Published in final edited form as:

Infect Control Hosp Epidemiol. 2017 April ; 38(4): 461–468. doi:10.1017/ice.2016.315.

Preferential use of nitrofurantoin over fluoroquinolones for acute uncomplicated cystitis and outpatient *Escherichia coli* resistance in an integrated health care system

Rebecca L. Pedela, PharmD¹, Katherine C. Shihadeh, PharmD¹, Bryan C. Knepper, MPH, MSc¹, Michelle K. Haas, MD^{1,2,3}, William J. Burman, MD^{1,2}, and Timothy C. Jenkins, MD^{1,2}

¹Denver Health, Denver, Colorado

²University of Colorado School of Medicine, Aurora, Colorado

³Denver Public Health, Denver, Colorado

Abstract

Objectives—To evaluate changes in outpatient fluoroquinolone (FQ) and nitrofurantoin use and resistance among *E. coli* isolates after a change in institutional guidance to use nitrofurantoin in preference to FQs for acute uncomplicated cystitis.

Design—Retrospective pre-intervention post-intervention study

Setting—Urban, integrated healthcare system

Patients—Adult outpatients treated for acute cystitis

Methods—Two time periods were compared: Jan 2003 – Jun 2007 when FQs were recommended as first-line therapy, and Jul 2007 – Dec 2012 when nitrofurantoin was recommended. The main outcomes were changes in FQ and nitrofurantoin use and FQ- and nitrofurantoin-resistant *E. coli* by time series analysis.

Results—5,714 adults treated for acute cystitis and 11,367 outpatient *E. coli* isolates were included in the analysis. After the change in prescribing guidance, there was an immediate 26% (95%CI 20 – 32%) decrease in FQ use ($P < .001$), and a non-significant 6% (95%CI –2 – 15%) increase in nitrofurantoin use ($P = .12$); these changes were sustained over the post-intervention period. Oral cephalosporin use also increased during the post-intervention period. There was a significant decrease in the trend of FQ-resistant *E. coli* (–0.4% per quarter [95%CI –0.6% – –0.1%], $P = .004$) between the pre- and post-intervention periods; a change in the trend of nitrofurantoin-resistant *E. coli* was not observed.

Conclusions—In an integrated healthcare system, a change in institutional guidance for acute uncomplicated cystitis was associated with a reduction in FQ use which may have contributed to a

Correspondence and reprint requests: Timothy Jenkins, MD, Denver Health, 660 Bannock Street, Denver, Colorado 80204, timothy.jenkins@dhha.org.

This work was presented in part at IDWeek 2014, Philadelphia, PA.

Potential conflicts of interest: All authors report no relevant conflicts of interest.

stabilization in FQ-resistant *E. coli*. Increased nitrofurantoin use was not associated with a change in nitrofurantoin resistance.

Keywords

acute cystitis; *Escherichia coli*; antimicrobial resistance; fluoroquinolone resistance; nitrofurantoin resistance; antimicrobial stewardship

Background

Antimicrobial resistance among bacterial pathogens is a growing public health threat.¹ Combating antimicrobial resistance is a national priority,² and treatment strategies for bacterial infections that prevent or limit the development of antimicrobial resistance are urgently needed. Urinary tract infections are among the most common bacterial infections treated in the ambulatory care setting, resulting in approximately 8 million antibiotic prescriptions each year in the United States.³ Treatment of urinary tract infections is increasingly difficult due to the emergence of antibiotic-resistant Gram-negative bacteria.⁴ Fluoroquinolone resistance among uropathogens such as *Escherichia coli* is particularly problematic.^{5,6}

Although fluoroquinolones are effective treatment options for urinary tract infections, their use has been associated with the emergence of antimicrobial resistance among both Gram-negative and Gram-positive pathogens,^{6–10} the development of *Clostridium difficile* infection,^{11–13} and potentially serious side effects.¹⁴ Because of this potential for so-called “collateral damage,” the 2010 update to the Infectious Diseases Society of America (IDSA) guideline for acute uncomplicated cystitis recommends first-line treatment with alternative agents such as nitrofurantoin, fosfomycin, or trimethoprim-sulfamethoxazole.⁴

At Denver Health, an urban, integrated public healthcare system, resistance to trimethoprim-sulfamethoxazole among urinary *E. coli* isolates reached 24% in 1999.¹⁵ In response, an institutional guideline for the treatment of outpatients with acute uncomplicated cystitis was developed recommending fluoroquinolones as first-line therapy. This resulted in a marked increase in outpatient fluoroquinolone use which was associated with a rapid increase in fluoroquinolone resistance among urinary *E. coli* isolates: from 1% in 1999 to 9.4% in 2005.⁶ The guideline was therefore revised in 2007 to direct providers to use nitrofurantoin for acute uncomplicated cystitis and to reserve fluoroquinolones for complicated urinary tract infections. This treatment strategy, mirroring the current IDSA guideline recommendations, has been in place at Denver Health since 2007, offering a unique opportunity to evaluate its long-term impact on antimicrobial resistance. The objectives of this study were to evaluate changes in fluoroquinolone and nitrofurantoin use following the change in recommended first-line therapy and to assess the effects on antimicrobial resistance among outpatient *E. coli* isolates.

Methods

Study Design, Setting, and Population

This was a retrospective, pre-intervention post-intervention study. Denver Health is an urban, integrated, safety-net healthcare system with a 477-bed hospital, emergency department and urgent care center, eight community health clinics, and fifteen school-based clinics.¹⁶ The study population included adults with a visit to the emergency department, urgent care center, or an outpatient clinic for acute cystitis during two periods: January 2003 – June 2007 when fluoroquinolones were the recommended first-line agents for acute uncomplicated cystitis (pre-intervention period) and July 2007 – December 2012 when nitrofurantoin was the recommended first-line agent (post-intervention period). This study was approved by the Colorado Institutional Review Board.

Outcome measures

The primary outcomes of interest were the changes in fluoroquinolone and nitrofurantoin use for acute cystitis and the changes in fluoroquinolone- and nitrofurantoin-resistant *E. coli* between the two periods. Secondary outcomes included the change in total outpatient fluoroquinolone use, the appropriateness of fluoroquinolone prescriptions, and the occurrence of urinary tract infection-related clinical events in the 28 days after the index visit.

Data Collection

Cases were included for analysis when a visit with a primary or secondary *International Classification of Diseases – 9th Revision* (ICD-9) diagnosis of acute cystitis (595.00, 599.00) was associated with an antibiotic prescription dispensed in the Denver Health system within 3 days of that visit. Pregnant women, prisoners, and patients less than 19 or greater than 89 years of age were excluded. Cases where the antibiotic prescription was filled more than 3 days after the index visit or where incomplete documentation prevented identification of the prescribed antibiotic were also excluded.

Antibiotics prescribed for acute cystitis were aggregated quarterly and expressed as the proportion of total antibiotic prescriptions for acute cystitis over time. To evaluate for changes in fluoroquinolone use for all possible indications that could have potentially impacted antimicrobial resistance, total quarterly fluoroquinolone prescriptions were aggregated and expressed as prescriptions per 1000 outpatient visits.

To assess the appropriateness of fluoroquinolone use during the period when nitrofurantoin was the recommended first-line agent, we manually reviewed the medical records of 100 randomly-selected patients prescribed a fluoroquinolone during this time period. Use of a fluoroquinolone was deemed appropriate in the following scenarios: documentation of an allergy, intolerance, or contraindication to nitrofurantoin, history of infection with an organism resistant to two or more antibiotic classes (multi-drug resistant organism), treatment of cases meeting criteria for complicated urinary tract infection as recommended in the institutional guideline (Supplemental Figure), or documentation of a co-infection in which nitrofurantoin monotherapy would be considered inappropriate (e.g., pneumonia).

Nitrofurantoin was considered contraindicated when the estimated creatinine clearance was less than 60 mL/min or when the most recent serum creatinine was greater than 1.4 mg/dL. Early and late return visits were defined as hospitalizations or emergency department, urgent care center, or outpatient clinic visits associated with a diagnosis of urinary tract infection, pyelonephritis, or renal abscess within 1 – 7 days and 8 – 28 days after the index visit, respectively.

To evaluate the association between changes in antibiotic use and antimicrobial resistance, all outpatient *E. coli* isolates in the Denver Health system during the study period were identified electronically from the microbiology laboratory database. Data were expressed as the proportion of *E. coli* isolates resistant to a fluoroquinolone or nitrofurantoin over time, by quarter.

Statistical Analyses

Interrupted time series analysis was used to assess changes in fluoroquinolone and nitrofurantoin use for acute cystitis, total outpatient fluoroquinolone use, and fluoroquinolone and nitrofurantoin resistance among outpatient *E. coli* isolates over time. For each outcome, we constructed an autoregressive integrated moving average model to evaluate: (1) the trend for the pre-intervention period; (2) the immediate effect of the intervention; (3) the trend in the post-intervention period; and (4) the change in slope from pre- to post-intervention. The maximum likelihood estimate method was used to construct each model. Correlation was assessed using the Durbin-Watson statistic. If the Durbin-Watson statistic was significant ($P < 0.05$) for either positive or negative autocorrelation, a lag was inserted into the model (starting with $n=1$ lag) until the statistic became non-significant ($P > 0.05$). As secondary analyses, we compared the aggregate use of individual antibiotics and the frequency of early and late return visits between the pre-intervention and post-intervention periods using the Chi-square test for proportions. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

45,099 visits involving a primary or secondary ICD-9 diagnosis of acute cystitis during the 10-year study period were identified. Of these, 5,714 were associated with an antibiotic prescription filled at a Denver Health pharmacy and were included for analysis. Demographic and clinical characteristics of patients in the pre-intervention and post-intervention periods were similar (Table 1). Patients were predominantly female. Diabetes mellitus was the most prevalent comorbid condition, present in nearly a quarter of patients. Compared with the pre-intervention period, visits to the emergency department were more common during the post-intervention period, while visits to outpatient clinics were less common (Table 1).

Antimicrobial use

After the change in institutional guidance recommending nitrofurantoin over fluoroquinolones for acute uncomplicated cystitis, an immediate 25.9% (95%CI 20.2 – 31.5%) decrease in fluoroquinolone use ($P < .001$) and a 6.0% (95%CI –2.1 – 15.0%)

increase in nitrofurantoin use ($P=.12$) was observed (Figure 1, Table 2). There were no subsequent significant trends in use during the post-intervention period. Collectively, fluoroquinolones accounted for 68.1% (95%CI 66.1 – 70.0%) of total prescriptions for acute cystitis during the pre-intervention period compared with 34.9% (95%CI 33.3 – 36.5%) during the post-intervention period ($P<.001$) (Table 3). Nitrofurantoin accounted for 16.2% (95%CI 14.7 – 17.8%) of total prescriptions for acute cystitis during the pre-intervention period and 28.1% (95%CI 26.6 – 29.6%) during the post-intervention period ($P<.001$). Of note, use of first- and third-generation cephalosporins also increased significantly during the post-intervention period (Table 3). In a pattern similar to fluoroquinolone use for acute cystitis, total outpatient fluoroquinolone use for any indication significantly decreased immediately following change in institutional guidance ($P<.001$) without a subsequent significant trend in use (Figure 2, Table 2).

In the review of 100 post-intervention period cases where a fluoroquinolone was prescribed, the fluoroquinolone was deemed appropriate in 80%. The indication for a fluoroquinolone was typically the presence of an institutional guideline criterion for complicated urinary tract infection, including male gender (35%), diabetes mellitus (25%), evidence of pyelonephritis (15%), presence of an indwelling urinary catheter (13%), recent treatment failure (10%), or an elevated serum creatinine (1.4 mg/dL) (6%).

Antimicrobial resistance

From 2003 through 2012, a total of 11,367 outpatient *E. coli* isolates with antibiotic susceptibility testing were available for analysis. The overall proportion of *E. coli* isolates resistant to a fluoroquinolone increased from 1.5% in 2003 to 7.6% in 2012 ($P<.001$). By time series analysis, there was a significant change in the trend of fluoroquinolone-resistant *E. coli* ($P=.004$) between the pre- and post-intervention periods (Figure 3, Table 2), from a steady increase from 2003 to 2007 to a plateau and slight decline thereafter. In contrast, there was no significant change in nitrofurantoin resistant-*E. coli* from 2003 to 2012.

Clinical outcomes

Overall, during the 28-day follow-up period after the index visit, early (1 – 7 days) and late (8 – 28 days) outpatient return visits for urinary tract infection and pyelonephritis occurred with similar frequency during the pre-intervention and post-intervention periods (Table 4). Hospitalizations for any reason, as well as early and late hospitalizations for urinary tract infection and pyelonephritis, did not differ significantly between the two study periods. No cases involved the development of a renal abscess. There were five cases of laboratory-confirmed *C. difficile* infection during the post-intervention period and no cases during the pre-intervention period.

Discussion

At our institution, a marked increase in fluoroquinolone-resistant *E. coli* prompted a change in the recommended treatment for acute uncomplicated cystitis from fluoroquinolones to nitrofurantoin. This change in prescribing guidance was associated with an immediate and sustained reduction in fluoroquinolone use and a modest increase in nitrofurantoin use.

These prescribing changes were associated with stabilization of the previously increasing trend of fluoroquinolone resistance among outpatient *E. coli* isolates and no significant change in the trend of nitrofurantoin resistance.

The IDSA recommends nitrofurantoin as a first-line agent for acute uncomplicated cystitis;⁴ however, to our knowledge, the impact of widespread nitrofurantoin use on community resistance patterns has not previously been evaluated. It is noteworthy that we did not observe an increase in nitrofurantoin resistance among *E. coli* over more than five years despite almost a 75% relative increase in nitrofurantoin use. This is in stark contrast to the previous observation at our institution where a substantial increase in fluoroquinolone use was associated with a marked increase in fluoroquinolone-resistant *E. coli*.⁶ In the present study, we also found that reductions in use of fluoroquinolones for acute cystitis and in total fluoroquinolone use were associated with a stabilization in the rate of fluoroquinolone-resistant *E. coli*. In aggregate, these findings lend support to the IDSA recommendation to preferentially use nitrofurantoin over fluoroquinolones for acute uncomplicated cystitis⁴ and have potential relevance to national efforts aimed at reducing antimicrobial resistance.²

Our findings linking a decrease in fluoroquinolone use with a decrease in fluoroquinolone resistance among *E. coli* are similar to previous reports.^{17–20} In combination with the lack of an increase in resistance to nitrofurantoin observed in our study, these findings may reflect important underlying differences in the mechanisms for developing antimicrobial resistance between fluoroquinolones and nitrofurantoin. For example, fluoroquinolones can induce the development of multi-drug efflux pumps. In addition, plasmid-mediated fluoroquinolone resistance can be transferred easily, leading to resistance across different antimicrobial classes.^{21,22} In contrast, nitrofurantoin resistance may come at a significant fitness cost to replicating *E. coli*; a trait ill-fitted to the widespread development and transfer of resistance genes.^{23,24}

There are several limitations to the present study that warrant further discussion. First, the pre-intervention post-intervention design is subject to period effect. It is therefore possible that the stabilization in the trend of fluoroquinolone-resistant *E. coli* was an epidemiologic trend unrelated to the observed change in fluoroquinolone use in the Denver Health system. For example, the Food and Drug Administration banned fluoroquinolones from animal agricultural in 2005²⁵ which could have affected resistance trends. However, the observed decrease in the trend in fluoroquinolone resistance in this study was sudden and closely temporally associated with the institution-wide reduction in fluoroquinolone use (Figure 3) suggesting they may be related; however, it is important to note that this association does not prove a causal link.

Next, the identification of visits using ICD-9 codes did not allow for the distinction between acute uncomplicated cystitis and complicated urinary tract infections where prescribing recommendations differ. The manual chart review of patients treated with fluoroquinolones demonstrated that a large proportion of cases met criteria for complicated urinary tract infection. This is likely why nitrofurantoin, recommended only in cases of acute uncomplicated cystitis, accounted for less than a third of prescriptions in the post-intervention period.

Another limitation is that a large number of visits with an ICD-9 diagnosis of acute cystitis were not associated with an antibiotic prescription. Since our ICD-9 search identified visits with either a primary or secondary diagnosis of cystitis, we captured visits that were not the initial presentation of cystitis (i.e., follow-up visits where a recent episode of cystitis was already treated), overestimating the number of actual episodes of acute cystitis. Second, because we were only able to identify antibiotic prescriptions filled at a Denver Health pharmacy (approximately 30% are filled outside of our system), the proportion of visits with an associated antibiotic prescription reflected in our data is an underestimate of the true proportion.

It is important to point out that we could not identify *E. coli* isolates specifically from cases of acute uncomplicated cystitis, where urine cultures are most often not sent; our microbiological data therefore represent a broader range of urinary tract infections (e.g., uncomplicated and complicated, upper and lower urinary tract) than was included for the antibiotic utilization assessment. Nevertheless, it is notable that a reduction in fluoroquinolone use for acute cystitis appeared to have an impact on antimicrobial resistance among *E. coli* isolates from a broad group of urinary tract infections. Since we did not collect resistance data for other antibiotics such as cephalosporins, it is not known whether the observed increase in use of cephalosporins was associated with increased resistance to these agents, such as through the emergence of extended-spectrum β -lactamase-producing organisms.

We did not have complete data on the effectiveness, safety, or tolerability of the antibiotic regimens used during the two time periods. We therefore cannot conclude based on the results of this study that the use of nitrofurantoin, despite its apparent lower impact on *E. coli* resistance, is the optimal treatment for acute uncomplicated cystitis. It is worth noting that although *C. difficile* infection was infrequent in both time periods, cases were only identified during the nitrofurantoin period. The continued use of fluoroquinolones in a substantial proportion of cases and the fact that our microbiology laboratory changed to a more sensitive *C. difficile* diagnostic test during the nitrofurantoin period limit the conclusions that can be drawn from these data.

In summary, these findings add to the evidence that local changes in antimicrobial use may impact antimicrobial resistance in the community. Specifically, we observed that in a large, integrated healthcare system, a reduction in fluoroquinolone use for acute cystitis was associated with stabilization of a previously increasing trend of outpatient fluoroquinolone-resistant *E. coli*; whereas, a modest increase in nitrofurantoin use did not have an apparent impact on nitrofurantoin-resistant *E. coli*. The longer-term impact of fluoroquinolone-sparing strategies for acute uncomplicated cystitis on community antimicrobial resistance will require further study; however, this study lends support to the IDSA recommendation to preferentially use nitrofurantoin over fluoroquinolones because of a lower likelihood of inducing resistance. This study helps to inform ongoing national antimicrobial stewardship initiatives aimed at addressing the growing threat of antimicrobial resistance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support. This work was supported in part by the National Institute of Allergy and Infectious Diseases, National Institutes of Health (TCJ: K23 AI099082).

The authors wish to thank Ron Cake, Matthew Archer, and Debora Gardner for their assistance with data acquisition as well as Mike Doody for his support in the initial conception and study design.

References

1. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. 2013. Available at: <http://www.cdc.gov/drugresistance/threat-report-2013/> Accessed 9 June 2014
2. National Action Plan for Combating Antibiotic-Resistant Bacteria. Mar. 2015 Available at: https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf Accessed April 6, 2015.
3. Shapiro DJ, Hicks LA, Pavia AT, Hersh AL. Antibiotic prescribing for adults in ambulatory care in the USA, 2007-09. *J Antimicrob Chemother.* 2014; 69:234-40.
4. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis.* 2011; 52:e103-20. [PubMed: 21292654]
5. Lautenbach E, Strom BL, Nachamkin I, Bilker WB, Marr AM, Larosa LA, 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; 38:655-62. [PubMed: 14986249]
6. Johnson L, Sabel A, Burman WJ, Everhart RM, Rome M, MacKenzie TD, et al. Emergence of fluoroquinolone resistance in outpatient urinary Escherichia coli isolates. *Am J Med.* 2008; 121:876-84. [PubMed: 18823859]
7. Chen DK, McGeer A, de Azavedo JC, Low DE. Decreased susceptibility of Streptococcus pneumoniae to fluoroquinolones in Canada. Canadian Bacterial Surveillance Network. *N Engl J Med.* 1999; 341:233-9. [PubMed: 10413735]
8. MacDougall C, Powell JP, Johnson CK, Edmond MB, Polk RE. Hospital and community fluoroquinolone use and resistance in Staphylococcus aureus and Escherichia coli in 17 US hospitals. *Clin Infect Dis.* 2005; 41:435-40. [PubMed: 16028149]
9. Ambrose PG, Bast D, Doern GV, Iannini PB, Jones RN, Klugman KP, et al. Fluoroquinolone-resistant Streptococcus pneumoniae, an emerging but unrecognized public health concern: is it time to resight the goalposts? *Clin Infect Dis.* 2004; 39:1554-6. [PubMed: 15546106]
10. Lautenbach E, Larosa LA, Kasbekar N, Peng HP, Maniglia RJ, Fishman NO. Fluoroquinolone utilization in the emergency departments of academic medical centers: prevalence of, and risk factors for, inappropriate use. *Arch Intern Med.* 2003; 163:601-5. [PubMed: 12622607]
11. Stevens V, Dumyati G, Fine LS, Fisher SG, van Wijngaarden E. Cumulative antibiotic exposures over time and the risk of Clostridium difficile infection. *Clin Infect Dis.* 2011; 53:42-8. [PubMed: 21653301]
12. Slimings C, Riley TV. Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis. *J Antimicrob Chemother.* 2014; 69:881-91.
13. Zilberberg MD, Reske K, Olsen M, Yan Y, Dubberke ER. Risk factors for recurrent Clostridium difficile infection (CDI) hospitalization among hospitalized patients with an initial CDI episode: a retrospective cohort study. *BMC Infect Dis.* 2014; 14:306. [PubMed: 24898123]

14. U.S. Food and Drug Administration. FDA Drug Safety Communication. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm500143.htm> Accessed June 10, 2016.
15. Burman WJ, Breese PE, Murray BE, Singh KV, Batal HA, MacKenzie TD, et al. Conventional and molecular epidemiology of trimethoprim-sulfamethoxazole resistance among urinary *Escherichia coli* isolates. *Am J Med.* 2003; 115:358–64. [PubMed: 14553870]
16. Gabow P, Eisert S, Wright R. Denver Health: a model for the integration of a public hospital and community health centers. *Ann Intern Med.* 2003; 138:143–9. [PubMed: 12529097]
17. Gottesman BS, Carmeli Y, Shitrit P, Chowders M. Impact of quinolone restriction on resistance patterns of *Escherichia coli* isolated from urine by culture in a community setting. *Clin Infect Dis.* 2009; 49:869–75. [PubMed: 19686074]
18. Pena C, Albareda JM, Pallares R, Pujol M, Tubau F, Ariza J. Relationship between quinolone use and emergence of ciprofloxacin-resistant *Escherichia coli* in bloodstream infections. *Antimicrob Agents Chemother.* 1995; 39:520–4.
19. Gallini A, Degris E, Desplas M, Bourrel R, Archambaud M, Montastruc JL, et al. Influence of fluoroquinolone consumption in inpatients and outpatients on ciprofloxacin-resistant *Escherichia coli* in a university hospital. *J Antimicrob Chemother.* 2010; 65:2650–7.
20. Lamikanra A, Crowe JL, Lijek RS, Odetoyin BW, Wain J, Aboderin AO, et al. Rapid evolution of fluoroquinolone-resistant *Escherichia coli* in Nigeria is temporally associated with fluoroquinolone use. *BMC Infect Dis.* 2011; 11:312. [PubMed: 22060770]
21. Wong-Beringer A, Nguyen LH, Lee M, Shriner KA, Pallares J. An antimicrobial stewardship program with a focus on reducing fluoroquinolone overuse. *Pharmacotherapy.* 2009; 29:736–43. [PubMed: 19476424]
22. Peterson LR. Squeezing the antibiotic balloon: the impact of antimicrobial classes on emerging resistance. *Clin Micro Infection.* 2005; 11(Suppl 5):4–16.
23. Sandegren L, Lindqvist A, Kahlmeter G, Andersson DI. Nitrofurantoin resistance mechanism and fitness cost in *Escherichia coli*. *J Antimicrob Chemother.* 2008; 62:495–503.
24. Poulsen HO, Johansson A, Granholm S, Kahlmeter G, Sundqvist M. High genetic diversity of nitrofurantoin- or mecillinam-resistant *Escherichia coli* indicates low propensity for clonal spread. *J Antimicrob Chemother.* 2013; 68:1974–7.
25. U.S. Food and Drug Administration. FDA Announces Final Decision About Veterinary Medicine. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108467.htm> Accessed June 9, 2016.

Figure 1.

Fluoroquinolone and nitrofurantoin prescriptions for acute cystitis over time. Data are expressed as the proportion of all antibiotic prescriptions for acute cystitis per quarter.

Figure 2.

Overall fluoroquinolone use in the Denver Health system over time. Data are expressed as the total number of fluoroquinolone prescriptions (for any indication) per 1000 outpatient visits

Figure 3. Fluoroquinolone and nitrofurantoin resistance among outpatient *E. coli* isolates over time. Data are expressed as the proportion of isolates resistant to the respective antibiotic per quarter.

Table 1

Demographic and clinical characteristics of the study population.

	Pre-intervention period N = 2191	Post-intervention period N = 3523
Female	1938, 88.5, (87.1–89.7)	2915, 82.7, (81.5–84.0)
Age, mean (standard deviation)	43.3, 17.8, (42.5–44.0)	45.3, 17.9, (44.8–45.9)
Diabetes mellitus	495, 22.6, (20.9–24.4)	855, 24.3, (22.9–25.7)
Elevated serum creatinine (≥ 1.4 mg/dL)	15, 0.7, (0.4–1.1)	93, 2.6, (2.2–3.2)
Dialysis-dependence	4, 0.2, (0.05–0.5)	52, 1.5, (1.1–1.9)
Cardiovascular disease	205, 9.4, (8.2–10.7)	371, 10.5, (9.6–11.6)
Chronic obstructive pulmonary disease	115, 5.3, (4.4–6.3)	265, 7.5, (6.7–8.4)
HIV infection	35, 1.6, (1.1–2.2)	61, 1.7, (1.4–2.2)
Immunosuppressing medication ^a	163, 7.4, (6.4–8.6)	464, 13.2, (12.1–14.3)
Hospitalization within 90 days of index visit	188, 8.6, (7.5–9.8)	422, 12.0, (11.0–13.1)
Location of visit		
Emergency department	481, 22.0, (20.3–23.7)	1289, 36.6, (35.0–38.2)
Urgent care	821, 37.5, (35.5–39.5)	1309, 37.2, (35.6–38.8)
Outpatient clinic	889, 40.6, (38.5–42.7)	925, 26.3, (24.8–27.7)

Data presented as n, %, (95% confidence interval) unless otherwise noted.

^a Includes corticosteroids, antineoplastic agents, monoclonal antibodies, immunomodulators, and anti-rejection immunosuppressants

Fluoroquinolone and nitrofurantoin use and resistance among outpatient *E. coli* isolates by time-series analysis.**Table 2**

	Pre-intervention period slope (95% confidence interval)	Immediate change in level after start of intervention (95% confidence interval)	P	Post-intervention period slope (95% confidence interval)	Change in slope between periods (95% confidence interval)	P
Antimicrobial use						
Fluoroquinolone prescriptions for acute cystitis, %	-0.4 (-0.8, 0.02)	-25.9 (-31.5, -20.2)	< .001	-0.3 (-0.6, -0.03)	0.06 (-0.4, 0.6)	.81
Nitrofurantoin prescriptions for acute cystitis, %	0.5 (-0.06, 1.2)	6.0 (-2.1, 15.0)	.12	-0.06 (-0.5, 0.4)	-0.6 (-1.4, 0.2)	.11
Total fluoroquinolone prescriptions per 1000 outpatient visits	-0.05 (-0.1, -0.009)	-2.1 (-3.0, -1.3)	< .001	-0.03 (-0.07, 0.02)	0.02 (-0.05, 0.1)	.50
Antimicrobial resistance						
Fluoroquinolone resistance among <i>E. coli</i> isolates, %	0.3 (0.1, 0.5)	1.3 (-1.3, 4.0)	.31	-0.03 (-0.2, 0.1)	-0.4 (-0.6, -0.1)	.004
Nitrofurantoin resistance among <i>E. coli</i> isolates, %	0.06 (-0.01, 0.1)	-0.9 (-1.9, 0.2)	.09	0.006 (-0.05, 0.06)	-0.06 (-0.1, 0.04)	.22

Table 3

Aggregate antibiotic prescriptions for acute cystitis by study period.

	Pre-intervention period N = 2191	Post-intervention period N = 3523	P
Fluoroquinolones	1491, 68.1, (66.1–70.0)	1228, 34.9, (33.3–36.5)	<.001
Nitrofurantoin	354, 16.2, (14.7–17.8)	989, 28.1, (26.6–29.6)	<.001
Trimethoprim-sulfamethoxazole	141, 6.4, (5.5–7.5)	190, 5.4, (4.7–6.2)	0.10
1 st -generation cephalosporin	106, 4.8, (4.0–5.8)	528, 15.0, (13.9–16.2)	<.001
Amoxicillin or amoxicillin-clavulanate	44, 2.0, (1.5–2.7)	64, 1.8, (1.4–2.3)	0.61
Doxycycline	24, 1.1, (0.7–1.6)	36, 1.0, (0.7–1.4)	0.79
Azithromycin	13, 0.6, (0.3–1.0)	111, 3.2, (2.6–3.8)	<.001
3 rd -generation cephalosporin	5, 0.2, (0.08–0.6)	350, 9.9, (9.0–11.0)	<.001
Other	13, 0.6, (0.3–1.0)	27, 0.8, (0.5–1.1)	0.45

Data presented as n, %, (95% confidence interval).

Table 4

Clinical outcomes within 28 days of the index visit.

	Pre-intervention period N = 2191	Post-intervention period N = 3523
Any return visit related to UTI	479, 21.9, (20.2–23.6)	805, 22.9, (21.5–24.3)
Any outpatient return visit related to UTI	444, 20.3, (18.6–22.0)	725, 20.6, (19.3–22.0)
Urinary tract infection	414, 18.9, (17.3–20.6)	669, 19.0, (17.7–20.3)
Early ^a	268, 12.2, (10.9–13.7)	427, 12.1, (11.1–13.2)
Late ^b	230, 10.5, (9.3–11.9)	387, 11.0, (10.0–12.1)
Pyelonephritis	50, 2.3, (1.7–3.0)	102, 2.9, (2.4–3.5)
Early ^a	43, 2.0, (1.5–2.6)	74, 2.1, (1.7–2.6)
Late ^b	24, 1.1, (0.7–1.6)	45, 1.3, (1.0–1.7)
Renal abscess	0	0
Any subsequent hospitalization	451, 20.6, (18.9–22.3)	738, 21.0, (19.6–22.3)
Any hospitalization related to UTI	61, 2.8, (2.2–3.6)	142, 4.0, (3.4–4.7)
Urinary tract infection	58, 2.7, (2.1–3.4)	129, 3.7, (3.1–4.3)
Early ^a	26, 1.2, (0.8–1.7)	69, 2.0, (1.6–2.5)
Late ^b	35, 1.6, (1.1–2.2)	64, 1.8, (1.4–2.3)
Pyelonephritis	6, 0.3, (0.1–0.6)	23, 0.7, (0.4–1.0)
Early ^a	6, 0.3, (0.1–0.6)	17, 0.5, (0.3–0.8)
Late ^b	0	7, 0.2, (0.1–0.4)
Renal abscess	0	0
Laboratory-confirmed <i>C. difficile</i> infection	0	5, 0.1, (0.06–0.3)

Data presented as n, %, (95% confidence interval). UTI, urinary tract infection.

^aOccurred within 7 days of the index visit^bOccurred 8 – 28 days after the index visit