Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials

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Background: Cystitis is a common infection. The alarmingly high resistance rates exhibited by contemporary uropathogens necessitate the re-evaluation of old antibiotics.

Objectives: To evaluate the effectiveness and safety of fosfomycin compared with other antibiotics for the treatment of patients with cystitis.

Methods: We performed a meta-analysis of randomized controlled trials (RCTs), generated from searches performed in PubMed, Scopus and Cochrane CENTRAL, which involved patients with cystitis treated with fosfomycin versus other antibiotics.

Results: Twenty-seven trials (eight double-blind) were included. Sixteen of these 27 trials involved exclusively non-pregnant female patients, 3 involved adult mixed populations of older age, 5 involved pregnant patients and 3 involved paediatric patients. Regarding clinical success, no difference was found in the comprehensive analysis regarding all comparators combined [10 RCTs, 1657 patients, risk ratio (RR) = 1.00, 95% confidence interval (CI) = 0.98–1.03] in trials involving non-pregnant females and in trials involving mixed populations. Insufficient relevant data were provided from trials involving paediatric and pregnant patients. No difference between fosfomycin and comparators was also found in all comparisons regarding the remaining effectiveness outcomes (namely microbiological success/relation/re-infection). Fosfomycin had a comparable safety profile with the evaluated comparators in non-pregnant women, mixed and paediatric populations, whereas it was associated with significantly fewer adverse events in pregnant women (4 RCTs, 507 patients, RR = 0.35, 95% CI = 0.12–0.97).

Conclusions: In the era of high drug resistance rates, reported even among community-acquired uropathogens, fosfomycin may provide a valuable alternative option for the treatment of cystitis in non-pregnant and pregnant women and in elderly and paediatric patients.

Keywords: fosfomycin tromethamine, microbiological eradication, pregnancy, safety

Introduction

Cystitis is a common bacterial infection. It affects mostly women of reproductive age, while incidence declines after the age of 40. It has been estimated that more than half of the women in United States will be diagnosed with an uncomplicated urinary tract infection (UTI) at some time during their life. This has considerable socio-economic implications.1–3

Antimicrobial resistance is a major concern worldwide. A particular concern has been raised regarding commonly isolated uropathogens, since their susceptibility profile has been constantly changing.4 Specifically, the emergence of uropathogens that are resistant to fluoroquinolones, as well as uropathogens, mainly Escherichia coli, that exhibit considerably high resistance due to the production of extended-spectrum β-lactamases (ESBLs), narrow our armamentarium against UTIs.5–7 Fosfomycin is a broad-spectrum antibiotic with pharmacokinetic and pharmacodynamic properties that favour its use for the treatment of UTIs.6,9 In this regard, a single-dose fosfomycin tromethamine oral treatment has been approved for the treatment of acute uncomplicated cystitis.10 On the other hand, fosfomycin seems
to play an important role in the treatment of infections beyond the urinary tract.\textsuperscript{11–14}

With these considerations in mind, we aimed to compare the effectiveness and safety profile of fosfomycin versus other antibiotics in patients with cystitis by performing a meta-analysis of relevant randomized controlled trials (RCTs).

\section*{Methods}

\subsection*{Literature search}

The PubMed database, Cochrane CENTRAL and Scopus were searched during the period between 26 October 2009 and 15 January 2010. References cited in relevant articles were also reviewed. A broad search was performed in PubMed under the general term ‘fosfomycin’. The search strategies used in the Cochrane Central Register of Controlled Trials and Scopus were ‘(fosfomycin) AND (urinary tract infection OR cystitis)’ and ‘(urinary tract infection OR cystitis) AND (fosfomycin) AND (female)’, respectively. The study selection was performed by two independent reviewers (A. G. T. and M. K.), who also evaluated the eligibility of the retrieved articles for inclusion in the meta-analysis and extracted the data.

\subsection*{Study selection criteria}

RCTs involving patients of any age with microbiologically confirmed or clinical suspicion of cystitis who were randomized to receive treatment with fosfomycin or other antibiotic agents were regarded as eligible for inclusion in the meta-analysis. Trials involving patients with anatomical or functional abnormalities of the urinary tract and/or patients with other factors predisposing to complicated cystitis, or patients with pyelonephritis, were excluded. Abstracts presented at scientific conferences and studies written in languages other than English, French, Spanish and Turkish were excluded.

\subsection*{Data extraction}

Data extracted from each of the included trials referred to the study design, quality assessment, characteristics of the study population, inclusion/exclusion criteria used, characteristics of the compared study treatments, follow-up visits performed, as well as specific outcomes that were evaluated in this meta-analysis.

\subsection*{Definitions}

\textit{Cystitis} was defined as the presence of symptoms that are suggestive of acute UTI, including painful urination (dysuria) and/or urinary urgency or frequency, in combination with a positive urine culture for a bacterial organism, and/or detected pyuria. \textit{Asymptomatic bacteriuria} in women was defined as the presence of at least two consecutive voided specimens yielding sufficient quantitative counts of similar organism(s).\textsuperscript{5,16}

\subsection*{Outcomes of the meta-analysis}

\textbf{Effectiveness outcomes}

The primary effectiveness outcome of our meta-analysis, clinical success, was defined as the complete (cure) and/or non-complete (improvement) resolution of symptoms at the end of treatment. Secondary effectiveness outcomes included: microbiological success (eradication), defined as the presence of a negative urine culture at the end of treatment; microbiological relapse, defined as the detection of the same pathogen as the one identified at the baseline urine culture at a long-term follow-up evaluation, after the acquisition of a sterile culture at a previous follow-up assessment, as well as microbiological re-infection, defined as the detection of a pathogen at a long-term follow-up evaluation, different from the one identified at the baseline culture, after the acquisition of a sterile culture at a previous follow-up assessment. The intention-to-treat population was defined as the numbers of patients that were randomized to receive the compared treatment regimens.

\textbf{Safety outcomes}

The safety outcomes of the meta-analysis included: adverse events, defined as any adverse event that was reported at any time during the study period; and study withdrawals due to adverse events.

\subsection*{Subgroup and sensitivity analysis}

Separate analyses regarding the effectiveness and safety outcomes were performed for each one of the subgroup of trials, involving patient populations with different characteristics, that were included in our meta-analysis. Separate analyses regarding all the outcomes were also performed to compare fosfomycin with each of the different types of antibiotic agent used in the subgroup of trials involving non-pregnant female patients. In a comprehensive analysis, we also evaluated fosfomycin versus all the compared antibiotic agents combined with regard to the evaluated outcomes.

In a sensitivity analysis we chose to evaluate microbiological effectiveness in trials comparing single-dose fosfomycin with single-dose regimens of other antibiotics, as well as in trials comparing single-dose fosfomycin with longer regimens of other antibiotics and we tested for differences between the above subgroups of trials.

We also performed sensitivity analyses in order to evaluate clinical and microbiological success in trials with a blinded design (double-blind and single-blind) trials, as well as in the remaining trials, and we tested for difference between these subgroups of trials.

\subsection*{Quality assessment}

We used the Jadad criteria to assess the methodological quality of each of the included trials. According to the Jadad criteria, one point was assigned to each trial for the presence of each of the following components: randomization; blinding; and reporting of data regarding study withdrawals. One point was awarded to the trial or subtracted when the randomization procedure was deemed appropriate or not, respectively. This was also applied with regard to the blinding procedure. The maximum score that could be awarded to a trial was 5 points. A score higher than 2 was considered as indicative of adequate methodological quality.\textsuperscript{17,18}

\subsection*{Statistical analysis}

The presented data were statistically analysed with the use of Review Manager (RevMan) v.5.0 Software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2008). Pooled risk ratios (RRs) and 95\% confidence intervals (CIs) were determined using a random effects model, in case of outcomes that were expressed as dichotomous variables. We used the \textit{x}\textsuperscript{2} test in order to assess statistical heterogeneity between the trials included in the meta-analysis. A \textit{P} value $<0.1$ was considered as indicative of significant heterogeneity among evaluated trials.

\section*{Results}

\subsection*{Selected studies}

Our searches in PubMed, the Cochrane Central Register of Controlled Trials and Scopus generated a total of 1697, 45 and 175 articles, respectively. A total of 27 individual trials were regarded as eligible
for inclusion in our meta-analysis. The detailed process of selection of the eligible trials is depicted in Figure 1 (flow diagram).

**Study characteristics**

The main characteristics of the 27 included trials are presented in Table 1. Eight of the 27 included trials were double-blind RCTs, 2 were single-blind RCTs, and the remaining 17 trials were open-label trials. Of note, all blinded studies were included in the subgroup of trials involving non-pregnant female patients. Eight of the included trials were multicentre RCTs. Ten of the 27 included trials were assigned a Jadad score $>2.$

![Flow diagram of the detailed process of selection of trials for inclusion in the meta-analysis.](https://academic.oup.com/jac/article-abstract/65/9/1862/721366)
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<th>Antibiotic group A (dosage, duration)</th>
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<td><strong>Non-pregnant females</strong></td>
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<td>Bozkurt, 200819</td>
<td>Double-blind RCT, Turkey, training and research hospital gynaecology clinic of urology</td>
<td>2</td>
<td>Adult women (mean age 36.2 ± 4.53 y) with uncomplicated UTIs</td>
<td>Clinical symptoms (dysuria, frequency, groin pain), with documented pyuria and bacteriuria on urinalysis (&gt;10^5 cfu/mL of urine)</td>
<td>Significant leucocytosis, burning pain, high fever and upper UTI</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>Ciprofloxacin (500 mg po, bid, 3 d)</td>
<td>100 (50 vs 50)</td>
<td>10 d post-treatment</td>
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<td>Gupta, 200520</td>
<td>RCT, USA, patients presenting to the university healthcare centre/recruited through advertisements at the University of Washington campus</td>
<td>2</td>
<td>Non-pregnant, in good general health women, 18–45 y, with acute uncomplicated cystitis</td>
<td>Confirmed pyuria measured by a haemocytometer, urine culture with &gt;10^5 cfu/mL of a uropathogen</td>
<td>Pregnancy/lactation, irregular use of contraceptives, chronic conditions (e.g. diabetes), known anatomical UT abnormalities, allergy to any of the three study drugs, recent (&lt;2 weeks) exposure to oral or parenteral antimicrobial agents, age &gt;65 years, hysterectomy, inability to swallow tablets</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>Ciprofloxacin (250 mg po, bid, 3 d) or nitrofurantoin (100 mg po, bid, 7 d)</td>
<td>62 (20 vs 42)</td>
<td>1–3 d, 10–14 d and 28–30 d after therapy</td>
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<td>Stein, 199971</td>
<td>Multicentre RCT, UK, ambulatory patients assessed by GPs</td>
<td>5</td>
<td>Healthy women, ≥12 y, with acute uncomplicated lower UTI</td>
<td>Clinical symptoms of acute uncomplicated UTI (dysuria, frequency, urgency), onset of symptoms ≤96 h, &gt;10^5 cfu/mL of a uropathogen in a clean-voided midstream urine sample</td>
<td>Evidence of pyelonephritis (temperature ≥101°F, pain or chills), pregnancy, lactation, known hypersensitivity to nitrofurantoin, structural or functional UT abnormalities, history of recurrent UTIs (&gt;3 during the past year), renal or hepatic dysfunction, antibiotic use within the last 2 d</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>Nitrofurantoin monohydrate/macrocrystal (100 mg po, 7 d)</td>
<td>749 (375 vs 374)</td>
<td>5–11 d after initial treatment dose, 5–11 d and 4–6 w after last day of medication</td>
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<td>Minassian, 199872</td>
<td>Multicentre RCT, UK, ambulatory patients</td>
<td>2</td>
<td>Women, 18–65 y, with uncomplicated lower UTI</td>
<td>Symptoms (dysuria, frequency, urgency) present ≤48 h, microbiologically significant count (≥10^5 (cfu)) in urine</td>
<td>Signs and symptoms of upper UTI ( loin pain, fever ≥38.5°C, rigour and vomiting), pregnancy, lactation, inadequate pregnancy precautions, UT abnormalities, iv drug users, antibacterial therapy &gt;2 w, sepsis, chronic GI disorders, renal impairment, folate deficiency, megaloblastic anaemia, malignancies, HIV infection, hypersensitivity towards agents being tested, any condition requiring treatment with any agent that could interact with the study drugs, unwillingness to participate/compel with protocol requirements, any subject considered unsuitable</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>Trimethoprim (200 mg po, bid, 5 d)</td>
<td>530 (350 vs 180)</td>
<td>7–9 d and 28–30 d</td>
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<td>Richaud, 1995$^3$</td>
<td>Double-blind, placebo-controlled RCT, France, ambulatory patients</td>
<td>5</td>
<td>Women, 18–80 y, with uncomplicated lower UTIs</td>
<td>Female patients, age 18–80 y, with UTI, bacteriuria &gt;10$^5$ cfu/mL in urine culture</td>
<td>Functional or anatomical UT abnormalities, history of recurrent UTIs (&gt;4 episodes/y), fever and symptoms of upper UTI, pregnancy, known hypersensitivity to any of the study drugs, absorption disorders in GI tract</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>Pefloxacin (800 mg po, single dose)</td>
<td>57 (29 vs 28)</td>
<td>7 d and 30 d post-treatment</td>
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<td>Elhanan, 1994$^4$</td>
<td>Open-label RCT, Israel, NR</td>
<td>3</td>
<td>Women, ≥16 y, with acute uncomplicated cystitis (positive leucocyte esterase test)</td>
<td>Clinical symptoms (dysuria, frequency, urgency of urination, absence of fever or flank pain) and pyuria (≥8 leucocytes/mm$^3$ mL) and positive urinary culture (≥10$^5$ cfu/mL of a microorganism susceptible to both medications used in the study), no antibiotic use ≤4 wk</td>
<td>Known anatomical or functional renal abnormalities, diabetes mellitus, pregnancy, immunocompromised women, known allergy to cephalosporins, history of UTI in previous 5 w</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>Cefalexin (500 mg po, qid, 5 d)</td>
<td>112 (58 vs 54)</td>
<td>5 d and 28 d</td>
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<td>Van Pienbroek, 1993$^5$</td>
<td>Double-blind, placebo-controlled RCT, Netherlands, ambulatory patients assessed by GPs</td>
<td>4</td>
<td>Non-pregnant women, ≥18 y, with acute uncomplicated lower UTI</td>
<td>Visiting their GP with acute dysuria, stranguria and/or urinary frequency</td>
<td>Signs and symptoms of a complicated or higher UTI, diabetes, known liver or kidney disease, known anatomical UT abnormalities, indwelling catheter, known allergy to study medications, recent use of immunosuppressive drugs, antibiotic treatment ≤2 wk, patients unable to read or write Dutch language, patients not suitable according to the GP</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>Nitrofurantoin (50 mg po, qid, 7 d)</td>
<td>231 (116 vs 115)</td>
<td>4 d, 9 d and 42 d</td>
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<tr>
<td>Cortes, 1992$^6$</td>
<td>Single-blind RCT, Spain, ambulatory patients</td>
<td>2</td>
<td>Women, 16–75 y, with uncomplicated lower UTI</td>
<td>Clinical symptoms compatible with lower UTI</td>
<td>Presence of general pathology, UT abnormalities with concomitant complicated infections, liver disease, prior antibiotic therapy, hypersensitivity to any of the study drugs, pregnancy</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>Pipemidic acid (400 mg, bid, 5–7 d) or po norfloxacin (400 mg, bid, 5–7 d)</td>
<td>106 (49 vs 36 vs 21)</td>
<td>3 d, 7 d and 28 d post-treatment</td>
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<tr>
<td>de Jong, 1991$^7$</td>
<td>Multicentre, open-label RCT, France, ambulatory patients assessed by GPs</td>
<td>2</td>
<td>Women, &gt;16 y, with uncomplicated lower UTI</td>
<td>Typical signs and symptoms of uncomplicated lower UTI, with confirmed bacteriuria &gt;10$^5$/mL</td>
<td>Severe renal impairment, abnormal UT, neurological bladder, lithiasis, tumour, clinical symptoms suggestive of higher infection (high fever, shivering back pain), recurrent UTI (&gt;4 in the past year), GI disease, unstable diabetes, hypersensitivity to study drugs, pregnancy</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>Norfloxacin (400 mg po, bid, 5 d)</td>
<td>68 (38 vs 30)</td>
<td>3–4 d and 25–30 d post-treatment</td>
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<td>Boerema, 1990&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Double-blind, placebo-controlled RCT, The Netherlands, ambulatory patients assessed by GPs</td>
<td>Symptomatic UTIs, documented pyuria and bacteriuria on urinalysis ($&gt;10^5$ cfu/mL urine)</td>
<td>Known structural (anatomical) or functional (neurological) UT abnormalities, pregnancy, lactation, concomitant infection, allergy to the test drugs or derivatives, concomitant antibiotic or antimicrobial treatment $&lt;$ 7 d prior to start of study</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>158 (79 vs 79)</td>
<td>2–3 d, 8–9 d and 6 w after first day of therapy</td>
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<td>Crocchiolo, 1990&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Open-label RCT, Italy, ambulatory patients assessed by GPs</td>
<td>Presence of symptoms suggesting acute lower UTI</td>
<td>Known hypersensitivity to either of the compounds studied, renal insufficiency, known UTI abnormalities, administration of any other antibacterial agent $&lt;$ 3 d, inadequate contraception use, evidence of renal insufficiency, known UT abnormalities (i.e. stones, previous surgery), antimicrobial use $&lt;$ 3 d</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>73 (38 vs 35)</td>
<td>5–10 d and 25–30 d post-treatment</td>
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<td>Harvard Davis, 1990&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Double-blind RCT, UK, ambulatory patients assessed by GPs</td>
<td>Symptoms suggestive of acute UTI (frequency, dysuria $+$ loin pain)</td>
<td>Known hypersensitivity to any study agent, pregnancy, inadequate contraception use, evidence of renal insufficiency, known UT abnormalities (i.e. stones, previous surgery), antimicrobial use $&lt;$ 3 d</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>51 (26 vs 25)</td>
<td>1 w and 6 w</td>
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<td>Naber, 1990&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Multicentre, single-blind RCT, Germany, ambulatory patients assessed by private practice urologists</td>
<td>Signs and symptoms of an acute uncomplicated UTI, $\leq$ 4 relapses/y</td>
<td>History of hypersensitivity/allergy to study medications or their derivatives, pregnancy, suspected pregnancy, lactation, antibiotic treatment within 3 d of study initiation, chronic UTI, renal function impairment, $CL_{CR} &lt; 20$ mL/min/1.73 m$^2$, diabetes mellitus, UT abnormalities, anatomical abnormalities, stones, neurogenic bladder, urine stoma, symptoms suggestive of upper tract disease (chills, fever, flank pain), recent sexually transmitted disease, use of anticonvulsives and/or cytotoxic drugs</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>562 (266 vs 131 vs 134) (31 patients with unclear study medication)</td>
<td>1 w and 4 w</td>
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<td>Neu, 1990&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Multicentre, double-blind RCT, Netherlands/Italy/Spain/Belgium, NR</td>
<td>Diagnosis of uncomplicated UTI, bacteriuria $&gt;10^5$ cfu/mL urine, isolated microorganism(s) susceptible to study drugs</td>
<td></td>
<td>Amoxicillin (3 g po, single dose)</td>
<td>158 (80 vs 78)</td>
<td>3–5 d, 5–9 d and 16–32 d</td>
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<td>Reynaert, 1990</td>
<td>RCT, Belgium, patients were residents of a university psychiatric centre</td>
<td>3</td>
<td>Women, 16–75 y, residents of university psychiatric centre, with acute uncomplicated UTI</td>
<td>Clear symptoms of uncomplicated UTI (dysuria, pollakiuria, without fever), cultures with bacterial count ≥10⁵ bacteria/mL</td>
<td>Renal insufficiency, other renal abnormalities, history of norfloxacin hypersensitivity or allergic reactions, history of chronic UTI, liver disease, pregnancy</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>Norfloxacin (400 mg po, bd, 3 d)</td>
<td>32 (16 vs 16)</td>
<td>5–10 d and an average 35.4 d vs 36 d after treatment initiation</td>
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<tr>
<td>Selvaggi, 1990</td>
<td>Double-blind RCT, Italy, ambulatory patients assessed by GPs</td>
<td>3</td>
<td>Women 12–75 y, with uncomplicated UTI</td>
<td>Symptoms of cystitis (dysuria, frequency, urgency etc)</td>
<td>History of complicated UTI, UT abnormalities, drug allergy, age &lt;12 y and &gt;75 y, pregnancy</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>Norfloxacin (800 mg po, single dose)</td>
<td>89 (45 vs 44)</td>
<td>7 d and 3 w</td>
</tr>
<tr>
<td>Caramalli, 1991</td>
<td>Open-label RCT, Italy, hospitalized patients</td>
<td>3</td>
<td>Elderly hospitalized patients (M/F), with acute or recurrent UTIs</td>
<td>Simple and complicated clinical forms (UT obstruction, indwelling catheters, post-surgical etc.), presence of &gt;10⁵ cfu/mL of susceptible bacterial strains isolated from midstream urine sample</td>
<td>NR</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td></td>
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<tr>
<td>Cooper, 1990</td>
<td>RCT, UK, ambulatory patients assessed by GPs</td>
<td>3</td>
<td>Adults (M/F) with symptoms suggestive of UTI</td>
<td>Patients of either sex complaining of dysuria and/or frequency</td>
<td>&gt;3 infections in previous 12 m, age &lt;16 y, pregnancy, lactation, penicillin allergy</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>Amoxicillin/clavulanic acid (175 mg po, tid, 5 d)</td>
<td>141 (72 vs 69)</td>
<td>5–10 d and 4–6 w post-treatment</td>
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<td>Ferraro, 1990</td>
<td>Open-label RCT, Italy, NR</td>
<td>1</td>
<td>Elderly subjects (15 M/4 F), &gt;50 y (mean age 68. y), with uncomplicated lower UTIs</td>
<td>Symptomatic infection of lower UT, caused by germs susceptible to study drugs, bacteriuria &gt;10⁵/mL</td>
<td>Anatomical and/or functional alterations of kidneys and excretory system, presence of foreign bodies (e.g. stone, catheter) in UT, signs of parenchymal infection (kidneys, prostate), diabetes, serious malfunction of the kidneys (Cr&lt;sups&gt;2&lt;/sups&gt; mL/min), immunosuppression, antibiotic or antimicrobial use discontinued &lt;1 w before study</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>Norfloxacin (400 mg po, bd, 7 d)</td>
<td>60 (30 vs 30)</td>
<td>3–5 d and 25–35 d after discontinuation of therapies</td>
</tr>
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<td>Estebanez, 2009</td>
<td>Open-label RCT, Spain, ambulatory patients seeking care from healthcentres</td>
<td>3</td>
<td>Adult pregnant women with asymptomatic bacteriuria&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Presence of ≥10² cfu/mL of the same microorganisms in two consecutive cultures from a patient without fever or symptoms of UTI</td>
<td>Antibiotics use 14 d prior to taking culture for any reason other than having UTI, allergy to penicillin, high-risk pregnancy, need for admittance to hospital, impossibility of performing follow-up, UT anomalies, infection due to microorganisms resistant to either of the two antibiotics, refusal to participate in the study, symptomatic UTI</td>
<td>Fosfomycin (3 g po, single dose)</td>
<td>Amoxicillin/clavulanate (500 mg po/125 mg po, tid, 7 d)</td>
<td>131 (65 vs 66)</td>
<td>10–14 d post-treatment and if culture sterile monthly until end of pregnancy</td>
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<td>Study</td>
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<tr>
<td>Bayrak, 2007</td>
<td>Turkey</td>
<td>Adult pregnant women in 2nd trimester of gestation with asymptomatic bacteriuria</td>
<td>Presence of leukocytosis, fever, urolithiasis, lower back pain, history of previous urological surgery, known UT abnormality</td>
<td>Fosfomycin (3 g po, single dose) Cefuroxime axetil (250 mg po, bid, 5 d)</td>
<td></td>
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<tr>
<td>Krcmery, 2001</td>
<td>Slovak Republic</td>
<td>Pregnant women, &gt;18 y, with acute cystitis</td>
<td>Presence of typical lower UTI symptoms (dysuria, urgency, frequency, suprapubic pain), pyuria (&gt;).10 leucocytes/HPF ×400) and significant bacteriuria (&gt;).10³ cfu/mL midstream urine)</td>
<td>Fosfomycin (3 g po, single dose) Cefuroxime (250 mg po, bid, 5 d)</td>
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<tr>
<td>Zinner, 1990</td>
<td>Italy</td>
<td>Adult pregnant women with symptomatic bacteriuria</td>
<td>Presence of typical lower UTI symptoms (dysuria, urgency, frequency, suprapubic pain), pyuria (&gt;).10 leucocytes/HPF ×400) and significant bacteriuria (&gt;.10³ cfu/mL midstream urine)</td>
<td>Fosfomycin (3 g po, single dose) Pipemidic acid (400 mg po, bid, 7 d)</td>
<td></td>
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<tr>
<td>Thoumin, 1990</td>
<td>Belgium</td>
<td>Pregnant women with asymptomatic bacteriuria</td>
<td>Significant bacteriuria (&gt;.10⁴ organisms/mL), absence of any UTI symptom</td>
<td>Fosfomycin (3 g po, single dose) Nitrofurantoin (100 mg po, bid, 7 d)</td>
<td></td>
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<tr>
<td>Poediatric trials</td>
<td>Principi, 1990</td>
<td>Children (M/F), 1 mo to 16 y, presumptively affected with lower UTI</td>
<td>Renal failure</td>
<td>Fosfomycin (2 g po, single dose, 1 g in children ≤1 y) Nitrofurantoin (5 mg/kg im, single dose)</td>
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<tr>
<td>Careddu, 1987</td>
<td>Italy</td>
<td>Children 1–14 y, (hospitalized/outpatients, M/F), with symptomatic and asymptomatic recurrent UTIs</td>
<td>2 urine cultures positive for same germ (&gt;.10⁴ cfu/mL)</td>
<td>Fosfomycin (2 g po, single dose) Pipemidic acid (200 or 400 mg po, in children weighing &gt;25 kg, bid, 7 d)</td>
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Continued
**Patient population characteristics**

Sixteen of the 27 included trials involved exclusively non-pregnant female patients with cystitis and 3 involved adult mixed populations, consisting of non-pregnant female and male patients with acute/recurrent UTI, symptoms suggestive of a UTI and patients with cystitis, respectively. Two of these three trials involved elderly patients. In addition, 5 of the 27 included trials involved pregnant female patients. Three of these five trials involved pregnant women with asymptomatic bacteriuria, and the remaining one involved pregnant women with symptomatic and asymptomatic bacteriuria. The remaining 3 of the 27 included trials involved paediatric patients with recurrent UTIs. One of these three trials involved a paediatric population with recurrent UTIs. The majority of the included trials involved outpatients.

In addition, most of the trials involving non-pregnant female patients included adult patients. However, seven of the trials from this subgroup included also adolescents and young adults. Two of the three trials involving non-pregnant female and male patients included elderly individuals. Four of the five trials that involved pregnant women included young adults. Regarding the subgroup of trials involving paediatric patients, the age distribution of the included children ranged from 1 month to 16 years.

**Characteristics of the treatment regimens compared**

**Types of antibiotic agents compared**

In all of the trials involving non-pregnant females the patients allocated to the fosfomycin treatment arm received a 3 g single-dose treatment with fosfomycin. Fosfomycin was compared with quinolones in nine of these trials. Specifically, fosfomycin was compared with norfloxacin in four trials, with ciprofloxacin in two trials, and with ofloxacin, pefloxacin and pipemidic acid, respectively. In two other trials involving non-pregnant female patients, fosfomycin was compared with trimethoprim, co-trimoxazole, b-lactams (cefalexin and amoxicillin, respectively) and in the remaining two with nitrofurantoin. In the subgroup of trials involving non-pregnant females and male patients, fosfomycin was compared with norfloxacin, netilmicin or amikacin, and clavulanate-potentiated amoxicillin. Regarding the subgroup of trials involving pregnant women, fosfomycin was compared with b-lactams in three trials (specifically, amoxicillin/clavulanate, ceftibuten, with pipemidic acid in one trial and with nitrofurantoin in the remaining trial). In the three paediatric trials fosfomycin was compared with netilmicin and with pipemidic acid.

**Duration of compared treatment regimens**

In 5 of the 27 included trials the single-dose fosfomycin treatment was compared with a single-dose treatment of pefloxacin, ofloxacin or co-trimoxazole, norfloxacin, trimethoprim and netilmicin or amikacin, respectively. In the
remaining 22 trials, fosfomycin was compared with longer treatment regimens. Specifically, the duration of the treatment regimens ranged from 3 to 7 days among these trials.

Outcomes
The data extracted from each of the included trials that were incorporated in the analyses regarding the outcomes of our meta-analysis are presented in Table S1 [available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)].

Effectiveness outcomes
Trials involving non-pregnant female patients
In the subgroup of trials involving non-pregnant female patients, no difference was observed regarding the primary outcome of our meta-analysis (clinical success) between patients treated with fosfomycin versus those treated with comparator(s) in the separate analyses, with the exception of one trial in which fosfomycin was found to be superior to trimethoprim.19 No difference was also observed in the comprehensive analysis including all the evaluated comparators (10 RCTs, 1657 patients, RR = 1.00, 95% CI = 0.98–1.03).19,21,26,28–31,33 Similarly, regarding cure, no difference was observed in the separate analyses, as well as in the comprehensive analysis (7 RCTs, 1272 patients, RR = 1.00, 95% CI = 0.96–1.03).19,21,24,26,30,31,33 No difference was observed regarding microbiological success between patients treated with fosfomycin versus those treated with comparator(s), either in the separate analyses comparing fosfomycin with each of the different types of antibiotic agents used or in the comprehensive analysis regarding fosfomycin versus all the comparators combined (12 RCTs, 1602 patients, RR = 1.02, 95% CI = 0.97–1.07).19,21–24,26–31,33 Specific data are presented in Figure 2.

No difference was also observed between patients treated with fosfomycin versus those treated with comparator(s) in the separate analyses, as well as in the comprehensive analysis regarding microbiological relapse (8 RCTs, 828 patients, RR = 0.84, 95% CI = 0.50–1.39)22–24,26,28,30,31,33 and microbiological re-infection (7 RCTs, 748 patients, RR = 1.26, 95% CI = 0.77–2.02).22,23,26,28,30,31,33

Trials involving non-pregnant male patients
No difference was observed regarding clinical success (3 RCTs, 286 patients, RR = 0.98, 95% CI = 0.87–1.11).35–37 No difference was also observed between patients treated with fosfomycin versus comparators regarding microbiological success (3 RCTs, 218 patients, RR = 1.01, 95% CI = 0.88–1.17).35–37 Data regarding the remaining effectiveness outcomes were not sufficient to perform a meta-analysis.

Trials involving pregnant patients
Data sufficient to perform a meta-analysis were provided only for microbiological success. Specifically, no difference was observed between patients treated with fosfomycin versus comparators (4 RCTs, 505 patients, RR = 1.00, 95% CI = 0.96–1.05).38,39,41,42

Trials involving paediatric patients
Data sufficient to perform a meta-analysis were provided only for microbiological success. Specifically, no difference was observed between patients treated with fosfomycin versus comparators regarding microbiological success (2 RCTs, 209 patients, RR = 0.98, 95% CI = 0.92–1.05).43,45

Sensitivity analyses
Regarding microbiological success, no difference was found between trials comparing single-dose fosfomycin regimens with single-dose comparator regimens and those comparing single-dose fosfomycin regimens with longer comparator regimens (7 RCTs, 964 patients, RR = 0.98, 95% CI = 0.91–1.05)23,30–32,35,41,45 versus 15 RCTs, 1728 patients, RR = 1.02, 95% CI = 0.99–1.05,19,21,22,24,26–29,31,33,41,42 respectively, P = 0.1 for the χ2 test for subgroup differences).

Only trials involving non-pregnant female patients were included in the second sensitivity analysis, since all of the trials included in the remaining subgroups did not have a blinded design. Specifically, no difference regarding clinical success was observed between trials with a double-blind design and the remaining trials (5 RCTs, 918 patients, RR = 1.01, 95% CI = 0.98–1.05,19,21,25,28,30 versus 4 RCTs, 707 patients, RR = 0.99, 95% CI = 0.96–1.03)24,26,29,31 respectively, P = 0.41 for the χ2 test for subgroup differences). Similarly, no difference regarding microbiological success was noted between trials with a double-blind design and the remaining trials (5 RCTs, 633 patients, RR = 1.01, 95% CI = 0.93–1.10)19,21,23,28,30 versus 7 RCTs, 979 patients, RR = 1.02, 95% CI = 0.94–1.1122,24,26,27,29,31,33 respectively, P = 0.71 for the χ2 test for subgroup differences). Specific data are shown in Figure 3.

Safety outcomes
Trials involving non-pregnant female patients
No difference was observed regarding the occurrence of adverse events in patients treated with fosfomycin versus those treated with comparator(s) either in the separate analyses or in the comprehensive analysis (13 RCTs, 2388 patients, RR = 1.25, 95% CI = 0.83–1.88)19,21–29,31–33.

No study withdrawals due to adverse events were observed either in the fosfomycin or comparator group in 11 of the 13 studies (involving a total of 1428 patients) included in the comprehensive analysis. In the remaining two trials patients were allocated to receive either fosfomycin or nitrofurantoin. No difference was observed with regard to the occurrence of study withdrawals due to adverse events (2 RCTs, 980 patients, RR = 2.01, 95% CI = 0.05–80.21).21,25

Trials involving non-pregnant female and male patients
No difference was observed regarding the occurrence of adverse events or study withdrawals due to adverse events in trials involving non-pregnant female and male patients (3 RCTs, 297
Figure 2. Microbiological success (eradication) in non-pregnant women with cystitis who were treated with fosfomycin compared with other antibiotic agents. Vertical line indicates no difference between the compared groups. Diamonds indicate pooled RRs (95% CI). Horizontal lines indicate 95% CIs. Squares indicate point estimates; the size of the squares indicates the weight that each individual study had in the meta-analysis.
patients, RR = 0.76, 95% CI = 0.29–1.96, and 3 RCTs, 297 patients, RR = 0.33, 95% CI = 0.03–3.08). Bar chart 5. Sensitivity analysis regarding microbiological success in double-blind versus single-blind/open-label trials involving non-pregnant female patients with cystitis who were treated with fosfomycin compared with other antibiotic agents. Vertical line indicates no difference between the compared groups. Diamonds indicate pooled RRs (95% CI). Horizontal lines indicate 95% CIs. Squares indicate point estimates; the size of the squares indicates the weight that each individual study had in the meta-analysis.

Trials involving pregnant patients

Adverse events occurred significantly less frequently in pregnant women treated with fosfomycin versus those treated with comparators (4 RCTs, 507 patients, RR = 0.35, 95% CI = 0.12–0.97). Specific data are presented in Figure 4. No study withdrawal due to adverse events occurred in either of the compared treatment groups in the three trials that provided relevant data. Bar chart 6. Systematic review

Trials involving paediatric patients

No adverse event occurred in either of the compared treatment groups in two of the three trials providing relevant data. Similarly, no study withdrawal due to adverse events occurred in either of the compared treatment groups in the three trials involving paediatric patients.

Discussion

The main finding of our meta-analysis is that a single-dose oral fosfomycin treatment was equal to the comparator regimens in terms of clinical effectiveness in non-pregnant female patients and mixed populations (non-pregnant female and male patients) of older ages with cystitis. This finding was consistent regarding microbiological effectiveness for the above-mentioned subpopulations, as well as for pregnant and paediatric patients. Fosfomycin also appears to have a comparable safety profile with the evaluated comparators in non-pregnant female, mixed populations of older age, and paediatric patients, whereas it was associated with significantly fewer adverse events in pregnant patients. Yet no difference was observed between fosfomycin and comparators regarding the severity
of adverse events, as inferred from study withdrawals due to adverse events, regarding all the evaluated subpopulations. Of note, study withdrawals due to adverse events were only noted in 4 of the 27 included trials. As opposed to our findings, a relevant previous meta-analysis and practice guideline regarding the treatment of cystitis, based on the evaluation of only three trials, reported that single-dose fosfomycin treatment is associated with inferior microbiological success when compared with a 5 day treatment with pipemidic acid, whereas no difference was found in the analysis of two trials involving a limited number of patients that compared a single dose of fosfomycin with a ≥5 day course of norfloxacin. In one of these three trials, fosfomycin treatment was also associated with significantly more adverse events. Yet our meta-analysis, pooling data from 27 relevant trials, contributes considerably to the clarification of the effectiveness and safety issues of fosfomycin treatment for cystitis.

Fosfomycin is an old, broad-spectrum antibiotic with pharmacokinetic and pharmacodynamic aspects that favour its use for the treatment of UTIs. Specifically, after a single 3 g oral dose of fosfomycin tromethamine, peak urine concentrations (above the minimal inhibitory concentrations of the common uropathogens) are achieved within 4 h and persist for 48 h. In addition, fosfomycin in combination with fluoroquinolones seems to have good in vitro antimicrobial activity against the P. aeruginosa biofilms that complicate UTIs. Fosfomycin alone or in combination with N-acetylcysteine is also reported to have the ability to reduce the viability of sessile cells as well as to disrupt the formation of biofilms by uropathogenic E. coli.

The aim of the antibiotic treatment of uncomplicated UTIs, apart from the resolution of symptoms, is the achievement of microbiological eradication and the prevention of microbiological relapse or re-infection. Short courses, including 3 day courses of co-trimoxazole and 5 day courses of fluoroquinolones, have been used for the treatment of uncomplicated UTIs. Yet the reported resistance rates of uropathogens for these agents in many clinical settings are alarmingly high. Single-dose antibiotic regimens are expected to be associated with enhanced compliance, lower cost and possibly fewer adverse events, in comparison with longer antibiotic regimens. Yet considerations regarding the achievement of microbiological eradication as well as the emergence of microbiological relapse or re-infection may arise. However, in our meta-analysis, single-dose fosfomycin treatment was found to be equally effective with the compared treatment regimens in regard to the above-mentioned outcomes. Additionally, in the subgroup analysis comparing single-dose fosfomycin treatment with single-dose treatment with other antibiotics, fosfomycin was not inferior to the comparators (including fluoroquinolones, trimethoprim and co-trimoxazole). Another potential drawback that may be associated with fosfomycin treatment is the emergence of resistance. This issue was evaluated in a limited number of trials included in our meta-analysis. Specifically, this issue was addressed in 5 of the 27 included trials (evaluating a sufficient number of microbial strains); one was rather recent (published in 2005), whereas the other trials were older (published between 1987 and 1998). No emergence of uropathogens resistant to fosfomycin was observed in these five studies.

According to our findings, fosfomycin also appeared to have a safety profile equal to that of the comparators in non-pregnant female patients and mixed populations of older age and paediatric patients. The severity of the reported adverse events, as indicated by study withdrawals due to adverse events, was also comparable. Notably, a single-dose oral fosfomycin regimen was associated with fewer adverse events compared with longer comparator regimens in pregnant women with cystitis or asymptomatic bacteriuria. However, one may consider that longer treatment regimens are expected to be associated with more adverse events in comparison with shorter regimens. Yet, fosfomycin tromethamine may provide a useful alternative option to β-lactams for the treatment of UTIs, as the use of quinolones and sulfamethoxazole is avoided in pregnant women. Additionally, treatment of asymptomatic bacteriuria in pregnancy is reported to reduce the risk of development of pyelonephritis and prevents adverse fetal outcomes such as premature labour and low birth weight. Fosfomycin had been assigned by the FDA to pregnancy category B. In addition, the pharmacokinetic aspects of fosfomycin in pregnant patients appear to be similar to those in non-pregnant patients. These aspects, along with the favourable safety profile, make fosfomycin a valuable treatment option for asymptomatic bacteriuria and cystitis in pregnant women.

### Figure 4
Adverse events in pregnant women with asymptomatic bacteriuria/cystitis who were treated with fosfomycin compared with other antibiotic agents. Vertical line indicates no difference between the compared groups. Diamond shapes indicate pooled RRs (95% CI). Horizontal line indicates 95% CIs. Squares indicate point estimates; the size of the squares indicates the weight that each individual study had in the meta-analysis.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fosfomycin</th>
<th>Comparators</th>
<th>Risk ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinner, 1990</td>
<td>14 (54.9%)</td>
<td>20 (59.2%)</td>
<td>0.63 [0.33, 1.20]</td>
<td>1990</td>
</tr>
<tr>
<td>Thoumsin et al, 1990</td>
<td>0 (11.0%)</td>
<td>3 (10.0%)</td>
<td>0.11 [0.01, 1.95]</td>
<td>1990</td>
</tr>
<tr>
<td>Bayrak et al, 2005</td>
<td>1 (15.0%)</td>
<td>4 (13.0%)</td>
<td>0.45 [0.04, 4.82]</td>
<td>2005</td>
</tr>
<tr>
<td>Estebanez et al, 2009</td>
<td>1 (19.1%)</td>
<td>11 (19.1%)</td>
<td>0.10 [0.01, 0.72]</td>
<td>2009</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>263 (100.0%)</td>
<td>244 (100.0%)</td>
<td>0.35 [0.12, 0.97]</td>
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</table>

### Table 9
Test for overall effect: Z = 2.01 (P = 0.04)
Regarding paediatric populations, fosfomycin may also play an important role in the treatment of UTIs since fluoroquinolones are restricted. Moreover, a single-dose treatment with fosfomycin may provide the advantage of ambulatory care in children with UTIs, as ambulatory treatment by using short-term, intravenous antibiotic therapy in infants with febrile UTIs has been recommended.\(^5\)

Our meta-analysis has limitations that should be taken into consideration in the evaluation of its findings. Firstly, considerable heterogeneity regarding the types of antibiotics used, the treatment durations and the clinical settings was observed among the included trials. Heterogeneity regarding the patient populations was also observed. In this regard, relevant subgroup analyses were performed in order to cope with this source of heterogeneity. In addition, the majority of the included trials focused mainly on microbiological, as opposed to clinical, outcomes of cystitis. Notably, more severe outcomes such as the development of pyelonephritis were also inadequately assessed by the included trials. Specifically, only one study involving pregnant patients reported that no difference was observed between the compared treatment groups regarding the development of pyelonephritis.\(^21\) Moreover, the majority of the included trials were old (published between 1987 and 1999). This might raise considerations regarding the antibiotic resistance of uropathogens, which is often observed in today’s clinical practice, a fact that may possibly compromise the extrapolation of the findings of our meta-analysis to today’s clinical practice. However, recently published studies indicate that fosfomycin exhibits considerably high antimicrobial activity against contemporary uropathogens,\(^22\) including those with ESBLs.\(^5\)

Furthermore, detailed data regarding the method of recording who performed the assessment of the evaluated adverse events were scarcely reported in the included trials, a fact that may have potentially influenced our findings. Specifically, the majority of the included trials reported on an overall incidence of adverse events that were mostly mild adverse events of gastrointestinal origin. Indeed, the severity of adverse events, as inferred from the evaluation of study withdrawals due to adverse events, was low. These findings are in accordance with post-marketing studies suggesting that fosfomycin is associated with adverse events of mild severity, whereas serious adverse events are rare.\(^5,25\)

Additionally, a considerable number of the included trials did not have a blinded design and consequently had a low Jadad score (specifically, 10 of the 27 included trials had a Jadad score >2 and were considered as trials of adequate quality). Notably, all of the trials involving mixed populations of non-pregnant female and male patients, pregnant patients and paediatric patients did not have a blinded design. Regarding the subgroup of trials involving non-pregnant female patients, microbiological success was evaluated in a sensitivity analysis but no significant difference between the trials with a blinded design and the remaining trials was found. Information regarding allocation concealment was also inadequately reported. Thus selection bias might have influenced our findings.

In conclusion, in the current era of alarmingly high antibiotic resistance rates, fosfomycin, specifically a single-dose oral treatment with fosfomycin tromethamine, may play an important role in the treatment of cystitis, not only in non-pregnant women but also in pregnant women and elderly and paediatric patients.

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**Transparency declarations**

None to declare.

**Supplementary data**

Table S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

**References**

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