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Effectiveness of fosfomycin tromethamine prophylaxis in preventing infection following transrectal ultrasound-guided prostate needle biopsy: Results from a large Canadian cohort

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ABSTRACT

Objectives: Rates of infection following transrectal ultrasound-guided prostate biopsy (TRUSPB) are increasing. The aim of this study was to evaluate the effectiveness of fosfomycin tromethamine (FMT) prophylaxis in preventing post-TRUSPB infectious complications.
Methods: This nested case–control study included patients undergoing TRUSPB in a Canadian tertiary-care hospital who developed post-TRUSPB bacteraemia or urinary tract infection. Four prophylaxis periods were defined: (i) ciprofloxacin, low-resistance period (CIPRO-LOW), 2002–2009; (ii) ciprofloxacin, high-resistance period (CIPRO-HIGH), 2010–October 2013; (iii) oral FMT, one dose (FOSFO1), December 2013–September 2015; and (iv) oral FMT, two doses (FOSFO2), November 2015–June 2016. Incidence rates of the infection were calculated.
Results: TRUSPB ($n = 9391$) resulted in 138 cases of urinary sepsis (58% with bacteraemia). The incidence rates were 1.8% (CIPRO-HIGH), 3.5% (FOSFO1; $P = 0.004$ vs. CIPRO-HIGH) and 2.7% (FOSFO2; $P = 0.19$ vs. CIPRO-HIGH). Although *Escherichia coli* remained the predominant pathogen with fosfomycin-based regimens, the proportion of infections caused by *Klebsiella* spp. was higher (20/66; 30.3%) than with ciprofloxacin-based regimens (2/77; 2.6%; $P < 0.0001$).
Conclusion: Independent risk factors for infection were the prophylactic regimen administered, presence of urological co-morbidities and diabetes. FMT was therefore not an effective alternative to ciprofloxacin for preventing post-TRUSPB urinary sepsis. These results highlight the need for novel antibacterial prophylaxis approaches.

1. Introduction

Prostate cancer is the most prevalent cancer in men, with 1.4 million cases worldwide [1]. Transrectal ultrasound-guided prostate biopsy (TRUSPB) is the gold standard for the diagnosis of prostate cancer. This procedure, however, can lead to complications such as infection, haematuria and haemospermia [2].

Antibiotic prophylaxis is generally used to decrease the risk of TRUSPB-related infections, as recommended both by the European and American urological associations [3,4]. Fluoroquinolones are the agents of choice because they have been shown to decrease the frequency of post-TRUSPB infection [5]. However, over the last decade several studies have demonstrated increasing rates of post-TRUSPB infections [6–8]. We previously documented the major role of resistance to ciprofloxacin in increasing rates of bacteraemia and febrile urinary tract infection (UTI) in patients undergoing TRUSPB [9]. Fosfomycin is an attractive alternative to fluoroquinolones in this setting because of its broad-spectrum activity against a wide range of Gram-positive and Gram-negative bacteria [10]. Furthermore, it is highly effective against *Escherichia*

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coli, the most common causative pathogen of post-TRUSPB infectious complications [10].

Therefore, a nested case–control study of patients diagnosed with post-TRUSPB infection in a tertiary-care hospital in Canada was conducted to evaluate the efficacy of fosfomycin trometh-amine (FMT) prophylaxis in preventing post-TRUSPB infectious complications.

2. Materials and methods

2.1. Population and design

The Centre hospitalier universitaire de Sherbrooke (CIUSSSE-CHUS) provides comprehensive hospital care for the 165 000 residents of Sherbrooke, Quebec, Canada, and is a referral hospital for a larger catchment population.

The study was approved by the CIUSSSE-CHUS Institutional Review Board. Using a clinical data warehouse, all patients who underwent TRUSPB between 1 January 2002 and 30 June 2016 ($n = 9391$) were identified. The same three urologists performed most of the prostate biopsies.

2.2. Selection of cases and controls

Cases were defined as patients with post-TRUSPB bacteraemia (at least one positive blood culture for a pathogen not considered a contaminant) or urinary sepsis (fever >38.0 °C or leukocytosis >12 000 white blood cells/mm^3, with a positive urine culture without bacteraemia) within 1 month of TRUSPB. Using a pseudorandom number generator, four controls for each case were randomly selected among all patients who underwent TRUSPB at CIUSSSE-CHUS.

2.3. Data collection

Demographic, clinical and laboratory data were collected from each patient's medical record. Clinical information included co-morbidities (diabetes mellitus and chronic obstructive pulmonary disease), urological risk factors (cystoscopy in the preceding month, permanent urinary catheter, benign prostatic hyperplasia, nephrostomy or double-J catheter) and information on the use of antimicrobials in the year preceding the biopsy. Procedure-related data included whether the biopsy was performed in the outpatient clinic or 'minor surgical' facilities, the number of core samples and the estimated prostate volume. From 2002–2007, 500 mg ciprofloxacin was used for prophylaxis orally twice daily for 3 days. In accordance with the recommendations of the American Urological Association [11], this regimen was updated in 2007 to a single 1 g dose of long-acting ciprofloxacin administered 2 h prior to the biopsy. Because of an increasing rate of infectious complications in the context of ciprofloxacin resistance, prophylaxis was modified again to a one-dose FMT regimen in 2013 (3 g orally the night before the procedure). Two years later, this regimen was increased to a two-dose FMT regimen (3 g orally the morning of the procedure, followed by 3 g orally 48 h later).

On the basis of our previous results [9], four prophylaxis periods were defined: (i) ciprofloxacin, low-resistance period (CIPRO-LOW, 2002–2009); (ii) ciprofloxacin, high-resistance period (CIPRO-HIGH, 2010–October 2013); (iii) FMT, single-dose (FOSFO1, December 2013–September 2015); and (iv) FMT, two doses (FOSFO2, November 2015–June 2016). To minimise overlap of regimens across study periods, patients treated within 1 month of regimen changes were excluded. Details of the prophylaxis were not recorded in the progress notes; however, immediately before TRUSPB, the urologists systematically asked all patients if they had taken their prophylactic medications and, if not, the procedure was postponed.

The potential impacts of infectious complications were also drawn from medical records, including 30-day mortality rate, vasopressor requirement, length of hospitalisation and duration of intensive care unit (ICU) stay, if any.

2.4. Antimicrobial susceptibility data

Up to 2007, minimum inhibitory concentrations (MICs) of various antibacterial agents against uropathogens were determined by the broth microdilution method. In 2008, the VITEK®2 system (bioMérieux, Marcy-l'Étoile, France) was introduced for bacterial identification and antimicrobial susceptibility testing. Resistance to antimicrobials was determined using Clinical and Laboratory Standards Institute (CLSI) criteria [12], except for ceftriaxone for which European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used [13]. The number of antibiotics tested for each isolate varied according to whether the specimen had been obtained at the outpatient clinic, emergency room or ward. Determination of FMT resistance was not systematically performed.

2.5. Data analysis

All data were double-entered and analysed with Stata Statistical Software: Release 14.1 for Mac (StataCorp LP, College Station, TX). Incidence rates of infections per 100 biopsies, along with their 95% confidence interval (CI), were calculated. Proportions were compared using χ^2 test or Fisher's test as appropriate, whereas continuous variables were compared using an unpaired *t*-test or Wilcoxon rank-sum test in cases that were not normally distributed.

Crude and adjusted odds ratios and their 95% CI were calculated using logistic regression analysis. Variables with a 10% level of significance in the univariate analysis were included in the unconditional logistic regression model. Variables were added individually and were retained only if they were still significant in the multivariate model, per the likelihood ratio test. The final model retained variables that significantly enhanced the fit at the $P < 0.05$ level. All tests were two-sided and a *P*-value of <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of cases and incidence

Among the 9391 patients who underwent TRUSPB during the study period, 138 cases (1.5%) of post-TRUSPB infections were identified, with a mean ± standard deviation patient age of 65.9 ± 7.2 years. The incidence of infection was significantly higher in patients receiving FOSFO1 than in patients receiving CIPRO-HIGH ($P = 0.0004$) (Table 1). Cases presented with infection a median of 2 days following TRUSPB.

Of the 138 patients with infection, 112 (81.2%) required hospitalisation for a median (interquartile range) duration of 3 days (2–4 days), with 12 being admitted to the ICU for 1–5 days. Eight patients required vasopressors, but none died within 30 days of the infection. Patients receiving FOSFO1 [risk ratio (RR) = 11.3, 95% CI 5.6–23.1; $P < 0.0001$] and FOSFO2 (RR = 9.5, 95% CI 4.0–22.4; $P = 0.05$) had a higher risk of hospitalisation for a post-TRUSPB infectious complication than patients receiving CIPRO-HIGH.

3.2. Microbiology

Escherichia coli was the most frequently isolated pathogen ($n = 99$; 71.7%). However, its proportion decreased when ciprofloxacin was replaced by FMT from 80.8% (63/78) to 48.6% (36/74)

Table 1
Incidence of infectious complications following transrectal ultrasound-guided prostate biopsy (TRUSPB), according to prophylaxis regimen.

Prophylaxis regimen	No. of infections	No. of biopsies	Incidence (%)	Risk ratio (95% CI)	*P*-value
Ciprofloxacin (low-resistance period)	20	4426	0.45	0.24 (0.15–0.41)	<0.00001
Ciprofloxacin (high-resistance period)	57	3139	1.82	1	–
Fosfomycin, one dose	49	1386	3.54	1.95 (1.34–2.84)	0.0004
Fosfomycin, two doses	12	440	2.73	1.50 (0.81–2.78)	0.19

CI, confidence interval.

($P < 0.0001$), whereas the proportion of *Klebsiella* spp. increased from 2.6% (2/77) to 27.0% (20/74) ($P < 0.0001$). Among the 129 cases with aerobic or facultative Gram-negative rods, the following susceptibility rates were observed: ciprofloxacin, 90/129 (69.8%); trimethoprim/sulfamethoxazole (SXT), 100/126 (79.4%); gentamicin, 112/128 (87.5%); ceftriaxone, 94/101 (93.1%); and meropenem, 102/102 (100%). The proportion of ciprofloxacin-susceptible cases was higher in patients receiving FMT (56/59; 94.9%) than in those receiving ciprofloxacin (35/71; 49.3%) ($P < 0.0001$).

Between 2015 and 2017, fosfomycin susceptibility testing was not performed systematically but rather selectively on ciprofloxacin- and SXT-resistant isolates. Susceptibility testing was thus available for 241 *E. coli* isolates from urine cultures. Among these, 2/241 (0.8%) were resistant to fosfomycin, 86/241 (35.7%) were resistant to ciprofloxacin and 83/241 (34.4%) were resistant to SXT.

3.3. Risk factors for post-TRUSPB infections

Factors associated with post-TRUSPB infections in the univariate analyses are shown in Table 2, whilst Table 3 displays the findings of the multivariate analysis. Independent risk factors associated with post-TRUSPB infections were the prophylaxis regimen, diabetes and the presence of urological co-morbidities (Table 3).

4. Discussion

This study demonstrates that FMT is not an effective alternative to ciprofloxacin for prophylaxis against post-TRUSPB infections. The incidence of bacteraemia or septic UTI with a one-dose regimen of FMT (administered the night before the procedure) was significantly higher than that of ciprofloxacin during a period of high ciprofloxacin resistance. The multivariable logistic regression

Table 2
Characteristics of patients with and without infectious complications following transrectal ultrasound-guided prostate biopsy (TRUSPB), 2002–2016.[a]

Risk factor	Controls ($n = 552$)	Cases ($n = 138$)	Crude OR (95% CI)	*P*-value
Age (years) (mean ± S.D.)	66.3 ± 7.8	65.9 ± 7.2	–	0.3
Prophylaxis regimen				
Ciprofloxacin (low-resistance period)	271 (49.1)	20 (14.5)	0.22 (0.13–0.39)	<0.0001
Ciprofloxacin (high-resistance period)	171 (31.0)	57 (41.3)	1	
Fosfomycin, one dose	82 (14.9)	49 (35.5)	1.79 (1.12–2.86)	0.02
Fosfomycin, two doses	28 (5.1)	12 (8.7)	1.29 (0.61–2.70)	0.6
No. of biopsies during procedure				
2–5	18 (3.3)	3 (2.2)	1	
6–9	114 (20.7)	11 (8.0)	0.58 (0.15–2.30)	0.4
10–16	420 (76.1)	124 (89.9)	1.77 (0.51–6.12)	0.4
PSA level (μg/L) [median (IQR)]	5.9 (4.6–8.5)	5.6 (4.0–7.5)	–	0.06
Prostate volume (cm^3) [median (IQR)]	43.7 (32–62)	47 (36–61)	–	0.2
Urological co-morbidities				
No	550 (99.6)	123 (89.1)	1	
Yes	2 (0.4)	15 (10.9)	33.54 (7.14–157.59)	<0.0001
Hospitalised in the previous month				
No	551 (99.8)	135 (97.8)	1	
Yes	1 (0.2)	3 (2.2)	12.24 (1.24–120.34)	0.03
Antibiotic treatment during the previous year				
No/unknown	532 (96.4)	130 (94.2)	1	
Yes	20 (3.6)	8 (5.8)	1.64 (0.70–3.80)	0.3
Residence				
Sherbrooke	218 (39.5)	76 (55.1)	1	
Elsewhere	334 (60.5)	62 (44.9)	0.53 (0.36–0.78)	0.001
Diabetes				
No	529 (95.8)	119 (86.2)	1	
Yes	23 (4.2)	19 (13.8)	3.67 (1.92–7.02)	<0.0001
Chronic obstructive pulmonary disease				
No	539 (97.6)	127 (92.0)	1	
Yes	13 (2.4)	11 (8.0)	3.60 (1.56–8.26)	0.003

OR, odds ratio; CI, confidence interval; S.D., standard deviation; PSA, prostate-specific antigen; IQR, interquartile range.
[a] Data are *n* (%) unless otherwise stated.

Table 3
Independent risk factors for infection following transrectal ultrasound-guided prostate biopsy (TRUSPB) in logistic regression analysis.

Risk factor	Adjusted OR (95% CI	*P*-value
Prophylaxis regimen		
Ciprofloxacin (low-resistance period)	0.20 (0.11–0.37)	<0.0001
Ciprofloxacin (high-resistance period)	1	
Fosfomycin, one dose	1.80 (1.10–2.94)	0.02
Fosfomycin, two doses	1.43 (0.66–3.09)	0.36
Diabetes		
No	1	
Yes	4.61 (2.24–9.46)	<0.0001
Urological co-morbiditsies		
No	1.00	
Yes	43.8 (8.99–212.9)	<0.0001

OR, odds ratio; CI, confidence interval.

model revealed that the odds of infection with the one-dose FMT regimen were significantly higher than that for ciprofloxacin during the high ciprofloxacin resistance period. A higher risk of hospitalisation for infection was also observed with the two FMT regimens.

A few studies have suggested a role for fosfomycin in the context of emerging fluoroquinolone resistance, with conflicting results. Moreover, they are difficult to compare because of heterogeneous study designs and outcomes. The cohort study by Ongün et al. loosely defined UTI on the basis of observed symptoms and included patients with negative urine cultures [14]. Lista et al. prospectively investigated only asymptomatic bacteriuria, a rather weak outcome [15], and concluded that FMT was a safe and effective alternative to ciprofloxacin even though the frequency of bacteriuria was higher in patients receiving FMT. Similar findings were reported in another study involving 202 patients receiving 3 g FMT 1–2 h before the procedure and 210 patients receiving ciprofloxacin and metronidazole ≥1 h before the procedure [16]. More recently, Cai et al. reported the potential of FMT to prevent post-TRUSPB febrile UTI in a cohort larger than that of previously published studies (FMT group, $n = 632$ patients; ciprofloxacin group, $n = 477$ patients) [17]. Their study showed lower rates of symptomatic UTIs and urosepsis among patients treated with FMT. However, the proportion of TRUSPB leading to febrile UTI in the ciprofloxacin group was markedly higher (7.8%) than that generally reported in the literature. Furthermore, 20% of the patients were excluded because of missing data, and this proportion was much higher in the ciprofloxacin group (189/666; 28%) than in the FMT group (73/705; 10%). Finally, their second dose of fosfomycin was administered 24 h after the procedure (compared with 48 h in the current study).

In contrast, our work summarises the experience of more than 9000 TRUSPBs, including 1826 procedures performed following FMT prophylaxis. It also focuses on bacteraemia and septic UTI, the most serious post-TRUSPB complications, resulting in hospitalisation in >80% of cases. This analysis also further explores the different hypotheses explaining FMT clinical failure: pharmacokinetics; tissue penetration; FMT resistance; and the impact of patient co-morbidities.

4.1. Fosfomycin tromethamine pharmacokinetics

When the FMT regimen was instituted in 2013 owing to resistance issues with ciprofloxacin, little was known about fosfomycin pharmacokinetics in the prostate. In 2015, Rhodes et al. reported adequate plasma and prostatic concentrations for highly susceptible organisms when procedures were performed 1–4 h following fosfomycin administration [18]. Fosfomycin 3 g confers >90% coverage for organisms with an MIC ≤4 μg/mL over the first 12 h post-dose period. In the FOSFO1 regimen, FMT was administered the evening before, i.e. >12 h before the procedure, presumably leading to suboptimal coverage.

4.2. Limited tissue penetration of fosfomycin tromethamine

Among 26 healthy men undergoing a transurethral prostate resection for benign prostatic hyperplasia, Gardiner et al. found that the mean overall prostate fosfomycin concentration was 6.5 μg/mL (median 2.97 μg/mL) [19], with potentially therapeutic concentrations up to 17 h after administration; the mean prostate-to-plasma ratio was 0.67, much lower than that for fluoroquinolones [20]. Moreover, fosfomycin prostatic concentrations may fall below the MICs 12 h after the procedure, when the iatrogenic epithelial break still exists. Altogether, these elements may explain the higher infection rates seen with the one-dose and two-dose FMT regimens.

4.3. Fosfomycin tromethamine resistance and selection

It is unlikely that the fosfomycin-associated infectious risk was caused by *E. coli* resistance to fosfomycin in this cohort. First, data from a Canadian surveillance study involving 868 urinary isolates of *E. coli* collected in 2010–2013 from outpatients attending 219 hospital clinics and emergency rooms showed that 99.4% of *E. coli* strains were susceptible to fosfomycin [21]. Moreover, our local data from a sample of urinary isolates ruled out a significant presence of fosfomycin-resistant *E. coli*.

However, a significant increase in the proportion of *Klebsiella* spp. was observed when fosfomycin prophylaxis was introduced. This is not surprising as the activity of fosfomycin against *Klebsiella* spp. is 8–16 times less effective than that against *E. coli* [22]. Fosfomycin use led to selective pressure on *Klebsiella* spp., facilitating its emergence in this setting. To our knowledge, we are the first authors to report this. Not only is it a good example of 'artificial selection' of a resistant flora by the introduction of a specific intervention, it also illustrates the need to monitor the ecological impacts of population-based antimicrobial interventions more broadly than with resistance alone.

4.4. Impact of co-morbidities

Diabetes mellitus and urological co-morbidities are independent risk factors for post-TRUSPB infection. Whilst the prevalence of diabetes mellitus has increased in our population [23], this fact does not, by itself, explain the increase in incidence over the study period. We tried to assess previous antibacterial exposure, but the retrospective nature of this study and lack of access to some outpatient antibacterial prescriptions raise the possibility that diabetes and urological co-morbidities represent surrogate markers for outpatient antibiotic prescriptions and colonisation with fluoroquinolone-resistant Gram-negative rods. More intensive prophylaxis regimens may be warranted in these populations and should be evaluated in prospective trials.

This study has several limitations. First, some patients who live outside Sherbrooke probably presented to local hospitals when developing post-TRUSPB infections, causing an underestimation of the true frequency of this complication. Second, the suboptimal documentation of antibacterials prescribed by physicians working outside the hospital may have led to residual confounding. Finally, caution must be exercised in concluding that FMT is inferior to ciprofloxacin, considering that the administration of ciprofloxacin was stopped in 2013 at our centre. At the same time, a significant increase in the percentage of ciprofloxacin-resistant *E. coli* has been observed in Canada [24]. It is likely that the rate of infections

would have continued to rise in 2013–2017 had ciprofloxacin still been used.

In conclusion, it was found that FMT was not an effective alternative to ciprofloxacin in preventing post-TRUSPB infections, especially a single-dose FMT regimen given the night before the procedure. Novel approaches for antibacterial prophylaxis (i.e. pre-procedure rectal swab screening, followed by a tailored regimen) need to be designed, evaluated and monitored over time. FMT might not be the 'magic bullet' against post-TRUSPB infections, but neither is the blind use of ciprofloxacin alone.

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Competing interests

AC declares a speaker's association with Paladin Labs. All other authors declare no competing interests.

Ethical approval

This study approved by the Centre hospitalier universitaire de Sherbrooke (CIUSSSE-CHUS) Institutional Review Board [IRB approval no. ##2015-655, 13-129].

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