ORIGINAL ARTICLE

Outbreak of Fluoroquinolone-Resistant *Escherichia coli* Infections after Transrectal Ultrasound–Guided Biopsy of the Prostate

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DESIGN. We conducted an investigation after identifying a cluster of 4 serious infections following transrectal ultrasound–guided biopsy of the prostate (TRUBP) during a 2-month period.

SETTING. Veterans Affairs medical center.

PATIENTS. Patients with urinary tract infection (UTI) after TRUBP and time-matched controls with no evidence of infection.

METHODS. The incidence of UTI within 30 days after TRUBP was calculated from 2002 through 2010. We evaluated the correlation between infection with fluoroquinolone-resistant gram-negative bacilli (GNB) and fluoroquinolone resistance in outpatient *Escherichia coli* urinary isolates and performed a case-control study to determine risk factors for infection with fluoroquinolone-resistant GNB. Processes for TRUBP prophylaxis, procedures, and equipment sterilization were reviewed.

RESULTS. An outbreak of UTI due to fluoroquinolone-resistant *E. coli* after TRUBP began 2 years before the cluster was identified and was correlated with increasing fluoroquinolone resistance in outpatient *E. coli*. No deficiencies were identified in equipment processing or biopsy procedures. Fluoroquinolone-resistant *E. coli* UTI after TRUBP was independently associated with prior infection with fluoroquinolone-resistant GNB (adjusted odds ratio, 20.8; $P = .005$). A prediction rule including prior UTI, hospitalization in the past year, and previous infection with fluoroquinolone-resistant GNB identified only 17 (49%) of 35 cases.

CONCLUSIONS. The outbreak of fluoroquinolone-resistant *E. coli* infections after TRUBP closely paralleled rising rates of fluoroquinolone resistance among outpatient *E. coli* isolates. The delayed detection of the outbreak and the absence of sensitive predictors of infection suggest that active surveillance for infection after TRUBP is necessary in the context of increasing fluoroquinolone resistance in the United States.

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Each year, an estimated 1 million US men undergo transrectal ultrasound–guided biopsy of the prostate (TRUBP).[1] Because the biopsy needle passes through the rectal mucosa, the TRUBP procedure is associated with a significant risk of infectious complications, including urinary tract infection (UTI), prostatitis, and bacteremia.[2-6] *Escherichia coli* is the most common cause of these infections.[7-10] In randomized trials, antibiotic prophylaxis has been shown to significantly reduce the frequency of infectious complications after TRUBP.[11] Fluoroquinolones are the most often utilized antibiotics for prophylaxis in the United States.[11,12] However, fluoroquinolone resistance in *E. coli* and other gram-negative bacilli (GNB) has increased steadily in recent years,[13,14] and there have been several reports of increasing rates of infection due to fluoroquinolone-resistant *E. coli* among patients undergoing TRUBP.[6-8,14-17]

On December 30, 2010, the infection control department at the Cleveland Veterans Affairs (VA) Medical Center became aware of a cluster of 4 serious infections after TRUBP during the prior 2 months that required hospital admission. Three of the 4 infections were due to fluoroquinolone-resistant *E. coli* and were associated with bacteremia. We conducted an investigation to determine the extent of the outbreak and to identify factors contributing to the increase in infections. A case-control study was performed to determine risk factors for infection with fluoroquinolone-resistant GNB after TRUBP. We hypothesized that prior exposure to fluoroquinolones and/or previous admission to the hospital would pre-

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dict most cases of infection with fluoroquinolone-resistant GNB after TRUBP.

METHODS

Study Setting

The Cleveland VA Medical Center is a 214-bed acute care facility that provides care to more than 95,000 veterans each year in northeast Ohio. Patients with an indication for prostate biopsy are referred to the urology department clinic. Approximately 30–40 TRUBP procedures are performed each month.

Outbreak Investigation

From January 2002 through July 2011, we calculated the incidence of UTI after TRUBP using the computerized medical record system. We identified patients who underwent TRUBP with a positive urine culture in the month after the procedure. A case of UTI associated with the procedure was defined as a patient with a positive urine culture plus signs or symptoms of UTI (ie, fever, dysuria, and/or suprapubic pain). Information on identification and susceptibility test results were obtained from the clinical microbiology laboratory.

We evaluated whether the increase in infections with fluoroquinolone-resistant GNB after TRUBP might be attributable to increasing rates of fluoroquinolone-resistant GNB in the Cleveland VA healthcare system. The prevalence of fluoroquinolone-resistant GNB submitted to the microbiology laboratory from 2002 through 2011 was calculated, stratified by inpatient versus outpatient isolates. The prevalence of fluoroquinolone-resistance GNB among outpatient isolates was correlated with the incidence of infections with these organisms after TRUBP.

To determine whether changes in the TRUBP procedure or processing of the equipment might have contributed to the increase in infections, the TRUBP procedure was reviewed with the urology department, and sterilization procedures were reviewed with the processing department.

Case-Control Study

Cases of UTI after TRUBP were categorized as fluoroquinolone-resistant GNB or fluoroquinolone-susceptible GNB infections. Cases due to other microorganisms were excluded from the analysis. Controls were selected for each case by selecting several of the patients without signs or symptoms of UTI undergoing TRUBP during the same week.

The medical records of the cases and controls were reviewed for demographic characteristics, medical conditions (ie, diabetes mellitus, immune deficiency, cerebrovascular disease, chronic kidney disease, spinal cord injury, and previous urologic abnormalities), admissions in the past year, antibiotic use in the past year, and biopsy-related factors (ie, prior prostate biopsy and type of prebiopsy prophylaxis).

Statistical Analysis

Correlation was determined by calculating Pearson's correlation coefficient. Categorical variables were described using proportions, and continuous variables were described using median and range. Univariable analysis was performed to calculate odds ratios (ORs). Ordinal variables with more than 2 strata were converted to dichotomous variables because of the small sample size. The Fisher exact test was used to test the strength of association among categorical variables, and the Wilcoxon rank sum test was used to test the strength of association among continuous variables. Continuous variables were described with median and range. Among the fluoroquinolone-resistant cases, factors with a P value less than .1 were placed into a multivariable model to determine adjusted ORs. A P value of 0.1 was selected rather than 0.2 because the small sample limited the number of variables that could be analyzed in a multivariable model.

RESULTS

Outbreak Investigation

From January 2002 through July 2011, 59 patients had positive urine cultures within 1 month after TRUBP. Fourteen patients were excluded from the analysis because there were no documented signs or symptoms of UTI. Of the 45 patients with UTI after TRUBP, 35 (78%) had fluoroquinolone-resistant GNB (34 *E. coli* and 1 *Klebsiella pneumonia*), 7 (16%) had fluoroquinolone-susceptible GNB (3 *E. coli*, 1 *K. pneumoniae*, 1 *Proteus mirabilis*, and 1 with *K. pneumonia* and *P. mirabilis*), and 3 (7%) had other microorganisms (1 *Enterococcus* species, 1 coagulase-negative *Staphylococcus*, and 1 methicillin-resistant *Staphylococcus aureus*). Of the 35 fluoroquinolone-resistant GNB isolates, 20 (57%) were susceptible to trimethoprim-sulfamethoxazole, 28 (80%) were susceptible to cefazolin, 10 (29%) were susceptible to ampicillin-sulbactam, and 31 (89%) were susceptible to gentamicin.

Of the 35 patients with UTI due to fluoroquinolone-resistant GNB after TRUBP, 18 (51%) required hospital admission, 1 (3%) was admitted to the intensive care unit, 7 (20%) had bacteremia with fluoroquinolone-resistant GNB, and 1 (3%) had a prostate abscess. The average length of hospital stay was 4.5 days (range, 2–187 days).

Figure 1 shows the incidence of TRUBP-related UTI per quarter between January 2002 and July 2011 and the concurrent yearly prevalence of fluoroquinolone resistance among outpatient *E. coli* urinary isolates. The prevalence of fluoroquinolone resistance increased in a nearly linear fashion from 4% in 2002 to 23% in 2010. The outbreak of infection due to fluoroquinolone-resistant GNB began 4 years prior to the time when the infection control committee was notified of the increase in serious infections, and the peak of the outbreak occurred 1 year prior to notification. The increase in fluoroquinolone resistance was closely correlated with the

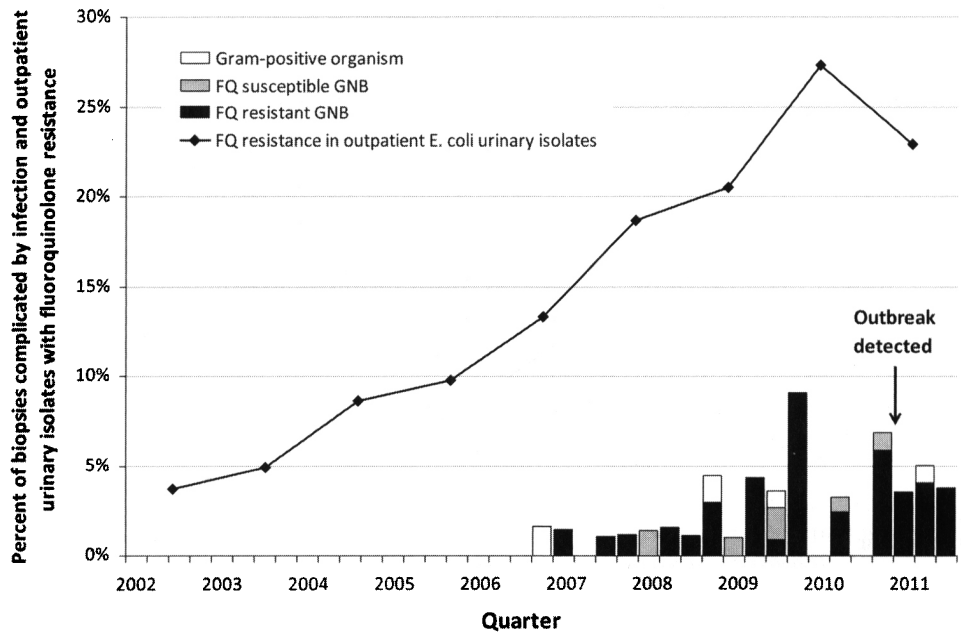

FIGURE 1. Incidence of urinary tract infection after transrectal ultrasound–guided biopsy of the prostate by organism and proportion of outpatient *Escherichia coli* urinary isolates resistant to fluoroquinolones (FQ) at the Cleveland Veterans Affairs Medical Center from January 2002 through August 2011. Isolates included 35 FQ-resistant gram-negative bacilli (GNB; 34 *E. coli* and 1 *Klebsiella pneumonia*), 7 FQ-susceptible GNB (3 *E. coli*, 1 *K. pneumoniae*, 1 *Proteus mirabilis*, and 1 patient with *K. pneumonia* and *P. mirabilis*), and 3 gram-positive organisms (1 *Enterococcus* species, 1 coagulase-negative *Staphylococcus* species, and 1 methicillin-resistant *S. aureus*).

increase in UTI due to fluoroquinolone-resistant GNB that began in 2007 ($r = 0.942$, $P < .001$).

A review of the TRUBP procedure did not reveal any changes during the outbreak period that might explain the increase in infections. A single experienced attending urologist supervised urology residents performing the procedure. Throughout the study period, 500 mg of oral ciprofloxacin was administered twice daily for 6 doses beginning the evening prior to the procedure. There was no change in the device used for TRUBP or in the procedures for equipment reprocessing. The reusable ultrasound probe was plasma sterilized after manual cleaning, and the other components of the device, including the needle and the needle holder, were disposable.

Case-Control Study

Table 1 provides a comparison of the characteristics of the 35 patients with fluoroquinolone-resistant GNB infections and 168 controls with no infection. The median age of the subjects was 64 years (range, 43–88 years). Of the 203 analyzed patients undergoing TRUBP, 183 (90%) were prescribed ciprofloxacin for prophylaxis, including 34 (97%) of 35 patients with fluoroquinolone-resistant GNB infections. On univariable analysis, prior UTI (OR, 3.5 [95% confidence interval (CI), 1.3–9.3]; $P = .01$), history of fluoroquinolone-resistant GNB infection (OR, 27.8 [95% CI, 3.1–2,247.7]; $P < .001$), and admission in the past 12 months (OR, 3.1 [95% CI, 1.2–7.6]; $P = .02$) were significantly associated with fluoroquinolone-resistant GNB. These 3 factors were placed into a multivariable model with prior UTI as the primary factor, followed by history of fluoroquinolone-resistant GNB infection and history of admission in the past 12 months. In this model, history of fluoroquinolone-resistant GNB infection (adjusted OR, 20.8 [95% CI, 2.8–199.9]; $P = .005$) remained significant as an independent predictor of infection. There was a trend toward significance for admission in the past 12 months (adjusted OR, 2.7 [95% CI, 1.0–7.8]; $P = .072$). When controlling for the other factors, prior UTI was no longer a significant factor. Notably, 18 (51%) of the 35 patients did not have any of these 3 potential risk factors for infection.

DISCUSSION

We report an outbreak of fluoroquinolone-resistant GNB infections after TRUBP that closely paralleled rising rates of fluoroquinolone resistance in outpatient *E. coli* isolates. There was no evidence that changes in the TRUBP procedure or inadequate device reprocessing contributed to the increase in infections. The outbreak was associated with significant morbidity and costs, with 51% of patients requiring hospital admission, including 20% with bacteremia. Other recent reports of increasing infections due to fluoroquinolone-resistant GNB after TRUBP have also demonstrated high frequencies of bacteremia and hospital admission.[11,12,14-17]

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TABLE 1. Univariable and Multivariable Analysis of Risk Factors for Infection due to Fluoroquinolone (FQ)–Resistant Gram-Negative Bacilli (GNB) after Transrectal Ultrasound–Guided Biopsy of the Prostate (TRUBP) versus Time-Matched Controls Undergoing TRUBP

Variable	Control (n = 168)	FQ-resistant GNB (n = 35)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	P	OR (95% CI)	P
Age, median (range), years	64 (43–88)	64 (51–81)	1.0 (0.9–1.0)	.60		
Diabetes mellitus	43 (25.6)	10 (28.6)	1.2 (0.5–2.6)	.68		
Systemic steroids	4 (2.4)	1 (2.9)	1.2 (0.1–11.1)	1		
Renal disease	10 (6.0)	4 (11.4)	2.1 (0.6–7.1)	.26		
Spinal cord injury	0	3 (8.6)				
History of FQ-resistant GNB infection	1 (0.6)	5 (14.3)	27.8 (3.1–247.7)	<.001	20.8 (2.2–199.9)	.005
History of urologic abnormality	39 (23.2)	9 (25.7)	1.2 (0.5–2.7)	.83		
Renal stones	10 (6)	0				
Chronic urinary catheter	2 (1.2)	1 (2.9)	2.4 (0.2–27.7)	.43		
Prior urinary tract infection	13 (7.7)	8 (22.9)	3.5 (1.3–9.3)	.01	2.4 (0.8–7.4)	.186
Urinary retention	21 (12.5)	1 (2.9)	0.2 (0.03–1.6)	.13		
Admission in past year	17 (10.1)	9 (25.7)	3.1 (1.2–7.6)	.02	2.7 (1.0–7.2)	.072
Antibiotic use in past year						
FQ	28 (16.7)	9 (25.7)	1.7 (0.7–4.1)	.23		
Penicillin	15 (8.9)	3 (8.6)	0.9 (0.3–3.5)	1		
Cephalosporin	11 (6.5)	5 (14.3)	2.4 (0.8–7.3)	.16		
Macrolide	8 (4.8)	3 (8.6)	1.9 (0.5–7.5)	.41		
Tetracycline	4 (2.4)	2 (5.7)	2.5 (0.4–14.1)	.28		
Trimethoprim-sulfamethoxazole	7 (4.2)	3 (8.6)	2.2 (0.5–8.8)	.38		

NOTE. Data are no. (%) of patients, unless otherwise specified.

One notable aspect of our report is that the outbreak began 2–4 years before it was discovered. This observation highlights the fact that our infection control program, like many others, did not perform routine surveillance for infectious complications after outpatient biopsy procedures because of the perceived low risk of infection. Given the increasing prevalence of fluoroquinolone resistance in *E. coli* throughout the United States, routine surveillance for infections after TRUBP is indicated when rates of fluoroquinolone resistance are high among outpatient *E. coli* isolates. There is also a need for data on rates of infection associated with other procedures where fluoroquinolones are routinely used for periprocedure prophylaxis.

There is uncertainty regarding which strategies are optimal for prevention of infections due to fluoroquinolone-resistant GNB after TRUBP in settings with a high prevalence of fluoroquinolone resistance in *E. coli*. One potential approach is to modify the periprocedure prophylaxis regimen for all patients undergoing TRUBP. In some reports, the addition of intramuscular gentamicin to ciprofloxacin has been associated with reductions in the incidence of infections due to fluoroquinolone-resistant GNB.[18] In contrast, substitution of amoxicillin-clavulanate for ciprofloxacin was associated with an increase in infections after TRUBP,[19,20] possibly as a result of suboptimal penetration of the prostate by amoxicillin-clavulanate.[21,22] An alternative strategy to prevent infections due to fluoroquinolone-resistant GNB after TRUBP is to modify the prophylaxis regimen only for patients at the highest risk of infection. Screening for rectal carriage of fluoroquinolone-resistant GNB prior to the procedure may allow targeted modification of the prophylaxis regimen based on susceptibility test results.[23]

Use of clinical risk factors could provide another method to identify a subset of high-risk patients who might benefit from modified prophylaxis. We found that a previous history of infection with a fluoroquinolone-resistant GNB was independently associated with infection with fluoroquinolone-resistant GNB after TRUBP. Unfortunately, only 14% of patients who developed fluoroquinolone-resistant GNB infections would have been identified by this risk factor. Moreover, the presence of 1 or more of 3 risk factors (previous history of infection with fluoroquinolone-resistant GNB, prior urinary tract infection, and hospital admission in the past year) was only 49% sensitive for detection of fluoroquinolone-resistant GNB infections after TRUBP.

Our study had some limitations. First, the study was conducted in a single VA institution. Additional studies are needed in other settings. Second, the study was retrospective and was limited to information present in the VA computerized medical record system. Although it is likely that most veterans undergoing TRUBP would receive care for complications within the VA healthcare system, it is possible that we underestimated the incidence of infections, history and duration of antibiotic exposure, and other risk factors if some patients received care outside the VA system. Third, the number of patients with infections was small, limiting the power to detect significant factors associated with infections. Fourth, we did not assess the extent of antimicrobial exposure as

indicated by total days of therapy and/or total number of agents prescribed. Finally, we relied on clinical cultures to detect infections. It is possible that prospective monitoring of patients would have resulted in identification of additional patients with mild infections.

In conclusion, we report an outbreak of fluoroquinolone-resistant *E. coli* infections after TRUBP that closely paralleled rising rates of fluoroquinolone resistance among outpatient *E. coli* isolates. The delay in detection of the outbreak and the absence of sensitive clinical predictors of infection suggest that active surveillance for infection after TRUBP is indicated in the context of increasing fluoroquinolone resistance in the United States.

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