J Antimicrob Chemother 2014; **69**: 3372–3378
doi:10.1093/jac/dku293 Advance Access publication 11 August 2014

Journal of Antimicrobial Chemotherapy

# Antibiotic prophylaxis for transrectal prostate biopsy—a new strategy

**Valeria Antsupova[1]*, Nis Nørgaard[2], Rasmus Bisbjerg[2], Jette Nygaard Jensen[1], Jonas Boel[1,3], Jens Otto Jarløv[1] and Magnus Arpi[1]**

[1]*Department of Clinical Microbiology, Herlev Hospital, University of Copenhagen, Herlev, Denmark;* [2]*Department of Urology, Herlev Hospital, University of Copenhagen, Herlev, Denmark;* [3]*Capital Region Pharmacy, Herlev Hospital, University of Copenhagen, Herlev, Denmark*

*Corresponding author. Department of Clinical Microbiology, Herlev Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark. Tel: +45-50529995; E-mail: valeria.antsupova@yahoo.dk

*Received 20 May 2014; returned 17 June 2014; revised 7 July 2014; accepted 7 July 2014*

**Background:** Fluoroquinolones are extensively used as prophylaxis for transrectal ultrasound-guided biopsy of the prostate (TRUBP). Emerging fluoroquinolone resistance and selection of multiresistant organisms warrant new prophylactic strategies. Pivmecillinam and amoxicillin/clavulanic acid have mutual synergistic activity and the combination of these agents has a broad coverage of the majority of microorganisms causing infectious complications after TRUBP and may be a valuable future prophylactic regimen.

**Patients and methods:** This was a retrospective cohort study of 2624 men that underwent TRUBP at a Danish university hospital. The patients were divided into three groups. Group 1 ($n=1220$) received ciprofloxacin before TRUBP, Group 2 ($n=240$) received a combination of pivmecillinam and amoxicillin/clavulanic acid before TRUBP and Group 3 ($n=1161$) received an extended prophylaxis with pivmecillinam and amoxicillin/clavulanic acid before and for 2 days after TRUBP.

**Results:** One hundred and ten out of 148 (74.3%) post-TRUBP infections were caused by *Escherichia coli*, *Klebsiella pneumoniae* or *Enterococcus faecalis*. Group 3 with the extended prophylaxis with pivmecillinam and amoxicillin/clavulanic acid had a significantly lower rate of bacteraemia (0.9%) as compared with Group 1 (1.8%) and Group 2 (3.7%). A significant fall in the proportion of ESBL-producing Enterobacteriaceae was observed from the period when ciprofloxacin was used as prophylaxis (8.1%) compared with the subsequent period when pivmecillinam and amoxicillin/clavulanic acid was used (5.9%).

**Conclusions:** The combination of pivmecillinam and amoxicillin/clavulanic acid is an attractive prophylaxis for TRUBP from a clinical, bacteriological and ecological point of view as compared with ciprofloxacin.

**Keywords:** prostate biopsy, prophylaxis, ciprofloxacin, pivmecillinam, amoxicillin/clavulanic acid

## Introduction

Transrectal ultrasound-guided biopsy of the prostate (TRUBP) is an essential procedure for verification of prostate cancer diagnosis and a frequently performed procedure in urology. However, this procedure has a number of complications, such as haematuria, haematospermia, asymptomatic bacteriuria, urinary tract infection (UTI), fever, bacteraemia and life-threatening sepsis.[1–4]

Several randomized controlled studies have demonstrated that antibiotic prophylaxis for TRUBP reduced the risk of sepsis and UTI after this procedure.[5,6] Clinical guidelines therefore recommend antibiotic prophylaxis to protect against severe infections after prostate biopsy.[7,8]

Fluoroquinolones, especially ciprofloxacin, have been the drug of choice for prophylaxis since the 1980s, mostly because of their rapid penetration and high concentration in the prostatic tissue and because of potent activity against a broad spectrum of clinically relevant pathogens in the urogenital tract.[7–12] In a randomized controlled study, Aron *et al.*[5] observed that infections after TRUBP significantly decreased when fluoroquinolones were used compared with placebo. A high consumption of fluoroquinolones in urological departments for decades has resulted in an increased rate of infections following TRUBP caused by fluoroquinolone-resistant organisms.[13–16]

The incidence of ESBL-producing bacteria has increased in many countries.[17,18] Many ESBL-producing bacteria are resistant not only to penicillins and cephalosporins, but also to fluoroquinolones and aminoglycosides, underscoring the need to find new strategies to combat this problem.[18–20] Strategies including new alternative antibiotic regimens to reduce the risk of infection, timing and duration of prophylaxis for TRUBP are warranted. The choice of prophylactic antibiotics should be based on the following properties: documented penetration into the prostate tissue, broad spectrum of antimicrobial activity against the most common pathogens of the urogenital tract, low-level antibiotic resistance and low selection pressure.

Pivmecillinam, a 6-β-amidinopenicillanic acid derivative discovered in the 1970s, has a documented high clinical effect on UTI caused by Enterobacteriaceae including ESBL-producing strains.[18,21] Jansåker *et al.*[21] recently demonstrated a clinical and bacteriological effect of pivmecillinam on ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* causing UTI. Pivmecillinam has the advantage of minor ecological impact on the normal intestinal and vaginal flora.[18,22]

Grabe *et al.*[23,24] showed the effectiveness of a short perioperative course with pivampicillin and pivmecillinam in transurethral prostatic resection. In a recent paper, Dewar *et al.*[18] discussed the emerging clinical role of pivmecillinam in the treatment of UTI in the context of MDR bacteria. They stressed the unique mode of action of pivmecillinam on the bacterial cell wall and suggested broadening of the antibacterial spectrum by a combination of pivmecillinam with another β-lactam antibiotic and/or a β-lactamase inhibitor, e.g. a combination of pivmecillinam and amoxicillin/clavulanic acid.[18]

Resistance to mecillinam has remained low since its introduction. A study conducted in 16 European countries and Canada between January 1999 and December 2000 found resistance to mecillinam to range from 1.2% (*E. coli*) to 5.2% (*Klebsiella* spp.).[25] Another large study during the period 2003–06 conducted in Europe and Brazil obtained similar results: 95.9% of *E. coli* isolates were susceptible to mecillinam.[26]

In this retrospective cohort study, we evaluated the prevalence of post-TRUBP infections and the antimicrobial resistance after antibiotic prophylaxis was changed from ciprofloxacin to a combination of pivmecillinam and amoxicillin/clavulanic acid.

## Patients and methods

We conducted a retrospective cohort study of 2624 men who underwent 2823 TRUBP procedures in the Department of Urology, Copenhagen University Hospital, Herlev, Denmark, from January 2010 to January 2013. All patients undergoing TRUBP were included. They were divided into three groups according to the prophylactic regimen. From January 2010 to August 2011, 1220 patients (1340 TRUBP procedures) received 500 mg of ciprofloxacin just before biopsy and 6 h after biopsy (Group 1). Due to increasing resistance to fluoroquinolones in the whole hospital, including the Department of Urology, the antibiotic prophylaxis for TRUBP was changed. This was part of the antibiotic stewardship programme in the entire hospital, which was introduced in 2011 with the primary goal to reduce the consumption of fluoroquinolones and cephalosporins. In August 2011, a combination of pivmecillinam and amoxicillin/clavulanic acid as a new antibiotic prophylaxis regimen for TRUBP was introduced. From August to November 2011, 240 patients (245 TRUBP procedures) were treated with a combination of 400 mg of pivmecillinam and 500/125 mg of amoxicillin/clavulanic acid the night before and 2 h before biopsy (Group 2). In November 2011, owing to a trend of increased infection rate, this antibiotic prophylaxis was extended. From November 2011 to January 2013, 1161 patients (1238 TRUBP procedures) received a combination of 400 mg of pivmecillinam and 500/125 mg of amoxicillin/clavulanic acid the night before and 2 h before biopsy followed by 2 days with three divided doses each day after biopsy (Group 3).

Three patients from Groups 2 and 3 who were allergic to penicillin were excluded from the study.

### *Surgical procedure*

All patients were referred because of elevated prostate-specific antigen and/or suspicious findings on digital rectal examination (DRE). They had 10 mL of Installagel® injected in the rectum and DRE and diagnostic transrectal ultrasound (TRUS) with volume estimation were performed.

TRUS was done using Hitachi 8500, Hitachi Preirus or BK Medical PRO Focus ultrasound systems and Hitachi EUP-U533 or BK Medical 8848 biplane transducers. Some patients also had an MRI scan before image fusion-guided biopsies. Depending on DRE, TRUS and MRI, 1–14 ultrasound-guided transrectal biopsies from the prostate were taken using Hitachi EUP-V53 or BK Medical 8818 transducers and the end-fire technique. All image fusion-guided biopsies were performed with Hitachi Preirus and Hitachi EUP-V53 systems. All biopsies were taken with an 18 gauge TruCut needle. There was no difference in the biopsy technique used by two attending urologists.

In accordance with several international studies, information on infectious complications, isolated microorganisms and antibiotic resistance after TRUBP was collected until 30 days after biopsy.[3,14,27] Data were extracted from the electronic patient records, the electronic patient medicine module and the laboratory information system at the Department of Clinical Microbiology (ADBakt, Autonik, Sweden).

The most frequent reasons for admission to the hospital after prostate biopsy were symptoms of infection such as fever >38°C, shivering and dysuria. Febrile patients with non-urological causes were excluded.

All blood and urine samples from patients that underwent prostate biopsy were analysed at the Department of Clinical Microbiology, Copenhagen University Hospital, Herlev, Denmark, during the whole study period. Samples were collected from patients presenting clinical symptoms of infection using local hospital guidelines. The BACTEC™ system was used for blood cultures.

Identification of microorganisms was performed using approved conventional methods.[28] Antimicrobial susceptibility testing was performed by disc diffusion according to EUCAST recommendations.[29] In the period from April 2012 to July 2013, susceptibility testing of ciprofloxacin was changed from a nalidixic acid disc to a ciprofloxacin disc. This period has not been included in the evaluation of time trends of ciprofloxacin resistance.

All organisms showing reduced susceptibility to cefpodoxime were tested for ESBL production by using the AmpC and ESBL Detection Set (Mast Group, UK).

### *Definitions*

UTI was defined as a mid-stream urine sample with $\geq 10^4$ cfu/mL of an organism. In patients with both bacteraemia and UTI with an identical organism isolated, only bacteraemia was recorded.

Pivmecillinam is an absorbable prodrug of mecillinam used for oral administration. Mecillinam in its hydrochloride dehydrate form is suitable for parenteral administration, but it is not absorbed when given orally.

### *Statistical analysis*

The data were analysed using the Statistical Package for the Social Sciences (SPSS) 19.0 for Windows (IBM Software, USA). Quantitative data are presented as numbers with percentages. Categorical variables were compared using either the $\chi^2$ test or Fisher's exact test. A binary logistic regression analysis was used to examine the association between possible predictive factors for the occurrence of bacteraemia and UTI after prostate biopsy. Analysis of variance was used to evaluate differences in the mean and median values between groups and the Bonferroni test was used as a *post hoc* test. Differences were considered statistically significant when *P* values were <0.05 on the two-sided test. A relative risk of 1.0 indicates no difference between comparison groups.

The study was approved by the Danish Data Protection Agency (I–suitnr. 02297 and id.no. HEH-2013-030).

## Results

A total of 2823 TRUBP procedures performed in 2621 patients with a median age of 67 years (range 32–98 years) were included in the study. There was no significant difference in the patients' ages and comorbidities between the groups. In total, the median interval between TRUBP and positive blood and positive urine culture was 2.5 days (range 1–15 days) and 4 days (range 0–30 days), respectively. When divided into three groups (Group 1, Group 2 and Group 3), the median interval between biopsy and positive blood culture was 2.4 days (range 1–11 days), 3.2 days (range 1–7 days) and 5.1 days (range 1–15 days), respectively. The interval between TRUBP and positive urine culture varied greatly in all groups. All patients with a positive blood culture had only one bacteraemic episode. Overall, Gram-positive pathogens were found in 16% and Gram-negative in 84% of all blood and urine cultures (Table 1).

Implementation of an antibiotic stewardship programme at our hospital in 2011 resulted not only in a reduction of ciprofloxacin consumption, but also in a stabilization of the level of ciprofloxacin resistance with no further increase in the Department of Urology. The consumption of ciprofloxacin and the rate of ciprofloxacin-resistant *E. coli* in the Department of Urology are presented in Figure 1.

After the antibiotic prophylaxis for TRUBP was changed, the ciprofloxacin consumption in the Department of Urology decreased significantly, while the use of pivmecillinam and amoxicillin/clavulanic acid increased from 6700 DDDs/1000 bed-days in 2010 to 15 793 DDDs/1000 bed-days in 2012 and from 150 DDDs/1000 bed-days to 9540 DDDs/1000 bed-days, respectively.

During the first period of the study (Group 1), 1340 TRUBP procedures were performed. All patients received ciprofloxacin. Of these patients, 24 (1.8%) were admitted because of symptoms of infection and had a positive blood culture, while 51 patients (3.8%) had a positive urine culture (Table 2). The most common microorganism in both blood and urine culture was *E. coli*: 16/24 (66.7%) and 22/51 (43.1%), respectively (Table 1). Of all *E. coli* isolates, 55.3% were ciprofloxacin resistant, 5.3% were gentamicin resistant, 21.1% were cephalosporin resistant and 15.8% produced ESBL. Three isolates of *E. coli* (7.9%) from blood and urine cultures were mecillinam resistant. One ESBL-producing *E. coli* isolate was resistant to mecillinam. Among all *E. coli* in blood cultures, 6.3% (1/16) were amoxicillin/clavulanic acid resistant. None of the bacteria was resistant to meropenem.

**Table 1.** Microorganisms isolated from blood and urine cultures after prostate biopsy

| | Culture results [*n* (%)] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1 | | Group 2 | | Group 3 | | all patients | |
| Microorganism | blood | urine | blood | urine | blood | urine | blood | urine |
| Gram-positive | | | | | | | | |
| *Staphylococcus aureus* | 1 (4.2) | 0 | 0 | 0 | 0 | 1 (2.5) | 1 (2.3) | 1 (1.0) |
| *Staphylococcus epidermidis* | 0 | 0 | 0 | 1 (7.7) | 0 | 0 | 0 | 1 (1.0) |
| *Streptococcus haemolyticus* group G | 0 | 1 (2.0) | 0 | 0 | 0 | 0 | 0 | 1 (1.0) |
| *Enterococcus faecalis* | 1 (4.2) | 9 (17.6) | 0 | 1 (7.7) | 0 | 4 (10.0) | 1 (2.3) | 14 (13.5) |
| *Enterococcus faecium* | 0 | 1 (2.0) | 0 | 0 | 0 | 2 (5.0) | 0 | 3 (2.9) |
| *Enterococcus* spp. | 0 | 0 | 0 | 0 | 0 | 2 (5.0) | 0 | 2 (1.9) |
| Gram-negative | | | | | | | | |
| *Escherichia coli* | 16 (66.7) | 22 (43.1) | 5 (55.6) | 8 (61.5) | 8 (72.7) | 25 (62.5) | 29 (65.9) | 55 (52.9) |
| *Klebsiella pneumoniae* | 1 (4.2) | 6 (11.8) | 1 (11.1) | 2 (15.4) | 0 | 1 (2.5) | 2 (4.5) | 9 (8.7) |
| *Klebsiella oxytoca* | 1 (4.2) | 4 (7.8) | 1 (11.1) | 0 | 0 | 0 | 2 (4.5) | 4 (3.8) |
| *Enterobacter cloacae* | 1 (4.2) | 1 (2.0) | 0 | 0 | 0 | 1 (2.5) | 1 (2.3) | 2 (1.9) |
| *Proteus mirabilis* | 0 | 2 (3.9) | 0 | 0 | 0 | 1 (2.5) | 0 | 3 (2.9) |
| *Proteus vulgaris* | 0 | 1 (2.0) | 0 | 0 | 0 | 0 | 0 | 1 (1.0) |
| *Flavobacterium* spp. | 0 | 0 | 1 (11.1) | 1 (7.7) | 0 | 0 | 1 (2.3) | 1 (1.0) |
| *Acinetobacter baumannii* | 0 | 0 | 0 | 0 | 1 (9.1) | 0 | 1 (2.3) | 0 |
| *Pseudomonas aeruginosa* | 1 (4.2) | 1 (2.0) | 1 (11.1) | 0 | 2 (18.2) | 1 (2.5) | 4 (9.1) | 2 (1.9) |
| *Pseudomonas* spp. | 0 | 1 (2.0) | 0 | 0 | 0 | 2 (5.0) | 0 | 3 (2.9) |
| *Agrobacterium* sp. | 1 (4.2) | 0 | 0 | 0 | 0 | 0 | 1 (2.3) | 0 |
| *Alcaligenes faecalis* | 0 | 1 (2.0) | 0 | 0 | 0 | 0 | 0 | 1 (1.0) |
| *Achromobacter piechaudii* | 0 | 1 (2.0) | 0 | 0 | 0 | 0 | 0 | 1 (1.0) |
| *Bacteroides* sp. | 1 (4.2) | 0 | 0 | 0 | 0 | 0 | 1 (2.3) | 0 |
| Total | 24 | 51 | 9 | 13 | 11 | 40 | 44 | 104 |

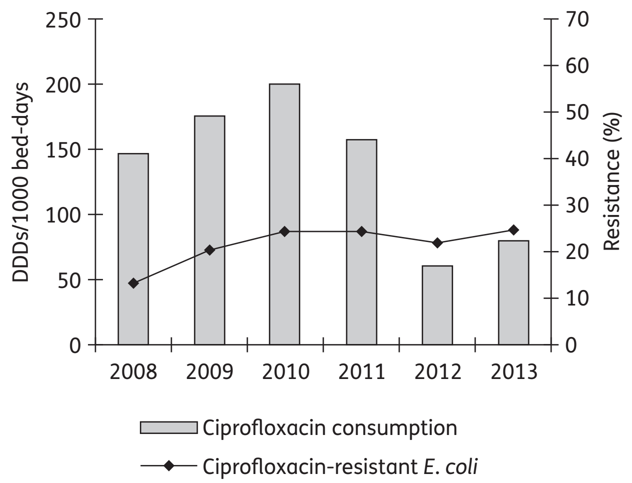


**Figure 1.** Ciprofloxacin consumption and the rate of ciprofloxacin-resistant *E. coli* in the Department of Urology from 2008 to 2013.

After the implementation of a new antibiotic prophylaxis with two doses of pivmecillinam and amoxicillin/clavulanic acid (Group 2), the incidence of bacteraemia increased to 3.7% (9/245 cases, $P=0.058$) (Table 2). Thirteen patients (5.3%) had positive urine cultures. The dominating cause of bacteraemia and UTI was *E. coli* (59.1% of all isolates) (Table 1). The incidence of ciprofloxacin resistance decreased from 55.3% to 23.1% ($P=0.045$). None of the bacteria was ESBL producing and one *E. coli* isolate was cephalosporin resistant. All *E. coli* isolates were susceptible to mecillinam and meropenem and one isolate was resistant to amoxicillin/clavulanic acid.

In Group 3 with the extended prophylaxis, the bacteraemia rate decreased significantly to 0.9% compared with Groups 1 and 2 (Table 2). Forty patients (3.2%) had positive urine cultures, which was lower than in Groups 1 and 2, but not significantly. Among these positive blood and urine cultures, 64.7% were caused by *E. coli* (Table 1).

The resistance rate for ciprofloxacin (12.1%) in Group 3 was not directly comparable to the rates in Groups 1 and 2 due to a change in the susceptibility testing of ciprofloxacin (from a nalidixic acid disc to a ciprofloxacin disc). Susceptibility testing with a ciprofloxacin disc in our laboratory generally showed a 10% lower resistance rate among *E. coli* as compared with a nalidixic acid disc. We therefore conclude that no further increase in the resistance rate occurred in Group 3. This stabilization was also observed in the total patient population in the Department of Urology (Figure 1).

There were no cases of ESBL-producing *E. coli*, but the rate of cephalosporin-resistant *E. coli* was 12.1%. One isolate was mecillinam and amoxicillin/clavulanic acid resistant. No isolates were meropenem resistant.

During the whole investigated period, 438 ESBL-producing Enterobacteriaceae isolates (*E. coli* 76.6%, *K. pneumoniae* 21.7% and *Proteus mirabilis* 1.6%) were isolated from 244 patients out of all patients admitted to the Department of Urology. A significant fall in the proportion of ESBL-producing Enterobacteriaceae was observed from 8.1% in the period when ciprofloxacin was used as prophylaxis for TRUBP as compared with 5.9% in the subsequent period when pivmecillinam and amoxicillin/clavulanic acid was used as prophylaxis ($P<0.01$).

We investigated the antibiotic coverage of mecillinam and amoxicillin/clavulanic acid alone and in combination for the most prevalent organisms causing infections after TRUBP in the Department of Urology. *E. coli*, *K. pneumoniae* and *Enterococcus faecalis* accounted for 110 out of a total of 148 isolates (74.3%). The proportion was 72.7% for blood isolates and 75.0% for urine isolates. The coverage was calculated for all isolates of *E. coli* ($n=1043$), *K. pneumoniae* ($n=168$) and *E. faecalis* ($n=2185$) that were isolated from patients admitted to the Department of Urology in the investigated period. The coverage of mecillinam alone using the EUCAST zone diameter for clinical breakpoints was 94.7% for *E. coli* and 97.6% for *K. pneumoniae*. All *E. faecalis* were resistant. EUCAST does not present clinical breakpoints for amoxicillin/clavulanic acid. Using the epidemiological breakpoints from EUCAST, the coverage was 72.5% for *E. coli* and 83.9% for *K. pneumoniae*. Almost all *E. faecalis* were ampicillin susceptible (99.5%). Overall, the combination of pivmecillinam and amoxicillin/clavulanic acid gave high coverage for the majority of pathogenic organisms that were involved in infections after TRUBP at our hospital. The few isolates of *Klebsiella oxytoca*, *Enterobacter cloacae*, *Proteus* spp. and *Staphylococcus aureus* would probably be sufficiently covered by the combination. Six isolates of *Pseudomonas aeruginosa* were not covered by the combination.

## Discussion

Infectious complications following TRUBP occur after the introduction of bacteria into the parenchyma of the prostate, the bloodstream, the urinary tract or any combination of the three from the hollow-core biopsy needle traversing the rectal wall and periprostatic tissue. Overall, our data are similar to studies demonstrating that 1%–4% of men who have TRUBP performed will develop an infection requiring hospital care.[2,17,30,31]

The portion of men who needed to be hospitalized for an infection within 30 days of having a prostate biopsy increased from

**Table 2.** Occurrence of positive blood and urine cultures after prostate biopsy

| Culture result | Total ($n=2823$) | Group 1 ($n=1340$) | Group 2 ($n=245$) | Group 3 ($n=1238$) | *P* value | RR (95% CI) Group 1 vs 2 | RR (95% CI) Group 2 vs 3 | RR (95% CI) Group 1 vs 3 |
|---|---|---|---|---|---|---|---|---|
| Positive blood culture | 44 (1.6%) | 24 (1.8%) | 9 (3.7%) | 11 (0.9%) | 0.004 | 0.478 (0.220–1.042) | 4.134 (1.732–9.870) | 2.016 (0.992–4.098) |
| Positive urine culture | 104 (3.7%) | 51 (3.8%) | 13 (5.3%) | 40 (3.2%) | 0.511 | 0.7 (0.387–1.266) | 1.683 (0.915–3.099) | 1.178 (0.784–1.769) |

RR, relative risk.

0.6% in 1996 to 3.6% in 2005 according to a study of 75 190 Canadian men.[3]

As reported by previous studies, *E. coli* was the most commonly found bacteria also in our patients with post-TRUBP infection. Several studies have documented increasing rates of fluoroquinolone resistance among patients hospitalized for infectious complications after prostate biopsy.[13–16,27] In our urological department, ciprofloxacin has been the standard antibiotic for prophylaxis for TRUBP and has also been widely used for treatment of different urological infections such as prostatitis and epididymitis. As a result, the number of ciprofloxacin-resistant microorganisms increased. In the first phase of our study when ciprofloxacin was used as prophylaxis for TRUBP, 55.3% of all *E. coli* strains isolated within a month after the biopsy were ciprofloxacin resistant. This reflects the high selective pressure of ciprofloxacin. This level of resistance appears similar to the recently published data from several other studies.[13,15] Hospitals with a high incidence of infectious complications after TRUBP caused by ciprofloxacin-resistant microorganisms should consider the use of an alternative prophylactic regimen.

The new combined prophylactic regimen fulfils several demands. It has a broad-spectrum activity against most common pathogens in the urogenital tract, few ecological disadvantages concerning the normal flora and low selection pressure as compared with ciprofloxacin. The documentation of an achievable prostatic concentration of pivmecillinam and amoxicillin/clavulanic acid is still insufficient and contradictory.

Currently, only a few studies on the penetration of these antibiotics into prostate tissue have been published. Juricic *et al.*[32] reported levels of 26.4 mg/L amoxicillin and 0.6 mg/L clavulanic acid, 15–120 min after administration of a single oral dose. Lipsky *et al.*[33] reported a prostatic concentration of amoxicillin of 3.8–7.2 μg/g after administration of amoxicillin/clavulanic acid. In contrast to these reports, Scaglione *et al.*[34] found the prostatic tissue concentrations of amoxicillin and clavulanic acid to be 0.77 and 0.15 mg/L, respectively.

Grabe and Forsgren[23] found a low concentration of mecillinam and ampicillin in prostate chips ($<$0.26 and 0.77 mg/L, respectively) for samples obtained 1–4 h after oral intake of 500 mg of pivampicillin and 400 mg of pivmecillinam. This is in contradiction to the results reported by Jeppesen and Frimodt-Møller.[35] They found considerably higher mean concentrations of mecillinam and ampicillin in patients undergoing transurethral resection of the prostate. After intravenous administration of 5 mg/kg mecillinam and 12 mg/kg ampicillin, the mean prostatic concentration of mecillinam after 1, 2 and 6 h was 4.9, 2.3 and 0.31 mg/L, respectively. Corresponding results for ampicillin were 16, 6.7 and 0.68 mg/L, respectively. They concluded that a serum prostatic tissue ratio of about 2:1 was obtainable. Differences in the methods used for the analysis of prostatic tissue concentration and different time lags between the administration of antibiotics and tissue sampling are probably the reason for the diverging results in the mentioned studies. Differences in the time elapsed from the administration of antibiotics to tissue sampling may have a major impact on the tissue concentration due to the short half-life of mecillinam and amoxicillin/clavulanic acid.

Kerrn *et al.*[36] investigated mecillinam susceptibility in 147 *E. coli* isolates from patients with UTI from general practices in Denmark using an agar dilution method for MIC determination. The $MIC_{50}$ and $MIC_{90}$ were 0.5 and 2.0 mg/L, respectively.

As early as 1976, Neu[37] demonstrated the synergy between mecillinam and clavulanic acid against many Enterobacteriaceae species, in particular *E. coli* and *K. pneumoniae*. Lampri *et al.*[38] investigated the synergy between mecillinam and clavulanic acid in 48 ESBL-producing *E. coli* in Greece. CTX-M-type enzymes were present in 87.2% of the isolates. The MIC of mecillinam for ESBL-producing *E. coli* ranged from 0.25 to 16 mg/L, with 97.9% being susceptible. The $MIC_{50}$ and $MIC_{90}$ were 1.0 and 4 mg/L, respectively. In the presence of clavulanic acid, 41 isolates (84.5%) showed a $\geq$3 2-fold dilution decrease in the MIC value compared with mecillinam alone. The MICs of the combination of mecillinam and clavulanic acid ranged from 0.06 to 0.5 mg/L and the $MIC_{50}$ and $MIC_{90}$ were 0.125 and 0.5 mg/L, respectively. Forty-seven of 48 isolates (97.9%) were susceptible in the presence of clavulanic acid, even if high inocula were used. Thomas *et al.*[39] reported mecillinam MICs for CTX-M ESBL-producing *E. coli* and *Klebsiella* isolates that were 0.125–2 mg/L at an inoculum of $10^4$ cfu/spot, rising to 1–16 mg/L at $10^6$ cfu/spot. The addition of clavulanic acid reduced the MICs at a high inoculum from 8–16 to 0.03–0.06 mg/L. Brenwald *et al.*[40] reported that the susceptibility of mecillinam appears little affected by AmpC β-lactamases, with no appreciable inoculum effect attributable to this type of β-lactamase.

The synergy between mecillinam and other β-lactams, such as amoxicillin, has been documented in several studies.[37,41] The synergy is most pronounced for isolates less susceptible to mecillinam.[37] Binding to different PBPs promotes the synergy. Mecillinam binds to PBP2 whereas amoxicillin primarily binds to PBP1A.[42]

Moreover, the synergy between amoxicillin and clavulanic acid is also well documented. The addition of clavulanic acid significantly expands amoxicillin's spectrum to include penicillinase-producing *E. coli*, *Klebsiella* spp., *P. mirabilis* and *S. aureus*.[43,44]

All three drugs (mecillinam, amoxicillin and clavulanic acid) in combination may mutually contribute to the synergy. The pronounced synergistic effect probably diminishes the MICs to levels that are obtainable in prostatic tissue and sufficient for TRUBP prophylaxis. This is supported by the clinical results in the present study.

The issue of the duration of antibiotic coverage after TRUBP has yet to be resolved. It is well documented that the overall infection rate after TRUBP in patients who received pre- and post-biopsy antibiotics is lower than in patients who received post-biopsy antibiotics alone, but there is no consensus on the duration of post-biopsy prophylaxis.[45,46]

Our study not only demonstrated the effectiveness of the combination of pivmecillinam and amoxicillin/clavulanic acid in the prevention of infections after prostate biopsy, but also underscores the importance of follow-up with antibiotics after biopsy, in our case for 2 days.

In the group of patients who received a combination of pivmecillinam and amoxicillin/clavulanic acid for 3 days, the incidence of bacteraemia decreased significantly compared with patients from the ciprofloxacin group and patients treated with a short course of pivmecillinam and amoxicillin/clavulanic acid. Moreover, our study demonstrated a positive trend in reducing infections caused by ciprofloxacin-resistant and ESBL-producing microorganisms after implementing the new prophylactic regimen. There are no indications that the use of the new prophylaxis protocol has resulted in increased rates of resistance to mecillinam and amoxicillin/clavulanic acid.

The antibiotic prophylaxis should be effective but should not disturb the microflora of the gut, which may result in a *Clostridium difficile* infection. Pivmecillinam is a prodrug for oral use that is well absorbed and has minimal effect on the ecological balance of the normal intestinal microflora. Currently, pivmecillinam is an available therapeutic option to treat uncomplicated infections caused by ESBL producers, but the combination with clavulanic acid has a markedly better susceptibility profile for a wider range of both ESBL- and AmpC-producing Enterobacteriaceae. This is promising not only for prophylaxis, but also for treatment of post-TRUBP infections.

Mecillinam is also available for parenteral use. This is a valuable alternative for treating ampicillin-resistant and mecillinam-susceptible Enterobacteriaceae as a substitute for piperacillin/tazobactam or cefuroxime. We have recently introduced this regimen for treatment of urosepsis at our hospital.

To our knowledge, this is the first large study of TRUBP that presents good clinical results after a change of the prophylaxis treatment from ciprofloxacin to a combination of pivmecillinam and amoxicillin/clavulanic acid. However, our study has some limitations. It is a retrospective cohort study, not a randomized controlled trial. We have not studied extended prophylaxis with ciprofloxacin. Higher doses of pivmecillinam could be an issue to increase the achievable prostatic concentration. Optimal dosage of pivmecillinam and amoxicillin/clavulanic acid, optimal dosing intervals and the duration of post-biopsy treatment remain to be elucidated. Reliable methods for determination of the prostatic concentration of mecillinam and amoxicillin/clavulanic acid is a warranted research issue.

In conclusion, the combination of pivmecillinam and amoxicillin/clavulanic acid is an attractive potential prophylaxis for TRUBP, from a clinical, bacteriological and ecological point of view, as compared with ciprofloxacin.

## Funding

This study was carried out as part of our routine work.

## Transparency declarations

None to declare.

### *Author contributions*

V. A. helped to develop the study design, conducted the acquisition of data and drafted the article with analysis and interpretation of data. N. N. helped with acquisition of data. R. B. helped with acquisition of data. J. N. J. helped with acquisition of data and with analysis and interpretation of data. J. B. helped with acquisition of data. J. O. J. helped to develop the study design. M. A. proposed the original idea of the study, helped to develop the study design, drafted the diagnostic methods and acted as a mentor throughout the process of the study, revising the analysis and interpreting data.

## References

**1** Loeb S, Carter HB, Berndt SI *et al*. Complications after prostate biopsy: data from SEER-Medicare. *J Urol* 2011; **186**: 1830–4.

**2** Loeb S, van den Heuvel S, Zhu X *et al*. Infectious complications and hospital admissions after prostate biopsy in a European randomized trial. *Eur Urol* 2012; **61**: 1110–4.

**3** Nam RK, Saskin R, Lee Y *et al*. Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. *J Urol* 2013; **189**: 12–8.

**4** Raaijmakers R, Kirkels WJ, Roobol MJ *et al*. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. *Urology* 2002; **60**: 826–30.

**5** Aron M, Rajeev TP, Gupta NP. Antibiotic prophylaxis for transrectal needle biopsy of the prostate: a randomized controlled study. *BJU Int* 2000; **85**: 682–5.

**6** Kapoor DA, Klimberg IW, Malek GH *et al*. Single-dose oral ciprofloxacin versus placebo for prophylaxis during transrectal prostate biopsy. *Urology* 1998; **52**: 552–8.

**7** Assaad El-Hakim S. CUA guidelines on prostate biopsy methodology. *Can Urol Assoc* 2010; **4**: 89–94.

**8** Heidenreich A, Bolla M, Joniau S *et al*. *Guidelines on Prostate Cancer*. European Association of Urology, 2013. http://www.uroweb.org/gls/pdf/09_Prostate_Cancer_LR.pdf.

**9** Charalabopoulos K, Karachalios G, Baltogiannis D *et al*. Penetration of antimicrobial agents into the prostate. *Chemotherapy* 2003; **49**: 269–79.

**10** Boerena JBJ, Dalhoff A, Debruyne FMY. Ciprofloxacin distribution in prostatic tissue and fluid following oral administration. *Chemotherapy* 1985; **31**: 13–8.

**11** Grabe M, Forsgren A, Björk T. Concentrations of ciprofloxacin in serum and prostatic tissue in patients undergoing transurethral resection. *Eur J Clin Microbiol* 1986; **5**: 211–2.

**12** Naber K, Sörgel F, Kinzig M *et al*. Penetration of ciprofloxacin into prostatic fluid, ejaculate and seminal fluid in volunteers after an oral dose of 750 mg. *J Urol* 1993; **150**: 1718–21.

**13** Zaytoun O, Vargo E, Rajan R. Emergence of fluoroquinolone-resistant *Escherichia coli* as cause of postprostate biopsy infection: implications for prophylaxis and treatment. *Urology* 2011; **77**: 1035–41.

**14** Mosharafa A, Torky M, El Said W. Rising incidence of acute prostatitis following prostate biopsy: fluoroquinolone resistance and exposure is a significant risk factor. *Urology* 2011; **78**: 511–4.

**15** Williamson D, Freeman J, Porter S. *Escherichia coli* bloodstream infection after transrectal ultrasound-guided prostate biopsy: implications of fluoroquinolone-resistant sequence type 131 as a major causative pathogen. *Clin Infect Dis* 2012; **54**: 1406–12.

**16** Lange D, Zappavigna C, Hamidizadeh R. Bacterial sepsis after prostate biopsy—a new perspective. *Urology* 2009; **74**: 1200–5.

**17** Horcajada JP, Busto M, Grau S *et al*. High prevalence of extended-spectrum β-lactamase-producing Enterobacteriaceae in bacteremia after transrectal ultrasound-guided prostate biopsy: a need for changing preventive protocol. *Urology* 2009; **74**: 1195–9.

**18** Dewar S, Reed LC, Koerner RJ. Emerging clinical role of pivmecillinam in the treatment of urinary tract infection in the context of multidrug-resistant bacteria. *J Antimicrob Chemother* 2014; **69**: 303–8.

**19** Livermore DM. Fourteen years in resistance. *Int J Antimicrob Agents* 2012; **39**: 283–94.

**20** Livermore DM, Canton R, Gniadkowski M *et al*. CTX-M: changing the face of ESBLs in Europe. *J Antimicrob Chemother* 2007; **59**: 165–74.

**21** Jansåker F, Frimodt-Møller N, Sjögren I *et al*. Clinical and bacteriological effects of pivmecillinam for ESBL-producing *Escherichia coli* or *Klebsiella pneumoniae* in urinary tract infections. *J Antimicrob Chemother* 2014; **69**: 769–72.

**22** Norrby SR. Mecillinam (amdinocillin) and pivmecillinam. In: Grayson ML, ed. *Kucers' The Use of Antibiotics Sixth Edition: A Clinical Review of Antibacterial, Antifungal and Antiviral Drugs*. London: Hodder Arnold/ASM Press, 2010; 152–9.

**23** Grabe M, Forsgren A. The effectiveness of a short perioperative course with pivampicillin/pivmecillinam in transurethral prostatic resection: bacteriological results. *Scand J Infect Dis* 1986; **18**: 575–81.

**24** Grabe M, Forsgren A, Hellsten S. The effectiveness of a short perioperative course with pivampicillin/pivmecillinam in transurethral prostatic resection: clinical results. *Scand J Infect Dis* 1986; **18**: 567–73.

**25** Kahlmeter G. An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: the ECO·SENS Project. *J Antimicrob Chemother* 2003; **51**: 69–76.

**26** Naber KG, Schito G, Botto H *et al*. Surveillance study in Europe and Brazil on clinical aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): implications for empiric therapy. *Eur Urol* 2008; **54**: 1164–75.

**27** Feliciano J, Teper E, Ferrandino M *et al*. The incidence of fluoroquinolone resistant infections after prostate biopsy—are fluoroquinolones still effective prophylaxis? *J Urol* 2008; **179**: 952–5.

**28** Murray P, Baron E, Jorgensen J *et al*. *Manual of Clinical Microbiology*. Washington: American Society for Microbiology, 2007.

**29** EUCAST. *Rationale for the Clinical Breakpoints*. 2010. http://www.eucast.org/documents/rd/.

**30** Hadway P, Barrett LK, Waghorn DJ *et al*. Urosepsis and bacteraemia caused by antibiotic-resistant organisms after transrectal ultrasonography-guided prostate biopsy. *BJU Int* 2009; **104**: 1556–8.

**31** Barrett LK, Hadway P, Waghorn DJ. Urosepsis after transrectal ultrasonography-guided prostate biopsy: reaudit following a shortened antibiotic prophylaxis regimen. *J Antimicrob Chemother* 2013; **68**: 2959–60.

**32** Juricic C, Klippel K, Sietzen W. Concentration of amoxycillin and clavunalate in the prostate tissue and in serum: a pharmacokinetic study. In: *Abstracts of the Fifteenth International Congress of Chemotherapy, Istanbul, 1987*. International Society of Chemotherapy Istanbul, Turkey.

**33** Lipsky BA, Byren I, Hoey CT. Treatment of bacterial prostatitis. *Clin Infect Dis* 2010; **50**: 1641–52.

**34** Scaglione F, Ferrara F, Logo R. Pharmacokinetics and tissue penetration of clavulanic acid and amoxicillin given in combination and in a single intake. In: *Abstracts of the Sixth Mediterranean Congress on Chemotherapy, Taormina, 1988*. Mediterranean Society of Chemotherapy, Italy.

**35** Jeppesen N, Frimodt-Møller C. Serum concentrations and penetration into prostate of mecillinam and ampicillin. *Curr Med Res Opin* 1984; **9**: 213–8.

**36** Kerrn MB, Klemmensen T, Frimodt-Møller N *et al*. Susceptibility of Danish *Escherichia coli* strains isolated from urinary tract infections and bacteraemia, and distribution of *sul* genes conferring sulphonamide resistance. *J Antimicrob Chemother* 2002; **50**: 513–6.

**37** Neu JC. Synergy of mecillinam, a β-amidinopenicillanic acid derivative, combined with β-lactam antibiotics. *Antimicrob Agents Chemother* 1976; **10**: 535–42.

**38** Lampri N, Galani I, Poulakou G *et al*. Mecillinam/clavulanate combination: a possible option for the treatment of community-acquired uncomplicated urinary tract infections caused by extended-spectrum β-lactamase-producing *Escherichia coli*. *J Antimicrob Chemother* 2012; **67**: 2424–8.

**39** Thomas K, Weinbren MJ, Warner M *et al*. Activity of mecillinam against ESBL producers *in vitro*. *J Antimicrob Chemother* 2006; **57**: 367–8.

**40** Brenwald NP, Andrews J, Fraise AP. Activity of mecillinam against AmpC β-lactamase-producing *Escherichia coli*. *J Antimicrob Chemother* 2006; **58**: 223–4.

**41** Grunberg E, Cleeland R. *In vivo* activity of the 6β-amidinopenicillanic acid derivative, mecillinam, chemically linked or combined in varying ratios with 6-aminopenicillanic acid derivatives. *J Antimicrob Chemother* 1977; **3** Suppl B: 59–68.

**42** Moosdeen F, Williams JD, Yamabe S. Antibacterial characteristics of YTR 830, a sulfone β-lactamase inhibitor, compared with those of clavulanic acid and sulbactam. *Antimicrob Agents Chemother* 1988; **32**: 925–7.

**43** Bush L, Johnson C. Ureidopenicillins and β-lactam/β-lactam inhibitor combinations. *Infect Dis Clin North Am* 2000; **14**: 409–33.

**44** Slocombe B, Beale A, Boon R. Antibacterial activity in vitro and in-vivo of amoxicillin in the presence of clavulanic acid. In: Neu HC, ed. *Progress and Perspectives on β-Lactamase Inhibition: A Review of Augmentin*. New York: Custom Communications. Postgraduate Medicine, 1984; 29–49.

**45** Taylor H, Bingham J. The use of prophylactic antibiotics in ultrasound-guided transrectal prostate biopsy. *Clin Radiol* 1997; **52**: 787–90.

**46** Shandera KC, Thibault GP, Deshon GE. Variability in patient preparation for prostate biopsy among American urologists. *Urology* 1998; **52**: 644–6.