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Concise Communication

Antimicrobial resistance patterns in urinary *E. coli* isolates after a change in a single center's guidelines for uncomplicated cystitis in ambulatory settings

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Abstract

Recommending nitrofurantoin to treat uncomplicated cystitis was associated with increased nitrofurantoin use from 3.53 to 4.01 prescriptions per 1,000 outpatient visits, but nitrofurantoin resistance in *E. coli* isolates remained stable at 2%. Concomitant levofloxacin resistance was a significant risk for nitrofurantoin resistance in *E. coli* isolates (odds ratio [OR], 2.72; 95% confidence interval [CI], 1.04–7.17).

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Escherichiae coli urinary tract infections (UTIs) are among the most common reasons for antibiotic use in ambulatory settings, resulting in >8.3 million ambulatory visits.[1] With increasing rates of antimicrobial resistance, healthcare systems have established antimicrobial stewardship programs to encourage the appropriate use of antibiotics.[2,3] Although antimicrobial stewardship programs can limit the misuse of antibiotics, they require close monitoring to identify antibiotic resistance trends as prescribing patterns change.[4]

At Denver Health, previous antimicrobial stewardship guidelines recommended trimethoprim-sulfamethoxazole (TMP-SMX) and levofloxacin to treat uncomplicated cystitis in nonpregnant, female adult patients.[5,6] With each guideline change, use of each antibiotic and resistance of *E. coli* to both antibiotics increased. In 2008, Denver Health changed its recommended treatment for uncomplicated UTI to nitrofurantoin and aligned its UTI stewardship program with Infectious Disease Society of America (IDSA) guidelines.[7]

In this study, we provide a descriptive analysis of the changes in nitrofurantoin and levofloxacin prescribing and changes in *E. coli* resistance with stewardship guideline changes. We additionally performed a retrospective case-control analysis to identify risk factors that may correlate with nitrofurantoin resistance.

Methods

Denver Health is a community safety-net hospital with a 525-bed main hospital, emergency department (ED), and 9 federally qualified community health clinics. We chose the study period of January 2008–December 2014 to include the time between the change in stewardship guidelines at Denver Health and the start of the study, and to be consistent with a previous analysis.[6] Using ambulatory data, we identified the number of nitrofurantoin and levofloxacin prescriptions per 1,000 outpatient prescriptions.

In our case-control analysis, episodes of uncomplicated cystitis due to *E. coli* were identified by their *International Classification of Disease, Ninth Revision* (ICD-9) code. Inclusion criteria included episodes of uncomplicated cystitis due to *E. coli* with an associated urine culture of >100,000 colony-forming units in ambulatory, nonpregnant female patients aged 18–89 years. We excluded UTIs treated in inpatient settings. We utilized manual chart review of the 12 months prior to the UTI development to identify risk factors and comorbid conditions associated with nitrofurantoin resistance, to ensure that patients had documentation of symptoms (eg, urinary frequency, hesitancy, urge, dysuria, pelvic pain) consistent with UTI, to exclude asymptomatic bacteriuria, and to exclude cases of ascending infection. If patients had multiple UTIs during the study period, we included only the first episode in our analysis.

Cases were defined as those patients with a nitrofurantoin-resistant *E. coli* isolate resistant to nitrofurantoin, and controls were defined as those with a nitrofurantoin-susceptible *E. coli* isolate. We randomly matched 2 controls to each case to adequately power the study and to avoid overmatching, which would limit our analysis of potentially significant risk factors for nitrofurantoin resistance.

To determine the significance of risk factors associated with nitrofurantoin resistance in *E. coli* UTIs, we performed an unadjusted logistic regression for each categorical variable. For continuous variables, we performed a *t* test. A statistical analysis was completed using SAS version 9.4 software (SAS Institute, Cary, NC). $P < .05$ was predetermined to be statistically significant.

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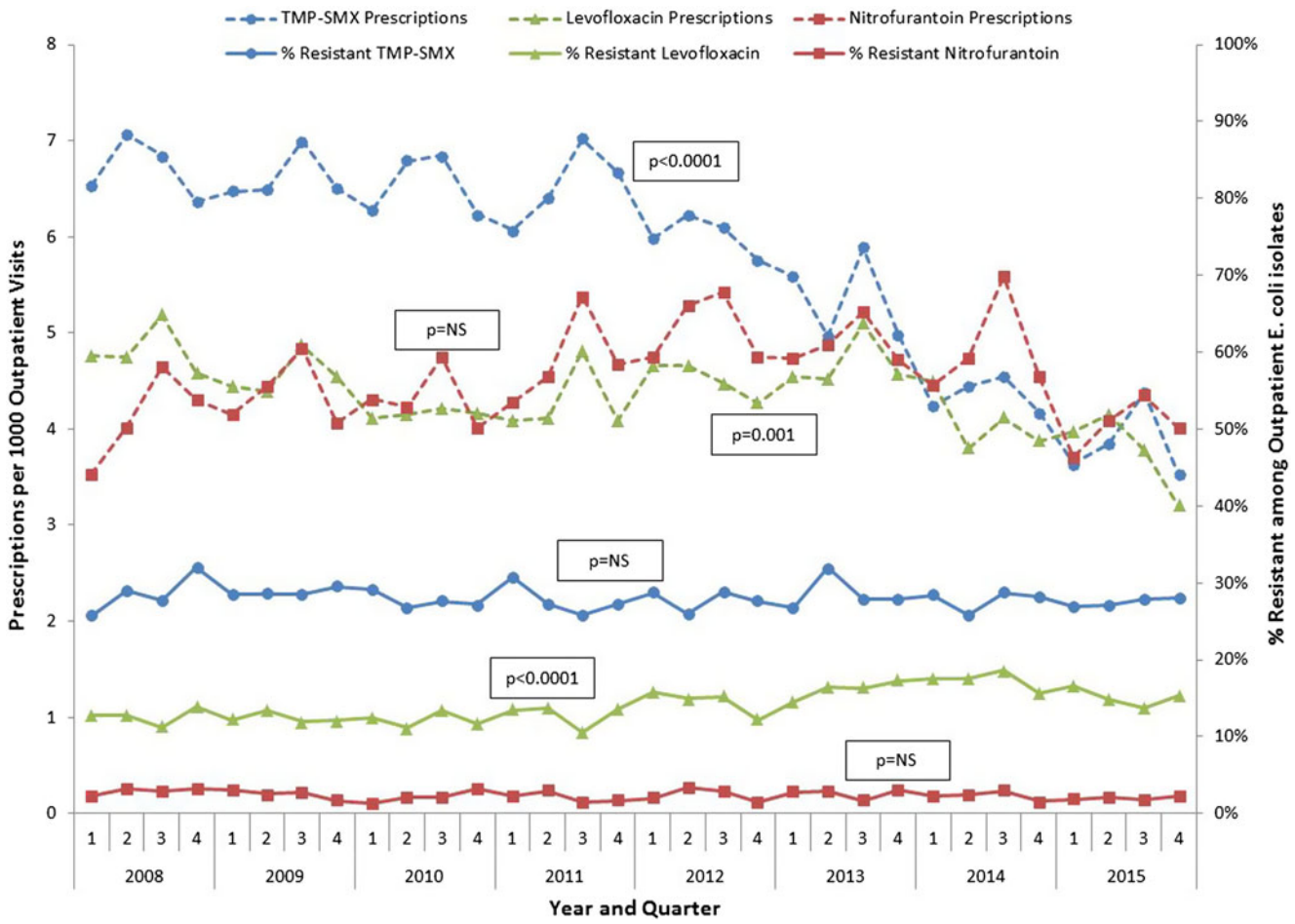

Fig. 1. Rate of nitrofurantoin, levofloxacin, and trimethoprim-sulfamethoxazole prescriptions per 1,000 outpatient visits and rate of *E. coli* isolate resistance for January 2008–December 2015.

This study was approved by the Colorado Multiple Institutional Review Board, and a waiver of consent was granted.

Results

In total, 2,104 *E.coli* UTIs were identified in nonpregnant, female, adult patients in ambulatory settings during the study period. Of all bacteria isolates, 39 *E. coli* isolates (1.9%) were resistant to nitrofurantoin. Among *E. coli* susceptibilities from all culture sources in the study period, nitrofurantoin resistance remained stable at 2% ($P = .16$). Resistance to levofloxacin increased from 13% to 15% ($P < .0001$), and resistance to TMP-SMX remained relatively stable from 26% to 28% ($P = .37$) (Fig. 1). The prescription rate for nitrofurantoin remained relatively stable from 3.53 to 4.01 per 1,000 outpatient visits ($P = .20$). During the study period, prescriptions of levofloxacin decreased from 4.76 to 3.2 per 1,000 outpatient visits ($P = .001$), and prescriptions of TMP-SMX decreased from 6.54 to 3.52 per 1,000 outpatient visits ($P < .0001$),

Within the case-control analysis, 38 cases of nitrofurantoin-resistant *E. coli* UTI met inclusion criteria (1 case was excluded due to pregnancy), and we matched 77 controls of nitrofurantoin-susceptible *E.coli* UTI. The most significant risk factor for nitrofurantoin resistance was the presence of concomitant levofloxacin resistance (odds ratio [OR], 2.72; 95% confidence interval [CI], 1.04–7.17; $P = .04$). We observed a nonsignificant trend toward nitrofurantoin-resistant *E. coli* in patients with diabetes mellitus (OR, 2.07; 95% CI, 0.914.71; $P = .08$), nitrofurantoin use in the preceding 12 months (OR, 2.15; 95% CI, 0.9–5.16; $P = .09$), and surgery in the previous 12 months (OR, 3.25; 95% CI, 0.96–11.04; $P = .06$). No significant risk for nitrofurantoin resistance was associated with the presence of chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), congestive heart failure (CHF), coronary heart disease, immunosuppressive medications, cirrhosis, or malignancy, nor amongst continuous variables including previous number of UTIs, duration of previous hospitalization, or duration of previous antibiotic exposure in the preceding 12 months to the study UTI.

Discussion

At Denver Health over a 7-year period, there appears to be benefit in treating uncomplicated cystitis using narrower-spectrum agents, limiting the development of antibiotic resistance locally. After changing UTI stewardship guidelines, there was increased, though not statistically significant, nitrofurantoin use, but there was no increase in *E. coli* resistance to nitrofurantoin. This finding is encouraging and contrasts with previous experiences at Denver Health with TMP-SMX and levofloxacin.

Within this single-center case-control analysis, the risk factor most associated with *E. coli* resistance to nitrofurantoin was concomitant resistance to levofloxacin. We observed nonsignificant

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trends toward nitrofurantoin resistance in the presence of diabetes, with the use of nitrofurantoin in the previous 12 months, and with surgery in the previous 12 months. There were no significant associations with other suspected risk factors for nitrofurantoin resistance.

Even when *E. coli* isolates acquire nitrofurantoin resistance, there appears to be less risk of developing resistance to other antimicrobial classes compared to levofloxacin-resistant isolates. One hypothesis for this occurrence is the mechanism of resistance to levofloxacin via efflux pumps; *E. coli* spp have been known to overexpress the *acrAB* efflux pump in times of stress.[8,9] Another proposed mechanism for nitrofurantoin-resistant isolates having less resistance with other antimicrobials is due to decreased nitrofurantoin delivery to the large intestine; there is less "collateral damage" with endogenous flora exposure to nitrofurantoin.[10] Additionally, nitrofurantoin's multimodal mechanism of action is thought to be protective in limiting resistance.

In terms of study limitations, the quality of the data was reliant upon the documentation available in the electronic health record and ICD-9 coding. During the study period, clinical documentation was hand written and scanned into an electronic health record, making legibility of documentation challenging. Additionally, direct causation of the risk factors identified for nitrofurantoin resistance could not be inferred from these results based upon the retrospective nature of this study. Lastly, the small sample size from a single institution for a single diagnosis limits the generalizability of the findings.

Further study should assess how frontline providers access antimicrobial stewardship guidelines and how often they adhere to guidelines. Additional research should assess risk factors for nitrofurantoin resistance among a larger cohort of patients to increase the generalizability of the results and limit the risk of type II error.

This study demonstrates that in changing antimicrobial stewardship guidelines to recommend nitrofurantoin for the treatment of uncomplicated UTIs, there is less risk of developing antimicrobial resistance locally. These findings support the use of narrower-spectrum agents in antimicrobial stewardship programs.

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References

1. Schappert SR, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2007. *Vital Health Stat* 2011;*169*:1–38.
2. Etienne M, Lefebvre E, Frebourg N, Hamel H, Pestel-Caron M, Caron F. Antibiotic treatment of acute uncomplicated cystitis based on rapid urine test and local epidemiology: lessons from a primary care series. *BMC Infect Dis* 2014;*14*:137.
3. Davey P, Marwick CA, Scott CL, *et al.* Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017;*2*:CD003543.
4. Zhanel GG, Hisanaga TL, Laing NM, *et al.* Antibiotic resistance in *Escherichia coli* outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). *Int J Antimicrob Agent* 2006;*27*:468–475.
5. Burman WJ, Breese PE, Murray BE, *et al.* Conventional and molecular epidemiology of trimethoprimsulfamethoxazole resistance among urinary *Escherichia coli* isolates. *Am J Med* 2003;*115*:358–364.
6. Johnson L, Sabel A, Burman WJ, *et al.* Emergence of fluoroquinolone resistance in outpatient urinary *Escherichia coli* isolates. *Am J Med* 2008;*121*:876–884.
7. Gupta K, Hooton TM, Naber KG, *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–e120.
8. Webber MA,Piddock LJV. The importance of efflux pumps in bacterial antibiotic resistance. *J Antimicrob Chemother* 2003;*51*:9–11.
9. Sulavik MC, Houseweart C, Cramer C, *et al.* Antibiotic susceptibility profiles of Escherichia coli strains lacking multidrug efflux pump genes. *Antimicrob Agents Chemother* 2001;*45*:1126–1136.
10. Paterson DL. "Collateral damage" from cephalosporin or quinolone antibiotic therapy. *Clin Infect Dis* 2004;*38* Suppl 4:S341–S345.

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