Fosfomycin trometamol for the prevention of infectious complications after prostate biopsy: A consensus statement by an international multidisciplinary group

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Abstract

Background: Transrectal ultrasound-guided prostate biopsy (TRPB) has been a standard of care for diagnosing prostate cancer but is associated with a high incidence of infectious complications.

Objectives: To achieve an expert consensus on whether fosfomycin trometamol provides adequate prophylaxis in TRPB, and discuss its role as prophylaxis in transperineal prostate biopsy (TPPB).

Methodology: An international multidisciplinary group of experts convened remotely to discuss how to best use fosfomycin in various clinical settings and patient situations. Six statements related to prostate biopsy and the role of fosfomycin were developed, based on literature searches and relevant clinical experience.

Results: Consensus was reached for all six statements. The group of experts was unanimous regarding fosfomycin as a preferred candidate for antimicrobial prophylaxis in TRPB. Fosfomycin potentially also meets the requirements for empiric prophylaxis in TPPB, although further clinical studies are needed to confirm or refute its utility in this setting.

Limitations: There is a risk of bias due to sponsorship by a pharmaceutical company.

Conclusions: Antimicrobial prophylaxis is mandatory in TRPB, and fosfomycin trometamol is an appropriate candidate due to low rates of resistance, a good safety profile, sufficient prostate concentrations, and demonstrated efficacy in reducing the risk of infectious complications following TRPB.

Patient summary: Patients undergoing transrectal ultrasound-guided prostate biopsy (TRPB) have a high risk of infectious complications, and antimicrobial prophylaxis is mandatory. However, increasing antimicrobial resistance, as well as safety concerns with fluoroquinolones, have restricted the number of antimicrobial options. Fosfomycin trometamol meets the requirements for a preferred antimicrobial in the prophylaxis of TRPB.

Keywords:

Antimicrobial prophylaxis

Fosfomycin trometamol

Infectious complications

Transperineal prostate biopsy

Transrectal prostate biopsy

Introduction

Biopsy of the prostate is the gold standard diagnostic test to confirm a diagnosis of prostate cancer [1]. The procedure is typically performed using a transrectal approach known as transrectal ultrasound-guided prostate biopsy (TRPB). The incidence of infectious complications after TRPB is concerning, particularly in the current era of increasing antimicrobial resistance; consequently, effective antimicrobial prophylaxis is mandatory.

Post-biopsy infections occur in approximately 5%–10% of men undergoing TRPB, with serious infections resulting in hospitalization for 1%–3% despite antimicrobial prophylaxis [1-3]. Finding the optimal prophylaxis is now problematic due both to the proliferation of resistant *Escherichia coli* [4], as well as to recent recommendations to discontinue fluoroquinolones, which have been the most commonly used antimicrobials for this purpose [5, 6].

A key consideration is that antibiotic choices must be made within the context of 'antimicrobial stewardship', which involves the appropriate selection of drug, dosage, and duration to prevent or cure infection while minimizing opportunities for the development or spread of resistant bacteria [7]. Antimicrobial stewardship – with its key objective of avoiding the 'collateral damage' of adverse ecological effects during antimicrobial therapy [8] – has been developed as a response to the dramatic increase in antimicrobial resistance among clinical bacteria over the past 20 years [9, 10].

A switch to transperineal prostate biopsy (TPPB) is now widely preferred, and is advocated in European guidelines, substantially owing to its lower infection hazard than for TRPB. TRPB however remains the preferred approach *pro tem* in North America and elsewhere, and we believe the procedure will continue in many jurisdictions.

Given the extent to which classical agents like co-trimoxazole and fluoroquinolones have been compromised by resistance and, in the case of fluoroquinolones, safety concerns, it is of paramount importance to identify alternative prophylactic regimens to make the procedure as safe as possible. The present review aims to assess whether fosfomycin trometamol provides adequate prophylaxis in TRPB and to briefly discuss its role as prophylaxis in TPPB.

Materials and methods

*Consensus process***.** On July 2nd, 2020, an international multidisciplinary group of experts met remotely to discuss how to best use fosfomycin trometamol in various clinical settings and patient situations. The Metaplan® moderation method was used to manage communication in the group.

This method is effective in highlighting different points of view by means of a joint electronic blackboard. The group identified prophylaxis in prostate biopsy and treatment of urinary tract infections (UTIs) as the main clinical settings for the use of fosfomycin trometamol.

A second virtual meeting, held on September 10th, 2020, used a qualitative approach to expand and refine topics that had arisen during the first session, with a focus on the characteristics of the prostate biopsy procedure and the pharmacokinetics, pharmacodynamics, and clinical experience with fosfomycin as prophylaxis in prostate biopsy.

Literature search. The consensus statements are based on papers identified by the authors and literature searches done by international guideline panels. A new search of the literature was conducted in PubMed with the search terms 'fosfomycin' and/or: 'prostate biopsy,' 'antimicrobial prophylaxis,' 'urinary tract infection,' 'transrectal,' 'transperineal,' 'resistance,' 'susceptibility,' 'transperineal,' 'resistance,' 'susceptibility,' and 'TRexit' [11]. Sixty papers were identified for review. Relevant clinical experience among authors was taken into account.

Outcomes. The group agreed to develop statements on the following issues related to prostate biopsy and the role of fosfomycin:

- *The need for antimicrobial prophylaxis to prevent infectious complications*
- *The impact of resistance, new European Medicines Agency (EMA) regulations, and antimicrobial stewardship*
- *The role of non-antimicrobial preventive measures*
- *The principles of antimicrobial prophylaxis and the choice of antimicrobials*
- *The role of fosfomycin as prophylaxis in transrectal prostate biopsy*
- *The role of fosfomycin as prophylaxis in transperineal prostate biopsy*

Writing process and ethics. A professional medical writer developed a draft report based on minutes from the Metaplan® discussions. The report was further developed, edited, and finalized by the authors. Zambon SpA provided financial support for group meetings and assistance from the medical writer.

Results

The need for antimicrobial prophylaxis to prevent infectious complications

The most important complications after TRPB are bacterial infections. We believe these are most often caused by the introduction of rectal bacteria into the bloodstream and the urinary tract when

the biopsy needle passes from the contaminated surgical field of the rectum into the prostate, which is regarded as a clean surgical field [11]. Despite the use of standard antimicrobial prophylaxis, symptomatic UTIs and sepsis occur, and can be life-threatening. Approximately 10% of patients will need antimicrobial treatment for infectious complications after TRPB [3]. The group supports the clear recommendations in the US [1] and European guidelines [6, 12] on the need for effective antimicrobial prophylaxis.

Risk factors, increasing the hazard of infection after biopsy include previous TRPB, an indwelling urinary catheter, urogenital infection, recent antimicrobial treatment, or hospital admission within the previous 6 months, immune-compromising conditions, and international travel [13]. A further risk factor is that the prostate itself may already be contaminated. The frequent finding of histological prostatitis in surgical specimens suggests that the pathogens of post-biopsy infections are not always introduced by the biopsy needle. The fact that the prostate can harbor pathogenic microorganisms is also demonstrated by studies of infertile men and those with prostatic pain [14-16].

Although the contamination risk of the procedure is reduced with a transperineal approach, the hospital setting and all patient-related risk factors remain present, as does the hazard of the prostate already carrying bacteria. The skin can (and should be) be disinfected, but the contamination category of the procedure is still challenged by the proximity of the surgical field to the anal opening and the fact that all specimens are taken with the same needle without cleansing in-between.

The Global Prevalence of Infections in Urology (GPIU) study of infective complications after TRPB, published in 2013, found no correlation between the number of biopsy cores and the rate of infective complications [17]. A systematic review from 2021 also reported no correlation [18]. Although there are no good studies addressing this issue in TPPB, we believe there is even less likelihood of finding a correlation due to the lower contamination status of the TPPB procedure. This applies regardless of whether the biopsy is taken in the urological outpatient unit as an image-fusion guided biopsy or as an in-bore MRI-guided prostate biopsy.

Although the rate of infectious complications seems to be lower after TPPB than TRPB [3, 6], the group believes that there is not yet enough evidence to abandon antimicrobial prophylaxis in TPPB. In general, the arguments for prophylaxis in TPPB are similar to those for prophylaxis in transurethral resection of the prostate.

Consensus statement: Antimicrobial prophylaxis is mandatory in TRPB and should not be abandoned in TPPB.

The impact of resistance, new EMA regulations, and antimicrobial stewardship

The incidence of infections following TRPB is associated with the growing prevalence of antimicrobial-resistant and multidrug-resistant (MDR) strains of *Escherichia coli* in the rectum [19, 20]. Increased rates of post-biopsy infection paralleled an increase in rectal fluoroquinolone-resistant bacterial carriage in Iranian men undergoing TRPB (odds ratio [OR], 4.73; 95% confidence interval [CI], 1.115–20.061; p=0.03) [21]. In a Finnish study, the presence of non-wild-type rectal *E. coli* was associated with post-TRPB infectious complications [22]. An analysis of urine cultures from urological patients in Norway identified that *E. coli* had become increasingly resistant to co-trimoxazole between 2013 and 2015 (resistance increased from 35% to >60%) [2].

Risk factors for fluoroquinolone resistance in bacteria from individual patients include previous TRPB, an indwelling urinary catheter, urogenital infection, international travel, or hospital admission within the previous 6 months [13]. The American Urological Association (AUA) recommends checking local antibiograms, specifically to assess current local prevalence rates of fluoroquinolone resistance and assessing risk factors for prostate biopsy infection [1].

The European Association of Urology (EAU) Urological Infections Guidelines Panel recommends urologists 'choose a specific antimicrobial based on their knowledge of local pathogen prevalence, the antimicrobial susceptibility profiles, and virulence' [6, 12]. Recommendations to develop local prophylactic protocols based on local resistance data stem from the GPIU study and analyses made by Tandogdu and colleagues [23, 24].

Trimethoprim and co-trimoxazole, as the established prophylactic agents for TRPB, are now unsuitable for empirical use in most countries, due to high resistance rates along with concerns regarding fluoroquinolone toxicity. A recently published EAU position paper on the prevention of infectious complications following TRPB states that the use of fluoroquinolones for perioperative antibiotic prophylaxis in prostate biopsy was suspended by the European Commission in March 2019 due to the risks of chronic severe side effects [6]. An 'augmented' antimicrobial prophylactic approach, based on adding additional antimicrobials when resistance was locally prevalent was shown to reduce infection-related complications post-prostate biopsy by 53% compared with historical rates [25]; however, this approach violates the principles of antimicrobial stewardship.

More generally, antimicrobial stewardship means that oral antimicrobials should be preferred to intravenous antimicrobials, targeted prophylaxis should be preferred to empirical prophylaxis, and antimicrobials with a low risk of collateral damage should be preferred to antimicrobials with high

risk [7]. Hospitalization and prophylaxis with intravenous broad-spectrum antimicrobials for prostate biopsy should be avoided [18]. These factors limit the number of potentially usable agents.

Consensus statement: Increasing antimicrobial resistance and demands for antimicrobial stewardship have significant impact on the spectrum of antimicrobials available for prophylaxis in TRPB. New EMA regulations ban the use of fluoroquinolones for infection prophylaxis in TRPB.

The role of non-antimicrobial preventive measures

Recent approaches utilized by urologists to prevent UTIs following TRPB include (i) rectal preparation with povidone-iodine, (ii) rectal swabs to screen for carriage of resistant bacteria followed by 'targeted prophylaxis,' and (iii) switching to TPPB to reduce the contamination category of the procedure [11, 18].

Non-antimicrobial strategies have been assessed in a systematic review and meta-analysis of 90 randomized controlled trials (n=16,941) [18]. This analysis identified that rectal preparation with povidone-iodine was associated with a significantly reduced risk of infectious complications (relative risk [RR] 0.50, 95% CI 0.38–0.65, p<0.000001; n=1,686 participants, 8 studies) and hospitalization (RR 0.38, 95% CI 0.21–0.69, p=0.002; n=620 participants, 4 studies).

In March 2019, the six hospitals that comprise the South East London Cancer Alliance switched from TRPB to TPPB under local anesthesia [11]. This initiative, called the UK TRexit, aims to replace TRPB with TPPB throughout the UK by the end of 2022. The success of such an approach can be seen in Norway, where the standard of care was changed from TRPB to TPPB following the widely publicized death of a 68-year-old man after TRPB [2]. An analysis of Norwegian Patient Registry data identified a local sepsis rate requiring hospitalization of 10%. Since switching to TPPB, the rate of post-biopsy infection at Oslo University Hospital has been close to zero [26].

To comply with the principles of antimicrobial stewardship and to reduce the risk of infectious complications following prostate biopsy, the Global Prevalence Study of Infections in Urology, which assessed data within the years 2010–2019, recommended clinicians switch to TPPB [3]. In Europe, the EAU recommends rectal cleansing with povidone-iodine and targeted prophylaxis based on local resistance for TRPB; however, to further reduce prostate biopsy-related infections, TPPB is preferred [6, 12].

Consensus statement: There are effective non-antimicrobial measures to reduce infectious complications in TRPB. The measures are disinfection of the anal canal with povidone-iodine and switching from TRPB to TPPB.

The principles of antimicrobial prophylaxis and the choice of antimicrobials

The value of prophylaxis is non-disputable in TRPB, but the duration of prophylaxis is a matter of debate.

Although unequivocal supportive evidence is lacking, it is a well-established principle that prophylaxis should provide infection protection for 24 hours after a surgical procedure with a risk of infection. Whilst augmenting the regimen and extending the duration of prophylaxis may further reduce rates of infections [25, 27], antimicrobial stewardship considerations stipulate that the duration of prophylaxis shall be as short as possible due to the risk of selecting resistance in the patient`s colonic flora and owing to negative collateral effects for society. The antimicrobial must cover expected pathogens, and be present in the exposed tissue and the bloodstream in effective concentrations at the time of exposure to these pathogens. Hence, the expected spectrum, pharmacodynamics, and pharmacokinetics of the antimicrobial are of great importance.

Consensus statement: The preferred antimicrobial should be present in the prostate, the urinary tract, and the bloodstream in the right concentration at the time of the biopsy and provide infection protection for 24 hours.

The role of fosfomycin as prophylaxis in transrectal prostate biopsy

Pharmacological aspects

Fosfomycin is a phosphoenolpyruvate analog produced by *Streptomyces* spp. and is also manufactured synthetically. It was discovered in 1969 [28, 29] and is available in a variety of formulations, including the oral agent fosfomycin trometamol (also known as fosfomycin tromethamine) ($C_3H_7O_4P \cdot C_4H_{11}NO_3$).

Fosfomycin disrupts the biosynthesis of the bacterial cell wall via irreversible inhibition of the enzyme MurA (UDP-N-acetylglucosamine-3-enolpyruvyl transferase), which is involved in peptidoglycan biosynthesis. This action is unique and occurs at an earlier step of cell wall synthesis compared with other widely used bacterial cell wall inhibitors (β-lactams or glycopeptides) (reviewed in [30-32]).

Antibacterial spectrum

Fosfomycin is active against Gram-positive and Gram-negative pathogens, including otherwise resistant and MDR strains [30, 33]. Resistance to fosfomycin can arise via intrinsic or acquired

mechanisms [32, 34]. In particular, fosfomycin can be deactivated by enzymes including FosA, FosB, and FosX, preventing action on MurA. Alternatively, a change in the MurA target, or its expression, caused by mutations in the *murA* gene or by increased *murA* expression can prevent or reduce the effect of fosfomycin on this target. Lastly, resistance can evolve due to mutations in the genes encoding fosfomycin transporters (i.e., *glpT* or *uhpT*), impeding uptake of fosfomycin by the pathogen [30, 32, 34-36].

In *E. coli,* the major mechanisms of resistance are (i) mutational loss of uptake systems or (ii) acquisition of plasmids encoding FosA [32]. There are few surveys reporting the prevalence of fosfomycin resistance in bowel-colonizing *E. coli*; however, studies of fosfomycin resistance in UTIs, which are also seeded by the gut flora, indicate resistance rates are generally <5%, whereas rates to fluoroquinolones and trimethoprim now commonly exceed 20%, and are much higher in developing countries [37, 38].

Fosfomycin-susceptible *E. coli* isolates can be identified from urinary samples by disk diffusion or Etest [39]. Alternatively, selective media containing a standard amount ciprofloxacin, trimethoprim, fosfomycin, or amoxicillin-clavulanic acid have been validated technically as sufficiently sensitive and specific for the detection of resistant Gram-negative bacilli in the rectal flora [40]. Fosfomycin prophylaxis is not recommended for patients known to carry microorganisms with minimum inhibitory concentrations (MICs) >4 mg/L in their rectal flora.

Safety profile

Fosfomycin trometamol has almost no known drug interactions and its safety profile is favorable, with gastrointestinal disturbances (i.e., diarrhea, nausea, dyspepsia, abdominal pain), nervous system disorders (i.e., headache, dizziness), and superinfections the most commonly reported adverse drug reactions [41]. Most events are short-lived and resolve spontaneously. Following a review of the safety and effectiveness of fosfomycin medicines, the EMA recommended, on June 9th, 2020, that fosfomycin trometamol, given orally, can continue to be used to prevent infection in men undergoing biopsy of the prostate [42].

Pharmacodynamics

The elimination half-life of fosfomycin is approximately 4 hours after oral intake, with the majority of the drug excreted unchanged in the urine by glomerular filtration (40%–50% of the dose); it is also excreted in feces (18%–28% of the dose) [41, 43]. Sufficient penetration of fosfomycin into prostatic tissue has been shown in healthy men undergoing transurethral resection of the prostate for benign prostatic hyperplasia [44]. Following a single 3 gram oral dose of fosfomycin the mean concentration of fosfomycin in the prostate was 6.5 ± 4.9 µg/g (range 0.7–22.1 µg/g), with therapeutic

concentrations detectable for up to 17 hours post-dose, supporting its use as a prophylactic antimicrobial before TRPB. Oral administration 1–4 hours prior to transurethral resection of the prostate was deemed optimal [45] to achieve initial antibacterial concentrations within the prostate.

Indications and dosage

In Europe, fosfomycin trometamol is indicated for the treatment of acute, uncomplicated cystitis in women and female adolescents (aged >12 years) and, relevant to this article, as perioperative antimicrobial prophylaxis for TRPB in adult men [41]. Fosfomycin tromethamine is indicated in the US to treat women with uncomplicated UTIs (acute cystitis) caused by susceptible strains of *E. coli* and *Enterococcus faecalis* [43]. The recommended fosfomycin dosage for treating uncomplicated UTIs in adults is a single 3-gram oral dose.

When used to prevent post-TRPB infectious complications, the recommended dosage is 3 grams 3 hours before the procedure plus 3 grams 24 hours after the procedure, as recommended by the EMA [41]. This regimen is evidenced by a recent network meta-analysis showing that two doses of fosfomycin are more effective in preventing post-TRPB UTIs than a single dose (Table 1) [46]. An older narrative review by Wagenlehner and colleagues [33] also recommended two doses of fosfomycin to prevent infectious complications after endourological interventions. Moreover, a large Canadian study (n=9,391) reported a significantly increased risk of infectious complications post-TRPB with single-dose fosfomycin compared with ciprofloxacin but not with a 2-dose fosfomycin regimen (these authors administered the second dose 48 hours after the procedure, not 24 hours) [47]. Single dose regimens nonetheless may deliver adequate antimicrobial prophylaxis for TRPB (Table 1) [48-51] if the dose is timed precisely. Dosing 3 hours before biopsy should provide sufficient concentrations in the prostate at the time of surgery, with drug concentrations continuing to increase for approximately 6 more hours. Given the delays and vagaries of the 'real world' the two-dose approach does, however, seem more prudent and need for antimicrobial coverage during the 24 hours after biopsy must not be underestimated.

A prospective randomized study suggests the addition of a third dose of fosfomycin (with dosing at 12 and 4 hours prior to and 24 hours after the procedure) was no more effective than the recommended two-dose regimen [52].

Clinical evidence

There is extensive evidence to support the use of fosfomycin as prophylaxis for TRPB (Table 1). Compared with standard fluoroquinolone-based therapy, fosfomycin prior to TRPB has been shown to significantly reduce the incidence of infectious complications [33, 53-57]. Thus, patients treated with fosfomycin as a prophylactic regimen for TRPB had significantly lower symptomatic UTI rates

compared with ciprofloxacin in a retrospective review of 1,109 patients from 7 Italian urological institutions, with fosfomycin dosages and timings as recommended here [55]. Moreover, significantly lower rates of febrile and afebrile UTIs were associated with fosfomycin compared with ciprofloxacin in a meta-analysis of four clinical studies published between 2012 and 2017 (n=2,331) [56]. This meta-analysis may have been limited by the inclusion of men from multiple countries (Egypt, Germany, Italy, Norway, and Turkey) who are likely to have diverse rates of resistance in their colonic flora, increasing the heterogeneity of the analyzed sample.

Consensus statement: Fosfomycin meets all the requirements for a preferred antimicrobial in the prophylaxis of TRPB. The statement is supported by high-level evidence from well-designed studies.

The role of fosfomycin as prophylaxis in transperineal prostate biopsy

The risk of infectious complications is lower after TPPB than after TRPB, with post-biopsy infections reported in up to 3% of TPPB patients [26, 58-61], regardless of whether antibiotic prophylaxis was used or not, compared with approximately 10% of TRPB patients, even with prophylaxis (as reported above).

However, the group believes prophylaxis should not yet be abandoned in TPPB until there is strong evidence to do so. The health care setting, exposed tissue, spectrum of expected pathogens, and the type of infectious complications are the same in TPPB as in TRPB. Given its prostatic penetration, the group regards fosfomycin as a good candidate for prophylaxis in TPPB and recommends clinical studies, including study arms without antimicrobial prophylaxis.

Consensus statement: Fosfomycin potentially meets the requirements for empiric prophylaxis in TPPB. Clarification of its future role in this setting requires further studies.

Discussion

Main statements

Antimicrobial prophylaxis is mandatory in TRPB. Increasing antimicrobial resistance, safety concerns apropos fluoroquinolones, and demands for stewardship have significantly impacted on the choices of antimicrobials available for this purpose. Disinfection of the anal canal with povidone-iodine and switching from a transrectal to a transperineal biopsy route are effective non-antimicrobial preventive measures.

When TRPB is performed an appropriate antimicrobial should be present in the exposed tissue in adequate concentration at the time of the biopsy and should provide protection against infection

for 24 hours. Fosfomycin trometamol is an ideal candidate for this purpose due to low resistance rates [62, 63] a good safety profile [41], adequate prostate penetration [44], and demonstrated effectiveness in reducing the risk of infectious complications following TRPB compared with fluoroquinolones [46, 55-57]. Fosfomycin has excellent activity against *E. coli*, including ESBL-producing and fluoroquinolone-resistant strains, and has a low impact on normal gastrointestinal flora.

There is a lack of evidence regarding antimicrobial prophylaxis in TPPB, but fosfomycin is a good candidate for empiric prophylaxis, and its role should be explored in future studies.

The group reached complete consensus on all statements.

Recommendations by others

To prevent UTIs following TRPB, the European Section of Infections in Urology (ESIU) and the EAU guidelines panel recommend perioperative antimicrobial prophylaxis [64]. As fluoroquinolones are no longer approved, there is consensus that the choice of alternative antimicrobials for prophylaxis should be based on local resistance rates, or should be targeted according to rectal swab culture, with either approach being followed in conjunction with povidone-iodine rectal preparation [6]. The ESMO 2020 Clinical Practice Guidelines for the diagnosis, treatment and follow-up of prostate cancer and the 2021 EAU position paper on the prevention of infectious complications following prostate biopsy recommend a transperineal approach to reduce prostate biopsy-related infections [6, 65], supported by perineal cleansing and antimicrobial prophylaxis. If TPPB is not feasible, TRPB is an appropriate second choice, together with povidone-iodine rectal preparation plus antimicrobial prophylaxis. Switching to TPPB has also been recommended by the GPIU study group to reduce the risk of infectious complications and comply with antimicrobial stewardship principles [3].

Guidelines on antimicrobial prophylaxis in TRPB have been published by the AUA [1]. Suggested measures to reduce infections in men undergoing TRPB are: (i) rectal flora sampling for targeted prophylaxis, with the antimicrobial choice dependent on the presence or absence of fluoroquinolone-resistance bacteria; (ii) augmentation of a fluoroquinolone with an additional antimicrobial; or (iii) a transperineal biopsy approach. It should be added that the AUA white paper update on the prevention and treatment of common complications related to prostate biopsy was published in 2017, prior to the recent upsurge in safety concerns regarding fluoroquinolones [42, 66].

Clinical perspectives

In TRPB, the primary issue is patient safety rather than antimicrobial stewardship, since infectious complications (i) represent a serious risk to the patient, (ii) have high associated costs and (iii) necessitate the prolonged use of broad-spectrum antimicrobials to achieve cure. An augmented antimicrobial prophylactic regimen based on local antibiograms could be utilized and was shown to reduce infection-related complications post-prostate biopsy by 53% compared with historical rates [25]. However, the use of multiple agents is not good stewardship.

TRPB is convenient and can be performed safely as an outpatient procedure with local anesthetic. Targeted prophylactic antimicrobials based on a prior rectal swab culture can be used to identify patients with resistant rectal flora at increased risk of sepsis [67]. Patients with risk factors for fluoroquinolone resistance [13] may particularly benefit from a prior rectal swab and targeted prophylaxis as well as from rectal disinfection, or switching to a transperineal approach [68]. However, rectal culture before TRPB incurs extra visits and costs and may not be appropriate for all patients.

TPPB can be performed safely as an outpatient procedure with local anesthetic. Early elevated complication rates were most likely due to mapping, and saturation biopsies with a large number of specimens. Modern TPPBs are image-fusion guided biopsies with the same number of specimens as in regular TRPB.

Nonetheless, comparison of complications following prostate biopsy identified a higher risk of hospital admission in patients undergoing TPPB (n=13,723) than TRPB (n=59,907) (12.3% vs. 2.4%, respectively; adjusted risk difference 9.7%, 95% CI 7.1–12.3), with a higher likelihood of readmission for urinary retention than for sepsis [69]. Thus, while a transperineal approach may reduce the risk of sepsis, other complications should be considered when choosing the optimal technique for prostate biopsy.

Established fluoroquinolone and co-trimoxazole regimens for prophylaxis in TRPB are heavily compromised by resistance and, in the case of fluoroquinolones, by safety concerns, making alternatives necessary. Until now, fosfomycin has primarily been used to treat uncomplicated UTIs in women, but it is licensed and suitable for use in TRPB, with an appropriate spectrum, few side effects, and efficacy demonstrated in clinical trials. In countries where the drug has been widely used for UTIs (e.g., Italy and Spain), the prevalence of resistance has remained below 5% [37]. There is no reason to anticipate that the prophylactic use in TRPB will lead to greater resistance selection.

Strengths and weaknesses

Strengths of this consensus report are the multidisciplinary, international representation of the group and the use of the Metaplan® technique to reduce the risk of dominance by key opinion

leaders. Most authors have research experience with fosfomycin. Sponsorship by a pharmaceutical company always implies a risk of bias.

Conclusions

Appropriate antimicrobial prophylaxis for the prevention of infectious complications in prostate biopsy is imperative, and the choice of antimicrobial must consider complication rates, local resistance rates, local procedural expertise, antimicrobial stewardship, and recommendations from international guidelines. Fosfomycin trometamol represents a valid choice for perioperative antimicrobial prophylaxis of TRPB in adult men due to its high susceptibility rate, retained activity against otherwise resistant and MDR Gram-negative bacteria (especially *E. coli*), short treatment duration, sufficient penetration into prostatic tissue, advantageous pharmacodynamics, and favorable safety profile. Fosfomycin is also a potential candidate for empiric prophylaxis in TPPB, given its penetration into the prostate, however supporting trial evidence are required.

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Table 1. Clinical evidence supporting fosfomycin trometamol as a valid choice for perioperative antimicrobial prophylaxis of transrectal prostate biopsy

Author names **Study design**	**Study aims**	**Treatment (No. pts)**	**Main outcome**	**Adverse events**
Ongun et al. 2012 [48] Retrospective evaluation	To retrospectively evaluate the efficacy of single-dose FT vs. FQ for the preoperative prophylaxis of TRPB.	Single oral dose FT 3 g taken the night before TRPB (n=104). FQ (CIP 500 mg bid for 5 d starting 1 day prior, or LEV 500 mg taken 1 hr prior to TRPB) (n=516).	Overall, 19 pts (3.0%) developed febrile UTIs after TRPB (FT, 1 pt [5.2%]; LEV, 4 pts [21%]; CIP, 14 pts [73.6%]), and 51 pts (8.2%) developed afebrile UTIs after TRPB (FT, 4 pts [7.8%]; LEV, 8 pts [15.6%]; CIP, 39 pts [76.4%]), with no between-group differences identified.	Not reported
Sen et al. 2015 [50] Prospective, randomized, and controlled clinical study	To demonstrate the efficacy, safety, and convenience of single-dose FT for the preoperative prophylaxis of TRPB.	Single oral dose FT 3 g taken the night before TRPB (n=150). Single oral dose CIP 500 mg taken 1 hr	Afebrile UTI rate was significantly lower in patients who received single-dose FT 3 g compared with oral CIP 500 g (1.3% vs. 6.0%; p=0.032); the background rate of fluoroquinolone-resistance was 35.7%.	None reported for either antimicrobial regimen.

		before TRPB (n=150).		
Fahmy et al. 2016 [49] Prospective, randomized study	To compare the incidence of infectious complications after TRPB with single-dose FT vs. standard FQ-based prophylaxis.	Single dose FT 3 g orally 1–2 hr prior to TRPB (n=202). CIP 500 mg + MET 500 mg 1 hr before TRPB then twice daily for 3 d after TRPB (n=210).	Infectious complications significantly reduced with FT compared with CIP+MET (1.9% vs. 8.5%; p=0.001). In pts who developed afebrile or febrile UTIs, FQ resistance was identified in 3 of 4 pts treated with FT and in 13 of 18 pts who received standard FQ treatment.	Not reported
Cai et al. 2017 [55] Retrospective, comparative cohort study	To compare the clinical outcomes of TRPB prophylaxis with FT vs. CIP.	FT 3 g orally 3 h before and 24 h after the first administration (n=632). CIP 500 mg bid for 5 d starting 1 d before the procedure (n=477).	Significantly lower rates of symptomatic UTIs (1.6% vs. 12.9%; p<0.001) and urosepsis (0.3 vs. 1.8 %; p=0.02) with FT vs. CIP.	Frequency of adverse events similar between FT and CIP (0.6 vs. 0.4 %; p=0.94).

Noreikaite et al. 2018 [53] Systematic review and meta-analysis (5 studies)	To compare the efficacy of FT with quinolone-based antimicrobial prophylaxis for TRPB.	FT (n=1,447) Quinolone-based (n=1,665)	Significantly lower incidence of overall UTIs in FT cohort vs. quinolone-based prophylaxis (RR 0.20; 95% CI 0.13–0.30); p<0.00001). Meta-analysis also favored FT for febrile (RR 0.24; 95% CI 0.14–0.41; p<0.00001), afebrile (RR 0.27; 95% CI 0.16–0.45; p<0.00001), and urosepsis (RR 0.20; 95% CI 0.06–0.69; p=0.01) vs. quinolone-based prophylaxis.	Equivalent adverse event profile for FT and quinolone-based prophylaxis.
Roberts et al. 2018 [54] Individual patient-data meta-analysis and systematic review (5 studies)	To compare FT vs. FQ antimicrobial prophylaxis for the prevention of TRPB-related infectious complications.	FT FQ (n=3,112)	Significantly lower risk of an infectious complication (OR 0.22; 95% CI 0.09–0.54) or of a Grade 2 infection (OR 0.13; 95% CI 0.07–0.26) with FT than FQ.	A low incidence of side effects to FT and FQ was reported across 4 studies.
D'Elia et al. 2019 [52] Prospective randomized study	To assess the efficacy and safety of a 2- vs. 3-dose FT regimen for prostate biopsy prophylaxis.	FT 3 g given 4 hr before and 24 hr after the procedure (n=162). FT 3 g given 12 hr and 4 hr before and	8 of 297 pts developed febrile UTI, with no statistically significant difference between the 2- vs. 3-dose FT regimen (3.7% versus 1.5%, respectively; p=0.29).	FT was safe and well-tolerated. No side effects or intolerance to FT were reported in either treatment group.

		24 hr after the procedure (n=135).		
de Oliveira Freitas et al. 2019 [56] Systematic review and meta-analysis (4 studies)	To systematically review the prophylactic effectiveness of FT vs. CIP after TRPB on literature published between January 1970 and June 2017. A meta-analysis was performed on 4 clinical studies published between 2012 and 2017.	FT (n=1,088) CIP (n=1,243)	FT prophylaxis was associated with significantly lower rates of febrile (OR 0.15, 95% CI 0.07–0.31; p<0.001) and afebrile (OR 0.21, 95% CI 0.12–0.38; p<0.001) UTIs than CIP.	Not reported
Carignan et al. 2019 [47] Nested case–control study	To evaluate the effectiveness of FT prophylaxis in preventing post-TRPB infectious complications in pts who underwent TRPB between 1 January 2002 and 30 June 2016 in a Canadian hospital.	FT1 (3 g >12 hr before TRPB; Dec 2013–Sept 2015) FT2 (3 g in the morning of TRPB and 3 g 48 hr later; Nov 2015–Jun 2016).	Increased incidence rates of post-TRPB urinary sepsis with single dose FT1 vs. CIP-HIGH (3.5% vs. 1.8%; p=0.0004) but not with a 2-dose FT2 regimen (2.7% vs. 1.8% vs.; p=0.19).	Not reported.

		CIP-LOW (2002–2009; low-resistance period) CIP-HIGH (2010–Oct 2013; high-resistance period) (n=9,391).		
Bonkat et al. 2020 [46] NMA	To review literature published between 1987 and 2019 on the use of FT vs. FQ to prevent post-TRPB UTIs and evaluate the efficacy of different FT dosing regimens.	NMA evaluated 6 articles (n=2,783) published between 2012 and 2018 with a primary outcome measure of overall incidence of UTIs, and also evaluated the efficacy of different doses of FT.	A lower incidence of overall UTIs was associated with both single and two-dose FT dosing regimens than FQ (OR 0.41, 95% CI 0.23–0.73 and OR 0.11, 95% CI 0.04–0.26, respectively). Significantly higher risk of developing postoperative UTIs with 1 vs. 2 FT dosing (OR 3.77, 95% CI 1.29–11.00).	Not reported
Morin et al. 2020 [57] Retrospective pre-/post-intervention study	To retrospectively compare the rates of post-TRPB urosepsis with CIP vs. CIP/FT in 2,287	Oral CIP 500 mg 2 hours prior to TRPB (n=1,090).	The incidence of urosepsis was significantly lower with CIP/FT than CIP alone (adjusted RR = 0.16 (95% CI 0.03–0.76; p=0.02).	Non-infectious complications after TRPB were similar between treatment

	patients who underwent TRPB from January 2012 to December 2015 in two Canadian hospitals.	Oral CIP 500 mg plus oral FT 3 g 2 hours prior to TRPB (n=1,197).		groups (Grade 1 = 0.4% vs. 0.1, and Grade 2 = 0.9% vs. 0.3% for CIP vs. CIP/FT).
Delory et al. 2021 [51] Observational, monocentric, prospective, cohort study	To assess the real-life efficacy and safety of single-dose FT versus FQ as antimicrobial prophylaxis for TRPB.	Single-dose FT 3 g taken 2 hr prior to TRPB (n=81). Single-dose FQ (CIP 500 mg, or LEV 500 mg, or ofloxacin 400 mg) taken 2 hr prior to TRPB (n=116).	Overall incidence of self-reported post-TRPB UTIs was similar in both treatment arms (9% vs. 15% for FT vs FQ; RR = 0.55; 95% CI, 0.22–1.40; p=0.209).	Post-TRPB adverse events were similar between treatment groups (36% vs. 31% for FT vs FQ; RR = 1.17; 95% CI, 0.64–2.15; p=0.602).

Abbreviations: bid, twice daily; CI, confidence interval; CIP, ciprofloxacin; Dec, December; FT, fosfomycin trometamol; FQ, fluoroquinolone; g, grams; hr, hours; Jun, June; LEV, levofloxacin; MET, metronidazole; n, number; NMA, network meta-analysis; Nov, November; Oct, October; pts, patients: OR, odds ratio; RR, relative risk; Sep, September; TRPB, transrectal ultrasound-guided prostate biopsy; UTIs, urinary tract infections.