Antibiotic prophylaxis for transrectal ultrasound-guided prostate needle biopsy: Compared efficacy of ciprofloxacin vs. the ciprofloxacin/fosfomycin tromethamine combination

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Abstract

Introduction: Some authors advocate an increase in post-prostate needle biopsy (PNB) infections associated with emergent quinolone resistance in *E. coli*, urging re-evaluation of antibiotic prophylaxis (antibioprophylaxis). In this study, we compared rates of post-PNB urosepsis associated with two oral regimens of antibioprophylaxis: ciprofloxacin (CIP) vs. ciprofloxacin and fosfomycin tromethamine combination (CIP/FOS).

Methods: This retrospective pre-/post-intervention study included all patients who underwent PNB in two Canadian hospitals from January 2012 to December 2015. The primary outcome was urosepsis within one month of PNB. Urosepsis rates were analyzed according to antibioprophylaxis using log-binomial regression, considering the propensity score weights of collected risk factor data.

Results: We reviewed 2287 PNB patients. A total of 1090 received CIP and 1197 received CIP/FOS. Urosepsis incidence with CIP was 1.1% (12/1090) and fell to 0.2% (2/1197) with CIP/FOS. Our analysis indicates that CIP/FOS significantly decreased the risk of urosepsis compared to CIP alone (adjusted relative risk [aRR] 0.16; p=0.021). The isolated pathogen was *E. coli* in 12/14 cases, including seven bacteremias. Among *E. coli* cases, seven strains were CIP-resistant. Eleven of 12 *E. coli,* including all CIP-resistant strains, were isolated in patients on CIP alone. One case of *B. fragilis* bacteremia occurred in the CIP/FOS group. No cases of *C. difficile* were identified in the three months post-PNB.

Conclusions: The adoption of CIP/FOS antibiotic prophylaxis significantly lowered the rate of post-PNB urosepsis. Conveniently, this regimen is oral, single-dose, and low-cost.

Introduction

Transrectal ultrasound-guided prostate needle biopsy (PNB) is a useful procedure for prostate cancer diagnosis and pathological staging.[1] Its main complications are macrohematuria, rectal bleeding, urinary retention, erectile dysfunction, needle tract seeding, and hematospermia. Infectious complications include cystitis, epididymitis, orchitis, prostatitis, and urosepsis.[1,2]

Although PNB is generally considered a safe procedure, infectious complication rates range from 0.1–7% and up to 3.1% of patients were noted to develop urosepsis.[2,3] The American Urological Association guidelines, therefore, recommend the use of antibiotic prophylaxis, more specifically fluoroquinolones (FQs) or first-, second-, or third-generation cephalosporins as first-line antibiotic prophylaxis (antibioprophylaxis), at least one hour prior to the procedure.[2]

Recent studies report rising rates of post-PNB infections associated with emergent FQ-resistant *E. coli* and extended-spectrum β-lactamase producing *E. coli* (ESBL), raising concerns about efficacy of these antibioprophylaxis regimens.[2,4-6] On the other hand, various mitigating strategies are suggested in the literature: rectal swab screening with directed antibioprophylaxis,[7,8] switching antibioprophylaxis,[7,9-11] and transperineal biopsy approach.[2,7]

Recently, some authors pointed out fosfomycin tromethamine (FOS) as being an attractive alternative because of its adequate levels in prostatic tissue obtained with a single 3 g oral dose, the low level of bacterial resistance, its broad spectrum of activity (including multidrug-resistant organisms), and its good safety profile.[10-12]

A series of post-PNB infections and the abovementioned FOS characteristics prompted us to modify our antibioprophylaxis regimen. The objective of our study was to compare rates of post-PNB urosepsis associated with two oral regimens of antibioprophylaxis: ciprofloxacin (CIP) vs. ciprofloxacin and fosfomycin tromethamine combination (CIP/FOS).

Methods

Study design and population

We conducted a retrospective, pre-/post-intervention study in two university-affiliated Canadian hospitals. In December 2013, CIP antibioprophylaxis was augmented to CIP/FOS combination. This antibioprophylaxis has, since then, become the new standard of care in our centers. Approval from our institutional ethical review board was obtained for this study (2016–2017/04-01-A C112).

The population was composed of all patients who underwent a PNB from January 2012 to December 2015 in these two centers and an affiliated outpatient clinic. Patients who did not receive either CIP or CIP/FOS combination for antibioprophylaxis prior to the biopsy were excluded. Group 1 was composed of patients who received oral CIP 500 mg two hours prior to the PNB, along with a sodium phosphate enema (January 2012 to November 2013). Group 2 was composed of patients who received oral CIP 500 mg and oral FOS tromethamine 3 g two hours prior to the PNB, along with a sodium phosphate enema (December 2013 to December 2015).

Biopsy procedure

PNBs were performed either in an outpatient urology clinic or in the endoscopy suite at the hospital by one of the nine certified Canadian urologists on our team. Patients were instructed to self-administer antibioprophylaxis and sodium phosphate enema two hours prior the procedure. Before the biopsy, urologists systematically verified if patients had taken their antibioprophylaxis and if they had specific infection symptoms (i.e., fever, chills, or lower urinary tract symptoms, such as urgency, frequency, dysuria, or suprapubic tenderness). If patients were symptomatic or did not follow protocol, PNB was postponed.

Before the procedure, transrectal periprostatic local anesthetic (lidocaine) was administered. With patients on the left-lying position, we performed transrectal ultrasound-guided prostate biopsy with a 10–12-core strategy using a Pro-Mag™ Ultra Automatic Biopsy Instrument with a disposable 18-gauge × 20–25 cm biopsy Argon Pro-Mag needle. All patients were instructed to seek medical attention at our two hospitals if they developed symptoms related to biopsy complication (i.e., severe bleeding, urinary retention, fever, chills, or lower urinary tract symptoms).

Data collection

Electronic medical records of all patients were reviewed for demographic, clinical, and microbiological data. Clinical information included emergency consultations, hospital admissions and risk factors for post-PNB infection distributed into comorbidities, infectious, and urological risk factors.[3,4,7,10,13] Microbiological data included available midstream-voided urine and blood cultures, as well as the pathogens and antibiotic susceptibility testing, as reported by clinical microbiological laboratories. Urine or blood cultures were only performed for symptomatic patients who presented at the emergency ward. We also evaluated development of *C. difficile* colitis up to three months post-PNB.

The main outcome was urosepsis defined by urinary tract infection (UTI) with bacteremia or as UTI with systemic inflammatory response syndrome (SIRS)[14] within one month of PNB. The clinical impacts of infectious complications were also documented and included 30-day mortality, vasopressor requirement, length of hospitalization, and length of stay at the intensive care unit (ICU).

Non-infectious complications were similarly documented and were graded according to the severity. Grade 1 included macrohematuria, hematospermia, and dysuria and grade 2 included acute urinary retention, significant rectal bleeding, and prostatic hematoma.[10]

Statistical analysis

To assess the risk factors' statistical significance, t-test, Mann-Whitney test, Fisher's exact test, or chi-squared test were used, as appropriate. For urosepsis incidence in the CIP and CIP/FOS groups, Wilson's 95% confidence intervals were used.

To account for baseline differences between the cohorts, inverse probability of treatment weighting adjusted analyses were performed. The propensity score was estimated using a logistic regression model. The comparison of infection rates between the two cohorts was made using log-binomial regression considering the propensity score weights, with $p<0.05$ marking statistical significance.

Results

A total of 2304 patients were assessed for eligibility. We excluded 17 patients from the study for incomplete demographic data: 11 in the CIP group, six in the CIP/FOS group. The CIP group was left with 1090 patients and the CIP/FOS group with 1197 patients. No infectious complications were found among the excluded patients upon chart review.

All patient clinical and laboratory characteristics at the time of the biopsy are found in Table 1. There were significant differences between the two study periods. More patients underwent cystoscopies in the month prior to PNB and repeat biopsies in the first group, while higher prostatic-specific antigen levels and more aggressive prostate cancer histological findings were observed in the second group.

Table 1. Characteristics of patients at the time of prostate needle biopsy and histological findings post-prostate needle biopsy

Risk factors	Ciprofloxacin (%) n=1090	Ciprofloxacin and fosfomycin (%) n=1197	p
Age, yr, average ± SD	65.2±7.7	65.0±7.5	0.6
Infection risk factors			
Urinary tract infections in the last 6 months	4 (0.4)	12 (1.0)	0.08
Extended-spectrum beta lactamase stool sample in the last 6 months	–	1 (0.1)	–
C. difficile stool sample in the last 6 months	–	–	–
Hospitalized in the previous month	19 (1.7)	18 (1.5)	0.7
Comorbidities			
Diabetes	132 (12.1)	142 (11.7)	0.9
Chronic obstructive pulmonary disease	23 (2.1)	35 (2.9)	0.2
Heart valve	8 (0.7)	4 (0.3)	0.2
Coronary artery disease	86 (7.9)	79 (6.6)	0.2
Urological risk factors			
Cystoscopy in the last month	47 (4.3)	31 (2.6)	0.02
Urinary catheter in the last month	6 (0.6)	5 (0.4)	0.6
Benign prostatic hyperplasia	448 (41.1)	500 (41.8)	0.7
Prostatic-specific antigen level, mg/ml (Q1;Q2;Q3)[a]	4.4; 5.7; 7.8	4.7; 6.0; 8.2	0.001
Repeat biopsy	403 (37.0)	374 (31.2)	0.004
Prostate cancer histological finding	626 (57.4)	773 (64.6)	<0.001

Data in parenthesis are percentages unless otherwise specified. [a]Quartiles were used because prostate-specific antigen data did not follow a standard deviation. SD: standard deviation; Q1;Q2;Q3: quartile 1, 2, and 3.

There was also a difference in the local antibiogram for CIP-susceptible *E. coli* rates between the two cohorts: it dropped from 86.8% to 85.1%.

In the month following PNB, 14 urosepsis cases were identified in the entire study population. The median hospital stay was two days (interquartile range [IQR] 1–3.25). One patient was sent to the ICU, none required the use of vasopressors, and there was no mortality within 30 days of PNB. A total of 13 patients received intravenous antibiotics during their hospitalization. The median time between biopsy and emergency consultation was one day (range 0–24).

Overall incidence was 1.1 urosepsis per 100 biopsies (95% confidence interval [CI] 0.63– 1.91%) in the CIP group (12/1090 patients). Of these cases, seven had bacteremia. *E. coli* was the only pathogen. All the FQ-resistant and ESBL *E. coli* strains were found in this group. In the CIP/FOS group, two urosepsis events were identified (2/1197), leading to an incidence of 0.2% (95% CI 0.05–0.61%). There was one case of *E. coli* urosepsis and one case with *Bacteroides fragilis* bacteremia. Detailed microbiological characteristics of cases are found in Table 2.

In the multivariate analysis, the urosepsis incidence rate was significantly lower in the CIP/FOS combination antibioprophylaxis group, giving an adjusted relative risk (aRR) of 0.16 (95% CI 0.03–0.76; p=0.02).

Other complications

One case of prostatitis, not meeting urosepsis criteria, with no identified pathogen was also found in the CIP group. This patient was excluded from analysis.

In patients who consulted at the hospital after PNB, there were a total of 4/1090 (0.4%) grade 1 and 10/1090 (0.9%) grade 2 post-PNB non-infectious complications among the CIP group. As for the CIP/FOS group, there were 1/1197 (0.1%) grade 1 and 3/1197 (0.3%) grade 2 non-infectious complications. All reported post-procedural non-infectious complications are displayed in Table 3.

No cases of *C. difficile* infection were identified in either group in the three months post-administration of antibioprophylaxis.

Discussion

Our study demonstrates that a CIP/FOS combination was associated with an 84% decrease in the incidence of urosepsis when compared to a CIP regimen. This reduction was statistically significant despite a low baseline incidence rate of post-PNB urosepsis and an increase in *E. coli* resistance in our centers throughout the study period.

Table 2. Microbiological characteristics of urosepsis patient during hospitalization

Group	Ciprofloxacin (%)	Ciprofloxacin and fosfomycin (%)	p
Urosepsis	12 (1.1)	2 (0.2)	0.02
Bacteremia	7 (0.6)	1 (0.1)	0.07
Escherichia coli	7	0	
Fluoroquinolone-resistant *E. coli*	5	0	
ESBL *E. coli*	2	0	
Bacteroïdes fragilis	0	1	
Bacteriuria	11 (1.0)	1 (0.1)	
Escherichia coli	11	1	
Fluoroquinolone-resistant *E. coli*	7	0	
ESBL *E. coli*	2	0	

Data in parentheses are percentages unless otherwise specified. ESBL: extended-spectrum beta-lactamase.

Table 3. Non-infectious complications after prostate biopsy

Group	Ciprofloxacin (%)	Ciprofloxacin and fosfomycin (%)
Grade 1	4 (0.4)	1 (0.1)
Macrohematuria	3	1
Dysuria	1	–
Hematospermia	–	–
Grade 2	10 (0.9)	3 (0.3)
Acute urinary retention	5	2
Rectal bleeding	4	1
Prostatic hematoma	1	–

Data in parenthesis are percentages unless otherwise specified.

In recent years, FQ antibioprophylaxis regimen has been used to cover most relevant urological pathogens.[15] However, many studies report increased post-PNB infections associated with increasing rates of FQ-resistant E. coli.[2,4-6] Considering there is an estimate of >1 million PNB annually in the U.S.[16] and that urosepsis can lead to hospitalization and serious health hazards,[2] antibioprophylaxis regimens need to be re-assessed.

We observed an increase in CIP-resistant E. coli at our institutions, as well as an increase in post-PNB infections, especially in 2013. This prompted us to change our antibioprophylaxis regimen to a CIP/FOS combination. At the time, there were no published studies on the use of FOS alone. We, therefore, elected to use CIP for its excellent enterobacteriæ coverage[15] and to add FOS to cover the CIP-resistant strains.

There were no cases of CIP-resistant or ESBL E. coli urosepsis in the CIP/FOS group, suggesting that FOS covered these multidrug-resistant pathogens. The wider spectrum of antimicrobial coverage afforded by this regimen could have led to increased post-PNB C. difficile cases, but none were identified in the three months post-procedure. The negligible influence of FOS on the microbiome when compared to other broad-spectrum antimicrobial agents and the lower propensity for significant microbiome disruption with single-dose regimens could explain this finding.[11]

Theoretically, the use of FOS alone, considering its pharmacokinetic characteristics and its broad spectrum, is a rational option for standalone antibioprophylaxis.[11] Even more so, many reports indicate low reported resistance rates to relevant pathogens.[12,17] According to a CANWARD surveillance prospective study on FOS susceptibility rates conducted from 2010–2013, 99.4% of 868 urinary E. coli isolates were susceptible to FOS.[18]

We have identified two European studies[10,19] published after our regimen choice that suggest standalone FOS as a viable option for antibioprophylaxis. There was also a meta-analysis by Roberts et al (n=3112) that demonstrated a significant reduction in post-PNB grade 2 infections (bacteremia, febrile UTI, urosepsis) with FOS (adjusted odds ratio [aOR] 0.13; 95% CI 0.07–0.26).[11] Their results reassuringly correlate with our own and even question the relevance of maintaining CIP in the CIP/FOS combination.

However, in one large, Canadian study (n=9527), use of single-dose FOS for antibioprophylaxis resulted in an increased risk of infectious complications compared to CIP alone (aOR 1.80; 95% CI 1.10–2.94; p=0.02). This increased risk was not corrected by adding a second dose of FOS 12 hours post-PNB (aOR 1.43; 95% CI 0.66–3.09; p=0.36).[20] A Klebsiella spp. breakthrough, most likely justified by the poor FOS coverage for this pathogen,[12] could explain this increased risk.

Before choosing the CIP/FOS combination as antibioprophylaxis for PNB in our centers, other mitigating strategies have also been contemplated. As advocated by some authors, we considered using rectal swab screening to direct antibioprophylaxis prior to PNB;[7,8] however, this strategy has mixed results in the literature. Some authors point out no difference in post-PNB infectious complications with targeted antibioprophylaxis,[21-25] along with an increased burden for clinical microbiology laboratories and urologists.[4] Also, it has been demonstrated that in a single individual, many clones of the same organism (i.e., E. coli) can subsist at the same time.[26,27] Antibioprophylaxis is, therefore, most often targeted only towards CIP-resistant clones and could neglect the resistance patterns of other clones.

Another approach would be to use intravenous or intramuscular antibiotics, such as gentamicin or amikacin.[2,4,9,12] According to one large study conducted by Jiang et al (n=15 236), augmented antibiotic prophylaxis composed of CIP and intramuscular gentamicin or intramuscular amikacin significantly reduced the rate of post-PNB urosepsis when compared to standalone CIP or targeted antibiotic prophylaxis (OR 0.35; 95% CI 0.16–0.76; p=0.008).[21] Many antibiotic prophylaxis regimens, such as this one, have demonstrated that they can diminish post-PNB infections and can add protection for CIP-resistant E. coli.[2,9,10] Unfortunately, these are administered either intramuscularly or intravenously, which is associated with an increased cost and logistical burden.

A transperineal approach for PNB has also been shown to diminish infectious complications and rectal bleeding, but it has a similar post-procedural hospitalization rate due to increased acute urinary retention.[3,7,28] Moreover, widespread adoption of transperineal approach was thought to be nearly impossible and too expensive, as it requires hospitalization and general anesthesia for all patients. However, some authors have recently advocated in-office transperineal prostate biopsy under local anesthesia without antibioprophylaxis. This approach was demonstrated to be safe, effective, and well-tolerated by patients, despite some concern over post-procedural urinary retention.[29,30] This alternative should be strongly considered, as it would nearly eliminate the need for antibioprophylaxis, therefore, supporting antimicrobial stewardship.

Until in-office, antibioprophylaxis-free transperineal prostate biopsies are widely accepted, it is our view that antibiotic prophylaxis regimens with low baseline resistance in target pathogens are preferable. Thus, FOS represents an excellent antibiotic alternative, which can be administered orally. The use of CIP/FOS combination antibioprophylaxis represents a valid and practical alternative to the abovementioned strategies.

Strengths and limitations

Our large study group enabled us to demonstrate statistically significant differences in urosepsis between the two regimens, despite its low incidence rate. The measured effect of an adjusted risk reduction of 0.16 is clinically significant but the small number of urosepsis cases leaves us with a relatively wide confidence interval (95% CI 0.03–0.76). The true effect may not be as notable as the measured effect but is at the worst end of our CI, compatible with a 24.4% decrease in post-PNB urosepsis rates, which we consider clinically meaningful.

This study has several limitations. First, this non-randomized and retrospective study has an inherent possibility of bias. Secondly, there were more cystoscopies in the month preceding the biopsy in the CIP group, which is a post-PNB infection risk factor that could influence the incidence rate of urosepsis. However, this statistical difference was taken into account in the multivariate analysis. Finally, even if patients were told to seek medical attention at both our institutions if specific symptoms occurred, it remains possible that patients consulted elsewhere (i.e., family physician, other hospitals) or did not seek medical care for minor complications. Our dataset may underestimate the true frequency of the total post-PNB complications, particularly uncomplicated UTI. However, we have no reason to believe that rates of consultations to other centers would change during our study period.

Conclusions

Our results show that the antibiotic prophylaxis combination of CIP and FOS tromethamine significantly lowered urosepsis rates following PNB. Benefits of this combination include single dose, low cost, and dodging the logistical burden of rectal swab screening and/or those associated with intravenous antibiotic prophylaxis administration. Further studies are needed to validate our findings and to evaluate the differences in the incidence of non-urosepsis complications.

Competing interests: Dr. Bergevin has been an advisory board member for AVIR, Merck, Pendopharm, and Verity; and has been a speaker for and received honoraria from AVIR, Janssen-Ortho, Merck, and Sunovion. Dr. Lapointe has has been an advisory board member for Abbvie, Astellas, and Janssen; and has participated in clinical trials supported by Abbvie and Ferring. The remaining authors report no competing personal or financial interests related to this work.

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