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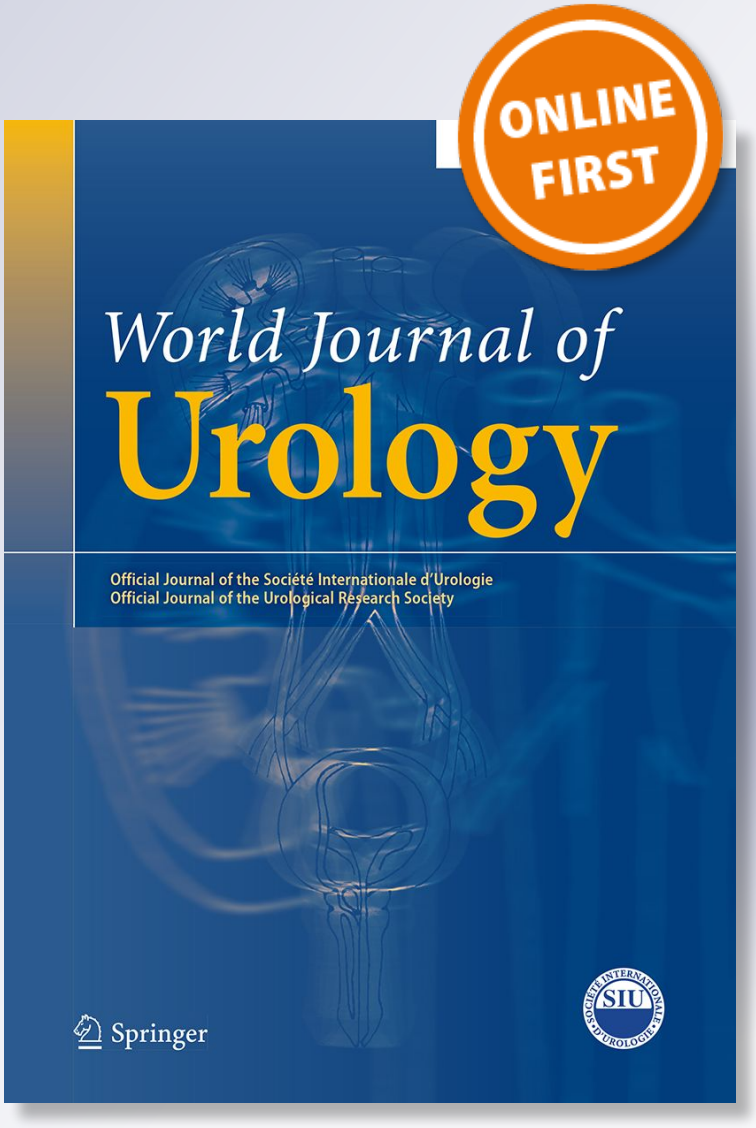

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ORIGINAL ARTICLE

Transrectal ultrasound guided prostate biopsy in the era of increasing fluoroquinolone resistance: prophylaxis with single-dose ertapenem

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Abstract
Purpose The aim of the study was to compare single-dose ertapenem (ERT) with the 3-day regime of ciprofloxacin (CIP) for prophylaxis of possible infections following transrectal prostate biopsy.
Methods Data from a consecutive group of 542 patients from January 2012 to January 2017 were retrospectively analysed. As preinterventional prophylaxis patient group A (179) received 500 mg CIP twice a day for three days, beginning on the day before the biopsy (until June 2013); group B (363) received a single dose of ERT 60 min prior to intervention. The first follow-up examination for all patients was between post-intervention days 2 and 3. The second follow-up examination was between day 15 and 30 following biopsy. Urine was cultured in all cases and any adverse drug reactions (ADRs) related to the antibiotic treatment were noted. We also recorded all clinically relevant morbidities requiring intervention (ischuria, macrohaematuria, symptomatic urinary tract infections and urosepsis), as well as those not requiring active intervention (macrohaematuria, decreased urinary stream, pain, haemospermia). The main study criterion was the symptomatic urinary tract infection rate and ADRs.
Results All 542 biopsied patients could be included in the study and the drop-out rate was zero. There were no significant differences between groups A and B with regards to complications not requiring intervention. There was, however, a significant reduction from 14.5% (group A) to 0.8% (group B) in infectious complications. This showed a significant correlation in favour of ERT ($p < 0.001$). Furthermore, in the ERT group there was also a distinct and significant reduction ($p > 0.001$) in the number of patients with bacteriuria (>10e4 cfu per ml urine) without fever (0.5%) compared to the CIP group (12.3%).
Conclusion A single-dose of 1 g of intravenous ERT applied 1 h before a scheduled transrectal prostate biopsy is a safe option and provides effective protection against infection-related complications arising from surgery.

Keywords Prostate biopsy · TRUS guided biopsy · Prostate cancer · Infectious complication · Transperineal versus transrectal prostate biopsy

Introduction

The transrectal ultrasound (TRUS) and transrectal guided prostate biopsy (TRUS-TRBx), together with the perineal conducted prostate biopsy (TRUS-TPBx) is currently the only means of diagnosing prostate adenocarcinoma. The most commonly applied technique in Europe is still the transrectal access, which is considered to be a safe procedure, even though differing degrees of complications can arise [1–3].

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Potential complications of prostate biopsy are divided into clinically relevant morbidities and those not requiring active intervention. These include transient macrohaematuria, decreased urinary stream, pain and haemospermia. Examples of clinically relevant events requiring pro-active management are urinary retention and bleeding (peranal, urethral or intravesical). Infections can range from complicated cystitis to acute prostatitis to full blown septicaemias [4, 5].

Although complications arising from infections after TRUS-TRBx were previously considered rare, in recent years there have been growing numbers of reports about increasing, particularly clinically relevant infection-related complications with severe acute prostatitis, sepsis and deaths [6].

The most common form of antibiotics owing to their wide spectrum against gram-positive and gram-negative bacteria is the fluoroquinolones.

These also have a favourable safety profile and effective penetration into the prostatic parenchyma [7–9]. Numerous randomised studies have shown their efficacy in reducing infection rates following prostate biopsies. Whereas prior to 2000 the incidence of ESBL-associated urosepsis following prostate biopsy was <1%, current reports show the rate to be between 2 and 3.6% [10–13], mainly as a result of *Escherichia coli* [14]. Ertapenem (ERT) was used in this study because it is approved as antibiotic prophylaxis for elective procedures via colorectal access. As a carbapeneme antibiotic, it also has a broad antimicrobial spectrum against gram-positive and gram-negative bacteria, especially against extended-spectrum beta-lactamase-(ESBL) and AmpC-producing enterobacteriaceae which might be of advantage in reducing infectious complications in patients undergoing prostate biopsy.

Materials and methods

Study design and cohort

This study is a retrospective data analysis. It draws on the complete medical data of a consecutive group of 542 patients with an indication for prostate biopsy between January 2012 up to and including January 2017. All patients had a standard 12-core prostate biopsy. Up to and including June 2013, all patients in group A were treated with 500 mg ciprofloxacin (CIP) twice a day for 3 days beginning the day before the biopsy. Contrary to EAU guidelines, this was not administered in 1-day regime, but in 3-day regime according to the Schaeffer study. This was because all efficacy analyses showed the bacteriological and clinical success rates to be consistently lower for 1-day than for 3-day treatment [15].

From July 2013 onwards (group B) and after consultation with an infectiologist in the institute, this approach was re-evaluated and amended. This was necessary due to cumulated infectious complications after transrectal biopsy under ciprofloxacin.

From July 2013 onwards, patients were given 1 g ERT in a single intravenous dose 60 min before surgery.

There were two follow-up examinations. The first on post-intervention day 2–3; the second between post-intervention days 15–30.

In the interests of medical safety monitoring any adverse events on the day of the intervention and the first follow-up examination were recorded. Also recorded were any clinically insignificant complications not requiring intervention:

mild transient haematuria (defined as macrohematuria not requiring intervention), perineal pain (documentated on a visual analoque scale [VAS] 0–10), peranal bleeding, decreased urinary stream (more than 5 ml/s), haemospermia.

Clinically significant complications were divided into:

1. Considerable macrohaematuria requiring treatment (bladder catheterisation with or without bladder irrigation).
2. Urinary retention (bladder catheterisation).

Clinically significant infectious complications were divided into:

1. Symptomatic and afebrile urinary tract infection (>10e4 cfu/ml mid-stream urine, body temperature <38 °C, pain or lower urinary tract symptoms [LUTS]).
2. Symptomatic, and febrile urinary tract infection (>10e4 cfu/ml mid-stream urine, body temperature >38 °C).
3. Positive blood cultures, septic shock.

For this purpose the following examinations were performed at the first and second follow-up appointments:

- Anamnesis with questions about dysuria, increased micturition frequency, voiding symptoms and perineal pain.
- Urine analysis, urine cultures
- Temperature
- Heart rate, breathing rate
- Leukocytes, blood cultures.

Clinical control examinations were scheduled as shown in Table 1.

The Clavien-Dindo Classification of Surgical Complications was not used in this study due to the fact that occurred complications were classified as grade II (Requiring

Table 1 Contact with patient and examinations—standard institute protocol

Type of examination	Preliminary examination	Intervention	Follow-up 1	Follow-up 2
Anamnesis	Medical history	ADRs	ADRs complications	ADRs complications
Uroflow	✓		✓ if decreased flow was mentioned	
Informed consens	✓			
Urine analysis	✓	✓	✓	✓
Urine culture	✓		✓	✓
Temperature			✓	✓
Heart rate	✓	✓	✓	✓
Breathing rate			✓ only with fever or clinical symptoms	✓ only with fever or clinical symptoms
Leucocytes	Blood count		With fever or complications	With fever or complications
Blood cultures			With fever	With fever

pharmacological treatment with drugs) complication which did not allow any differentiation.

Microbiological processing

Microbiological processing was in a specialised central microbiological laboratory in accordance with current EUCAST guidelines for antibiotic sensibility evaluation.

Inclusion and exclusion criteria

All patients with the indication for prostate biopsy in accordance with EAU [16, 17] were included in the study. They were all fully informed about the forthcoming procedure. Exclusion criterion was a urinary tract infection on the day of the intervention, diagnosed by means of urine strip test (exclusion of a positive leucocyte esterase and nitrite test). Also excluded were patients with known antibiotics resistance or ciprofloxacin, resp. ertapenem allergy.

Ethical considerations

Data collection and analysis was in acc. with the Declaration of Helsinki. The approval of the local Bavarian ethics committee was not required due to the retrospective design and the fact that ertapenem is approved for elective procedures via colorectal access and has the authorisation numbers EU/1/02/216/001 and EU/1/02/216/002. All patient data was anonymised.

Prostate-biopsy

The prostate biopsy was performed with a 18-gauge × 25 cm disposable biopsy pistol without prior colonic irrigation in the lithotomy position. An ultrasound generator Hitachi-Avius was used; the ultrasound probe was the EUP-V53 W (4.0–8.0 MHz). The local anaesthetic was given transrectal with 10 ml Scandicain 1% [mepivacaine] in each seminal vesicle angle.

Statistics

Statistical analysis was by means of the Mann–Whitney-*u*-test with SPSS 17.0 software.

Results

Patient cohort

The data from a total of 542 patients was retrospectively evaluated according to TRUS-TRBx. Of these, 179 patients were in group A (prophylaxis with CIP) and 363 patients in group B (prophylaxis with ERT). Drop-out rate during data processing was zero. There was no significant difference in clinical parameters such as age, PSA-level, rectal examination findings and the presence of diabetes mellitus. This also applied to patients who underwent a second biopsy or antibiotics treatment during the final 6 weeks (see Table 2).

Complications of TRUS-TRBx without infectious background

The most common non-infectious complication following prostate biopsy was macrohaematuria (72.6% in group A and 68.3% in group B), followed by peranal bleeding and decreased urine stream. All non-infectious complications decreased significantly over time (day of intervention vs. follow-up 1 vs. follow-up 2). Neither was there any significant difference for this type of complication between groups A and B. All non-infectious complications are given in Table 3.

Table 2 Patients' clinical data at the time of the prostate biopsy

	Group A	Group B	Statistics
Number of patients	179	363	
Age (±SD)	67.8 (±5.9)	68.9 (±6.5)	p-value = 0.64552
PSA-level (±SD)	7.16 (SD ± 2.20)	7.52 (SD ± 3.08)	p-value = 0.95216
DRE pos. finding (in %)	29 (16.2)	34 (9.4)	p-value = 0.99202
Diabetes (in %)	8 (4.5)	26 (7.2)	p-value = 0.87288
Repeat biopsy	32 (17.8)	73 (20.1)	p-value = 0.42277
Antibiotic treatment within the final 4 weeks	5 (2.7)	8 (2.2)	p-value = 0.76864

SD Standard deviation

Table 3 Non-infectious complications following prostate biopsy

Complication	Intervention		p-value	Follow-up 1		p-value	Follow-up 2		p-value
	Group A	Group B		Group A	Group B		Group A	Group B	
Mild transient hematuria (in %)	130 (72.6)	248 (68.3)	0.87288	22 (12.3)	38 (10.5)	0.97606	06 (3.4)	11 (3.0)	0.88076
Perineal pain[e]	20 (11.2)	35 (9.6)	0.88866	8 (4.5)	9 (2,5)	0.96810	0 (0)	2 (0.6)	0.99288
Decreased urinary stream	46 (25.7)	140 (38.6)	0.54850	15 (8.4)	10 (2.8)	0.87288	n.e.	n.e.	n.e.
Haemato-spermia	n.e.	n.e.	n.e.	29/34 (85.3)	66/73 (90.4)	0.67448	n.e.	n.e.	n.e.
Severe haematuria-[a] (in %)	0 (0)	0 (0)	n.s.	0 (0)	0 (0)	n.s.	0 (0)	0 (0)	n.s.
Peranal bleeding[b,c]	53 (29.6)	120 (33.1)	0.74896	06 (3.4)	11 (3.0)	0.88076	n.e.	n.e.	n.e.
Urinary retention[d]	0 (0)	1 (0.3)	n.s.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.

n.e. not evaluated; *n.s.* not significant

[a] Catheterisation required following biopsy and/or bladder irrigation

[b] All forms of peranal bleeding were recorded

[c] No patient required intervention for peranal bleeding

[d] Catheterisation until the following day

[e] Documented on a VAS (0–10)

Complications of TRUS-TRBx with infectious background

A symptomatic urinary tract infection according to TRUS-TRBx was only recorded for 29 of the entire cohort of 524 men (5.4%). Symptomatic urinary tract infections were defined as such if the bacterial count in urine was >10e4 cfu per ml urine and the patient had clinical symptoms and/or fever. The distribution of such infections in group A was 26/179 (14.5%) and in group B 3/363 (0.8%). This showed a significant correlation in favour of ERT ($p < 0.001$). Furthermore, there was also a distinct and significant reduction ($p > 0.001$) in the number of patients with bacteriuria (>10e4 cfu per ml urine) without fever in the ERT group (0.5%) compared to the CIP group (12.3%). Results are shown in Table 4.

CIP patients were treated with 1 g ERT per day until the antibiogram became available, after which they were given oral antibiotics if possible, with treatment lasting 10 days. At the second follow-up examination the urine analyses of all patients were found to be bacteria-free and without clinical symptoms.

ERT patients should have received 3 daily intravenous doses of piperacillin-tazobactam 4.5 g until the antibiogram became available. A recommended alternative was a daily single oral dose of 3 g fosfomycin/trometamol. All three patients opted for fosfomycin/trometamol and continued treatment according to the test conditions when the

Table 4 Infectious complications following prostate biopsy

Complication	Follow-up 1		*p*-value	Follow-up 2		*p*-value
	Group A	Group B		Group A	Group B	
Significant infectious complications such as	26/179 (14.5)	3/363 (0.8)	<0.001	0 (0)	0 (0)	n.s.
Symptomatic and afebrile urinary tract infection	22/179 (12.3)	2/363 (0.5)	<0.001	0 (0)	0 (0)	n.s.
Symptomatic and febrile urinary tract infection	4/179 (2.2)	1/363 (0.3)	<0.05	0 (0)	0 (0)	n.s.
SIRS	1 (0)	0 (0)	0.623	0 (0)	0 (0)	–
Urosepsis	1 (0)	0 (0)	0.623	0 (0)	0 (0)	–
Positive blood culture	2/4 (50)	0 (0)				

n.s. not significant; *SIRS* systemic inflammatory response syndrome

antibiogram became available. At the second follow-up examination, the urine analyses of all patients were found to be bacteria-free and without clinical symptoms.

Patients who developed fever after the prostate biopsy benefited significantly from ERT prophylaxis ($p < 0.05$). SIRS criteria (fever and leucocytosis) and a (mild) urosepsis (criteria of ACCP/SCCM Consensus Conference) therefore, only occurred in group A. One CIP patient, on being diagnosed of coliform bacteria in urine microscopy, was treated in the out-patient department with a single daily dose of 1 g ERT. Treatment was continued on the basis of resistance testing for a total of 10 days. At the second follow-up examination the patient was found to be symptom-free with normal urine status. No patients required hospitalisation. Identified bacterial strains are shown in Table 5. The most common causative bacteria for infectious complications in group A was *E. coli* with 82.4% followed by *Klebsiella* and *Proteus mirabilis*. In group A 60.7% of *E. coli* were fluoroquinolone resistant and even 17.4% were ESBL-producing *E. coli*. In comparison, all infectious complications in group B were caused by *E. coli*.

Adverse drug reactions

Twelve patients from each group developed diarrhoea (p value = 0.976) after taking the prescribed antibiotics. No other side effects were noted.

Discussion

In accordance with the guidelines of the European (EAU) and American Urological Association (AUA) it is consensus to administer fluoroquinolones as antibiotic prophylaxis prior to TRUS-TRBx due to their broad spectrum against gram-positive and gram-negative bacteria. They have a favourable safety profile and effectively penetrate prostate parenchyma [7–9]. Numerous randomised studies have shown that they can effectively reduce infection rates following prostate biopsies [18]. The extensive application of this group of substances has caused the development of fluoroquinolone-resistant bacteria, particularly coliform bacteria, which produce beta-lactamases with an extended spectrum (ESBL) and which are becoming an increasing problem. Whereas prior to 2000 the incidence of ESBL-associated urosepsis following prostate punch biopsy was <1%, current reports show this to have increased between 2 and 3% [10–12] mainly as a result of *E. coli* [14]. These alarming figures, and the fact that resistance to fluoroquinolones given for infectious complications following TRUS-TRBx has been found to be as high as 73.6% [2, 19], demonstrates the urgent need for the development of new alternative antibacterial prophylaxis strategies for patients requiring a prostate biopsy.

Table 5 Bacterial strains found in patients with symptomatic urinary tract infection

	Group A (ciprofloxacin)	Group B (ertapenem)
Total identified bacterial stains	28 in 26 patients	3 in 3 patients
E. coli (in %)	23 (82.4)	3 (100)
E. coli—fluoroquinolone resistant (in %)	17 (60.7)	2 (66.7)
E. coli—ESBL (in %)	4 (17.4)	1 (33.3)
Klebsiella species (in %)	4 (14.3)	–
Klebsiella species—fluoroquinolone resistant (in %)	2 (7.1)	–
Proteus mirabilis	1 (3.6)	–

In this retrospective study, we were able to show that prophylaxis with ERT could provide a feasible and promising alternative for patients undergoing a TRUS-TRBx. Treatment with ERT that resulted in significantly fewer infection-related complications with a drug-safety level comparable to the generally accepted standard (prophylaxis with CIP).

If these findings are compared with the current literature, it can be seen that various groups are currently researching alternative antibiotic strategies. These studies can generally be divided into those that supplement the accepted standard (CIP) with an additional antibiotic (augmented prophylaxis, and those with fluoroquinolone treatment. The latter topic has been addressed in an innovative paper by Lista et al. [20]. In a prospective randomised study with 671 patients Lista showed that preinterventional prophylaxis with two doses of 3 g fosfomycin-trometamol at an interval of 48 h provided a feasible alternative to 500 mg ciprofloxacin twice a day for 5 days and is equally safe and effective. This correlation was also confirmed in a recently published study. A retrospective study with more than 1100 patients in seven Italian centres compared the prophylactic efficacy of ciprofloxacin and Fosfomycin-Trometamol for TRUS-TRBx. Not only was there a significant reduction in symptomatic urinary tract infections (UTI) from 12.9 to 1.6% ($p < 0.001$), but the urosepsis rate among patients dropped from 1.8 to 0.3% ($p < 0.003$) with a similar level of drug safety. The study population exhibited a surprisingly high rate (73.6%) of fluoroquinolone-resistant bacteria among patients with symptomatic urinary tract infections [19]. In view of this data this observational study was also able to show a comparably significant reduction in bacteria without fever from 12.3 to 0.5% ($p < 0.001$) and for bacteria with fever from 2.2 to 0.3% ($p < 0.05$). Our data was also in line with this and showed a high percentage of fluoroquinolone-resistant bacteria (*E-coli* and *Klebsiella*) of 67.7% (vs. 73.6% [19]). In a small prospective study, Samarinas et al. [21]. compared the prophylactic efficacy for TRUS-TRBx of a single shot of 1 g meropenem with a 3-day regime of ciprofloxacin. This study also showed a similarly distinct and significant reduction in symptomatic urinary tract infections with fever from 16.3 to 1.2% ($p < 0.001$) with meropenem. Data for ertapenem is still only rudimentary. A study with just nine patients scheduled for TRUS-TRBx and exhibiting multiresistant *E. coli* in the rectal smear, for example, was able to show that after testing for resistance, prophylaxis with ERT did not result in infectious complications [22]. There is also a further paper on ERT in the category of augmented antibiotics prophylaxis. In a prospective study in New Zealand men scheduled for TRUS-TRBx were given amoxicillin/clavulanate (AMC) orally for three days and ciprofloxacin (CIP) twice a day, respectively. In addition, patients with a high risk of post-biopsy sepsis (defined as previous prostate biopsy, recurrent urinary tract infections, CIP treatment in the previous 12 months, diabetes, immunosuppression) were also given ERT. Whereas six (6.7%) of the 170 men examined after TRUS-TRBx with AMC and CIP developed urosepsis, there were no cases or urosepsis in the high-risk group with additional ERT ($p < 0.05$). In summary, it can be established that in comparison with the current literature, our study recorded a similar reduction in infectious complications and could, therefore, present an attractive and effective alternative to antibiotic prophylaxis for TRUS-TRBx, particularly considering the low adverse effects profile. A limitation in this study is its retrospective design. With its consecutive group of patients in an institution with the same physician, the study design does, however, correspond to Real World Data. It remains to be seen whether these results can be confirmed in further randomised, controlled and possibly multicentric studies. A further limitation arises from the number of actual occurrences of diagnosed urosepsis (SIRS plus UTI), which is too low to confirm key assertions and increase the level of evidence. On the other hand, however, our two groups exhibited statistically significant differences with regard to symptomatic urinary tract infections. A further weakness of the study is the relatively long period during which data was collected and the fact that the two groups were generated consecutively. As the results are skew in favour of ERT, however, this appears unlikely. It can be assumed that there were fewer resistances among ciprofloxacin patients during earlier examinations than among ERT patients at later examinations. New medical implications in urology, particularly for TRUS-TRBx, arise from the distinct increase in fluoroquinolone-resistant *Enterobacteriaceae.* In view of the high rate of new cases throughout the world [23], despite decreases in many places, and the high number of TRUS-TRBx in the context of the Active-Surveillance Programme, current recommendations for concrete prophylaxis must be reconsidered. Our findings show that ERT could be a possible and effective contender. ERT was chosen in our institute on the basis of its microbiological sensitivity not only to fluoroquinolone-resistant *Enterobacteriaceae,* but also to multiresistant (to acylamino penicillin, cephalosporin, fluoroquinolone) gram-negative bacteria. Besides, it has a longer half-life than other carbapenems and the single daily dose renders this agent ideal for outpatient use. ERT has also been approved for use in Europe since 2002 and its adverse effects profile is low. An allegedly ostensible disadvantage of ERT is the singularity that it can only be administered in intravenous or intramuscular form. Ultimately, a large majority of patients in our institute opted for intravenous administration, which also has the advantage of providing immediate access for emergency medication in the case of an allergic reaction. Apart

from this there is one further aspect that requires consideration. It involves the possible risk of developing resistance to carbapenem-resistant Enterobacteriaceae. We know of no studies showing resistance development following the prophylactic use of an antibiotic. The risk of resistance development also appears unlikely, as a key factor of resistance development is the indiscriminate use of antibiotics. This, however, does not apply to prophylaxis. Unlike CIP for example, ERT will not find extensive clinical application, if only because of the intravenous administration method.

For the sake of completeness, it also has to be mentioned that numerous other strategies for reducing infection rates are being also under examination [6], for example, disinfection of biopsy needles after removing a tissue cylinder [24], rectal disinfection and suppositories [25–27]. Other authors promote goal-directed, test-based antibiotic prophylaxis following rectal smear [28, 29], or augmented antibiotic prophylaxis [30, 31], in addition to the possibility of perineal access.

Summary

The single-dose of 1 g intravenous ERT applied 1 h before the scheduled prostate biopsy is a safe option and provides effective protection against infection-related complication arising from prostate biopsy.

Author's contribution M Bader: Manuscript editing. M Seitz: Protocol/Data collection/Data analysis/Manuscript writing/editing. C Stief: Manuscript editing. D Tilki: Data analysis/Manuscript editing. R Waidelich: Manuscript editing.

Compliance with ethical standards

Conflict of interest All authors have nothing to declare and no competing financial interests in relation to the work described.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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