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Increasing Risk of Infectious Complications After Transrectal Ultrasound–Guided Prostate Biopsies: Time to Reassess Antimicrobial Prophylaxis?

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Abstract

Background: An increasing risk of infectious complications following transrectal ultrasound–guided prostate needle biopsy (PNB) has been observed recently in some centers.

Objective: To delineate the risk factors associated with post-PNB bacteremia and/or urinary tract infection (UTI) and determine why this risk has risen over time.

Design, setting, and participants: A case–control study in a Canadian tertiary-care center. Cases were all patients who developed bacteremia and/or UTIs after PNB between 2002 and 2011; controls were randomly selected among patients who underwent a PNB without such complications.

Outcome measurements and statistical analysis: Crude and adjusted odds ratios and their 95% confidence intervals were calculated using logistic regression.

Results and limitations: A total of 5798 PNBs were performed during the study period, following which there were 48 cases of urinary sepsis (42% with bacteremia). The incidence increased from 0.52 infections per 100 biopsies in 2002–2009 to 2.15 infections per 100 biopsies in 2010–2011 ($p < 0.001$). *Escherichia coli* was the predominant pathogen (75% of cases). Among 42 patients whose post-PNB infection was caused by aerobic or facultative Gram-negative rods, 22 patients (52%) were infected by pathogens resistant to ciprofloxacin. Independent risk factors for post-PNB infection were diabetes, hospitalization during the preceding month, chronic obstructive pulmonary disease, and performance of the biopsy in 2010–2011. In 2010–2011, the minimal inhibitory concentrations for ciprofloxacin increased compared with 2002–2009 ($p < 0.03$). The major limitation of the study was its retrospective hospital-based nature, which hampered data collection on outpatient antibiotic prescriptions.

Conclusions: In the past 2 yr, ciprofloxacin resistance contributed to the increasing incidence of post-PNB infections in our center. Novel antibacterial prophylaxis approaches need to be evaluated.

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1. Introduction

In 2008, prostate cancer was diagnosed in 340 000 men and caused nearly 71 000 deaths across the European Union [1]. In the United States, it is estimated that >1 million ultrasound-guided prostate needle biopsies (PNBs) are performed annually [2]. Complications include hematuria, hemospermia, bacteremia, and urinary tract infections (UTIs) [3]. Fluoroquinolones (FQs) are the most frequently used antibacterial prophylaxis before transrectal prostate biopsy. They are attractive because of their high bioavailability, antimicrobial spectrum, and high concentrations in prostatic tissues. Randomized controlled trials have demonstrated their efficacy in decreasing the risk of sepsis after PNB [4,5], and ciprofloxacin for 1 d is currently recommended by European, US, and Canadian expert committees [6–8].

Lately, increasing post-PNB infectious complication rates have been observed in Europe and North America [9–12]. Some of these prior studies have mentioned the potential impact of increasing FQ resistance on antibacterial treatment prior to biopsy, but they were descriptive, lacked a control group [10,11], did not evaluate risk factors [11], or lacked a microbiologic definition of the outcomes [9,12]. Consequently, no mitigating strategy has been proposed.

To delineate the respective contribution of antimicrobial resistance, patient-related risk factors, and procedure-related risk factors in the emergence of post-PNB infections, we conducted a case–control study of patients diagnosed with post–prostate biopsy infections between 2002 and 2011 in a secondary- and tertiary-care hospital in Canada.

2. Patients and methods

2.1. Population and design

The Centre Hospitalier Universitaire de Sherbrooke (CHUS) provides all hospital care to the 155 583 residents of Sherbrooke, Quebec, Canada; most hospital care for the rest of the Estrie region (total population: 309 975) in southern Quebec; and referral services for a larger catchment population. The study population included all patients who underwent a PNB between January 2002 and June 2011 at CHUS; two urologists performed most of the prostate biopsies.

The CHUS institutional review board approved this study. Data extracted from a clinical data warehouse included comprehensive information from each patient's computerized hospital record and discharge diagnoses based on the International Classification of Diseases, 9th and 10th revisions. We used this database to identify all patients who underwent prostate ultrasonography and prostate biopsy from January 1, 2002, to June 30, 2011 ($n = 5798$).

2.2. Selection of cases and controls

Cases were defined as patients experiencing post-PNB bacteremia (positive blood cultures for a pathogen not considered as a contaminant) or UTI (fever and/or leucocytosis with a positive urine culture but without bacteremia) within 1 mo of PNB. For each case, four unmatched controls were selected randomly among all patients who underwent a PNB at CHUS during the study period using the statistical package's pseudorandom number generator.

2.3. Data collection

Demographic, clinical, and laboratory information was collected from each patient's medical record. Clinical information included comorbidities, urologic risk factors (cystoscopy in the preceding month, permanent urinary catheter, benign prostatic hyperplasia, nephrostomy, or JJ catheter), and information on use of antibacterials in the year preceding the biopsy. Data related to the procedure included whether the biopsy was done in the outpatient clinic or in minor surgical facilities, the number of core samples, and the estimated prostate weight. Between 2002 and 2007, the prophylaxis used was 500 mg of ciprofloxacin by mouth twice a day for 3 d. Since late 2007, following recommendations by the American Urological Association [7], this prophylaxis has been changed to a single dose of long-acting ciprofloxacin (1 g) administered ≥ 2 h prior to the prostate biopsy. The details of the prophylaxis were not recorded in the progress notes; however, all patients were systematically asked by the urologist right before PNB if they had taken their ciprofloxacin, and if they had not, the procedure was postponed. Before 2006, patients were advised to self-administer a cleansing enema at home before the biopsy, but this procedure was discontinued because of a lack of supporting data, increased patient costs, and inconvenience [8]. Prebiopsy urine cultures were not routinely obtained.

The potential impact of the infectious complications included the 30-d mortality, need for vasopressors, length of hospitalization, and length of intensive care unit (ICU) stay (if any).

Until 2007, minimal inhibitory concentrations (MICs) of various antibacterials against uropathogens were determined using broth microdilution. In 2008, Vitek 2 (Biomérieux, Marcy-L'Étoile, France) was introduced for bacterial identification and antibiotic susceptibility testing. Resistance to antibacterials was determined using the Clinical and Laboratory Standards Institute criteria [13], except for ceftriaxone, for which European breakpoints were used [14]. The number of antibiotics tested for each isolate varied according to whether the specimen had been obtained at the outpatient clinic, in the emergency room, or on a ward.

2.4. Data analysis

Data were double entered and analyzed with Stata 11.2 for Mac (StataCorp, College Station, TX, USA). Crude and adjusted odds ratios and their 95% confidence intervals were calculated using logistic regression. Proportions were compared using the chi-square or Fisher test, whenever appropriate, while continuous variables were compared using an unpaired *t* test or Wilcoxon rank sum test in case of nonnormality.

Variables to be included in the unconditional logistic regression model were selected after univariate analysis by applying a 10% level of significance. Variables were added one at a time and retained only if they were still significant in the multivariate model as per the likelihood ratio test. The final model retained variables that significantly enhanced the fit at the $p < 0.05$ level.

3. Results

3.1. Characteristics of cases and incidence

We identified 5798 PNBs during the study period, following which we documented 48 cases of postprocedure infections (42% with bacteremia). Median age of cases was 66.7 yr (interquartile range [IQR]: 61.8–72.0 yr). Incidence was 0.71% in 2002–2003, 0.65% in 2004–2005, 0.15% in 2006–2007, and 0.69% in 2008–2009, but it increased to 2.15% in 2010–2011 (Fig. 1). Cases occurred a median of 3 d (IQR: 1–7 d) after PNB. Thirty-two patients (66.7%) needed to be hospitalized for a median duration of 4 d (IQR: 3–5 d).

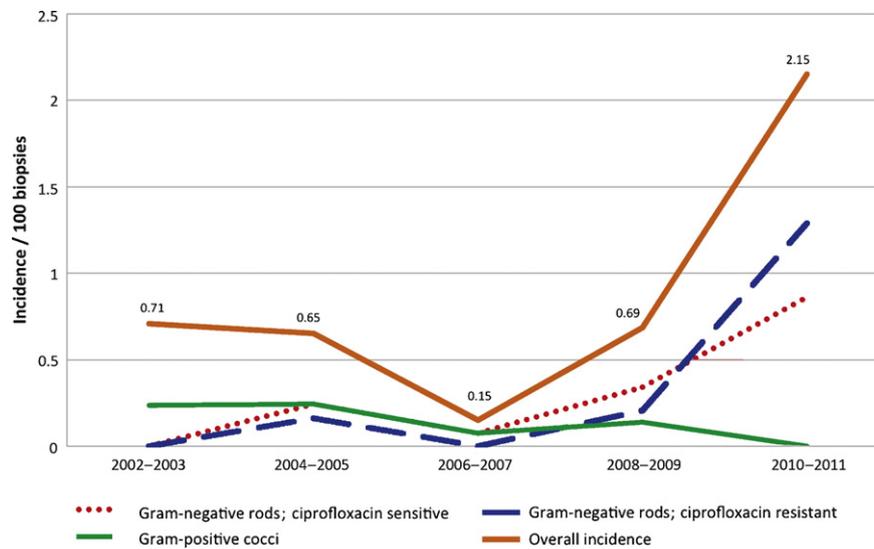


Fig. 1 – Incidence of infectious complications after transrectal ultrasound-guided prostate biopsy: Centre Hospitalier Universitaire de Sherbrooke, 2002–2011.

Of these 32 patients, 5 were admitted to the ICU (duration, range: 2–6 d), and one needed vasopressors. No patient died within 30 d of his infection.

Escherichia coli was the most frequent pathogen ($n = 36$; 75%) among cases, followed by *Enterobacter* and *Citrobacter* species ($n = 3$; 6% each). Gram-positive cocci accounted for only 10% of cases. Among the 42 cases with aerobic or facultative Gram-negative rods (GNRs), the following susceptibility rates were observed: ciprofloxacin, 20 of 42 cases (48%); trimethoprim-sulfamethoxazole, 31 of 41 cases (76%); gentamicin, 32 of 41 cases (78%); ceftriaxone, 26 of 28 cases (93%); and meropenem, 26 of 26 cases (100%).

Among the 46 cases for whom it was possible to identify the treatment received (for 2 patients, emergency room notes did not mention any treatment plan), 27 patients (59%) were treated with an initial regimen that included ciprofloxacin. Ciprofloxacin-resistant bacteria were isolated in all 5 patients who did not receive an adequate antibacterial treatment ≤ 24 h after presentation.

3.2. Risk factors for post-prostate needle biopsy infections

Factors associated with post-PNB infections in univariate analyses are shown in Table 1, and Table 2 displays the findings of the multivariate analysis. Several variables were associated with post-PNB infections in univariate analysis, but they were no longer significant after adjusting for confounders. The independent risk factors associated with post-PNB infections were having a biopsy performed in 2010–2011, diabetes, chronic obstructive pulmonary disease (COPD), and hospitalization during the preceding month.

To further investigate temporal changes in incidence, we compared the characteristics of cases diagnosed during 2002–2009 (low-incidence period) compared with the characteristics of cases identified in 2010–2011 (high-incidence period) (Table 3). Among cases diagnosed in the latter period, there were fewer hospitalizations during the

previous month as well as more core samples obtained during the procedure compared with their counterparts of 2002–2009. Ciprofloxacin resistance was more common in the latter period ($p = 0.03$).

4. Discussion

The incidence of post-PNB infections has increased in several centers in North America and Europe [9,12], and we now document a similar trend in another region of Canada. While the underlying causes have not yet been delineated, the geographic spread of this problem suggests the presence of some systemic factors.

We found no evidence that deficiencies in infection control could explain this increasing risk of post-PNB infections. Cases did not cluster; the risk did not vary according to the facility at which the biopsy was performed or with the rank of cases within the daily program. Some authors have suggested that a higher number of needle core samples may translate into a higher incidence of infection [9]. The current practice in our center is to obtain 12 needle core samples, and we found no difference in the number of needle core samples between cases and controls. In univariate analyses, post-PNB infections were associated with the procedure being carried out by urologist 3, who, between 2002 and 2005, performed biopsies simultaneously with cystoscopy without screening for asymptomatic bacteriuria. This practice was abandoned in 2005.

Having a biopsy performed in 2010–2011, recent hospitalization, diabetes mellitus, and COPD were independent risk factors for a post-PNB infection. However, the number of patients with diabetes, COPD, and recent hospitalization was limited, especially in 2010–2011, and cannot account for temporal changes in risk. While the prevalence of diabetes mellitus has increased in our population [15], as elsewhere in North America, this fact would not by itself suffice to explain the substantial increase in incidence during 2010–2011.

Table 1 – Characteristics of patients with and without post–prostate biopsy infection, Centre Hospitalier Universitaire de Sherbrooke, 2002–2011

Risk factors	Cases, no. (%), n = 48	Controls, no. (%), n = 192	Crude odds ratio	95% confidence interval	p value
Age, yr, median	66.7	66.1	–	–	NS [†]
Year of biopsy					
2002–2009	23 (47.9)	150 (78.1)	1		
2010–2011	25 (52.1)	42 (21.9)	3.88	1.95–7.73	<0.001
Site where procedure was performed					
Minor surgical facility	31 (64.6)	119 (62.0)	1		
Outpatient clinic	17 (35.4)	73 (38.0)	0.89	0.46–1.73	NS
Preceded on the same day by a patient who developed postbiopsy infection					
No	44 (91.7)	181 (94.3)	1		
Yes	4 (8.3)	11 (5.7)	1.50	0.45–4.94	NS
Prebiopsy cleansing enema					
No	37 (77.1)	134 (69.8)	1		
Yes	11 (22.9)	58 (30.2)	1.46	0.69–3.06	NS
Urologist performing the procedure					
Urologist 1	7 (14.6)	50 (26.0)	1		
Urologist 2	37 (77.1)	136 (70.8)	1.94	0.81–4.67	NS
Urologist 3	4 (8.3)	4 (2.1)	7.14	1.30–39.3	0.008
Biopsy done by a radiologist	0 (0)	2 (1.0)	0	–	–
Biopsies during procedure, no.					
2–5	4 (8.3)	12 (6.3)	1.71	0.47–6.23	NS
6–9	13 (27.1)	67 (34.9)	1	–	–
10–16	31 (64.6)	113 (58.9)	1.41	0.69–2.90	NS
Rank of the biopsy during the day, median	5	6	–	–	NS [†]
Prostate-specific antigen level, mg/ml, median	6.1	6.0	–	–	NS [†]
Prostate volume, cm ³ , median	50	43	–	–	NS [†]
Cystoscopy done on the same day as biopsy					
No	42 (87.5)	185 (96.4)	1		
Yes	6 (12.5)	7 (3.7)	3.78	1.19–12.01	0.03
Urologic comorbidities					
No	45 (95.7)	191 (99.5)	1		
Yes	2 (4.3)	1 (0.5)	8.49	0.73–98.03	0.1
Hospitalized in the last month					
No	44 (91.7)	190 (99.0)	1		
Yes	4 (8.3)	2 (1.0)	8.63	1.48–50.4	0.02
Antibiotic treatment during the last year					
No/unknown	45 (97.8)	189 (98.4)	1		
Yes	1 (2.2)	3 (1.6)	1.4	0.14–13.85	NS
Residence					
Sherbrooke	24 (50.0)	113 (58.9)	1		
Elsewhere	24 (50.0)	79 (41.2)	1.43	0.76–2.71	NS
Diabetes					
No	41 (85.4)	184 (95.8)	1		
Yes	7 (14.6)	9 (4.2)	3.93	1.33–11.65	0.02
Chronic obstructive pulmonary disease					
No	41 (85.4)	185 (96.4)	1		
Yes	7 (14.6)	7 (3.7)	4.51	1.47–13.87	0.039
Dementia					
No	44 (95.8)	192 (100.0)	1		
Yes	2 (4.2)	0 (0.0)	–	–	0.039
Chronic renal failure					
No	45 (93.8)	190 (99.0)	1		
Yes	3 (6.3)	2 (1.0)	6.33	1.00–39.96	0.06
Metastatic neoplasm					
No	45 (93.8)	191 (99.5)	1		
Yes	3 (6.2)	1 (0.5)	12.7	1.24–130.71	0.026

NS = not significant.

† Wilcoxon rank sum test.

Furthermore, the prevalence of COPD has not changed, the number of hospital admissions at our center is stable, and performance of the procedure in 2010–2011 remained associated with the outcome even after adjustment for these other independent risk factors.

Several arguments suggest that the higher risk of infection in 2010–2011 was driven by an increase in ciprofloxacin

resistance in *E coli* and a concomitant decrease in the efficacy of ciprofloxacin prophylaxis in patients undergoing PNB. First, over the last decade we have experienced an increase in the prevalence of resistance to ciprofloxacin among *E coli* strains isolated from patients with UTIs in general, presumably reflecting changes in the strains that colonize the patients' gastrointestinal tracts [16]. Second, the recent

Table 2 – Independent risk factors for post–prostate biopsy infection in logistic regression analysis

Risk factors	Adjusted odds ratio	95% confidence interval	p value
Year of biopsy			
2002–2009	1.00		
2010–2011	4.74	2.31–9.73	<0.001
Diabetes			
No	1.00		
Yes	4.78	1.45–15.78	0.01
Chronic obstructive pulmonary disease			
No	1.00		
Yes	5.66	1.69–18.89	0.005
Hospitalized in the last month			
No	1.00		
Yes	8.83	1.29–60.54	0.03

increase in post-PNB infections was more pronounced for ciprofloxacin-resistant than for ciprofloxacin-susceptible pathogens (Fig. 1), and there was a commensurate decrease in ciprofloxacin susceptibility among pathogens isolated

from patients with post-PNB infections in 2010–2011 (Table 3). Third, even among *E coli* isolates deemed susceptible, the MIC increased during the latter period. Taken together, these results suggest that ciprofloxacin resistance was indeed the main factor responsible for the recent increase in incidence of postbiopsy infections in our center. Prospective studies would also make it possible to determine whether an FQ-resistant sequence type 131 *E coli* played a role in the rise of postbiopsy sepsis, as in other centers [17].

Recent hospitalization is a risk factor for community-onset febrile UTIs caused by ciprofloxacin-resistant bacteria [18] and was recently shown to be a risk factor for post-PNB infections in England [19]. This risk factor most likely represents acquired colonization with pathogens with decreased sensitivity to FQ. Diabetic patients have an increased propensity to develop infections in general, and hyperglycemia-related impairment of the immune response may lead to an increase in postbiopsy infections. In vitro studies have shown that glycosuria enhances the

Table 3 – Characteristics of patients with post-prostate biopsy infection, 2002–2009 compared with 2010–2011

Risk factors	2002–2009, no. (%), n = 23	2010–2011, no. (%), n = 25	p value
Age, yr, median	67.8	66.2	NS
Site where procedure was performed			
Minor surgical facility	14 (60.9)	17 (68.0)	
Outpatient clinic	9 (39.1)	8 (32.0)	NS
Urologist performing the procedure			
Urologist 1	3 (13.0)	4 (16.0)	
Urologist 2	17 (73.9)	20 (80.0)	
Urologist 3	3 (13.0)	1 (4.0)	NS
Core samples during procedure, no., median	8	12	<0.001 [†]
Prostate volume, cm ³ , median	52	47	NS [†]
Prostate-specific antigen level, mg/ml, median	7.0	5.5	NS [†]
Ciprofloxacin minimal inhibitory concentration, mg/l [‡]			
≤0.25	5 (62.5)	4 (16.0)	
0.5	0 (0)	6 (24.0)	
1.0–2.0	0 (0)	0 (0)	
4.0	3 (37.5)	15 (60.0)	0.03
Hospitalized in the last month			
No	19 (82.6)	25 (100.0)	
Yes	4 (17.4)	0 (0.0)	0.05
Antibiotic treatment during the preceding year			
No/unknown	20 (95.2)	25 (100.0)	
Yes	1 (4.8)	0 (0.0)	NS
Cystoscopy done on the same day as biopsy			
No	18 (78.3)	24 (96.0)	
Yes	5 (21.7)	1 (4.0)	NS
Urologic comorbidities			
No	21 (95.5)	24 (96.0)	
Yes	2 (8.7)	1 (4.0)	NS
Diabetes			
No	18 (78.3)	23 (92.0)	
Yes	5 (21.7)	2 (8.0)	NS
Chronic pulmonary obstructive disease			
No	19 (82.6)	22 (88.0)	
Yes	4 (17.4)	3 (12.0)	NS
Metastatic neoplasm			
No	20 (87.0)	25 (100.0)	
Yes	3 (13.0)	0 (0.0)	NS

NS = not significant.

The number of subjects may not be equal to the total number in some categories because of unknown/missing values.

[†] Wilcoxon rank sum test.

[‡] Isolates before 2007 excluded because a different antibiotic susceptibility testing method was used.

growth of uropathogenic *E coli* [20], and diabetes was an independent risk factor for fever after PNB in a recent post hoc analysis of a European randomized trial [12]. Nicotine use delays primary healing and increases the risk of some infections [6], which might explain the association with COPD. COPD and diabetes might also represent residual confounding. We tried to assess previous antibacterial exposure, but the retrospective nature of our work and lack of access to some outpatient antibacterial prescriptions raise the possibility that these two factors, and especially COPD, may represent surrogate markers for outpatient antibiotic prescription and colonization with FQ-resistant GNRs.

How should this increased risk of post-PNB infections be addressed? In the context of increasing ciprofloxacin resistance and creeping MICs, the current recommendation of using a ciprofloxacin prophylaxis of duration ≤ 24 h needs to be reexamined [8]. In patients colonized with bacteria harboring a ciprofloxacin MIC of 0.5–2 $\mu\text{g/ml}$ (ciprofloxacin sensitive/intermediate), prostatic concentrations following a single dose of ciprofloxacin may fall below these MICs 24–48 h after the procedure [21], when there is still an iatrogenic epithelial break.

An alternative would be to give all patients a single dose of an antibiotic toward which *E coli* and other GNRs are less likely to be resistant, for example, amikacin. This drug achieves concentrations in the prostate that are lower than quinolones, but amikacin is bactericidal and has urine concentrations that exceed peak plasma levels 25- to 100-fold [22]. The drug may therefore be effective against the urine and bloodstream isolates seen in our patients. Amikacin was also recently shown to reduce post-PNB infections in addition to supplying an FQ-based prophylaxis [23], as did gentamicin in another study [24]. A single dose would not lead to significant nephrotoxicity or ototoxicity. However, we emphasize that antibiotic prophylaxis for PNB needs to be tailored to local resistance patterns. For example, isolates with CTX-M β -lactamases frequently exhibit cross-resistance to amikacin [25]. In centers at which extended-spectrum β -lactamase strains are highly prevalent [26], carbapenems could be considered for prophylaxis—especially ertapenem, given its long half-life. Such alternate prophylaxis should be considered especially for patients who have received an FQ in the last year, who are more likely to be colonized with FQ-resistant *E coli* [16].

Another approach would be to screen for ciprofloxacin-resistant GNRs in rectal swabs prior to a transrectal prostate biopsy (using selective media), followed by a course of a customized prophylaxis regimen [27,28]. However, this procedure would represent a substantial burden for clinical microbiology laboratories and would fail to detect ciprofloxacin-sensitive isolates with borderline MICs, which accounted for half of our post-PNB infections in 2010–2011. Another problem is that because of the relative instability of ciprofloxacin in broths or agars, there is no commercially available ciprofloxacin-containing media. Screening for asymptomatic bacteriuria would presumably be of little help, as demonstrated by others [29], given that most causal pathogens probably originate from the rectum.

Our study also provided hints for the improved management of patients presenting with sepsis after a PNB, a serious infection whose treatment required hospital admission in two-thirds of cases and ICU admission in 15% of cases. The use of ciprofloxacin as an empirical antimicrobial was inappropriate given the frequency of resistant strains. Empirical treatment should include either a third-generation cephalosporin or a carbapenem (if extended-spectrum β -lactamase strains are a concern) and vancomycin for Gram-positive coverage.

Our study had limitations. First, some patients who lived outside Sherbrooke may have presented to local hospitals when developing post-PNB infections, causing an underestimation in the true frequency of this complication. Second, the measurement of antibacterials ordered by physicians working outside the hospital was suboptimal and may have led to residual confounding. Third, the exact prescription for antibacterial prophylaxis (a single dose compared with a 3-d regimen) was generally not documented in the progress notes.

5. Conclusions

We found that emerging resistance to ciprofloxacin is the most likely cause of the increasing risk of infectious complications after PNB. Creeping ciprofloxacin MICs may even contribute to the increase in cases caused by FQ-susceptible strains. Novel approaches for antibacterial prophylaxis need to be designed and evaluated.

Author contributions: Alex Carignan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Carignan, Valiquette, Pépin.

Acquisition of data: Lapointe, Roussy.

Analysis and interpretation of data: Carignan, Pépin.

Drafting of the manuscript: Carignan.

Critical revision of the manuscript for important intellectual content: Carignan, Valiquette, Sabbagh, Roussy, Lapointe, Pépin.

Statistical analysis: Carignan.

Obtaining funding: Carignan, Pépin.

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