Supplementary Online Content

Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-day nitrofurantoin vs single-dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2018.3627

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Additional Study Exclusion Criteria and Definitions

Exclusion criteria

The study's inclusion criteria are listed in the main manuscript. All exclusion criteria are listed here:

- Male sex
- Pregnancy or planned pregnancy
- Known carriage of nitrofurantoin- or fosfomycin-resistant uropathogens(s)
- Concomitant antimicrobial therapy
- Use of any antibiotics in the past 7 days
- Known or suspected hypersensitivity or allergy to fosfomycin or nitrofurantoin
- History of lung or liver reaction or peripheral neuropathy after use of nitrofurantoin or other nitrofurans in the past
- Pre-existing polyneuropathy
- G6PD deficiency
- Symptoms consistent with urinary tract infection (UTI) in the preceding 4 weeks
- Active upper UTI (e.g. pyelonephritis, urosepsis: fever > 38.0, flank pain, chills)
- Symptoms/signs suggestive of vaginitis or sexually transmitted infection
- Indwelling catheter, nephrostomy, ureter stent or other foreign material
- Otherwise complicated UTI:
    - A history of anatomical or functional abnormalities of the urogenital tract:
        - Congenital abnormalities
        - Polycystic kidney disease
        - Obstruction or stricture of renal pelvis, ureter or urethra
        - Kidney stones
        - Cystocele
        - Cystic diverticulae
        - Change of anatomical proportions (e.g. after ureter implantation)
        - Chronic vesico-urethral reflux
        - Neurogenic bladder
- Severe chronic renal (creatinine clearance < 30 ml/min)* or hepatic dysfunction
- Porphyria
- Immunosuppression:
    - Untreated infection with the human immunodeficiency virus (HIV)

Use of high-dose systemic corticosteroids or other immunosuppressive medication (immunophilins, interferons, monoclonal antibodies, and mycophenylate)

    - Chemotherapy
    - Treatment with radiation
- Critical illness requiring intensive care
- Planned surgery within the next 6 weeks
- Inability to take oral drugs
- Participation in another prospective clinical trial
- Previous enrolment in the proposed study
- Inability to understand or to follow the study protocol

**Renal insufficiency at inclusion*

At the Geneva site, creatinine levels were measured at inclusion unless (1) there was a level drawn (with documentation available) in the previous three months and (2) the patient reported no known renal issues during that interval. At the other sites, routine blood draws for all patients at inclusion were not considered feasible, so patients' self-report was relied on at screening. If any candidate reported a history of renal sufficiency, a creatinine level was then drawn and the creatinine clearance calculated.

Definitions

Resistant bacteria were defined as those with phenotypic resistance to at least one agent in one or two antibiotic classes.

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Multiresistant bacteria were resistant to at least one agent in three or more antibiotic classes.

Positive urine culture: The laboratories reported growth according to the Wilson/Gaido algorithm (see Box).[1] In general, common uropathogens (*e.g.*, *Escherichia coli*) were treated as such even when not the only isolate. Mixed flora was reported, however when three or more different pathogens were present in the same amount. Of note, while baseline cultures with mixed flora were considered to be "positive" cultures, they could not be included in analyses for microbiologic outcomes given the lack of any clearly identified pathogen.

Box 1. Algorithm for reporting urine culture growth. Adapted from Wilson and Gaido.[1]

Probability of contamination, no. of microorganisms	Quantification, cfu/ml	Interpretation
Low probability*		
1	$<10^2$	Probable contaminant
1	$\geq 10^2$	Significant isolate
2	$<10^2$ for each	Probable contaminants
2	$\geq 10^2$ for each	Significant isolates
2	$\geq 10^2$ for 1	Significant isolate & contaminant
≥3	$\geq 10^5$ for 1	Significant isolate & contaminants
≥3	$\geq 10^5$ for each	Probable contaminants
High probability**		
1	$<10^2$	Probable contaminant
1	$\geq 10^2$	Significant isolate
2	$\geq 10^5$ for each	Significant isolates
2	$\geq 10^5$ for 1	Significant isolate & contaminant
2	$<10^5$ for each	Probable contaminants
≥3	$\geq 10^5$ for 1	Significant isolate & contaminants
≥3	$\geq 10^5$ for each	Probable contaminants

*Urine specimens obtained via aspiration (suprapubic, bladder, ureter, renal pelvis, kidney) or single catheterization; specimens obtained in the operating room, and urine specimens from patients receiving antimicrobial therapy

**Urine specimens obtained via the clean catch technique, indwelling catheters, nephron-/ureterostomy tubes

A *serious adverse event* was defined in line with FDA reporting guidelines[9] as a medical event that does one or more of the following:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

The nitrofurantoin dosing regimen

Several dosing regimens for nitrofurantoin are recommended in various countries; they range from 200 mg to 400 mg daily in two to four divided doses. Current treatment and dosage regimens of nitrofurantoin for lower UTI are summarized at right. The choice of 100 mg tid was made because this is the regimen most often recommended/approved in European countries; a duration of five days has proven sufficient for efficacy in acute uncomplicated UTI.[10]

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Country	Year	Dose	Duration (d)
USA[2]	1999	100 mg bid	7
Netherlands[3]	1999	100 mg tid	3
Scotland[4]	2006	Not stated	3
Netherlands[5]	2006	100 mg tid	5
France[6]	2008	100 mg tid	5
Belgium[7]	2008	100 mg tid	3
USA & Europe[8]	2010	100 mg bid	5

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eTable 1. Baseline Urine Culture Results by Site (Intention-to-Treat Population).

Baseline urinary cultures by site	Geneva	Lodz	Petah-Tiqva
Number of patients	**186**	**200**	**127**
Number, baseline cultures obtained (%)	**183 (98)**	**197 (99)**	**107 (84)**
Number of positive* cultures (%)	**169 (92)**	**136 (69)**	**72 (67)**
***Escherichia coli* (%**)**	**112 (66)**	**93 (68)**	**25 (35)**
- nitrofurantoin-resistant (%)	0 (0)	6 (7)	0 (0)
- fosfomycin-resistant (%)	0 (0)	1 (1)	0 (0)
- co-trimoxazole-resistant (%)	20 (18)	22 (24)	9 (36)
- fluoroquinolone-resistant (%)	13 (12)	9 (10)	5 (20)
- ESBL (%)	4 (4)	2 (2)	3 (12)
***Klebsiella* spp. (%**)**	**10 (6)**	**11 (8)**	**6 (8)**
- nitrofurantoin-resistant (%)	3 (30)	0 (0)	0 (0)
- fosfomycin-resistant (%)	2 (20)	0 (0)	0 (0)
- co-trimoxazole-resistant (%)	2 (20)	3 (27)	1 (17)
- fluoroquinolone-resistant (%)	1 (10)	0 (0)	1 (17)
- ESBL (%)	1 (10)	0 (0)	2 (33)
***Proteus* spp. (%**)**	**12 (7)**	**2 (1)**	**3 (4)**
- nitrofurantoin-resistant (%)	2 (17)	0 (0)	1 (33)
- fosfomycin-resistant (%)	2 (17)	0 (0)	1 (33)
- co-trimoxazole-resistant (%)	4 (33)	1 (50)	0 (0)
- fluoroquinolone-resistant (%)	2 (17)	0 (0)	0 (0)
- ESBL (%)	0 (0)	0 (0)	0 (0)
***Enterococcus* spp. (%**)**	10 (6)	16 (12)	1 (1)
Group B Streptococcus (%)**	5 (3)	5 (4)	3 (4)
***Enterobacter* spp. (%**)**	1 (1)	7 (5)	1 (1)
Mixed flora (%)**	48 (28)	13 (10)	30 (42)
Other (%)§**	10 (6)	2 (1)	15 (7)

*Positive culture was defined as the growth of $\geq 10^3$ cfu/ml of at least one uropathogen; laboratory reporting of culture growth is described in detail above. 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.

** Some cultures had polymicrobial growth.

§*Citrobacter koseri*, Morganella spp., *Staphylococcus aureus*, *Staphylococcus saprophyticus*, *Streptococcus anginosus*

eTable 2. Multiple Imputation of Missing Data.

We computed multiple imputation using M=20 imputations and adjusted the imputation model for site, age, number of urinary symptoms/signs, previous antibiotic use and any previous urinary tract infection (these variables predict both outcome and missingness).

	Odds ratio	95% CI	P
Complete data (logistic regression), MAR (n=470)	1.75	1.19-2.58	0.004
Complete data (mixed effects logistic regression*), MAR (n=470)	1.76	1.19-2.60	0.004
MAR, K=20 (logistic regression) (n=512)**	1.66	1.13-2.42	0.009
MAR, K=20 (mixed effects logistic regression) (n=512)	1.67	1.14-2.45	0.008

*Mixed effects logistic regression model with site as a random factor.

**One patient had no baseline variables and was not considered in multiple imputation.

MAR: missing at random

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eTable 3. Sensitivity Analyses for Missing Primary Outcome Data for Nitrofurantoin (n=11) and Fosfomycin (n=17).

eTable 3A: "Best-case scenario": assumes missing nitrofurantoin and fosfomycin cases are all successes through day 28.

	Nitrofurantoin	Fosfomycin	% Difference (95% CI)	P value*
Number of patients	255	258		
Clinical resolution (%)	**182 (71)**	**156 (61)**	**10 (3-19)**	**.009**
Clinical failure (%)	66 (26)	94 (36)		
Indeterminate (%)	7 (3)	8 (3)		

eTable 3B: "Worst-case scenario": assumes missing nitrofurantoin and fosfomycin cases are all failures by day 28.

	Nitrofurantoin	Fosfomycin	% Difference (95% CI)	P value*
Number of patients	255	258		
Clinical resolution (%)	**171 (67)**	**139 (54)**	**13 (5-21)**	**.002**
Clinical failure (%)	77 (30)	111 (43)		
Indeterminate (%)	7 (3)	8 (3)		

eTable 3C: "Extreme superiority": assumes all missing nitrofurantoin cases are successes through day 28 and all missing fosfomycin cases are failures by day 28.

	Nitrofurantoin	Fosfomycin	% Difference (95% CI)	P value*
Number of patients	255	258		
Clinical resolution (%)	**182 (71)**	**139 (54)**	**18 (9-26)**	**<.001**
Clinical failure (%)	66 (26)	111 (43)		
Indeterminate (%)	7 (3)	8 (3)		

eTable 3D: "Counterintuitive outcomes": assumes all missing nitrofurantoin cases are failures and all missing fosfomycin cases are successes through day 28.

	Nitrofurantoin	Fosfomycin	% Difference (95% CI)	P value*
Number of patients	255	258		
Clinical resolution (%)	**171 (67)**	**156 (61)**	**6 (-2-15)**	**.120**
Clinical failure (%)	77 (30)	94 (36)		
Indeterminate (%)	7 (3)	8 (3)		

*Chi square test, one degree of freedom.

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eTable 4. Post-Hoc Analyses: Clinical Response When Indeterminate Cases With Clinical Improvement are Considered Clinical Successes in (A) Intention-to-Treat and (B) Per-Protocol Populations.

A: Intention-to-treat population	Nitrofurantoin	Fosfomycin	% Difference (95% CI)	P value*
Number of patients	255	258		
Clinical response at day 28 (primary outcome)				
Clinical resolution (%)	**177 (73)**	**145 (60)**	**13 (4-21)**	**.004**
Clinical failure (%)	66 (27)	94 (39)		
Indeterminate, no improvement (%)	1 (0.4)	2 (0.8)		
Missing	*11 (4)*	*17 (7)*		
Clinical response at day 14 (secondary outcome)				
Clinical resolution (%)	190 (77)	168 (68)	9 (1-17)	.03
Clinical failure (%)	56 (23)	75 (30)		
Indeterminate, no improvement (%)	1 (0.4)	4 (1.6)		
Missing (%)	*8 (3)*	*11 (4)*		

B: Per-protocol population	Nitrofurantoin	Fosfomycin	% Difference (95% CI)	P value*
Number of patients	237	237		
Clinical response at day 28 (primary outcome)				
Clinical resolution (%)	**175 (74)**	**144 (61)**	**13 (5-21)**	**.002**
Clinical failure (%)	61 (25.7)	91 (38.3)		
Indeterminate, no improvement (%)	1 (0.4)	2 (0.8)		
Clinical response at day 14 (secondary outcome)				
Clinical resolution (%)	183 (77)	161 (68)	9 (1-17)	.03
Clinical failure (%)	53 (22.4)	72 (30.4)		
Indeterminate, no improvement (%)	1 (0.4)	4 (1.6)		

*Chi square test, one degree of freedom.

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eTable 5. Post-Hoc Analyses: Clinical Response When Indeterminate Cases are Considered Failures in (A) Intention-to-Treat and (B) Per-Protocol Populations.

A: Intention-to-treat population	Nitrofurantoin	Fosfomycin	% Difference (95% CI)	P value*
Number of patients	255	258		
Clinical response at day 28 (primary outcome)				
Clinical resolution (%)	**171 (70)**	**139 (58)**	**12 (4-21)**	**.004**
Clinical failure (%)	73 (30)	102 (42)		
Missing	*11 (4)*	*17 (7)*		
Clinical response at day 14 (secondary outcome)				
Clinical resolution (%)	184 (74)	162 (66)	9 (1-17)	.03
Clinical failure (%)	63 (26)	85 (34)		
Missing (%)	*8 (3)*	*11 (4)*		

B: Per-protocol population	Nitrofurantoin	Fosfomycin	% Difference (95% CI)	P value*
Number of patients	237	237		
Clinical response at day 28 (primary outcome)				
Clinical resolution (%)	**169 (71)**	**138 (58)**	**13 (5-21)**	**.003**
Clinical failure (%)	68 (29)	99 (42)		
Clinical response at day 14 (secondary outcome)				
Clinical resolution (%)	178 (75)	155 (65)	10 (2-18)	.02
Clinical failure (%)	59 (25)	82 (35)		

*Chi square test, one degree of freedom.

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eTable 6. Clinical Response Among Patients With *E. coli* in Baseline Urine Cultures.

E. coli in baseline urine cultures	Nitrofurantoin	Fosfomycin	% Difference (95% CI)	P value*
Number of patients randomized	255	258		
Clinical response at day 28				
Patients with day 28 data available	103	111		
Clinical resolution (%)	80 (78)	55 (50)	28 (15-40)	<.001
Clinical failure (%)	19 (18)	54 (48)		
Indeterminate, no improvement (%)	4 (4)	2 (2)		
Clinical response at day 14				
Patients with day 14 data available	105	114		
Clinical resolution (%)	88 (84)	67 (59)	25 (13-36)	<.001
Clinical failure (%)	14 (13)	45 (39)		
Indeterminate, no improvement (%)	3 (3)	2 (2)		

*Chi square test, one degree of freedom.

eTable 7. Bacteriologic Response Among Patients With *E. coli* in Baseline Urine Cultures.

E. coli in baseline urine cultures	Nitrofurantoin	Fosfomycin	% Difference (95% CI)	P value*
Number of patients randomized	255	258		
Bacteriologic response at day 28				
Patients with day 28 data available	98	109		
Bacteriologic success (%)	71 (72)	63 (58)	14 (2-27)	.03
Bacteriologic failure (%)	27 (28)	46 (42)		
Bacteriologic response at day 14				
Patients with day 14 data available	99	111		
Bacteriologic success (%)	84 (85)	78 (70)	15 (3-25)	.01
Bacteriologic failure (%)	15 (15)	33 (30)		

*Chi square test, one degree of freedom.

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eTable 8. Adverse Events by Treatment Group in the Intention-to-Treat Population.
Adverse events considered possibly or probably related to the study antibiotic are documented; no events were classified as certainly related.

Event		Nitrofurantoin (n=255)	Fosfomycin (n=258)
	Missing (%)	*7 (3)*	*11 (4)*
At least one adverse event	None (%)	228 (92)	232 (94)
	Mild (%)	7 (3)	4 (2)
	Moderate (%)	13 (5)	10 (4)
	Severe (%)	0 (0)	1 (0.4)
Nausea ± vomiting	None (%)	241 (97)	242 (98)
	Mild (%)	4 (2)	1 (0.4)
	Moderate (%)	3 (1)	4 (2)
Diarrhea	None (%)	245 (99)	242 (98)
	Mild (%)	2 (1)	3 (1)
	Moderate (%)	1 (0.4)	2 (1)
Abdominal cramping	None (%)	246 (99.6)	244 (99)
	Mild (%)	0 (0)	1 (0.4)
	Moderate (%)	1 (0.4)	2 (1)
Fatigue	None (%)	245 (99)	247 (100)
	Mild (%)	1 (0.4)	0 (0)
	Moderate (%)	2 (1)	0 (0)
Increased vaginal discharge	None (%)	245 (99)	246 (99.6)
	Mild (%)	2 (1)	1 (0.4)
	Moderate (%)	1 (0.4)	0 (0)
Headache	None (%)	247 (99.6)	246 (99.6)
	Mild (%)	0 (0)	0 (0)
	Moderate (%)	1 (0.4)	1 (0.4)
Dizziness	None (%)	246 (99)	245 (99)
	Mild (%)	1 (0.4)	0 (0)
	Moderate (%)	1 (0.4)	1 (0.4)
	Severe (%)	0 (0)	1 (0.4)
Other	None (%)	241 (97)	244 (99)
	Mild (%)	4 (2)	0 (0)
	Moderate (%)	3 (1)	3 (1)

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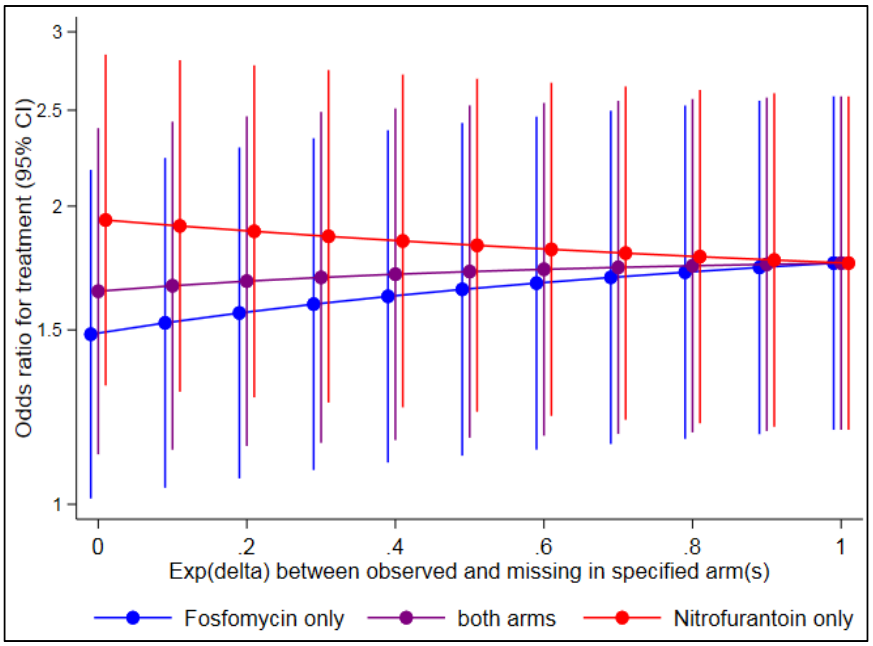
eFigure. Sensitivity of the Fosfomycin-Versus-Nitrofurantoin Comparison for Failure by Day 28 to Missing Data Not-at-Random Using a Pattern Mixture Model Approach.



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eReferences

1. Wilson ML, Gaido L. Laboratory diagnosis of urinary tract infections in adult patients. *Clin Infect Dis.* 2004;38(8):1150-1158.
2. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clin Infect Dis.* 1999;29(4):745-758.
3. van den Broek PJ, van Everdingen JJ. ['Urinary tract infections'--revised CBO guideline. Dutch Institute for Quality Assurance]. *Ned Tijdschr Geneeskd.* 1999;143(49):2461-2465.
4. Beckford-Ball J. Management of suspected bacterial urinary tract infection. *Nurs Times.* 2006;102(36):25-26.
5. van Pinxteren B, van Vliet SM, Wiersma TJ, Goudswaard AN. [Summary of the practice guideline 'Urinary-tract infections' (second revision) from the Dutch College of General Practitioners]. *Ned Tijdschr Geneeskd.* 2006;150(13):718-722.
6. [AFSSAPS Practice recommendations for diagnosis and antibiotic therapy of adult community urinary tract infections]. *Med Mal Infect.* 2008;38 Suppl 3:S203-252.
7. Acute cystitis in women: Belgian guidelines.
8. Gupta K, Hooton TM, Naber KG, et al. 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):e103-120.
9. FDA. Adverse Event Reporting. https://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm. Accessed September 5, 2017.
10. 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.

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