Febrile Infection in Post-Prostate Biopsy: Results of a Ten-Year Single-Institution Study in South Taiwan

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Abstract

Background: Post-biopsy infection is one of the major concerns of urologists and patients for prostate biopsy. Many efforts have been made to reduce the infection rate. We conducted a study at a single institution with the goal of describing the bacteriology and incidence trends of febrile infections following trans-rectal ultrasound (TRUS)-guided biopsy of the prostate.

Materials and Methods: From January 1998 to December 2002 (Period 1 of the study), January 2003 to August 2005 (Period 2), September 2005 to October 2007 (Period 3), and November 2007 to December 2009 (Period 4), 1,406 patients underwent prostate biopsy at our hospital. All biopsies were conducted under TRUS guidance without preparation by enemas. Several steps were taken to reduce infectious complications following biopsy, including a shift to levofloxacin prophylaxis starting from Period 3 of our study and thorough instructions in post-biopsy self-care starting from the beginning of Period 4. The incidence and bacteriology of urinary tract infection (UTI) following the prostate biopsies were reviewed from chart records.

Results: Twenty-eight of 514 (5.4%), 13 of 276 (4.7%), nine of 274 (3.2%), and three of 342 (0.9%) patients had post-biopsy febrile infections during the four periods of the study, respectively. Fifteen of 28 (53.5%), four of 13 (30.8%), five of nine (55.6%), and zero of three patients, respectively, had positive cultures of blood, urine, or both during the four study periods. *Escherichia coli* was the pathogen isolated most commonly and ampicillin- and fluoroquinolone-resistant strains of this organism were identified at a high frequency. The times to onset of fever after biopsy in the four study periods were 1.5 ± 1.3 d, 3.7 ± 2.7 d, 2.2 ± 1.6 d, and 2.5 ± 0.9 d, respectively.

Conclusions: Ampicillin- and fluoroquinolone-resistant strains of *E. coli* were the uropathogenic bacteria identified most commonly after prostate biopsy at our hospital. The incidence of UTI following prostate biopsy can be reduced by explaining instructions for medication and self-care thoroughly to patients undergoing such biopsy.

PROSTATE CANCER (PC) remains the most common malignant tumor and second leading cause of cancer deaths in Western countries [1]. In Taiwan, it has been the fifth most common malignant and seventh leading cause of cancer deaths in males for more than 5 y. More than 4,000 men in Taiwan are now diagnosed annually with PC [2]. There has been an obvious increase in the annual detection rate of this cancer since the late 1990s, in Taiwan as well as in other Asian countries [3,4]. Despite the increase in the rates of detection, malignant tumors of the prostate have not been detected at an earlier stage [5], and about 750 patients with PC die each year. An explanation for this may be that patients or physicians are concerned with complications related to biopsy for PC, and

particularly with "urosepsis." Several reports have described the complications and morbidity associated with transrectal ultrasound (TRUS)-guided prostate biopsy [6,7], which in many cases increased hospitalization rates and cost [8]. Consequently, it is important to understand how to eliminate the complications related to biopsy for PC and the morbidity and anxiety they provoke.

Several strategies have been reported and used effectively in reducing the frequency of urinary tract infection (UTI) following TRUS-guided biopsy, including various protocols of empiric antibiotic prophylaxis [9,10] and the use of pre-biopsy enemas [11–13], although the preventive role of enemas in reducing post-biopsy infections remains controversial

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[11–13]. The pathogens involved in UTI after transrectal biopsy of the prostate have also been investigated. Uropathogenic strains of *Escherichia coli* are the most frequent cause of symptomatic UTI [14]. Following prostate biopsy via the rectum, bacteriuria and bacteremia can be detected in 44% and 16% of patients, respectively [13]. Most cases of these two conditions are asymptomatic, but some may contribute to fatal sepsis [15]. The aim of this study was to report the bacteriology and trend in incidence of febrile infection following biopsy of the prostate and the steps taken to reduce the incidence of such infection.

Patients and Methods

The data collection and protocol for the study were approved by the institutional review board at National Cheng Kung University Hospital. Men with either increasing concentrations of prostate-specific antigen (PSA) (>4.0 ng/mL) or abnormal digital rectal examinations and who underwent a TRUS-guided biopsy of the prostate from January 1998 to January 2009 were enrolled into the study. All of the patients in the study underwent conventional two-dimensional (2D) gray-scale TRUS before biopsy in accord with similar procedures described previously [5]. Several strategies were applied to reduce the incidence of post-biopsy infectious complications, including instructions to patients about medication and self-care, and the timing, dosage and type of prophylactic antimicrobial agents the patients were given (Table 1). Before August 2005, the strategy for biopsy was to take bilateral sextant core specimens of prostate with or without additional targeted cores. The prophylactic antimicrobial agents used in about two-thirds of the study patients were pipemidic acid/metronidazole, and the remainder were cephalothin or trimethoprim/sulfamethoxazole plus metronidazole, or others. The patients' medication instructions included discontinuation of anticoagulants (aspirin warfarin) for at least 5 d and the time of initiation of antibi-

otic dosing, which varied widely depending on the orders of the urologists in the study. The duration of medication was 3 d (in Periods 1 and 2 of the study). From September 2005 to October 2007, the technique for biopsy was shifted to a systematically random basis, with the taking of 10 biopsy cores with or without additional targeted cores. For patients with a stone-hard prostate and markedly high concentrations of PSA, the number of biopsy cores was reduced to fewer than 10. The use of prophylactic antimicrobial agents was changed largely to levofloxacin plus metronidazole, but the instructions to patients for their medication did not change (Period 3). After November 2007, the instructions for medication were modified. On the day of the visit for biopsy, all of the patients were asked to take prophylactic antimicrobial agents 1 h before biopsy and immediately after biopsy, and to then continue taking their medication for 2 d. After the patients had undergone biopsy, four items were thoroughly explained to each patient or the patient's family, including the correct method of antibiotic use, indications for re-visiting the emergency department (such as high fever or massive bleeding), the need for avoiding any activities that involved abdominal straining, and the need for defecation without hard stool or watery diarrhea (Period 4).

When a patient was sent to the emergency department because of a high fever, profiling was done for infection, including blood and urine cultures. All bacteria isolated in urine or blood cultures were identified and tested for antibiotic susceptibility at our hospital through use of the standard routine methods [16]. In addition, all of the patients in the study were asked on their return visit following biopsy about whether they had experienced a post-biopsy fever. The incidence of febrile infection, bacteriology of urine and blood specimens, and time to the emergency department following the development of fever were recorded retrospectively via a chart review. All such complications were classified as being of grade II according to the Clavien classification of surgical complications [17].

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY SUBJECTS

Study Period	1	2	3	4
Date	January 1998 ~ December 2002	January 2003 ~ August 2005	September 2005 ~ October 2007	November 2007 ~ December 2009
Main prophylactic antibiotics	Pipemidic acid plus metronidazole	Pipemidic acid plus metronidazole	Levofloxacin plus metronidazole	Levofloxacin plus metronidazole
Biopsy strategy	Bilateral sextant	Bilateral sextant	Random 10 cores	Random 10 cores
Instructions	Varied	Varied	Varied	Scrupulous instructions
Patients (n)	514	276	274	342
Age (years)				
Median	71	71	71	71
25th–75th percentile	65–76	66–76	64–76	64–76
Prostate volume (mL)				
Median	42.8	43.1	46	43.8
25th–75th percentile	30.6–62.0	29.5–64.2	32.9–66.1	30.9–62.8
PSA (ng/mL)				
Median	16.4	16.2	14.4	12.6
25th–75th percentile	7.8–41.6	9.0–32.6	7.8–34.5	7.7–32.6
Biopsy cores, mean $\pm$ SE	5.4 $\pm$ 1.9	5.9 $\pm$ 1.3	7.1 $\pm$ 1.9	7.9 $\pm$ 2.3

PSA = prostate-specific antigen.

Statistical analyses

The basic characteristics of study subjects (i.e., patients' age, prostate volume, PSA, and number of biopsy cores) and incidence of febrile infections were analyzed for statistical significance or curve-fit analysis using the Prism GraphPad Prism 5.00 software package for Windows (GraphPad Software, San Diego, CA). Values were expressed as the mean $\pm$ SD or median with 25th–75th percentile values.

Results

In general, 10 random core biopsy specimens of prostate were taken and a third-generation fluoroquinolone (levofloxacin) was given in Period 3 of the study, and bilateral sextant core specimens were taken and a first-generation fluoroquinolone (piperidic acid) was given in Periods 1 and 2. The patients in Period 4 received more thorough instructions about the use of medications than did those in Period 3. In total, 514, 276, 274, and 342 patients, respectively, underwent prostate biopsy in Periods 1, 2, 3, and 4. The median age of the patients in these four groups was 71 y, and the median prostate volumes were 42.8 mL, 43.1 mL, 46 mL, and 43.8 mL, respectively. The median serum concentrations of PSA in the four patient groups were 16.4 ng/mL, 16.2 ng/mL, 14.4 ng/mL, and 12.6 ng/mL, respectively, and the numbers of biopsy core specimens were 5.4 ± 1.9 , 5.9 ± 1.3 , 7.1 ± 1.9 , and 7.9 ± 2.3 , respectively (mean $\pm$ SD) (Table 1).

Twenty-eight (5.4%), 13 (4.7%), nine (3.3%), and three (0.9%) patients, respectively, had febrile infections following prostate biopsy in periods 1, 2, 3, and 4 of the study. Fifteen of 28 (53.5%), four of 13 (30.7%), and five of nine (55.6%) patients, respectively, had positive cultures of either blood or urine samples in the first three periods of the study. Nine of 28 (32.1%), three of 13 (23%), and three of nine (33.3%) patients had positive blood cultures in the first three periods of the study. Around 20–33% of the patients had positive blood cultures. *Escherichia coli* was the bacterial species isolated most commonly from the patients in Periods 1 and 2 of the study, followed by *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Staphylococcus saprophyticus*. In contrast, the only bacterial species isolated from the patients in Period 3 of the study was *E. coli*. The times to onset of fever among the patients in the four study periods were 1.5 ± 1.3 d, 3.7 ± 2.7 d, 2.2 ± 1.6 d, and 2.5 ± 0.9 d, respectively (Table 2).

In total, 17 strains of *E. coli* were isolated and 13 (76.4%) were resistant to ampicillin; in contrast, 14 (82.4%) of the *E. coli*

strains were sensitive to either amoxicillin–clavulanic acid, or ampicillin–sulbactam. All of the isolated strains of *E. coli* were sensitive to the aminoglycoside class (e.g., gentamicin). Of the 17 strains of *E. coli* that were isolated, 15 (88.2%) were sensitive to the cephalosporin class, except two resistant to cephalothin. In addition, eight (47%), five (30%), and four (23%) of the isolated strains of *E. coli*, respectively, were sensitive, intermediate sensitive, and resistant to the quinolone class (e.g., ofloxacin–pefloxacin, levofloxacin, ciprofloxacin, and lomefloxacin). Resistance to trimethoprim/sulfamethoxazole was found in all seven strains of *E. coli* tested for sensitivity to this agent. All four isolated strains of *K. pneumoniae* were sensitive to the antimicrobials used in the study, except for ampicillin. One of two isolated strains of *P. aeruginosa* showed resistance to tobramycin, and the isolated strain of *S. saprophyticus* was resistant to oxacillin and vancomycin (Supplementary Table 1).

Discussion

Two approaches have been used in an attempt to reduce the incidence of UTI following transrectal prostate biopsy in our institution during the past decade, including a shift of prophylactic antimicrobials from first-generation to third-generation fluoroquinolones and thorough instruction of patients in the use of medications. As a result, the incidence of prostate biopsy-associated UTI has decreased from 4.7%–5.4% to 0.90%. Recent studies in the literature have reported varying incidence rates of post-biopsy UTI or sepsis, ranging from 0.5% to 9.3% [8,14,18–21]. Some methods have been investigated for reducing infectious complications of prostate biopsy. Taylor et al. showed that targeted antimicrobial prophylaxis based on rectal swab cultures may reduce the incidence of post-operative infectious complications and cost of care in patients undergoing TRUS-guided prostate biopsy [22]. In contrast, Koc et al. reported that in a randomized controlled trial of 180 patients, washing of the biopsy needle with povidone-iodine solution did not reduce the rate of infection after transrectal needle biopsy of the prostate [23]. Bruyere et al., in a prospective cohort of 353 patients, reported that the routine bacterial culture of urine before prostate biopsy was not useful for antibiotic prophylaxis [24]. None of the patients in our study were requested a pre-biopsy enema. Interestingly, a protective effect against infectious complications of bowel preparation or enema before biopsy is controversial [18,19], and some urologists do not request any form of

TABLE 2. INCIDENCE OF URINARY-TRACT INFECTION FOLLOWING TRANS-RECTAL ULTRASOUND-GUIDED PROSTATE BIOPSY

Study period	1	2	3	4
Number (%)	28 (5.4)	13 (4.7)	9 (3.3)	3 (0.9)
Positive culture, n (%)	15 (53.5)	4 (30.7)	5 (55.5)	0
Urine	4 (14.3)	0	1 (11.1)	0
Blood	9 (32.1)	3 (23)	3 (33.3)	0
Both urine and blood	2 (7.1)	1 (7.7)	1 (11.1)	0
Bacterial species, n (%)				
<i>Escherichia coli</i>	9 (60)	3 (75)	5 (100)	0
<i>Klebsiella pneumoniae</i>	3 (20)	1 (25)	0	0
<i>Pseudomonas aeruginosa</i>	2 (13.3)	0	0	0
<i>Staphylococcus saprophyticus</i>	1 (6.7)	0	0	0
Mean presentation days since biopsy (day, mean $\pm$ SD)	1.5 ± 1.3	3.7 ± 2.7	2.2 ± 1.6	2.5 ± 0.9

bowel preparation before biopsy [15]. Despite this, one meta-analysis showed that the risk of bacteremia was diminished in an "antibiotic + enema group" as compared with an antibiotic-only group [25]. Despite the decrease in incidence of post-biopsy infection in our study, we did not find any correlation with the time of onset of post-biopsy fever such as age, prostate volume, PSA concentration, study period, number of biopsy cores, and types of used antibiotics. A possible explanation for this is that post-biopsy fever or sepsis may be devastating, and that its rapid onset in the period 1 of the study (i.e., before 2003) was the result of insufficient instruction to patients, with variations in drug efficacy or patient compliance. With the prophylactic use of levofloxacin, the time to onset of post-biopsy infection did not change significantly with scrupulous instructions to patients even as the incidence declined.

Several studies have focused on evaluating the prediction of risk factors in needle biopsy of the prostate. Loeb et al. reported that prostate enlargement and diabetes mellitus were associated significantly with an increased risk of fever after such biopsy, whereas more years of biopsy during the study year was the only factor significantly with an increased risk of hospital admission in a multivariable analysis [8]. Interestingly, Zaytoun et al. found that recent use of anticoagulant/antiplatelet therapy (defined as use within 10 d before biopsy) increased the risk of developing both infectious complications and clinical hematospermia [18]. Kim et al. reported that biopsy performed as an outpatient procedure without a cleansing enema ($p=0.001$) and a history of cerebrovascular accident ($p=0.048$) were statistically significant predictors of risk [26].

In our study, *E. coli* was the pathogen isolated most frequently from patients with infectious complications of prostate biopsy, which was consistent with previous findings [15,20,26,27]. Soto et al. investigated the association of in vitro biofilm formation by strains of *E. coli* with their ability to cause cystitis, pyelonephritis, or prostatitis, and found that the strains causing prostatitis produced biofilms in vitro more frequently than did those causing cystitis and pyelonephritis, and that this was associated with a higher frequency of expression of the virulence factor hemolysin [28]. Because the needle used for TRUS-guided biopsy of the prostate apparently introduces bacteria from the rectum into the urine or blood [13], most strains of *E. coli* isolated after such biopsy are of enteric origin. However, it may not be appropriate to translate this evidence for the source of acute prostatitis into prostate biopsy-related prostatitis. Indeed, the phylogenetic distribution of uropathogenic *E. coli* (UPEC) and that of fecal strains of the organism is different [28]. Uropathogenic strains show greater expression of virulence factors (i.e., hemolysin, aerobactin, yersiniabactin, P-fimbriae, and type 1 fimbriae) and a greater ability to form in vitro biofilm than do intestinal strains of *E. coli* [28]. This finding also reflects the importance of the correct use of prophylactic antibiotics in TRUS-guided biopsy of the prostate, and of a sufficiently high intraprostatic drug concentration to eradicate the fecal strains of *E. coli* responsible for prostatitis [22].

We found that some of the strains of *E. coli* isolated from patients in our study were resistant to same fluoroquinolone drugs (e.g., ciprofloxacin, levofloxacin, and lomefloxacin), and that most were sensitive to the majority of drugs of the cephalosporin class. Because the fluoroquinolones reach a

higher concentration in prostate tissue than do other antimicrobials [29], most of the prophylactic antimicrobials used in clinical trials have been fluoroquinolones, with varying protocols for their administration [8,15], including that in the present study. We also found that the incidence of infectious complications was reduced further when patients were instructed thoroughly about the use of their prophylactic antimicrobial medications. Because mineral-fortified meals or drinks may interfere with the absorption of fluoroquinolones [30], it is important to let patients know the factors of which they should be aware in their use of these medications.

Our study had several limitations. First, it was retrospective in design. Also, the incidence of infectious complications of TRUS-guided prostate biopsy as an end point was too low to provide statistical reliability. Beyond this, only data for symptomatic febrile patients were recorded, and some patients with subclinical manifestations of infection may not have been evaluated. Additionally, the study is lacking a cost-effectiveness analysis. Additional modalities may help to reduce the incidence of infection following TRUS-guided biopsy of the prostate, but they may influence patient compliance and effectiveness. For example, a pre-biopsy enema may not be an effective procedure for all patients, and particularly for elderly patients treated on an outpatient basis.

Conclusions

We found that the incidence of febrile UTI following TRUS-guided prostate biopsy decreased at our hospital across the periods of our study. This decrease was associated with the steps we took to reduce the incidence of such infection, including changes in the antimicrobial agents used to prevent such infection and the institution of thorough instructions to patients in their use of the antibiotics administered for this purpose. We believe that in addition to the proper selection of prophylactic antibiotics, such instructions before and after biopsy constitute an important strategy for reducing infectious complications following biopsy of the prostate.

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Author Disclosure Statement

The authors declare no conflict of interest.

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