Antibiotic resistance in patients undergoing serial prostate biopsies: risk factors and impact on clinical outcomes

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Introduction: *We evaluate the rate of developing ciprofloxacin resistance in patients undergoing repeat prostate biopsies (PBx), associated risk factors, and impact on complications.*

Materials and methods: *We retrospectively evaluated pre-procedural rectal culture (RCx) data in men undergoing PBx from 1/1/2016 to 1/15/2021. Univariate and multivariate logistic regression were utilized to identify risk factors associated with development of antibiotic resistance. Complication rates were compared between ciprofloxacin-sensitive and ciprofloxacin-resistant patients.*

Results: *A total of 743 men underwent initial RCx. Initial RCx detected ciprofloxacin resistance in 22% of patients. A history of diabetes ($p = 0.01$), > 2 prior prostate biopsies ($p = 0.01$), and ciprofloxacin use ($p = 0.002$) were significant risk factors for ciprofloxacin resistance on initial RCx. The rate of new ciprofloxacin resistance following biopsy with standard ciprofloxacin prophylaxis on 1st and 2nd exposure was 17.2% and 9.1% respectively. The number of biopsy cores, interval antibiotic exposure and interval procedures performed between first and second RCx were not significant predictors of developing ciprofloxacin resistance. Patients who received a non-ciprofloxacin antibiotic between first and second RCx did not develop ciprofloxacin resistance. Antibiotic resistance profile did not significantly affect the rate or type of complications after various prostate procedures.*

Conclusions: *Serial exposure to standard antibiotic prophylaxis for PBx and associated procedures can lead to development of ciprofloxacin resistance after each subsequent exposure. This carries important implications for serial biopsy and highlights the role for RCx prior to repeat biopsy.*

Key Words: prostate biopsy, prostate cancer, antibiotics, resistance, surveillance

Introduction

Transrectal ultrasound guided prostate biopsy (TR-PBx) remains the mainstay method for diagnosing prostate cancer. More than one million TR-PBx are performed annually in the United States.[1] The UCSF Cancer of the Prostate Strategic Urologic Research Endeavor registry and several other contemporary population-based registries have documented a sharp increase in the uptake of active surveillance and localized treatment.[2] Therefore, localized treatment has evolved to include techniques such as partial gland ablation cryoablation and high intensity focused ultrasound (HIFU) ablation. As a result, the rate of biopsy procedures for follow up surveillance has increased commensurately.

Complications following TR-PBx have been well documented and include urinary tract infection

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(UTI), prostatitis, epididymoorchitis, bacteremia, and sepsis exacerbated in part by growing antibiotic resistance.[3] Multiple studies report infection rates following TR-PBx ranging from 0.1% to 7% along with emergency department presentations (0%-6%), hospitalizations (up to 4%), and severe sepsis (0%-1%).[4-8] The most common cause of infection is fluoroquinolone-resistant E. coli secondary to the translocation of GI flora to the urinary system.[9] FQ-based prophylaxis is recommended by the European Association of Urology and the American Urological Association due to their broad coverage and favorable prostatic drug penetration[10,11] and 90% of urologists report using empiric FQ prophylaxis.[12] The overall rate of FQ resistance in a 2014 meta-analysis was found to be 17.1% with a rate of 12.8% in studies which performed cultures prior to administration of antibiotic prophylaxis.[10] Given that antibiotic resistance has been classified by the CDC as a global threat,[3] pre-biopsy antibiotic selection presents a unique challenge in balancing post-procedure morbidity with responsible antibiotic stewardship.

This study examines risk factors contributing to initial FQ resistance and those that contribute to the development of resistance on subsequent cultures and attempts to correlate resistance status to post-procedural complication rates.

Materials and methods

IRB approval was obtained (NYU s022-00020) to retrospectively chart review patients undergoing primary RCx between 1/12016 and 1/15/2021 by a single surgeon. All men scheduled to undergo prostate biopsy were cultured. A small percentage of men were cultured but did not ultimately undergo any biopsy. Demographic data and the four medical co-morbidities which have been associated with post-prostate biopsy complications (diabetes, COPD, cardiac valve surgery, and BPH)[13] were also collected for each patient. Clinical data including information on antibiotic use prior to the first RCx, number of prior prostate biopsies, and history of allergy to antibiotics was collected. If present, subsequent RCx data out to five RCx was recorded for every included patient. Any procedures and/or antibiotic use between each subsequent RCx were also noted. Procedures included TR-PBx and transperineal prostate biopsy (TP-PBx), robotic radical prostatectomy/pelvic lymph node dissection, focal therapy (cryotherapy, HIFU), brachytherapy, fiducial marker placement, and rectal spacer placement.

Rectal culture

RCx were obtained on all men presenting for PBx. RCx results demonstrating FQ-resistance were assessed for sensitivity and antibiotic prophylaxis was adjusted accordingly. At our institution, RCx swabs are transferred within 2 hours to the laboratory in AMIES transport medium (Thermo Fisher Scientific ESwab, Waltham, MA, USA) and plated on MacConkey agar and MacConkey agar with ciprofloxacin (1 mg/L). After incubation at 37C for 24 hours, ciprofloxacin-resistant (CR) strains are identified with the Vitek 2 System (Biomerieux, Lyon, France), and the MIC for ciprofloxacin is determined either with the Vitek 2 System or Etest (Biomerieux, Lyon, France).

Prostate biopsy

Prostate biopsy was performed as previously described.[14] Men with negative RCx received a 3-day course of ciprofloxacin starting one day prior to biopsy. In men who reported allergy to fluoroquinolones, trimethoprim-sulfamethoxazole was administered instead. Intramuscular ceftriaxone (1 gm) was administered at the time of biopsy and intramuscular gentamicin was utilized in the setting of penicillin allergy. Culture-directed antibiotics (3-day regimen) were prescribed in the event of a rectal culture demonstrating resistance to ciprofloxacin. Patients were instructed to administer a rectal enema the night prior to the biopsy. Povidone-iodine disinfection and formalin needle disinfection are not part of our standard protocol.

Assessment of ciprofloxacin resistance and associated risk factors

The rate of CR on initial and repeat RCx was calculated and risk factors associated with development of CR were analyzed. A univariate logistic regression model was developed to determine factors associated with CR on initial RCx. Multivariable logistic regression model was then generated from significant factors on univariate analysis. Chi-squared tests were used to compare history of antibiotic use to the risk of demonstrating ciprofloxacin resistance on first culture.

The cohort of men who were pan-sensitive to antibiotics on first RCx and then subsequently underwent a second RCx were analyzed using the same statistical approach outlined above to determine factors associated with the development of CR. Interim use of antibiotics, interim record of prostate related procedures, and rates of post-procedural complications were included the univariate and subsequent multivariate analysis in determining risk factors for antibiotic resistance on repeat RCx. All analysis was performed w/ STATA Statistical Software (v10).

Results

Factors associated with initial resistance to ciprofloxacin

A total of 743 patients underwent initial RCx with demographic information shown in Table 1. The majority (79%) of patients underwent just one RCx during the duration of the study while 111 (15%) patients underwent two cultures, and 46 (6%) patients underwent more than two cultures. A total of 298 (40.1%) patients had undergone a prior prostate biopsy; of these patients, 188 (63.1%) patients had at least one positive biopsy (Grade Group 1 or greater). Most patients (85%) did not report an allergy to any prescription medications. The most common comorbidity in our cohort was BPH (27%) based on reported use of common alpha-blockers and 5-alpha reductase inhibitors and/or a diagnosis listed under past medical history upon chart review. A total of 205 (27%) patients reported use of antibiotics prior to first RCx with 86 patients (11.6%) reporting use within 6 months. One hundred twenty-four patients (16.7%) specifically reported ciprofloxacin use with 42 patients (5.7%) reporting ciprofloxacin use within 6 months of initial RCx.

Predictors of ciprofloxacin resistance on initial RCx are presented in Table 1. A history of diabetes (OR 1.83 [1.12-3.00], p = 0.01) and > 2 prior prostate biopsies (OR 3.81 [1.30-11.1], p = 0.01) were significant risk factors for CR on initial RCx. Additionally, ciprofloxacin use prior to initial RCx was a significant predictor of resistance (p = 0.002). The number of ciprofloxacin exposures appears to significantly increase the risk of ciprofloxacin resistance on first RCx (OR 1.23 [1.01-1.52], p = 0.047). However, the timing of ciprofloxacin use – specifically within 6 months of RCx, did not increase the risk of resistance (p = 0.17).

Factors associated with development of ciprofloxacin resistance on subsequent rectal cultures

A total of 111 patients underwent second RCx. Median time between 1st and 2nd RCx was 359 days. Table 2 illustrates factors associated the development of CR at second RCx. Twenty percent of patients received no interval antibiotics, 38% received 1-2 antibiotics, and 42% received three or more antibiotics. These included antibiotics as part of the standard TR-PBx protocol as well as those related to other procedures and isolated infections. Regarding prostate-related procedures, the 111 patients underwent a total of 136 procedures. Twenty-six percent underwent no interval procedure, 41% underwent 1 interval procedure, and 32% underwent two or more procedures. Specifically, 55% underwent TR-PBx, 28% underwent focal cryoablation, 15% underwent TP-PBx, and 2% underwent HIFU. The median number of biopsy cores was 16. None of these characteristics were significant contributors to the development of CR at 2nd RCx. Of patients who were sensitive to ciprofloxacin on initial RCx who developed CR on 2nd RCx, none underwent a transabdominal procedure such as prostatectomy.

Figure 1 demonstrates the rate of CR over time in our cohort of 743 patients. Initially, 167 patients (22%) were found to be CR. Of the 576 patients initially sensitive to ciprofloxacin, 356 subsequently received ciprofloxacin, and 81 underwent a second RCx. Of these patients, 14 (17%) developed CR of which 4 had concurrent ceftriaxone resistance. All 4 patients were resistant to ceftriaxone at initial RCx. No patients who received a non-ciprofloxacin antibiotic between 1st and 2nd RCx and underwent 2nd RCx developed CR. Of the 81 patients described above, 67 remained sensitive to ciprofloxacin and 35 received a second dose of ciprofloxacin between 2nd and 3rd RCx. Eleven patients underwent 3rd RCx and just one patient (9%) developed CR.

Rates of complications for procedures performed after 1st and 2nd rectal cultures

Table 3 depicts the complication rates for patients undergoing TR-PBx (performed after 1st RCx) and after the second set of procedures (performed after 2nd RCx). A total of 429 TR-PBx were performed after initial RCx. Three hundred forty one were performed on ciprofloxacin-sensitive patients and 88 procedures performed on ciprofloxacin-resistant patients. Twelve complications were reported for an overall complication rate of 2.8%. The rate of urinary retention was 1.4% (n = 6), bleeding (as defined by visit to emergency department with chief complaint of hematuria) 0.7% (n = 3). Infectious complications (defined by a positive urine culture and/or fever) were reported at a rate of 0.5% (n = 2). The overall rate of complications in ciprofloxacin-sensitive patients was 2.3%, n = 8 (0% infectious) while the overall complication rate in ciprofloxacin-resistant patients was 4.5%, n = 4 (2.3% infectious).

After 2nd rectal culture, a total of 90 TR-PBx were performed. Sixty-four procedures were performed on ciprofloxacin sensitive patients and 26 procedures performed on ciprofloxacin resistant patients. A total of 2 complications were reported for an overall complication rate of 2.2%. One episode each of urinary retention and significant hematuria were reported (1.1% each). Both events occurred in ciprofloxacin-sensitive patients.

TABLE 1. **Cohort characteristics and risk factors for developing antibiotic resistance**

Cohort characteristics	**N (%)**	**Odds ratio (95% CI)**	**p value**
Number of patients	743		
Age (median [IQR])	65 [60-71]	1.00 (0.98-1.01)	0.50
BMI (median [IQR])	27 [24-29]	1.00 (0.95-1.03)	0.80
Total number of rectal cultures		n/a	n/a
1 culture	586 (79%)		
2 cultures	109 (15%)		
3 cultures	36 (5%)		
4+ cultures	12 (1%)		
Antibiotic allergy		1.13 (0.66-1.81)	0.70
NKDA	631 (85%)		
Penicillin	71 (10%)		
Fluroquinolone	22 (3%)		
Aminoglycoside	13 (2%)		
Other	18 (2%)		
Race		1.15 (0.79-1.66)	0.47
White	487 (66%)		
Black	29 (4%)		
Asian	120 (16%)		
Other	107 (14%)		
Co-morbidities			
None	452 (61%)	Ref	Ref
DM	106 (14%)	1.83 (1.12-3.00)	0.01*
COPD	16 (2%)	0.24 (0.03-1.87)	0.20
History of cardiac valve surgery	15 (2%)	1.04 (0.28-3.81)	0.90
BPH	204 (27%)	0.78 (0.51-1.17)	0.20
History of prior Bx			
0	457 (62%)	Ref	Ref
1	226 (30%)	1.40 (0.94-2.04)	0.10
2	45 (6%)	1.44 (0.65-2.81)	0.42
> 2	15 (2%)	3.81 (1.30-11.10)	0.01*
History of prior antibiotic use			0.25
Yes	205 (27.5%)		
No	538 (72.4%)		
History of prior ciprofloxacin use			0.002*
Yes	124 (16.7%)		
No	619 (83.3%)		
History of prior antibiotic use within 6 months			0.20
Yes	86 (11.6%)		
No	657 (88.4%)		
History of prior ciprofloxacin use within 6 months			0.17
Yes	42 (5.7%)		
No	701 (94.3%)		
Doses of Cipro	Median: 0.3 (0.23-0.34)	1.23 (1.01-1.52)	0.047*

BMI = body mass index; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; BPH = benign prostatic hyperplasia. Baseline demographics of patients who underwent initial rectal culture and associated odds ratios for demonstrating ciprofloxacin resistance on initial culture. Univariate analysis was first performed and significant characteristics were then analyzed using multivariate analysis. (*) indicates statistically significant ($p < 0.05$) characteristics

TABLE 2. **Cohort characteristics and risk factors for developing antibiotic resistance on 2nd rectal culture**

Cohort characteristic	N (%)	Odds ratio	p value
Number of patients	111		
Interval antibiotic use		0.53 (0.21-1.3)	0.17
No interval antibiotic use	22 (20%)		
1-2 interval antibiotics	42 (38%)		
3+ interval antibiotics	47 (42%)		
Interval Intervention		0.57 (0.24-1.39)	0.2
No interval intervention	29 (26%)		
1 interval intervention	46 (41%)		
2+ interventions	36 (32%)		
Number of biopsy cores (median [IQR])	16 (0-17.5)	0.99 (0.94-1.003)	0.65
Procedure type			
Total procedures	136		
Transrectal prostate biopsy	75 (55%)		
Focal cryoablation	38 (28%)		
Transperineal prostate biopsy	20 (15%)		
HIFU	3 (2%)		

Cohort characteristics for patients who underwent both initial and 2nd rectal culture. Interval interventions including antibiotic exposure and procedures were analyzed for possible contribution to increasing the odds ratio of developing resistance between the two cultures. Univariate analysis was first performed, though given the lack of significance, no multivariate analysis was attempted.

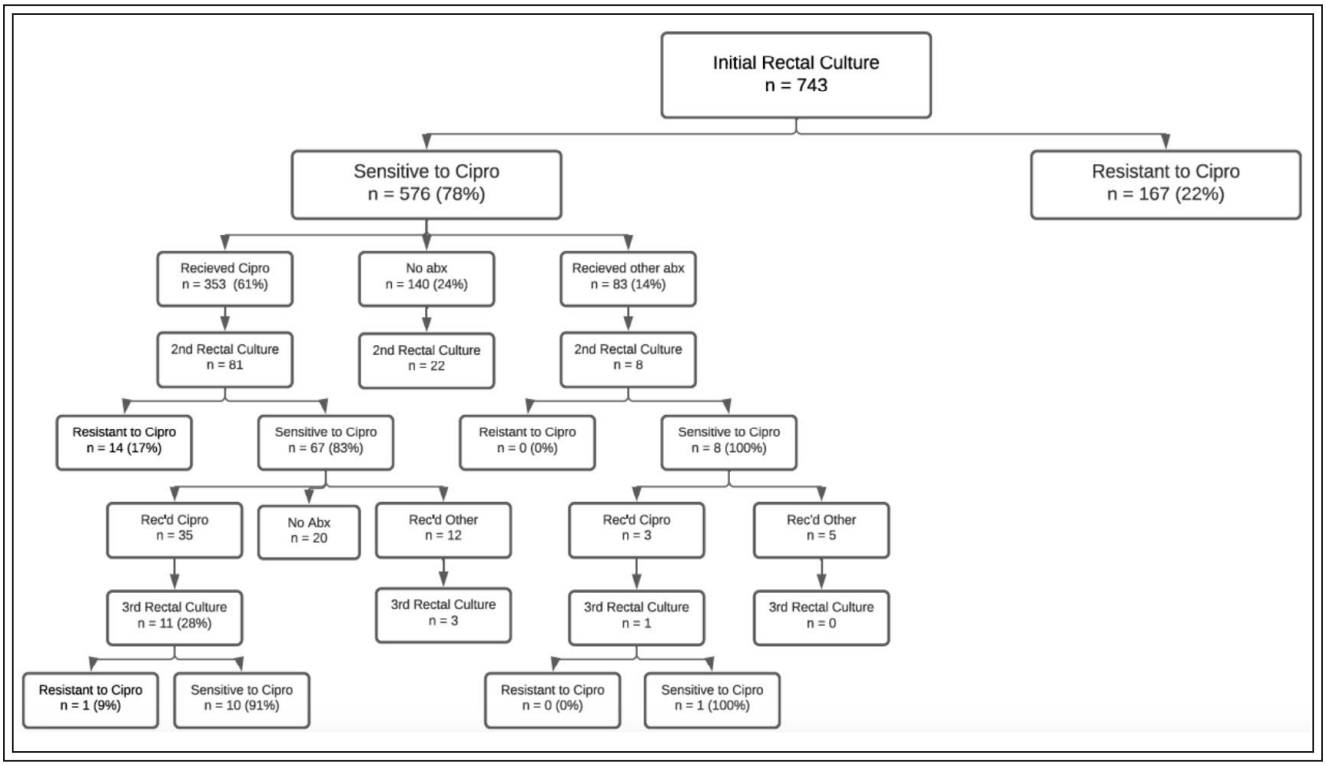

Figure 1. Rate of developing ciprofloxacin resistance in our cohort through three series of rectal cultures with associated interval antibiotic use.

TABLE 3. **Complication rates after TR-PBx**

	Number of procedures	Infection	Bleeding	Retention	Other	Overall
Between 1st and 2nd rectal culture						
Ciprofloxacin sensitive patients	341	0	3 (0.9%)	4 (0.9%)	1 (0.3%)	8 (2.3%)
Ciprofloxacin resistant patients	88	2 (2.3%)	0	2 (2.4%)	0	4 (4.5%)
Total	429	2 (0.5%)	3 (0.7%)	6 (1.4%)	1 (0.2%)	12 (2.8%)
Between 2nd and 3rd rectal culture						
Ciprofloxacin sensitive patients	64	0	1 (1.5%)	1 (1.5%)	0	2 (3.5%)
Ciprofloxacin resistant patients	26	0	0	0	0	0
Total	90	0	1 (1.1%)	1 (1.1%)	0	2 (2.2%)

Complications rates after 1st and 2nd TR-PBx performed after 1st and 2nd series of rectal cultures, respectively. Results are stratified by resistance status and type of complication as determined by chart review. TR-PBx = transrectal prostate biopsy.

Discussion

The incidence of prostate cancer in 2021 was reported to be nearly 250,000 in the United States resulting in 34,000 deaths by the American Cancer Society. More than 1 million PBx are performed each year in the United States and Europe.[1] Despite growing adoption of TP-PBx, TR-PBx remains the primary method for diagnosing prostate cancer. Growing antibiotic resistance, demonstrated to occur largely in parallel with increased antibiotic use, has been classified by the CDC as a global threat.[3] With increasing use of active surveillance[2] and developing interest in partial gland ablation pathways, prostate cancer management increasingly requires the use invasive diagnostic procedures. Repeat peri-procedural prophylaxis contributes to the documented rise in ciprofloxacin resistance from 15% in 2013 to 45% in 2016.[15] This study provides further insight into the rate of rise for men undergoing serially exposure to ciprofloxacin.

The reported rate of FQ resistance in North America ranges between 12.7 to 25% with a mean of 19%.[16] This is consistent with the rate of FQ resistance of 22% in the current study. In addition, multiple studies have reported risk factors for FQ resistance and have identified history of previous prostate biopsy, diabetes, chronic prostatitis, recent UTI, recent positive urine culture, older age, higher PSA density, and heart valve replacement as possible contributors.[16-18] This study highlights the increased risk of antibiotic resistance as demonstrated by RCx results in patients with a history of diabetes, > 2 prior prostate biopsies, and fluoroquinolone exposure. This finding has also been demonstrated by Liss and colleagues.[18] We do concede that the number of patients with a history of > 2 prostate biopsies was low at just 15 and the confidence interval was wide. In addition, the history of ciprofloxacin exposure was dose-dependent and not time-dependent. These findings suggest that RCx data should be obtained on men with these clinical characteristics and selection of either an alternative antibiotic prophylaxis or consideration of a transperineal approach for men for whom RCx is unable to be performed.

Furthermore, this study measured the rate of new resistance following FQ exposure associated with PBx, defining the rate of "FQ burn." The burn rate following a single exposure was approximately 17%, or approximately 1 in 6 men. The burn rate decreased to 9% after a 2nd FQ exposure, indicating that FQ prophylaxis may remain effective in men undergoing serial biopsies but confirming continued sensitivity requires pre-procedural RCx. Cohen et al reported a 10.6% rate of developing resistance to fluoroquinolones in patients who were sensitive at initial RCx and a 10.6% rate of developing resistance from second to third RCx.[19] Interestingly, the interval use of antibiotics and number of interval procedures or biopsy cores did not correlate with increased of FQ resistance. Pradere et al similarly found no difference in infectious complications/hospitalizations for the number of biopsy cores taken[20] and Steensels et al examined 342 patients undergoing PBx with RCx and reported that repeat biopsy was not a risk factor for FQ resistance though the use of FQ < 6 months before biopsy did appear to be a factor.[21]

After initial RCx, the overall complication rate in patients undergoing TR-PBx was 9.3%, with 3.2% infectious in nature which is comparable to widely quoted rates of complication after transrectal procedures.[1] We also found that there was a slightly increased rate of infectious complications in patients

who were resistant to ciprofloxacin. The data is mixed regarding the importance of targeted antibacterial prophylaxis. While Jiang et al found no significant different in sepsis rates after transrectal prostate biopsy in patients receiving targeted therapy versus empiric therapy,[22] other reports have demonstrated high infection and sepsis rates in patients who demonstrate fluoroquinolone resistance likely due to lack of culture-directed prophylactic antibiotic therapy.[23,24] However, in our cohort every patient regardless of resistance profile received targeted antimicrobial prophylaxis. Thus, our results underscore that the use of culture-directed antibiotics is effective in lowering the infection rate of FQ-resistant patients to match or even best that of FQ-sensitive patients.

Our data demonstrates a very low development of resistance to antibiotics such as ceftriaxone despite routinely administering a single dose of intramuscular ceftriaxone to patients immediately prior to biopsy, a practice which has been shown to lower post-procedural hospitalization rates compared to use of ciprofloxacin alone.[25] Given that duration of prophylaxis has not been standardized and no data supports prolonged use of antibiotics,[26-28] it is possible that shortening the duration of fluoroquinolone use prior to biopsy may lead to decreased development of resistance.

Another strategy is to broaden antibiotic prophylaxis with agents such as ceftriaxone or gentamicin. In the long term, this strategy risks facilitating the development of multi-drug resistant organisms. Ultimately, as rates of antibiotic resistance continue to rise, an increasing role for directed prophylaxis will likely be needed as demonstrated by Glick et al who found that culture-directed prophylaxis significantly lowered rates of infection compared to "provider discretion" and "augmented" (empiric prophylaxis plus 2nd agent from antibiogram) protocols,[29] corroborating findings by Jiang et al.[22]

A third possible solution is the increased utilization of TP-PBx which has been demonstrated to lead to decreased infectious complications[20] with some studies suggesting that no prophylaxis is necessary for the transperineal approach.[30] Though conflicting data demonstrating a lack of difference in the rate of infectious complications and increased episodes of urinary retention associated with TP-PBx have served as barriers to widespread adoption of this technique.[31]

The limitations of this study stem from the retrospective nature of the evaluation and arguably a prospective comparison controlling for risk factors and antibiotic exposure would serve to strengthen the results. Given that several factors have been identified in multiple studies, a prospective study examining RCx specifically for high-risk patients compared to empiric antibiotics for low-risk patients is warranted. Furthermore, we did not perform sequencing to determine the lineage of the resistant cultures. We also did not follow up on FQ-related morbidity, an increasingly important metric when discussing antibiotic stewardship.

Conclusions

Transrectal prostate biopsy remains a critical tool in the prostate cancer diagnostic and surveillance pathway and minimizing infectious complications associated with this procedure is a critical goal for urologists. This study supports the selective use of pre-biopsy rectal culture in men with risk factors for fluroquinolone resistance, and further highlights the need to assess for increasing rates of resistance in men undergoing repeat procedures. Utilization of culture-directed prophylaxis along with employment of transperineal prostate biopsy techniques allow urologists to provide improved safety for men requiring repeat and routine prostate tissue sampling and prevent the development of multi-drug resistant organisms. □

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