

AUA/SUNA White Paper on the Incidence, Prevention and Treatment of Complications Related to Prostate Needle Biopsy

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INTRODUCTION

In the United States, prostate cancer is the most common, non-skin related malignancy with an estimated 241,740 new diagnoses in 2012. Prostate cancer is also the second leading cause of cancer-related death with an estimated 28,170 deaths expected in 2012.¹ The use of a serum prostate-specific antigen (PSA) test and digital rectal examination are currently the recommended screening methods for prostate cancer; however, the diagnosis is made only with prostate needle biopsy. Transrectal ultrasound (TRUS)-guided prostate biopsy has mostly replaced the original techniques of digitally guided or transperineal biopsy.²

Complications related to prostate biopsy can range from mild and self-limited to severe and life threatening. The most common complications following prostate biopsy include infection, bleeding, and urinary retention.³⁻⁶ Infection-related complications following prostate biopsy include asymptomatic bacteriuria, urinary tract infection, febrile urinary tract infection, and sepsis.⁷ Of greatest concern are recent reports of an increasing number of men requiring hospitalization as a result of significant infectious complications following prostate biopsy.⁸ Although many factors may be responsible for these recently reported trends, the emerging pattern of fluoroquinolone-resistant bacteria⁹⁻¹⁴ and the lack of an evidence-based, standardized regimen for peri-procedural antimicrobial prophylaxis for prostate biopsy appear to be the most important etiologic factors responsible for these trends.¹⁵

The purpose of this document is to provide a critical review of the literature addressing the incidence, etiology, risk factors, prevention, and treatment of prostate biopsy-related complications. Special emphasis is placed on the prevention, identification and management of infection-related complications following prostate biopsy.

INDICATIONS FOR BIOPSY

The indications for prostate biopsy are not within the scope of this document, and available evidence for prostate biopsy indications may be reviewed within the AUA PSA Best Practice Statement¹⁶ As with all procedures, patients must receive extensive counseling and informed consent regarding the risks and benefits of this procedure.

COMPLICATIONS FOLLOWING PROSTATE BIOPSY

INFECTION/SEPSIS

Most prostate biopsies are performed transrectally, and introducing rectal bacteria into the urinary tract is a significant concern. Studies have indicated that transient asymptomatic bacteriuria will occur following prostate biopsy in approximately 5% of men who receive appropriate antimicrobial prophylaxis.⁷ Fewer men (2-3%) will develop a symptomatic urinary tract infection (dysuria, frequency, urgency, etc.), which can usually be treated effectively with oral antimicrobials.⁷

Despite antimicrobial coverage, there still remains the potential for introduction of rectal bacteria into the bloodstream (bacteremia) followed by sepsis. Sepsis is a clinical syndrome characterized by a systemic inflammatory reaction to an infectious process.¹⁷ The symptoms of sepsis are nonspecific, and may include fever, hypothermia, tachypnea, tachycardia, altered mental status, and hypotension (Table 1). Any patient who presents with a fever following a prostate biopsy should be assessed for the presence of sepsis. Septic shock refers to acute circulatory failure (hypotension) that persists despite adequate fluid resuscitation.

Table 1. Signs and Symptoms of Sepsis. Adapted from Levy MM, Fink MP, Marshall JC, et al¹⁷

General
Fever (>38.3° C)
Hypothermia (<36° C)
Tachycardia >90/min
Tachypnea
Hypotension (SBP<90mm Hg)
Altered mental status
Significant edema or positive fluid balance
Oliguria

Ileus

Altered mental status/lethargy

Laboratory

WBC >12,000/mm³ or < 4000/mm³

Normal WBC with >10% immature forms

Creatinine increase >0.5mg/dL

INR >1.5 or aPTT>60 secs

Thrombocytopenia (platelet count <100,000/mm³)

Hyperglycemia (plasma glucose >120 mg/dL) in the absence of diabetes

Hyperlactatemia (>1 mmol/L)

Etiology

Infectious complications following prostate biopsy occur after introduction of coliform bacteria into the parenchyma of the prostate, the bloodstream, the urinary tract, or any combination of the three from the hollow core biopsy needle traversing the rectal wall and periprostatic tissue.¹⁸

Several studies have documented increasing rates of fluoroquinolone resistance among patients hospitalized for infectious complications after prostate biopsy^{14,19,20} as well as in community hospital antibiograms. Resistance is mediated by chromosomal mutation, changes in membrane permeability, development of efflux pumps, and perhaps by more than one of these factors in a stepwise fashion. Antimicrobial overuse may be driving resistance to fluoroquinolones and other antimicrobials. Resistance is recognized to occur when bacteria are exposed to antimicrobials below minimum inhibitory concentration (MIC), ie, when antimicrobials are underdosed or used repetitively.²¹ Supporting these observations, one study documented that 22% of patients undergoing a rectal swab before prostate biopsy harbor fluoroquinolone-resistant bacteria.¹⁸ Use of fluoroquinolones in livestock and veterinary practice may also contribute to resistance.²² Fluoroquinolone resistance is currently the most important etiologic factor contributing to infectious complications following prostate biopsy. Residual bacteria in the lubricant^{23,24} or

improperly prepared needle guides²⁵ used in prostate biopsy have also been suggested as potential mechanisms for bacterial contamination.

Incidence epidemiology /cost

The incidence of infectious complications following prostate biopsy in large multi-institutional studies ranges from 0.1%-7%, depending upon the antimicrobial prophylactic regimen used.¹⁸ The risk of hospitalization for infectious complications in contemporary studies ranges from 0.6-4.1%.²⁶ In one large study of 75,000 patients undergoing prostate biopsy in Canada, the overall risk of hospitalization after prostate biopsy was 1.9%, with 72% of those hospitalizations related to infection; moreover, the incidence rose sharply over the 10-year period.²⁶ Loeb and colleagues compared infection-related hospitalizations following prostate biopsy in 17,472 Medicare patients to a control population of 134,977 men and found a significantly increased risk of hospitalization within 30 days in the study group. As many as 1.1% of patients undergoing prostate biopsy required hospitalization for infection-related complications⁸, with rising rates of hospitalization in the later years of the study. Although cost data is somewhat limited, another study calculated that the average cost of hospital admission due to infection after prostate biopsy was \$5900.²⁷

Risk factors

A number of studies have identified potential risk factors for post-prostate biopsy infectious complications. The most common of these risk factors appears to be exposure to antimicrobials within 6 months prior to biopsy. One study noted that men who had been treated with 3 weeks of fluoroquinolone antimicrobials to see if their PSA would decrease and subsequently had a biopsy

showed a 3-fold increase in sepsis compared to those who had not received antimicrobials.⁶ Another noted a 4-fold relative risk for infection in those recently exposed to antimicrobials.²⁸ A number of studies have found a 3-fold or greater incidence of acute prostatitis among men with fluoroquinolone exposure within 6 months prior to biopsy.^{29,30} Studies report that about 22% of men undergoing prostate biopsy harbor fluoroquinolone resistant *E. coli* strains in their fecal flora and the presence of these resistant bacteria is a significant risk factor for post-biopsy infection.^{14,18} Furthermore, the use of fluoroquinolones in the 6 months prior to biopsy is associated with an increased risk of detecting resistant bacteria in the fecal flora. These findings may explain why recent fluoroquinolone exposure may increase the risk for infectious complications after prostate biopsy.

Hospital employees and their family members appear to be at higher risk of prostate biopsy related infectious complications as well, and often demonstrate multi-drug resistant bacteria on culture.³¹ A recent paper documented 3 physicians who developed multi-drug resistant sepsis – one of whom died.³² Recent international travel also appears to be a risk factor for prostate biopsy related infectious complications. Indiscriminate antimicrobial use in some locales can affect the bowel flora of travelers. One study noted a 2.7-fold relative risk for infection after prostate biopsy among those who had recently returned from abroad.²⁸ Prior prostate biopsy also appears to be a risk for an infectious complication, but most studies attribute this to previous antimicrobial exposure. A large study of nearly 5000 prostate biopsies did not detect an association between complication rates and the number of biopsy cores.³ There are no recent data on infection rates comparing biopsies performed in an ambulatory versus an inpatient setting.

Prevention

As per the AUA Best Practice Statement, TRUS-guided prostate biopsy, performed through a grossly contaminated field, requires important preventative considerations. There is wide variation in the approach to the topical preparation of the rectum. Some studies found no benefit to either preprocedural povidine-iodine²⁰ or sodium biphosphate enemas.³³ However, another study found that a bisacodyl suppository rectal preparation the night before or morning of the procedure decreased infectious complications.⁵

No standard for topical preparation of the rectum prior to prostate biopsy has been established. The literature suggests that antimicrobial administration combined with mechanical enema preparation to evacuate the rectal vault results in a decreased risk of bacteremia as compared to antimicrobials alone, although the practice does not seem to affect the rates of fever between the two groups and hospitalization rates were never studied.⁷

With respect to antimicrobial prophylaxis, a large randomized controlled trial of 537 patients receiving oral ciprofloxacin or placebo before prostate biopsy revealed the incidence of bacteriuria to be significantly lower in the antimicrobial group.³⁴ In a 3-arm randomized controlled trial of 231 patients comparing placebo versus a single dose of oral ciprofloxacin plus tinidazole versus the same combination twice a day for 3 days, the incidence of all infectious complications, and specifically urinary tract infection was significantly lower in both antimicrobial groups. Moreover, the single dose was as effective as the 3-day dosing.³⁵ Subsequent randomized clinical trials have confirmed the equivalence of single-dose or one-day regimens compared to 3-day regimens.^{36,37}

Antimicrobials of choice listed in the AUA Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis are shown in Table 2.³⁸

Table 2. Adapted from AUA Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis (2008) (Reviewed and validity confirmed 2011, updated February 2012)³⁸

Procedure	Organisms	Prophylaxis	Antimicrobial(s) of Choice	Alternative Antimicrobial(s)	Duration of Therapy
Transrectal prostate biopsy	Intestine	All	Fluoroquinolone 1st/2nd/3rd generation cephalosporin	Aminoglycoside (Aztreonam) + metronidazole or clindamycin	≤24 hours

According to the AUA Best Practice Statement, all antimicrobials should be administered via the intramuscular or intravenous routes, except for the oral administration of fluoroquinolones and trimethoprim sulfamethoxazole.³⁸

In patients with risk factors for infectious complications following prostate biopsy the surgeon should consider the use of an alternative anti-microbial regimen.

Infectious endocarditis associated with genitourinary procedures is not readily prevented by antimicrobial prophylaxis, and overall, the risk of antimicrobial-associated adverse events exceeds the benefit from prophylactic antimicrobial therapy solely to prevent infectious endocarditis in patients undergoing genitourinary procedures.³⁸ However, the American Heart Association does suggest that for patients with prosthetic heart valves, previous infectious endocarditis, or certain forms of congenital heart disease, it may be reasonable that a

prophylactic antimicrobial regimen includes an agent active against enterococci (amoxicillin or ampicillin).³⁹

Rectal swabs have been used to assess rectal flora prior to prostate biopsy, as mentioned previously, and indicate a prevalence of about 22% of men harboring fluoroquinolone resistant bacteria.^{14,18} However, it remains undetermined if pre-procedural assessment of rectal flora with rectal swabs significantly reduces the number of infectious complications following prostate biopsy. Taylor and colleagues targeted specific antimicrobial prophylaxis based on rectal swab results.¹³ These authors were able to show a reduction in post-prostate biopsy infections from 2.6% to 0% and a cost savings per infectious complication averted. Despite the study's limitations (single center, non-randomized, small cohort of patients), its findings recommend the need for further study of antimicrobial prophylaxis based on the results of pre-procedure rectal swabs to reduce the number of infectious complications.

The need for routine urine culture prior to prostate biopsy is unclear; urine culture appears only to be useful in the decision to refrain from prostate biopsy when bacterial growth is evident.¹⁰

The use of urinalysis or urine dipstick prior to prostate biopsy is widespread; however, there are no published studies to document its benefit.

Treatment of infection

Post-prostate biopsy infections may be serious and, if unrecognized, can lead to significant morbidity or even death.⁴⁰ Patients must be counseled to contact their physician immediately if they have fever, lethargy, difficulty voiding, testicular swelling or symptoms suggestive of a urinary tract infection. Infectious complications after prostate biopsy include cystitis, epididymoorchitis, prostatitis, and urosepsis. If a patient demonstrates signs or symptoms of

sepsis, immediate intravenous hydration and broad-spectrum antimicrobials should be initiated. Once culture sensitivities have been ascertained, antimicrobials may be adjusted appropriately. Initial therapy must cover *E. coli* (the most common pathogen) as well as numerous other organisms. Prior to treatment, a urine culture (and blood cultures if the patient is febrile) should be obtained. Because of widespread ampicillin- and fluoroquinolone-resistance, alternative empiric antimicrobials should be selected.

Older studies evaluating resistance patterns in patients with post-prostate biopsy sepsis noted high rates of resistance to many of the commonly used antimicrobials and recommended the use of a second or third generation cephalosporin, amikacin, or carbapenem.^{4, 29} More recent studies have noted significant resistance to fluoroquinolones (90%), piperacillin (72%), trimethoprim/sulfamethoxazole (44%) and even gentamicin (22%).¹⁹ However, most of the current literature notes no or minimal resistance to the carbapenems (imipenem and meropenem) and amikacin.^{6, 19, 28-30, 41} In addition, the second- and third-generation cephalosporins maintain reasonably good sensitivities as well.^{19, 41} Clinicians may choose from these options but should be familiar with their local antibiogram.

BLEEDING

According to the AUA best practice statement, significant bleeding episodes may occur in 1-4% of patients after prostate biopsy.³⁸ The rates of any bleeding complications (significant or otherwise) are difficult to determine as the literature demonstrates great variability in reported bleeding rates. Recent data suggest that hematuria is present in 23-84%, rectal bleeding in 17-45%, and hematospermia in 12-93% of men after prostate biopsy. However relatively few

patients perceive hematuria (6%), rectal bleeding (3%), and hematospermia as a major/moderate problem following prostate biopsy (27%).⁴²⁻⁴⁵

Risk factors

The literature does not point to any clear risk factors for bleeding after prostate biopsy. One study indicated that large prostate volume was associated with an increased risk of post procedure bleeding.⁴⁵ Contrary to what might be expected, extended core protocols do not appear to be associated with increased bleeding.^{46,47}

Recommendations for anticoagulation

The literature is mixed on the use of anticoagulant/antiplatelet medications during prostate biopsy. Some studies suggest an increase in minor bleeding complications or bleeding duration^{48,49} although variably defined, while others do not.^{50,51} When examined in meta-analyses, continuation of aspirin did not appear to increase the risk for overall or severe bleeding complications, however the risk of minor bleeding was increased.^{52,53} Neither of these meta-analyses specifically addressed aspirin dosage, though there may be some indication that among the studies upon which the meta-analyses were based, the studies of low-dose aspirin were the ones most often demonstrating no increased risk of bleeding.^{52,53} The data regarding prostate biopsy during warfarin or clopidogrel treatment was too limited to draw conclusions.^{51 53-55} While the literature suggests that continued use of these medications does not predispose patients to significant bleeding, prostate biopsy is rarely an urgent procedure. It therefore may be appropriate to consider discontinuing these medications prior to the biopsy within enough time for platelet or coagulative function to recover.

Treatment of bleeding

Severe rectal bleeding may be managed initially with bed rest, volume resuscitation, and transfusion. If the patient's condition does not improve while under observation, options for management include digital compression, rectal tamponade with an inflated condom, colonoscopy with injection of epinephrine and polidocanol or use of sclerotherapeutic agents, angiography with embolization, transrectal exploration, and suturing.^{56, 57} Hematuria may be managed similarly with bed rest, volume resuscitation and transfusion. Cystoscopy with coagulation of bleeding points may be used in more severe cases.

URINARY RETENTION

Urinary retention occurs in 0.2-1.1% of men undergoing prostate biopsy.^{3, 45, 46, 58} Men with larger prostate volumes⁴⁶ and higher International Prostate Symptom Scores⁴⁵ are at increased risk for post prostate biopsy retention. Data suggest that starting higher-risk patients on an alpha blocker prior to prostate biopsy may prevent episodes of urinary retention.⁴⁰

MORTALITY

Overall, prostate biopsy carries with it a very low risk of mortality. The overwhelming majority of published series and population-based cohorts list no deaths (0 deaths out of 2258) or very few deaths (1 death out of 2023).^{59, 60} These estimates can be unreliable either due to insufficient sample size or inability to track patients after they have left the medical center. Therefore, the best estimates of the procedure's risk of mortality come from population-based cohort studies. Analysis of a population based registry from Ontario, Canada (N=75,190) suggests a 30-day mortality of 0.09% among men undergoing prostate biopsy²⁶ while an analysis of SEER-

Medicare (N=17,472) reports the rate to be 0.31%.⁸ The Canadian study noted no significant difference in mortality between those diagnosed with benign or malignant disease among those undergoing biopsy but did not determine the difference between those undergoing biopsy and a "healthy" control group. The SEER-Medicare analysis noted the 30-day mortality among those biopsied was actually lower than that of a comparable control population (OR 0.29, 95% CI 0.22-0.38), most likely because of a bias towards selecting a healthier cohort to undergo prostate biopsy. Those biopsied patients admitted to the hospital for infection-related complications had a much higher mortality (OR 12.02, 95% CI 8.59-16.80) compared with healthy controls not undergoing biopsy.

REPROCESSING OF EQUIPMENT

According to the Spaulding system for reprocessing medical devices, any devices entering sterile tissue are considered critical items. Because prostate biopsy needle guides have long, narrow lumens that are easily contaminated by blood and feces during procedures and because their lumens contact biopsy needles that penetrate sterile tissues, manufacturers, along with the US Food and Drug Administration (FDA) and the US Centers for Disease Control and Prevention (CDC), recommend cleaning and then heat sterilization for all reusable prostate biopsy needle guides.

However, due to the lack of comparative effectiveness data between steam sterilization and high-level disinfection, high-level disinfection is an acceptable practice. According to a study by William Rutala and colleagues, high-level disinfection resulted in complete inactivation of *Pseudomonas* organisms in the internal lumen of the needle guide when equipment was properly

disassembled, cleaned and high level disinfected.⁶¹ Rectal transducers and reusable prostate biopsy guns are semi-critical, heat sensitive devices and may be disinfected using high-level methods. The manufacturers' recommendations for sterilization and high level disinfection methods that are compatible with specific devices should be reviewed and followed.⁶²

In June 2006, the CDC received a report of *Pseudomonas aeruginosa* infections related to reusable needle guides being improperly cleaned and sterilized. Due to the reported infections, the FDA issued a public health notification regarding reprocessing of reusable prostate biopsy needle guides.⁶³ According to the FDA recommendations, reusable ultrasound transducer assembly parts should be disassembled for cleaning after each use. The cleaning should be done with a brush, properly sized for the lumen of each device being cleaned. All heat-sensitive parts, such as the ultrasound transducer, should be cleaned, dried and placed into high-level, liquid disinfectant. According to the FDA, sterile water should always be used to rinse the transducer of residual germicide. Tap water is contraindicated as it may re-contaminate the processed transducer. The use of organic solvents, such as isopropyl alcohol, can damage transducers and should not be used in cleaning or disinfection. The device should be thoroughly dried before reuse or storage. Single-use needle guides, single use biopsy needles and single use combination biopsy gun/needles should be properly disposed of immediately after the biopsy is completed.

Specific guidelines for refilling and using ultrasound gel bottles are lacking. To prevent cross-infection among multiple patients it is important that the dispenser tip of the bottle does not come in direct contact with patients, staff, the transducer, or the environment at any time. Use of single-sterile packets of ultrasound gel for prostate biopsy should be considered. Prevention measures should include staff training and competency testing on hand washing as well as safe

use and reprocessing of equipment. According to the CDC, infection control rounds/audits should be conducted annually to ensure compliance with reprocessing standards and policies.

(For specific cleaning/reprocessing instructions see appendix A).⁶³

SUMMARY

1. Complications related to prostate biopsy include infection/sepsis, bleeding, urinary retention, and in rare instances death. There may be an increasing number of patients requiring hospitalization for infection-related complications. Urologists should properly inform their patients about all potential risks of prostate biopsy.
2. Factors associated with an increased risk of infection-related complications of prostate biopsy include exposure to antimicrobials within 6 months of biopsy, recent international travel, and hospital employment. Family members of hospital employees also appear to be at an increased risk of infection-related complications.
3. The presence of fluoroquinolone-resistant bacteria in the fecal reservoir is becoming more prevalent due to increased, inappropriate, or repetitive prescribing; inadequate dosing; veterinary practices; and the ability of bacteria to mutate and develop resistance. Clinicians should be familiar with their local hospital antibiograms to assess patterns of bacterial resistance.
4. The AUA Best Practice Statement on prophylaxis for prostate biopsy indicates fluoroquinolones or 1st-, 2nd-, or 3rd-generation cephalosporins are the antimicrobials of choice. Single-dose regimens appear to be as effective as those spanning 1- or 3-days. Except

for the oral administration of fluoroquinolones and trimethoprim sulfamethoxazole, all antimicrobials should be administered via the intramuscular or intravenous routes. In patients with risk factors for infectious complications following prostate biopsy the surgeon should consider the use of an alternative anti-microbial regimen.

5. Sepsis following prostate biopsy is serious and can lead to significant morbidity and potentially mortality. Significant bacterial resistance to fluoroquinolones, piperacillin, trimethoprim/sulfamethoxazole and gentamicin has been reported. Empiric intravenous treatment with carbapenems, amikacin, or second and third generation cephalosporins can be considered until culture sensitivities are known.
6. Although rarely perceived as a major problem, a substantial proportion of patients undergoing prostate biopsy experience some degree of bleeding. Discontinuation of anticoagulant medications prior to the prostate biopsy may be warranted.
7. Prostate biopsy equipment places patients at high risk for infection when contaminated with microorganisms and must be processed between patients. Steam sterilization is the preferred method for reprocessing reusable, heat-stable medical devices, including prostate biopsy needle guides; however, high-level disinfection is an acceptable alternative. Rectal transducers are semi-critical, heat sensitive devices which must be high-level disinfected in accordance with the manufacturer's recommendations for the specific device. Single use items should be properly disposed of after the biopsy is completed.

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CLEANING/REPROCESSING OF TRANSDUCERS

- Wear personal protective equipment (ie, gloves, apron, face shield)
- Disassemble the transducer and remove needle guide and condom sheath with gloved hands
- Remove organic materials immediately after procedure before microorganisms have an opportunity to dry
- Clean transducer with disposable gauze pad or disposable soft towel, running water and nonabrasive liquid soap or enzymatic cleaner (refer to manufacture recommendations)
- Dry transducer with disposable paper towel
- Inspect device for cracks or residual soil

High level disinfection for heat sensitive transducers

- Use test strip to check minimum effective concentration level of disinfectant
- Submerge into high-level disinfection solution, flush any channels with disinfectant ensuring concentrate reaches all portions of transducer
- Follow FDA cleared label claim as recommended exposure times vary by solution
- Rinse with sterile water and flush all lumens carefully
- Dry thoroughly
- Store appropriately to ensure the device is not contaminated

At time of procedure, ultrasound transducer should be covered with a condom sheath to prevent contamination during the procedure.

CLEANING/REPROCESSING OF REUSABLE NEEDLE GUIDES

- Remove from transducer
- Disassemble all parts for cleaning after each use
- Remove visible contaminants from exterior with a soft gauze pad or disposable soft towel
- Soak guide in enzymatic cleaning solution
- Brush lumen with clean properly sized brush, ensuring all surfaces and channels are thoroughly cleaned and brushed--refer to manufacturer instructions for cleaning brush specifications
- Rinse with water
- Steam sterilization is the preferred method for reprocessing heat-stable medical devices, including many prostate biopsy needle guides. However high-level disinfection is an acceptable alternative.
- Package and store to ensure sterility
- Dispose of single-use needle guides properly after biopsy and do not reuse

USE OF BIOPSY NEEDLES AND GUNS

- Dispose of single-use biopsy needles or guns properly after biopsy
 - Thoroughly clean and rinse reusable biopsy guns to remove any soiling after procedure
 - Use manufacturer recommendations when disinfecting reusable biopsy guns
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