# Antibiotic Prophylaxis with Different Antibiotic Regimen In Prostate Biopsy Patients

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# ANTIBIOTIC PROPHYLAXIS WITH DIFFERENT ANTIBIOTIC REGIMEN IN PROSTATE BIOPSY PATIENTS

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***ABSTRACT***

***Objective:*** *To know the incidence of urinary tract infection (UTI) with different antibiotic prophylaxis for transrectal ultrasonography (TRUS) prostate biopsy.* ***Material & Method:*** *The study included 34 patients at Soetomo Hospital Surabaya, who were divided into 2 groups, each group consisting of 17 patients. In the first group patients received 1000 mg of ciprofloxacin orally, in the second group cefotaxime 1000 mg iv was given prior to biopsy. The two groups were compared in terms of UTI incidence as observed from the blood levels of leukocytes, C-reactive protein (CRP) and urine culture 3 days after the procedure.* ***Results:*** *Based on blood leukocyte levels, there was no statistically significant difference between the two groups (p = 0,74 and p = 0,42). So was the comparison of CRP levels. There was no other significant difference found (p = 0,53 and p = 0,27). From the results of urine culture, the ciprofloxacin group had positive urine culture results lower than the cefotaxime group (29,4% : 35,3%), although it was not statistically significant (p = 1,0).* ***Conclusion:*** *Based on the parameters of blood leukocytes levels, CRP and urine culture, there were no differences in the incidence of UTI after biopsy in the two groups.*

***Keywords:*** *TRUS prostate biopsy, UTI, ciprofloxacin, cefotaxime.*

***ABSTRAK***

***Tujuan Penelitian:*** *Penelitian ini membandingkan angka kejadian ISK pada penggunaan ciprofloxacin 1.000 mg oral dengan cefotaxime 1.000 mg iv sebagai antibiotika profilaksis transrectal ultrasonography (TRUS) biopsi prostat.* ***Bahan & Cara:*** *Penelitian ini melibatkan 34 pasien yang terbagi menjadi 2 kelompok dengan masing-masing kelompok terdiri dari 17 pasien. Kelompok pertama merupakan pasien yang diberikan ciprofloxacin 1.000 mg oral dan kelompok kedua diberikan cefotaxime 1.000 mg iv sebelum dilakukan TRUS biopsi prostat. Dari kedua kelompok tersebut dibandingkan angka kejadian ISK yang dilihat dari parameter kadar leukosit darah, C-reactive protein (CRP) dan kultur urine 3 hari setelah prosedur.* ***Hasil Penelitian:*** *Berdasarkan parameter kadar leukosit darah, secara statistik tidak ada perbedaan yang bermakna antara kedua kelompok (p = 0,74 dan p = 0,42). Begitu juga dengan perbandingan kadar CRP, tidak didapatkan perbedaan yang bermakna (p = 0,53 dan p = 0,27). Dari hasil kultur urine, kelompok ciprofloxacin memiliki hasil kultur urine positif lebih rendah dibanding kelompok cefotaxime (29,4% : 35,3%) meskipun secara statistik tidak berbeda bermakna (p = 1,00).* ***Simpulan:*** *Tidak didapatkan adanya perbedaan angka kejadian ISK pada pemberian dua macam antibiotik profilaksis.*

***Kata Kunci:*** *TRUS biopsi prostat, ISK, ciprofloxacin, cefotaxime.*

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## INTRODUCTION

Urinary tract infection (UTI) is a urothelium inflammatory response against bacterial invasion usually associated with bacteriuria and pyuria.[1,2] Examination of the body temperature and blood leukocytes can be used as a classic sign of infection and are part of the systemic inflammatory response syndrome (SIRS).[3]

C-reactive protein (CRP) is an acute phase protein detected since acute inflammatory phase. CRP is secreted from 4-6 hours after the stimulus and is independent, in which CRP level is affected only when the stimulus is removed or there is provision of anti-inflammatory drugs. To diagnose sepsis, CRP has the best cut-off point on the levels of 50 mg/l with

a sensitivity of 98,5% and a specificity of 75%. Therefore, CRP is an accurate marker of infection.[3,4]

On laboratory examination, gold standard for diagnostic establishment of UTI is urine culture in a significant value obtained when the bacteria colonies more than 105 colony forming units (CFU)/ml.[1,2,5,6]

Transrectal ultrasonography (TRUS) prostate biopsy is a diagnostic instrumentation in the field of urology for the early detection of prostate malignancies. Since first introduced by Hodge et al in 1989, this technique continues to evolve and become a gold standard for early detection of prostate malignancies.[7] Because it is invasive by inserting a biopsy needle to penetrate into the prostate through the rectum, this examination carries the risk of rectal bacteria entering the urinary tract resulting UTI.[8] The incidence of UTI in TRUS prostate biopsy without antibiotic prophylaxis is 10-44%,[8-10] with the most common bacterial causes being Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and Enterococcus sp.[11]

Infections caused by anaerobic bacteria are very rare, even from a study conducted by Breslin et al. in patients who underwent TRUS prostate biopsy. They did not get an infection due to anaerobic bacteria.[12] With the high rate of UTI, many studies have been conducted on antibiotic prophylaxis for TRUS prostate biopsy. Oral antibiotics are administered by 93,3%, intramuscular 3,5% and combination 3,3%.[9]

Ciprofloxacin is a quinolone derivatives of carboxylic acids that have broad spectrum antibacterial activity against gram-positive and gram negative bacteria, including those resistant to aminoglycosides and beta-Lactam antibiotics. Even in patients with impaired renal function, ciprofloxacin was safely administered at an adjusted dose.[13] There will be a proportional increase in peak serum concentration and area under curve (AUC) along with increasing oral doses of ciprofloxacin up to 1,000 mg.[14] From the data obtained at the Section of Clinical Microbiology Soetomo Hospital Surabaya, ciprofloxacin has a high sensitivity against UTI-causing bacteria, such as E. coli (45%), Klebsiella pneumoniae (55%), Pseudomonas aeruginosa (53%), and Enterobacter (48%) (Department of Clinical Microbiology, Soetomo Hospital, 2010).

Whereas, the duration of antibiotic prophylaxis is still being debated. However, from a study conducted by Aron et al. and Briffaux et al. it was found that there was no significant difference in the incidence of UTI between single dose of antibiotics compared with antibiotics up to 3 days after the procedure.[11,15]

On a randomized control trial (RCT) in England it was found that the antibacterial activity of ciprofloxacin includes four common bacterial cause of UTIs (Escherechia coli, Klebsiella pneumoniaea, Pseudomonas aeruginosa and Enterococcus sp) with the best dose is 1.000 mg single dose, 30 minutes before biopsy.[16]

At the Installation of Minimally Invasive Urology (IIU), Department of Urology, Soetomo Hospital Surabaya, we use cefotaxime 1000 mg intravenous (iv) as a single dose of antibiotic prophylaxis for TRUS prostate biopsy in patients with sterile urine culture results. Cefotaxime was chosen because it has a broad spectrum antibacterial, against both gram-positive and gram-negative and included in the formulary of ASKES and JAMKESMAS as well. However, the use of cefotaxime can only be parenteral, either intramuscular (im) or intravenous (iv). This makes patients undergoing TRUS prostate biopsy to be less comfortable than if antibiotic prophylaxis is administered enterally. Besides, financially, antibiotic injection types will be more expensive when compared with the type of oral antibiotics.

Therefore, this study selected 1.000 mg of oral ciprofloxacin as a prophylactic antibiotic because it has broad spectrum antibacterial activity against gram-positive and gram negative bacteria, including those resistant to aminoglycosides and beta-Lactam antibiotics. In addition, oral ciprofloxacin is also included in the formulary of ASKES and JAMKESMAS.

## OBJECTIVE

Comparing the incidence of UTI in patients with post-TRUS prostate biopsy with prophylactic antibiotic ciprofloxacin 1000 mg single oral dose with cefotaxime 1.000 mg iv single dose with a parameter of blood leukocytes, CRP, and urine culture.

## MATERIAL & METHOD

This is a randomized study, which was conducted from January to June 2011, with a total of 34 patients who met the inclusion criteria study. With randomization, patients were then divided into 2

groups with each group consisted of 17 patients. The first group was patients who underwent TRUS prostate biopsy with prophylactic antibiotic cefotaxime 1000 mg iv single dose and the second group were patients who underwent TRUS prostate biopsy with prophylactic antibiotic ciprofloxacin 1.000 mg oral single dose.

Inclusion criteria in this study were BPH LUTS patients to be subjected to TRUS prostate biopsy, and had sterile urine culture. All patients were asked about medical history, history of previous surgery and the use of antibiotics.

Laboratory tests include CBC, CRP, renal function tests, urinalysis and urine culture. Examination of renal function and urine culture was to rule out the existence of renal insufficiency and UTI (bacteria colonies > 105 cfu/ml). This laboratory examination was done unless the examination of renal function was repeated 3 days after the procedure. Especially for culture examination of urine, the sample was taken just before biopsy (at the same day) and 3 days after the biopsy from midstream urine. Plain abdominal x-ray was taken to ensure that no foreign bodies in the urinary tract (DJ Stents, urinary tract stones, and foreign bodies).

Analyses were performed descriptively and inferentially. Descriptive analysis was performed in bacteria identification. Inferential analysis was performed using Chi Square comparison test. The significance level used was 0,05.

## RESULTS

In table 1, no statistically significant difference in age distribution of the two groups (p = 0,78).

Based on the patient's clinical parameters, cefotaxime and ciprofloxacin group statistically showed no significant difference (Table 2), pulse (p = 0,98) and temperature (p = 0,61). Of laboratory tests, blood leukocyte level in ciprofloxacin group was higher than that in cefotaxime group, but it was not statistically significant (p = 0,26). In contrast, blood CRP levels was higher in cefotaxime group than that in ciprofloxacin group, although it was not statistically significant (p = 0,57).

From Table 3, in the parameter of blood leukocytes, there is an increase in blood leucocytes after treatment in cefotaxime group, although it was not statistically significant (p = 0,74). In contrast, the

**Table 1.** Age difference between groups.

| Age (year) | Groups *Cefotaxime* 1000 mg | Groups *Ciprofloxacin* 1000 mg | p value |
|---|---|---|---|
| | n = 17 (%) | n = 17 (%) | |
| < 60 | 3 (17,7) | 4 (23,5) | |
| 60 – 70 | 10 (58,8) | 10 (58,8) | |
| > 70 | 4 (23,5) | 3 (17,6) | |
| Mean ± SD | 65,5 ± 8,0 | 64,8 ± 6,9 | 0,78 |
| Range | 48 – 81 | 51 – 78 | |

**Table 2.** Characteristics of the samples.

| Variables | Cefotaxime | Ciprofloxacin | *p* |
|---|---|---|---|
| Pulse (x/mnt) | 79,17 ± 1,74 | 79,29 ± 2,22 | 0,98 |
| Temperature (°C) | 36,62 ± 0,09 | 36,64 ± 0,11 | 0,61 |
| Leuko (x1000/mm$^3$) | 7,49 ± 2,04 | 8,21 ± 1,63 | 0,26 |
| CRP (mg/l) | 4,21 ± 1,89 | 3,75 ± 2,71 | 0,57 |

**Table 3.** Sample characteristics before and after treatment.

| Variables | Antibiotics | Pre Biopsy | Post Biopsy | *p* |
|---|---|---|---|---|
| Pulse (x/mnt) | *Cefotaxime* | 79,17 ± 1,74 | 79,64 ± 1,45 | 0,33 |
| | *Ciprofloxacin* | 79,29 ± 2,22 | 79,17 ± 1,59 | 0,82 |
| Temperature (°C) | *Cefotaxime* | 36,62 ± 0,09 | 36,62 ± 0,09 | 1,00 |
| | *Ciprofloxacin* | 36,64 ± 0,11 | 36,64 ± 0,08 | 1,00 |
| Leuko (x1000/mm$^3$) | *Cefotaxime* | 7,49 ± 2,04 | 7,65 ± 1,53 | 0,74 |
| | *Ciprofloxacin* | 8,21 ± 1,63 | 8,01 ± 1,62 | 0,42 |
| CRP (mg/l) | *Cefotaxime* | 4,21 ± 1,89 | 4,52 ± 2,02 | 0,53 |
| | *Ciprofloxacin* | 3,75 ± 2,71 | 4,30 ± 2,42 | 0,27 |

ciprofloxacin group shows decreased levels of blood leucocytes after treatment, although not statistically significant (p = 0,42). Based on the parameters of blood CRP, both cefotaxime and ciprofloxacin groups revealed elevated levels of blood CRP after treatment, but it was again not statistically significant (p = 0,53 and p = 0,27).

Ciprofloxacin group (table 4) had lower positive urine culture than the cefotaxime group (29,4% : 35,3%). Although it was not statistically significant (p = 1,00).

There were 4 patients (11,8%) with non-significant bacteriuria. Klebsiella pneumoniae of > 105 cfu/ml were found in 5 patients (14,7%) of the total sample. Pseudomonas aeruginosa of > 105 cfu/ml and Burkholderia cepacia of > 105 cfu/ml each was found only in 2 patients (11,8%) in the cefotaxime group. The remaining 19 patients (55,9%), revealed sterile urine culture (Table 5).

In all of those patients, either the patient's complaints, physical examination (pulse and temperature) or laboratory (blood leukocytes and CRP) results 3 days after the procedure revealed no signs of infection (Table 6).

In patients with positive urine culture results (Table 7), both cefotaxime and ciprofloxacin groups in regard with complaints, physical examination (pulse and temperature), and laboratory tests (blood leukocytes and CRP) did not show any signs of infection.

Based on the variable rate, differences in changes of vital signs between groups of cefotaxime and ciprofloxacin groups were not significant (p = 0,41) (Table 8). So was the temperature (p = 1,00). From the results of laboratory tests, the difference between changes in blood leukocyte levels of cefotaxime and ciprofloxacin groups was not significant (p = 0,50). So was CRP levels between the two groups (p = 0,74).

**Table 4.** Urine culture results after treatment.

| Culture results | Groups | | Total |
|---|---|---|---|
| | *Cefotaxime* | *Ciprofloxacin* | |
| Positive | 6 (35,3%) | 5 (29,4%) | 11 (32,4%) |
| Negative | 11 (64,7%) | 12 (70,6%) | 23 (67,6%) |
| Total | 17 (100%) | 17 (100%) | 34 (100%) |

**Table 5.** Types of bacteria in the urine culture after treatment.

| Culture Results cfu/ml | Groups | | Total |
|---|---|---|---|
| | *Cefotaxime* | *Ciprofloxacin* | |
| *E.coli* < $10^3$ | 3 (17,6%) | 1 (5,9%) | 4 (11,8%) |
| *E.coli* > $10^5$ | 0 (0%) | 2 (11,8%) | 2 (5,9%) |
| *Klebsiella pneumoniae* > $10^5$ | 2 (11,8%) | 3 (17,6%) | 5 (14,7%) |
| *Pseudomonas aeruginosa* > $10^5$ | 2 (11,8%) | 0 (0%) | 2 (5,9%) |
| *Burkholderia cepacia* > $10^5$ | 2 (11,8%) | 0 (0%) | 2 (5,9%) |
| Sterile | 8 (47,1%) | 11 (64,7%) | 19 (55,9%) |
| Total | 17 (100%) | 17 (100%) | 34 (100%) |

**Table 6.** Characteristics of patients with urine culture results < 103 cfu/ml.

| Post Biopsy Culture | Antibiotics | Pulse (x/mnt) | Temperature (°C) | Blood leukocytes (x1000/mm$^3$) | CRP (mg/l) | Complaints |
|---|---|---|---|---|---|---|
| *E. coli* | *Cefotaxime* | 80 | 36,7 | 6,0 | 4,0 | - |
| *E. coli* | *Cefotaxime* | 78 | 36,7 | 5,0 | 3,0 | - |
| *E. coli* | *Cefotaxime* | 78 | 36,5 | 6,6 | 4,0 | - |
| *E. coli* | *Ciprofloxacin* | 78 | 36,5 | 8,8 | 9,4 | - |

**Table 7.** Characteristics of patients with positive urine culture results.

| Post Biopsy Culture | Pulse (x/mnt) | Temp. (°C) | Blood leukocytes (x1000/mm$^3$) | CRP (mg/l) | Complaints | Antibiotics |
|---|---|---|---|---|---|---|
| *Burkholderia cepacia* | 80 | 36,5 | 6,5 | 5,0 | - | *Cefotaxime* |
| *Burkholderia cepacia* | 82 | 36,7 | 10,4 | 7,0 | - | *Cefotaxime* |
| *Klebsiella pneumoniae* | 80 | 36,5 | 7,2 | 1,9 | - | *Cefotaxime* |
| *Klebsiella pneumoniae* | 80 | 36,7 | 6,5 | 2,8 | - | *Cefotaxime* |
| *Pseudomonas Sp* | 82 | 36,7 | 7,8 | 4,0 | - | *Cefotaxime* |
| *Pseudomonas Sp* | 78 | 36,7 | 9,0 | 4,2 | - | *Cefotaxime* |
| *E. coli* | 80 | 36,5 | 10,5 | 4,7 | - | *ciprofloxacin* |
| *E. coli* | 76 | 36,6 | 8,4 | 4,0 | - | *ciprofloxacin* |
| *Klebsiella pneumoniae* | 80 | 36,5 | 9,6 | 3,3 | - | *ciprofloxacin* |
| *Klebsiella pneumoniae* | 80 | 36,5 | 8,8 | 3,0 | - | *ciprofloxacin* |
| *Klebsiella pneumoniae* | 78 | 36,6 | 7,8 | 8,0 | - | *ciprofloxacin* |

**Table 8.** Differences in changes of vital signs and laboratory.

| Variables | Antibiotics | | *p* |
|---|---|---|---|
| | Cefotaxime (mean) | Ciprofloxacin (mean) | |
| Pulse | 0,47 ± 1,94 | -0,11 ± 2,17 | 0,41 |
| Temperature | 0,00 ± 0,12 | 0,00 ± 0,09 | 1,00 |
| Blood leukocytes | 0,15 ± 1,94 | -0,20 ± 1,00 | 0,50 |
| CRP | 0,31 ± 2,07 | 0,54 ± 1,96 | 0,74 |

## DISCUSSION

This study found that most of the patients were distributed in the age group of 60-70 years, both in cefotaxime and ciprofloxacin groups. Cefotaxime group had an age range 48-81 years and the ciprofloxacin group had an age range 51-78 years. No statistically significant difference were seen in age distribution of the two groups.

From the results of laboratory examination 3 days after treatment, there was an increase in blood leucocytes in cefotaxime group, while in the ciprofloxacin group there was decreased level of blood leukocytes, although neither was statistically significant (p = 0,74 and p = 0,42). Although there were differences, blood leukocyte levels in both groups were still within normal limits (4.000-12.000/mm$^3$). Based on the parameters of blood CRP, both cefotaxime and ciprofloxacin groups showed elevated levels of blood CRP after treatment, but was not statistically significant (p = 0,53 and p = 0,27). Although increased, the levels of CRP both groups remained within normal limits (< 10 mg/l).

Based on the results of urine culture 3 days after treatment, ciprofloxacin group was found to have positive urine culture results lower than the cefotaxime group (29,4% : 35,3%), although it was not statistically significant (p = 1,00).

There were 4 patients (11,8%) with non-significant bacteriuria, i.e. with the results of urine E. coli culture of < 103 cfu/ml, 3 patients (17,6%) in cefotaxime group, and 1 patient (5,9%) in ciprofloxacin group. In these patients, the examination of pulse and temperature revealed no significant increase of blood leukocytes and CRP examination found no signs of infection. However, we still cannot excluded the possibility of contamination during urine sampling in these patients.

In the United States, in 1998 Kapoor et al. conducted a multicenter study comparing ciprofloxacin 500 mg single dose with placebo as prophylaxis antibiotic of TRUS prostate biopsy. They found 3% in ciprofloxacin group and 8% in placebo group with positive urine culture. This figure is smaller than the results of our research, which is 29,4% in the ciprofloxacin group and 35,3% in the cefotaxime group. However, in Kapoor's et al. study there were 2% of patients with urosepsis requiring hospitalization, although all of the patients

recovered without sequelae.[17] In our study, none of the patients with positive urine culture results were accompanied by signs of sepsis. In all of the patients, either from physical examination or laboratory investigations, there were no signs of inflammation caused by infection.

This study obtained a total of 11 patients (32,3%) with positive urine culture results. Mostly we found Klebsiella pneumoniae culture, as many as 45,5% of total bacteria, followed by E. coli, Pseudomonas aeruginosa and Burkholderia cepacia, each 18,1%. These results are in contrast to previous studies in which E. coli was the bacteria most commonly found. Kapoor et al. found 76% of urine culture results were E. coli, while Aron et al found 77,7%.[11,17]

Although E. coli is the bacteria most commonly found in the rectum (108-1010/ml), other Enterobacteriacea family, including Klebsiella pneumoniae, are also found in the rectum. Both bacteria are normal flora in human digestive tract. Despite normal flora, the bacteria are opportunistic. E. coli, for example, has endotoxin, production of capsule and pili that enable it to attach to the host, so that when the immune system is weak, E. coli entering into the urinary tract will begin to colonize and cause infection. So does Klebsiella pneumoniae, although included in opportunistic bacterial pathogens, it also has endotoxin, capsules adhesion proteins and resistant to various antimicrobial drugs.[18] With its ability to cause infection, when the bacteria is moving from its original habitat, they can lead to urinary tract infection.

Pseudomonas aeruginosa is commonly found in the digestive tract of adults. Pathogenicity of Pseudomonas aeruginosa, for example, is the exotoxin A and some hemolysin and proteolytic enzymes production that can destroy cells and tissues. These bacteria are opportunistic pathogens, meaning that these bacteria can cause infection if there is lower resistance, which can result in community or hospital acquired infections.[19] Interestingly, this study acquired Burkholderia cepacia culture results. These bacteria are not the normal flora of the digestive tract and urinary tract. Burkholderia cepacia is one of the genus Pseudomonas whose species including aerobic, gram negative, and straight rod bacteria. These bacteria can survive at a relatively low temperature (up to 4°C), and have the optimum temperature to grow and thrive at temperatures of 30-37°C. Natural habitat is in water, soil, and vegetation. Among the species of Burkholderia, B. cepacia is the most frequently found. Because the bacteria are less likely to cause infection in humans, knowledge of virulence is also very minimal. Because of its ability to survive in the hospital environment, Burkholderia cepacia is able to colonize and infect hospitalized patients. Transmission can be caused by patient contact with tools or medical fluids that have been contaminated.[19] In this case, the possibility of transmission of the bacteria can come from those that already colonize the gastrointestinal tract or the use of needle biopsy at IIU. Burkholderia cepacia is sensitive to several antibiotics, including ciprofloxacin, piperacillin, ceftazidime, imipenem, chloramphenicol, and trimethoprim/sulfamethoxazole.[19]

In this study, although the number of bacteria obtained was > 105 cfu/ml, we did not find any signs of inflammation caused by UTI. This is because, despite the colonization of bacteria, the immune system, assisted by prophylaxis antibiotics we have given earlier, was more predominant than the virulence of the bacteria.

## CONCLUSION

Cefotaxime and ciprofloxacin can be used as antibiotic prophylaxis in prostate biopsy.

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# Antibiotic Prophylaxis with Different Antibiotic Regimen In Prostate Biopsy Patients

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