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Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women
A Randomized Clinical Trial

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IMPORTANCE The use of nitrofurantoin and fosfomycin has increased since guidelines began recommending them as first-line therapy for lower urinary tract infection (UTI).

OBJECTIVE To compare the clinical and microbiologic efficacy of nitrofurantoin and fosfomycin in women with uncomplicated cystitis.

DESIGN, SETTING, AND PARTICIPANTS Multinational, open-label, analyst-blinded, randomized clinical trial including 513 nonpregnant women aged 18 years and older with symptoms of lower UTI (dysuria, urgency, frequency, or suprapubic tenderness), a positive urine dipstick result (with detection of nitrites or leukocyte esterase), and no known colonization or previous infection with uropathogens resistant to the study antibiotics. Recruitment took place from October 2013 through April 2017 at hospital units and outpatient clinics in Geneva, Switzerland; Lodz, Poland; and Petah-Tiqva, Israel.

INTERVENTIONS Participants were randomized in a 1:1 ratio to oral nitrofurantoin, 100 mg 3 times a day for 5 days (n = 255), or a single 3-g dose of oral fosfomycin (n = 258). They returned 14 and 28 days after therapy completion for clinical evaluation and urine culture collection.

MAIN OUTCOMES AND MEASURES The primary outcome was clinical response in the 28 days following therapy completion, defined as clinical resolution (complete resolution of symptoms and signs of UTI without prior failure), failure (need for additional or change in antibiotic treatment due to UTI or discontinuation due to lack of efficacy), or indeterminate (persistence of symptoms without objective evidence of infection). Secondary outcomes included bacteriologic response and incidence of adverse events.

RESULTS Among 513 patients who were randomized (median age, 44 years [interquartile range, 31-64]), 475 (93%) completed the trial and 377 (73%) had a confirmed positive baseline culture. Clinical resolution through day 28 was achieved in 171 of 244 patients (70%) receiving nitrofurantoin vs 139 of 241 patients (58%) receiving fosfomycin (difference, 12% [95% CI, 4%-21%]; $P = .004$). Microbiologic resolution occurred in 129 of 175 (74%) vs 103 of 163 (63%), respectively (difference, 11% [95% CI, 1%-20%]; $P = .04$). Adverse events were few and primarily gastrointestinal; the most common were nausea and diarrhea (7/248 [3%] and 3/248 [1%] in the nitrofurantoin group vs 5/247 [2%] and 5/247 [1%] in the fosfomycin group, respectively).

CONCLUSIONS AND RELEVANCE Among women with uncomplicated UTI, 5-day nitrofurantoin, compared with single-dose fosfomycin, resulted in a significantly greater likelihood of clinical and microbiologic resolution at 28 days after therapy completion.

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Supplemental content

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Given increasing antimicrobial resistance, guidelines for the treatment of uncomplicated lower urinary tract infections (UTIs) were modified in 2010 to recommend nitrofurantoin and fosfomycin as first-line agents[1]; their use has since increased exponentially.[2] These antibiotics were commercialized in 1953 and 1971, respectively, in an era of less-stringent methodologic standards for drug testing and results reporting, which required neither randomization nor intention-to-treat (ITT) analyses. Thus, uncertainties regarding clinical efficacy persist, particularly for single-dose fosfomycin. While meta-analyses of randomized clinical trials evaluating nitrofurantoin for lower UTI suggest efficacy comparable with that of newer agents, such as fluoroquinolones,[3,4] the same has not been observed for fosfomycin. In a randomized clinical trial conducted in the 1990s that, to our knowledge, has not yet been published (PubMed database searched on February 25, 2018), the efficacy rate for fosfomycin was 70% compared with rates of 96% and 94% for ciprofloxacin and trimethoprim/sulfamethoxazole, respectively.[5]

There may be a microbiologic and pharmacologic basis for decreased efficacy. Mechanisms of resistance to fosfomycin, some of which are plasmid encoded, were described soon after the drug's approval in Europe.[6] While reported *Escherichia coli* resistance rates have been low,[7] most data were collected before the shift to its widespread use in 2011. In communities using fosfomycin regularly, significant increases in resistance have been observed, as demonstrated in Spain in 2008.[8] The single-dose regimen may be insufficient[1,5] for effective bactericidal activity given the drug's at least partially time-dependent killing[9,10] and the high interindividual variability observed in urinary concentrations.[11]

Thus far, nitrofurantoin and fosfomycin have been compared in few randomized clinical trials.[12,13] The purpose of this study was to assess the comparative efficacy of 5-day nitrofurantoin and single-dose fosfomycin for clinical resolution of uncomplicated UTI.

Key Points

Question What is the effect of 5-day nitrofurantoin, compared with single-dose fosfomycin, on clinical resolution of uncomplicated lower urinary tract infection (UTI) in women?

Findings In this randomized clinical trial that included 513 women with uncomplicated UTI, clinical resolution at 28 days occurred in 70% of patients in the nitrofurantoin group vs 58% of patients in the fosfomycin group, a statistically significant difference.

Meaning Five-day nitrofurantoin may be a better alternative to single-dose fosfomycin for treating uncomplicated UTI in women.

Methods

Study Design and Population

This open-label/analyst-blinded, multicenter, randomized clinical trial was conducted from October 2013 to May 2017 at 3 sites (Geneva, Switzerland; Lodz, Poland; and Petah-Tiqva, Israel) and included adult women aged 18 years and older presenting with at least 1 symptom of acute lower UTI (dysuria, urgency, frequency, or suprapubic tenderness) and a urine dipstick test result positive for either nitrites or leukocyte esterase.[14] The statistical analysis plan and full trial protocol are available in Supplement 1 and Supplement 2, respectively. Main exclusion criteria were pregnancy and lactation; suspected upper UTI (presence of fever, chills, or flank pain); antibiotic use or any symptoms consistent with UTI in the preceding 4 weeks; indwelling urinary catheter or otherwise complicated UTI; immunosuppression (untreated infection with HIV, ongoing chemotherapy or radiation therapy, use of high-dose corticosteroids or other immunosuppressive medication); and renal insufficiency (creatinine clearance <30 mL/min). Additional exclusion criteria and definitions are available in the eAppendix in Supplement 3.

Both hospitalized and ambulatory patients were recruited, with the former hospitalized for other medical reasons and recruited on development of urinary symptoms, and the latter attending walk-in clinics or their primary care physicians' offices due to their symptoms. The study was reviewed and approved by the independent ethics committees of each site and by the Swiss Agency for Therapeutic Products (2013DR4095). All participants provided written informed consent before their inclusion.

Randomization

The randomization sequence was computer-generated and used randomly permuted blocks of 4 to 12 allocations within site. Assignments were concealed from study investigators via opaque sealed envelopes until patient enrollment, and allocated treatment to either nitrofurantoin or fosfomycin in a 1:1 ratio.

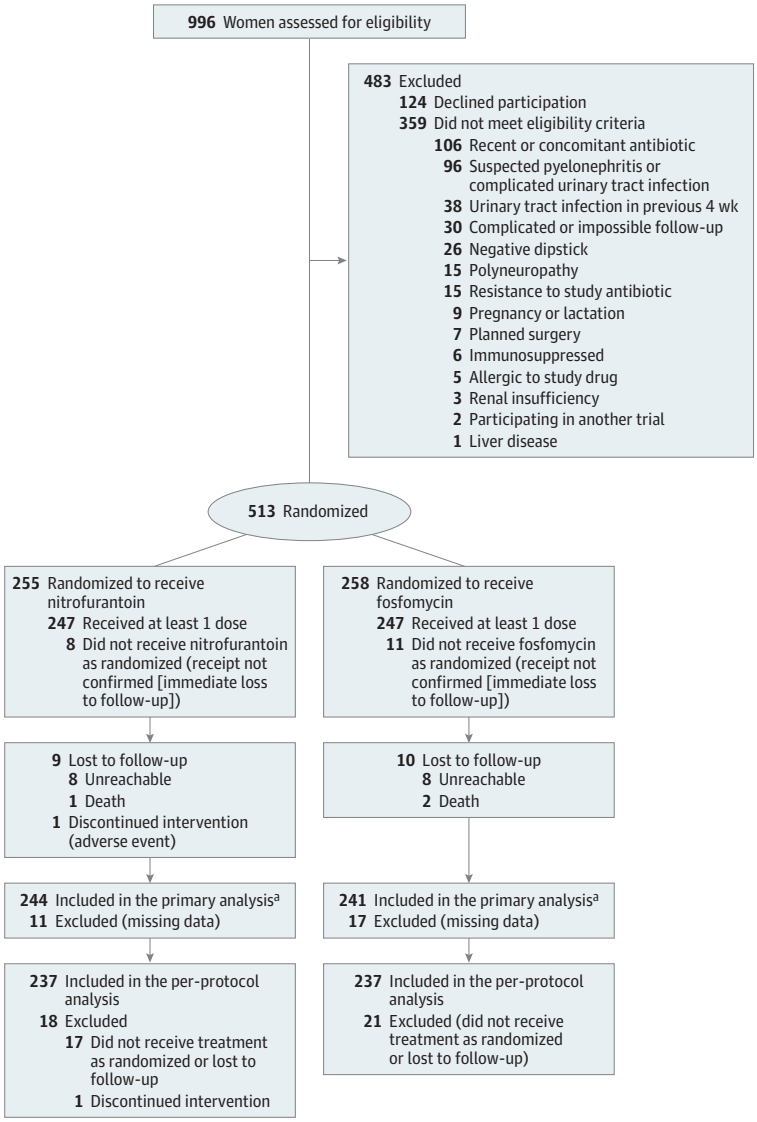
Intervention and Procedures

Participants were randomly assigned to either oral macrocrystalline nitrofurantoin, 100 mg 3 times a day for 5 days (the most commonly recommended regimen in Europe; eAppendix in Supplement 3) or a single 3-g dose of oral fosfomycin tromethamine and instructed to contact study investigators in the absence of clinical improvement. They attended 2 follow-up visits at 14 (±2) and 28 (±7) days after completion of antibiotic therapy; urine cultures were collected at all scheduled and unscheduled visits. Because of fosfomycin's purported long half-life,[15] antibiotic therapy was considered completed in both groups on day 5 after randomization.

Outcomes and Definitions

The primary outcome was clinical response in the 28 (±7) days following completion of therapy, defined as clinical resolution (complete resolution of symptoms and signs of UTI without prior failure), failure (need for additional or change in antibiotic treatment due to a UTI or discontinuation due to lack of efficacy), or indeterminate (either persistence of symptoms without objective evidence of infection

Figure. Study Flowchart of the Nitrofurantoin and Fosfomycin Groups



Both the intention-to-treat and per-protocol populations were analyzed. The intention-to-treat population included all patients randomized and the per-protocol population, those with at least 80% medication adherence, no major protocol deviations, and available primary outcome data.

[a] Data on the primary outcome were available for 244 of 255 patients (96%) randomized to nitrofurantoin and 241 of 258 patients (93%) randomized to fosfomycin; 7 and 4 patients in these groups, respectively, had clinical failure before being lost to follow-up. The only major protocol deviation documented in either group was nonadherence to the study antibiotic.

or any extenuating circumstances precluding a classification of clinical resolution or failure). Clinical resolution was thus a lack of prior failure with complete resolution of symptoms at the date of the examination, indeterminate response was a lack of prior failure yet with persistence of symptoms without objective evidence of infection, and clinical failure at any time point was carried through to the end of the study.

A secondary outcome was bacteriologic response at 14 (±2) and 28 (±7) days after therapy completion, defined as resolution (eradication of the infecting strain with no recurrence of bacteriuria [$<10^3$ colony-forming units {cfu}/mL] during follow-up) or failure (bacteriuria $\geq 10^3$ cfu/mL with the infecting strain). Other secondary outcomes included clinical response at 14 (±2) days after therapy completion, duration of symptoms after treatment initiation, incidence of progression to pyelonephritis or urosepsis, lost days of work due to hospital admission, incidence of adverse events (considered possibly, probably, or certainly related to the study antibiotic) throughout the study period, incidence of confirmed UTI at baseline, incidence of baseline resistance to either study antibiotic and other UTI-targeted antibiotics, and emergence of phenotypic bacterial resistance throughout the study period.

Confirmed UTI required the presence of at least 1 of the 4 urinary symptoms required for inclusion and a positive urine culture ($\geq 10^3$ cfu/mL).[14] Positive cultures could be mixed (containing >1 uropathogen); laboratory reporting of culture growth is further detailed in the online supplement, as are other definitions (eAppendix in Supplement 3).

Women deemed at increased risk for carriage of resistant bacteria had at least 1 of the following: systemic antibiotic exposure (≥1 dose) or hospitalization in an acute or long-term care center in the previous 12 months, UTI fulfilling

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic by Site	Nitrofurantoin (n = 255)	Fosfomycin (n = 258)
Age, median (IQR) [range], y	43 (31-63) [18-101]	46 (31-66) [18-93]
Geneva	43 (31-58) [18-101]	37 (26-54) [18-91]
Lodz	51 (33-65) [19-90]	58 (40-68) [18-88]
Petah-Tiqva	37 (27-59) [18-83]	42 (30-60) [19-93]
Outpatient at the time of inclusion, No. (%)	237 (93)	238 (92)
Geneva	77 (82)	74 (80)
Lodz	98 (100)	102 (100)
Petah-Tiqva	62 (98)	62 (97)
No. of symptoms, median (IQR)[a]	3 (2-4)	3 (2-4)
Geneva	3 (2-4)	3 (2-4)
Lodz	3 (2-4)	3 (2-4)
Petah-Tiqva	4 (3-5)	4 (3-5)
Urine culture positive at inclusion, No. (%)[b]	194 (76)	183 (71)
Geneva	88 (94)	81 (91)
Lodz	68 (70)	68 (68)
Petah-Tiqva	38 (73)	34 (62)
At risk for resistant organisms, No. (%)[c]	220 (86)	232 (90)
Geneva	60 (65)	68 (74)
Lodz	97 (99)	100 (98)
Petah-Tiqva	63 (100)	64 (100)
Antibiotic therapy for any reason in the past year, No. (%)	131 (51)	137 (53)
Geneva	31 (33)	39 (42)
Lodz	97 (99)	95 (93)
Petah-Tiqva	3 (5)	3 (5)
Any previous UTI, No. (%)[d]	41 (16)	43 (17)
Geneva	9 (10)	20 (21)
Lodz	6 (6)	8 (9)
Petah-Tiqva	26 (41)	15 (23)

Abbreviations: IQR, interquartile range; UTI, urinary tract infection.

[a] A total of 9 symptoms were assessed; they included at least 1 of the following: dysuria, frequency, urgency, or suprapubic tenderness; and they may have additionally included flank and/or lower back pain, nausea, subjective fever, or a subjective feeling of chills.

[b] Positive culture was defined as the growth of 10^3 colony-forming unites/mL or more of at least 1 uropathogen; laboratory reporting of culture growth is described in detail in the eAppendix in Supplement 3. All patients were symptomatic at baseline, thus those with a positive culture had confirmed UTI.

[c] Systemic antibiotic exposure (≥1 dose) or hospitalization in an acute or long-term care center in the previous 12 months, UTI fulfilling criteria for health care–associated infection, recent (in the preceding 12 months) carriage of resistant organisms, or stay of at least 1 month in a high-risk country (any country in the Mediterranean basin excluding France, South or Southeast Asia, the Middle East, Africa, and Central or South America).

[d] Self-reported.

criteria for health care–associated infection,[16] recent (in the preceding 12 months) carriage of resistant organisms, or stay of at least 1 month in a high-risk country (any country in the Mediterranean basin excluding France, South or Southeast Asia, the Middle East, Africa, and Central or South America).

Laboratory Methods

Voided midstream urine specimens were collected in sterile containers and transported within 24 hours to each site's central laboratory, where specimens were cultured according to published recommendations.[17] Cultures were reported to be positive when 10^3 cfu/mL or more of at least 1 bacterium was detected (see the eAppendix in Supplement 3 for more details). Resistances were determined in Poland and Israel via Clinical and Laboratory Standards Institute[18] and in Switzerland via European Committee on Antimicrobial Susceptibility Testing[19] break points.

Statistical Methods

Sample Size

The sample size calculation was driven by a superiority hypothesis based on previously reported clinical response rates with nitrofurantoin and fosfomycin of 90% and 80%, respectively.[12,20,21] Assuming these rates and attrition of roughly 12%, 300 participants per group were necessary to show clinical superiority by 10% or more of nitrofurantoin with 90% power and 5% 2-sided significance in the treatment of this common infection. Delays in study launch and limited budgets curtailed the planned recruitment period, which was thus closed when 513 patients were enrolled, ensuring 80% power. A minimal clinically important difference of 10% was chosen in line with guidance provided by the Infectious Disease Society of America[22] and given previous studies' findings suggesting at least a 10% difference in clinical resolution between treatment groups.[12,20,21]

Study Populations

The ITT population consisted of all patients randomized to either study antibiotic and the per-protocol population of those who took the study antibiotic with at least 80% adherence and for whom no major protocol deviations were documented. There were no significant differences between the ITT and per-protocol populations in outcomes (eAppendix in Supplement 3); unless otherwise specified, ITT results are reported.

Analyses

Analyses were performed with blinding to treatment allocation. Baseline characteristics are described by frequencies, medians, and interquartile ranges (IQRs). The incidence of clinical and bacteriologic resolution was compared between treatment groups using the χ^2 test; incidence of adverse events and other outcome measures with events numbering less than 10 were compared using the Fisher exact test. Patients who had documented clinical failure and were then lost to follow-up were included in the primary outcome analysis of any failure by day 28, while those whose response status was unknown before dropout were considered missing; missing values were excluded from the primary analysis.

Post-hoc analyses were performed to quantify the potential of missing data for primary outcomes only: multiple imputation for missing at random was used,[23] with M = 20 imputations and adjustment of the imputation model for

site, age, number of urinary symptoms and signs, previous antibiotic use, and any previous UTI. Sensitivity analyses were conducted with worst- and best-case scenarios, indeterminate clinical responses treated alternatively as failures, or, among those with improvement, successes, and using the rctmiss command in Stata for missing-not-at-random assumptions. Post-hoc analyses were also conducted to evaluate clinical and microbiologic response among patients with confirmed *E coli* infections. Bivariable regression models were constructed to assess associations between clinical failure and baseline demographic, clinical, and microbiologic characteristics.

Post-hoc mixed effects logistic regression models were constructed to take into account potential site variability on the intercept of the model in this multicenter trial. An interaction term between the treatment effect and *E coli* baseline positivity was introduced to assess differences in treatment effects in patients with and without *E coli* infections. Statistical tests were 2-sided with a significance level of .05. Because there was no adjustment for multiple comparisons, secondary end point analyses should be interpreted as exploratory. All analyses were performed using Stata (StataCorp).

Results

Study Population

Of 996 patients screened, 513 were enrolled and randomized, 255 to nitrofurantoin and 258 to fosfomycin (ITT population; **Figure**). Within the ITT population, receipt of the study intervention was confirmed among 494 women (96%), with thereafter 20 patients lost to follow-up, so that ultimately 474 (92%) composed the per-protocol population.

Baseline Demographics

The median age was 44 years (IQR, 31-64; **Table 1**). Baseline characteristics were similar by treatment group. Women in Lodz tended to be older and to have taken antibiotics more frequently in the year prior to inclusion as compared with those in Geneva and Petah-Tiqva. Nearly 90% of all women were at risk for resistant organisms, more than half of them due at least in part to the consumption of antibiotics in the previous year.

Baseline Urine Cultures

Of the 487 baseline urine cultures obtained, 377 (77%) were positive (**Table 2**; eTable 1 in Supplement 3). Among these, *E coli* (230/377 [61%]), *Klebsiella* spp (27/377 [7%]), *Enterococcus* spp (27/377 [7%]), and *Proteus* spp (17/377 [5%]) predominated. There were no significant differences in epidemiology in the 2 treatment groups; baseline antibiotic resistance among *E coli* isolates in Petah-Tiqva was increased but differences were not statistically significant. Patients randomized there had higher rates of *E coli* either producing extended-spectrum beta-lactamase (3/25 [12%] vs 4/112 [4%] and 2/93 [2%] in Geneva and Lodz, respectively) and/or fluoroquinolone resistance (5/25 [20%] vs 13/112 [12%] and 9/93 [10%]). Yet only in Lodz, Poland (where nitrofuran derivatives are sold over the counter[24]), was baseline resistance among *E coli* isolates to nitrofurantoin detected (6/93 [7%]; $P = .004$). The Lodz site also had the study's only *E coli* strain resistant to fosfomycin at baseline (1/93 [1%]). Conversely, only in Geneva was any baseline resistance to study drugs detected among *Klebsiella* spp, with 3 of 10 (30%) and 2 of 10 (20%) strains resistant to nitrofurantoin and fosfomycin, respectively.

Table 2. Baseline Urinary Isolates and Their Susceptibilities by Treatment Allocation

	No. (%)	
	Nitrofurantoin (n = 255)	Fosfomycin (n = 258)
Baseline cultures obtained	243 (95)	244 (95)
Positive cultures[a]	194 (80)	183 (75)
Escherichia coli[b]	111 (57)	119 (65)
Nitrofurantoin resistant	2 (1)	4 (3)
Fosfomycin resistant	0 (0)	1 (1)
Co-trimoxazole resistant	26 (23)	25 (21)
Fluoroquinolone resistant	13 (12)	14 (12)
Extended-spectrum beta-lactamase	7 (6)	2 (1)
Klebsiella spp[b]	20 (10)	7 (4)
Nitrofurantoin resistant	3 (15)	0 (0)
Fosfomycin resistant	2 (10)	0 (0)
Co-trimoxazole resistant	4 (20)	2 (29)
Fluoroquinolone resistant	1 (5)	1 (14)
Extended-spectrum beta-lactamase	2 (10)	1 (14)
Proteus spp[b]	7 (4)	10 (5)
Nitrofurantoin resistant	6 (86)	9 (90)
Fosfomycin resistant	0 (0)	2 (20)
Co-trimoxazole resistant	3 (42)	2 (20)
Fluoroquinolone resistant	2 (29)	0 (0)
Extended-spectrum beta-lactamase	0 (0)	0 (0)
Enterococcus spp[b]	13 (7)	14 (7)
Group B *Streptococcus*[b]	7 (4)	6 (3)
Enterobacter spp[b]	5 (3)	4 (2)
Mixed flora[b]	51 (26)	40 (21)
Other[b,c]	10 (5)	7 (4)

[a] Positive culture was defined as the growth of 10^3 colony-forming units/mL or more of at least 1 uropathogen; laboratory reporting of culture growth is described in detail in the eAppendix in Supplement 3. All patients were symptomatic at baseline, thus those with a positive culture had confirmed urinary tract infection. Patients with mixed flora at baseline could not be analyzed for microbiologic outcomes.

[b] Some cultures had polymicrobial growth.

[c] *Citrobacter koseri*, *Morganella* spp, *Staphylococcus aureus*, *Staphylococcus saprophyticus*, and *Streptococcus anginosus*.

Clinical Outcomes

Clinical Response

At 28 days after therapy completion, 171 of 244 patients (70%) receiving nitrofurantoin had maintained clinical resolution vs 139 of 241 (58%) receiving fosfomycin (difference, 12% [95% CI, 4%-21%]; $P = .004$; **Table 3**). Data were missing for 28 randomized patients (6%), and 15 patients (3%) completing follow-up had "indeterminate" clinical response.

Table 3. Clinical and Microbiologic Outcomes

Clinical and Bacteriologic Outcome	No./Total No. (%) Nitrofurantoin (n = 255)	Fosfomycin (n = 258)	Difference, % (95% CI)	*P* Value[a]
Primary Outcome				
Clinical response at 28 d[b]				
Clinical resolution	171/244 (70)	139/241 (58)	12 (4-21)	.004
Clinical failure	66/244 (27)	94/241 (39)		
Indeterminate	7/244 (3)	8/241 (3)		
Missing[c]	11 (4)	17 (7)		
Secondary Outcomes				
Clinical response at 14 d				
Clinical resolution	184/247 (75)	162/247 (66)	9 (1-17)	.03
Clinical failure	56/247 (23)	75/247 (30)		
Indeterminate	7/247 (3)	10/247 (4)		
Missing[c]	8 (3)	11 (4)		
Microbiologic response at 28 d[b]				
Culture obtained/baseline culture positive	175/194 (90)	163/183 (89)		
Bacteriologic success through 28 d	129/175 (74)	103/163 (63)	11 (1-20)	.04
Bacteriologic success failure by 28 d	46/175 (26)	60/163 (37)		
Microbiologic response at 14 d				
Culture obtained/baseline culture positive	177/194 (91)	165/183 (90)		
Bacteriologic success through 14 d	146/177 (82)	121/165 (73)	9 (0.4-18)	.04
Bacteriologic success failure by 14 d	31/177 (18)	44/165 (27)		

[a] Calculated using χ^2_1 test.

[b] Clinical response was defined as clinical resolution (complete resolution of symptoms and signs of urinary tract infection without prior failure), failure (need for additional or change in, antibiotic treatment due to a urinary tract infection, or discontinuation due to lack of efficacy), or indeterminate (either persistence of symptoms without objective evidence of infection or any extenuating circumstances precluding a classification of clinical resolution/failure). Microbiologic response was defined as resolution (eradication of the infecting strain with no recurrence of bacteriuria [$<10^3$ colony-forming units/mL] during follow-up) or failure (bacteriuria $\geq 10^3$ colony-forming units/mL with the infecting strain).

[c] Number of patients with missing data on this outcome measure and thus not included in this analysis (see eTables 2 and 3 in Supplement 3 for multiple imputation and sensitivity analyses for missing data).

Post-hoc multiple imputation and sensitivity analyses for both missing data (worst- and best-case scenarios, missing not at random) and indeterminate responses (treated alternatively as failures or, among those with some clinical improvement, successes) confirmed the robustness of this outcome in all scenarios (eTables 2-5 and eFigure in Supplement 3). Mixed effects models with site as a random effect provided an odds ratio for failure by day 28 after fosfomycin therapy of 1.76 (95% CI, 1.19-2.60; *P* = .004).

Clinical response at the earlier point of 14 days after therapy completion also differed significantly between groups, with 184 of 247 patients (75%) receiving nitrofurantoin experiencing clinical resolution vs 162 of 247 (66%) receiving fosfomycin (difference, 9% [95% CI, 1%-17%]; *P* = .03; Table 3). Patients in either treatment group with early clinical failure (due to persistence of symptoms rather than recurrence after initial improvement) returned for additional antibiotic therapy at the same point after inclusion (mean [SD] of 6.3 [3.8] and 6.5 [3.6] days in the nitrofurantoin and fosfomycin groups, respectively).

In post-hoc analyses of the subgroup of patients with *E coli* infections, the difference in clinical response between treatment groups was more pronounced: through day 28, 80 of 103 (78%) vs 55 of 111 (50%) patients in the nitrofurantoin and fosfomycin groups, respectively, had clinical success (difference, 28% [95% CI, 15%-40%]; *P* < .001); there were 4 and 2 indeterminate outcomes, respectively (eTables 6 and 7 in Supplement 3). The test of interaction was significant (*P* < .001) when comparing treatment effect sizes in patients with *E coli* infections vs those without (odds ratios for failure after fosfomycin therapy: 4.48 [95% CI, 1.99-10.10] and 0.92 [95% CI 0.55-1.54], respectively).

Duration of Symptoms

The median duration of initial symptoms was 1 day longer in women receiving nitrofurantoin (4 days [IQR, 2-14] vs 3 days [IQR, 2-14]; *P* = .30).

Pyelonephritis and Other Morbidities

The development of pyelonephritis was rare. It occurred in 1 of 246 (0.4%) and 5 of 247 (2%) women in the nitrofurantoin and fosfomycin groups, respectively (difference, 1.6% [95% CI, −0.5% to 4.2%]; *P* = .22). There were no urosepsis events, and no lost days of work due to hospital admission (5/7 patients with pyelonephritis were retired; the remaining 2 were treated as outpatients).

Adverse Events

Adverse events were reported relatively infrequently and occurred with similar proportions in both treatment groups (eTable 8 in Supplement 3). Among patients with follow-up of at least 1 week following randomization, 21 of 248 (8%) and 16 of 247 (6%) in the nitrofurantoin and fosfomycin groups, respectively, reported at least 1 event. All events occurring with 1% or more frequency were gastrointestinal in nature and were of mild or moderate intensity (eTable 8 in

Supplement 3). Six serious adverse events (eAppendix in Supplement 3) occurred within the study period; none were deemed related to the study antibiotic or the UTI at inclusion.

Bacteriologic Outcomes

Bacteriologic Success

As with clinical response, patients receiving nitrofurantoin had significantly more bacteriologic success: among those with positive baseline cultures, 146 of 177 (82%) and 121 of 165 (73%) saw no recurrence on day 14 in the nitrofurantoin and fosfomycin groups, respectively (P = .04; Table 3). The difference remained at day 28, when both groups saw an overall decrease in success, with 129 of 175 (74%) and 103 of 163 (63%), respectively (difference, 11% [95% CI, 1%-20%]; P = .04).

Again in post-hoc analyses restricted to patients with *E coli* infections, the difference was wider, with the nitrofurantoin group achieving 72% bacteriologic success (71/98) vs a rate of 58% in the fosfomycin group (63/109) (difference, 14% [95% CI, 2%-27%]; P = .03) by day 28 (eTable 7 in Supplement 3).

Emergence of Resistance Among Patients With Bacteriologic Recurrence

Within 14 days after nitrofurantoin therapy, 1 of 109 patients (1%) with initially nitrofurantoin-susceptible *E coli* had recurrence with a newly nitrofurantoin-resistant strain and by day 28, another saw recurrence of an *E coli* strain with new intermediate resistance. Neither experienced clinical failure, and the first was treated with fosfomycin. Her recurrent strain was also resistant to fosfomycin, but the initial strain's susceptibility to this antibiotic was not tested. No emergence of resistance to fosfomycin could be documented.

Discussion

Among women with uncomplicated UTI, a 5-day course of nitrofurantoin compared with single-dose fosfomycin resulted in a significantly greater likelihood of clinical and microbiologic resolution at 28 days after therapy completion.

A purely clinical response was chosen as the primary outcome because it is the most meaningful to patients and, by extension, determines further medical pathways (ie, additional medical encounters with or without further laboratory work-up or additional antibiotic consumption). The use of a composite primary outcome incorporating both clinical and microbiologic responses would have excluded all patients without an available positive culture at baseline (up to 30% of patients in earlier studies,[25] and 27% of randomized patients in this one).

In earlier nondynamic studies (which do not assess potential bacterial regrowth over time), fosfomycin was reported to possess high levels of in vitro activity against *E coli* and other uropathogens,[7] yet in this trial's post-hoc analysis of women with *E coli* infections, only 50% of those receiving fosfomycin experienced and maintained clinical resolution. The gap between those laboratory observations and fosfomycin's in vivo efficacy[5] suggests that pharmacokinetics, pharmacodynamics, or both play a major role in its ability to achieve clinical and in vivo microbiologic success. There is doubt that a single 3-g dose can reach adequate, or adequately durable, concentrations in urine.[11]

New evidence from more contemporary laboratory studies appears to confirm the role of pharmacodynamics: in an in vitro dynamic bladder infection model, significant rates of rapid regrowth of *E coli*, *Klebsiella* spp, and other uropathogens were observed following single-dose fosfomycin administration, with apparent amplification of resistant subpopulations.[26]

The perception that there is little baseline resistance to fosfomycin may be inaccurate: regions with increasing consumption have proportionately increasing resistance. A longitudinal study conducted in Spain documented an increase in fosfomycin resistance from 4% to 11% between 1997 and 2009, corresponding to a 340% increase in the drug's consumption during that time.[8] Fosfomycin is an antibiotic with a wide spectrum of activity, particularly against multidrug-resistant organisms,[27] and a favorable safety profile, but its continued oral administration at an insufficient dose may rapidly diminish its usefulness, especially for invasive infections requiring intravenous administration of this drug.

Although patients taking nitrofurantoin experienced superior clinical and microbiologic outcomes, the drug's overall response rate in this trial was lower than anticipated given earlier reported success rates of up to 90%.[3,12,28] A few factors may explain the discrepancy, among them the relatively high incidence of non-*E coli* infections in this population. Nearly 80% of *E coli* infections were treated successfully with nitrofurantoin; *Proteus* spp have intrinsic resistance and *Klebsiella* spp resistance of up to 50%, depending on the region.[29] And in earlier trials comparing nitrofurantoin with other UTI agents, definitions of "clinical" success often allowed for improvement in symptoms without full resolution[30] or used microbiologic success with high bacterial counts as the cutoff. Two other trials comparing these drugs in the 1990s found clinical and microbiologic cure rates of 82% to 95% and 87% to 96%, respectively.[12,13] Both trials defined clinical cure as symptomatic improvement and reported per-protocol results only; patients withdrawing because of clinical failure were excluded from analyses. In both trials, a reduction in urine culture counts from 10^5 to 10^4 cfu/mL qualified as microbiologic success.

Baseline resistance rates to nitrofurantoin are also increasing; participants with *E coli* infections in Poland, where nitrofuran derivatives have been sold over the counter for the past 5 years, had significantly higher baseline resistance to nitrofurantoin than those at the other sites where the drug is obtained by prescription only (6% vs 0%).[24] Nonetheless, currently these rates are low relative to those of other antibiotics, and nitrofurantoin's role in guidelines and clinical practice as a fluoroquinolone-sparing agent remains essential.[31,32]

Both drugs led to few adverse events, with no serious adverse events occurring in relation to either. The more serious adverse effects of nitrofurantoin, pulmonary and hepatotoxicity, were neither expected in this trial of short-course therapy[33] nor observed.

Limitations

This study has several limitations. First, it was conducted open label. The open design became inevitable in light of the costs of sachet-packaged fosfomycin dummies, which would have totaled more than a quarter of the trial's budget. The open design may have introduced some level of measurement bias given a subjective primary end point. However, there was consistency between clinical and microbiologic outcomes. Second, laboratory analyses were not centralized, potentially introducing heterogeneity in microbiologic methods. Third, recruitment and follow-up in Israel did not reach original targets due to political events occurring soon after the site's launch. Fourth, the 3 sites had some differences among patients (age and local resistance prevalences with, in Poland, over-the-counter sales of nitrofuran derivatives coincident with the trial's launch).

Conclusions

Among women with uncomplicated UTI, 5-day nitrofurantoin, compared with single-dose fosfomycin, resulted in a significantly greater likelihood of clinical and microbiologic resolution at 28 days after therapy completion.

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REFERENCES

1. Gupta K, Hooton TM, Naber KG, et al; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52(5):e103-e120.

2. European Centre for Disease Prevention and Control. Trend of antimicrobial consumption by country. https://ecdc.europa.eu/en/antimicrobial-consumption/database/trend-country. Accessed February 25, 2018.

3. Huttner A, Verhaegh EM, Harbarth S, Muller AE, Theuretzbacher U, Mouton JW. Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. *J Antimicrob Chemother*. 2015;70(9):2456-2464.

4. Zalmanovici Trestioreanu A, Green H, Paul M, Yaphe J, Leibovici L. Antimicrobial agents for treating uncomplicated urinary tract infection in women. *Cochrane Database Syst Rev*. 2010;(10):CD007182.

5. Fosfomycin for urinary tract infections. *Med Lett Drugs Ther*. 1997;39(1005):66-68.

6. Kahan FM, Kahan JS, Cassidy PJ, Kropp H. The mechanism of action of fosfomycin (phosphonomycin). *Ann N Y Acad Sci*. 1974;235(0):364-386.

7. Maraki S, Samonis G, Rafailidis PI, Vouloumanou EK, Mavromanolakis E, Falagas ME. Susceptibility of urinary tract bacteria to fosfomycin. *Antimicrob Agents Chemother*. 2009;53(10):4508-4510.

8. Oteo J, Bautista V, Lara N, et al; Spanish ESBL-EARS-Net Study Group. Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli. *J Antimicrob Chemother*. 2010;65(11):2459-2463.

9. Michalopoulos AS, Livaditis IG, Gougoutas V. The revival of fosfomycin. *Int J Infect Dis*. 2011;15(11):e732-e739.

10. Mazzei T, Cassetta MI, Fallani S, Arrigucci S, Novelli A. Pharmacokinetic and pharmacodynamic aspects of antimicrobial agents for the treatment of uncomplicated urinary tract infections. *Int J Antimicrob Agents*. 2006;28(suppl 1):S35-S41.

11. Wijma RA, Koch BCP, van Gelder T, Mouton JW. High interindividual variability in urinary fosfomycin concentrations in healthy female volunteers [published online September 1, 2017]. *Clin Microbiol Infect*. doi:10.1016/j.cmi.2017.08.023

12. Stein GE. Comparison of single-dose fosfomycin and a 7-day course of nitrofurantoin in female patients with uncomplicated urinary tract infection. *Clin Ther*. 1999;21(11):1864-1872.

13. Van Pienbroek E, Hermans J, Kaptein AA, Mulder JD. Fosfomycin trometamol in a single dose versus seven days nitrofurantoin in the treatment of acute uncomplicated urinary tract infections in women. *Pharm World Sci*. 1993;15(6):257-262.

14. Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *Urol Clin North Am*. 2008;35(1):1-12, v. v.

15. Borsa F, Leroy A, Fillastre JP, Godin M, Moulin B. Comparative pharmacokinetics of tromethamine fosfomycin and calcium fosfomycin in young and elderly adults. *Antimicrob Agents Chemother*. 1988;32(6):938-941.

16. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control*. 2008;36(5):309-332.

17. Garcia LS, Isenberg HD. *Clinical Microbiology Procedures Handbook*. 3rd ed. Washington, DC: ASM Press; 2010.

18. CLSI. *M100-S25 Performance Standards for Antimicrobial Susceptibility Testing: Twenty-Fifth Informational Supplement*. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.

19. European Committee on Antimicrobial Susceptibility Testing. http://www.eucast.org/. Accessed November 28, 2017.

20. Gupta K, Hooton TM, Stamm WE. Isolation of fluoroquinolone-resistant rectal Escherichia coli after treatment of acute uncomplicated cystitis. *J Antimicrob Chemother*. 2005;56(1):243-246.

21. Ernst EJ, Ernst ME, Hoehns JD, Bergus GR. Women's quality of life is decreased by acute cystitis and antibiotic adverse effects associated with treatment. *Health Qual Life Outcomes*. 2005;3:45.

22. Infectious Diseases Society of America. White paper: recommendations on the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens. *Clin Infect Dis*. 2012;55(8):1031-1046.

23. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30(4):377-399.

24. Huttner A, Brossier C, von Dach E, et al. Increasing nitrofurantoin resistance in Escherichia coli urinary isolates in a country with over-the-counter antibiotic sales. Presented at: 27th European Congress on Clinical Microbiology and Infection; April 22, 2017; Vienna, Austria.

25. Giesen LG, Cousins G, Dimitrov BD, van de Laar FA, Fahey T. Predicting acute uncomplicated urinary tract infection in women: a systematic review of the diagnostic accuracy of symptoms and signs. *BMC Fam Pract*. 2010;11:78.

26. Abbott IJ, Meletiadis J, Belghanch I, et al. Fosfomycin efficacy and emergence of resistance among Enterobacteriaceae in an in vitro dynamic bladder infection model [published online December 14, 2017]. *J Antimicrob Chemother*. doi:10.1093/jac/dkx441

27. Neuner EA, Sekeres J, Hall GS, van Duin D. Experience with fosfomycin for treatment of urinary tract infections due to multidrug-resistant organisms. *Antimicrob Agents Chemother*. 2012;56(11):5744-5748.

28. Iravani A, Klimberg I, Briefer C, Munera C, Kowalsky SF, Echols RM. A trial comparing low-dose, short-course ciprofloxacin and standard 7 day therapy with co-trimoxazole or nitrofurantoin in the treatment of uncomplicated urinary tract infection. *J Antimicrob Chemother*. 1999;43(suppl A):67-75.

29. Mezzatesta ML, La Rosa G, Maugeri G, et al. In vitro activity of fosfomycin trometamol and other oral antibiotics against multidrug-resistant uropathogens. *Int J Antimicrob Agents*. 2017;49(6):763-766.

30. Spencer RC, Moseley DJ, Greensmith MJ. Nitrofurantoin modified release versus trimethoprim or co-trimoxazole in the treatment of uncomplicated urinary tract infection in general practice. *J Antimicrob Chemother*. 1994;33(suppl A):121-129.

31. Slekovec C, Leroy J, Huttner A, et al. When the precautionary principle disrupts 3 years of antibiotic stewardship: nitrofurantoin in the treatment of urinary tract infections. *J Antimicrob Chemother*. 2014;69(1):282-284.

32. Stewardson AJ, Vervoort J, Adriaenssens N, et al; SATURN WP1 Study Group; SATURN WP3 Study Group. Effect of outpatient antibiotics for urinary tract infections on antimicrobial resistance among commensal Enterobacteriaceae: a multinational prospective cohort study. *Clin Microbiol Infect*. 2018;S1198-743X(18)30031-4.

33. Muller AE, Verhaegh EM, Harbarth S, Mouton JW, Huttner A. Nitrofurantoin's efficacy and safety as prophylaxis for urinary tract infections: a systematic review of the literature and meta-analysis of controlled trials. *Clin Microbiol Infect*. 2017;23(6):355-362.