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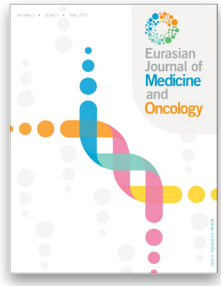


Research Article

# Prostate Biopsy to Diagnose Acute Bacterial Prostatitis: Current Microbiological Spectrum, Sensitivity to Antibiotics, and Clinical Findings in Turkey

**Hakan Turk,[1] Sitki Un,[2] Gamze Asli Sener,[3] Mehmet Yoldas,[1] Firat Akdeniz,[4] Erkan Arslan[5]**

[1]Department of Urology, Dumlupınar University Evliya Celebi Training and Research Hospital, Kutahya, Turkey
[2]Department of Urology, Denizli State Hospital, Denizli, Turkey
[3]Departement of Medical Microbiology, Katip Celebi University Ataturk Training and Research Hospital, Izmir, Turkey
[4]Department of Urology, Trabzon Kanuni Research and Training Hospital, Trabzon, Turkey
[5]Department of Urology, Harran University Faculty of Medicine, Sanlıurfa, Turkey

## Abstract

**Objectives:** Ultrasound-guided transrectal prostate biopsy is considered the standard procedure for diagnosing prostate cancer. However, minor complications, such as hematuria, hematospermia, and rectal bleeding, as well as clinically significant complications, such as urinary tract infections and acute bacterial prostatitis (ABP) can occur. ABP is an acute disease requiring immediate treatment. The aim of this study was to evaluate the clinical presentation, microbiological profile, antibiotic susceptibility, and treatment of patients with ABP that developed after a transrectal prostate biopsy.

**Methods:** The records of a total of 3550 patients who underwent an ultrasound-guided transrectal prostate biopsy in the clinic between September 2012 and December 2017 were retrospectively examined. The age, prostate volume, prostate-specific antigen level, number of cores per prostate biopsy, biopsy indications, and urine and blood culture results of those with ABP were recorded.

**Results:** Among 3550 patients who had undergone prostate biopsy, ABP developed in 195 (5.4%) following biopsy. Of these, 37 (39.3%) had initiated antibiotherapy treatment elsewhere before admission to this clinic. A positive urine culture was detected in 101 (51.7%) and a positive blood culture in 43 (22%) of the 195 patients diagnosed with ABP. The microorganisms were identified as *Escherichia coli* (141 patients), *Klebsiella* spp. (1 patient) and *Enterococcus faecalis* (2 patients). *E. coli* was the most common bacteria and was isolated in 98 (97%) of all urine cultures.

**Conclusion:** In complicated urinary tract infections, clinicians should consider antibiotic resistance patterns, particularly in terms of extended-spectrum beta-lactamase-producing strains, and should make the required changes for the treatment to be successful according to the culture results. To reduce the rate of this complication, frequent use of antibiotics should be avoided in primary healthcare centers.

**Keywords:** Antibiotherapy, prostate biopsy, sepsis, urine culture, uropathogenic bacteria

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Ultrasound-guided transrectal prostate biopsy is considered as the standard procedure for diagnosing prostate cancer. Although this procedure is generally considered to be safe, complications may rarely occur. These include minor complications such as hematuria, hematospermia, and rectal bleeding as well as clinically significant complications such as urinary tract infections, acute bacterial prostatitis (ABP), epididymo-orchitis, and urosepsis. [1] The rate of complications associated with infections following prostate biopsy has been reported to be 1.7–11.3%.

**Address for correspondence:** Hakan Turk, MD. Dumlupinar Universitesi Evliya Celebi Egitim ve Arastirma Hastanesi Uroloji Anabilim Dalı, Kutahya, Turkey
**Phone:** +90 555 551 68 85 **E-mail:** hkntrk000@hotmail.com
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[2, 3] ABP is characterized by symptoms such as fever, chills, rectal and perineal pain, frequent urination, and dysuria. Fatigue and muscle and joint pain can also accompany. The National Institutes of Health has defined four categories of prostatitis: acute bacterial, chronic bacterial, chronic prostatitis/chronic pelvic pain syndrome, and asymptomatic. ABP is an acute disease requiring immediate treatment. Generally, in-patient treatment is required due to complications such as urosepsis.[4] Pathogens causing ABP can be detected in urine culture. In the setting of systemic symptoms, most physicians recommend intravenous (i.v.) antibiotics, such as beta-lactam agents, aminoglycosides, or quinolones, either alone or in combination with supportive measures including i.v. hydration and catheter drainage if patients cannot void.[5] In the present study, we aimed to evaluate the clinical presentation, microbiological profile, antibiotic susceptibility, and treatment of patients with ABP that developed after transrectal prostate biopsy.

## Methods

The Institutional Review Board approved this study and waived the requirement of informed consent. A total of 3550 patients who had undergone ultrasound-guided transrectal prostate biopsy in four clinics between September 2014 and December 2017 were retrospectively examined. Biopsy specimens were obtained using an automated biopsy gun with an 18-gauge-needle. All patients were started on prophylactics, two doses of 500 mg ciprofloxacin at the day of biopsy and aminoglycoside therapy for patients who had received antibiotic treatment within the last 3 months. The age, prostate volume, prostate-specific antigen levels, number of cores per prostate biopsy, biopsy indications, and urine and blood culture results of those with ABP were recorded. The diagnosis of ABP was established upon fever higher than 38°C, >5–10 white blood cells/high power field leukocytes in urine sediments, and positive urine and/or positive blood cultures.[6] Standard blood biochemistry tests, semi-quantitative urine dip stick tests, and urine cultures for microbiological examinations were performed for all patients.

Midstream clean-catch urine was collected in a sterile urine container for performing a microbiological examination. Quantitative cultivation was performed on 5% sheep blood agar and eosin methylene blue agar, simultaneously with the direct microscopic examination of urine samples submitted to the laboratory. Agar plates were incubated at 37°C for 18–24 h. Bacterial identification and antimicrobial susceptibility tests of patients having positive culture growth on plaques were performed using the automated identification system VITEK 2 (Biomerioux-France) or the Kirby-Bauer disk diffusion method according to the criteria of the Clinical Laboratory Standards Institute; the antibiotic sensitivity of bacteria was detected with respect to the measured zone diameter.[7]

Patients suspected of having ABP were hospitalized at the urology clinic and i.v. fluid administration and empirical antibiotic treatment were initiated. Then, these patients were treated with sensitive antibiotics and discharged with full recovery.

## Results

In this study, 3550 patients were determined to have undergone prostate biopsy, and ABP developed in 195 (5.4%) of them, following biopsy. The mean age of all patients was 63.3±12.07 years, while the mean prostate volume 38.1 cm3 (range, 24-90 $cm^3$) in those with ABP. The mean number of cores per prostate biopsy was 12 (range, 8-16). Patients were admitted with fever or other symptoms 36 h after undergoing prostate biopsy on average. Table 1 presents

**Table 1.** Initial characteristics of patients with acute bacterial prostatitis

| | Total (195) | |
|---|---|---|
| Mean age (years) | 63.3 | |
| Symptoms | | |
| Fever | 190 | |
| Pain* | 150 | |
| Dysuria | 180 | |
| Retention | 29 | 8 epicystostomy, 21 Foley catheter |
| Obstructive symptoms | 145 | |
| Storing symptoms | 130 | |
| Initial urinalysis | | |
| Hematuriaα | 151 | |
| Pyuriaβ | 187 | |
| PSA (ng/mL) | 12.3 | |
| TRUS (mL) | 38.1 | |

PSA, prostate-specific antigen; TRUS, transrectal ultrasound. *Suprapubic pain, arthralgia, and myalgia; α: >4 red blood cells/high power field; β: >4 white blood cells/high power field.

**Table 2.** Microbial spectrum of patients with acute bacterial prostatitis

| | Patients (%) |
|---|---|
| Sterile urine | 94 (48.2) |
| *Escherichia coli* | 98 (97) |
| *Klebsiella spp.* | 1 (1) |
| Enterococci | 2 (2) |
| ESBL *E. coli* | 13 (13.2) |

**Table 3.** Sensitivity of bacterial strains to antibiotics in patients with ABP

| | *E. coli* sensitivity (%) | *Klebsiella spp.* sensitivity (%) | *Enterococcus* sensitivity (%) |
|---|---|---|---|
| Tigecycline | 100 | 100 | 100 |
| Ampicillin | 12.2 | 100 | 100 |
| Amoxicillin+clavulanic acid | 43.8 | | |
| Ampicillin+sulbactam | 36.3 | | |
| Piperacillin+tazobactam | 89.4 | | |
| Trimethoprim/Sulfamethoxazole | 30.4 | | |
| Cefuroxime | 52.7 | | |
| Cefotaxime | 47 | | |
| Ceftriaxone | 48.5 | | |
| Cefoperazone | 28.5 | | |
| Cefoperazone+sulbactam | 85.1 | | |
| Ceftazidime | 46.2 | | |
| Ertapenem | 100 | | |
| Cefepime | 37.2 | | |
| Ciprofloxacin | 11.2 | 0 | 0 |
| Gentamicin | 44.2 | 0 | 0 |
| Amikacin | 86.5 | | |
| Imipenem | 100 | | |
| Meropenem | 100 | | |
| Cefazolin | 47.9 | | |
| Cefepime | 37.2 | | |
| Nitrofurantoin | 82.9 | | |
| Phosphomycin | 96.8 | | |

symptoms seen at the time of admission. Acute urinary retention developed in 29 patients (14.8%) during treatment; a 16-Fr Foley catheter was inserted in 21 patients, and an epicystostomy was inserted in 8 patients. The urine culture was negative in 94 (48.2%) patients who developed ABP. Of these, 37 (39.3%) had been initiated on antibiotherapy elsewhere, before admission to our clinic. Positive urine culture was detected in 101 (51.7%) and positive blood culture was detected in 43 (22%) of the 195 patients with ABP, and the microorganisms were *Escherichia coli* (141 patients), *Klebsiella spp.* (1 patient), and *Enterococcus faecalis*.[2] *E. coli* was the most common bacteria and was isolated in 98 (97%) of all urine cultures (Table 2). An overview of the resistance to antimicrobial drugs in ABP patients is shown in Table 3. The most commonly used empirical antibiotics were ertapenem, ampicillin+amikacin and ceftriaxone. The empirical antibiotics used are shown in Table 4. In 69 (35.3%) patients receiving empirical antibiotherapy, treatment was changed because of urine culture results and/or failed response to empirical antibiotherapy. Sepsis developed in 5 patients and was responsible for the death of 2 patients. After treatment, abscess developed in 1 patient, recurrence was detected in 4 patients, and chronic prostatitis was diagnosed in 10 patients (Table 5). All patients who had recurrence or were diagnosed with chronic prostatitis were identified to have been initiated on antibiotherapy before they were admitted to our clinic.

## Discussion

ABP is a serious infection that can be diagnosed based on clinical findings and urine cultures. ABP is usually caused by uropathogenic bacteria and manifests with symptoms such as fever, chills, rectal pain, frequent urination, and dysuria. Pyuria, microscopic hematuria, and bacteriuria can be seen. ABP patients may present with symptoms of urinary tract infection and sometimes with sepsis. In ABP patients, prostate massage, rectal examination, and transrectal ultrasonography may cause bacteremia and sepsis.[8] The most common causative organisms of ABP are gram-negative bacteria (90%), particularly *E. coli* (50–80% of patients). In our patients, *E. coli* was the most common isolated bacteria.

Among gram-positive bacteria (10%), *Enterococcus* spp. and *Staphylococcus aureus* are observed most frequently.[9] The increasing prevalence of gram-positive pathogens may represent a change in the epidemiology of the disease due to treatment. In some cases, prostatitis is caused by

**Table 4.** Distribution of empirical antibiotics

| | |
|---|---|
| No antibiotic | 2 |
| Ampicillin-sulbactam+Amikacin | 41 |
| Ciprofloxacin | 14 |
| Trimethoprim/sulfamethoxazole | 1 |
| Ertapenem | 80 |
| Imipenem | 3 |
| Meropenem | 2 |
| Piperacillin+tazobactam | 6 |
| Ceftriaxone | 32 |
| Cefuroxime | 4 |
| Cefoperazone+sulbactam | 7 |
| Levofloxacin | 2 |
| Gentamicin | 1 |
| Total | 195 |

atypical pathogens.[10, 11] Sterile urine cultures in ABP patients may be because of the previous use of antibiotics.

The most serious complications of transrectal ultrasonography-guided prostate biopsies are bacterial infections. Colonic bacteria carried into the prostate tissue during biopsy may cause infection.[12] Bacteremia has been reported to occur in 16-73% of patients, while bacteriuria in 36-44% of patients; *E. coli* was the most commonly isolated bacteria.[13]

Etienne et al.[14] evaluated 371 patients and reported that half of them were treated with combination antibiotic therapy. They stated that aminoglycosides were added in 80% and third-generation cephalosporins in 56% of the cases of combination therapies. They found that empirical antibiotic therapy failed in 16% of patients, but the treatment initiated according to culture and antibiogram results failed in 7% of patients.[14] In our study, empirical antibiotic therapy was initiated in 35.3% of patients and modified by culture results or clinical unresponsiveness. The most frequently changed empirical treatment was penicillin+aminoglycosides.

Urine cultures were reported to be positive in 60-80% of ABP patients in whom the threshold for bacteriuria was considered as 104 CFU/ml.[14, 15] This percentage was found to be 35.4 in the series of Lee et al.,[16] and the most frequently isolated bacteria was *E. coli*. Those authors argued that starting empirical antibiotic therapy without obtaining urine culture results would be sufficient for treating treatment ABP.[16] In our study, however, growth rate in urine culture was determined as 51.7%.

Although prophylaxis with fluoroquinolones is effective for preventing infectious complications in many patients who have undergone transrectal prostate biopsy, it has been reported in the literature that infections resistant to fluoroquinolones are also observed after performing biopsy.[6, 17-21] Ciprofloxacin-resistant pathogens and nosocomial

**Table 5.** Characteristics of the course of infection in acute bacterial prostatitis

| | Total | Acute retention foley (14) | Acute retention epicystostomy (4) |
|---|---|---|---|
| Abscess | 1 | 1 | |
| Recurrence | 4 | 2 | |
| Progression to chronic prostatitis | 10 | 5 | 1 |
| Urosepsis | 5 | 2 | |
| Exitus | 2 | | |

Includes only patients available to follow-up over 6 months.

acquisition or prior instrumentation have been associated with increased antibiotic resistance and higher clinical failure rates.[22] In our study, pathogens isolated in urine cultures were observed to be resistant to fluoroquinolones in 81.1% of the patients. For this reason, we used aminoglycosides for patients who had a history of pre-biopsy antibiotherapy.[23] Therefore, we believe that fluoroquinolones have no place in the empirical treatment of ABP after performing prostate biopsy.

The use of blood cultures in the diagnosis of ABP patients is still controversial and does not yield desired outcomes. In addition, the diagnostic and prognostic significance of blood cultures has not been sufficiently proven.[14] The microbiological failure rate of blood cultures in urinary tract infections is high (75%).[24] Blood cultures are theoretically successful for diagnosing and treating patients with negative urine cultures. However, blood culture results are obtained late; this has a negative impact on its usability. In their study in which the role of blood cultures in the diagnosis and treatment of ABP patients was evaluated, Etienne et al showed that blood cultures were positive in 21% of the patients and that this has a 5% contribution to making the diagnoses.[25] In our study, the blood cultures of 43 (22%) patients were positive. Thirty-two (74.4%) patients with positive blood cultures had the same pathogen in urine cultures. The treatment of only 1 (0.5%) patient was altered with respect to blood culture.

Drug concentrations are high in urine, seminal fluid, and prostate tissue but low in prostate fluid. In humans, the concentrations of alkaline drugs such as trimethoprim and clindamycin are high in the prostate. Acidic drugs such as beta-lactams can be detected at low levels.

Penicillin G can reach low concentrations in the prostate, while piperacillin can reach high concentrations; successful outcomes can be obtained in the treatment of ABP. Cephalosporins are detectable in therapeutic levels in the prostate tissue and fluid. However, aztreonam, imipenem, and

some aminoglycosides can reach levels over the minimal inhibitory concentration in the prostate tissue for most organisms belonging to the family Enterobacteriaceae. Prostate concentrations of minocycline and doxycycline are at least 40% of their serum concentrations. High concentrations of erythromycin and other macrolides can be achieved in the prostate. Clindamycin and trimethoprim easily pass into the prostatic fluid and are detectable in the prostate fluid at concentrations that can exceed plasma levels. The prostate concentrations of sulfamethoxazole, even with trimethoprim, are very low. However, the prostate levels of nitrofurantoin remain below the therapeutic level.

Parenteral antibiotic therapy, at least initially, is recommended for patients with ABP and systemic symptoms. Broad-spectrum beta-lactams, piperacillin-tazobactam, cephalosporin, or cephalosporin+aminoglycoside is recommended options for patients who have recently received antibiotherapy or have serious infections.[26]

Regarding the patients in the present study, the most commonly initiated empirical treatment was ampicillin-sulbactam+aminoglycoside and ertapenem. However, ampicillin-sulbactam+aminoglycoside has been the most altered empirical treatment due to the culture results or unresponsiveness to them.

The most important method to prevent antibiotic resistance is to use them rationally. Non-compliance with the antibiotic use policy, prophylaxis with fluoroquinolones, and bacteria producing extended-spectrum beta-lactamases are important for developing resistance. For antibiotic prophylaxis in ultrasound-guided transrectal prostate biopsy, it is recommended to use a single dose of ceftriaxone, without the short-term use of fluoroquinolone.[27] Data have shown that knowledge on the susceptibility of uropathogens to antibiotics will guide the treatment planning of urinary tract infections.[28]

While planning empirical treatment, clinicians should consider local drug-resistance properties.[26] Antibiotics used in prophylaxis should be replaced if necessary depending on resistance to the local drug. We determined resistance to fluoroquinolone in over 80% in our ABP patients. Therefore, we also consider local resistance to fluoroquinolones in planning treatment. In our experience, patients in a good general condition can be treated with oral antibiotics. Treatment of AMP usually lasts for 2 weeks, although it can continue for up to 4 weeks in complicated cases.[10]

Resistance to fluoroquinolone is increasingly becoming a major problem, and these cases require treatment with third-generation cephalosporins or carbapenem. Resistance to ciprofloxacin was 55% in 2011, while it has been recently reported to reach 90%.[12] In our study, resistance to ciprofloxacin was detected in 50% of strains, while it was lower (42%) for inpatients. The highest sensitivity to tigecycline, cefoperazone-sulbactam, colistin, amikacin, imipenem, and meropenem was detected in *Klebsiella* strains. Similar rates were found for Proteus strains. However, ciprofloxacin, amikacin, third-generation cephalosporins, or ciprofloxacin+gentamicin is very effective for treating ABP. Increasing resistance to fluoroquinolones is being reported in studies on antibiotic resistance. In light of this fact, it is clear that we will need different antibacterial agents. It is crucial to consider the consequences of antibiotic resistance during antibiotic selection.

An inflammatory pattern in the primary biopsy is not associated with a decrease in prostate cancer incidence at repeated saturation prostate biopsy; therefore, only an accurate clinical evaluation including more parameters (PCA3, multiparametric magnetic resonance imaging) may select men who need to undergo rebiopsy in the presence of a persistent suspicion of cancer.[29]

## Conclusion

To the best of our knowledge, this is the first report recording the clinical and microbiological aspects of ABP in Turkey. This survey may help clinicians select the appropriate empirical treatment. Patients with ABP should be hospitalized without delay, and parenteral antibiotics and fluid therapy should be initiated. Due to the frequent use of fluoroquinolones, serious resistance against these drugs is a matter of fact. Therefore, broad-spectrum beta-lactam antibiotics, piperacillin, tazobactam, ertapenem, cephalosporins, or cephalosporin+aminoglycoside are the recommended options for the empirical treatment of patients who have recently been treated with antibiotics and who have had serious infections. In complicated urinary tract infections, clinicians should consider antibiotic resistance patterns, particularly in terms of extended-spectrum beta-lactamase-producing strains, and should make required changes according to the culture results to make the treatment successful. ABP is a serious complication that can occur after prostate biopsy. To reduce the rate of this complication, frequent use of antibiotics should be avoided in primary healthcare centers. Previous antibiotherapies should be taken into consideration in planning prophylaxis during its application prior to prostate biopsy.

### Disclosures

**Ethics Committee Approval:** The study was approved by the Local Ethics Committee.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship contributions:** Concept – H.T., S.U., E.A.; Design – H.T., G.A.S., F.A.; Supervision – S.U., F.A.; Materials – H.T., M.Y., E.A.;

Data collection &/or processing – H.T., S.U., F.A., E.A.; Analysis and/or interpretation – H.T., G.A.S.; Literature search – H.T., S.U.; Writing – H.T., S.U.; Critical review – G.A.S., E.A.

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