

Transrectal Prostate Biopsy-Associated Prophylaxis and Infectious Complications: Report of a Query to the Emerging Infections Network of the Infectious Diseases Society of America

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Background. Fluoroquinolone-resistant infections after transrectal prostate biopsy (TRPB) are increasing.

Methods. Members of the Emerging Infections Network, a consortium of adult infectious diseases physicians sponsored by the Centers for Disease Control and Prevention and the Infectious Diseases Society of America, were administered an electronic 9-question survey regarding post-TRPB infections and associated prophylaxis. Results were compared with respondent characteristics.

Results. The overall response rate was 47% (552 of 1180). Of the 552 respondents, 234 (42%) reported that this problem was not applicable to their practice. The remaining 318 (58%) reported that, despite widespread recent changes in prophylactic regimens, fluoroquinolone monotherapy still was most common, but diverse alternate or supplemental oral and parenteral antibiotics (including imipenem) also were used. Reports of culture-guided prophylaxis were rare (9%). The most common duration of prophylaxis was a single prebiopsy antibiotic dose. However, 16%–23% of respondents reported prophylaxis continuing for ≥ 24 hours postbiopsy. Post-TRPB infections were reported as being more frequent now than 4 years ago, with sepsis and genitourinary presentations predominating, but with osteomyelitis, endocarditis, and epidural abscess also occurring. Infection isolates reportedly were usually resistant to the prophylactic regimen.

Conclusions. Emerging Infections Network members perceive post-TRPB infections as increasingly frequent, caused by resistant strains, and involving serious illness. Prophylactic approaches, although in flux, still usually entail ciprofloxacin monotherapy, which often is given for excessive durations. Multiple opportunities exist for infectious diseases specialists to partner with proceduralists in devising, studying, and implementing improved prophylaxis regimens for TRPB.

Keywords. antimicrobial resistance; infection; prophylaxis; prostate biopsy; sepsis.

Transrectal prostate biopsy (TRPB) confers a risk of postbiopsy urinary tract infection and sepsis. Historically, this risk was held to an acceptably low level by the

use of periprocedural prophylaxis with oral ciprofloxacin [1]. Over the past decade, however, paralleling the rising prevalence of fluoroquinolone resistance in *Escherichia coli*, reports have appeared of increasing rates of post-TRPB infections due to fluoroquinolone-resistant *E coli*, accompanied by calls for alternative approaches to prophylaxis [2–4].

No consensus has yet emerged for how best to prevent post-TRPB infections in the current era of widespread ciprofloxacin resistance. Advocates exist for both broader-spectrum universal prophylaxis using various single- or multiple-drug regimens [5–10] and culture-guided individualized prophylaxis [11–14]. However, the supporting evidence is scant, of low-to-moderate quality

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(eg, none derives from randomized trials), and inconsistent. Existing guidelines are in flux [15, 16]. How these recent developments have affected clinical practice is poorly understood.

Accordingly, we surveyed members of the Emerging Infections Network (EIN) of the Infectious Diseases Society of America (IDSA) [17] to determine how different institutions are dealing with prophylaxis for TRPB, what complications they are encountering, and how both of these may have changed recently. We report here the results of that survey.

METHODS

Emerging Infections Network

The EIN is a network of infectious diseases physicians in North America that was established in 1995 by the Centers for Disease Control and Prevention to create a provider-based emerging infections sentinel network [17]. EIN members who receive surveys are physician members of IDSA who are actively involved in the practice of infectious diseases.

Survey

The survey was designed initially by 2 of the authors (J. R. J. and S. E. B.). Then, it was revised based on input from several expert colleagues who piloted and critiqued it.

The survey was first distributed electronically or by facsimile on May 21, 2014 to all 1180 EIN members who have an adult infectious diseases practice. Survey reminders were sent to non-responders twice, at 8 and 15 days after the initial request.

The survey consisted of brief introductory text and 9 questions. All EIN surveys, including this one, include an “opt-out” pathway, which allows members who are not involved in the aspect of infectious disease practice being queried to answer “not applicable”. For this survey, members were able to respond by e-mail that TRPB prophylaxis and its associated complications were not relevant to their practices without answering any specific survey questions.

Statistical Analysis

Responses were compiled and summary statistics were calculated for response rates (both overall and stratified by member characteristics) and survey content results. Respondent geographical location was classified according to the 9 United States census divisions [18], Canada, and Puerto Rico. Physician employment was classified as hospital/clinic, private/group practice, university/medical school, and state government. Type of hospital/clinic was classified as community, non-university teaching, university, city/county, Veterans Affairs (VA) or Department of Defense (DOD) hospital, or other. Experience in infectious diseases practice was classified as <5 years since infectious diseases fellowship training (including current fellows), 5 to 14 years postfellowship experience, 15 to 24 years, and ≥25 years postfellowship experience. Interest in infection control

practice was inferred based on being a hospital epidemiologist, being an infection control committee member, having indicated this interest on the EIN new member survey, and/or being a member of the Society of Hospital Epidemiologists of America. Comparisons of proportions were tested using Fisher’s exact test or a χ^2 test, with $P < .05$ as the criterion for significance.

RESULTS

Survey Respondents

Overall, survey responses were received from 552 (47%) of the 1180 adult infectious disease physician members who had ever responded to an EIN survey. Response rates were similar by geographic region.

Response rates were higher for members with ≥15 years post-fellowship infectious diseases experience, compared with those with less experience (300 of 567 [53%] vs 252 of 613 [41%]; $P < .0001$). Response rates also varied significantly in relation to hospital/clinic type, being highest for VA and DOD hospitals (45 of 80 members [56%]), lowest for community hospitals (148 of 354 [42%]), and intermediate for city/county hospitals (21 of 41 [51%]), non-University teaching hospitals (159 of 327 [49%]), and University hospitals (173 of 371 [47%]) (for overall comparison, $P = .04$).

Of the 552 respondents, 234 (42%) indicated that TRPB prophylaxis and its complications were not applicable to their practice; they exited the survey at that point. The other 318 respondents (58%), who completed the survey (implying that TRPB prophylaxis and its complications were applicable to their practice), did not differ by geographical distribution from the “not applicable” respondents (data not shown). However, the survey-completing respondents were significantly more likely than the “not applicable” respondents to be in private or group practice, to be affiliated with a community or non-University teaching hospital, to have been in practice ≥15 years, and to have an interest in infection control (Table 1).

Table 1. Respondent Characteristics Associated With Reporting Prophylaxis for Prostate Biopsy as “Not Applicable” to Respondent’s Practice

Characteristic	No. of Respondents (Column %)		P Value
	“Not Applicable” (n = 234)	Others (n = 318)	
Employment = private or group practice	40 (17%)	121 (38%)	<.001
Location = community or non-University teaching hospital	101 (43%)	206 (65%)	<.001
Practice duration ≥15 years postfellowship	109 (47%)	191 (60%)	.005
Interest in infection control	108 (46%)	206 (65%)	<.001

Prophylactic Regimens

Among the 318 respondents who considered prostate biopsy prophylaxis relevant to their practice and who reported on “What are the urologists/interventional radiologists in your primary institution currently using for prophylaxis?”, 66 (21%) were not sure. Of the 252 who were sure, 55% specified a single-agent regimen, which overwhelmingly was ciprofloxacin monotherapy (Table 2). In contrast, 33% specified a combination regimen, predominantly a fluoroquinolone plus another agent (an aminoglycoside, a second- or third-generation cephalosporin, or trimethoprim-sulfamethoxazole), whereas 12% indicated that it varied in relation to specific factors.

When we ranked different prophylactic antibiotics according to reported frequency of use, either alone or as part of a combination regimen (number of cited uses, % of the 252 respondents who specified one or more drugs), fluoroquinolones dominated (186, 74%), followed distantly by aminoglycosides (44, 17%), third-generation cephalosporins (33, 13%), trimethoprim-sulfamethoxazole (18, 7%), and second-generation cephalosporins (17, 7%). Aztreonam and carbapenems were used rarely (4 and 3, respectively; 2% and 1%), and fosfomycin was not used at all. (Percentages sum to >100% because respondents could select “all that apply”).

Table 2. Frequency of Use of Specific Regimens as Prophylaxis for Transrectal Prostate Biopsy

Category	Specific Drug(s)	Frequency of Use, no. (% of 252 ^a)
Single agent	Any of below	138 (55%)
	Fluoroquinolone alone	120 (48%)
	Aminoglycoside alone	2 (0.8%)
	Second-generation cephalosporin alone	5 (2%)
	Third-generation cephalosporin alone	7 (3%)
	Carbapenem alone	3 (1.2%)
	Cefazolin alone	1 (0.4%)
Combination	Any of below	84 (3%)
	Fluoroquinolone + aminoglycoside	21 (8%)
	Antibiotic combination not specified	12 (5%)
	Fluoroquinolone + third-generation cephalosporin	12 (5%)
	Fluoroquinolone + trimethoprim-sulfamethoxazole	8 (3%)
	Fluoroquinolone + second-generation cephalosporin	5 (2%)
	25 other combinations (≤3 respondents each)	26 (10%)
Other	Either of below	96 (38%)
	Variable (by provider, history, culture, etc)	30 (12%)

^a 252, number of respondents (among the 318 who indicated implicitly that prostate biopsy prophylaxis is applicable to their practice) after excluding the 66 who answered “not sure” regarding prophylactic regimens.

Table 3. Duration of Antimicrobial Prophylaxis for Transrectal Prostate Biopsy

Duration	Number of Respondents (% of 214 ^a)
Single dose before procedure	119 (56%)
Several doses for a total of ≤24 hours	46 (21%)
>24 hours to <72 hours (1–2 days)	37 (17%)
≥72 hours (3 or more days)	12 (6%)

^a 214, number of respondents (among the 318 who indicated implicitly that prostate biopsy prophylaxis is applicable to their practice) after excluding the 104 (33%) who answered “not sure” for duration of prophylaxis.

Duration of Therapy

Prophylactic treatment duration varied greatly (Table 3). The most commonly reported duration was a single preprocedure dose (56%, excluding “not sure” responses). Nonetheless, durations >24 hours still accounted for 23% of responses (excluding “not sure” responses).

Revised Approaches to Prophylaxis

A change within the past 4 years in the locally used prophylactic regimen for TRPB was affirmed by 28% of 318 respondents (44% of those with an opinion), denied by 37%, and reported as unknown by 37%. Use of stool culture screening to guide prophylaxis was affirmed by 9% of respondents, denied by 75%, and reported as unknown by 16%. Involvement of the respondent, or of his/her infectious diseases colleagues (including pharmacists), in discussions with providers who perform TRPB regarding modifying prophylaxis for TRPB was affirmed by 43% of respondents (54% of those with an opinion), denied by 37%, and reported as unknown by 20%.

Posttransrectal Prostate Biopsy Infections

Overall, 233 respondents (ie, 73% of the 318 who considered prophylaxis for TRPB applicable to their practice; 42% of 552 total respondents) reported having seen at least 1 post-TRPB infection in the past 4 years, and they shared their impressions regarding frequency trends and characteristics of such infections (Figure 1). For infection frequency now compared with 4 years ago, the most frequent response was “increased” (39% of 233, or 63% of those with an opinion), followed by “no change” (27%, or 37%). In contrast, “decreased” was comparatively rare (8%, or 11%).

The dominant clinical presentations reported were sepsis and other types of systemic infection, followed by localized infections of genitourinary tract (Table 4). However, the clinical spectrum included osteomyelitis, endocarditis, and epidural abscess, with 3% of respondents reporting fatalities (Table 4). According to 49% of the 233 respondents (56% of those with an opinion), infection isolates were usually, almost always, or always resistant to the prophylactic regimen (Table 5).

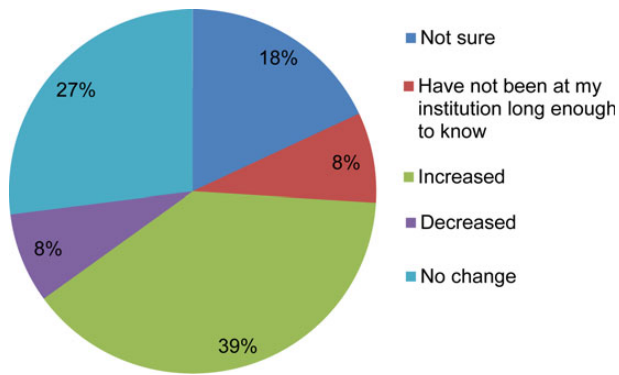


Figure 1. Reported change from 4 years ago to present in frequency of postprostate biopsy infections at respondent's institution. Results are for the 233 respondents who reported having encountered at least 1 post-biopsy infection in the past 4 years. The corresponding proportions after excluding the "not sure" and "have not been at my institution long enough to know" groups (combined, 26% of total) are as follows: increased, 63%; no change, 37%; and decreased, 11%.

DISCUSSION

This recent Internet-based survey of members of the EIN, who are adult infectious disease physicians practicing in North America [17], yielded multiple novel findings regarding recent trends related to post-TRPB infections, including what to our knowledge is the first broad survey of current approaches to prophylaxis. These findings have potentially important implications for the prevention and management of such infections.

First, antibiotic prophylaxis for TRPB reportedly is still dominated by fluoroquinolone monotherapy, an increasingly

Table 4. Infections Occurring After Transrectal Prostate Biopsy

Type of Infection	Frequency, no. (% of 233 Respondents) ^a
Sepsis ^b , pyelonephritis, and/or febrile urinary tract infection (UTI), ±documented bacteremia	207 (89%)
Acute prostatitis	101 (43%)
Acute lower urinary tract infection (UTI, cystitis)	96 (41%)
Recurrent or chronic UTI/prostatitis	29 (12%)
Orchitis and/or epididymitis	20 (9%)
Death	6 (3%)
Other ^c	8 (3%)
Not sure	2 (0.9%)

^a 233 respondents reported having encountered at least 1 postbiopsy infection. Data sum to >233 (and percentages to >100%) because multiple responses were allowed per respondent.

^b The single most common response was sepsis alone (n = 76).

^c Other infections included vertebral osteomyelitis (n = 4), prostatic abscess with bacteremia (n = 1), enterococcal endocarditis (n = 1), and epidural abscess (n = 1).

Table 5. Frequency of Resistance to Locally Used Prophylactic Antimicrobial Regimen Among Infection Isolates From Postprostate Biopsy Infections

Frequency of Resistance to Prophylactic Regimen	No. of Respondents (% of 203 ^a)
Always or almost always	32 (16%)
Usually	82 (40%)
Occasionally	69 (34%)
Rarely	18 (9%)
Never	2 (1%)

^a 203 respondents remained (among the 233 who reported having encountered at least 1 postbiopsy infection) after excluding the 30 who answered "not sure" for frequency of resistance.

questionable approach given the rising prevalence of fluoroquinolone resistance among relevant pathogens, especially *E coli* [1, 19]. Widespread mistrust of fluoroquinolone monotherapy is suggested by the reportedly already-extensive use of alternate or supplemental antibiotics, including aminoglycosides, cephalosporins, and trimethoprim-sulfamethoxazole and, in several instances, even carbapenems. There was no reported use of fosfomycin, an oral agent with broad activity against fluoroquinolone-resistant uropathogens [20, 21], possibly due to its higher cost compared with other oral agents or concerns about promoting resistance. This diversity of reported prophylactic regimens, which seems fairly haphazard, likely reflects the absence of high-quality evidence in this field to inform rational regimen selection, and it points out a pressing need for new, well designed, and adequately powered clinical trials [22].

Second, whereas 28% of respondents indicated that their local prophylactic regimen has changed recently, only 9% reported local use of culture-guided antibiotic selection. Culture-guided prophylaxis has been assessed in at least 4 prepost or retrospective observational studies [11–14]. Although only 1 of these documented a statistically significant reduction in post-biopsy sepsis [12], meta-analysis of 3 of these studies indicated a significant overall benefit [23]. In contrast, expanded-spectrum universal prophylaxis has been examined in at least 6 studies [5–10], 5 of which showed statistically significant benefit, although 1 of these would have lost statistical significance if adjusted for multiple comparisons [8]. Our findings suggest that in North America today, the culture-based approach is less popular than empirical broad-spectrum therapy, possibly because of its comparative complexity and/or limited supporting evidence. However, considering the predictable undesirable effects of widespread use of broad-spectrum therapy, especially "last-resort" agents such as ertapenem [9], the short-term appeal of universal broad prophylaxis may lead to larger problems in the long-term. Here, again, well designed comparative clinical trials are needed [22]. Still, even high-quality, randomized, controlled trials may not provide relevant answers for institutions with

E coli susceptibility profiles differing significantly from those in the studies.

Third, duration of prophylactic therapy also varied widely, with a disturbingly large fraction of use extending beyond the recommended and evidence-based single preprocedure dose [16, 24]. This identifies an important opportunity for education and, possibly, systems-based interventions to reduce the duration and optimize the timing of pre-TRPB prophylaxis, as has been done for surgical procedures [15]. Here again, however, a glaring evidence deficit exists, because the pharmacokinetics of drug delivery to the rectum, prostate, and periprostatic tissues after oral or parenteral antibiotic administration are poorly defined [25, 26], as are the pharmacodynamics of drug exposure at these sites relative to infection risk.

Fourth, post-TRPB infections are perceived generally as increasing, led by sepsis and genitourinary infections, but also involving diverse body sites, eg, spine, cardiac valves, and epidural space. This finding, which is consistent with published case reports and single-site surveillance studies [1, 12, 27–32], supports that post-TRPB infections represent a widespread and non-trivial problem, warranting greater attention from specialists in infectious diseases and infection prevention.

Fifth, the high reported frequency of resistance to the prophylactic regimen among post-TRPB infection isolates suggests that inadequate spectrum of coverage, rather than other possible factors (eg, nonadherence, timing of administration, dose size, etc), likely underlies the increasing infection rate. This both emphasizes the need for modified prophylactic regimens that take into account current resistance trends and underscores the importance of not basing empirical therapy for post-TRPB infections on the drugs that were used prophylactically. Unfortunately, anecdotal evidence suggests that fluoroquinolone agents remain providers' "go-to" choice for treating suspected genitourinary-source infections, regardless of the patient's recent antibiotic exposure history [27, 33, 34]. This identifies an additional need for education of relevant providers and systems-based interventions, in this instance to steer empirical therapy toward more rational and appropriate regimens.

In this regard, many respondents, despite considering prostate biopsy-related infections relevant to their practice, were unsure what prophylaxis regimens were used at their institution for this procedure. It is likely that such awareness is even lower among generalists who care for patients presenting with postbiopsy infections, a situation that predictably would predispose to suboptimal empirical therapy.

Regarding survey validity and generalizability, the response rate was relatively high (47% among EIN members who have responded to at least 1 survey), and the respondents represented a broad range of geographical areas, practice types, and practice setting. The only indications of response bias were that, compared with nonrespondents, respondents were more likely to work at a VA or DOD hospital and to have been in practice

≥15 years, both of which might be associated with being more aware of post-TRPB infections and their upward incidence trend.

In addition, specific subsets of EIN members consider prophylaxis for TRPB especially relevant to their practice. These include individuals in private practice and/or practicing at community and non-University teaching hospitals (possibly because of closer collegial relationships with urologists and primary providers, or because prostate biopsy is done more commonly in these settings), those with more years in practice (possibly from having encountered more of these infections over time), and those interested in infection prevention. However, despite the statistical association of an interest in infection prevention with regarding TRPB prophylaxis as applicable to one's practice, fully 108 of 314 (34%) of infection prevention-interested respondents selected "not applicable". Although this may indicate that TRPB is not performed at their institution, or that their personal infection prevention role excludes post-TRPB infections, it also may identify an opportunity for consciousness-raising and inclusion of TRPB-related infections within the purview of formal infection prevention activities, which currently often neglect this topic.

It can be hoped that the latest recommendations from the US Preventive Services Task Force regarding restricted use of prostate-specific antigen (PSA) screening for prostate cancer will reduce the number of TRPB procedures and, consequently, the number of post-TRPB infections [35]. Still, PSA screening and performance of biopsies doubtless will continue, including for serial surveillance of men diagnosed with low-grade prostate cancer on an initial biopsy. Therefore, a need will remain for the design and implementation of optimal prophylactic and empirical treatment regimens. Infectious diseases physicians and infection prevention specialists have unique expertise that is sorely needed in this field. Ideally, they should become more involved, including in generating the high-quality evidence needed to guide appropriate decision making.

Study limitations include the incomplete (albeit relatively high) response rate; reliance on recall, opinion, and second-hand information from infectious diseases physicians; uncertain generalizability of the findings to non-EIN members and to other practice settings; and lack of granularity regarding the rationale for the selected prophylactic regimens and whether infectious diseases physicians were involved in their selection. Strengths include the broad representation of diverse practice settings across North America; detailed information about the prophylactic regimens used, duration of treatment, and infectious complications; and the ability to stratify respondents according to locale, employment type, practice setting, duration of practice, and interest in infection prevention.

CONCLUSIONS

In summary, survey respondents reported recent shifts at their institution in antimicrobial prophylaxis for TRPB, away from

traditional fluoroquinolone monotherapy, which nonetheless still predominates, toward (as-yet largely untested) alternative regimens involving single or multiple drugs, with minimal use of culture-guided drug selection. They perceive post-TRPB infections as increasingly frequent, usually presenting with sepsis but also localizing to diverse nongenitourinary anatomical sites, and usually involving organisms resistant to the selected prophylactic regimen. Numerous evidence gaps are apparent. Several opportunities exist for infectious diseases specialists to help fill these evidence gaps and to use new or existing knowledge to address more effectively the challenge of post-TRPB infections in this era of emerging antimicrobial resistance.

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