of renal impairment and whether it was performed.
- Approach of prescription (empiric or targeted), outcome (discharged or died), and culture tests (name of pathogen, date, source, minimum inhibitory concentration (MIC), interpretation, upgrade or downgrade).

Statistical analysis

The collected data were entered into the Statistical Package for the Social Sciences (IBM SPSS) via SPSS version 23.0 (IBM Corp, Armonk, NY, USA) and checked for clarity. Descriptive statistics, including frequency and percentages, were employed to summarize patient sociodemographic characteristics, medical history, disease comorbidities, and current admission status. Continuous variables, such as age and treatment duration, were summarized using the mean and standard deviation or the median and interquartile range (IQR), as appropriate. To examine associations between categorical variables, the chi-square test or Fisher's exact test was applied, with a p value of less than 0.05 considered statistically significant, to determine if there were meaningful relationships between the variables under study.

Ethical considerations

Ethical approval was obtained from the *Institutional Review Boards* (IRBs) *of An-Najah National University*. Permission letters were also received from the respective hospital administrator (An-Najah National University Hospital) to conduct the study. We confirm that all the information that was collected from the medical records is for scientific research purposes only and that this information was kept completely confidential and would not be used for purposes other than this study. No one will have access to information or data except the researchers. Identifiable information was replaced with numerical codes, maintaining privacy throughout the study.

Results

Clinical and sociodemographic characteristics of patients treated with fluoroquinolones

During the 2-year study period, 692 patients met the study inclusion criteria. Among these patients, 283 patients (40.9%) received oral ciprofloxacin, and 409 patients (59.1%) received oral levofloxacin. The 283 patients who were treated with ciprofloxacin had a median age (IQR) of 55 (38–63), and the majority were aged older than 50 years (25.4%). The female sex was

Table 1 Clinical and sociodemographic characteristics of patients treated with fluoroquinolones

Variable	Ciprofloxacin *N* (%) *N* = 283	Levofloxacin *N* (%) *N* = 409
Age (years)		
0–18	18(2.6)	4(0.6)
19–24	24(3.5)	22(3.2)
25–50	65(9.4)	113(16.3)
> 50	176(25.4)	270(39)
Median (IQR)	55 (38–63)	58 (42–67)
Gender		
Female	181 (64)	156 (38.1)
Male	102 (36)	253(61.9)
Comorbidities		
Cardiovascular disease	148(52.3)	224(53.7)
Hematological malignancy	121(42.76)	147(35.3)
Diabetes mellitus	88(31.1)	137(32.9)
Solid malignancies	48(17)	98(23.5)
Chronic kidney disease	24(8.5)	68(16.3)
Neurology-psychology disorders	22(7.8)	24(5.8)
Liver diseases	20(7.1)	31(7.4)
Thyroid disorders	14(4.9)	17(4.1)
Respiratory disease	10(3.5)	29(7)
Acute kidney injury	10(3.5)	25(6)
Blood disorders *	10(3.5)	17(4.1)
Immune disorders ^	8(2.8)	15(3.6)

^ other than autoimmune hepatitis

*other than hematological malignancy

Patients have multiple underlying conditions, resulting in 1355 instances

Table 2 Patient distribution among hospital departments

Ward	Ciprofloxacin *N* (%) *N* = 283 (100%)	Levofloxacin *N* (%) *N* = 409(100%)
Medical ward	70 (24.7)	187(45.7)
Oncology department	80 (28.2)	91(22.2)
Bone marrow transplant	40 (14.1)	77(18.8)
Cardiac intensive care unit	77(27.2)	21(5.1)
Medical intensive care unit	8 (2.8)	24(5.9)
Surgical intensive care unit	6 (2.1)	9(2.2)
Pediatric intensive care unit	2 (0.7)	0

predominant, with 181 patients (64%), and the male to female ratio was 0.5630:1.

The 409 patients who were administered levofloxacin had a median age (IQR) of 58 (42–67), with 270 (39%) being above the age of 50. Male sex was predominant, with 253 patients (61.9%), and the male-to-female ratio was 1:1.622.

With respect to comorbidities among patients treated with fluoroquinolones, cardiovascular diseases were reported in 148 (52.3%) patients treated with ciprofloxacin, followed by hematological malignancies in 121 patients (42.76%), diabetes mellitus in 88 patients (31.1%), solid malignancies in 48 patients (17%), and chronic kidney disease in 24 patients (8.5%).

Cardiovascular disease also occurred in 224 patients (53.7%) who received levofloxacin, followed by hematological malignancies in 147 patients (35.3%), diabetes mellitus in 137 patients (32.9%), solid malignancies in 98 patients (23.5%), chronic kidney disease in 68 patients (16.3%), and other conditions, as listed in Table 1.

Patient distribution among hospital departments

Among the patients who were prescribed ciprofloxacin, 80 patients (28.2%) were in the oncology department, followed by 77 patients (27.2%) in the cardiac intensive care unit, 70 patients (24.7%) in the medical department, and 40 patients (14.1%) in the bone marrow transplant unit. For levofloxacin, 187 patients (45.7%) were in the medical ward, 91 patients (22.2%) were in the oncology department, and 77 were in the bone marrow transplant unit (18.8%); Table 2.

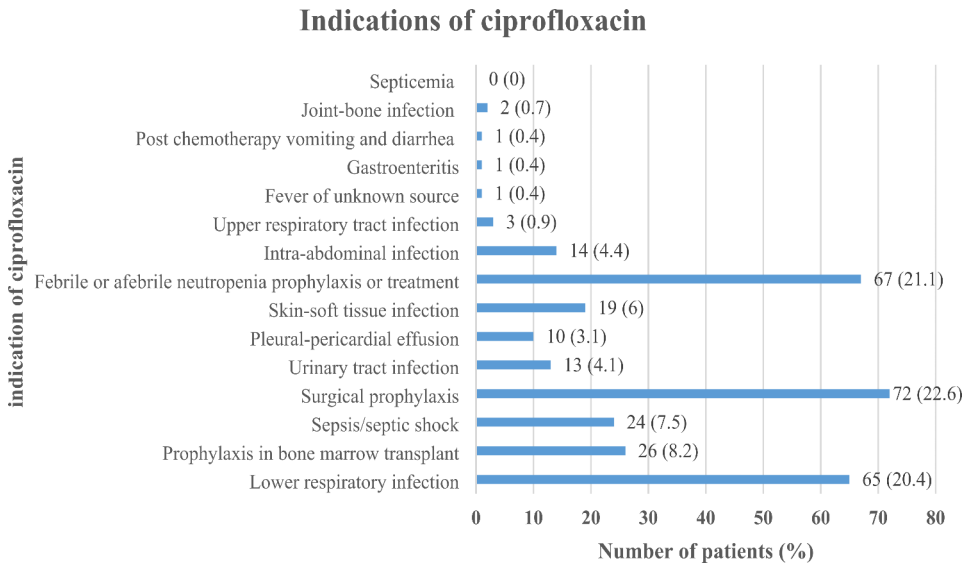

Fig. 1 Indications for prescribing ciprofloxacin

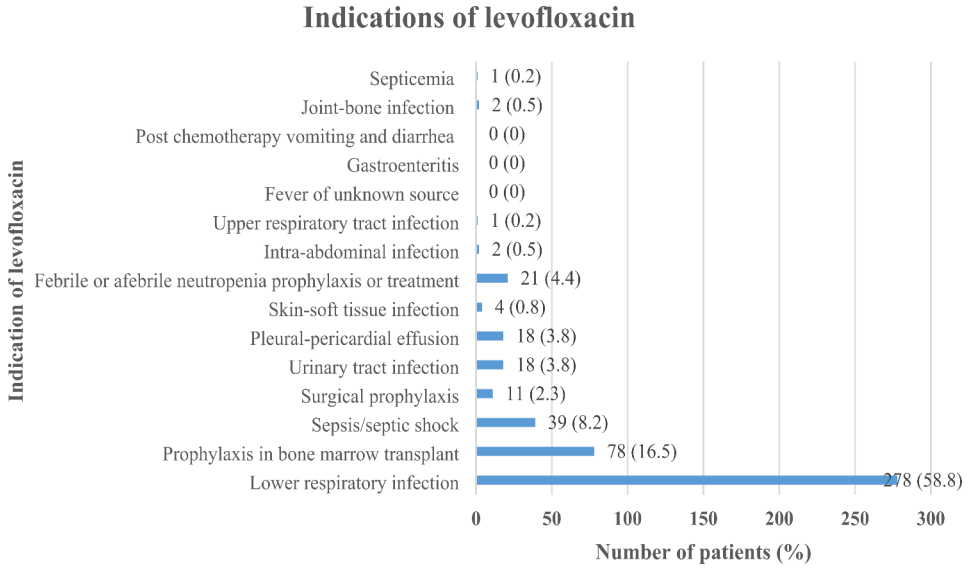

Fig. 2 Indications for prescribing levofloxacin

Indications for prescribing fluoroquinolones

The most common indication for ciprofloxacin use was surgical prophylaxis, administered to 72 patients (22.6%). Other notable reasons included prophylaxis or treatment of febrile neutropenia in 67 patients (21.1%), management of lower respiratory tract infections in 65 patients (20.4%), prophylaxis for bone marrow transplantation in 26 patients (8.2%), and treatment of sepsis or septic shock in 24 patients (7.5%); (Fig. 1). For levofloxacin, the primary indication was lower respiratory tract infections, which accounted for 278 patients (58.8%). Infections related to bone marrow transplantation were the second most common reason, comprising 78 patients (16.5%). Additionally, sepsis and septic shock were indications for 39 patients (8.2%); (Fig. 2).

Antibiotic combinations with fluoroquinolones

Given that some patients had combination regimens with ciprofloxacin or levofloxacin to treat their infections, the most common antibiotic combinations with ciprofloxacin were cefuroxime, ceftazidime, vancomycin, and piperacillin-tazobactam, with percentages of 27%, 15.5%, 14.7%, and 13.5%, respectively. However, the most common antibiotic combinations with levofloxacin were ceftazidime, piperacillin-tazobactam, vancomycin, and metronidazole, which accounted for 37.2%, 18.6%, 10.8%, and 6.7% of the cases, respectively.

Notably, a total of 596 patients were treated with more than one antibiotic in addition to either ciprofloxacin (252) or levofloxacin (344). Details can be found in Table 3.

Dosing regimens of prescribed fluoroquinolones

We evaluated the dosing regimens for the prescribed fluoroquinolones, including the dosage, duration, and frequency of the ciprofloxacin and levofloxacin regimens. The median dose of ciprofloxacin (IQR) was 500 mg (250–750), and the treatment duration lasted for a median (IQR) of six days (4–7). The most prevalent administration frequency in 261 patients (92.2%) was twice daily. Three times a day was the least common frequency of administration, representing 0.4% of the instances. The median MIC was 4 ([IQR]: 0.25–5). For levofloxacin, the median dose (IQR) was 750 mg (500–750), and the median duration of treatment (IQR) was 7 days (4–8). The most prevalent administration frequency was once daily in 339 individuals (81.3%). The median MIC was 8 ([IQR]: 0.25–8). For more details, please refer to Table 4.

The sensitivity of fluoroquinolones was evaluated in isolates that were tested for fluoroquinolones, with 44.8% of the isolates exhibiting sensitivity and 55.2% demonstrating resistance from a total of 34 cultures.

Dose adjustment in cases of renal impairment

The dosage regimen for all patients with renal impairment was adjusted accordingly. The proportion of these patients was 26.3% (182) of the total patients. For ciprofloxacin, 87 (47.8%) of the patients had adjusted doses, and for levofloxacin, 95 patients (52.2%) had adjusted doses.

Approaches to antibiotic treatment, intervention, and overall patient outcomes

In this study, 89% of patients received ciprofloxacin empirically, with 94.7% being discharged. Targeted therapy was administered to only 31 patients (11%), while 14.8% of the interventions involved upgrading to

Table 3 Antibiotic combinations with fluoroquinolones

Combined with	**Ciprofloxacin *N* (%) *N**= 252 (100%)**
Ceftazidime	39(15.5)
Piperacillin-tazobactam	34(13.5)
Vancomycin	37(14.7)
Cefuroxime	68(27)
Ceftriaxone	12(4.8)
Metronidazole	7(2.8)
Meropenem	4(1.6)
Amikacin	10(4)
Clindamycin	7(2.8)
Gentamycin	4(1.6)
Amoxicillin-clavulanic acid	8(3.2)
Trimethoprim-sulfamethoxazole	7(2.8)
Colistin	6(2.4)
Chloramphenicol	3(1.2)
Others	6 (2.4)
Combined with	**Levofloxacin N (%) N*= 344 (100%)**
Ceftazidime	128(37.2)
Piperacillin-tazobactam	64(18.6)
Vancomycin	37(10.8)
Ceftriaxone	22(6.4)
Metronidazole	23(6.7)
Meropenem	19(5.5)
Amikacin	6(1.7)
Clindamycin	9(2.6)
Gentamycin	9(2.6)
Amoxicillin-clavulanic acid	4(1.2)
Trimethoprim-sulfamethoxazole	5(1.5)
Cefazolin	7(2)
Tigecycline	3(0.9)
Ertapenem	3(0.9)
Others	5(1.5)

* N specifies the number of cases that received second or third antibiotic in addition to quinolone, some cases received quinolone only without combination

Table 4 Dosing regimens for prescribed fluoroquinolones

Variable	Ciprofloxacin *N* (%) Total 283	Levofloxacin *N* (%) Total 409
Doses(mg) (median, IQR)	500 (250–750)	750(500–750)
Mean ± Standard deviation	573.76 ± 116.99	740.22 ± 51.59
Minimum	250	250
Maximum	750	740
Duration (days) (median, IQR)	6(4–7)	7 (4–8)
Mean ± Standard deviation	7.42 ± 5.18	6.87 ± 3.42
Minimum	2	2
Maximum	58	22
Frequency		
Once daily	21(7.4)	339 (81.3)
Twice daily	261(92.2)	1(0.2)
Three times daily	1(0.4)	1(0.2)
Every other day	0	68(16.3)
Minimum inhibitory concentration (median, IQR)	4 (0.25-5)	8 (0.25-8)
Mean ± Standard deviation	3.23 ± 3.11	6.34 ± 5.52
Minimum	0.06	0.12
Maximum	8	16

Table 5 Approach to antibiotic treatment, intervention, and overall patient outcomes

Variable	Ciprofloxacin *N* (% of available data) *N* = 283(100%)	Levofloxacin *N* (% of available data) *N* = 409(100%)	*P* value
Approach			
Empiric	252(89)	400(97.8)	0.000
Targeted	31(11)	9(2.2)	
Outcome of treatment			
Discharged	268 (94.7)	375(91.7)	0.128
Died	15(5.3)	34(8.3)	
Intervention			
Stopped	215(76)	326 (79.7)	0.495
Upgrade	42(14.8)	50(12.2)	
Downgrade	26(9.2)	33(8.1)	

broader spectrum agents, and 9.2% were downgraded. Discontinuation of ciprofloxacin was observed in 76% of the patients. Conversely, 97.8% of patients were treated empirically with levofloxacin, and 91.7% were discharged. Among the interventions with levofloxacin, 12.2% involved upgrading, 8.1% were downgraded, and 79.7% were discontinued. Statistical analysis revealed a significant association between the choice of antibiotic and the approach to therapy. Levofloxacin was significantly more likely than ciprofloxacin to be used as empiric therapy ($p<0.001$), whereas ciprofloxacin was more likely to be used as targeted therapy ($p<0.001$). A chi-square test for independence indicated no significant association between the type of antibiotic and the treatment outcome, whether discharged or deceased ($p=0.128$). Furthermore, there was no significant association between the type of antibiotic and the nature of the intervention, whether it was upgraded, downgraded, or discontinued ($p=0.595$). As illustrated in Table 5.

Microbiological profile of organisms isolated from positive clinical samples

Among the positive cultures ($n=35$) of clinical samples obtained from patients treated with ciprofloxacin, positive urine cultures were the most commonly reported (40%), with *Enterococcus* and methicillin-resistant *Staphylococcus aureus* (MRSA) accounting for the greatest proportion of the isolated pathogens (22.7% for each). Compared with other sample types, positive urine cultures were significantly more common ($p<0.001$). For the wound samples, which accounted for 31.4% of the positive cultures, the most common microorganisms isolated were *Enterococcus* spp., *Escherichia coli*, *Pseudomonas aeruginosa*, and MRSA, each accounting for 15.8% of the positive cultures. The prevalence of these pathogens in wound samples was significant ($p<0.05$). Other clinical samples, including peripheral blood cultures (11.4%), bile cultures (5.7%) and central blood cultures (5.7%), were also obtained. Sputum and trap cultures each accounted

for 2.9%, which constituted the lowest percentage of positive cultures. The details are listed in Table 6.

For levofloxacin, a total of 21 positive cultures were reported. Urine and peripheral blood cultures comprised the greatest proportion of positive cultures (28.6% for each). Positive sputum cultures (19%) and trap culture samples (14.3%) had the lowest percentages, followed by central blood samples (4.8%) and wound samples (4.8%). The majority of bacteria isolated from the urine sample were extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales* (57.1%, $p<0.001$), *Escherichia coli* (14.3%, $p<0.05$), *Morganella morganii* (14.3%, $p<0.05$), and *Pseudomonas aeruginosa* (14.3%, $p<0.05$). With respect to positive peripheral blood cultures, the most frequently isolated microorganism was *Staphylococcus hominis* (33.3%, $p<0.001$). The details are shown in Table 7.

Sensitivity pattern of the isolated pathogens to the tested fluoroquinolones

Fifty pathogens were tested for susceptibility to ciprofloxacin; 24 (48%) were sensitive, and 26 (52%) were resistant to ciprofloxacin. Among the gram-positive bacteria isolated, the sensitivity rates to ciprofloxacin were as follows: *Streptococcus oralis (100%)*, *Haemophilus influenzae (100%)*, vancomycin-resistant *Enterococci* (50%), *Staphylococcus hominis* (50%), *Enterococcus* spp. (37.5%), and methicillin-resistant *Staphylococcus aureus (37.5%).* The sensitivity rates for the following gram-negative pathogens varied among the isolates: *Pseudomonas aeruginosa* (71.4%), *Escherichia coli* (42.9%), and others (Table 8).

A small number (8) of the isolates were tested for levofloxacin susceptibility. Among these strains, 2 (25%) were sensitive, and 6 (75%) were resistant to levofloxacin. Among the gram-positive bacteria isolated, *Staphylococcus hominis* had 50% sensitivity, and *Staphylococcus capitis* had 100% sensitivity. However, both *Streptococcus oralis* and methicillin-resistant *Staphylococcus aureus* were 100% resistant to levofloxacin, and *Staphylococcus hominis* and vancomycin-resistant *Enterococci* had resistance rates of 50% and 20%, respectively. Among the gram-negative bacteria, 33.3% of the ESBL-producing *Enterobacterale*s were resistant. Details on the sensitivity rate can be found in Table 9.

Table 6 Microbiological profile of organisms isolated from positive samples for ciprofloxacin

Source *N*(%) *N* = 35	Microorganism	*N* (100%) Microorganism	*P* value
Wound	*Escherichia coli*	3(15.8)	0.001
11(31.4)	ESBL-producing *Escherichia coli*	1(5.3)	0.039
	Morganellamorganii	1(5.3)	0.039
	Enterococcus	3(15.8)	0.002
	Coagulase-negative *Staphylococci*	1(5.3)	0.039
	Klebsiella pneumonia	2(10.5)	0.004
	Acinetobacter baumannii	2(10.5)	0.008
	Pseudomonas aeruginosa	3(15.8)	0.001
	Methicillin-resistant *Staphylococcus aureus*	3(15.8)	0.002
Bile fluid	Vancomycin-resistant *Enterococci*	1(50)	0.007
2(5.7)	*Pseudomonas aeruginosa*	1(50)	0.049
Peripheral blood	Gram-positive bacilli	1(25)	0.014
4(11.4)	*Pseudomonas aeruginosa*	1(25)	0.096
	Staphylococcus hominis	1(25)	0.028
	Staphylococcus aureus	1(25)	0.014
Central blood	*Pseudomonas aeruginosa*	1(50)	0.049
2(5.7)	*Staphylococcus epidermidis*	1(50)	0.007
Urine	*Streptococcus oralis*	2(9.1)	0.002
14(40)	ESBL-producing *Escherichia coli*	4(18.2)	0.000
	Enterococcus	5(22.7)	0.000
	Klebsiella pneumonia	2(9.1)	0.007
	Acinetobacter baumannii	2(9.1)	0.013
	Pseudomonas aeruginosa	1(4.5)	0.302
	Staphylococcus hominis	1(4.5)	0.097
	Methicillin-resistant *Staphylococcus aureus*	5(22.7)	0.000
Sputum 1(2.9)	*Haemophilus Influenzae*	1(100)	0.004
Trap culture 1(2.9)	*Pseudomonas aeruginosa*	1(100)	0.025

Table 7 Microbiological profile of organisms isolated from positive samples for levofloxacin

Source *N* (%) *N* = 21	Microorganism	*N* (100%)	*P* value
Wound 1(4.8)	ESBL-producing *Enterobacterales*	1(100)	0.000
Peripheral blood 6(28.6)	*Escherichia coli*	1(16.7)	0.029
	ESBL-producing *Enterobacterales*	1(16.7)	0.085
	Staphylococcus hominis	2(33.3)	0.000
	Staphylococcus capitis	1(16.7)	0.015
	Methicillin-resistant *Staphylococcus aureus*	1(16.7)	0.015
Central blood 1(4.8)	*Staphylococcus hominis*	1(100)	0.005
Urine 6(28.6)	*Escherichia coli*	1(14.3)	0.029
	Morganellamorganii	1(14.3)	0.015
	ESBL-producing *Enterobacterales*	4(57.1)	0.000
	Pseudomonas aeruginosa	1(14.3)	0.029
Sputum 4(19)	*Escherichia coli*	1(20)	0.019
	ESBL-producing *Enterobacterales*	1(20)	0.058
	Pseudomonas aeruginosa	1(20)	0.019
	ESBL-producing *Escherichia coli*	2(40)	0.000
Trap culture 3(14.3)	*Streptococcus oralis*	1(33.3)	0.007
	Klebsiella pneumonia	1(33.3)	0.007
	Acinetobacter baumannii	1(33.3)	0.007

Table 8 Ciprofloxacin sensitivity profile of the isolated pathogens

Gram- positive bacteria	**Sensitive** ***N* (%)**	**Resistant** ***N* (%)**
Streptococcus oralis	2 (100)	0
Vancomycin-resistant *Enterococci*	1 (50)	1 (50)
Enterococcus	3 (37.5)	5 (62.5)
Coagulase-negative *Staphylococci*	0	1 (100)
Haemophilus Influenzae	1 (100)	0
Staphylococcus hominis	1 (50)	1 (50)
Staphylococcus epidermidis	0	1 (100)
Staphylococcus aureus	1 (100)	0
Methicillin-resistant *Staphylococcus aureus*	3(37.5)	5 (62.5)
Gram- negative bacteria	**Sensitive** **N (%)**	**Resistant** **N (%)**
ESBL-producing *Escherichia coli*	1 (100)	0
Escherichia coli	3(42.9)	4 (57.1)
MorganellaMorganii	1 (100)	0
ESBL-producing *Enterobacterales*	1 (100)	0
Klebsiella pneumonia	1 (33.3)	2(66.7)
Acinetobacter baumannii	0	4(100)
Pseudomonas aeruginosa	5(71.4)	2(28.6)

Table 9 Levofloxacin sensitivity profile of the isolated pathogens

Gram- positive bacteria	**Sensitive *N* (%)**	**Resistant *N* (%)**
Streptococcus oralis	0	1(100)
Vancomycin-resistant *Rnterococci*	0	1(20)
Staphylococcus hominis	1 (50)	1 (50)
Staphylococcus capitis	1(100)	0
Methicillin-resistant *Staphylococcus aureus*	0	1(100)
Gram- negative bacteria	**Sensitive N (%)**	**Resistant N (%)**
ESBL-producing *Enterobacterales*	0	2(33.3)

Discussion

Fluoroquinolones are commonly prescribed agents in different parts of the world owing to their broad-spectrum activity against a wide range of bacterial pathogens [5, 23, 24]. In contrast, descriptions of its prescribing practices, including indications, doses, treatments, and resistance profiles, in local settings are lacking. Therefore, it is imperative to determine the actual utilization pattern in such environments to provide evidence-based recommendations for educational resources and antibiotic stewardship programs to optimize local antibiotic prescribing guidelines. By doing so, treatment failure, mortality, the spread of antimicrobial resistance, and overall health costs can be improved.

In this study, a greater patient flow was observed in the inpatient setting for levofloxacin (~60%) than for ciprofloxacin for bacterial infections, possibly because levofloxacin has greater bioavailability and a longer duration of action, enabling once-daily dosing, which may increase patient compliance [25]. This study included 283 patients who received ciprofloxacin, comprising 102 (36%) males and 181 (64%) females. The median age of the patients was 55 years, suggesting that adults aged older than 50 years were more likely to be prescribed ciprofloxacin (25.4%). A total of 93.6% of our participants included in the ciprofloxacin trial were older than eighteen years. Interestingly, our findings align with those of a previous hospital-based retrospective cross-sectional study, which was conducted to evaluate the medical records of patients who had taken ciprofloxacin and was published in 2020 in four governmental Ethiopian hospitals, namely, HiwotFana Specialized University Hospital, Jugel Hospital, Federal Harar Police Hospital, and Southeast Command III Hospital; this study also reported a majority of participants (91.6%) aged older than eighteen years but a greater proportion of males (50.8%) [5].

In this study, the majority of prescriptions originated from medical wards, accounting for 37.1% of all prescriptions. Ciprofloxacin prescriptions accounted for 24.7% of all medical wards. Similar findings were reported from local hospitals in the central Norway Regional Health Authority [7]. This can be explained by a retrospective observational study conducted at NNUH to study the epidemiology of *Pseudomonas* among admitted patients and the antibiotic resistance profile of the isolated pathogen [26]. One study revealed that the majority of patients with positive *Pseudomonas* growth were in the internal medical ward (21.1%), and fluoroquinolones were used to treat this infection in 23.3% of the patients [26]. Other wards where patients were treated with fluoroquinolones included oncology, bone marrow transplant, and cardiac, medical and surgical intensive care units (ICUs). The opposite findings were reported from Ethiopian hospitals, where the majority of fluoroquinolone treatments were reported from outpatient departments, accounting for 91.4%, compared with the medical ward, which constituted just 6.1% [5].

Febrile and afebrile neutropenia are common and potentially life-threatening complications of myelosuppressive chemotherapy among oncology patients, especially those with hematological malignancies [27, 28]. Fluoroquinolones are commonly used to reduce the incidence of chemotherapy-induced neutropenia episodes. In our study, 8.2% of patients who received ciprofloxacin and 16.5% of patients who received levofloxacin were for prophylaxis during bone marrow transplantation, and 21.1% of ciprofloxacin patients and 4.4% of levofloxacin patients received these agents for febrile or afebrile neutropenia prophylaxis or treatment; both constitute approximately one-quarter of the sample. An article published in November 2023 reviewed the pros and cons of fluoroquinolone prophylaxis in patients with hematological malignancies, hematopoietic stem cell transplantation, and high-risk, prolonged neutropenia by reviewing the current guidelines, practices, and evidence [13]. This study concluded that this practice is supported by an older meta-analysis that reported a lower mortality rate [29–32], whereas a later meta-analysis failed to show the same benefits because of the lower effectiveness of fluoroquinolones as a result of the high resistance rate [33–36]. The aim of this study was to develop alternative approaches other than universal fluoroquinolone prophylaxis, especially in centers with high resistance rates. Other concerns regarding the use of fluoroquinolone prophylaxis include increased rates of bloodstream infections with fluoroquinolone-resistant *Enterobacterales* [37], *ESBL-producing Enterobacterales* [38], and multidrug- and carbapenem-resistant *P. aeruginosa* [39, 40]. To further emphasize local data, a study published in 2023 to determine the antibiotic resistance profiles and associated factors of *Pseudomonas* infections among patients admitted to NNUH, similar to our study, concluded that among isolates of *Pseudomonas aeruginosa*, those with antibiotic resistance to *Pseudomonas regimens* had the highest resistance to meropenem and ciprofloxacin (23.4%). Multidrug resistance was detected in 108 (58.4%) isolates [26].

With respect to chemotherapy-induced neutropenia, another study published in 2023 explored the pros and cons of the use of fluoroquinolone prophylaxis in patients with neutropenia or who underwent hematopoietic stem cell transplantation, as this topic is controversial, with international guidelines providing conflicting recommendations. This practice should be guided by individualized risk assessment on the basis of clinical characteristics and local antimicrobial resistance [41].

The results of this study also revealed that lower respiratory tract infection, mainly pneumonia, was one of the

top indications for ciprofloxacin and levofloxacin, followed by sepsis, septic shock and prophylaxis in bone marrow transplantation. The broad-spectrum antibacterial activity of fluoroquinolones, their very good bioavailability and their appropriateness for treating patients with multiple infections and those with gram-negative infections justifies their common use in these indications [14]. Similar findings were reported from a study conducted to evaluate levofloxacin prescribing patterns in intensive care units, where community-acquired pneumonia was the most common indication [8], and from Necker-Enfants Malades University Hospital in Paris [42].

In this study, ciprofloxacin and levofloxacin were used most commonly in combination with another antibiotic. The most common coprescribed antibiotics were cefuroxime, ceftazidime, piperacillin-tazobactam and vancomycin. In contrast, in this study, in eastern Ethiopia, doxycycline, metronidazole and ceftriaxone were the primary coprescribed antibiotics [5].

Resistance to commonly employed bacteria has increased to alarming levels owing to excessive and inappropriate indications, doses or durations of treatment. However, the combination of antibiotics remains an acceptable salvage approach for managing complicated multidrug-resistant infections. This approach must be supported by antibiotic stewardship programs for modifying existing guidelines by providing evidence-based recommendations on the basis of hospital antibiograms to optimize antibiotic prescribing practices. The susceptibility of gram-positive bacteria to quinolones varies significantly across species and generations of fluoroquinolones. Methicillin-susceptible *Staphylococcus aureus* (MSSA) generally shows good susceptibility to newer fluoroquinolones, whereas methicillin-resistant *Staphylococcus aureus* (MRSA) and *enterococci* often exhibit significant resistance. Resistance mechanisms include mutations in target enzymes, efflux pumps, and plasmid-mediated resistance. The clinical use of quinolones for gram-positive infections should be guided by susceptibility testing and the consideration of alternative antibiotics to minimize resistance development.

In our study, the combination of ciprofloxacin with cefuroxime was used for surgical prophylaxis in cardiac surgery, mainly via coronary artery bypass graft (CABG), for 4 days. However, a study supported by the European Association for Cardiothoracic Surgery (EACTS) guidelines revealed that the regimen used for prophylaxis was mainly cefuroxime alone or combined with other antibiotics (vancomycin or gentamicin). Other options include flucloxacillin alone or in combination with another antibiotic (ciprofloxacin, gentamicin) or amoxicillin–clavulanic acid alone or in combination with gentamicin. The antimicrobial prophylaxis regimens used for penicillin allergy patients in this study included teicoplanin or vancomycin in combination with ciprofloxacin [43]. Another study supported by guidelines was developed jointly by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA). This work represents an update to the previously published ASHP Therapeutic Guidelines on Antimicrobial Prophylaxis in Surgery, as well as guidelines from the IDSA and SIS. The use of cefazolin or cefuroxime as surgical prophylaxis in cardiac surgery has been recommended [44]. Therefore, it is recommended that the guidelines, especially in cardiac surgeries, be followed to prevent collateral effects associated with the use of fluoroquinolones as routine prophylactic agents.

Strengths and limitations

This groundbreaking Palestinian study investigated the use of fluoroquinolone antibiotics and the microbial profiles of patients receiving them at a major hospital. Although the large sample size of 692 patients provided valuable insights, the retrospective nature of the study meant that it relied on existing medical records, which may have contained incomplete or missing information, especially regarding local pathogen susceptibility patterns. Additionally, the generalizability of the findings may be limited, as the study was conducted at a single hospital within Palestine. Finally, the two-year timeframe (July 1st, 2021, to June 30th, 2023) might not fully capture potential variations in antibiotic prescribing and resistance trends over time. In particular, some levofloxacin cultures have limitations, as NNUH laboratories tend to use VITEK®, which is a fully automated system that performs bacterial identification and antibiotic susceptibility testing. This system sometimes selects ciprofloxacin only from fluoroquinolones when the intended sensitivity test is for levofloxacin. This resulted in only 8 pathogens (from 23 total pathogens for levofloxacin) being identified as R or S to levofloxacin. Finally, due to lack of data, it was not feasible to compare the use of these fluoroquinolones in relation to COVID-19 pandemic.

Conclusions and recommendations

Fluoroquinolone antibiotics, specifically levofloxacin and ciprofloxacin, are extensively utilized in a variety of patient populations, including elderly individuals. Patients frequently have underlying medical conditions such as hematological malignancies and cardiovascular diseases. The use of antibiotics varied by department; the highest rates were found in cardiac intensive care and oncology. Levofloxacin and ciprofloxacin were prescribed most frequently for respiratory tract infections and surgical procedures, respectively. Combinations of

ciprofloxacin or levofloxacin with other antibiotics are commonly used to treat complex infections. Although most patients' dosing regimens comply with guidelines, many modifications are needed because of differences in kidney function. The unique resistance patterns of the isolated pathogens to every fluoroquinolone guided the selection of the right antibiotic. According to previous studies, the use of fluoroquinolones may be excessively widespread, and treatment response guides decisions about stopping or switching antibiotics.

Future research and clinical implications

- Long-term research should be carried out to track the prevalence of fluoroquinolones, resistance trends, and changes over time. Variables such as patient demographics, disease incidence, and the use of interventions were considered.
- Antimicrobial stewardship programs in health care facilities should be strengthened to optimize fluoroquinolone use, support rational prescribing behaviors, and reduce the potential harm of antimicrobial resistance. The significance of monitoring kidney function and adjusting the fluoroquinolone dosage on the basis of individual needs is emphasized. This reduces the possibility of negative effects while ensuring safe use.
- Patient cohorting techniques, improved sanitation, and more stringent infection control measures should be implemented. This reduces infections linked to healthcare settings and stops the spread of organisms that are resistant to drugs.
- Medical professionals should be continuously instructed on the appropriate ways to prescribe antibiotics. This covers thorough safety data as well as antibiotic stewardship techniques.
- Medical specialists, such as infection control specialists, pharmacists, microbiologists, and clinicians, have made cooperative efforts. This group can create antimicrobial resistance tactics that are suitable for local culture.

Abbreviations

ASHP	American Society of Health-system Pharmacists
EACTS	European Association for Cardiothoracic Surgery
ESBL	Extended-spectrum beta-lactamase
FDA	Food and Drug Administration
ICUs	Intensive Care Units
IDSA	Infectious Diseases Society of America
IQR	Interquartile range
IRB	Institutional Review Board
MIC	Minimum inhibitory concentration
NNUH	An-Najah National University Hospital
SHEA	Society for Healthcare Epidemiology of America
SIS	Surgical infection society
SPSS	Statistical Package for the Social Sciences

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Author contributions
The first draft of the manuscript was written by A.Z., M.A.O., and M.H.H, who also collected the data and performed the analysis. A.S. and A.A. offered logistical support, designed the study, and assisted in producing the final version of the manuscript. S.H.Z., B.M.A., and S.W.A. conceptualized and designed the study, analyzed and coordinated the data, organized and supervised the field study, critically reviewed the manuscript, interpreted the results, and contributed to writing the final version. Finally, all the authors approved the final manuscript.

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Data availability
The data from our surveillance are not available in the public domain owing to privacy and ethical restrictions, but anyone interested in using the data for scientific purposes is free to request permission from the corresponding authors.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the *Institutional Review Boards (IRBs) of An-Najah National University*. The collected data were exclusively utilized for clinical research endeavors, ensuring confidentiality and nondisclosure for any other purpose. Patient identities were safeguarded through coding. As retrospective data were utilized, the *IRB of An-Najah National University* waived the need for informed consent. The authors ensured adherence to pertinent guidelines and regulations in conducting all methods.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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