Impact of fluoroquinolone susceptibility suppression on discharge prescribing for acute uncomplicated cystitis.

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ABSTRACT

- **Introduction**: Fluoroquinolones (FQ) are associated with multiple adverse effects and increasing resistance. Though only recommended as alternative therapy, FQ are still often prescribed as primary treatment of acute uncomplicated cystitis (AUC). Previous data suggests that suppression of FQ susceptibilities may reduce inpatient prescribing; however, FQ prescribing at hospital discharge may actually increase. The purpose of this study was to investigate the impact of FQ susceptibility suppression on discharge prescribing for AUC.
- **Methods**: This was a retrospective, quasi-experimental analysis in adult inpatients at a 350-bed academic medical center. Incidence of FQ prescribing at discharge was compared a year before and after the intervention of FQ susceptibility suppression, which occurred in March of 2018, for patients with pan-susceptible urine isolates for *Klebsiella* sp. and *E. coli*. Appropriateness of prescribing and risk factors for FQ use were also assessed. Exclusion criteria included pyelonephritis, urinary hardware, pregnancy, concomitant infections treated with FQ, and organisms not susceptible to FQ. Risk ratios of FQ use were calculated for pre-/post-groups and stratified by discharging team for adjusted rates (aRR) using Cochran-Mantel-Haenszel approach. For secondary outcomes, Chi-Square statistics were utilized and generalized regression models were used to assess odds of FQ use among variables.
- **Results**: Overall discharge FQ prescribing decreased from 41.1% to 21.1% after the intervention, which corresponded to a 53% lower adjusted risk (aRR 0.47 [95% CI 0.28-0.81]). One hundred percent of FQ use was inappropriate, largely due to organism susceptibility to a guideline-preferred agent (n = 38). After adjusting for the intervention and clustering of discharge team, the odds of outpatient FQ use was 3.46 times higher for uninsured vs. insured patients, and 13.4 times higher among those who received FQ while inpatient.
- **Conclusions**: Suppression of FQ susceptibilities on pan-susceptible urine isolates for *Klebsiella* sp. and *E. coli* was associated with decreased FQ prescribing at discharge for AUC. Patients receiving FQ while inpatient were 13.4 times more likely to be continued on a FQ at discharge. Overall, prescribing of FQ for AUC was inappropriate, demonstrating the need for focused stewardship at discharge beyond FQ susceptibility suppression policies.

BACKGROUND

- Cystitis is defined as "uncomplicated" as long as it occurs exclusively in pre-menopausal women without other complicating factors (i.e. pyelonephritis, pregnancy, or known urological abnormalities/comorbidities). [1]
- *Escherichia coli* and *Klebsiella* spp. are the most common bacterial pathogens associated with AUC. [1]
- Current guidelines recommend first-line treatment of AUC with either nitrofurantoin, sulfamethoxazole/trimethoprim, or fosfomycin (which is often cost-prohibitive). β-lactams (e.g. cephalexin) may also be used for definitive therapy, or for empiric therapy based on local antibiograms. [1]
- FQ (i.e. levofloxacin and ciprofloxacin) should be reserved only for alternative therapy for AUC, due to the inherent risks associated with these agents and the broader coverage they provide. [2]
- FQ have been associated with many adverse effects, including cardiac arrhythmias, QT-interval prolongation, aortic aneurysm/dissection, and *Clostridioides difficile* superinfection. The U.S. FDA has issued black box warnings regarding tendonitis and tendon rupture, exacerbation of muscle weakness in patients with myasthenia gravis, peripheral neuropathy, and central nervous system effects. Additionally, *Escherichia coli* resistance rates to levofloxacin have been found to be 29.3% higher for hospital-acquired UTI vs. community-acquired UTI. [3,4]
- Treatment of AUC remains one of the most frequent reasons for FQ use today, and over 30 million oral FQ prescriptions were dispensed overall in the U.S. in 2014. [1,4]
- Previous studies have reported marked improvement in inpatient FQ prescribing, as well as *Escherichia coli* and *Pseudomonas aeruginosa* susceptibilities, after suppression of microbiological FQ susceptibility results. [3,5]
- However, Vaughn et al. found that most (66.6%) FQ treatment days occurred after hospital discharge, and that hospitals with FQ stewardship interventions actually had twice as many new starts after discharge (15.6% vs. 8.4%; *P* = 0.003). [6]
- Our institution implemented a FQ susceptibility suppression policy on pan-susceptible urine isolates for *Escherichia coli* and *Klebsiella* spp. starting in March 2018.

STUDY OBJECTIVES

Primary: Compare the incidence of FQ prescribing for AUC at discharge, pre- and post-implementation of a policy to suppress FQ microbiological susceptibility results

Secondary: (1) Compare the appropriateness of FQ prescribing for AUC at discharge, pre- and post-implementation of a policy to suppress FQ microbiological susceptibility results

(2) Identify risk factors for FQ use at discharge

METHODS

Retrospective, quasi-experimental analysis at a single-center, 350-bed academic medical institution

Inclusion
- Inpatient adults (age ≥18 years old)
- Urine cultures resulted between March 2017 – March 2019
- (+) urine culture for *E. coli* or *Klebsiella spp* (≥10^5 CFU)
- Diagnosis of cystitis or UTI during hospital admission
- Prescribing of any oral antibiotic at discharge

Exclusion
- Pregnancy
- Not first admission during study period, or ED visit only
- Organism not susceptible to FQ, or none reported
- Pyelonephritis, or other infection treated with FQ
- Nephrostomy tubes/stents, or indwelling catheter

Data Collection

- **03/01/17 to 03/31/2019 (March 2018 excluded as wash-out period)**
- Screened 600 pre-group and 600 post-group:
  - Patient demographics (including PMH, insurance status, discharging medical team)
  - Laboratory data (i.e. CBC, CMP, QTc)
  - Inpatient/discharge antibiotics
  - Bacterial culture/susceptibility results with colony count:
    - **Breakpoints (μg/mL) defined as**: ciprofloxacin ≤ 1, levofloxacin ≤ 2, cefazolin ≤ 16, nitrofurantoin ≤ 32, and sulfamethoxazole/trimethoprim ≤ 2/38 [7]

Primary Objective: Comparison of FQ Prescribing Incidence

- Calculated change in percentage of discharge FQ use pre- and post-implementation of suppression policy
- Risk ratios for FQ use were calculated for pre- and post-groups
- Stratified by discharging team for adjusted rates using a Cochran-Mantel-Haenszel approach

Secondary Objective (1): Comparison of FQ Prescribing Appropriateness

- Qualitative comparison pre- and post-implementation of suppression policy
- **Inappropriate FQ prescribing defined as**:
  - Susceptibility to another preferred agent:
    - sulfamethoxazole/trimethoprim
    - nitrofurantoin
    - cephalexin
  - Without contraindications, allergies, or prior adverse effects to these agents

Secondary Objective (2): Identification of Risk Factors for FQ Use

- Chi-square statistics were utilized and generalized estimating equation regression models were used to assess odds of FQ use among variables.

RESULTS

There were no statistically significant differences in demographics between pre- and post-groups

Table 1- Antibiotic Use

	Pre-group (n = 56)	Post-group (n = 69)	RR (95% CI)	p-value
Primary Outcome: Discharge FQ Antibiotic, n (%)	23 (41.1)	15 (21.7)	0.47 (0.28-0.81)	0.005
Discharging Team, n (%)				
Hospitalist	8 (34.8)	11 (37.9)	1.09 (0.53-2.26)	0.815
Neurology/Neurosurgery	3 (20.0)	0 (0)	N/A	0.239
Medicine Team	5 (100)	1 (7.7)	0.08 (0.01-0.51)	0.001
Trauma	2 (66.7)	1 (20.0)	0.3 (0.04-2.06)	0.464
Family Medicine	1 (50.0)	1 (33.3)	0.67 (0.08-5.54)	1.000
Other	4 (50.0)	1 (10.0)	0.2 (0.03-1.45)	0.118

RESULTS

Table 2- Risk Factors for FQ Use

Variable	Individual Variables		Multiple Variable Model	
	OR (95% CI)	P-value	aOR (95% CI)	P-value
Post- vs. Pre-Group	0.304 (0.133-0.692)	0.005	0.493 (0.138-1.762)	0.277
Inpatient FQ Use	10.529 (3.692-30.03)	<.001	13.43 (3.821-47.205)	<.001
Insurance	0.500 (0.188-1.335)	0.167	0.289 (0.113-0.744)	0.01
Male Gender	1.529 (0.441-5.304)	0.504		
CrCL	1.006 (1-1.012)	0.045		
SCr	1.119 (0.858-1.459)	0.407		
Allergies	0.843 (0.373-1.904)	0.68		
WBC	1.036 (0.909-1.182)	0.596		
Platelets	1.003 (0.999-1.007)	0.176		
Age	0.982 (0.957-1.008)	0.179		

Table 3- FQ Inappropriateness

Variable	Total (n = 38)	Pre-group (n = 23)	Post-group (n = 15)	p-value
FQ Inappropriateness, n (%)	38 (100)	23 (100)	15 (100)	N/A
Reason for FQ Inappropriateness				N/A
CI/ADE	4	1	3	
Allergy	1	1	0	
Susceptible to preferred agent	33	21	12	

DISCUSSION

- Suppression of FQ susceptibilities for pan-susceptible urine isolates for *Klebsiella* spp. and *Escherichia coli* led to a 50% decrease in FQ prescribing at discharge for AUC (but not significant for multivariate analysis).
- The ability to use other preferred agents (i.e. cephalexin, nitrofurantoin, and/or sulfamethoxazole/trimethoprim) was the primary reason for the inappropriateness of FQ use.
- Patients who were uninsured or received a FQ while inpatient were much more likely to be discharged on a FQ. Conversely, those discharged from a medicine team were less likely to be prescribed a FQ at discharge, possibly due to the nature of a teaching team populated with faculty, residents, and students from both medical and pharmacy professions.
- Antimicrobial stewardship programs should consider suppressing FQ susceptibility results on pan-susceptible urine cultures to reduce the incidence of both inpatient and discharge FQ prescribing for AUC. Additional stewardship measures are still needed to ensure appropriateness of discharge FQ prescribing.

LIMITATIONS

- Patient data obtained exclusively from retrospective chart review.
- Not all possible patients within the timeframe were screened due to study feasibility.
- Inclusion of both men and woman of all ages, which is outside the proper definition of AUC.
- Disparity in timing between patients included in the pre- and post-implementation groups.
- Our rate of 27% β-lactam allergy is much higher than the 10% normally referenced. However, there was no statistical difference in β-lactam allergy between pre- and post-groups (26.8% vs. 28.2%, *P* = 0.863), and allergies overall were not significantly correlated with FQ use in multivariate analysis (OR 0.843 [95% CI 0.373-1.904], *P* = 0.68). Therefore, it is unlikely that this increase influenced our results.
- Change in FQ susceptibility breakpoints for *Enterobacteriaceae* during the 2-year study (decreased from ≤1 to ≤0.25 μg/mL and from ≤2 to ≤0.5 μg/mL for ciprofloxacin and levofloxacin, respectively), although our lab did not implement the changes. [7]
- Nitrofurantoin CrCL cutoff reduced from 60 to 30 mL/min during the 2-year study. [8]

REFERENCES

1. Gupta K, et al. *Clin Infect Dis* 2011;52(5):e103–e120.
2. FDA News Release, FDA Website, 07/10/18.
3. Langford B, et al. *J Clin Microbiol* 2016;54:2343–2347.
4. Van T, et al. *J Clin Microbiol* 2019; 57:e02072-18.
5. White B, et al. (Abstract) ID Week; April 2019.
6. Vaughn V, et al. *Clin Infect Dis* 2019; iy102:1-8. Published online ahead of print February 13, 2019.
7. CLSI 2019. M100-S29. Clinical and Laboratory Standards Institute, Wayne, PA.
8. AGS Beers Criteria Update Expert Panel. *J Am Geriatr Soc*. 2019;67(4):674-694.