CAT
Critically Appraised Topic

Bacterial sepsis with fluoroquinolone resistant *E. coli* after prostate biopsy — Is fluoroquinolone prophylaxis still effective?

Author: Deborah Steensels
Supervisor: Prof. Dr. J. Verhaegen & Prof. Dr. H. Van Poppel
Search/methodology verified by: Prof. Dr. P. Vermeersch
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CLINICAL BOTTOM LINE

The starting point of this critically appraised topic was the perception that an increased number of patients are being admitted for post-transrectal ultrasound-guided prostate biopsy (TRUSPB) sepsis at our center, and the concern of increasing ciprofloxacin resistance. In order to verify these speculations, a retrospective and prospective study was conducted.

First, a retrospective chart review of patients who presented back to our hospital with urosepsis after TRUSPB from 2003 to 2009 was performed. The overall incidence of urosepsis with positive blood cultures after TRUSPB was 0.95% (54/5663 biopsy procedures). However, the estimate of incidence was retrospective and assumed that all patients with sepsis after prostate biopsy reported back to our hospital. Therefore, the number of cases reported was likely an underestimation. Our study has shown that fluoroquinolone resistant infections after prostate biopsy are increasingly noted. The incidence of urosepsis was 0.39% from 2003 to 2005 and 1.41% from 2006 to 2009 (p-value < 0.01). Sepsis occurred in 33 patients after the first biopsy (1.01%), and in 21 patients after a repeat biopsy (2.23%) (p-value < 0.01), indicating that patients who underwent a repeat biopsy have a higher risk of developping sepsis. This is most likely explained by the higher incidence of chronic prostatitis in these patients.

Additionally, we started a prospective study to determine the local distribution of faecal pathogens and their susceptibility in patients undergoing TRUSPB starting on 1 December 2009. Today, this study is still ongoing. Of the first 100 patients who underwent TRUSPB, 21 had faecal ciprofloxacin resistant *E. coli* strains. Sepsis occurred in three patients. This high number indicates that the true incidence of sepsis after prostate biopsy at the University Hospital of Leuven is much higher than determined with our retrospective study. In these three cases, the sepsis was caused by ciprofloxacin resistant *E. coli*, and all patients had a history of previous use of quinolones less than six months before biopsy.

Since third generation cephalosporins are highly active against these quinolone resistant strains we would recommend intramuscular ceftriaxone as an alternative option for patients with a high risk of infectious complications and/or faecal carriage of quinolone resistant strains before biopsy. Quinolone resistant organisms will continue to be a problem after a TRUSPB. No single protocol can guarantee a perfect prophylaxis regimen before TRUSPB. Instead, the physician should consider several factors, including previous fluoroquinolone treatment and pre-existing chronic prostatitis, and tailor treatment on an individual case basis.

CLINICAL/DIAGNOSTIC SCENARIO

Prostate cancer rarely causes symptoms until it is advanced. Thus, suspicion of prostate cancer resulting in a recommendation for prostatic biopsy is most often raised by abnormalities found on digital rectal examination (DRE) or by serum prostate-specific antigen (PSA) elevations. The exact cutoff level of what is considered to be a normal PSA value has not been determined, but values of less than 2.5 ng/mL for younger men and slightly higher for older men are often used. Although there is controversy regarding the benefits of early diagnosis, it has been demonstrated that an early diagnosis of prostate cancer is best achieved using a combination of DRE and PSA.

Transrectal ultrasound (TRUS)–guided, systematic needle biopsy is currently the most reliable method, at present, to ensure accurate sampling of prostatic tissue in men considered at high risk for harboring prostatic cancer on the basis of DRE and PSA findings.

As nearly universal as the approach, as nearly universal is the technique, namely a TRUS-guided biopsy using an 18- gauge needle to obtain a tissue core. Since the landmark study by Hodge and colleagues demonstrating the superiority of TRUS guidance compared with digitally guided biopsy, the TRUS-guided biopsy technique has become the worldwide accepted standard in prostate cancer diagnosis. Performance (sensitivity, specificity, positive and negative predictive values) of all other diagnostic tests (eg, DRE and PSA assay) is calculated according to the assignment (cancer present vs absent) made by prostate biopsy. Recognizing the fact that all sampling procedures, including prostate biopsies, incur the risk of returning false-negative results (ie, cancer is present but missed by the biopsies), calculation of the statistical performance characteristics of all other tests using biopsy outcomes as the gold standard are inherently incorrect and biased. Similarly, when comparing the statistical performance of various biopsy strategies, usually the most extensive strategy is chosen as the gold standard to define disease presence or absence, and the performance of all other strategies is calculated on the basis of that particular strategy, again incurring a significant bias due to the remaining false-negative rate of even the most extensive sampling strategy.

On initial biopsy, a minimum of 10 systemic, laterally directed cores is recommended, eventually with more cores in larger glands. Extended prostate biopsy schemes, which require cores weighted more laterally at the base (lateral horn) and medially to the apex, show better cancer detection rates without increasing adverse events.

The risks and complications of TRUS-guided prostate biopsy are well known. Most of these complications are minor, such as pain, dysuria, rectal bleeding, hematuria, hematospermia and urinary retention. Clinically significant infectious complications include fever, urinary tract infection (UTI), acute bacterial prostatitis, orchiepididymitis and sepsis. However, there is no gold standard for preparing a patient before prostate biopsy.

Several studies have demonstrated the value of antibiotic prophylaxis before TRUSPB. However, there is wide variation in the prophylactic antibiotic regimens used by the urologist with no consensus on the most appropriate type of antibiotic or its duration.
The American Urological Association recommends a fluoroquinolone or second- or third-generation cephalosporin as the antimicrobial agent of choice, and an aminoglycoside plus metronidazole or clindamycin as the alternate. The recommended duration is ≤ 24 hours, with extended coverage for ≤ 3-4 days in patients with comorbid conditions.

Fluoroquinolones, such as ciprofloxacin, are one of the most commonly used prophylactic antibiotics for TRUSPB. These antimicrobial agents have a broad spectrum of activity against gram-positive and gram-negative bacteria. Because fluoroquinolones are potent, non-toxic, orally administered, penetrate prostatic tissue well, and have a long-lasting urinary bactericidal activity, they are frequently used for urologic patients for the treatment of UTIs and surgical prophylaxis. However, the sensitivity of *Escherichia coli*, the most common cause of infectious complications after TRUSPB, to fluoroquinolones is decreasing.

Each year, approximately 800 TRUS-guided prostate biopsies are performed at our center.
Because of the perception that increased numbers of patients are being admitted for post-TRUSPB sepsis at our center, and the concern of increasing ciprofloxacin resistance, we conducted this study. A retrospective chart review of patients who presented back to our hospital with urosepsis after TRUSPB from 2003 to 2009 was performed. Additionally, a prospective study was conducted in every patient who underwent TRUSPB starting on 1 December 2009, to determine the local distribution of faecal pathogens and their susceptibility. Today, this prospective study is still ongoing.

QUESTION(S)

1) What is the incidence of sepsis following transrectal ultrasound-guided prostate biopsy at our center? Did rates of infective complications increase in recent years with the emerging fluoroquinolone resistance?

2) What are the predisposing factors of sepsis after TRUSPB?

3) What is the incidence of ciprofloxacin resistant faecal strains before TRUSPB at our center?

4) Is fluoroquinolone prophylaxis still effective? Should we reassess our practices?

SEARCH TERMS

1) MeSH Database (PubMed): "prostate biopsy AND antibiotic prophylaxis", "prostate biopsy AND sepsis", "prostate biopsy AND fluoroquinolones", "prostate biopsy AND bacteremia", "prostate biopsy AND complications"
2) PubMed Clinical Queries (from 1966; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi): Systematic Reviews; Clinical Queries using Research Methodology Filters (diagnosis + specific, diagnosis + sensitive, prognosis + specific)

RELEVANT EVIDENCE/REFERENCES

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APPRAISAL

I. Sepsis following TRUS-guided prostate biopsy: a retrospective study

A. Objectives

First, to determine the incidence of sepsis following transrectal ultrasound-guided prostate biopsy at our center, and to investigate whether rates of infective complications increased in recent years with the emerging fluoroquinolone resistance. Secondly, to evaluate potential predisposing factors of sepsis after prostate biopsy, with the aim of improving patient counseling and the safety of the procedure. Moreover, to calculate the total average cost of this complication. Finally, to review the literature on the incidence of infectious complications after TRUSPB and the use of antibiotic prophylaxis in this setting.

B. Material and methods

We retrospectively reviewed a group of 54 men who presented with sepsis due to *E. coli* (positive blood culture) after undergoing TRUS biopsy at our center from 2003 to 2009. Every patient who underwent TRUSPB from 01/01/2003 to 31/12/2009 was first screened for positive blood cultures. Next, only those patients who had positive blood cultures with *E. coli* within 30 days after taking the biopsy were retained.

The biopsies were performed by 2 radiologists using the same protocol. With the patient in the left decubitus position, TRUS was performed with a multi-planar multi-frequency probe (75MHz) attached to the ultrasound scanner. Prostate biopsies were taken with an 18 Gauge x 20 cm Biopsy cut with the automated spring loaded gun mechanism. They were obtained at the apex, middle and base of the left and right prostate lobes in the parasaggittal plane. The prostate volume as measured on the TRUS determined the number of cores of prostate biopsies. At our center, patients receive 500 mg levo- or ciprofloxacin 12 to 1 hour before the procedure and 500 mg/day for 3 days after the procedure.

The medical records of all patients with sepsis occurring within 30 days after biopsy were reviewed for history of prostate pathology (including prostatitis), medical comorbidities, risk factors for urosepsis, use of prophylactic antibiotics, causative organisms, and antibiotic sensitivity patterns in both blood and urine cultures. Other factors such as onset of sepsis in relation to TRUS biopsy and length of hospitalization were recorded. Attachment 1 shows the questionnaire which was filled out for each patient included in our study.

C. Results

From 2003 to 2009, 5663 biopsy procedures were performed in 4204 patients at our center. Of the 4204 patients, 3264 underwent their first biopsy and 940 already underwent one or more previous biopsies. Clinically, none of the patients were suspected of having a urinary tract infection or acute prostatitis before biopsy.

The overall incidence of urosepsis after TRUSPB is 0.95% (54/5663 biopsy procedures). However, the estimate of incidence was retrospective and assumed that all patients with sepsis after prostate biopsy reported back to our hospital. Therefore, the number of cases reported was likely an underestimation, because some patients may have reported to other hospitals and were not captured by this study.

Of the 4204 patients, 54 (1.28%) reported back to our hospital with urosepsis. Sepsis occurred after the first biopsy in 33 patients (1.01%), and occurred after a repeat biopsy in 21 patients (2.23%). Table 1 lists the results of the patient data. The difference is statistically significant (p-value < 0.01), which indicates that patients who underwent a repeat biopsy have a higher risk of developping sepsis. This is most likely explained by the higher incidence of chronic prostatitis in these patients. Of the 33 patients who underwent their first biopsy, 10 were noted to have chronic prostatitis, compared to 15 of the 21 patients who underwent a repeat biopsy. This difference is statistically significant (p-value < 0.01).

Table 1 — Patient characteristics

	Total % (range)	**First biopsy % (range)**	**Repeat biopsy % (range)**
Percentage patients with urosepsis	1.28	1.01	2.23
Median age	61.5 (45-82)	60.4 (46-82)	63.3 (45-75)
Median PSA before biopsy	7.4 (0.7-20.3)	6.9 (0.7-20.3)	8.1 (1.8-14.3)
PSA at presentation	44.0 (6.0-160.1)	49.3 (6.0-160.1)	31.2 (8.8-51.4)
CRP at presentation	103.8 (3.4-330.2)	110.6 (7.4-330.2)	92.5 (3.4-257.9)
WBC count at presentation	10.4 (1.6-27.4)	10.4 (2.7-27.4)	10.5 (1.6-25.6)
Creatinine at presentation	1.2 (0.6-2.6)	1.1 (0.8-2.09)	1.2 (0.6-2.6)
Mean interval of biopsy to sepsis (days)	3 (1-26)	2 (1-10)	4 (1-26)
Mean length of hospitalization (days)	5 (2-12)	5 (2-11)	5 (2-12)
Profylactic regimen			
Ciprofloxacin	57.4% (31/54)		
Levofloxacin	7.4% (4/54)		
Norfloxacin	1.8% (1/54)		
Ofloxacin	1.8% (1/54)		
Amoxicillin-clavulanate	3.7% (2/54)		
Nitrofurantoin	1.8% (1/54)		
Trimethoprim/sulfamethoxazole	3.7% (2/54)		
Unknown	22.2% (12/54)		

In order to find out whether the incidence of urosepsis increased over the years at our center, we compared the number of patients who reported back to our hospital from 2003 to 2005 with the period starting from 2006 to 2009. The incidence of urosepsis was 0.39% (10/2550 biopsy procedures) from 2003 to 2005 and 1.41% (44/3112 biopsy procedures) from 2006 to 2009. The difference is statistically significant (p-value < 0.01), which confirms the observation that increased numbers of patients are being admitted for post-TRUSPB sepsis at our center. It should however be noted that this observation was the starting point for this evaluation.

Of the 54 men, 42 were noted to have received antibiotic prophylaxis. We cannot exclude that one or more of the remaining 12 patients received prophylaxis. The mean age of the patients was 61.5 years. The median interval between TRUSPB and presentation to the emergency room with symptoms of urosepsis was 3 days. Most patients (87%) presented back to the hospital 1-3 days after taking the biopsy, only 3 patients were admitted more than 10 days after biopsy. The median length of hospital stay was 5 days (range 2-12 days).
Mean PSA, CRP and leukocyte count at presentation was 44.0 ng/mL, 103.8 mg/L and 10.4 $x10^9$ cells/L, respectively.

The average cost (including hospital stay, medical and paramedical fees and medication) that was associated with the hospitalization of these 54 patients will be calculated by the administration of UZ Leuven. The results are not yet available.

All 54 patients had by definition a positive blood culture comprising *E. coli*. Urine cultures were sterile in 20 patients (37%). Only 34 (63.0%) harbored *E. coli* in both blood and urine samples. Urine samples were also analyzed for resistance and sensitivity patterns. Table 2 shows an overview of antibiotics to which the blood bacterial isolates were resistant. Indicated are the number of isolates that were resistant to a givin antibiotic as well as the corresponding percentage.
The overall incidence of fluoroquinolone resistance was 59.3% (32/54 patients). However, because of the retrospective character of our study, we cannot verify whether the patients actually received ciprofloxacin as antibiotic prophylaxis or not.

Table 2 — Percentage of antibiotic resistance in 54 *E. coli* blood culture isolates

Antibiotic	% resistance (number of patients)
Amoxicillin	74.1% (40/54)
Amoxicillin-clavulanate	7.4% (4/54)
Cefuroxime	1.8% (1/54)
Piperacillin/tazobactam	0% (0/54)
Levofloxacin	59.3% (32/54)
Gentamicin	20.4% (11/54)
Tobramycin	3.7% (2/54)
Trimethoprim/sulfamethoxazole	64.4% (29/45)
Nitrofurantoin	3.4% (1/29)

Table 3 shows the percentage sensitivity to a given antibiotic of fluoroquinolone resistant strains. Only 18.75% of the fluoroquinolone resistant strains were sensitive to amoxicillin, whereas 71.87% were sensitive to amoxicillin-clavulanate. All strains (100%) were sensitive to piperacillin/tazobactam. Therefore, this antibiotic agent could be used succesfully to treat these septic patients. Treatment varied between patients. All patients were treated empirically before positive culture results. The majority of the patients were treated with intravenous amikacin-cefotaxim. In addition, all patients were perscribed antibiotics on discharge. There were no cases of septic shock and no deaths.

Table 3 — Percentage of antibiotic sensitivity of fluoroquinolone resistant strains

Antibiotic	% sensitivity of ciprofloxacin resistant strains (number of patients)
Amoxicillin	18.75% (6/32)
Amoxicillin-clavulanate	71.87% (23/32)
Cefuroxime	87.5% (28/32)
Cefotaxime	100% (32/32)
Ceftazidime	100% (32/32)
Piperacillin/tazobactam	100% (32/32)
Amikacin	93.7% (30/32)
Gentamicin	71.87% (23/32)
Tobramycin	68.75% (22/32)
Trimethoprim/sulfamethoxazole	37.5% (12/32)
Nitrofurantoin	89.47% (17/19)

D. Discussion

In our series of 4,204 patients the overall incidence of sepsis was 0.95%. This result is consistent with the reported rates in the literature. Attachment 2 shows the results of several studies who determined the incidence of infectious complications after TRUSPB.

In a randomized, double-blind, controlled study reported in 1998 Kapoor et al noted that using ciprofloxacin during transrectal prostate biopsy resulted in a 3% incidence of urinary tract infections (UTI) compared to 5% in the placebo group. In their series 2% of patients were hospitalized due to febrile UTIs, although none were ciprofloxacin treated patients. Aron et al reported that infective complication rates can be decreased 3-fold when fluoroquinolones are used compared to placebo (8% vs 25%). In the 2000 series by Aron et al all UTIs yielding positive cultures after prostate biopsy were susceptible to fluoroquinolones. In 1998 Sieber et al reported only 2 cases of UTI that were resistant to fluoroquinolones in a series of 4,439 TRUSBPs with fluoroquinolone prohylaxis.

But are these values still valid in our dynamic environment of antimicrobial resistance? Recent trends have shown that fluoroquinolone resistant infections after prostate biopsy are increasingly noted. In 2003 Tal et al reported on 23 patients who were hospitalized with clinical UTIs and in whom bacteria showed high resistance to fluoroquinolones after transrectal prostate biopsy. In 2004 Otrock et al noted that 50% of patients hospitalized with clinical UTIs after transrectal prostate biopsy were infected with fluoroquinolone resistant *E. coli*. A population based study as recent as March 2010 was conducted by Nam et al. More than 75,000 men who underwent TRUSPB in Ontario, Canada, between 1996 and 2005 were included. The study demonstrated that hospital admission rates for complications increased from 1% to 4% during the 10-year period, primarily due to an increasing rate of infection related complications. At our center, we also found a significant increase of the incidence of sepsis after prostate biopsy over the 6-year study period.

In the literature, we have found 11 case reports of septic shock, 6 case reports of life-threatening meningitis and one case of disseminated intravascular coagulation with fluoroquinolone resistant *E. coli* after transrectal prostate biopsy.

Should we reassess our practices? Is fluoroquinolone prophylaxis still effective? Do rates of infective complications after transrectal prostate biopsy differ in the current setting of emerging fluoroquinolone resistance?
There is high evidence that the use of antibiotic prophylaxis reduces the incidence of post-biopsy bacteriuria and bacteremia. However, no reference standard is available for preparing a patient before prostate biopsy, especially regarding the use of antibiotics.
Fluoroquinolones are the most frequently used antibiotics for prophylaxis before transrectal prostate biopsy. A summary of several studies who compare different antibiotic prophylaxis treatments is given in attachment 3.
In a single urological centre, Ho et al (2009) performed an interventional study that compared ciprofloxacin with the combination of ciprofloxacin and gentamicin IM. After the introduction of IM gentamicin, the number of hospitalisation secondary to febrile UTI was reduced from 3.3% to 1.3%. This represented a 50% reduction but the difference was not statistically significant. They concluded that the addition of gentamicin IM to oral ciprofloxacin is a safe and effective prophylactic antibiotic regimen in reducing the incidence of sepsis after TRUSPB.
Horjacada et al (2009) compared their old preventive protocol, that is, amoxicillin-clavulanate 500 mg tid for 3 days with a new protocol, that is, 2g cefoxitin 1 hour before the procedure and ciprofloxacin 750 mg p.o. bid for 4 days. The incidence of bacteremia was significantly lower during the period of new preventive protocol. They concluded that cefoxitin could be used as prophylaxis in centers with high prevalence of ESBL-producing enterobacteriaceae.
In 2002 Cormio et al compared the efficacy of short-term parenteral prophylaxis with piperacillin-tazobactam (2250 mg I.M. twice daily for 2 days) with long-term oral ciprofloxacin (500 mg p.o. twice daily for 7 days). The rate of asymptomatic bacteriuria was similar, but patients in the cipro-group required further treatment, with one needing hospitalization. They recommend short-term prophylaxis with piperacillin-tazobactam despite its disadvantages of cost and parenteral administration.

Not only is there no agreement on the agent to be used, neither do urologists agree on the duration of prophylaxis for TRUSPB. Anyway, it is important to administer antimicrobials over shorter periods to increase antimicrobial agent efficiency, decrease the selection of antibiotic-resistant strains, and improve cost-effectiviness. Six studies of which five randomized controlled trials and one non-randomized prospective study compared the incidence of infective events between a single dose and 3-day course of a fluoroquinolone as antibiotic prophylaxis for TRUSPB. Briffaux et al (2009) found no argument for the use of more than one dose of antibiotic prophylaxis. Cam et al found similar complication rates between these groups. These results were also found by Aron et al, they conclude that continuing the antibiotic prophylaxis for 3 days offers no benefit over single-dose prophylaxis.
Shigemura et al investigated the incidence of infectious febrile complications and mean serum WBC count and CRP. For both outcome parameters, no significant difference was found between the 1-day and 3-day group. However, WBC count and CRP elevation tended to be smaller in the 1-day group, which indicates that 600 mg/day of levofloxacin for 1 day may be more effective for preventing infectious complications than 300 mg/day for 3 days.

Schaeffer et al found that in terms of microbiological efficacy, prophylaxis with one dose of ciprofloxacin was statistically no worse than a 3-day regimen. However, the clinical succes rates were consistently lower for the 1-day than for the 3-day treatment. For patients with diabetes mellitus and a history of prostatitis all treatment failures were found among those treated with 1-day regimen. They conclude that for patients undergoing TRUSPB, there might be a role for 3-day preventive therapy, possibly for those with diabetes or a history of prostatitis. Petteffi et al also concluded that long term antimicrobial prophylaxis presents a trend towards lower incidence of infectious complications.
At our center, patients receive 500 mg levo- or ciprofloxacin 12 to 1 hour before the procedure and 500 mg/day for 3 days after the procedure.

Enemas were not given before biopsy in our protocol, because, to the best of our knowledge, no consensus exists in the literature regarding the impact of a bowel-cleansing enema before biopsy (Table 4). In 1981, Brown et al. reported that a povidone-iodine enema provided a safe and effective means for preventing bacteremia and bacteriuria. On the contrary, Vallancien et al. attributed the increased complication rate for patients undergoing enema before biopsy to rectal irritation promoting bacterial dissemination. In a prospective randomized study, Lindert et al. proposed that bacteremia might be minimized by a prebiopsy enema. In their study, bacteremia following prostate biopsy occurred in 4% (1 of 25) of patients who had prebiopsy enemas compared with 28% (7 of 25) of those who did not. This study therefore provided a theoretical basis for using a prebiopsy rectal preparation for the prevention of infectious complications. Huang et al. reported that a phosphate-based enema combined with povidone-iodine is effective in reducing postprostate biopsy infectious complications (9.23 versus 0%).

Table 4 — Benefits of pre-biopy enema?

Author	Population	Complications – Enema	Complications – No enema	Remarks
Park et al, 2009	N= 481	0.3%	6.6%	
Huang et al, 2006	N= 222	0%	9.23%	phosphate enema combined with povidone-iodine administered by a doctor at the hospital versus phosphate enema administered by the patient at home
Lindert et al, 2000	N= 50	4%	28%	Transient bacteremia
Vallencien et al, 1991	N=59	20%	9%	
Brown et al, 1981	N= 40	19%	69%	Transient bacteremia

Our study has shown that fluoroquinolone resistant infections after prostate biopsy are increasingly noted. One of the possible causes of the increasing resistance to fluoroquinolones is the previous wide use of these drugs.

In a case-control study of the risk factors for the acquisition of ciprofloxacin-resistant isolates in a Veterans Affairs Medical Center (Muder et al), previous fluoroquinolone use was significantly more frequent among patients with resistant isolates than among controls (58% vs 20%) and was the single most important risk factor on multivariate analysis. In a multivariate analysis of 611 gram-negative isolates from community-acquired UTIs from 15 centers in Turkey, the use of ciprofloxacin more than once in the past year was associated with ciprofloxacin resistance (Arslan et al).
In a study involving single-dose prophylaxis (Wagenlehner et al) with ciprofloxacin in urologic procedures, resistant *E. coli* were isolated from 3% of patients before prophylaxis, which increased to 12% after prophylaxis, indicating how quickly resistance can develop over a 7-day period. Furthermore, between the years 2000 and 2007, ciprofloxacin resistance among *E. coli* urinary isolates rose from 20% to 25%.
Also, some studies have reported on the development of quinolone-resistant strains of *E. coli* in the stool of patients receiving fluoroquinolone prophylaxis. Shigehara et al. considered that the previous use of levofloxacin might cause bacterial selection in the rectum, and *E. coli* resistant to levofloxacin might then appear in the rectum for a certain period.
These findings might suggest that the antibiotic prophylaxis regimen should be revised by using a shorter period of fluoroquinolones or parenteral administration of different groups of antibiotics before repeat biopsy. In order to determine the incidence of ciprofloxacin resistant *E. coli* strains in the rectum before biopsy, we conducted a prospective study at the department of urology of the University Hospital of Leuven starting on 1 december 2009. This study is described in part II.
A 2004 study on the incidence of UTI after TRUSPB at a tertiary care center in Lebanon (Otrock et al) concluded that, given the increasing incidence of antibiotic resistance among the Enterobacteriaceae, antimicrobial prophylaxis should be re-evaluated and the universal administration of quinolones alone or in combination with aminoglycosides should be reconsidered.

In addition to the fluoroquinolone-resistant strains of *E. coli*, many studies have addressed the emergence of ESBL-producing *E. coli*. A number of case-control studies have consistently shown that previous use of third-generation cephalosporins and the previous use of fluoroquinolones remain as independent risk factors for infections caused by ESBL-producing organisms. Kanafani et al. reported that the most notable risk factor for acquiring infections with ESBL-producing organisms was antibiotic consumption within 30 days of infection with an odds ratio of 7. Lautenbach et al. have also shown that the previous use fluoroquinolone increased the risk of ESBL-producing *E. coli* and *K. pneumoniae* infections.
If we continue to use fluoroquinolones as the mainstay of antibiotic prophylaxis for TRUSBP, we will probably continue to see an increasing emergence of ESBL-producing bacteria. This could translate into more post-TRUSBP prostatitis and other infectious complications. Clinicians must be aware of this and should promptly initiate an alternative antibiotic determined by their local distribution of pathogens and susceptibility. Many have suggested using either a second- or third-generation cephalosporin or carbapenem (if the patient is at high risk).

Others recommend combination therapy of ciprofloxacin and another antibiotic agent such as trimethoprim/sulfamethoxazole, or antibiotic cycling for long-term prophylaxis, especially for the high-risk patient. These would be the patients who, based on their medical history, have had frequent exposure to antibiotics and are thus more likely to develop infections as a result of the presence of resistant bacteria. Long-term antibiotic cycling regimes have been found to be successful at decreasing colonization with antibiotic resistant bacteria in several hospital settings and also increased the effectiveness of empirical antibiotic selection.

E. Conclusion

We have reported a regional case series of sepsis after prostate biopsy in the University Hospital of Leuven. The rate of *E. coli* resistance to fluoroquinolone antibiotics has been increasing worldwide. Although antimicrobial prophylaxis has been shown to decrease the risk of infectious complications, no standardized regimen has been agreed on for prophylaxis for TRUSPB. The morbidity of infectious complications, as seen in these 54 patients, highlights the need for reporting these complications and randomized controlled trials to standardize the antimicrobial prophylaxis.

Although the incidence of sepsis following a TRUSPB is low, it is potentially fatal. If treatment is delayed or inadequate therapy is administered, patients will develop septic shock which could be fatal. However, early appropriate antimicrobial therapy is usually successful. In order to perform early treatment, it is important to inform them the risk of infectious complications after a TRUSPB and to caution them to consult a hospital immediately if fever occurs within at least two weeks following a TRUSPB. TRUS patients should be provided with a letter to present to health care providers if they develop signs of sepsis. The letter should indicate that they have recently undergone a TRUS biopsy with ciprofloxacin prophylaxis and that ciprofloxacin should not be used for treatment of their sepsis. This ensures that ciprofloxacin resistance needs to be suspected and that appropriate treatment should be tailored according to the resistance profiles dictated by the local resistance profiles of the center, the patient's medical history, and should be adjusted according to the culture and sensitivity reports of each individual patient.

Quinolone resistant organisms will continue to be a problem after a TRUSPB, and urologists must exert more effort to prevent and treat such infections by obtaining a careful history, cautious informed consent, and appropriate antimicrobial treatment. No set protocol can guarantee a perfect prophylaxis regimen before and after TRUSPB or efficient treatment of the patient after sepsis has developped. Instead, the physician should consider several factors and tailor treatment on an individual case basis.

One limitation of this study was the retrospective nature of data collection. The estimate of incidence was retrospective and assumed that all patients with sepsis after prostate biopsy reported back to our hospital. Therefore, the number of cases reported was likely an underestimation, because some patients may have reported to other hospitals and were not captured by this study.

II. Local distribution of faecal pathogens and their susceptibility in patients undergoing TRUSPB: a prospective study

A. Objectives

First, to determine the prevalence of faecal carriage of quinolone-resistant *E. coli* strains before TRUSPB at our center and to evaluate potential predisposing risk factors. Next, to investigate the evolution of ciprofloxacin resistance of *E. coli* strains at our center, and to compare alternative options for antibiotic prophylaxis before prostate biopsy.

B. Material and methods

The prospective study was conducted at the department of urology starting on 1 december 2009. Each patient who underwent TRUSPB at our center, was included in the study.

Rectal swabs were obtained just before taking the biopsy. These swabs were transferred to the laboratory in a transport medium and plated according to protocol on MacConkey agar and on MacConkey agar with ciprofloxacin 1 mg/L. The agar plates were incubated at 37° for 24 hours. Ciprofloxacin resistant strains were indentified with VITEK® and the minimal inhibitory concentration was determined using an E-test according to National Committee for Clinical Laboratory Standards guidelines.

In order to correlate the presence of fluoroquinolone resistant strains with plausible risk factors, a questionnaire was filled out for each patient by the urologist. With this questionnaire (see attachment 4) we tried to determine whether the number of previous prostate biopsies, the presence of chronic prostatitis, and/or the long term use of fluoroquinolones short before taking biopsies correlates with a higher risk of fluoroquinolone resistant faecal strains.

C. Results

Given the current widespread use of fluoroquinolones in both humans and animals, it is probable that fluoroquinolone resistant *E. coli* are increasingly likely to be present in the colonic flora.

First, we determined the incidence of ciprofloxacin resistant *E. coli* strains from rectal swabs that were taken before biopsy. Of the first 100 patients who underwent TRUSPB, 23 had a negative culture (no growth on MacConkey or MacConkey + ciprofloxacin 1 mg/L). For 55 patients, there was growth on MacConkey but not on MacConkey + ciprofloxacin 1 mg/L. So these patients harbored ciprofloxacin sensitive strains. There was growth on both MacConkey agar and on MacConkey + ciprofloxacin 1 mg/L for 22 patients, of which 21 with *E. coli*. Thus we found that 21% of the patients harbored faecal ciprofloxacin resistant *E. coli* strains. One patient's rectal swab was positive for a ciprofloxacin resistant *P. aeruginosa* strain.

In parallel, we investigated the evolution of ciprofloxacin resistance among *E. coli* isolated from urine at our institute over a 6-year period. The percentage of resistance to several antibiotic agents of *E.coli* from urine cultures from 2003 to 2009 is shown in Table 5.

Table 5 – Percentage of antibiotic resistance of *E.coli* from urine cultures from 2003 to 2009

Antibiotic agent	2003	2004	2005	2006	2007	2008	2009
ciprofloxacin	14.94 % (140/937)	17.28 % (192/1111)	16.45 % (189/1149)	21.33 % (269/1261)	22.21 % (309/1391)	22.57 % (321/1422)	22.19 % (286/1289)
levofloxacin	/	/	/	22.19 % (249/1122)	22.49 % (318/1414)	22.77 % (326/1432)	23.04 % (300/1302)
norfloxacin	13.98 % (131/937)	16.92 % (188/1111)	16.00 % (184/1149)	20.29 % (255/1261)	20.33 % (282/1391)	21.45 % (305/1422)	22.78 % (293/1286)
ofloxacin	15.43 % (148/959)	17.25 % (193/1119)	16.97 % (198/1167)	17.22 % (26/151)	/	/	/
ampicillin	43.47 % (416/957)	46.20 % (517/1119)	46.87 % (547/1167)	48.74 % (619/1270)	50.57 % (715/1414)	52.83 % (757/1433)	53.92 % (702/1302)
amoxicillin-clavulanate	6.14 % (59/961)	5.54 % (62/1119)	6.17 % (72/1167)	5.91 % (75/1270)	7.57 % (107/1414)	10.33 % (148/1433)	12.90 % (168/1302)
piperacillin-tazobactam	0.42 % (4/958)	0.63 % (7/1119)	0.43 % (5/1167)	0.16 % (2/1270)	0.21 % (3/1414)	0.28 % (4/1433)	0.77 % (10/1301)
cefuroxim	5.53 % (53/958)	7.06 % (79/1119)	6.61 % (77/1165)	5.20 % (66/1269)	6.79 % (96/1414)	7.89 % (113/1433)	8.76 % (114/1302)
cefazolin	10.65 % (75/704)	7.09 % (20/282)	12.94 % (151/1167)	14.84 % (23/155)	25.0 % (1/4)	/	/
cefotaxim	1.56 % (15/959)	5.27 % (59/1119)	2.06 % (24/1167)	1.10 % (14/1269)	2.97 % (42/1414)	3.42 % (49/1433)	4.45 % (58/1302)
ceftazidim	1.77 % (17/960)	5.36 % (60/1119)	0.60 % (7/1167)	0.39 % (5/1269)	0.99 % (14/1414)	1.05 % (15/1433)	1.46 % (19/1302)
meropenem	0.10 % (1/960)	0%	0%	0%	0%	0%	0%

Table 6 – Percentage of antibiotic resistance of ciprofloxacin resistant *E.coli* from urine cultures from 2003 to 2009

Antibiotic agent	2003	2004	2005	2006	2007	2008	2009
ampicillin	82.14 % (115/140)	85.94 % (165/192)	86.77 % (164/189)	88.85 % (239/269)	86.73 % (268/309)	90.65 % (291/321)	88.81 % (254/286)
amoxicillin-clavulanate	48.57 % (68/140)	45.31 % (87/192)	34.92 % (66/189)	39.03 % (105/269)	38.19 % (118/309)	52.02 % (167/321)	60.49 % (173/286)
piperacillin-tazobactam	2.14 % (3/140)	8.33 % (16/192)	3.17 % (6/189)	3.35 % (9/269)	2.91 % (9/309)	2.49 % (8/321)	6.64 % (19/286)
cefuroxim	46.04 % (64/139)	67.61 % (192/284)	47.62 % (90/189)	41.64 % (112/269)	42.72 % (132/309)	42.06 % (135/321)	48.25 % (138/286)
cefazolin	67.65 % (69/102)	73.68 % (28/38)	72.49 % (137/189)	81.48 % (22/27)	/	/	/
cefotaxim	5.71 % (8/140)	27.08 % (52/192)	15.87 % (30/189)	7.81 % (21/269)	13.59 % (42/309)	17.76 % (57/321)	15.38 % (44/286)
ceftazidim	5.71 % (8/140)	27.60 % (53/192)	17.46 % (33/189)	7.81 % (21/269)	15.53 % (48/309)	18.69 % (60/321)	17.13 % (49/286)
meropenem	0 % (0/140)	0 % (0/192)	0 % (0/189)	0 % (0/269)	0 % (0/309)	0 % (0/321)	0 % (0/286)

These results show a significant increase in ciprofloxacin resistance between 2003-2005 and 2006-2009 (p-value < 0.01). This increase in fluoroquinolone resistance correlates with the increasing incidence of post-TRUSPB sepsis at our center during the same period (as described above). Furthermore, the percentage of resistance to ciprofloxacin of *E. coli* strains from urine samples was 22.19% in 2009, which is similar to the percentage of ciprofloxacin resistant *E. coli* strains isolated from rectal swabs with our prospective study, namely 21%.
Additionally, we evaluated the evolution of antibiotic resistance of ciprofloxacin resistant *E. coli* from urine cultures from 2003 to 2009 at our center. Table 6 shows the results.

During our prospective study, sepsis occurred in three patients of the first 100 and all of them were caused by ciprofloxacin resistant *E. coli*. This high number indicates that the true incidence of sepsis after prostate biopsy at the University Hospital of Leuven is much higher than determined with our retrospective study. Today, this prospective study is still ongoing.

Of the first 100 patients included in this study, 69 received ciprofloxacin (or levofloxacin) at least 1 hour before taking the biopsy, including all three patients who reported back to the hospital with urosepsis. A substantial number of patients (27) received ciprofloxacin during or after the procedure, and four patients received a non-fluoroquinolone as prophylaxis.
In the three cases of sepsis, all of the patients had a history of previous use of quinolones less than six months before the biopsy was taken. Patient one had also a history of chronic prostatitis and orchitis. Two of them underwent their first biopsy, the third underwent already 2 previous prostate biopsies. The patients' characteristics are shown in Table 7.

Table 7 — Patient characteristics

Patient No.	**1**	**2**	**3**
Age (year)	70	70	61
Biopsy indication	elevated PSA	elevated PSA	elevated PSA
Biopsy date	22/12/2009	28/12/2009	30/12/2009
Date of hospitalization	23/12/2009	29/12/2009	01/01/2010
History of biopsy	third	first	first
PSA (µg/L)	14.33	13.0	4.66
Pathology	no malignancy	invasive adenocarcinoma	no malignancy
Medical history	- chronic prostatitis and orchitis - post-TRUSPB sepsis (2007) - sleep apnea	drug eluting stent 05/2009	- hip prosthesis - sleep apnea
Antimicrobial history	several cures of fluoroquinolone in the past	30 days fluoroquinolone before biopsy	6 weeks fluoroquinolone starting from 09/09/2009

In order to find out if patients who underwent a repeat biopsy are at higher risk for faecal carriage of quinolone resistant strains than patients who underwent their first biopsy, we performed a fisher's exact test. Of the first 100 patients, 55 had a first biopsy of which 9 patients harbored a ciprofloxacin resistant *E. coli*. On the other hand, 13 out of 45 patients who underwent a repeat biopsy were found positive for a ciprofloxacin resistant *E. coli*. Thus, we found 16.4% patients with resistant strains in the "first biopsy-group" and 28.9% patients in the "repeat biopsy-group". However, the difference was not statistically significant (p-value = 0.15).

An overview of the antimicrobial susceptibility of the blood isolates of these patients is shown in Table 8. The blood cultures were positive for *E. coli*, all resistant to fluoroquinolones and one was also resistant to gentamicin. None of the isolates produced an extended-spectrum β-lactamase.

Table 8 — Antimicrobial susceptibility of fluoroquinolone resistant *E. coli* isolated from three cases

Patient No.	**1**	**2**	**3**
levofloxacin	R	R	R
amoxicillin	R	R	R
amoxicillin/clavulanate	I	I	S
piperacillin/tazobactam	S	S	S
meropenem	S	S	S
cefazolin	R	S	S
cefuroxime	S	S	S
cefotaxim	S	S	S
ceftazidim	S	S	S
amikacin	S	S	S
gentamicin	S	S	R
tobramycin	S	S	R
temocillin	S	S	S
trimethoprim/sulfamethoxazole	R	R	R
R = resistant, S = sensitive			

D. Discussion

According to a cross-sectional study conducted by Lautenbach et al in 2005, the sensitivity of perirectal and rectal swabs compared to stool samples was 90% and the specificity was 100%. They demonstrated that rectal swabs, as used in this study, have excellent sensitivity and specificity for detection of gastrointestinal tract colonization with fluoroquinolone-resistant *E. coli*.

The risk factors for acquisition of urinary tract infection caused by quinolone resistant *E. coli* were identified by Ena et al. They reported that previous use of quinolones and the presence of a urinary tract disorder (prostatic obstruction, lithiasis, neoplasm, and recurrent urinary tract infection) were the strongest risk factors.

In 2010, Simsir et al assessed the relationship between sepsis and age, serum total prostate-specific antigen level (PSA), PSA density, prostate volume, number of biopsies, number of repeated biopsies, accompanying diagnosis of prostatitis, presence of urethral catheter and presence of diabetes mellitus. Of the 2,023 patients, 62 (3.06%) developped sepsis within 5 days after biopsy. In this study, one of the risk factors for sepsis was having a urinary catheter. There is controversy over this issue in the literature. However, the fact that 19.2% of cases with a urethral Foley catheter had a sepsis is significant. The most important reason for this is that urethral catheters are an ideal medium for bacterial colonization. Another risk factor for sepsis was the number of biopsy cores. The increase in the number of cores increases the inoculation of microorganisms, found in the rectal mucosa, to the prostate tissue. It is obvious that the amount of cumulative bacteria transferring from the rectum to the prostate will be directly related to the development of infection and its severity. Moreover, of the 396 patients with a diabetic history, septic manifestations were observed in 32 (8.1%). This result supports the findings of Aus et al, who showed the relationship between diabetes mellitus and sepsis.
Our retrospective study has indicated that patients who underwent a repeat biopsy have a higher risk of developping sepsis. However, we found no significant difference between patients who underwent a repeat biopsy and those who underwent their first biopsy as regards to the risk for faecal carriage of quinolone resistant strains.

Yagci et al determined the prevalence of and risk factors for the faecal carriage of quinolone-resistant *E. coli* strains and its relationship with the use and duration of quinolone therapy on an inpatient and outpatient basis. Fluoroquinolone use in the previous 6 months was found to be a risk factor for quinolone-resistant *E. coli* carriage before therapy or hospitalization. The prevalence of quinolone-resistant *E. coli* strains in faecal flora increased steadily with the duration of quinolone therapy.
Shigehara et al. considered that the previous use of levofloxacin might cause bacterial selection in the rectum, and *E. coli* resistant to levofloxacin might then appear in the rectum for a certain period. In the three cases described in this report, all of the patients had a history of previous use of quinolones less than six months before the biopsy was taken. One patient had also a history of chronic prostatitis and orchitis. This highlights the potential importance of reviewing a patient's history before prescribing a prophylaxis regimen.
At our center, the use of fluoroquinolones in the previous 6 months before biopsy, the presence of chronic prostatitis and the presence of diabetes mellitus are considered as the strongest risk factors. Patients who have a history of infectious complications after a previous prostate biopsy are also considered at risk. It is therefore important to evaluate those prebiopsy patient-related risk factors by obtaining a thorough history.

Based on the results shown in Table 6, alternative options for antibiotic prophylaxis before prostate biopsy could be determined. In addition to a regimen's efficacy in preventing infection, its cost-effectiveness and clinical applicability should be considered.
In 2006, a University Hospital in Spain chose amoxicillin-clavulanate for antibiotic prophylaxis before TRUSPB instead of ciprofloxacin, because in their country the prevalence of quinolone resistance was high (23%) at that time.

Although there is limited experience for the use of amoxicillin-clavulanate, it has been considered as an alternative to quinolones for antibiotic prophylaxis in TRUSPB, its use has been previously described, and it is well tolerated for few days and easy to administer. In our center, the sensitivity to amoxicillin-clavulanate was only 39.51% in 2009 (Table 6), which makes this antibiotic agent a poor choice for prophylaxis.

Piperacillin-tazobactam, another combination β-lactam-β-lactamase inhibitor, has also demonstrated its efficacy as prophylaxis inTRUSPB. As mentioned before, Cormio et al compared the efficacy of short-term parenteral prophylaxis with piperacillin-tazobactam (P/T) with long-term oral ciprofloxacin. The rate of asymptomatic bacteriuria was similar, but patients in the cipro-group required further treatment, with one needing hospitalization. They recommend short-term prophylaxis with piperacillin-tazobactam despite its disadvantages such as the need for parenteral administration and its cost. At our center, the sensitivity to piperacillin-tazobactam of fluoroquinolone resistant strains isolated from urine samples is high (Table 6). These results show that piperacillin-tazobactam could be used as an alternative antibiotic agent for TRUSPB prophylaxis in patients with a high risk of faecal carriage of quinolone resistant strains. However, we would not recommend its use because of the important drawbacks as mentioned above.

Another alternative is the combination therapy of trimethoprim-sulfamethoxazole and ciprofloxacin, which is considered at the Vancouver General Hospital (University of British Columbia). However, our retrospective study pointed out that, in patients with urosepsis, the sensitivity to sulfamethoxazole of ciprofloxacin resistant strains was only 37.5%.

Third generation cephalosporins are highly active against these quinolone resistant *E. coli* strains. At our center, the sensitivity to cefotaxim was 84.62% in 2009. Therefore, we would recommend ceftriaxone as an alternative option for patients with a high risk of infectious complications and/or faecal carriage of quinolone resistant strains before biopsy. Like other third-generation cephalosporins, ceftriaxone has broad spectrum activity against Gram-positive and Gram-negative bacteria. In most cases, it is considered to be equivalent to cefotaxime in terms of safety and efficacy. Ceftriaxone is completely absorbed following IM administration with mean maximum plasma concentrations occurring between 2 and 3 hours post-dose. It has a long elimination half-life (5.8 to 8.7 hours) and a small degree of nonlinearity in its pharmacokinetics which can be ignored in its clinical applications. The recommended dose is 1 gram intramuscular, 30 minutes before taking the biopsy.

Ceftriaxone does not increase the risk of an allergic reaction among patients with penicillin allergy. Penicillin-allergic patients have shown an increased incidence of allergic reactions to cephalothin, cephaloridine, cephalexin, cefadroxil, cefazolin, and cefamandole. However, the risk has been overestimated because most studies reporting this cross-reactivity were flawed (because penicillins were contaminated with cephalosporins) and then failed to account for the fact that penicillin-allergic patients have a 3-fold increased risk of allergic reactions even to nonrelated drugs. For patients truly allergic to penicillin, the risk of a reaction from a cephalosporin with side chains that differ from penicillin/amoxicillin (cefuroxime, cefpodoxime, cefdinir, and ceftriaxone, as endorsed by the AAFP) is so low that use is justified and medico-legally defensible by the currently available evidence.

Alternatively, a rectal swab could be obtained in patients with a history of fluoroquinolone use to screen for faecal carriage of quinolone resistant *E. coli* strains.
A possible drawback of this strategy is the practical applicability at the department of urology. The swab has te be taken at least 24 hours and preferrably 48 hours before biopsy. This means that patients who attented the outpatient clinic will have to come back to the hospital, after the results of the culture are known. On the other hand, this strategy would allow us to reserve broad spectrum antibiotic agents such as ceftriaxone for those high risk patients who have quinolone-resistant *E. coli* strains in the rectum.

E. Conclusion

During our prospective study, sepsis occurred in three patients of the first 100 and all of them were caused by ciprofloxacin resistant *E. coli*. This high number indicates that the true incidence of sepsis after prostate biopsy at the University Hospital of Leuven is much higher than determined with our retrospective study. Today, this prospective study is still ongoing.

The percentage of ciprofloxacin resistant *E. coli* strains isolated from rectal swabs with our prospective study is high (21%). This is similar to the percentage of resistance to ciprofloxacin of *E. coli* strains isolated from urine samples in 2009. Given the increasing incidence of antibiotic resistance among *E. coli* at our center, antimicrobial prophylaxis should be re-evaluated and the universal administration of quinolones should be reconsidered.
The use of fluoroquinolones in the previous 6 months before biopsy, the presence of chronic prostatitis and the presence of diabetes mellitus are considered as the strongest risk factors for infectious complications after TRUSPB. Patients who have a history of infectious complications after a previous prostate biopsy are also considered at risk. It is therefore important to evaluate those prebiopsy patient-related risk factors by obtaining a thorough history.
Based on the susceptibility results at our center (shown in Table 6), alternative options for antibiotic prophylaxis before prostate biopsy could be determined. Not only should a regimen's efficacy in preventing infection be considered, but also its cost-effectiveness and clinical applicability. Third generation cephalosporins are highly active against these quinolone resistant strains. Therefore, we would recommend intramuscular ceftriaxone as an alternative option for patients with a high risk of infectious complications and/or faecal carriage of quinolone resistant strains before biopsy. Alternatively, a rectal swab could be obtained in patients with a history of fluoroquinolone use to screen for faecal carriage of quinolone resistant *E. coli* strains.
Finally, post-biopsy complications involving fluoroquinolone-resistant *E. coli* should be reported through a user-friendly, nationwide system. This could provide precious and instructive information concerning the incidence and risk factors of sepsis after transrectal ultrasound-guided prostate biopsy.

TO DO/ACTIONS

1) Continue our prospective study at the University Hospital of Leuven.

2) Create a system to report post-biopsy complications involving fluoroquinolone-resistant *E. coli*.

3) Review our current antimicrobial prophylaxis regimen for TRUSPB in consultation with the urologists.

ATTACHMENTS

Attachment 1 – Retrospective study: questionnaire of patient characteristics

Attachment 2 – Studies on incidence of infectious complications after TRUSPB

Attachment 3 – Studies on antibiotic prophylaxis for TRUSPB

Attachment 4 – Prospective study: questionnaire of patient characteristics

Attachment 1 – Retrospective study: questionnaire of patient characteristics

Critically Appraised Topic 2009-2010

Bacteriemie met fluorochinolone resistente *E.coli* na uitvoering van een prostaatbiopsie: een reden tot nieuwe aanpak?

Deborah Steensels

Supervisie: Prof. Dr. J. Verhaegen

Dossierstudie:

- Initiële PSA
- PPA
- Datum biopsie
- Aantal biopsies
- Resultaat biopsie
- Antibioticum voor chemoprofylaxe
- Datum opname op spoed
- Biologische parameters na spoedopname (wijzend op infectie):
    - CRP?
    - PSA spoed?
    - WBC?
    - Creatinine? (stijging bij septische shock)
- Symptomatologie van de patiënt
- Resistentiepatroon *E.coli*
- Behandeling bacteriemie:
    - Welke antibiotica?
    - Hoelang?
- Evolutie van de patiënt (restletsels, overlijden)
- Risicoprofiel van de patiënt:
    - Hoge leeftijd?
    - Chronische prostatitis?
    - Urineweginfecties in het verleden?
    - Langdurig gebruik van chinolones?
    - Prebiopsie bacterurie?
    - Diabetes?
    - Immunosuppressie?
    - Steroïden gebruik?

Attachment 2 – Studies on incidence of infectious complications after TRUSPB

Author	Study type	Population	Prophylactic regimen	Outcome parameter	Outcome	Remarks
Lange et al, 2009	Retrospective review	N= 24/4749	Ciprofloxacin starting 1 day before the biopsy for 3 days	-incidence of sepsis -use of prophylactic AB -onset of sepsis -length of hospitalization -results of blood & urine culture -antibiotic sensitivity	-Incidence (number) of urosepsis: 0.5% (24) -Number of patients who received prophylactic AB: 22/24 -Median interval between biopsy and hospitalization: 2d -Median length of hospital stay: 4d -Number of positive blood cultures: 16/24 -> all with *E.coli* -Number of positive urine cultures: 12/24 -> 11 with *E.coli*, 1 with *E.cloacae* -Percentage of ciprofloxacin resistance: Blood isolates 100% Urine isolates 92%	Number of cases is likely underestimated
Young et al, 2008	Retrospective review	N= 5/1423	Fluoroquinolone the morning of or 1 hour before biopsy +/- gentamicin 80 mg I.M. 1h before biopsy	-incidence of sepsis -medical history -use of prophylactic AB -onset of sepsis -length of hospitalization -results of blood & urine culture -antibiotic sensitivity	-Estimated incidence of sepsis: 0.1-0.9% -Medical history: 3/5 DM 2/5 significant urologic history 1/5 significant surgical history 5/5 exposure to AB in the 21 months before biopsy -Antimicrobial prophylaxis: 5/5 fluoroquinolone p.o. before biopsy 4/5 gentamicin 80 mg I.M. 1h before biopsy -Median interval between biopsy and hospitalization: 2d -Median length of hospital stay: 7.2d -Blood & urine cultures: all positive with fluoroquinolone resistant *E.coli* strains (3/5 ESBL)	Study across 4 hospitals in southern California
Özden et al, 2008	Retrospective review	N= 1339	Ciprofloxacin 500 mg p.o. twice daily for 5 days, beginning 24h before biopsy	-incidence of acute bacterial prostatitis -onset of sepsis - results of urine culture -antibiotic sensitivity	-Incidence of acute bacterial prostatitis: 2.1% → after 1st biopsy: 1.3% → after repeat biopsy 6.8% -Median interval between biopsy and hospitalization: 3d -Percentage of positive urine cultures: 61% (17/28) -Percentage of ciprofloxacin resistance: 76.5% -Overall incidence of fluoroquinolone resistance: 1% (13/1339)	Significant difference between the 2 groups

Feliciano et al, 2008	Retrospective review	N= 1273	Levofloxacin 3x250 mg/d p.o. or Gatifloxacin 3x200 mg p.o. starting 1 day before biopsy	-annual & overall incidence of infective complications and fluoroquinolone resistant infections -onset of infective symptoms -results of blood & urine culture -antibiotic sensitivity	-Overall incidence of infective complications: 2.4% -Annual incidence of infective complications: 2004: 1.7% 2005: 1.6% 2006: 4.8% -Percentage of positive blood and/or urine culture: 61% (19/31) -Percentage of fluoroquinolone resistance: 79% (15/19) -Overall incidence of fluoroquinolone resistance: 1.2% -Annual incidence of fluoroquinolone resistance: 2004: 0.6% 2005: 0.8% 2006: 2.6% -Median interval between biopsy and symptoms: 5.3d	3 times higher incidence in 2006 compared to that in 2004 and 2005 4.3 and 3.3 times higher incidence in 2006 compared to that in 2004 and 2005, respectively
Shigahara et al, 2007	Retrospective review	N= 457	Levofloxacin 200 mg p.o. twice daily for 4 days, beginning 24h before biopsy + Isepamicin 200 mg I.V. 30 min before biopsy	-incidence of acute bacterial prostatitis -results of blood & urine culture -antibiotic sensitivity	-Incidence of acute bacterial prostatitis: 1.3% → after 1st biopsy: 0.5% → after repeat biopsy: 4.7% -Number of positive urine cultures: 6/6 -> *E.coli* -Number of positive blood cultures: 3/6 -> *E.coli* -Percentage of ciprofloxacin resistance: 100%	Significant difference
Otrock et al, 2004	Retrospective review	N= 207	-58%: ciprofloxacin -42%: ciprofloxacin + gentamicin	-primary endpoint: development of UTI that required hospitalization -secondary endpoints: duration of hospitalization and duration of antibiotic treatment	-Incidence of UTI requiring hospitalization: 6.3% → cipro-only: 5% → cipro + genta: 8% -Mean hospital stay: 9.2d -Number of positive urine cultures: 8/13 -> *E.coli* -Number of positive blood cultures: 6/13 -> *E.coli* -Percentage of ciprofloxacin resistance: 100% -Mean duration of antibiotic treatment: 23.2d	No significant difference
Raaijmakers et al, 2002	Retrospective review	N= 5802	Trimethoprim-sulfamethoxazole 960 mg before and after biopsy	-incidence of minor complication: expected side effects requiring no additional treatment -incidence of major complications: adverse effects requiring additional treatment	-Incidence of minor complications: Hematospermia: 50.4% Hematuria > 3d: 22.6% -Incidence of major complications: Fever: 3.5% Urinary retention: 0.4% Hospital admission: 0.5%	

Tal et al, 2002	Prospective study	N= 23	95.7% op the patients received antibiotic prophylaxis, including 69.5% with fluoroquinolones	-clinical presentation -results of blood & urine culture -antibiotic sensitivity -length of hospitalization	-Percentage of positive urine cultures: 60.8% -> 92.9% *E.coli* -Percentage of positive blood cultures: 26.1% -> 100 % *E.coli* -Percentage of fluoroquinolone resistance: → all patients: 75.6% → patients with fluoroquinolone prophylaxis: 97.0% -Median length of hospital stay: 5.7d	
Griffith et al, 2002	Prospective observational study	N= 400	Low risk: Levofloxacin 500 mg p.o. single dose 30-60 min before biopsy High risk: +2 additional doses levofloxacin for patients at increased risk of infectious complications	-complications -number of biopsy cores -prostate size -cancer detection rates	-Incidence of infectious complications: Low risk group: 0.27% High risk group: 0% -Mean number of biopsy cores: 7 -Mean prostate volume: 49.75 cc -Percentage of prostate cancer: 23%	High risk criteria: prostate > 75 cc, DM, recent steroid use, severe voiding dysfunction, immune compromise
Lindert et al, 2000	Randomized prospective study	N= 50	No antibiotics before biopsy Ciprofloxacin 500 mg + metronidazole 500 mg p.o. immediately after all cultures were obtained	-incidence and predisposing factors of bacteremia and bacteriuria -value of pre-biopsy enema	-Percentage of positive urine cultures: → pre-biopsy: 48% → post-biopsy: 44% -Predisposing factors of bacteriuria: • Statistically significant correlation of increasing patient age with bacterial growth in the pre- and post-biopsy urine culture • No correlation with PSA, number of biopsies, obstructive voiding symptoms, prostate volume, enema administration, cancer, post-biopsy hematuria, pre- or post-biopsy dysuria or post-biopsy urinary frequency -Percentage of positive post-biopsy blood cultures: 16% -Predisposing factors of bacteremia: • Highly statistically significant correlation of bacterial growth in blood cultures with the lack of an enema • No correlation with patient age, history of dysuria and/or UTI, PSA, number of biopsies, obstructive voiding symptoms, prostate volume, cancer or post-biopsy hematuria or voiding symtoms -Percentage of positive prostate biopsy tissue cultures: 50% → 65.8% of the organisms were of enteric origin	-Patients with history of prosthetic devices and/or VHD were excluded -No enema: 28% with positive blood culture Enema: 4% with positive blood culture

					-Predisposing factors of positive prostate biopsy tissue cultures: • Statistically significant correlation with a larger prostate and higher AUA symptom score • No correlation with history of UTI or dysuria -Percentage of postive cultures of swabs from the biopsy needle: 74% → 70.1% of the organisms were of enteric origin	-Prostate tissue and blood culture growth correlated with bacterial growth in the biopsy needle cultures → most bacteremia results from seeding of the prostate and blood from the rectum via the biopsy needle
Sieber et al, 1997	Retrospective review	N= 4439	Ciprofloxacin 500 mg p.o. twice dialy for 8 doses beginning the day before biopsy	-Symptomatic urinary tract infection rate	-Incidence (number) of symptomatic UTI: 0.1% (5) → 3 cases of sepsis	Low infection rate associated with this prophylaxis regimen
AB = antibiotics, p.o. = per os, I.M. = intramuscular, I.V. = intravenous, UTI = urinary tract infection, DM = diabetes mellitus, VHD = valvular heart disease, GUI = genitourinary infection.						

Attachment 3 – Studies on antibiotic prophylaxis for TRUSPB

Author	Study type	Population Control/ intervention	Inclusion criteria	Intervention/ control	Outcome parameter	Outcome	Remarks
Ho et al, 2009	Retrospective cohort study & prospective interventional cohort study	N= 741 374 / 367	-No bacteriuria -No ciprofloxacin or gentamicin allergy and/or renal impairment -No VHD -No other sources of fever	-Retrospective: Ciprofloxacin 500 mg p.o. twice daily for 3d -Prospective: Ciprofloxacin 500 mg p.o. twice daily for 3d + gentamicin 80 mg I.M.	-Hospitalisation secondary to sepsis within 1 wk -Isolated bacteria and its susceptibility	- Incidence of sepsis Cipro-only 3.3% Cipro + Genta 1.3% -Number of positive blood cultures with ciprofloxacin resistant *E. coli*: Cipro-only 9/10 Cipro + Genta 1/10	Difference not statistically different
Horjacada et al, 2009	Retrospective cohort study & prospective interventional cohort study	N= 411 204 / 207	-No positive urinary dipstick test -No non-adherence to AB prophylaxis -No altered coagulation parameters	-Retrospective: Amoxicillin/clavulanate 2x500 mg/d starting 1 day before biopsy for 3 days -Prospective: Cefoxitin 2g 1h before biopsy + ciprofloxacin 2x750 mg/d p.o. starting 1 day before for 4 days	-Incidence of bacteremia	-Incidence of bacteremia: Old protocol 4.4% (ESBL) New protocol 0.9% (non-ESBL) -Incidence of septic shock: Old protocol 1.4% New protocol 0%	Difference statistically significant
Briffaux et al, 2008	RCT	N= 288 139 / 149	-No contra-indications to ciprofloxacin -No risk factors for infection -No AB 1 wk prior -No UTI -No VHD	-Single dose ciprofloxacin2x 500mg 2h before biopsy -3-day dose ciprofloxacin (2x500 mg 2h before biopsy + 1x500 mg every 12h for a total of 3 days)	-Bacteriuria >10^3 CFU/ml -Incidence of clinical symptoms and UTI	-Number of patients with bacteriuria: Single dose group: 1 (cipro S) 3-day group: 1 (cipro R) -Incidence of clinical symptoms: Single dose group: 2.4% 3-day group: 9.2%	No argument for the use of more than one dose
Cam et al, 2008	RCT	N= 400 139 / 131 / 130	- No AB prior -No bacteriuria	-Ceftriaxone 1g I.M. 30 min before biopsy - Ciprofloxacin 500 mg p.o. twice daily for 3 days - Single dose ciprofloxacin 500 mg p.o. 60 min before biopsy	-Incidence of minor complications -Incidence of major complications requiring hospitalisation	-Incidence of minor complications: Group 1: 108.7% Group 2: 113% Group 3: 110.8% -Incidence of major complications: Group 1: 2.1% Group 2: 2.4% Group 3: 1.6%	-Similar complication rates between all groups -Minor: pain, dysuria, hematospermia, hematuria, mild fever, rectal bleeding -Major: vasovagal episode, urinary retention, acute prostatitis, sepsis

Schaeffer et al, 2007	RCT, double blinded	N= 497 247 / 250	-No bacteriuria -No hypersensitivity to quinolone agents -No VHD -No renal or hepatic insufficiency -No CNS disorder that might predispose to seizures -No indwelling catheter -No AB 7d prior	-1-day ciprofloxacin XR 1000 mg -3-day ciprofloxacin XR 1000 mg	-Primary efficacy variable: bacteriological succes rates (negative urine cultures) -Secondary efficacy variable: clinical succes rates (absence of a genitourinary infection or a procedure-related non-genitourinary infection)	-Bacteriological succes rates: 1-day group 94.8% 3-day group 98.0% -Clinical succes rates: 1-day group 96.7% 3-day group 98.5% -Potential predictors of microbiological failure: DM -Potential predictors of clinical failure: history of prostatitis	-Difference not statistically significant -Difference statistically significant -For patients with DM and a history of prostatitis: all failures among those treated with 1-day regimen
Lindstedt et al, 2006	Open comparative study	N= 1322 791 / 531	-No bacteriuria -No indwelling catheter -No history of repeated UTI, prostatitis or febrile genitourinary infection -No hypersensitivity to ciprofloxacin -No artificial heart valves -No steroid medication	-Lund: single high dose ciprofloxacin 750 mg p.o. 2h before biopsy - Malmö: single high dose ciprofloxacin 750 mg p.o. just before biopsy	-Incidence of febrile genitourinary infection -Result of urine culture taken 2-4 weeks after biopsy	-Incidence of febrile GUI: Overall 0.9% Lund 0.8% Malmö 1.1% -Urine cultures: Negative 91% 10^4-10^5 4.8% > 10^5 4.3%	Rate of septicaemia 0.17%
Puig et al, 2006	Retrospective study	N= 1018 614 / 404	-No prior history of urinary infection or prostatitis	-no AB -ciprofloxacin 500 mg/12h p.o. from 12h before until 5d after biopsy	-Incidence of minor complications (expected side effects) -Incidence of major complications (adverse side effects that required hospitalisation)	-Number of patients with minor infectious complications: No AB group 32 Cipro group 5 -Number of patients with major infectious complications: No AB group 31 Cipro group 10	Differences statistically significant NNT= 25.1 NNT= 38.8
Shigemura et al, 2005	Non-randomized prospective study	N= 236 124 / 112	-No pyuria	-Levofloxacin 600 mg for 1 day -Levofloxacin 300 mg for 3 days	-Incidence of febrile infectious complications -Evolution of serum WBC count and CRP: d0 (10 min before biopsy) d1 (1 day after biopsy) d7 (7 days after biopsy)	-Incidence of febrile infectious complications: 1-day group 1.61% 3-day group 1.79% -Mean serum WBC count & CRP: No significant difference between 2 groups but WBC count and CRP elevation tends to be smaller in 1-day group	-No significant difference -600 mg/day for 1 day may be more effective for preventing infectious complication

Petteffi et al, 2002	RCT, simple blinded	N= 105 51 / 54	-No allergy to norfloxacin -No long term indwelling catheter -No AB (chronic or within 30d) -No leucopenia with granulocytes count < 1000 mL -No VHD or valvular prothesis	-Short term: norfloxacin 400 mg p.o. single dose 1h before biopsy -Long term: nofloxacin 400 mg p.o. 1h before + twice daily during 72h	-Incidence of minor complications -Continuous variables: hematocrit, hemoglobin, total WBC, bands percentage -Categorical events: fever, urine culture, emergency management, empirical AB, hospitalization	-Incidence of minor complications: Short term 78% Long term 74% -Continuous variables: no statistical difference - rates of fever: Short term 15% Long term 2% -positive urine cultures: Short term 29% Long term 7%	-No significant difference -Trend towards higher incidence of major complications with short term prophylaxis
Cormio et al, 2002	RCT	N= 138 72 / 66	-No indwelling catheter -No AB or immunosuppressive drugs -No positive mid-stream urine cultures before biopsy	-Piperacillin/tazobactam (P/T) 2250 mg I.M. twice daily for 2 days -Ciprofloxacin 500 mg p.o. twice daily for 7 days	-Incidence of bacteriuria (> 10^5 CFU/mL)	-Incidence of positive MIU cultures: P/T group 2.8% Cipro group 4.5%	-Difference not statistically significant -Patients in cipro-group required further treatment
Aron et al, 2000	RCT, patient blinded	N= 231 75 / 79 / 77	-No UTI -No indwelling catheter	-Single dose ciprofloxacin 500 mg + tinidazole 600 mg p.o. + placebo until 3d -Ciprofloxacin 500 mg + tinidazole 600 mg p.o. twice daily for 3d -Placebo 3d	-Bacteriuria (48h post-biopsy) -Fever (> 38°C) -Bacteraemia	-Incidence bacteriuria: Placebo 18.6% Prophylaxis 5-7.8% -incidence fever: Placebo 6.7% Prophylaxis 2.5-2.6% -Incidence bacteraemia: Placebo 2.7% Prophylaxis 0-1.3% -Incidence overall infective complications: Placebo 25.3% Prophylaxis 7.6-10.4%	No significant difference between single dose and 3d of AB

Isen et al, 1999	RCT	N= 110 23 / 42 / 45	-No AB 3d prior -No VHD, indwelling catheter, DM, steroid use, prostatitis	-Single dose ofloxacin 400 mg p.o. -Single dose TMP/SMX 160/800 mg p.o. -No AB	Bacteriuria 7-10d post biopsy	-Incidence bacteriuria No AB 26.1% Ofloxacin 4.8% TMP/SMX 6.7%	-Difference significant between no-AB group and AB group. -No significant difference between 2 AB schemes.
Kapoor et al, 1998	RCT, double blinded	N= 457 230 / 227	-No bacteriuria -No AB or endoscopic manipulation 1 wk prior -No indwelling catheter	-Single dose ciprofloxacin 500 mg p.o. -Placebo	-Bacteriuria > 10^4 CFU/ml 15d post-biopsy -Symptomatic UTI	-Incidence bacteriuria: Placebo 8% Cipro 3% - Incidence symptomatic UTI: Placebo 5% Cipro 3%	
Crawford et al, 1982	RCT, patient blinded	N= 48 25 / 23	-No UTI -No AB 2 wk prior -No VHD or prothesis	-Carbenicillin 1d prior + 1d post biopsy -Placebo	-Bacteriuria (>10^5 CFU/ml) 2+14d post biopsy -Bacteraemia -Fever (>38.5°C)	-Incidence bacteriuria day 2 - day 14 Placebo 36% - 20% Carbenicillin 8.6% - 8.6% -Incidence bacteraemia: Placebo 16% Carbecillin 22% -Incidence fever: Placebo 48% Carbecillin 17%	
RCT = Randomized controlled trial, AB = antibiotics, p.o. = per os, UTI = urinary tract infection, CFU = colony forming units, NNT = number needed to treat, TMP/SMX = trimethoprim/sulfamethoxazole, DM = diabetes mellitus, VHD = valvular heart disease, GUI = genitourinary infection.							

Attachment 4 – Prospective study: questionnaire of patient characteristics

Critically Appraised Topic 2009-2010

Bacteriemie met fluorochinolone resistente *E.coli* na uitvoering van een prostaatbiopsie: een reden tot nieuwe aanpak?

Naam Patiënt:	
EAD nummer:	
Datum biopsie:	

Initiële PSA :	
PPA :	
Aantal voorafgaande biopsies :	
Antibioticum voor chemoprofylaxe 1u voor biopsie :	○ Ciprofloxacine ○ Levofloxacine ○ Andere:
Chronische prostatitis :	Ja / Nee
Langdurig gebruik van chinolones in het verleden :	Ja / Nee **Zoja:** ✓ reden van gebruik: ✓ aantal dagen: ✓ tijdstip van inname: < 6 maanden geleden > 6 maanden geleden

Opmerkingen: