RISK FACTORS FOR AMBULATORY URINARY TRACT INFECTIONS CAUSED BY HIGH MIC-FLUOROQUINOLONE SUSCEPTIBLE *E. COLI* IN WOMEN

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ABSTRACT

BACKGROUND: Several studies have reported an increasing prevalence of high MIC fluoroquinolone susceptible *E. coli* (high MIC-FQSEC) which are the *E. coli* isolates with reduced susceptibility to FQs. High MIC-FQSEC potentially results in development of fully FQ-resistance and delayed response to FQ therapy. To date, risk factors for infection caused by high MIC-FQSEC have never been successfully identified. Our study aimed to identify risk factors for ambulatory urinary tract infections (UTIs) caused by high MIC-FQSEC in women.

METHODS: We conducted a case-control study of female subjects with UTIs caused by FQSEC at outpatient services within University of Pennsylvania Health System, Philadelphia. Of subjects in whom FQSEC (a levofloxacin-MIC<4 mcg/mL) were isolated on urine culture, we included only those who met our study criteria of UTIs. Cases were subjects with UTIs caused by high MIC-FQSEC (a levofloxacin-MIC≤0.12 mcg/mL) and controls were subjects with UTIs caused by low MIC-FQSEC, (a levofloxacin-MIC>0.12 but <4 mcg/mL). Cases and controls were compared with regard to demographics, comorbid conditions, and recent use of medications (particularly antibiotics) within the 90 days prior to the UTI onset. We obtained all necessary data from HUP clinical microbiology laboratory database and Penn data store.

RESULTS: Two thousand and one female subjects with FQSEC-UTIs were included during May 1, 2008 to April 30, 2011. A total of 91.8% had low MIC-FQSEC UTI while 8.2% had high MIC-FQSEC UTI. Mean age was 56.9+/-22.6 years among cases and 57.3+/-22.0 years among controls. Approximately one-fourth of subjects in both groups had at least one underlying diseases. Independent risk factors for high MIC-FQ susceptibility identified by multiple logistic regression are shown in table3.

CONCLUSION: In addition to Asian race and having chronic renal diseases, recent use of nitrofurantoin was identified as a risk factor. Since this study was conducted among a relatively healthy population with a low prevalence of recent antibiotic use, we did not have enough power to identify any associations between high MIC-FQSEC and other uncommonly used antibiotics.

BACKGROUND:

Over the past decade, the prevalence of FQ resistance among uropathogen has been constantly increasing. Furthermore, several studies have reported an increasing prevalence of high MIC fluoroquinolone susceptible *E. coli* (high MIC-FQSEC) which are the *E. coli* isolates with reduced susceptibility to FQs. High MIC-FQSEC potentially results in development of fully FQ-resistance and delayed response to FQ therapy. Thus far, the risk factors for infections caused by high MIC-FQSEC have never been successfully identified. Our study objective was to identify risk factors for UTIs caused by high MIC-FQSEC in women.

METHODS

SETTINGS: The study was conducted at outpatient services within University of Pennsylvania Health System (UPHS), Philadelphia during May 1, 2008 to April 30, 2011. The UPHS network consists of a broad range of healthcare facilities including one university hospital, two community hospitals, two specialty centers, six community practices and a number of outpatient clinical practices.

STUDY DESIGN: Case-control study

STUDY SUBJECTS: Adult female subjects (age ≥18 years) who had a positive urine culture for FQSEC and met the study definition for UTIs. We included only the first episode of UTI if a given patient had more than one episodes of UTI during the study period. To be eligible to our study, a given patient must register to the UPHS system for at least 3 months prior to the index date. The index date was the date that a urine specimen with FQSEC was collected.

DEFINITION FOR UTIs: By using data retrieved from the EPIC/Medview database, only those who met our criteria for UTIs (Table 1) within 7 days before or 7 days after the index date were considered as having E. coli UTI.

Table 1. Study definition of UTIs

To be diagnosed of UTI, the eligible subjects must meet both criterion 1 and criterion 2.	
Criterion 1	Patient has a positive urine culture ≥10^5cfu/ml, with >2 species of organisms
Criterion 2	At least one of the following a)Dipstick test positive for leukocyte esterase and/or nitrate b)Pyuria (≥10 white blood cells (wbc) /mm^3 or ≥ 3 wbc /HPF of unspun urine) c)Physician diagnosis of a urinary tract infection (ICD-9 code) ▪ 599.0 Urinary tract infection, site not specified ▪ 590.x Infection of kidney ▪ 595.0 Acute cystitis ▪ 597.x Urethritis, not sexually transmitted diseases

IDENTIFICATION OF CASES AND CONTROLS: Cases were subjects with UTIs caused by high MIC-FQSEC (a levofloxacin-MIC≤0.12 mcg/mL) and controls were subjects with UTIs caused by low MIC-FQSEC, (a levofloxacin-MIC>0.12 but <4 mcg/mL). We included only the first episode of UTI if a given patient had more than one episodes of UTI during the study period.

DATA COLLECTION: Data on potential risk factors including age, race, clinic site and service, previous hospitalization, comorbid conditions, previous and current medications used and microbiological results were obtained from the Penn data Store. Urine culture results within 90 days prior and after the index date as well as the MIC data were obtained from the clinical microbiology laboratory database.

STATISTICAL ANALYSIS: A 2-tailed p-value of <0.05 was considered significant. All statistical calculations were performed by using STATA, version 12.0.

RESULTS

Two thousand and one female subjects with FQSEC-UTIs were enrolled into our study. A total of 91.8% (1,836/2,001) had low MIC-FQSEC UTI while 8.2% (164/2001) had high MIC-FQSEC UTI. Baseline characteristics between cases and controls are shown in the table 2. Mean age was 56.9+/-22.6 years among cases and 57.3+/-22.0 years among controls. Approximately one-fourth of subjects in both groups had at least one underlying diseases. By comparing previous drug exposure between two groups, the high MIC group was more likely to previously expose to overall antibiotics [95%CI: 1.80; 0.67-4.12;p=0.15], nitrofurantoin [95%CI: 5.65; 0.51-39.73; p=0.08] and H2 blocker agents [95% CI: 2.12; 0.39-7.51; p=0.20]. However, these findings did not reach statistical significance in bivariable analysis. The variables that remained independent risk factors for high MIC-FQSEC UTI after multivariable analysis are shown in table 3. Independent risk factors for high MIC-FQ susceptibility included Asian race [95%CI: 2.92; 1.29-6.58; p=0.02], having renal diseases [95%CI: 2.18; 1.15-4.14; p=0.02] and previous exposure to nitrofurantoin [95%CI: 8.86; 1.95-40.29; p=0.04].

CONCLUSION:

Our study was the largest study that specifically designed to identify risk factors for high MIC-FQSEC UTI. Our study revealed three independent risk factors including Asian race, having underlying renal disease and previous exposure to nitrofurantoin. Data from chart-review confirmed that previous exposure to nitrofurantoin was a proxy of recurrent UTI episodes that did not meet our study definitions for UTIs. Since this study was conducted among a relatively healthy population with a low prevalence of recent antibiotic use, we did not have enough power to identify any associations between high MIC-FQSEC and other uncommonly used antibiotics. Further studies are needed to explore the association between Asian race and high MIC-FQSEC UTIs.

Table 2. Baseline characteristics between cases and controls

Variables	High MIC (N=165)		Low MIC (N=1,836)		Unadjusted Odds Ratio (95% CI)	p-value
	N	%	N	%		
Demographics						
Age (Mean+/-SD)	56.91±22.57		57.34±21.98		0.99 [0.99-1.00]	0.81
Race						
White	64	39.0	766	41.7	Ref	0.02
Black	77	47.0	931	50.8	1.00 [0.71-1.41]	
Asian	8	4.9	34	1.9	2.82 [1.25-6.34]	
Other/Unknown	15	9.1	105	5.7	1.71 [0.94-3.11]	
Co-morbidity						
Charlson index (mean+/-SD)	0.45	0.79	0.4	0.72		0.35
At least 1 underlying diseases	45	27.4	476	25.9	1.08 [0.74-1.56]	0.67
Acute Myocardial Infarction	7	4.3	45	2.5	1.77 [0.66-4.05]	0.16
Congestive Heart Failure	16	9.8	78	4.3	2.44 [1.29-4.34]	0.001
Peripheral Vascular Disease	4	2.4	48	2.6	0.98 [0.24-2.59]	0.57*
Cerebrovascular disease	12	7.3	131	7.1	1.03 [0.51-1.91]	0.93
Dementia	1	0.6	8	0.4	1.40 [0.03-10.56]	0.54*
COPD	6	3.7	86	4.7	0.77 [0.27-1.79]	0.55
Rheumatoid disease	2	1.2	12	0.7	1.88 [0.20-8.54]	0.32*
Peptic Ulcer	2	1.2	10	0.5	2.25 [0.24-10.70]	0.26*
Mild Liver Disease	1	0.6	13	0.7	0.86 [0.02-5.80]	0.99*
Moderate/Severe Liver disease	0	0	6	0.3	-	0.99*
Diabetes without complication	2	1.2	23	1.3	0.97 [0.11-4.00]	0.66*
Diabetes with complication	4	2.4	17	0.9	2.68 [0.65-8.33]	0.09*
Hemiplegia or Paraplegia	2	1.2	13	0.7	1.73 [0.19-7.75]	0.35*
Renal disease	12	7.3	68	3.7	2.05 [1.00-3.93]	0.02
Cancer	8	4.9	134	7.3	0.65 (0.27-1.35]	0.25
Metastatic cancer	4	2.4	37	2	1.22 [0.31-3.45]	0.57*

Table 3. Independent risk factors for high MIC-FQ susceptibility by multiple logistic regression

Variables	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	p-value
Race			
▪ White	Ref	Ref	0.02
▪ Black	1.00 [0.71-1.41]	0.99 [0.70-1.39]	
▪ Asian	2.82 [1.25-6.34]	2.92 [1.29-6.58]	
▪ Other/Unknown	1.71 [0.94-3.11]	1.72 [0.94-3.15]	
Renal diseases	2.05 [0.99-3.93]	2.18 [1.15-4.14]	0.02
Previous exposure to Nitrofurantoin	5.65 [0.51-39.73]	8.86 [1.95-40.29]	0.005

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