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Trends in Fluoroquinolone Use in a Tertiary Healthcare Institution in the Republic of Serbia: A Retrospective Study (2012–2024)

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Fluoroquinolones are widely used broad-spectrum antibiotics in hospital practice; however, their irrational use is closely associated with the development of antimicrobial resistance and adverse effects. This study analyzed long-term trends in fluoroquinolone use at the University Clinical Center Niš, a large tertiary healthcare institution in Serbia, over a thirteen-year observation period (2012–2024).

A retrospective analysis of hospital use of ciprofloxacin, levofloxacin, and moxifloxacin was conducted using the methodology of defined daily doses per 100 bed-days (DDD/100 BD), in accordance with WHO ATC/DDD standards.

During the observed period, significant annual fluctuations in fluoroquinolone use were identified. Ciprofloxacin use declined between 2012 and 2014, followed by a notable increase in 2017, then a decrease during 2018–2019 corresponding to European regulatory restrictions, and a subsequent rise again in 2022. Levofloxacin use showed a gradual increase over time, with a marked rise during the COVID-19 pandemic (2020–2021), while moxifloxacin use increased after its introduction in 2019, particularly during the pandemic period.

Total fluoroquinolone consumption reached its highest levels during the pandemic years, after which it declined, although it remained higher compared to the beginning of the observed period.

These results indicate substantial variability in fluoroquinolone use at the University Clinical Center Niš, influenced by regulatory measures, the COVID-19 pandemic, and likely local antibiotic prescribing strategies. Continuous monitoring of antibiotic use may contribute to the development and evaluation of targeted antimicrobial stewardship strategies aimed at more rational and critical use of fluoroquinolones in hospital settings.

Key words: fluoroquinolones, antibiotic consumption, antimicrobial resistance, defined daily dose, COVID-19, ciprofloxacin, levofloxacin, moxifloxacin

Trendovi upotrebe fluorohinolona u tercijarnoj zdravstvenoj ustanovi Republike Srbije: retrospektivna studija (2012–2024.)

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Fluorohinoloni su široko korišćeni antibiotici širokog spektra u bolničkoj praksi, ali je pri tome njihova neracionalna primena usko povezana sa razvojem antimikrobne rezistencije i neželjenim efektima. Ovo istraživanje analiziralo je dugoročne trendove upotrebe fluorohinolona u Univerzitetskom kliničkom centru Niš, velikoj tercijarnoj zdravstvenoj ustanovi u Srbiji, tokom trinaestogodišnjeg perioda praćenja (2012–2024.). Sprovedena je retrospektivna analiza bolničke upotrebe ciprofloksacina, levofloksacina i moksifloksacina, primenom metodologije definisanih dnevnih doza na 100 bolničkih dana (DDD/100 BD) u skladu sa WHO ATC/DDD standardima. Tokom posmatranog perioda uočene su značajne godišnje oscilacije u upotrebi fluorohinolona. Upotreba ciprofloksacina opadala je u periodu od 2012. do 2014. godine, nakon čega je usledio značajan porast u 2017. godini, zatim smanjenje upotrebe u periodu od 2018. do 2019. koje vremenski odgovaraju evropskim regulatornim ograničenjima, kao i naknadni ponovni porast u 2022. godini. Upotreba levofloksacina pokazala je postepen rast tokom vremena, sa izraženim porastom tokom pandemije COVID-19 (2020–2021.), dok je upotreba moksifloksacina porasla nakon njegovog uvođenja 2019. godine, naročito tokom pandemijskog perioda. Ukupna potrošnja fluorohinolona dostigla je najviše vrednosti tokom pandemijskih godina, a potom je opala, iako je ostala viša u poređenju sa početkom posmatranog perioda. Ovi rezultati ukazuju na značajnu varijabilnost u primeni fluorohinolona u Univerzitetskom kliničkom centru Niš pod uticajem regulatornih mera, pandemije COVID-19 i verovatno lokalnih strategija propisivanja antibiotika. Kontinuirani nadzor upotrebe antibiotika može doprineti razvoju i evaluaciji ciljanih strategija antimikrobnog nadzora usmerenih ka racionalnijoj i kritičnoj primeni fluorohinolona u bolničkim uslovima.

Ključne reči: fluorokinoloni, potrošnja antibiotika, antimikrobna rezistencija, definisana dnevna doza, COVID-19, ciprofloksacin, levofloksacin, moksifloksacin

INTRODUCTION

Fluoroquinolones are among the most commonly prescribed medications in hospital settings. The reasons for their widespread use include their bactericidal activity, broad spectrum of action, and excellent tissue penetration (1). Ciprofloxacin, levofloxacin, and moxifloxacin are the most frequently used fluoroquinolones in clinical practice (2). However, their excessive use can rapidly lead to the selection of resistant strains of *Escherichia coli*, *Klebsiella pneumoniae*, and other pathogens (3). Therefore, the implementation of rational use principles for these drugs represents one of the key objectives of antimicrobial stewardship programs (4, 5).

The COVID-19 pandemic (2020–2021) further complicated antibiotic use strategies (6). Although COVID-19 is a viral disease, hospitals worldwide reported excessive empirical use of antibiotics in patients with COVID-19 due to concerns about secondary bacterial infections. In many cases, broad-spectrum antibiotics (including fluoroquinolones, macrolides, and cephalosporins) were administered despite the low rate of confirmed bacterial coinfections (7). Such irrational antibiotic use during pandemic waves halted the declining trends achieved in previous years and led to an increase in resistance among certain microorganisms in the post-pandemic period (8).

This study focused on the University Clinical Center Niš (UCC Niš), one of the largest teaching hospitals in Serbia (approximately 1,400 beds), which provides healthcare services to the population of the southeastern region of the country. Fluoroquinolone use at UCC Niš was analyzed over the period from 2012 to 2024. The aim of the study was to present temporal trends in fluoroquinolone use in this institution, with particular emphasis on periods of changes in international guidelines and the COVID-19 pandemic. The obtained results are intended to contribute to the development of local and regional guidelines aimed at improving the rational use of antibiotics and combating antimicrobial resistance.

MATERIALS AND METHODS

A retrospective study of antibiotic consumption was conducted at the University Clinical Center Niš (UCC Niš), a tertiary academic healthcare institution in Niš, Serbia. This hospital serves as a referral center for approximately 2 million inhabitants of the region. The focus of the study was on three fluoroquinolone antibiotics commonly used in adult patients: ciprofloxacin (CIP), levofloxacin (LEV), and moxifloxacin (MOX). CIP and LEV were available throughout the entire observation period, while MOX was introduced into clinical practice at the end of 2018.

Annual consumption data for each of these antibiotics were obtained from the electronic database of the Department of Clinical Pharmacology. The data included the total amount of each antibiotic dispensed for hospital use, which was subsequently converted into defined daily doses (DDD) in accordance with the World Health Organization (WHO) ATC/DDD standards for each drug.

In order to adjust consumption to the level of hospital activity and enable comparability across different years, as well as with other healthcare institutions, the results were expressed as DDD per 100 bed-days (DDD/100 BD). This standardized measure is recommended by the WHO and the European Centre for Disease Prevention and Control for monitoring hospital antibiotic consumption.

The study involved analysis of retrospective drug consumption data without any individual patient data; therefore, informed consent was not required, and ethical committee approval was not considered necessary.

RESULTS

The annual consumption of CIP, LEV, and MOX, expressed as defined daily doses per 100 bed-days (DDD/100 BD), at UCC Niš from 2012 to 2024 is presented in Table 1. At the beginning of the observed period, CIP was the dominant fluoroquinolone in use, while in later years a significant increase in LEV consumption was observed. MOX consumption was negligible until its introduction into clinical practice in 2019.

The data indicate pronounced fluctuations in the use of these agents, with clearly identifiable years of sharp increases and periods of declining consumption, which are described in more detail below.

Table 1. Annual fluoroquinolone consumption at UCC Niš (DDD per 100 bed-days). *Note: "0" indicates that no use was recorded in the given year (MOX was not in use prior to 2019).*

Year	CIP (DDD/100 BD)	LEV(DDD/100 BD)	MOX(DDD/100 BD)
2012	5,18	0,38	0
2013	3,84	0,66	0
2014	1,90	1,11	0
2015	2,71	1,83	0
2016	3,26	3,03	0
2017	10,51	1,61	0
2018	3,49	4,93	0
2019	1,99	2,13	0,71
2020	2,81	6,41	2,51
2021	2,90	8,01	2,19
2022	9,25	3,09	0,33
2023	2,62	4,81	1,38
2024	3,44	3,05	2,04

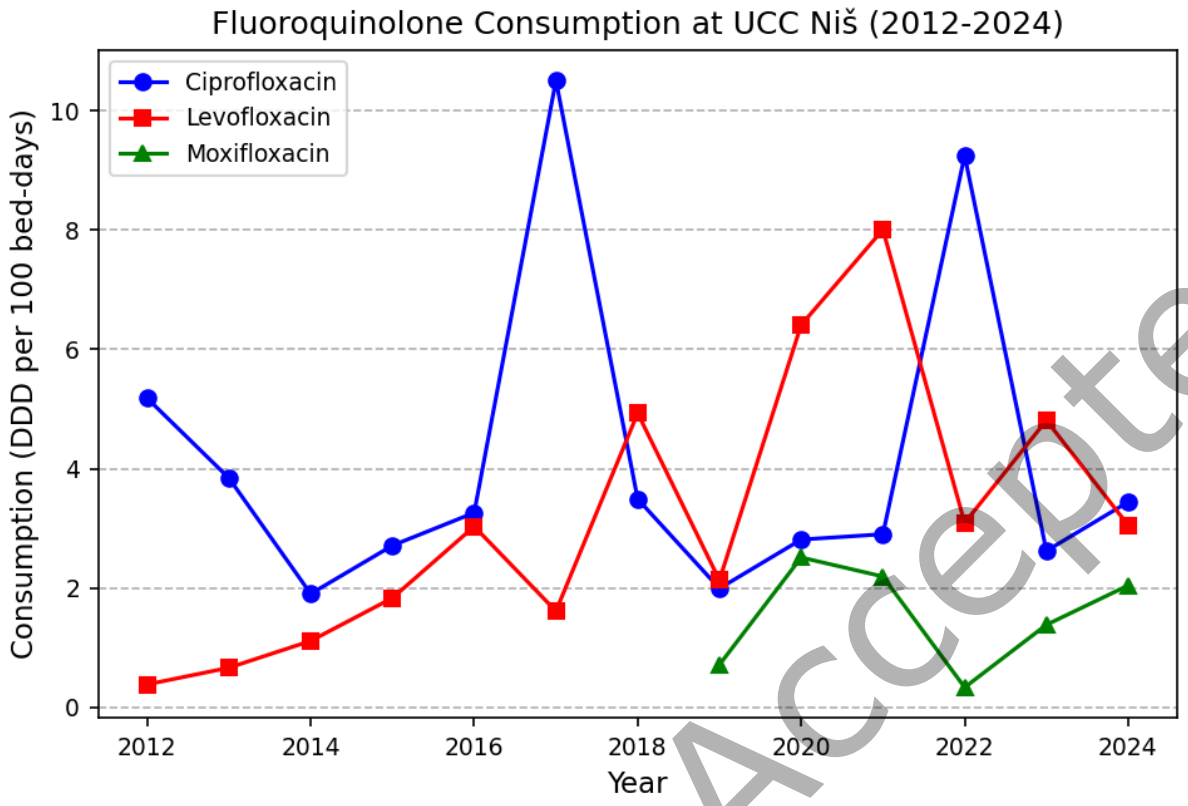

Figure 1. Annual consumption of ciprofloxacin (CIP), levofloxacin (LEV), and moxifloxacin (MOX) at UCC Niš during the period 2012–2024, expressed as DDD per 100 bed-days.

The use of CIP (blue line in Figure 1) at UCC Niš during the observed period was characterized by pronounced annual fluctuations. Following an initial decrease in consumption from 5.18 DDD/100 BD in 2012 to a minimum of 1.90 DDD/100 BD in 2014, representing a 63.3% reduction, a sharp increase in use was observed, reaching a marked peak of 10.51 DDD/100 BD in 2017. This value represents the highest recorded level of consumption for any fluoroquinolone during the entire observation period.

Between 2018 and 2019, a significant decrease in CIP consumption was recorded, with a 43% reduction in 2019 to a value of 1.99 DDD/100 BD. This trend temporally coincides with the recommendations of the European Medicines Agency (EMA) regarding restrictions on fluoroquinolone use. During the COVID-19 pandemic years (2020–2021), CIP consumption remained relatively low; however, in 2022 a renewed increase was observed, reaching 9.25 DDD/100 BD, representing a 219% increase compared to the previous year. This was followed by another decline, with values of 2.62 DDD/100 BD in 2023 and 3.44 DDD/100 BD in 2024, further confirming the marked variability in ciprofloxacin use throughout the observed period.

LEV (red line in Figure 1) showed a different consumption pattern, with a pronounced long-term increasing trend, particularly during the pandemic period. LEV consumption gradually increased from 0.38 DDD/100 BD in 2012 to 3.03 DDD/100 BD in 2016, representing a total

increase of 697%. A further rise was observed in 2020, when consumption was 16 times higher compared to the baseline value in 2012. The highest level of consumption of this fluoroquinolone was recorded in 2021, reaching 19.51 DDD/100 BD.

Following the pandemic peak, a significant decrease in LEV use was observed, dropping to 3.09 DDD/100 BD in 2022, representing a 61.4% reduction. In the subsequent period, consumption stabilized, with values of approximately 3.05 DDD/100 BD in 2024. Despite the reduction compared to the pandemic period, consumption remained higher than in the early years of observation.

MOX (green line in Figure 1) was introduced into clinical practice later than the other studied fluoroquinolones, and its consumption was negligible until 2019. During the COVID-19 pandemic period, a significant increase in use was observed, with a 253.5% rise, reaching 2.51 DDD/100 BD in 2020. This pandemic-related increase was followed by a marked decline in consumption, dropping to 0.33 DDD/100 BD in 2022. After reaching this minimum, MOX consumption increased again, rising by 318.2% in 2023, followed by an additional increase of 47.8% in 2024.

An overall assessment of total consumption of all three fluoroquinolones provides a broader picture of the use of this antibiotic class. In the initial period, a decrease was observed from 5.56 DDD/100 BD in 2012 to 3.01 DDD/100 BD in 2014, representing a total reduction of 45.9%. This was followed by an increase in consumption in 2015 (50.8%) and 2016 (38.5%), culminating in 2017 with nearly a twofold increase compared to the previous year.

Between 2018 and 2019, a significant decrease in fluoroquinolone consumption was recorded, followed by a sharp increase during the COVID-19 pandemic, with a 142.9% rise in 2020 and an absolute peak in 2021 (13.10 DDD/100 BD). After the pandemic maximum, a gradual downward trend in consumption was observed, with a notable decline of 30.5% in 2023.

Encouragingly, total consumption in 2024 (8.53 DDD/100 BD) was lower compared to the years with the highest consumption levels. This suggests a degree of progress at the end of the observed period in reducing excessive fluoroquinolone use compared to the pandemic peaks or the spike observed in 2017. However, the challenge for the future remains to maintain a lower and more stable level of consumption, with a desirable continued downward trend in accordance with the principles of rational antibiotic use strategies.

DISCUSSION

Long-term monitoring of antibiotic consumption in hospital settings represents a key component of antimicrobial stewardship and serves as a foundation for evaluating the effects of restrictive measures and rational antibiotic use programs (9,10).

During the observed period, pronounced fluctuations in fluoroquinolone consumption were recorded. CIP consumption showed an initial decline from 2012 to 2014, which is consistent with the general European trend of reduced fluoroquinolone use following concerns about antimicrobial resistance and adverse effects associated with this drug class (11,12). A similar pattern of reduced fluoroquinolone use in hospital settings has also been reported in ECDC

Point Prevalence Survey (PPS) studies, which indicated a gradual decrease in their use across most EU countries during the second half of the 2010s (13).

Veličković-Radovanović et al., in their analysis of antibiotic consumption at the Clinical Center Niš for the period 2011–2014, reported marked fluctuations in fluoroquinolone use, along with a high level of resistance of *Escherichia coli* and *Klebsiella pneumoniae* to CIP in urinary and intra-abdominal infections (14). These findings are consistent with the results of our study, which, over an extended observation period (2012–2024), also demonstrates unstable patterns of fluoroquinolone consumption in the same institution.

However, in 2017, a significant increase in CIP consumption was observed, which may indicate local clinical or organizational factors, such as changes in treatment protocols, the occurrence of nosocomial infections caused by Gram-negative pathogens, or a lack of alternative therapeutic options. Similar fluctuations in the consumption of individual fluoroquinolones have been described in other European tertiary centers, particularly in countries with traditionally higher levels of antibiotic consumption (15).

In contrast to CIP, LEV consumption showed a gradual increase during the period 2012–2016, which is consistent with its increasingly frequent use in the treatment of respiratory infections and hospital-acquired pneumonia. The introduction of MOX in 2019 coincides with a broader European trend toward the use of "respiratory fluoroquinolones," particularly in the treatment of severe pneumonia (16).

An important regulatory milestone was the 2018 decision of the European Medicines Agency (EMA), which recommended restrictions on the use of fluoroquinolones due to the risk of serious and potentially long-lasting adverse effects (17). Following this decision, many European countries reported a significant decline in fluoroquinolone consumption, both in outpatient and hospital settings (12,18). In this context, the reduction in fluoroquinolone consumption at UCC Niš during 2018–2019 can be interpreted.

The effectiveness of antimicrobial stewardship programs in reducing fluoroquinolone consumption has been confirmed in several studies. Bertolino et al., through studies conducted in tertiary hospitals in Italy, demonstrated a significant decline in overall fluoroquinolone consumption over a decade: analysis of hospital data for the period 2015–2024 showed a reduction of approximately 58% in DDD/100 bed-days following the introduction of regulatory measures and strengthening of stewardship programs (19). In a study from a tertiary hospital center in southern Poland (650 beds), the implementation of a restrictive policy with mandatory pre-authorization led to a marked reduction in fluoroquinolone consumption in the urology department, from 358.9 to 43.4 DDD/1,000 patient-days during the period 2018–2023 (20).

In contrast, at UCC Niš during the period 2012–2024, no formal fluoroquinolone restriction policy was in place; therefore, although reductions in consumption were observed in certain years, they were not sustained. Such comparisons suggest that the implementation of clearly defined restrictive measures may have a more significant and long-lasting impact on reducing fluoroquinolone use in hospital settings.

The COVID-19 pandemic period (2020–2021) was characterized by a significant increase in LEV and MOX consumption at UCC Niš. This finding is consistent with numerous international studies indicating excessive empirical use of antibiotics in hospitalized COVID-19 patients, despite the low prevalence of bacterial coinfections. Meta-analyses have shown

that more than 70% of COVID-19 patients received antibiotics without microbiological confirmation of bacterial infection (6,8).

A similar increase in fluoroquinolone consumption during the pandemic has been reported in other hospital centers, particularly in countries with already high baseline antibiotic use, including those outside Europe (21). These data suggest that even established antimicrobial stewardship systems were partially compromised during the pandemic.

Data from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) indicate substantial variability in antibiotic consumption across European countries, with those traditionally having lower consumption exhibiting overall lower use of antibacterial agents compared to countries with higher antibiotic use (22). In this context, the consumption levels observed at UCC Niš further highlight the need to strengthen measures aimed at promoting rational antibiotic use.

CONCLUSION

Our study demonstrates that fluoroquinolone consumption at UCC Niš during the period from 2012 to 2024 was characterized by significant year-to-year variability, reflecting the combined influence of regulatory changes, the COVID-19 pandemic, and likely national antibiotic prescribing guidelines. Although reductions in consumption were observed in certain periods, they were not sustained in the long term, indicating insufficient long-term control of fluoroquinolone prescribing.

Finally, the extended observation period covered in this study highlights the importance of continuous monitoring of antibiotic consumption as a fundamental tool for evaluating the effectiveness of regulatory and stewardship interventions, as well as for guiding future strategies aimed at combating antimicrobial resistance.

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