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Review Article

Rediscovering the value of fosfomycin trometamol in the era of antimicrobial resistance: A systematic review and expert opinion

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ABSTRACT

The worldwide prevalence of uncomplicated lower urinary tract infections (uUTIs) caused by multidrug-resistant *Escherichia coli* is increasing. To address this emergency, international guidelines recommend reducing administration of fluoroquinolones, in the context of growing resistance and the long-lasting and potentially disabling side effects of these drugs. The favoured drug to replace fluoroquinolones is fosfomycin trometamol (FT), a well-known derivate of phosphonic acid with broad-spectrum activity against Gram-negative and Gram-positive bacteria, including multidrug-resistant (MDR) strains. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) recently reduced the susceptibility breakpoint for *E. coli* from 32 mg/L to 8 mg/L regarding FT used for uUTIs. This might lead to increased appropriate use of oral fosfomycin target therapy against *E. coli* and other microorganisms, and may be associated with a high likelihood of success. For species such as *Klebsiella* spp, particularly MDR strains, the absence of clinical breakpoints might lead to reduced use of oral fosfomycin, particularly if minimum inhibitory concentration is not available. To address this issue, this review presents an overview of the preclinical evidence on the activity of FT, and a systematic review of the clinical activity of FT in uUTIs in women, and in the prevention of infectious complications after prostate biopsy. The findings indicate that the safety and microbiological and clinical effectiveness of a single oral dose of FT are similar to that for comparator regimens with longer treatment schedules in women with uUTI, and FT can be considered a viable alternative to fluoroquinolones for antimicrobial prophylaxis in prostate biopsy. These observations and a broad clinical experience support the empirical use of FT for treating uUTI and indicate that FT is a promising candidate to effectively counteract antibiotic-resistant uUTIs throughout Europe.

1. Introduction

Acute, uncomplicated lower urinary tract infection (uUTI) is among the most common indications for antibiotic use [1,2]. *Escherichia coli* represents the main cause of UTIs, accounting for 80–90% of cases [3,4].

Surveillance data indicate that the incidence of UTIs caused by multidrug-resistant *E. coli* is increasing worldwide, with considerable variation by country, from 5% in Spain to 90% in India [5,6]. This leads to an increased risk for first-line treatment failure and reduces the possibility of treating these infections effectively [7,8]. International guidelines recommend reducing prescriptions for fluoroquinolones to manage uUTIs, in the context of growing resistance and the long-lasting and potentially disabling side effects of these drugs [2,9]. The latest European Association of Urology and Infectious Diseases Society of America guidelines on urological infections recommend the first-line use of fosfomycin trometamol (FT) to manage this condition [2,10].

Fosfomycin is a derivate of phosphonic acid that inhibits bacterial cell wall synthesis and has a broad spectrum of activity against Gram-negative (particularly *E. coli* isolates) and Gram-positive bacteria, including multidrug-resistant (MDR) strains [11,12]. This

Abbreviations: uUTI, uncomplicated lower urinary tract infection; FT, fosfomycin trometamol; EUCAST, European Committee on Antimicrobial Susceptibility Testing; AUC, area under the curve of plasma concentrations; RCT, Randomised controlled trial; PK/PD, pharmacokinetic/pharmacodynamic.

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activity has been maintained for over four decades with a relatively low resistance rate, as confirmed in a recent surveillance study involving Belgium, UK, Italy, Spain and Russia that demonstrated fosfomycin activity against 96.4% of *E. coli* isolates *in vitro* [3,13,14]. Furthermore, fosfomycin has an exclusive mechanism of action; therefore, the possibility of cross-resistance to other antibacterial agents is low [15–17].

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) recently reduced the susceptibility breakpoint for *E. coli* from 32 mg/L to 8 mg/L (susceptible [S] ≤8 mg/L; resistant [R] >8 mg/L) regarding the trometamol formulation of fosfomycin used for uUTIs [18]. This might lead to increased appropriate use of oral fosfomycin target therapy against *E. coli* and other microorganisms, and may be associated with a high likelihood of success. For species such as *Klebsiella* spp., particularly MDR strains, the absence of clinical breakpoints might lead to reduced use of oral fosfomycin, particularly if minimum inhibitory concentration (MIC) is not available. However, the change in breakpoint would not impact on the choice of empirical therapy for uUTI.

To address these issues, a group of Italian experts from different specialities attended an online meeting in September 2022 to critically analyse the rationale behind the EUCAST breakpoint update and discuss the clinical value of FT in the era of antimicrobial resistance.

The aim of this paper was to present an overview of the preclinical evidence on the activity of FT, and to provide a systematic review of the clinical activity of FT used for the management of uUTIs in women and in the prevention of infectious complications after prostate biopsy. An expert opinion on the most recent updates in this field is also provided.

2. Methods

2.1. Search criteria for preclinical evidence

A search was conducted on PubMed and Embase for studies evaluating the preclinical activity of FT up to 15 September 2022. Different combinations of pertinent keywords (e.g., FT and susceptibility testing; FT and pharmacokinetic [PK]; FT and pharmacodynamic [PD]) were used, focusing on papers published in English and with no time restriction. If relevant, documents from the authors' collection of literature were considered. Papers were selected for inclusion according to their relevance to the topic, as judged by the authors.

2.2. Search criteria for clinical evidence

A search was conducted on PubMed and Embase for studies evaluating the clinical activity of FT for treating uUTIs in female patients or for antimicrobial prophylaxis for prostate biopsy up to 15 September 2022. The Boolean operators "AND"/"OR" were used along with controlled MeSH and free pertinent terms relevant to the clinical literature search. The following queries were used on PubMed: ((urinary tract infection) OR cystitis AND (Humans[Mesh] AND English [lang])) AND (fosfomycin) AND (Humans[Mesh] AND English [lang]); ((prostate biopsy AND (Humans[Mesh] AND English [lang])) AND (fosfomycin) AND (Humans[Mesh] AND English [lang])). Different combinations of pertinent keywords were used for the Embase search (fosfomycin AND uncomplicated urinary tract infection; fosfomycin AND prostate biopsy).

2.2.1. Types of publications

Regarding clinical evidence, only human studies performed on adult patients published in English in the last 10 years (2012–2022) were included. Clinical trials, randomised controlled trials (RCTs), observational studies, and systematic reviews with meta-analyses were considered. Other publications, including letters, editorials, reviews, thesis, and abstracts, were not evaluated.

2.2.2. Study eligibility criteria

The eligibility criteria for clinical studies included in this systematic review were designed according to the Population Intervention Comparators Outcomes Study framework. The population included patients with clinically suspected and/or microbiologically confirmed acute uncomplicated cystitis or patients undergoing antimicrobial prophylaxis for prostate biopsy. The intervention of interest was treatment with FT. There were no inclusion restrictions on the type of control treatment used in the selected studies. Cure or improvement at the end of FT treatment, intended as the resolution and/or the non-complete resolution of symptoms, or microbiological eradication, were defined as clinical or microbiological success and were used as the primary outcome for studies evaluating the management of uUTIs in women. The primary outcome for studies evaluating the prophylactic use of FT was all types of post-biopsy infectious complications.

The authors independently screened the titles and abstracts of the research literature. The full-text manuscripts for the studies selected were reviewed for inclusion. Any disagreement about inclusion was resolved by discussion.

2.2.3. Data extraction and analysis

Data were extracted and grouped according to the interventions evaluated. There was a lack of uniformity in treatment regimens; therefore, a meta-analysis was not performed and instead a narrative description of the included studies was provided.

3. Results

3.1. Preclinical evidence

3.1.1. Microbiological aspects

According to the literature, FT shows broad-spectrum bactericidal activity against *Haemophilus* spp., staphylococci, and most enteric Gram-negative bacteria, as well as bactericidal and bacteriostatic activity against enterococci (including *Enterococcus faecalis* and *Enterococcus faecium*, irrespective of vancomycin resistance) [19–22]. FT also shows activity against most *E. coli*, including those producing extended-spectrum beta-lactamases [13,23–26]. *Serratia* spp. and *Klebsiella* spp. show higher MICs (from 0.5 to 128 μg/mL and from 0.25 to 512 μg/mL, respectively). *Pseudomonas aeruginosa* susceptibility to FT is variable, with MICs starting from 4 and up to ≥512 μg/mL [23]. Resistance to FT has been reported for nearly all *Acinetobacter baumannii* isolates, although a synergistic effect of FT with amikacin, colistin, and sulbactam has been reported in different studies [27]. Modification of membrane transporters to prevent fosfomycin entering the bacterial cell has been identified as a mechanism of acquired resistance and acquisition of plasmid-encoded genes that inactivate fosfomycin and MurA mutations [28]. Mutation frequency is higher among *P. aeruginosa* and *Klebsiella* spp. compared with *E. coli* and is associated with fosfomycin concentration [28]. In vitro studies showed that for very low MIC, FT might also be effective against species with resistance genes (FosA), such as *Klebsiella* spp. [29].

3.1.2. Pharmacokinetic properties

FT is a monobasic anionic salt that is metabolised to fosfomycin after absorption, with activity against Gram-negative and Gram-positive strains depending on concentration. FT shows a long-lasting *in vitro* post-antibiotic effect; the area under the curve (AUC)/MIC ratio is the main PK/PD parameter related to efficacy for Enterobacterales [16,30–32]. The compound is stable and soluble

in the acidic gastric environment and is rapidly absorbed following oral administration, with good bioavailability (34–58%) [19,33]. Absorption is not affected by age, but is lower with food intake (37% vs. 30% in fasting and with food, respectively), as is the maximum serum concentration [15,24].

FT plasma concentrations reach 24–32 mg/L following the administration of a single dose (3 g), generally within 2–2.5 h. There is a linear relationship between the AUC of plasma concentrations, the peak plasma concentrations and the dosage [17,30–32]. The half-life is 5–7 h, and the distribution volume is 0.3–0.4 L/kg, which is higher than that of extracellular fluids, thus indicating good distribution in the extravascular compartment [17,32,33]. FT is not bound to plasma proteins; its tissue distribution is wide, and clinically relevant concentrations are achieved in the bladder wall, kidneys, seminal vesicles, and prostate [19,31,33,34]. Fosfomycin concentrations were measured in prostate tissues 3 and 12 h after a single 3 g FT dose. At 3 h, an average of 20.78±2.35 μg/g FT was reported in prostate tissues, and serum fosfomycin concentration was 25.63±3.66 μg/mL [35]. Twelve hours after drug administration, fosfomycin was present at a concentration of 4.92±0.89 μg/g in prostate tissues and 6.75±0.82 μg/mL in serum [35]. Comparable results were obtained in a more recent study involving patients undergoing prostate transurethral resection for benign prostatic hyperplasia. Seventeen hours after the administration of a single 3 g FT dose, average fosfomycin concentration was 6.5±4.9 μg/g (range, 0.7–22.1 μg/g) in the prostate, and therapeutic plasma concentrations were reported up to 17 h after drug administration [36]. In addition, recent PK data support the use of a subsequent dose of FT approximately 27 h after elimination of the first dose. The second dose is intended to boost FT concentrations in peripheral compartments (prostate and seminal vesicles) and plasma, which could lead to effective levels at the target sites and eradication of remnant pathogen foci [34]. Fosfomycin is excreted unmetabolised in the urine through glomerular filtration. Urinary recovery ranges from 30 to 60%, and high urinary concentrations are reached within 4 h and maintained over time, with large interindividual and intrasubject variability, and a reported peak concentration of 1.982±1.257 mg/L [16,32,37,32]. Mean urinary concentrations are >100 mg/L until 48 h after a dose, thus enabling the maintenance of sufficiently high levels with very high urinary AUC/MIC ratios and Cmax/MIC and a strong bactericidal activity primarily on *E.coli* [15–17,24,32–34,37,38].

FT is associated with a low incidence of side effects and has a high tolerability profile. The most reported adverse events are generally related to the gastrointestinal tract (e.g., diarrhoea), although these are generally mild and have a low incidence of 2–3%, which is lower than that reported for beta-lactams [16,39].

3.2. FT for the treatment of uUTI

3.2.1. Study characteristics

A total of 83 potentially relevant articles evaluating the clinical activity of FT for the treatment of uUTIs were identified through PubMed and Embase searches. After initial screening for duplicates and evaluation of full text for eligibility, nine studies were considered in the systematic review (Fig. 1). These were five RCTs and four systematic reviews with meta-analysis. Antibiotics used as comparators in meta-analyses included fluoroquinolones (two studies), β-lactams (three studies), cephalosporins (one study), sulfonamides (three studies), trimethoprim (three studies), and nitrofurantoin (four studies). One RCT compared 5-day nitrofurantoin treatment with single-dose FT. Substitutes for antibiotics (uva ursi extract, BNO 1045: coated tablet containing ibuprofen and lovage root, centaury and rosemary leaf powders) were evaluated in four RCTs and compared with the immediate use of FT. Table 1 reports the principal characteristics of the included studies.

3.2.2. Clinical and microbiological assessment

Meta-analyses showed that the microbiological and clinical remission rates of single-dose oral FT were similar to those with longer treatment schedules with fluoroquinolones, sulfonamides, trimethoprim, β-lactams and cephalosporins [11,40–42]. The RCT by Huttner and collaborators showed that 5-day 100 mg nitrofurantoin (three times a day) was associated with a greater probability of clinical resolution (difference, 12% [95% confidence interval (CI), 4–21]; P=0.004) and microbiological resolution (difference, 11% [95% CIs, 1–20]; P=0.04) after therapy completion at 28 days than that with a single 3-g dose of FT [43]. Meta-analyses by Konwar, Wang, and Cai indicated that there were no significant differences in any outcome between these antibiotic regimens [11,41,42].

3.2.2.1. Effectiveness of antibiotic substitutes. Initial treatment with uva ursi extracts (2 × 105 mg tablets, three times a day for 5 days) was found to correlate with a potential reduction of antibiotic use and a greater symptom burden, greater rate of pyelonephritis and fever than initial use of a single dose of FT (3 g) [44].

The phytodrug, Canephron®N (BNO 1045) was non-inferior to a single 3-g FT dose, based on the number of additional antibiotics used by patients for treating uUTIs [45]. In addition, assessment of patient-reported outcomes through the Acute Cystitis Symptom Score showed that scores were comparable in BNO 1045 and FT groups at day 1 and then decreased during the treatment (day 4 and day 8 assessment) and at late follow-up (day 38) [46]. However, there was a lower mean reduction of symptoms with this treatment than with a single 3-g FT dose (P=0.0166) [45].

The initial treatment of uUTIs with ibuprofen was related to fewer courses of antibiotics but showed a greater overall symptom burden, with more pyelonephritis, than immediate use of FT (single 3-g dose) [47].

3.2.3. Safety outcomes

There were no serious adverse events related to FT reported in the studies considered; the most frequent events were mainly gastrointestinal [41,43,45]. There were no significant differences in the number of patients who reported an adverse event between FT and other antibiotics regimens [41,43,45]. The use of uva ursi extract or ibuprofen as substitutes for initial antibiotic therapy was associated with more safety concerns, such as a higher occurrence of pyelonephritis [44,47].

3.3. FT antimicrobial prophylaxis for prostate biopsy

3.3.1. Study characteristics

A total of 38 potentially relevant articles evaluating FT antimicrobial prophylaxis for prostate biopsy were identified through PubMed and Embase searches. After screening for duplicates and evaluating full text for eligibility, ten studies were included in the systematic review (Fig. 2). Retrieved studies comprised four RCTs, two retrospective studies, and four systematic reviews with meta-analysis. All studies compared the use of FT with fluoroquinolones-based prophylaxis, except for one RCT that compared the use of different FT doses (two or three 3 g daily doses). One meta-analysis evaluated the use of seven different antimicrobial interventions. The main characteristics of included studies evaluating the activity of FT in the prevention of infectious complications after prostate biopsy are summarised in Table 2.

3.3.2. Clinical and microbiological assessment

The four meta-analyses retrieved in the database search showed that patients who received prophylaxis with FT were less likely to develop prostate biopsy-related infectious complications and

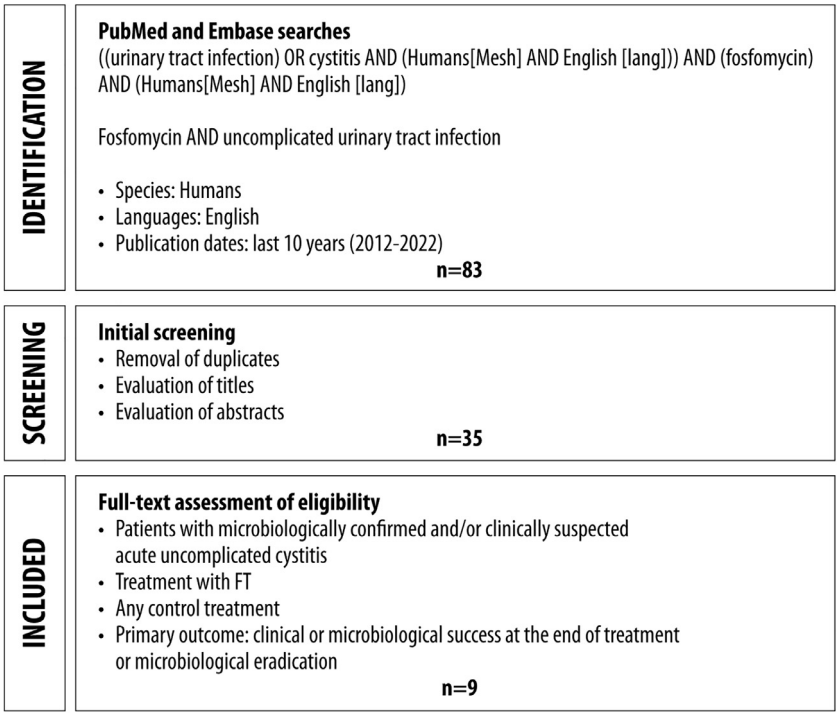

Fig. 1. Search strategy for articles evaluating the clinical activity of FT for the treatment of uUTIs.

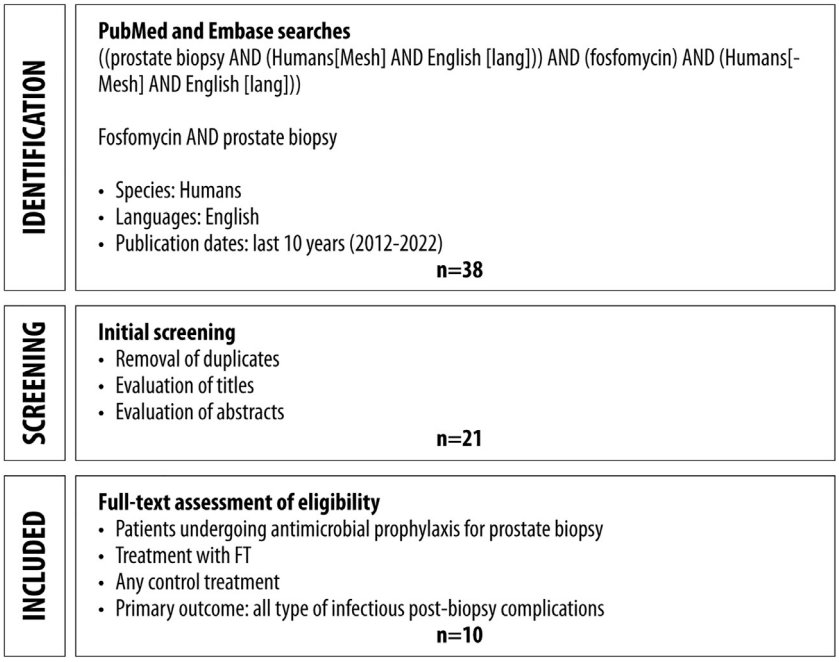

Fig. 2. Search strategy for articles evaluating FT antimicrobial prophylaxis for prostate biopsy.

severe, resistant infections than those who received fluoroquinolones (ciprofloxacin or levofloxacin), as shown by the significantly lower incidence of uUTI in the fosfomycin cohorts (P=0.02 to P<0.00001) [48–51]. Similar results were reported in the retrospective studies by Cai and Ongün, which showed a lower rate of symptomatic infections in patients treated with FT compared with those treated with ciprofloxacin or levofloxacin [52,53]. No infective complications were observed in patients involved in the RCT by Kisa and collaborators, in which FT was compared with ciprofloxacin [54]. There were no statistically significant differences in the total number of complications between FT and ciprofloxacin in the RCTs by Lista (P=0.017) and Van Besien (P=0.59) [55,56]. However, the likelihood of antibiotic resistance in patients with bacteriuria was greater in patients treated with ciprofloxacin in the RCT by Lista (P=0.0004) [55].

No difference in clinical outcomes was found between the two or three daily doses of 3g FT tested by D'Elia and collaborators [57].

Table 1
Main characteristics of included studies evaluating the activity of FT in the management of uUTIs.

Reference (Author, year)	Study design	Comparator treatment	Primary endpoint	Study population	Main conclusions
Yan 2021 [35]	Systematic review and meta-analysis	Fluoroquinolones, trimethoprim-sulfamethoxazole, nitrofurantoin and β-lactams	To compare the efficacy and safety of quinolones with trimethoprim-sulfamethoxazole (TMP/SMX), nitrofurantoin, fosfomycin, and β-lactams	47 RCTs comprising a total of 8992 patients	Clinical and bacteriological remission rates of quinolones were similar to those for TMP/SMX and fosfomycin
Konwar 2022 [36]	Systematic review and meta-analysis	Nitrofurantoin	To compare the efficacy and safety of nitrofurantoin with FT	Four RCTs (one for asymptomatic bacteriuria in pregnancy) comprising a total of 1497 patients	No significant differences in clinical and microbiological outcomes were found within 4 weeks of treatment
Gágyor 2021 [32]	Randomised controlled trial	Herbal treatment with uva ursi (UU) extract	To evaluate whether initial treatment with UU can be considered an alternative to antibiotics in uUTIs without increasing symptom burden and complication frequency compared with FT treatment	398 patients randomly allocated to receive UU (n=207) or FT (n=191)	Excluding the trial drug FT, the subsequent/additional antibiotic use was higher in the UU group (23% vs. 44%). UU was associated with a higher symptom burden and more safety concerns than FT
Alidjanov 2020 [39]	Double-blind, randomised, multicentre, phase III non-inferiority trial	Phytodrug Canephron®N (BNO 1045)	To measure the patient-reported outcomes through the Acute Cystitis Symptom Score (ACSS) in women with uUTI treated with BNO 1045 or FT	657 patients randomly allocated to receive BNO 1045 (n=325) or FT (n=332)	Mean sum scores of the ACSS-typical domains were comparable between groups during treatment (day 1, day 4, and day 8 assessment) and at late follow-up on day 38
Wang 2020 [37]	Systematic review and meta-analysis	Antibiotics used as comparators included β-lactams and cephalosporins, sulfonamides, trimethoprim and nitrofurantoin	To compare the efficacy and safety of single-dose FT vs. other antibiotics in women with uUTI and pregnant women with uUTI or asymptomatic bacteriuria	21 studies comprising a total of 4589 patients	Single-dose FT has equivalent clinical and microbiological efficacy to comparator antibiotics
Cai 2020 [12]	Systematic review and meta-analysis	Antibiotics used as comparators included fluoroquinolones, trimethoprim, cotrimoxazole, nitrofurantoin and β-lactams	To compare the effectiveness and safety profile of FT *vs.* comparator antibiotics in women with uUTIs	15 studies comprising a total of 2295 patients	Single-dose FT has equivalent clinical and microbiological effectiveness and safety to comparator regimens in women with uUTI. FT is associated with high patient compliance
Huttner 2018 [41]	Randomised clinical trial	Nitrofurantoin	To compare the clinical and microbiological efficacy of nitrofurantoin and fosfomycin in women with uncomplicated cystitis	513 women randomised in a 1:1 ratio to 5-day oral nitrofurantoin (n=255) or single-dose FT (n=258)	Significantly greater likelihood of clinical and microbiological resolution with 5-day nitrofurantoin compared with a single 3-g dose of FT at day 4 (P=0.016). Comparable likelihood of resolution at the end of treatment and at the follow-up period (28 days)
Wagenlehner 2018 [38]	Double-blind, parallel-group, randomised, multicentre, non-inferiority phase III trial	Phytodrug Canephron®N (BNO 1045)	To determine whether herbal therapy with BNO 1045 is non-inferior to FT according to the proportion of patients who need additional antibiotics to treat uUTIs	657 patients randomly allocated to receive BNO 1045 (n=325) or FT (n=332)	BNO 1045 was non-inferior to FT according to the number of patients who received additional antibiotics to treat uUTIs. This treatment was associated with a lower mean reduction of symptoms compared with a single 3-g dose FT (P=0.0166)
Gágyor 2015 [40]	Randomised clinical trial	Ibuprofen	To evaluate whether treatment of uUTIs with ibuprofen can reduce the rate of additional antibiotic prescriptions without a significant increase in symptoms, recurrences, or complications	494 women randomised to receive FT (n=246; 243 analysed) or ibuprofen (n=248; 241 analysed)	The 248 women in the ibuprofen group receiving significantly fewer courses of antibiotics, had a significantly higher total symptom burden and more pyelonephritis

3.3.3. Safety outcomes

In all the included studies, the rate of adverse events for antibiotic prophylaxis with FT was lower than or comparable with the rate with fluoroquinolones [48–57].

4. Discussion

The monobasic anionic salt FT has a low molecular weight and can reach clinically relevant concentrations in the bladder and prostate gland [15,16,36]. FT has bioavailability of up to 50%, with a 2-h plasma concentration up to 30 mg/L, and a 4-hour urinary concentration of 1000–5000 mg/L after a single 3-g oral dose [16,58].

The (tentative) epidemiological cut-off values for FT on the EUCAST website range from 4 mg/L (CI 1–4) for *E. coli* to 128 mg/L (CI 64–256) for *K. pneumoniae* and 128 mg/L (95% CIs) for *Enterococcus* spp. Bacteria most frequently isolated in uUTIs present an MIC of <4 mg/L (*E. coli*) or 8 mg/L (*Proteus mirabilis*) [59]. High

Table 2
Main characteristics of included studies evaluating the activity of FT for the prevention of infectious complications following prostate biopsy.

Reference (Author, year)	Study design	Comparator treatment	Primary endpoint	Study population	Main conclusions
Pilatz 2020 [42]	Systematic review and meta-analysis	Seven different antimicrobial interventions	To evaluate the evidence for different antibiotic prophylaxis regimens	59 RCTs comprising a total of 14 153 patients	In countries where fluoroquinolones are allowed, a minimum of a full 1-day administration is recommended. In countries with a ban on fluoroquinolones, fosfomycin is a good alternative
Roberts 2018 [43]	Individual patient-data meta-analysis	Quinolone-based antibiotic prophylaxis (ciprofloxacin or levofloxacin)	To analyse available evidence comparing FT to fluoroquinolone-based prophylaxis to prevent transrectal ultrasound-guided prostate biopsy related to infectious complications	Five studies (three prospective randomised trials and two retrospective cohort studies) comprising a total of 3112 patients	Patients who received FT prophylaxis were less likely to develop infections, as well as severe and resistant infections, after the biopsy than those who received fluoroquinolone-based prophylaxis
Lista 2014 [49]	Prospective randomised comparison trial	Ciprofloxacin	To evaluate the efficacy and safety of antibiotic prophylaxis in prostate biopsy by comparing two antibiotic regimens: FT and ciprofloxacin	671 patients randomly allocated to receive FT (n=359) or ciprofloxacin (n=312)	FT prophylaxis is as effective and safe as ciprofloxacin, which carries a lower resistance rate
D'Elia 2019 [51]	Randomised clinical trial	Two vs. three FT doses	To evaluate the efficacy and safety of a prostate biopsy prophylaxis protocol using two vs. three fosfomycin doses	297 patients randomly allocated to receive two (n=325) or three (n=332) FT doses	There was no significant difference in clinical outcome between the two dosage regimens. The low fever and prostatitis rate indicate that FT prophylaxis is safe and effective
Noreikaite 2018 [44]	Systematic review and meta-analysis	Quinolone-based antibiotic prophylaxis (ciprofloxacin or levofloxacin)	To compare the efficacy of fosfomycin with quinolone-based antibiotic prophylaxis for transrectal ultrasound-guided prostate biopsy (TRUSBP)	Five studies comprising a total of 3112 patients (1447 and 1665 patients were included in the FT and fluoroquinolone cohorts, respectively)	A significantly lower incidence of UTI in the fosfomycin cohort was reported ($P<0.00001$). Urine cultures from FT patients showed significantly lower resistance rates ($P<0.0001$). The adverse effect profile between the two cohorts was similar
Van Besien 2019 [50]	Prospective randomised study	Ciprofloxacin	To investigate whether switching ciprofloxacin to fosfomycin in the case of fluoroquinolone-resistant rectal bacteria influences the incidence of infectious complications after transrectal prostate biopsy	204 patients randomised to FT (n=202) or ciprofloxacin (n=202)	The total number of complications (major and minor) did not differ between groups ($P=0.59$)
Kisa 2017 [48]	Prospective, randomised trial concerning risk factors	Ciprofloxacin	To compare fosfomycin with ciprofloxacin use in prophylaxis	513 women randomised in a 1:1 ratio to 5-day oral nitrofurantoin (n=255) or single-dose FT (n=258)	No infective complications were observed. Ciprofloxacin may be used liberally in patients without risk factors but should be given according to the rectal swab results in patients at risk. Fosfomycin may be used independently of risk factors and rectal swab results
Cai 2017 [46]	Retrospective study	Ciprofloxacin	To compare FT and ciprofloxacin for antibiotic prophylaxis in transrectal prostate biopsy	1109 patients who received ciprofloxacin (n=477) or FT (n=632)	Antibiotic prophylaxis with FT had a lower rate of adverse events and a lower rate of symptomatic UTIs than ciprofloxacin
Freitas 2019 [45]	Systematic review and meta-analysis	Ciprofloxacin	To assess the comparative prophylactic effectiveness of FT vs. ciprofloxacin in men who underwent transrectal ultrasonography-guided prostate needle biopsy	4 RCTs comprising a total of 2331 patients	Antibiotic prophylaxis with FT was associated with lower rates of infectious complications than ciprofloxacin
Ongün 2012 [47]	Retrospective study	Quinolone-based antibiotic prophylaxis (ciprofloxacin or levofloxacin)	To evaluate the efficacy of single-dose fosfomycin prophylaxis as an alternative to fluoroquinolone-based prophylaxis in TRUSBP	620 patients who underwent TRUSBP and received a single dose of FT or a single dose of levofloxacin or oral ciprofloxacin	Most febrile UTIs occurred in patients who received levofloxacin (21%) or ciprofloxacin (74%). Among patients with afebrile UTI, 8% received FT, 16% received levofloxacin, and 76% received ciprofloxacin. The ease of use of FT, reducing the rate of fluoroquinolone-resistant infections, shows that it could be an effective alternative for antimicrobial prophylaxis

FT concentrations in urine (>100 mg/L), even 48 h post-antibiotic administration, promote uropathogen killing [15,16,32,37,38]. This observation, along with evidence from the literature, supports the empirical use of FT for the management of uUTI, even for resistant isolates, in populations including pregnant women and older women [13,14,60,61].

Although the administration of oral fosfomycin dates back to the 1970s, *E. coli* resistance to this molecule is still rare, reflecting the slow adaptation rate to FT [3,13,15].

Clinical evidence from the last 10 years indicates that the microbiological effectiveness and safety of single-dose oral FT are similar to that for comparator regimens with longer treatment

schedules in women with clinically suspected or microbiologically confirmed uUTI [11,40–42]. These clinical data are supported by the similar resistance rate to fosfomycin among uropathogens, as demonstrated by Kahlmeter and collaborators [62]. These authors reported resistance to FT of <2% in *E. coli* [62]. In addition, FT has been associated with high patient compliance [11].

The RCT by Huttner and collaborators showed that 5-day nitrofurantoin resulted in a greater probability of resolution at 28 days after therapy completion compared with single-dose FT [43]. However, these conclusions should be viewed with caution. Concerns surrounding these conclusions include the modality of uUTI diagnosis, the study schedule, recruiting and follow-up (the three sites had differences regarding local resistance prevalence and patients' age), the antibiotics administration modality, in terms of dose and timing, and the microbiological responses assessed as secondary outcomes [43]. Moreover, this was an open-label study, which may account for some level of measurement bias, and there may have been heterogeneity in microbiological methods as laboratory analyses were not centralised [43]. An editorial by Vallée and Bruyère highlighted some points to consider in the interpretation of this paper, such as the inclusion of hospitalised women (which may exclude patients with uncomplicated cystitis), and the rationale for prolonged antibiotic treatment (5–7 days of nitrofurantoin instead of a fosfomycin single dose) in the era of antibiotic crisis, when limiting the duration of antibiotic treatment appears essential [63].

First-line use of antibiotics for the treatment of the acute phase of uUTIs is supported by current guidelines [10]. Nevertheless, to counteract the abuse of antibiotics and increasing rates of antimicrobial resistance, studies have sought to determine whether effective substitutes for antibiotics can be used to treat uUTIs [46]. The phytodrug, BNO 1045, and ibuprofen were shown to be no less effective than a single 3-g dose of FT, based on the number of patients who received additional antibiotics to treat uUTIs [45,47]. However, these treatments were associated with a greater total symptom burden [45,47]. Consequently, these results must be interpreted carefully. Generally, this treatment option cannot be recommended as a first approach and should be proposed to patients with mild-to-moderate infection in a shared care approach or as part of a late antibiotic prescribing strategy [47].

Evidence from the literature on the prophylactic use of FT to prevent infectious complications after prostate biopsy includes the ease of use and safety of FT, and the lower rates of resistant infections and hospitalisations compared with fluoroquinolones, which indicate that this molecule is a viable and effective alternative drug, particularly in countries where fluoroquinolones are not allowed [48–53,55]. Notably, lower rates of adverse events, infectious complications, and symptomatic UTIs have been reported with FT compared with ciprofloxacin [51,52].

5. Conclusions

According to the literature published in the last 10 years, clinical and microbiological effectiveness and safety of single-dose oral FT are similar to that for comparator regimens that have longer treatment schedules in women with microbiologically confirmed or clinically suspected uUTI. FT is an effective alternative drug to fluoroquinolones for antimicrobial prophylaxis in prostate biopsy. These observations, along with a broad clinical experience, support the empirical use of FT for treating UTIs, and indicate that FT is a promising candidate to effectively address antibiotic-resistant UTIs throughout Europe.

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