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Prevalence and Significance of Fluoroquinolone Resistant *Escherichia coli* in Patients Undergoing Transrectal Ultrasound Guided Prostate Needle Biopsy

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Abstract

Purpose—We estimated the prevalence of fluoroquinolone resistant *Escherichia coli* in patients undergoing repeat transrectal ultrasound guided prostate needle biopsy and identified high risk groups.

Materials and Methods—From January 2009 to March 2010 rectal swabs of 136 men from 3 institutions undergoing transrectal ultrasound guided prostate needle biopsy were obtained. There were 33 men with no previous biopsy who served as the controls. Participants completed questionnaires and rectal swab culture was obtained just before performing the prostate biopsy. Selective media was used to specifically isolate fluoroquinolone resistant *E. coli* and sensitivities were obtained. The patients were contacted via telephone 7 days after the procedure for a followup questionnaire.

Results—A total of 30 patients had cultures positive for fluoroquinolone resistant bacteria for an overall rate of 22% (95% CI 15, 29). Patients with diabetes and Asian ethnicity had higher risks of resistant rectal flora colonization (OR 2.3 and 2.8, respectively). However, differences did not reach statistical significance ($p = 0.09$ and $p = 0.08$, respectively). Patients with no prior biopsy had a positive rate of 15% (5 of 33) compared to 24% (25 of 103) in those with 1 or more prior biopsies (OR 1.8, $p = 0.27$). Five patients (3.6%) had post-biopsy fever while only 1 of those patients had a positive rectal swab.

Conclusions—Using selective media to isolate fluoroquinolone resistant *E. coli* from the rectum before transrectal ultrasound guided prostate biopsy, we isolated organisms in 22% of patients with a wide resistance pattern. This protocol may be used to provide information regarding targeted antibiotic prophylaxis before transrectal prostate biopsies.

Keywords

prostate; biopsy; drug resistance; microbial; fluoroquinolones; postoperative complications

Transrectal ultrasound guided biopsy is the standard procedure for histological diagnosis of prostate carcinoma. Approximately 800,000 biopsies are performed in the United States alone each year.¹ Infectious complications from prostate biopsy include fever, urinary tract infection, acute bacterial prostatitis, epididymo-orchitis and sepsis.² The infection rate in larger studies has been estimated at 0.1% to 7% depending on the prophylactic routine.²⁻⁶ The most common organism responsible for these infectious complications is *E. coli*.^{2,6-10} Other studies have shown that infections and hospital admissions after transrectal prostate biopsy, including sepsis, have increased at alarming rates during the last decade.^{6-8,11,12} Our group previously reported that men diagnosed with sepsis after repeat transrectal prostate biopsy in our surrounding hospitals in Southern California all had fluoroquinolone resistant *E. coli*.⁷ The proposed mechanism of infection is likely the introduction of bacteria into the bladder and bloodstream from the rectum. However, the prevalence of fluoroquinolone resistant *E. coli* in the rectum at the time of biopsy is unknown. Therefore, we determined the prevalence of fluoroquinolone resistant bacteria in men undergoing transrectal prostate biopsy by using a novel selective media that targeted fluoroquinolone resistant *E. coli*. We also examined risk factors associated with the harboring of these organisms.

METHODS

Between January 2009 to March 2010 we enrolled male patients older than 35 years old who were to undergo TRUS guided prostate needle biopsy. Institutional review board approval was obtained at the 3 participating institutions. After informed consent patients completed the AUA symptom score, Charlson comorbidity index questionnaire, Total Illness Burden Index for Prostate Cancer, as well as questions designed to determine their risk of prior fluoroquinolone exposure such as previous cystoscopy, recent antibiotic intake and hospital admission in the year before the biopsy. Patients were asked if they had ever had a previous biopsy and, if so, how and when. The patients underwent an antibiotic prophylaxis and bowel preparation regimen ordered by their physician and compliance with these regimens was recorded. Immediately before the transrectal prostate biopsy a rectal culture was obtained by the physician performing the biopsy using a culturette (Venturi Transystem® swabs). Rectal swabs were collected from 136 patients undergoing TRUS guided prostate biopsy from 3 separate institutions in California (University of California-Irvine, Long Beach Veterans Affairs Medical Center and Kaiser Permanente Orange County). The swabs were placed directly into 5 ml brain heart infusion broth containing 10 µg/ml ciprofloxacin: Liss formulation (Hardy Diagnostics, Santa Maria, California) developed to screen for fluoroquinolone resistant bacteria, and incubated overnight at 35C in ambient air. Subsequently the broth was subcultured to MacConkey agar with 10 µg/ml ciprofloxacin: Liss formulation. The plates were inoculated by transferring 0.1 ml broth onto the media and streaking for isolation, and were incubated overnight at 35C in ambient air. All enteric gram-negative bacilli were characterized on the Vitek® 2 using GN and AST-GN30 cards (BioMérieux, Durham, North Carolina) for identification and susceptibility testing,

respectively (see figure). All patients were contacted by telephone interview 7 days after the biopsy to complete a followup questionnaire. Responses to questions pertaining to fever, lower urinary tract symptoms, presentation to another hospital or doctor, newly prescribed antibiotics, hematuria and pain (present or absent) were documented. Patients were grouped according to culture result, which was positive or negative for fluoroquinolone resistant bacteria. These groups were compared with respect to descriptive characteristics and factors before and after biopsy using a t test or Mann-Whitney test for continuous variables and Pearson chi-square test for categorical variables (see table). Multivariate analysis was performed using multiple logistic regression analysis to examine the independent effects of demographic and preoperative factors. All variables with suggestive p values on univariate analysis were included in the multivariate analysis and $p = 0.05$ was considered statistically significant.

RESULTS

Patient characteristics are presented in the table. Of the total of 136 men (median age 65 years) 103 had undergone previous transrectal prostate biopsy (median 3 biopsies). The 3 institutions contributed 36 (26%), 61 (45%) and 39 (29%) patients, respectively. Only 4 patients failed to complete the questionnaires (3%). However, the majority of men could not remember the dates of previous biopsies. Ciprofloxacin prophylaxis before prostate biopsy was used in all patients except 4 in the study. Two dosing regimens were recognized, with 38 (28%) patients taking 1 dose of 500 mg ciprofloxacin the morning of the biopsy and 94 (69%) taking 3 doses of 500 mg ciprofloxacin starting the day before the biopsy. Gentamicin was added to the prophylactic regimen in 30 (22%) patients just before biopsy and was used in 79% of those taking the single dose of ciprofloxacin before biopsy. In terms of bowel preparation 88 (68%) of the patients used a single Dulcolax® (bisacodyl) suppository the morning of the biopsy and 42 (32%) had a self-administered Fleet® enema. The bowel preparation and antibiotic prophylactic regimen did not alter the rate of a positive pre-biopsy rectal culture for fluoroquinolone resistant *E. coli* ($p = 0.59$ and $p = 0.38$, respectively). Other patient pre-biopsy patient characteristics are displayed in the table.

Race/ethnicity, diabetes and previous number of biopsies did have a possible significant effect on the rate of positive pre-biopsy rectal swab for fluoroquinolone resistant *E. coli*. Four racial/ethnic backgrounds were identified in the study including 96 (70%) white, 16 (12%) black, 12 (9%) Hispanic and 12 (9%) Asian. While there were no significant differences when 4 race/ethnic categories were compared, the Asian population had a 42% (5 of 12) positive rate for ciprofloxacin resistant *E. coli* at the time of biopsy vs 20% (25 of 124) in other ethnicities (OR 2.8, $p = 0.08$). Of 22 patients with diabetes 8 (36%) had a positive culture whereas only 22 of 110 men without diabetes (20%) had a positive culture (OR 2.3, $p = 0.09$). The number of previous prostate biopsies was recorded, and 33 (24.3%) had no prior biopsy, 60 (44.1%) had 1 and 43 (31.6%) had more than 1. Risk of resistant infection was higher for those men with 1 or more prior biopsy (OR 1.8), although this difference did not reach statistical significance ($p = 0.27$). On multivariate analysis Asian ethnicity, diabetes and prior biopsies were associated with increased risk of colonization by resistant *E. coli* (OR 3.0, 2.4 and 2.3, respectively), although p values did not reach the 5% significance level ($p = 0.09$, $p = 0.09$ and $p = 0.15$, respectively). Numbers were small and

power was limited (less than 40%) for detection to be significant using $p = 0.05$ for the observation of increased risks.

During the procedure the presence of nodules, calcifications, vasovagal episodes, rectal bleeding and immediate hematuria as well as the number of cores taken were recorded. No statistically significant associations to a positive culture were noted (t test $p = 0.83$, $p = 0.93$, $p = 0.86$ and $p = 0.66$, respectively). The patients were contacted by telephone for an interview 7 days after prostate biopsy, and were asked if they had any fevers, hematuria, suprapubic pain, and whether they had presented to a physician, hospital or emergency department in that period in which 125 (80%) were successfully contacted. These factors showed no significant association with harboring fluoroquinolone resistant bacteria. However, 5 (4%) patients had a subjective fever after the prostate biopsy and only 1 of 5 (20%) had a positive rectal screen for resistant *E. coli*. One patient presented to the hospital with fever and urinary symptoms for treatment, but urine and blood cultures were negative, as was the pre-biopsy rectal swab for fluoroquinolone resistant bacteria. Men with benign prostatic hyperplasia did not have an increased risk of harboring fluoroquinolone resistant bacteria vs those diagnosed with prostate cancer ($p = 0.581$).

A total of 30 patients (22%) had a positive culture for fluoroquinolone resistant bacteria. Using selective media *E. coli* was isolated from 29 (97%) patients. One nonfermenting bacteria, *Brevundimonas diminuta/vesicularis*, was isolated from 1 patient. The *E. coli* isolates were further investigated regarding their resistance profile (see figure). Of these fluoroquinolone resistant bacteria, extended spectrum beta-lactamase *E. coli* represented 15% (5 of 33 colonies) of the bacteria. The fluoroquinolone resistant bacteria were also resistant to multiple antibiotics but none were resistant to amikacin or imipenem.

DISCUSSION

It is estimated that 192,000 men will be diagnosed with and more than 27,000 men will die of prostate cancer this year.¹³ Given this finding, prostate cancer screening with PSA has undergone exponential growth during the last decade. In turn, this has led to more prostate biopsies being performed to investigate the increase in PSA. One of the most common risks of transrectal prostate biopsies is complications from infection, the most dreaded of which is sepsis.² The AUA Best Practice Statement for antibacterial prophylaxis recommends use of a fluoroquinolone as a first line therapy for the prevention of infection from transrectal prostate biopsy.¹⁴ However, a recent study of more than 75,000 Canadian men showed an increase in hospital admission rates within 30 days of prostate biopsy from 1.0% in 1996 to 4.1% in 2005, with 76% of admissions due to infection.¹¹ In addition to other investigators our group previously reported men diagnosed with sepsis after repeat transrectal prostate biopsy in 4 Southern California hospitals and all had blood cultures positive for fluoroquinolone resistant *E. coli*.^{6,7,9,10} Before our report Feliciano et al investigated more than 1,200 men and found 31 (2.4%) presented with infection symptoms.⁶ Of those cases 50% were due to resistant bacteria for an overall rate of 1.2% fluoroquinolone resistant infections.

The proposed mechanism of infection involves the biopsy needle passing through the rectal mucosa with fecal contamination seeding the bladder and vasculature, rather than the bladder being the origin.¹⁵ To prevent these infections broad spectrum oral antibiotics with or without bowel preparation have been used.^{4,5,11} Nevertheless, due to the increasing rates of bacterial resistance to fluoroquinolones, post-biopsy infection rates are increasing. Therefore, we examined the prevalence of rectal flora bacteria and their resistance profiles immediately before prostate biopsy. Batura et al found a 10.6% prevalence of ciprofloxacin resistance in 500 British men undergoing transrectal prostate biopsy using rectal swabs obtained before biopsy.¹⁵ We found a prevalence of 22% of patients harboring fluoroquinolone resistant *E. coli*. A total of 33 men (15%) receiving a first time biopsy had a positive culture and the rate increased to 24% in the repeat biopsy group. However, the increase was not significant on univariate or multivariate analysis. Although the increased number of fluoroquinolone resistant *E. coli* can be explained by previous exposure of patients to fluoroquinolone at prior biopsies, another possible reason for the overall increased rate of fluoroquinolone resistance compared to other studies was our development of a customized isolation protocol using broth enhancement and selective agar media containing ciprofloxacin, ie Liss broth and media. The concept of this protocol is to allow for specimens with low numbers of fluoroquinolone resistant *E. coli* to be isolated, thus possibly increasing the sensitivity of the screening culture.

Patient characteristics were evaluated to determine if there were other risk factors associated with fluoroquinolone resistance. Previous reports have suggested that various comorbidities, diabetes, indwelling Foley catheters and extended biopsies do place the patient at increased risk for infectious complications after transrectal prostate biopsy, including sepsis.^{7,16,17} The presence of diabetes in our patient population was 16.7% and we noted an increased risk that was not statistically significant ($p = 0.09$).¹⁶ Interestingly we also found that the Asian population may be at increased risk for fluoroquinolone resistance (univariate $p = 0.08$, multivariate $p = 0.08$). The Asian population in our study only represented 12 (8.8%) patients. However, 5 (42%) patients had fluoroquinolone resistant bacteria isolated. Recent surveillance reports from Asian countries estimate a prevalence of 30% to 74% of fluoroquinolone resistant *E. coli* in China and Japan, and a 74% rate of nalidixic acid resistance in Vietnam.^{16,18,19} Due to the small numbers of these higher risk subgroups our ability to detect a statistically significant difference was decreased and a larger study population is needed to confirm these results.

Five patients (4%) reported a subjective fever after the biopsy and only 1 had a positive screening culture for ciprofloxacin resistant *E. coli*. Therefore, 1 in 30 patients (3.3%) harboring fluoroquinolone resistant organisms had a subjective fever. However, this finding may be confounded by the addition of gentamicin to some antibiotic regimens. One patient (0.8%) was admitted to the hospital for fever for 3 days, yet blood and urine cultures were negative. Nam et al noted that increasing hospital admission rates were more commonly associated with a benign diagnosis rather than a diagnosis of prostate cancer.¹¹ In our investigation there was no difference in the positive culture rate in those patients diagnosed with prostate cancer or benign prostatic hyperplasia and a positive screening culture ($p = 0.58$). There were 29 patients with cultures positive for fluoroquinolone resistant *E. coli* and 1 with *B. diminuta/vesicularis* in whom further antimicrobial susceptibility testing was

performed (see figure). There are few reports in the literature of *Brevundimonas* spp. causing clinical infection. However, 1 study included 7 patients (1 isolate from the urinary tract) and showed fluoroquinolone resistance suggesting an intrinsic factor of the bacteria itself.²⁰ Although this is an interesting finding, we are unsure of its clinical significance.

Given these findings we recommend that just as urine culture is obtained before instrumentation of the urinary tract to guide appropriate antibiotic prophylaxis, rectal swab screening cultures may provide a targeted antibiotic approach to transrectal procedures. Despite the relatively high rate of detection of fluoroquinolone resistant *E. coli* on our screening cultures, the infectious complication rate was still less than 1%. Therefore, the use of rectal culture before transrectal prostate biopsy may not improve already low infection rates, but rather provide a targeted approach to antibiotic prophylaxis. We may also prevent further use of antibiotics with known side effects that are not providing appropriate prophylaxis and are potentiating further antibiotic resistance. We caution against using these results to change antibiotic prophylactic regimens without culture proven fluoroquinolone resistance.

CONCLUSIONS

Transrectal ultrasound guided prostate biopsy is a common procedure that can result in significant morbidity which is occurring at an increasing rate due to the increasing prevalence of fluoroquinolone resistant *E. coli* in rectal flora worldwide. We describe the use of selective media to isolate fluoroquinolone resistant *E. coli* that may be used to provide information regarding targeted prophylaxis before transrectal prostate biopsies. Populations that may be at increased risk for harboring fluoroquinolone resistant *E. coli* are patients undergoing repeat biopsy, Asian patients and patients with diabetes mellitus. Further study of these observed results with larger patient numbers is indicated.

Acknowledgments

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Study received institutional review board approval.

Abbreviations and Acronyms

AUA	American Urological Association
PSA	prostate specific antigen
TRUS	transrectal ultrasound

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Resistance pattern for fluoroquinolone resistant *E. coli*

Patient characteristics before biopsy

	Total (%)	Mean	SE	Fluoroquinolone Resistance				p Value
				No. (%)	Mean	SE	No. (%)	
Age	136	64.51	0.58	30	65.70	1.02	106	0.69
Body mass index	136	28.42	0.35	30	28.51	0.68	106	0.19
PSA	136	10.78	3.49	30	5.83	0.50	106	0.41
Prior biopsies	136	1.37	0.13	30	1.30	0.19	105	0.15
TRUS size	133	59.74	2.99	29	51.54	4.08	104	3.62
Doses before biopsy (500 mg ciprofloxacin)	132	5.48	0.10	28	5.50	0.22	103	0.11
AUA symptom score	128	11.67	0.73	29	10.59	1.42	99	0.85
Charlson comorbidity index	136	3.49	0.18	30	4.00	0.44	106	0.19
Total Illness Burden Index for Prostate Ca	130	3.62	0.28	30	4.03	0.75	100	0.28
Race:	136 (100)			30 (22)			106 (78)	0.38 [†]
White	96 (70.6)			20 (20.8)			76 (79.2)	
Hispanic	12 (8.8)			2 (16.7)			10 (83.3)	
Black	16 (11.8)			3 (18.8)			13 (81.2)	
Asian	12 (8.8)			5 (41.7)			7 (58.3)	
<i>Asian compared to all other ethnicities</i>								
Prior biopsies:	136 (100)			30 (22)			106 (78)	0.08 [†]
0	33 (24.3)			5 (15.2)			28 (84.8)	0.27 [†]
1	60 (44.1)			17 (28.3)			43 (76.7)	
2 or More	43 (43.1)			8 (18.6)			35 (81.4)	
Diabetes:	132 (100)			30 (23)			102 (77)	0.09 [†]
No	110 (83.3)			22 (20.0)			88 (80.0)	
Yes	22 (16.7)			8 (36.4)			14 (63.6)	
History of urinary tract infections:	132 (100)			30 (23)			102 (77)	0.82 [†]
No	116 (87.9)			26 (22.4)			90 (77.6)	
Yes	16 (12.1)			4 (25)			12 (75)	

	Total (%)	Fluoroquinolone Resistance						p Value
		Mean	SE	No. (%)	Mean	SE	No. (%)	
Family members in health care:	132 (100)			30 (23)			102 (77)	0.77 [†]
No	108 (81.8)			24 (22.2)			84 (77.8)	
Yes	24 (18.2)			6 (25)			18 (75)	
Hospitalized for illness (12 mos):	132 (100)			30 (23)			102 (77)	0.96 [†]
No	114 (86.4)			26 (22.8)			88 (77.2)	
Yes	18 (13.6)			4 (22.2)			14 (77.8)	

* t Test.

[†] Chi-square test.