Original Article

Fluoroquinolone stewardship at a community health system: A decade in review

Elena A. Swingler PharmD, MBA, BCIDP1, Matthew Song PharmD, BCIDP1, Sarah E. Moore PharmD, BCIDP1, Brian C. Bohn PharmD, BCIDP2, Paul S. Schulz MD1, Alan D. Junkins PhD, D(ABMM)3 and Ashley M. Wilde PharmD, BCIDP1

1Norton Infectious Diseases Institute, Norton Healthcare, Louisville, Kentucky, 2Department of Pharmacy, Barnes-Jewish Hospital, St. Louis, Missouri and 3Department of Microbiology, Norton Healthcare, Louisville, Kentucky

Abstract

Objective: To describe inpatient fluoroquinolone use and susceptibility data over a 10-year period after the implementation of an antimicrobial stewardship program (ASP) led by an infectious diseases pharmacist starting in 2011.

Design: Retrospective surveillance study.

Setting: Large community health system.

Methods: Fluoroquinolone use was quantified by days of therapy (DOT) per 1,000 patient days (PD) and reported quarterly. Use data are reported for inpatients from 2016 to 2020. Levofloxacin susceptibility is reported for Pseudomonas aeruginosa and Escherichia coli for inpatients from 2011 to 2020 at a 4 adult-hospital health system.

Results: Inpatient fluoroquinolone use decreased by 74% over a 5-year period, with an average decrease of 3.45 DOT per 1,000 PD per quarter (P < .001). Over a 10-year period, inpatient levofloxacin susceptibility increased by 57% for P. aeruginosa and by 15% for E. coli. P. aeruginosa susceptibility to levofloxacin increased by an average of 2.73% per year (P < .001) and had a strong negative correlation with fluoroquinolone use, r = −0.99 (P = .002). E. coli susceptibility to levofloxacin increased by an average of 1.33% per year (P < .001) and had a strong negative correlation with fluoroquinolone use, r = −0.95 (P = .015).

Conclusions: A substantial decrease in fluoroquinolone use and increase in P. aeruginosa and E. coli levofloxacin susceptibility was observed after implementation of an antimicrobial stewardship program. These results demonstrate the value of stewardship services and highlight the effectiveness of an infectious diseases pharmacist led antimicrobial stewardship program.

(Received 8 July 2022; accepted 12 October 2022)

Antimicrobial resistance is a global public health threat mainly driven by the misuse of antimicrobials. Fluoroquinolone antibiotics have historically been prescribed for a wide variety of infections, including mild, uncomplicated infections for which alternatives may be preferred. Consequently, increasing antimicrobial resistance has been reported, particularly among Enterobacterales and Pseudomonas spp. Antimicrobial resistance greatly limits empiric and definitive treatment options for potentially serious infections. For example, for Pseudomonas spp infections, fluoroquinolones are the only antibiotic class currently available for enteral administration. Fluoroquinolone exposure has not only been associated with fluoroquinolone-resistant strains but also with methicillin-resistant Staphylococcus aureus and extended-spectrum β-lactamase–producing organisms.

In addition to driving resistance, fluoroquinolones have been associated with serious and potentially permanent musculoskeletal and central nervous system adverse events resulting in regulatory action by the Food and Drug Administration. Their use also carries a moderate to high risk of Clostridioides difficile infection compared with other antibiotic classes, and fluoroquinolones have been linked to the emergence and spread of the hypervirulent 027/BI/NAP1 strain.

In response to the concerns outlined above, many health systems have employed antimicrobial stewardship interventions to reduce fluoroquinolone use, antimicrobial resistance, and C. difficile infections. Interventions usually consist of formulary restriction and prospective audit and feedback, sometimes in conjunction with education and guidelines for optimal antibiotic use. Evidence to support fluoroquinolone-targeted interventions is heterogeneous regarding intervention types, duration, and...
outcomes measured. Overall, stewardship interventions are supported by favorable outcomes of reductions in fluoroquinolone use, resistance, and C. difficile infection rates. In this report, we describe fluoroquinolone use and susceptibility data over a 10-year period at a large community health system with an antimicrobial stewardship program (ASP).

Methods
This retrospective surveillance study was conducted at Norton Healthcare, a large, integrated health system of 4 adult hospitals licensed for ~1,600 beds in Kentucky. Inpatient fluoroquinolone use and susceptibility data were analyzed in the context of a growing ASP.

Antimicrobial stewardship program
The current ASP at our health system started in 2011 with 1 full-time infectious diseases pharmacist and 1 part-time infectious diseases physician. Initially, the ASP focused on formulary optimization, guidelines for optimal antimicrobial use, order-set updates, and provider and pharmacist education. Fluoroquinolone use was addressed primarily through order-set revisions to discourage routine use. After maximizing the antimicrobial stewardship benefit that could be achieved at the system level, the infectious diseases pharmacist in charge of the ASP focused on providing prospective audit and feedback for patients on broad-spectrum antimicrobials, including fluoroquinolones. In 2017, the ASP expanded to include 4 full-time infectious diseases pharmacists (1 at each hospital within the health system) and was able to consistently provide prospective audit and feedback for a larger number of patients. The ASP continues to be supported by a part-time infectious diseases physician leader, but prospective audit and feedback is performed by the pharmacists. Formulary restriction of fluoroquinolones was not utilized at our health system.

Antibiotic use
Inpatient levofloxacin and ciprofloxacin antibiotic use is expressed as days of therapy (DOT) per 1,000 patient days (PD) and is reported quarterly. DOT was calculated using administration records obtained from the electronic health record. Inpatient fluoroquinolone use data are reported for 2016 to 2020. Data were not readily retrievable for inpatient use before 2016.

Microbiology
Levofloxacin susceptibility data for P. aeruginosa and E. coli were obtained from the health system’s antibiograms, which were collated annually for each hospital. Antibiograms were created using only the first isolate of a given species per patient per year and included nonsurveillance samples from inpatient and emergency department patients. Antibiotic susceptibility testing was performed on the MicroScan WalkAway system (Beckman Coulter, Brea, CA). Susceptibility was reported using the Clinical and Laboratory Standards Institute (CLSI) breakpoints established prior to 2019. Adult hospital susceptibility rates were aggregated and weighted according to the number of isolates per hospital per year. The results were reported as the proportion of fluoroquinolone-susceptible isolates among all clinical isolates for each species. Microbiologic data were reported for the period of 2010 to 2020 for inpatients.

Statistical analysis
Line graphs were produced to show changes in fluoroquinolone DOT per 1,000 PD and changes in susceptibility to levofloxacin in E. coli and P. aeruginosa over time. Linear regression was used to produce trend lines and to describe changes over time. Beta coefficients, 95% confidence intervals, and P values were reported. Scatter plots were produced to plot fluoroquinolone DOT per 1,000 PD versus susceptibility to levofloxacin in E. coli and P. aeruginosa. Pearson correlation coefficients were produced to assess ecological associations between DOT per 1,000 PD and susceptibilities. The Pearson correlation coefficient, r, and P values were reported. All statistical analyses were performed in R version 4.1.2 software (R Foundation for Statistical Computing, Vienna, Austria). P values < .05 were deemed statistically significant.

Results
Antibiotic use
Inpatient fluoroquinolone use decreased from 83.5 DOT per 1,000 PD in quarter 1 of 2016 to 21.4 DOT per 1,000 PD in quarter 4 of 2020, representing a 74% decrease over a 5-year period. Fluoroquinolone use decreased over time by an average of 3.45 DOT per 1,000 PD per quarter, \( \beta = -3.45 \) (95% CI, -3.80 to -3.09; \( P < .001 \)) (Fig. 1).

Microbiology
Inpatient levofloxacin susceptibility increased for P. aeruginosa by 57% (absolute increase of 30%) and for E. coli by 15% (absolute increase of 10%) from 2010 to 2020. P. aeruginosa susceptibility to levofloxacin increased by an average of 2.73% per year, \( \beta = 2.73 \) (95% CI, 1.94–3.51; \( P < .001 \)) (Fig. 2). We detected a strong negative association between fluoroquinolone use and P. aeruginosa susceptibility to levofloxacin, \( r = -0.99 \) (\( P = .002 \)). E. coli susceptibility to levofloxacin increased by an average of 1.33% per year, \( \beta = 1.33 \) (95% CI, 0.91–1.75; \( P < .001 \)) (Fig. 3). We also detected a strong negative association between fluoroquinolone use and E. coli susceptibility to levofloxacin, \( r = -0.95 \) (\( P = .015 \)).

Discussion
The ASP efforts at our health system appear to be successful at reducing inpatient fluoroquinolone use and antimicrobial resistance among P. aeruginosa and E. coli isolates.

The results of this study add to the growing body of evidence that demonstrates the importance of persistent and well-resourced hospital-based ASPs. Several meta-analyses have summarized favorable outcomes for individual stewardship interventions as well as full programs on antibiotic use and resistance, clinical outcomes, adverse events, C. difficile infections, and costs. For these reasons, the ASP at our health system is valued and has expanded to provide comprehensive services across the health system. The desirable trends in fluoroquinolone use and susceptibility reported here provide further justification for our program.

We detected a 74% decrease in fluoroquinolone use over 5 years and an absolute increase of 30% and 10% in levofloxacin-susceptible P. aeruginosa and E. coli isolates, respectively, over 10 years. ASP implementation is typically accompanied by an ~20% decrease in total antimicrobial use, which is consistent with studies reporting on fluoroquinolone use specifically. Resistance reduction rates vary widely between studies. We detected a greater reduction in use and resistance than has typically been
Antimicrobial Stewardship & Healthcare Epidemiology

Our results provide support for non–restriction-focused ASP services. Most current evidence for ASP impact on gram-negative fluoroquinolone resistance includes formulary restriction as the main intervention.\textsuperscript{13} However, 2 studies have described interventions that included prospective audit and feedback without a restriction component.\textsuperscript{24,29} The interventions were successful in both studies, demonstrating a significant decrease in fluoroquinolone use and absolute increase of 9%–16% in fluoroquinolone-susceptible \textit{P. aeruginosa} isolates over an ~5-year period, which is in line with our results. Our study is unique because it not only provides fluoroquinolone susceptibility trends over 10 years but also has a longer stewardship intervention period than the 2 studies.

Another strength of our study is the utilization of order-set optimization and prospective audit and feedback as the core stewardship intervention, which can be adopted in virtually any hospital setting without the need for around-the-clock staff support, as might be required by some formulary restriction models. We might have observed even greater benefits if our system employed formulary restriction in addition to prospective audit and feedback and order-set optimization. When considering longitudinal antimicrobial stewardship activities, ASPs should periodically re-evaluate their approaches and adapt their activities based on needs and resources.

Antimicrobial stewardship activities at our health systems are primarily pharmacist driven, which is similar to other stewardship programs.\textsuperscript{38} Pharmacists, particularly those with infectious diseases expertise, are uniquely qualified to provide robust antimicrobial stewardship and therapeutic optimization.\textsuperscript{11,12} Leveraging pharmacists’ drug expertise appears to have been successful in reducing both antimicrobial use and antimicrobial resistance at our health system. In addition to empowering pharmacists to perform stewardship activities and promoting their expertise within our health system, investment in staffing likely contributes to the successes described. Various recommendations of ratios of antimicrobial stewardship staff to hospital beds exist, but our ratio of 1 full-time infectious diseases pharmacist to 400 beds may allow for more robust prospective audit and feedback and higher impact relative to ASPs with fewer staff members.\textsuperscript{35}

This study had several limitations. Fluoroquinolone use data were not available for inpatients before 2016. How use correlated with susceptibility before this time remains uncertain, but other than the stewardship activities described, there were no other clinical interventions, operational changes, or changes in infection prevention practices that could have significantly influenced susceptibility. Based on first-hand knowledge of stewardship activities and prescribing patterns prior to 2016, we know the use of fluoroquinolones was substantially higher in 2011 and decreased over time. We could not assess the impact of our program in a quasi-experimental study design due to lack of data prior to the intervention period. We also did not report use and antimicrobial resistance trends for other antibiotic classes, which may have inadvertently increased. However, this is unlikely given that our program did not focus solely on fluoroquinolone use but addressed other broad-spectrum antibiotics in parallel. Susceptibility interpretations for fluoroquinolones were designated based on CLSI breakpoints before the change in 2019.\textsuperscript{34} Application of updated breakpoints likely would have resulted in decreased susceptibility rates; however, this would have been a major confounding factor, and for the purposes of this review, utilizing a consistent breakpoint likely more accurately reflects trends over time.

In our health system, fluoroquinolone use substantially decreased and \textit{P. aeruginosa} and \textit{E. coli} levofloxacin susceptibility increased after the implementation of an ASP. These results
demonstrate the value of stewardship services and highlight the effectiveness of an infectious diseases pharmacist–led ASP.

Acknowledgments. The authors thank Stephen Furmanek, MPH, MS, for his assistance with the statistical analysis of this study.

Financial support. No financial support was provided relevant to this article.

Conflicts of interest. All authors report no conflicts of interest relevant to this article.

References

1. Antimicrobial resistance. World Health Organization website. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. Published 2021. Accessed June 29, 2022.

2. Linder JA, Huang ES, Steinman MA, Gonzales R, Stafford RS. Fluoroquinolone prescribing in the United States: 1995 to 2002. Am J Med 2005;118:259–268.

3. Lautenbach E, Strom BL, Nachamkin I, et al. Longitudinal trends in fluoroquinolone resistance among Enterobacteriaceae isolates from inpatients and outpatients, 1989–2000: differences in the emergence and epidemiology of resistance across organisms. Clin Infect Dis 2004;38:655–662.

4. Polk RE, Johnson CK, McClish D, Wenzel RP, Edmond MB. Predicting hospital rates of fluoroquinolone-resistant Pseudomonas aeruginosa from fluoroquinolone use in US hospitals and their surrounding communities. Clin Infect Dis 2004;39:497–503.

5. Sanchez GV, Master RN, Karlowsky JA, Bordon JM. In vitro antimicrobial resistance of urinary Escherichia coli isolates among US outpatients from 2000 to 2010. Antimicrob Agents Chemother 2012;56:2181–2183.

6. Parienti J-J, Cattoir V, Thibon P, et al. Hospital-wide modification of fluoroquinolone policy and metillin-resistant Staphylococcus aureus rates: a 10-year interrupted time-series analysis. J Hosp Infect 2011;78:118–122.

7. Weber SG, Gold HS, Hooper DC, Karchmer AQ, Carmeli Y. Fluoroquinolones and the risk for methicillin-resistant Staphylococcus aureus in hospitalized patients. Emerg Infect Dis 2003;9:1415–1422.

8. Rodríguez-Baño J, Navarro MD, Romero L, et al. Risk-factors for emerging bloodstream infections caused by extended-spectrum beta-lactamase-producing Escherichia coli. Clin Microbiol Infect 2008;14:180–183.

9. FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. Food and Drug Administration website. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-updates-warnings-oral-and-injectable-fluoroquinolone-antibiotics. Published 2016. Accessed June 29, 2022.

10. Deshpande A, Pasupuleti V, Thota P, et al. Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. J Antimicrob Chemother 2013:68:1951–1961.

11. Vardakas KZ, Trigkidis KK, Boukouvella E, Falagas ME. Clostridium difficile infection following systemic antibiotic administration in randomised controlled trials: a systematic review and meta-analysis. Int J Antimicrob Agents 2016;48:1–10.

12. He M, Miyajima F, Roberts P, et al. Emergence and global spread of epidemic healthcare-associated Clostridium difficile. Nat Genet 2013:45:109–113.

13. Pitiriga V, Vrioni G, Saroglou G, Tsakris A. The impact of antibiotic stewardship programs in combating quinolone resistance: a systematic review and recommendations for more efficient interventions. Adv Ther 2017;34:854–865.

14. Song M, Wilde A. An opt-out approach to antimicrobial stewardship utilizing electronic alert recommendations at a community hospital. Open Forum Infect Dis 2017;4:S277.

15. Baur D, Primrose Gladstone B, Burkert F, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. Lancet Infect Dis 2017;17:990–1001.

16. Feazel LM, Malhotra A, Perencevich EN, Kaboli P, Diekema DJ, Schweizer ML. Effect of antibiotic stewardship programmes on Clostridium difficile incidence: a systematic review and meta-analysis. J Antimicrob Chemother 2014:69:1748–1754.

17. Karanika S, Paudel S, Grigoras C, Kalbasi A, Mylonakis E. Systematic review and meta-analysis of clinical and economic outcomes from the implementation of hospital-based antimicrobial stewardship programs. Antimicrob Agents Chemother 2016:60:4840–4852.

18. Schuts EC, Hulscher ME, Mouton JW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis 2016;16:847–856.

19. Schuts EC, Boyd A, Muller AE, Mouton JW, Prins JM. The effect of antibiotic restriction programs on prevalence of antimicrobial resistance: a systematic review and meta-analysis. Open Forum Infect Dis 2021;8:1–9.

20. Chin J, Green SB, McKamey LJ, et al. Restriction-free antimicrobial stewardship initiative targeting fluoroquinolone reduction across a regional health-system. Infect Prev Pract 2019;11:e100019.

21. Jones KA, Onwubiko UN, Kubes J, et al. Reductions in inpatient fluoroquinolone use and postdischarge Clostridiodes difficile infection (CDI) from a systemwide antimicrobial stewardship intervention. Antimicrob Steward Healthc Epidemiol 2021;1:e32.

22. Boel J, Andreassen V, Jarlwo JO, et al. Impact of antibiotic restriction on resistance levels of Escherichia coli: a controlled interrupted time series study of a hospital-wide antibiotic stewardship program. J Antimicrob Chemother 2016;71:2047–2051.

23. Cook PP, Gooch M. Long-term effects of an antimicrobial stewardship program at a tertiary-care teaching hospital. Int J Antimicrob Agents 2015:45:262–267.

24. Hecker MT, Son AH, Murphy NN, et al. Impact of syndrome-specific antimicrobial stewardship interventions on use of and resistance to fluoroquinolones: an interrupted time-series analysis. Am J Infect Control 2019:47:869–875.

25. Wu H, Liu H, Lin Y, Hsieh P, Lee Y. Correlation between levofloxacin consumption and the incidence of nosocomial infections due to fluoroquinolone-resistant Escherichia coli. J Microbial Infect Dis 2016:49:424–429.

26. Lewis GI, Fang X, Gooch M, Cook PP. Decreased resistance of Pseudomonas aeruginosa with restriction of ciprofloxacin in a large teaching hospital’s intensive care and intermediate care units. Infect Control Hosp Epidemiol 2012:33:368–373.

27. Falagas ME, Bliztiotis IA, Michalopoulos A, et al. Effect of a policy for restriction of selected classes of antibiotics on antimicrobial drug cost and resistance. J Chemother 2007:19:178–184.

28. Gottesman BS, Carmeli Y, Shitrit P, Chowers M. Impact of quinolone restriction on resistance patterns of Escherichia coli isolated from urine by culture in a community setting. Clin Infect Dis 2009:49:869–875.

29. Lafaurie M, Porcher R, Donay J, Touratier S, Molina J. Reduction of fluoroquinolone use is associated with a decrease in methillin-resistant Staphylococcus aureus and fluoroquinolone-resistant Pseudomonas aeruginosa isolation rates: a 10-year study. J Antimicrob Chemother 2012:67:1010–1015.

30. Barlam TF, Childs E, Zieminski SA, et al. Perspectives of physician and pharmacist stewards on successful antibiotic stewardship program implementation: a qualitative study. Open Forum Infect Dis 2020;7:ofaa229.

31. Garau J, Bassetti M. Role of pharmacists in antimicrobial stewardship programs. Int J Clin Pharm 2018:40:948–952.

32. Bessessen MT, Ma A, Clegg DF, Fugit RV, Pepe A, Goetz MB. Antimicrobial stewardship programs: comparison of a program with infectious diseases pharmacist support to a program with a geographic pharmacist staffing model. Hosp Pharm 2015;50:477–483.

33. Pulcini C, Morel CM, Tacconelli E, et al. Human resources estimates and funding for antibiotic stewardship teams are urgently needed. Clin Microbiol Infect 2017:23:785–787.

34. Clinical and Laboratory Standards Institute. Fluoroquinolone breakpoints for Enterobacteriaceae and Pseudomonas aeruginosa, first edition. CLSI rationale document MR02. Wayne, PA: CLSI; 2019.