Published in final edited form as:

J Urol. 2015 February ; 193(2): 552–556. doi:10.1016/j.juro.2014.08.008.

Resistance in the Rectal Carriage of Men in an Active Surveillance Cohort: Longitudinal Analysis

Jason E. Cohen, Patricia Landis, Bruce J. Trock, Hiten D. Patel, Mark W. Ball, Paul G. Auwaerter, Edward Schaeffer, and H. Ballentine Carter*

James Buchanan Brady Urological Institute and Department of Urology, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Abstract

Purpose—Rectal swabs can identify men with fluoroquinolone resistant bacteria and decrease the infection rate after transrectal ultrasound guided prostate biopsy by targeted antimicrobial prophylaxis. We evaluated the rate of fluoroquinolone resistance in an active surveillance cohort with attention to factors associated with resistance and changes in resistance with time.

Materials and Methods—We evaluated 416 men with prostate cancer on active surveillance who underwent rectal swabs to assess the rate of fluoroquinolone resistance compared to that in men undergoing diagnostic transrectal ultrasound guided prostate biopsy. The chi-square test and Student t-test were used to compare categorical and continuous variables, respectively. Poisson regression analysis was used for multivariate analysis.

Results—On the initial swab fluoroquinolone resistance was found in 95 of 416 men (22.8%) on active surveillance compared to 54 of 221 (24.4%) in the diagnostic biopsy cohort ($p = 0.675$). Diabetes was found in 4.0% of the fluoroquinolone sensitive group vs 14.7% of the resistant group ($p < 0.001$). Biopsy history was not associated with resistance. Of those with a resistant first swab 62.9% had a resistant second swab and 88.9% of those with 2 resistant swabs showed resistance on the third swab. Of men with a sensitive first swab 10.6% showed resistance on the second swab and 10.6% of those with 2 sensitive swabs had resistant third swabs.

Conclusions—One of 4 men who present for surveillance and diagnostic trans-rectal ultrasound guided prostate biopsy have rectal flora resistant to fluoroquinolone. Resistance is significantly associated with diabetes but the number of prior biopsies is not. Men with fluoroquinolone resistant flora tend to remain resistant with time.

Keywords

prostatic neoplasms; biopsy; fluoroquinolones; drug resistance; bacterial; diabetes mellitus

One of the major complications of TRUSB is infection in the genitourinary system and sepsis. Rectal flora most likely enter the genitourinary tract or bloodstream through perforation of the bowel mucosa during the procedure.¹ Antibiotic prophylaxis has become

an important measure to prevent these complications with FQ used to prevent infectious complications.^{2,3} The 2008 AUA Best Practice Policy Statement recommends FQ prophylaxis before TRUSB along with preferred second line agents.⁴ Despite this recommendation there have been increasing rates of infection related complications after TRUSB.^{5,6} The increase is thought to be due to FQ resistant organisms in the rectal carriage.^{5,7}

Previous studies demonstrated that rectal swabs and resistance profiles of the rectal flora are effective for preventing post-procedure infectious complications, mainly by identifying FQ resistant bacteria.^{1,8} These findings led some groups to adopt rectal culture and directed prophylactic therapy before TRUSB. FQ resistance in the rectal carriage was reported in 10% to 22% of men who undergo TRUSB. FQ resistance is associated with previous heart valve replacement, diabetes and FQ use in the prior 3 months.^{8,9} However, to our knowledge no longitudinal study has been done to assess trends in resistance patterns in individuals with time.

We evaluated the rate of FQ resistance, the factors associated with resistance and the trends in resistance with time in a well characterized AS program. The resistance rate was compared to that in men not on AS who were undergoing diagnostic TRUSB.

METHODS

Study Cohort

The AS program at JHH is an institutional review board approved, open enrollment, longitudinal study consisting of men with very low to low risk prostate cancer who elect close followup as an alternative to curative intervention after a diagnosis of prostate cancer.¹⁰ A total of 1,297 men were enrolled in the AS cohort as of February 2014. Starting in July 2012 rectal swabs were performed in all men at JHH undergoing diagnostic and surveillance TRUSB in an effort to decrease post-TRUSB infectious complications. In the AS cohort a total of 717 swabs had been performed in 416 men as of May 2014.

We queried the AS database and the electronic medical records for FQ resistance (specifically ciprofloxacin resistance) in individual swabs, antibiotic resistance profiles, medical history, demographic data and biopsy history. Infection rates were not included in this study because this outcome was not prospectively included in our cohort. Information such as previous antibiotic use and hospitalizations in the last 6 months was also not available.

As a comparison cohort we determined the FQ resistance rate in 221 men who presented to JHH for diagnostic biopsy during the period when rectal swabs were done in the AS cohort (February 2013 to February 2014). Men who underwent diagnostic swabs at JHH under the same protocol as the AS cohort served as controls to determine whether the resistance rate in the AS cohort differed from that in men who presented for prostate biopsy without a prostate cancer diagnosis. Additional data such as medical and biopsy history were not available and these men did not serve as controls in the remaining analysis.

Rectal Swabs

Rectal swabs were performed in clinician office about 2 to 4 weeks before TRUSB. The swabs were incubated in broth containing ciprofloxacin for 24 hours at 35C. If there was evidence of bacterial growth in the broth, it was transferred to a MacConkey agar plate, a MacConkey agar plate with 10 µg/ml ciprofloxacin plate and 5% sheep blood agar plate. Gram staining was done to confirm gram-negative rods. The plates were incubated for 24 hours at 35C. If there was growth on the ciprofloxacin containing plate, organism identification and antimicrobial susceptibility testing were done on isolates from the nonselective plates using the BD PhoenixTM Automated Microbial System. If there was no evidence of growth in the broth containing ciprofloxacin, it was incubated an additional 24 hours before the swab was reported as negative for FQ resistant gram-negative rods.

The targeted prophylaxis approach was used. Patients with sensitive swabs received ciprofloxacin prophylaxis based on the standard empirical prophylaxis protocol described in the 2008 AUA Best Practice Policy Statement.⁴ Those with resistant swabs received alternative prophylaxis based on the swab resistance profile, which is standard practice at JHH.¹¹

All men were advised to discontinue medication interfering with platelet function 10 days before biopsy and to administer an enema on the morning of biopsy.

Statistical Analysis

The chi-square test and Student t-test were used to compare categorical and continuous variables, respectively. Multivariate Poisson regression analysis was done to calculate the RR of potential independent risk factors associated with FQ resistant flora in the AS cohort. The results of rectal swabs of men with a rectal swab history were compared to those of men who underwent an initial swab. The demographic and antibiotic resistance status of men not on AS who underwent rectal swabs and TRUSB at JHH served as controls.

Potential risk factors used in analysis included diabetes, increased cholesterol, hypertension and heart disease (congestive heart failure, coronary artery disease or a history of myocardial infarction). Presence of a risk factor was determined by the problem list in the electronic medical record.

RESULTS

FQ Resistance Rates in AS Cohort vs Controls

During the study period 416 men on AS and 221 controls underwent rectal swabs. There was no statistically significant difference in age between the 2 groups. Of the AS group 91% were white compared to 72% of controls (chi-square test $p < 0.001$). Of 416 men in the AS cohort with a rectal swab 95 (22.8%) had FQ resistance on the first swab compared to 54 of 221 (24.4%) with rectal swabs in the control group (chi-square test $p = 0.675$).

FQ Resistance Trends

Resistance rates were determined for other widely used antibiotics in swabs reported to be FQ resistant. Resistance was found for ampicillin in 79% of swabs, trimethoprim-sulfamethoxazole in 57%, tetracycline in 55%, aminoglycosides in 23%, cephalosporins in 20% and piperacillin-tazobactam in 1% (fig. 1).

FQ resistance was observed in 95 of the 416 first swabs (22.8%) of men in the AS cohort. Of the 54 men who showed resistance on the first swab and who had a second swab the rate was almost threefold higher (62.9%). The rate was fourfold higher (88.9%) in the 8 men in whom a third swab was done who showed resistance on the first 2 swabs. In contrast, FQ resistance was found in only 10.6% of the second swabs of the 179 men who showed sensitivity on the first swab and in 10.6% of the third swabs of the 47 who showed sensitivity on the first 2 swabs (fig. 2).

Factors Associated with FQ Resistance

FQ resistance on the first rectal swab of a patient was not significantly associated with age, race, PSA, prostate volume, hypertension, dyslipidemia or heart disease. There was no significant difference in the number of biopsies or the time between the most recent biopsy and rectal swab performance between men with FQ resistance and sensitivity (tables 1 and 2, and fig. 3).

The prevalence of diabetes in men with FQ resistance was significantly different from that in men without diabetes (14.7% vs 4.0%, chi-square test $p < 0.001$). Diabetes was significantly associated with FQ resistance on multivariate Poisson regression analysis adjusted for age, PSA, prostate volume, hypertension, hypercholesterolemia, heart disease, biopsy in the previous 6 months and number of biopsies before the swab (RR 2.60, 95% CI 1.37–4.93, $p = 0.003$, table 2).

DISCUSSION

In the last decade the hospital admission rate after TRUSB has been increasing due to infectious complications despite the AUA recommendation of FQ prophylaxis before the procedure.^{5,6} It was theorized that the increase in infectious complications is due to FQ resistant coliforms in the rectal carriage of men who undergo TRUSB.⁷ The infectious complication rate decreased when targeted antimicrobial prophylaxis based on rectal swabs to determine the resistance profiles of the rectal carriage was done before TRUSB.⁸

In past studies of the characteristics of men with FQ resistance the resistance rate was 10% to 22% and risk factors for resistance included recent FQ use, diabetes and heart valve replacement.^{6,8–10} It is unclear whether the number and timing of previous TRUSB procedures correlate with FQ resistance. To our knowledge no previous study has been done of resistance trends with time in individual patients.

In this series we found similar rates of resistance in an AS cohort and a comparison group (22.8% and 24.4%, respectively) undergoing diagnostic biopsy at the same hospital during the same period. Although the resistance rates were similar in the 2 groups, it is possible that

this may not translate into similar infection rates. Infection rates will be compared in further studies of the outcomes of rectal swabs. In terms of race there was a statistically significant difference in the proportion of men who were white in each group. This is consistent with a previous study showing the under representation of black men on AS.¹²

A diabetes history was significantly associated with FQ resistance in the current study, as in previous studies. However, the number of previous biopsies and time between the most recent biopsy and the swab were not significantly associated with resistance. This suggests that although most of the men received FQ prophylaxis, this alone did not appear to skew toward the development of resistance.

There were substantial rates of resistance to other common antibiotics in the men with FQ resistant rectal swabs. Notably 57% and 23% of these men were resistant to trimethoprim-sulfamethoxazole and aminoglycosides, respectively. These antibiotics are suggested as second line alternatives for prophylaxis. Thus, the significant rates of resistance to these alternative antibiotics in men with FQ resistance suggests that targeted prophylaxis rather than blindly using a second line agent may be a safer approach.⁴ Future studies should be done to analyze patterns of resistance to antimicrobials other than FQ because these agents will likely become increasingly important.

To our knowledge this is the first study to evaluate resistance trends longitudinally, that is in a small subset of patients during 6 months. Of the men with resistant first swabs 63% had resistant second swabs and of those with 2 resistant swabs 89% were resistant. Of the men with sensitive first swabs resistance had developed in 11% by the time of the second swab and of those with 2 sensitive swabs 11% had resistant third swabs. Changes in resistance profiles in a minority of men suggest that repeat rectal swabs may be needed to capture resistance profiles in those who undergo surveillance biopsies in an AS program.

Proper prophylaxis prevents infection but whether a man has infectious complications after TRUSB is complex. The rates of infectious complications are not as high as those of FQ resistance, which suggests that exposure to bacteria does not necessarily lead to infection. Most likely more pathogenic species or certain rectal micro-environments lead to infections and proper prophylaxis curbs such infections.

The strengths of this study include a large sample size, a significant subset of men who underwent followup swabs, longitudinal followup, a comparison group, and the similar biopsy protocol and microbiological assays performed during the study period. Limitations include the retrospective nature of the study, the lack of a complete medical history for all men, including an antibiotic administration history and hospitalizations 6 months before the swab. In addition, results may not be generalized to all men who undergo TRUSB, given that the study was performed at 1 center and mostly in white men.

CONCLUSIONS

One of 4 or 5 men who presented to an academic medical center for TRUSB had rectal flora resistant to FQ. This finding was significantly associated with diabetes but not with prior biopsy history. Most men with FQ resistant flora remained resistant with time. Rectal swabs

may have an important role in targeting prophylaxis if the FQ resistance rate continues to increase. As a followup study we plan to evaluate the rate of infectious complications in men on AS before and after beginning targeted prophylaxis.

Abbreviations and Acronyms

AS	active surveillance
AUA	American Urological Association
FQ	fluoroquinolone
JHH	Johns Hopkins Hospital
TRUSB	transrectal ultrasound guided prostate biopsy

References

1. Batura D, Rao GG, Nielson PB, et al. Prevalence of antimicrobial resistance in intestinal flora of patients undergoing prostatic biopsy: implications for prophylaxis and treatment infections after biopsy. *BJU Int.* 2010; 106:1017. [PubMed: 20346055]
2. Lange D, Zappavigna C, Hamidizadeh R, et al. Bacterial sepsis after prostate biopsy—a new perspective. *Urology.* 2009; 74:1200. [PubMed: 19815258]
3. Burden HP, Ranasinghe W, Persad R, et al. Antibiotics for transrectal ultrasonography-guided prostate biopsy: are we practising evidence-based medicine? *BJU Int.* 2008; 101:1202. [PubMed: 18336604]
4. Wolf, JS., Jr; Bennett, CJ.; Dmochowski, RR., et al. Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis. Linthicum: American Urological Association; 2007.
5. Nam RK, Saskin R, Lee Y, et al. Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. *J Urol.* 2010; 183:963. [PubMed: 20089283]
6. Loeb S, Carter HB, Berndt SI, et al. Complications after prostate biopsy: data from SEER-Medicare. *J Urol.* 2011; 186:1830. [PubMed: 21944136]
7. Liss MA, Chang A, Santos R, et al. Prevalence and significance of FQ resistant *Escherichia coli* in patients undergoing transrectal ultrasound guided prostate needle biopsy. *J Urol.* 2011; 185:1283. [PubMed: 21334021]
8. Duplessis CA, Bavaro M, Simmons MP, et al. Rectal cultures before trans-rectal ultrasound guided biopsies reduce post-prostatic biopsy infection rates. *Urology.* 2012; 79:556. [PubMed: 22386395]
9. Steensels D, Slabbaert K, De Wever L, et al. FQ-resistant *E. coli* in intestinal flora of patients undergoing transrectal ultrasound-guided prostate biopsy—should we reassess our practices for antibiotic prophylaxis? *Clin Microbiol Infect.* 2012; 18:575. [PubMed: 21958149]
10. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J Clin Oncol.* 2011; 29:2185. [PubMed: 21464416]
11. Taylor AK, Zembower TR, Nadler RB, et al. Targeted antimicrobial prophylaxis using rectal swab cultures in men undergoing transrectal ultrasound guided prostate biopsy is associated with reduced incidence of postoperative infectious complications and cost of care. *J Urol.* 2012; 187:1275. [PubMed: 22341272]
12. Sundi D, Ross AE, Humphreys EB, et al. African American men with very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy: should active surveillance still be an option for them? *J Clin Oncol.* 2013; 31:2991. [PubMed: 23775960]

Figure 1.
Percent of men with resistance to various antimicrobials among 105 with FQ resistance.
TMZ-SMX, trimethoprim-sulfamethoxazole. *Pip-Tazo*, piperacillin/tazobactam.

Figure 2.
Number of swabs and FQ resistance vs sensitivity

Figure 3.
Number of men with FQ resistant bacteria by number of prior biopsies.

Table 1

Univariate comparison of FQ resistance on first swab in AS cohort by demographic data and clinical findings before swab

	FQ Sensitive	FQ Resistant	p Value
Median age (IQR):			
At diagnosis	66.0 (62.7, 69.8)	66.0 (61.9, 68.5)	0.362
At 1st swab	70.5 (67.3, 74.5)	70.8 (66.8, 74.0)	0.745
% White	91.2	93.6	0.772
Median PSA (IQR)	4.5 (2.6, 7.1)	5.1 (3.3, 7.1)	0.277
Median prostate vol (IQR)	60.0 (43.0, 80.0)	62.0 (44.0, 78.0)	0.832
% Diabetes	4.0	14.7	<0.001
% Hypertension	42.9	50.6	0.223
% Hypercholesterolemia	47.0	49.4	0.701
% Heart disease *	13.8	9.6	0.324
Median mos most recent prostate biopsy-swab (IQR)	8 (6, 13)	10 (6, 17)	0.984
Prostate biopsy before rectal swab:			
% 12 Mos	0.70	0.68	0.804
% 6 Mos	0.33	0.35	0.691
Median No. (IQR)	3.5 (2, 6)	4.0 (3, 6)	0.106

* Previous diagnosis of congestive heart failure or coronary artery disease, or history of myocardial infarction.

Table 2

Multivariable Poisson regression analysis of FQ resistance on first swab in AS cohort by clinical findings before swab

	RR (95% CI)	p Value
Age:		
At diagnosis	1.05 (0.89–1.25)	0.535
At 1st rectal	0.98 (0.84–1.14)	0.754
PSA/1.0 ng/ml	1.05 (0.98–1.14)	0.132
Prostate vol/cc	0.99 (0.98–1.00)	0.084
Diabetes (yes vs no)	2.60 (1.37–4.93)	0.003
Hypertension (yes vs no)	1.10 (0.68–1.77)	0.701
Hypercholesterolemia (yes vs no)	0.93 (0.57–1.52)	0.787
Heart disease (yes vs no)*	0.73 (0.35–1.53)	0.405
Prostate biopsy before swab:		
In prior 6 mos (yes vs no)	1.19 (0.72–1.96)	0.481
No.	1.09 (0.91–1.33)	0.330

* Previous diagnosis of congestive heart failure or coronary artery disease, or history of myocardial infarction.