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MINIREVIEW

Cutting to the Core of the Issue: Emerging Strategies To Reduce Prostate Biopsy-Related Infections

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Over 1 million men undergo biopsy in the United States each year to evaluate for prostate cancer (S. Loeb, H. B. Carter, S. I. Berndt, W. Ricker, and E. M. Schaeffer, J Urol 186:1830–1834, 2011, http://dx.doi.org/10.1016/j.juro.2011.06.057). In recent years, there has been a rise in infectious complications related to these procedures. This review aims to provide an overview of the guidelines that direct transrectal prostate biopsy, to describe associated infection, and to evaluate the published data driving the current trend toward prebiopsy screening for resistant organisms.

The average American man has about a 1 in 7 chance of developing prostate cancer over his lifetime and a 1 in 30 chance of dying from this disease (1). An initial recommendation for annual prostate-specific antigen (PSA) screening was made for men over age 50 by both the American Cancer Society and the American Urological Society in 1992 and was widely adopted thereafter.

PROSTATE CANCER SCREENING

PSA is secreted by prostate epithelial cells and is not specific for prostate cancer. Blood levels can be elevated in response to other stimuli, such as prostatitis or urinary tract infections (UTIs), benign prostatic hyperplasia (BPH), ejaculation, or following digital rectal examination (DRE). Several medications can also affect PSA levels, including 5α-reductase inhibitors used to treat BPH, ketoconazole, and herbal supplements such as palmetto.

While there is no PSA level below which prostate cancer can be "ruled out," there is a positive correlation between the presence of cancer and increasing PSA levels. National Comprehensive Cancer Network (NCCN) guidelines recommend that men with a PSA level of >3.0 ng/ml undergo evaluation for benign disease, repeat PSA, and DRE in order to inform decisions about proceeding to biopsy, with some panel members recommending against prespecified thresholds (1). Recent large-scale randomized trials have used cutoff values from 2.5 to the conventional cutoff of 4.0 ng/ml (2). While there is no true abnormal threshold, the likelihood of biopsy increases with increasing PSA values.

PSA screening has been shown to prevent one death by prostate cancer for every 1,000 men tested over a 10-year period in men between the ages of 55 and 69, with less clear evidence in other age groups (3). While screening may reduce the risk of prostate cancer mortality, it is not without significant risk of harm due to complications of the procedure and overdetection and overtreatment of indolent disease. American Urological Association (AUA) guidelines now recommend against routine screening in men under 55 and over 69 (3). These guidelines state that men aged 55 to 69 years, for whom there is the greatest evidence of benefit, should be a part of a shared decision-making process that includes discussion of mortality from comorbid conditions, individual risk, influence of screening on life expectancy, and the possibility of morbidity from prostate cancer or its treatment (3). In contrast, the U.S. Preventative Task Force made a recommendation in 2012 that the risks of PSA screening outweigh the benefits in men of all ages, following their 2008 recommendation that men 75 and older not be tested. Since those recommendations, there has been a decrease in screening and detection of early-stage prostate cancer (4). A detailed analysis of the benefits and limitations of prostate cancer screening are beyond the scope of this review but are discussed at length in a recent series of articles in The Pathologist entitled "The Great Prostate Debate" (5).

Among every 1,000 men who undergo screening, 100 to 120 are expected to demonstrate an elevated PSA value, and most of these men will go on to have a biopsy, resulting in over 1 million prostate biopsies in the United States each year (2). Tissue for histopathological examination is most commonly obtained by transrectal ultrasound (TRUS)-guided biopsy, in which an ultrasound probe and biopsy needle are placed in the rectum and tissue cores are collected by sampling through the rectum wall into the prostate. NCCN guidelines recommend collection of 12-core biopsies. Of those patients who undergo biopsy, one-fourth will receive a diagnosis of prostate cancer (3). While TRUS-guided prostate biopsy is generally considered a safe procedure and can be performed in the outpatient setting, about one-third of men will experience symptoms or complications related to the procedure, with approximately 4% requiring hospitalization within 30 days (3).

COMPLICATIONS OF PROSTATE BIOPSY

The most common complications of prostate biopsy include bleeding, pain, and infection. Minor bleeding is common, with less than 1% of men experiencing bleeding severe enough to require hospitalization (6). Up to 90% of men report discomfort with the procedure, and NCCN guidelines now recommend consideration of topical lidocaine gel or injectable nerve block to decrease patient discomfort (1, 6).

Infectious complications following prostate biopsy can range from those confined to the genitourinary tract (urinary tract infection [UTI], epididymitis, prostatitis) to sepsis. Approximately 4% of men who undergo this procedure will experience febrile

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UTI, with up to 0.6% developing severe sepsis and septic shock (7). Less commonly, infections such as endocarditis, osteomyelitis, and epidural abscess have been reported (8). A survey of adult infectious disease physicians in the United States conducted in 2014 indicated an increasing frequency of postbiopsy infections over the previous 4 years (8). A review of the Medicare population revealed that risks of serious complications following prostate biopsy have largely remained stable over time, with the exception of the risk of infection. This study demonstrated an increase in hospitalizations due to infection within 30 days of biopsy between the years of 1991 and 2007, with year of procedure being significantly associated with risk of infectious complications (9). A Canadian study evaluating men for bacteremia or culture-positive UTI within 1 month of prostate biopsy established an increase from 0.71 infections per 100 biopsies from 2002 to 2003 to 2.15 infections per 100 biopsies from 2010 to 2011 (10).

The AUA best practice policy statement recommends prophylaxis with a fluoroquinolone or a first-, second-, or third-generation cephalosporin for ≤24 h prior to transrectal prostate biopsy (11), with infectious disease practitioners reporting ciprofloxacin alone as the most common regimen (8). Fluoroquinolones are an attractive option for prophylaxis in these procedures, as this class of drugs achieves a high concentration in the prostate after oral administration (12).

Escherichia coli is the most common organism isolated from patients presenting with post-TRUS biopsy sepsis, causing 75% to 90% of associated infections (13). A series of recent studies reviewed by Williamson et al. reported that the majority of *E. coli* isolates recovered from infections were fluoroquinolone resistant, and furthermore, that a number exhibited additional antimicrobial resistance, primarily third-generation cephalosporin resistance or the identification of extended-spectrum β-lactamases (ESBL) or gentamicin resistance (13). Liss et al. reported that patients' fluoroquinolone-resistant colonizing bacteria are the sources of most infections, demonstrating that pulsed-field gel electrophoresis profiles were indistinguishable for nine patients with paired isolates available from prebiopsy rectal screening and postbiopsy infection (14).

Increasing rates of community carriage of fluoroquinolone-resistant *E. coli*, along with growing numbers of post-prostate biopsy infections, have led urologists to consider whether the current recommendations, based on studies conducted at a time when resistance was much less common, are still appropriate. A number of approaches have been considered to prevent infection, including prebiopsy enema, povidone-iodine or chlorhexidine disinfection of the rectum, or bisacodyl suppository, with mixed results (7, 15). No recommendations for topical preparation prior to biopsy have currently been established by the AUA. Disinfection of the biopsy needle with 10% formalin between the collection of each core sample has been reported to reduce the incidence of infection and has been adopted by some urologists (16). A transperineal approach to biopsy, which prevents contamination with rectal flora, has also been evaluated with mixed results (7).

NEW APPROACHES TO INFECTION PREVENTION

Two strategies for the prevention of infection that have gained attention are (i) augmented antimicrobial prophylaxis regimens and (ii) targeted prophylaxis guided by prebiopsy screening for rectal colonization with ciprofloxacin-resistant organisms. Common augmented regimens that have been described include addition of a second antimicrobial, such as gentamicin, cefazolin, or piperacillin-tazobactam, to a fluoroquinolone or the use of gentamicin with or without clindamycin (17). Targeted regimens described in the literature generally involve the use of a single antimicrobial agent to which an identified ciprofloxacin-resistant organism is shown to test as susceptible, typically a cephalosporin, gentamicin, or trimethoprim-sulfamethoxazole (15, 17). An advantage of the augmented prophylaxis approach is that it does not require a patient visit for prebiopsy culture collection or the costs associated with the culture. However, the use of prophylaxis based on culture and susceptibility results potentially allows narrower and more directed therapy, which is appealing from an antibiotic stewardship perspective.

INCREASING FLUOROQUINOLONE RESISTANCE AND COLONIZATION

Ciprofloxacin has historically demonstrated very good activity against *Enterobacteriaceae*, with over 77,000 clinical *E. coli* isolates reported from two surveillance networks in 2000 demonstrating 4% to 5.5% resistance to ciprofloxacin (18). Resistance rates increased dramatically over the following decade. Data collected on hospitalized patients with urinary tract infections from 24 sites in the United States between 2009 and 2011 indicated that 28.5% of non-ESBL *E. coli* in community-associated infections were ciprofloxacin-resistant, while 36.3% of hospital-associated infections demonstrated resistance (19).

A meta-analysis examining the prevalence of fluoroquinolone-resistant rectal flora in men undergoing transrectal prostate biopsy reported the mean rate of colonization with fluoroquinolone-resistant organisms as 22.8% (15). Nine studies, conducted in North America, Spain, Turkey, and Columbia, were included in the analysis. Roberts et al. further categorized colonization rates based on the timing of the culture, reporting a pooled prevalence of 12.8% when cultures were collected prior to prophylaxis and 20.4% in those cultures that were collected postprophylaxis (20). While this suggests that increased levels of fluoroquinolone resistance are the result of selective pressure, a study of mothers and twins conducted by Gurnee et al. demonstrated that ciprofloxacin-resistant *E. coli* was found in the stool of up to 20% of subjects over the approximate 2.5-year course of sample collection (21). No significant relationship was found between antibiotic use and the recovery of ciprofloxacin-resistant organisms in these subjects (21). Resistance to at least one other antimicrobial tested was identified in 51% of ciprofloxacin-resistant isolates, suggesting that gastrointestinal colonization with multidrug-resistant *Enterobacteriaceae* is not uncommon in the community (21).

RISK FACTORS FOR POSTBIOPSY INFECTION

Rectal culture of over 2,600 men prior to prostate biopsy revealed that men who were colonized with fluoroquinolone-resistant *E. coli* were more likely to develop infection (6.6% versus 1.6%) and to require hospitalization (4.4% versus 0.9%) within 30 days of the procedure (22). Exposure to antimicrobial agents in the 6 months prior to biopsy has been identified in several studies as a risk factor for infection (23–25). Increased risk has also been seen in hospital employees and their family members and people who have traveled internationally (24, 26–28). The AUA published a white paper in 2012 that included the recommendation that physicians should consider an alternative antimicrobial regimen in patients with risk factors for infection, with current AUA alterna-

TABLE 1 Recent publications evaluating prophylaxis modifications

Study	Study size (no. preintervention/ no. intervention)	Design[a]	Significant reduction	Culture protocol (μg Cipro MAC[d])
Summers et al., 2015 (35)	2,759/166	Empirical vs targeted	No	10
Liss et al., 2015 (30)	3,553/1,802	Empirical vs targeted[b]	No	10
Dai et al., 2015 (36)	173/314	Empirical vs targeted	No	1
Cook et al., 2015 (37)	264/242	Empirical vs targeted	Yes	1
Womble et al., 2015 (17)	5,028/4,087	Empirical vs targeted or augmented	Yes[c]	10
Farrell et al., 2015 (38)	543/143	Empirical vs targeted	Yes	10

[a] Emperical prophylaxis encompasses nonculture-directed prophylaxis chosen by the physician, typically single agent and most commonly ciprofloxacin.
[b] This study combines single-agent (75%) and augmented (25%) prophylaxes into a single category of empirical prophylaxis.
[c] No significant difference was detected between targeted and augmented prophylaxes.
[d] Cipro MAC, MacConkey agar with ciprofloxacin.

tive prophylaxis regimens comprised of trimethoprim-sulfamethoxazole or an aminoglycoside (29).

HOW DO AUGMENTED AND TARGETED PROPHYLAXES AFFECT INFECTION RATES?

Two of the largest studies to address these questions were quality improvement initiatives in the state of Michigan and urology departments in Southern California that evaluated infection rates following a quality intervention (17, 30). The Michigan study demonstrated a 53% decrease in biopsy-infection-related hospitalizations for the combined intervention of either augmented or targeted prophylaxis compared to the standard prophylaxis chosen by the physician (17). It should be noted that, in this study, 23.5% of patients received augmented prophylaxis by physician choice in the preintervention period. There was no significant difference in postimplementation hospitalization rates between the augmented and targeted groups; however, this difference may have been difficult to detect, as only 5.3% of subjects received culture-directed prophylaxis (17). The California study compared targeted prophylaxis to empirical prophylaxis, which included both single-agent and augmented approaches (75% single agent and 25% augmented). No significant decrease in sepsis postintervention was observed, even when single-agent empirical prophylaxis was considered separately from augmented prophylaxis (30). Many smaller studies have shown a trend toward reduction but did not reach statistical significance, as they may not have been powered adequately to detect differences. A group of studies published in 2015 that address the effectiveness of empirical versus targeted and/or empirical prophylaxis, with mixed results, is shown in Table 1.

Based on the 2015 meta-analysis findings, targeted antibiotic use in 27 patients would prevent one additional infection (15). This conclusion is based on a comparison of single-dose fluoroquinolone prophylaxis to culture-directed antimicrobial regimens and does not take into account the use of augmented prophylaxis as an alternative approach (15).

LACK OF A COMMON APPROACH TO PROPHYLAXIS AND SCREENING

Of note, there is significant variability in how prophylaxis and cultures are managed in these studies, which may contribute to differences in outcomes. Antimicrobial regimens varied in both antimicrobial selection and duration, and culture collection occurred from 30 days to shortly before procedures (20). Laboratories reported using MacConkey agar containing both 1 μg and 10 μg/ml ciprofloxacin for screening cultures (Table 1).

The Clinical and Laboratory Standards Institute (CLSI) breakpoint for *Enterobacteriaceae* susceptibility to ciprofloxacin is ≤1 μg/ml, with ≥4 μg/ml interpreted as resistant, allowing the possibility of failure to detect resistant Gram-negative organisms using the 10 μg/ml screening agar that is commonly employed. However, susceptibility data from more than 16,000 worldwide *E. coli* isolates available in the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC distribution website demonstrate that less than 3% of resistant *E. coli* had MIC values between 4 and 8 μg/ml, with the greatest number of resistant isolates having an MIC of 32 μg/ml (31). A study evaluating organisms from men undergoing prostate biopsy demonstrated that all ciprofloxacin-resistant *E. coli* had MIC values of >32 μg/ml, suggesting that media containing 10 μg/ml of ciprofloxacin should effectively detect the majority of resistant *E. coli* (14). A comparison of screening culture methods evaluating direct plating and broth enrichment with 1 and 10 μg/ml of ciprofloxacin-containing media found no significant differences in the detection of ciprofloxacin-resistant *E. coli* between any of the methods tested (32).

MOLECULAR SCREENING

Commercial molecular methods are currently available to screen for colonization with specific pathogens (e.g., *Streptococcus agalactiae* in obstetrics patients) and organisms with particular resistance profiles (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA] and vancomycin-resistant enterococci [VRE]). In the future, this approach may be used to screen men for carriage of resistant organisms prior to prostate biopsy. A multiplex quantitative PCR (qPCR) approach has been developed to rapidly identify *E. coli* clonal groups sequence type 69 (ST69) and ST131 (along with subclone ST131-H30), which are associated with fluoroquinolone (ST131) and trimethoprim-sulfamethoxazole (both) resistance. Sensitivities reported for the detection of resistance to fluoroquinolones (75%) and trimethoprim-sulfamethoxazole (74%) are not adequate for clinical use, but this study may serve as a starting point for the development of rapid molecular testing for this application (33).

ST131 has disseminated globally and is responsible for much of the increase in antimicrobial-resistant extraintestinal *E. coli* infections (34). Fluoroquinolone resistance in *E. coli*, including ST131, is most commonly mediated by mutations in the quinolone resistance-determining region (QRDR) of genes encoding DNA gyrase and topoisomerase IV, *gyrA* and *parC*. However, resistance can also result from porin mutations, efflux pumps, and the acquisition of plasmid-mediated quinolone resistance genes. The molecular testing presented, and this approach in general, suffers from several limitations when utilized as an indirect test of fluoroquinolone resistance. This method would fail to detect organisms other

than *E. coli* or those belonging to a different clonal group than the most common, which may be particularly important in geographic regions in which different fluoroquinolone-resistant clones are found (34). Additionally, resistance mediated by the less common mechanisms described, and not associated with a particular clonal group, would not be detected.

PROPOSED IMPLEMENTATION PLAN

For those laboratories that choose to implement screening culture, the following information is offered for guidance and is based on published practices and opinion. Rectal swabs should be collected as close to the time of scheduled biopsy as is practicable while still allowing time for the completion of cultures and appropriate prophylaxis to occur.

MacConkey agar with ciprofloxacin is available commercially in concentrations of 1 μg/ml from Remel (catalog no. R01545; Lenexa, KS) and 10 μg/ml from Hardy Diagnostics (catalog no. G258; Santa Maria, CA). While there is no statistically significant difference between recovery from 1 μg/ml and 10 μg/ml media, more false-positive results occur when using 1 μg/ml, which adds to the cost of culture through the use of additional media and personnel time. Broth enrichment may be performed, and brain heart infusion (BHI) containing 10 μg/ml ciprofloxacin is available from Hardy Diagnostics (catalog no. K258). However, broth enrichment is not recommended, as it has been shown to yield a significant increase in false-positive results, requiring additional evaluation and adding to cost, without a concurrent statistically significant improvement in sensitivity (32). Direct plating onto MacConkey agar with 10 μg/ml ciprofloxacin is likely to be the most streamlined and cost-effective procedure.

Swabs should be plated on MacConkey agar with ciprofloxacin along with standard MacConkey agar in order to evaluate sample adequacy as evidenced by the presence of enteric bacteria. If there is no growth on the standard MacConkey agar, the sample may be considered unacceptable and recollection requested. Plates should be examined for growth at 24 h and 48 h, and each colony type of organism that grows on the ciprofloxacin-containing media should be identified and susceptibility testing should be performed.

Working together with urologists, labs should develop a reporting structure that allows physicians to easily choose appropriate antimicrobial agents for prophylaxis. This process offers the opportunity to utilize lab information systems and electronic medical record systems to create result reporting pathways and treatment recommendations based on screening results.

CONCLUSIONS

While there may not yet be consensus as to whether augmented prophylaxis or screening culture is the most effective way to reduce infectious complications of prostate biopsy, it is apparent that the current recommendations do not adequately address this problem. Microbiology labs are likely to continue to be called upon to provide information to urologists regarding carriage of ciprofloxacin-resistant organisms. To provide the most useful information for tailoring prophylaxis, it will be important to identify and perform susceptibility testing on all ciprofloxacin-resistant organisms recovered from screening cultures given the potential for resistance to other agents commonly used for prophylaxis. Increases in these requests will allow the opportunity to collect large amounts of data using a standardized approach to truly understand the role that screening plays in preventing prostate-biopsy-associated infections. We should seize this opportunity to work with our colleagues in urology to demonstrate the value of the microbiology lab to play a role in the development of new guidelines.

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