

TRUS

A Urologist's Perspective



INFECTION ASSOCIATED WITH TRANSRECTAL ULTRASOUND GUIDED BIOPSIES OF THE PROSTATE

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In 2010, an article appeared in the *Journal of Urology* (1) that caught the attention of urologists. It preceded what is now recognized as an increasing threat to the safety profile of one of the most common procedures performed by urologists; namely, transrectal ultrasound-guided (TRUS) prostate biopsy. That article published by Nam, et al. from the University of Toronto used a hospital and cancer registry database to estimate hospital admissions due to complications after prostate biopsy and to compare data from 1996 to 2005. The incidence of post-TRUS biopsy admissions increased from 1% to 4.1%. 72% of the admissions were for infection. A study from the U.S. (2) reviewed the Medicare database to compare the rate of serious complications after prostate biopsy to those experienced by a control group of patients who did not have a prostate biopsy. The 7% rate of hospitalizations was almost three times greater than in the non-biopsy group. The United States and Canadian studies provided confirmatory information.

The American Urological Association (AUA) Best Practice Policy Statement advises antimicrobial prophylaxis (prevention with antibiotics) in all patients having a transrectal prostate biopsy and recommends fluoroquinolones (namely Cipro and Levaquin) as the antibiotic of choice(3) However, currently no uniform protocol addresses the escalating problem of fluoroquinolone resistant organisms that are responsible for the majority of urinary tract

infections and, more significantly, for bloodstream infection, after diagnostic transrectal ultrasound guided biopsy of prostate. That this is an issue of increasing importance and concern is confirmed by the attention received at this year's annual AUA meeting where a number of presentations dealing with the problem were presented. An aging and healthier male population, the entry of a large cohort of baby-boomer men into the sixth and seventh decades of life where prostate cancer is most frequently diagnosed, will expand the population of men eligible for prostate biopsy. TRUS biopsy protocols have been incrementally adding to the number of samples (cores) taken per biopsy session. Against the background of this expanding denominator of individuals and biopsy cores obtained, even small percentage increments of the incidence of urinary and bloodstream infection translates into significant absolute numbers of patients that may be affected.

Most reports investigating this issue consist of retrospective 5-10 year analyses from single institutions. Patients with complications attributed to prostate biopsy are identified by culture results, emergency room visits, and hospital admissions reported within 30 days following the biopsy. In three studies of about 1000 patients each reported at the 2011 AUA, the overall urinary tract infection rate ranged from 1-3%; the blood stream infection rate was approximately 0.5%. A 0.4% sepsis rate (blood stream infection) after prostate biopsy was reported in the large European prostate screening trial. (4) The vast majority of these infections were secondary to a common intestinal flora, *E. coli*, which were

fluoroquinolone resistant. Recommendations from these retrospective studies emphasized the importance of a heightened state of awareness among the physicians and the patients to identify risk factors for infection and sepsis. (See Table 1) In addition, suggestions for alternative antibiotic protocols were made. The importance of prospective registries to more accurately document the incidence, cost and outcome of post biopsy infection was stressed.

The AUA meeting provided a prospective study. (5) It reported from Northwestern University in Chicago compared two regimens. One regimen, termed the standard/empiric protocol,

employed in 213 patients prescribed a quinolone given 2 hours before and 12 hours after the procedure. The second regimen, termed the targeted protocol, employed in 43 patients used the results of a rectal swab culture to detect fluoroquinolone resistance prior to the prostate biopsy and direct prophylaxis. If the rectal swab cultures do not show fluoroquinolone resistance, a fluoroquinolone is given 2 hours prior to the prostate biopsy. If resistance is detected, the appropriate antimicrobial based on bacterial sensitivity is selected and administered.

Six of the 43 (14%) rectal swabs demonstrated fluoroquinolone resistant bacteria (five E. coli, one Klebsiella – both

common bacteria in the gastrointestinal tract). None of the patients receiving targeted therapy experienced a urinary tract infection. Four (2.3%) of the patients using the standard/empiric protocol developed infections, one with bloodstream sepsis. An economic analysis was done. The cost of a rectal swab culture was \$13. The mean cost of treating an infection was \$2153 (\$619 – \$5271).

While large prospective studies will be necessary to further define populations at risk and appropriate action to reduce risk factors, a pre-biopsy rectal swab can identify fluoroquinolone resistant organisms. Even more important, these swabs can identify the sensitivity of rectal bacteria to other antibiotics, which can lead to more effective targeted antibiotic regimens. (5)

TABLE 1. RISK FACTORS for Infection After Prostate Biopsy	
Significant Risk	Moderate Risk
<ul style="list-style-type: none"> • Possible Exposure to Fluoroquinolone-Resistant Bacteria, Through: • Occupation as Healthcare Worker (nurse, lab, janitorial, food service, etc.) <ol style="list-style-type: none"> 1. Recent or prolonged hospitalization 2. Recent or frequent travel abroad – especially to underdeveloped countries 3. Living in the same household with any of the above. • Possible Development of any Fluoroquinolone-Resistant Bacteria, Through: <ol style="list-style-type: none"> 1. Recent use of quinolone antibiotics (Cipro, Levaquin, Avelox, etc.) 2. Prolonged use of quinolone antibiotics • Previous History of infection after prostate biopsy 	<ul style="list-style-type: none"> • Diabetes • Compromised immune system • Recent or prolonged use of steroids or other immune-suppressing drugs

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INFECTION ASSOCIATED WITH PROSTATE **BIOPSIES** *Helpline Perspective*

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If you have **RISK FACTORS** for infection (see Table 1, page 25),
some type of **PREVENTION** is **PRUDENT**

This article was inspired by a recent Helpline call, where a local physician explained his disturbing experience involving infection after a prostate biopsy. The situation became critical and required hospitalization. He had good medical care and gained complete recovery. However, he had a family member – also a physician – who experienced the same serious problem at an earlier date. This call illuminated an issue that healthcare professionals may be at higher risk for resistance to the antibiotic commonly used before prostate biopsy – Cipro or Levaquin (fluoroquinolones). This is likely due to their exposure to fluoroquinolone-resistant bacteria, predominantly E. coli. (see Table 1, page 25). If our healthcare system is not protecting our healthcare professionals, then we have missed “do no harm” at a significant level. Small percentages of other men are also at risk, but patient empowerment is a solution.

The issue of infection after prostate biopsy is a serious one, as discussed in the corresponding article by Dr’s Schellhammer and Schaeffer. But it is critical to find a way to take the issue from fear to understanding. To clarify the issue for men, the following factors must be stressed.

Infection after transrectal (TRUS) prostate biopsy is:

UNCOMMON, even rare - occurring in less than 10% of men biopsied. Most studies document less than 5% (1,2,3,4) and some studies even show less than 1% of patients. As always, there is a range in statistics between studies, but it is fair, even conservative to say that over 90% of men do not have symptoms of infection after prostate biopsy. This makes it a rare side effect.

Understanding percentages associated with side effects is essential – especially in reference to side effects that are serious and require medical attention. Unfortunately, some discussions on side effects lack this part of the issue. This can make it impossible for a patient to move from fear to understanding, which is the basis for empowerment. When discussing side effects, always research and ask about percentages.

“Although increasing in numbers, Infection after biopsy still occurs in less than 10% of men. Many studies document less than 5% of men.”

Infection from biopsy is also greatly **PREDICTABLE**. This comes from identifying risk factors for infection, and risk factors for an inability to respond to the commonly prescribed antibiotics. (See Table 1, page 25). Almost all men who experience infection after prostate biopsy have risk factors listed in this table. My physician caller, for example, had at least 2 risk factors in the Significant column of Table 1. He now has 3 significant risk factors with a “previous history” of infection post biopsy. He is currently considering another biopsy, but is taking clear steps to prevent any subsequent infection. *This leads us to the next factor – infection is...*

PREVENTABLE. Although there is no uniform urology protocol for prevention of biopsy infection after TRUSP, probably the best information to date comes from several studies presented in 2011, where simple, inexpensive rectal swabs were performed before transrectal biopsy. (2,3,5) These swabs can be studied for both antibiotic resistance – and antibiotic sensitivity. Since *E. coli* bacteria, which is resistant to Cipro and/or Levaquin, is the primary culprit (5,9), evaluating the intestinal region that will be introduced to needle biopsy is certainly one scientific and reasonable solution.

It is likely that men who have risk factors for infection from TRUSP biopsies will have to request the rectal swab procedure. But if you have risk factors (Table 1, page 25), some type of prevention is prudent.

Some studies have shown that pre-biopsy enemas do little to prevent infection in a man who has risk factors. However, one 2011 study did show some effectiveness with

bisacodyl suppositories administered the night before, or morning of TRUSP (7). Some studies have also shown that urine testing before and after biopsy, can help detect infection or the causative bacteria (3).

Dr Stan Brosman, urologist and longtime PCRI Board member, recently commented that generic Cipro may not be as effective as name brand Cipro. One clinical approach he has observed is that, “More and more doctors are administering an injectable agent such as Gentimycin or Tobramycin prior to the procedure.”

Additional prostate imaging may also be helpful in reducing the number of biopsy cores a man endures over time – especially for those men who have a history of negative biopsies, and a rising PSA. Some areas of the prostate are inaccessible through the transrectal approach – especially the anterior (front) of the prostate. MRI (see Prostate MRI: Information for Patients and Families; PCRInsights, Nov 2010) or color Doppler ultrasound (see Active Surveillance with Color Doppler Monitoring; PCRInsights, Feb 2007) may help visualize these areas, which may lead to more targeted biopsy needles.

It is also possible, that in some men, transperineal biopsy may be considered. This type of biopsy avoids the rectum, and therefore the quinolone-resistant *E. coli* risk. It administers cores through the perineum, which is the skin between the legs – very similar to the procedure used for brachytherapy (seed implantation). In this situation, rectal bacteria are avoided, and the indicated antibiotic is targeted to skin bacteria, not intestinal. The

transperineal biopsy is usually done in the hospital, under spinal or general anesthesia, so additional risks need to be factored in. But transperineal biopsy can reach areas of the prostate that transrectal biopsy cannot, so this may be another benefit. It usually renders 20 or more cores, which is a current, general definition for saturation biopsy. Transperineal saturation biopsy is also common protocol for any man considering targeted therapy for his prostate cancer – such as focal cryo, HIFU, or laser.

Last, but not least – infection is **TREATABLE**. Infection after prostate biopsy can come on quickly, or be delayed. Symptoms may present within hours or days. (9). Simply watching for signs of infection can catch the condition early when it is very treatable. **Urinary symptoms may include frequency, urgency, or burning. Cloudy urine may be observed. Flu-like symptoms such as fever and chills should be acknowledged as possible signs of infection. It is recommended that you seek medical attention promptly if you are experiencing any of these symptoms after transrectal prostate biopsy. A phone call to the urologist’s office – yes, even after hours – is advisable.** There are after hour procedures in place for situations such as this. Like anything else, early detection is the key.

IV antibiotics are sometimes used, as are other types of antibiotics if fluoroquinolones fail. See Table C for list of some antibiotics which have been shown effective in small studies. It is likely an infectious disease (ID) physician will be utilized for antibiotic selection. Feel free to ask.

Weighing Risk vs BENEFIT

This discussion of infection risk is only half of the necessary discussion to make a prostate biopsy decision. The other half is an essential discussion of benefit. Risk vs Benefit is always a reasonable and empowering approach to any medical decision.

There are several unique and critical benefits to prostate biopsy. See Table A.

First and foremost – nothing except pathology (produced by biopsy) can actually “diagnose” prostate cancer. (10, 11) Imaging cannot diagnose. PSA cannot diagnose. Neither can PCA3. The word “diagnose” means there is no longer scientific speculation, but certainty. Diagnose means that your medical chart is now given a certain ICD-9 code (185.0 for prostate cancer) which means your insurance company will now pay for your prostate cancer treatment and prostate cancer tests. Imaging, PSA, and PCA3 tests are all important elements of evidence, but their purpose is to point to the probability of cancer, not certainty. They all point to need to biopsy – or not.

Second, pathology is the only thing that can diagnose pre-cancerous cells in the prostate. Studies have identified two different types of pre-cancerous prostate cells: (1) ASAP (atypical small acinar proliferation) and (2) High Grade PIN (prostatic intraepithelial neoplasia). Since these cells have been reported to not produce excess PSA (11), they can be an important finding that most men would want to know about, as it could lead to a more aggressive PC prevention strategy. For example, 5-alpha reductase inhibitors (both Proscar and Avodart) have been shown to have action against pre-cancerous cells (12).

A third benefit is diagnosing prostatitis in the prostate tissue, or “inflammation”. Prostatitis can be challenging to diagnose, so pathology can be helpful. A man who understands he has prostatitis can make dietary changes, or treatment decisions regarding the inflammation. He can also have a better understanding of his own PSA and free % PSA better, since prostatitis usually affects both.



Fluoroquinolone antibiotics (sometimes called quinolone) include **Cipro** (ciprofloxacin), **Levaquin** (levofloxacin), **Avelox** (moxifloxacin), and **Floxin** (ofloxacin).

TABLE A. BENEFITS of PATHOLOGY Produced by Prostate Biopsy

Pathology CAN	Can PSA?	Can Imaging?	Can PCA3?
Diagnose Cancer	No. Helpful, but not definitive.	No. Helpful, but not definitive.	No. Helpful, but not definitive.
Identify Aggressiveness of Cancer (Gleason)	No.	No. Helpful, but not definitive.	No.
Diagnose Pre-Cancerous Cells (ASAP or High Grade PIN)	No.	No.	No.
Diagnose Inflammation (Prostatitis)	No. Helpful, but not definitive.	No. Helpful, but not definitive.	No.

TABLE B. Antibiotic alternatives to quinolones for prevention (Pre-Biopsy) (AUA) (6)

oral (duration <= 24 hrs)

1. Cefaclor: 500 mg PO [q8h]
2. Cefprozil: 500 mg PO [q12h]
3. Cefuroxime: 500 mg PO [q12h]

IV (duration <= 24 hrs)

4. Cefoxitin: 1 - 2 g IV [q8h]
5. Ceftizoxime: 1 g IV [q8h]
6. Ceftazidime: 1 g IV [q12h]
7. Ceftriaxone: 1 - 2 IV single dose
8. Cefotaxime: 1 g IV [q8h]
9. Aztreonam: 1 - 2 g IV [q8h]
10. Clindamycin: 600 mg IV [q8h] (also good for penicillin allergy)

TABLE C. Antibiotics shown to be effective against quinolone-resistant E. coli

1. Nitrofurantoin, co-amoxiclav (9)
2. mikacin (13)
3. meropenem (8,13)
4. imipenem (3,4)
5. cefiximine (8)
6. piperacillin-tazobactam (3,8)
7. piperacillin/tazobactam (3)

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