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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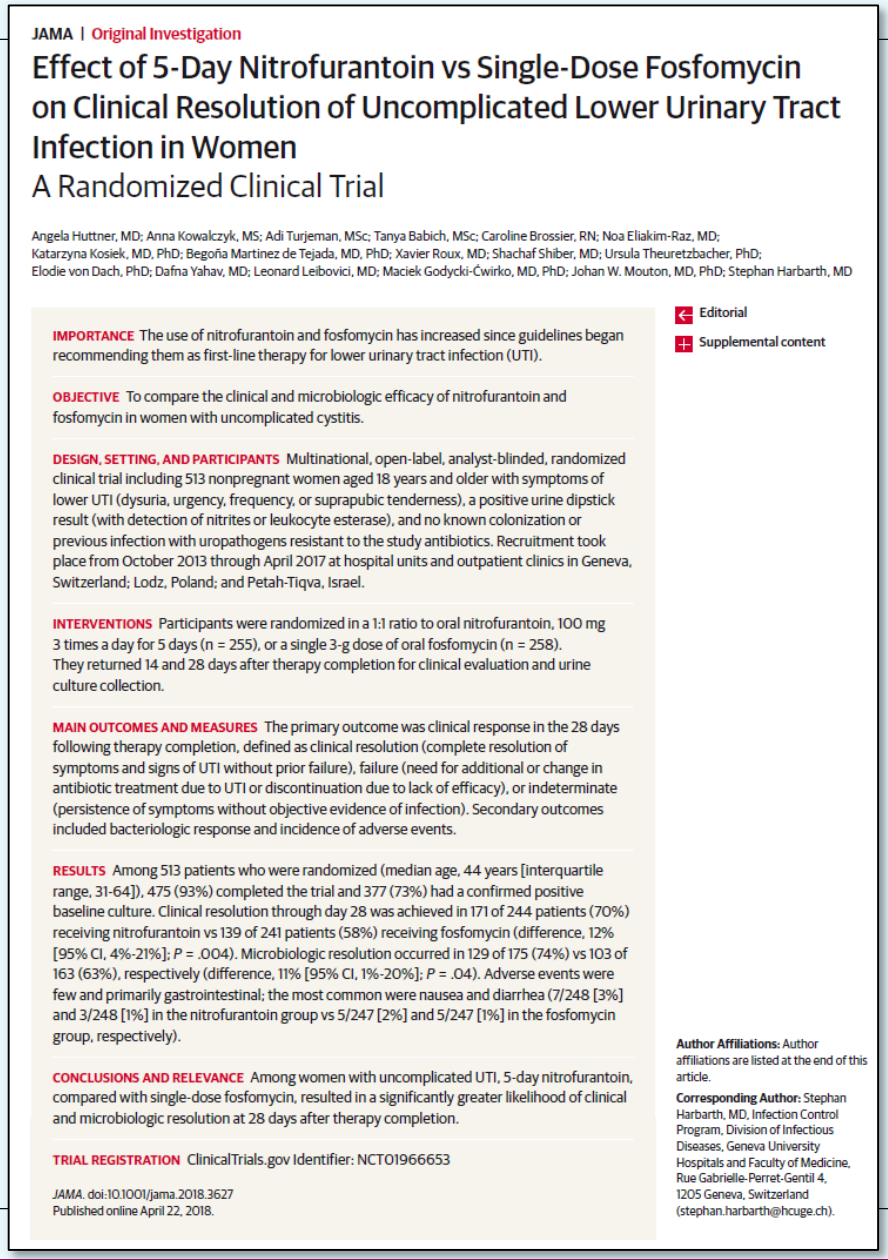

JAMA | Original Investigation

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.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01966653

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Editorial

Supplemental content

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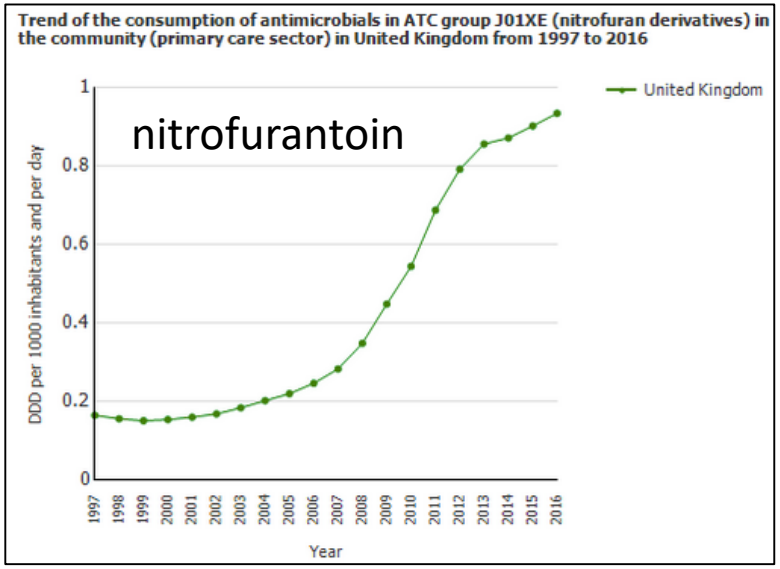
Conflict of interest disclosure

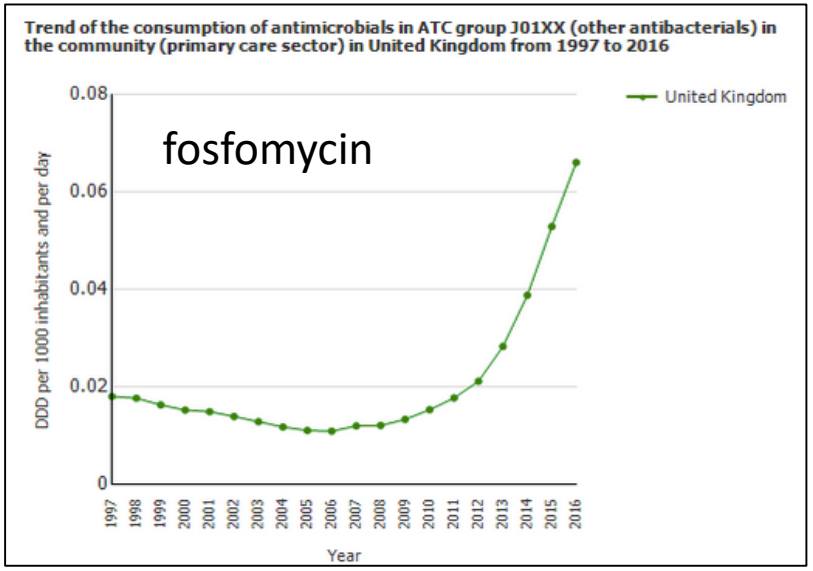
The AIDA Project:
Preserving old antibiotics for the future

A European Union 7th Framework Program (FP7) project

Nitrofurantoin vs fosfomycin for urinary tract infection in women: a randomized clinical trial

- Nitrofurantoin and fosfomycin have been recommended as first-line therapy for lower, uncomplicated urinary tract infection since 2011
  - Their use has since increased exponentially





Nitrofurantoin vs fosfomycin for urinary tract infection in women: a randomized superiority trial

- These “old antibiotics” were approved in an era of less stringent methodologic standards
- Nitrofurantoin’s efficacy is not perfect but it’s been proven

J Antimicrob Chemother 2015; **70**: 2456–2464
doi:10.1093/jac/dkv147 Advance Access publication 11 June 2015

Journal of Antimicrobial Chemotherapy

Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials

- Fosfomycin? Not so much…

Nitrofurantoin vs fosfomycin for urinary tract infection in women: a randomized clinical trial

- Doubts regarding fosfomycin:
  - 1997 US double-blind RCT
  - >1000 women with lower UTI received
  - Fosfomycin, TMP/SMX or ciprofloxacin

	Fosfomycin (N=771)	**TMP/SMX (N=197)**	**Ciprofloxacin (N=222)**
Microbiologic success	77%	93%	93%
Clinical success	70%	94%	96%

Nitrofurantoin vs fosfomycin for urinary tract infection in women: a randomized clinical trial

Sites in Geneva (CH), Tel Aviv (IL), Lodz (PL)

SCREENING | **RANDOMIZATION** | **FOLLOW-UP**

Adult women with symptoms of cystitis & positive urine dipstick

nitrofurantoin
100 mg tid for 5 days
n = 300

fosfomycin
single 3 g dose
n = 300

Primary outcome:
Clinical response
through day 28 post-therapy

Visit 1 — D0
Visit 2 — D14 post-therapy
Visit 3 — D28 post-therapy

Huttner A, Kowalczyk A, Turjeman A, et al. *JAMA.* 2018;319(17):1781–1789. doi:10.1001/jama.2018.3627

Nitrofurantoin vs fosfomycin for urinary tract infection in women: a randomized clinical trial

Geneva, Tel Aviv, Lodz

- Entry criteria
  - Inclusion criteria:
    - Age ≥18 years
    - Adult with dysuria, urgency, frequency, suprapubic tenderness
    - Positive urine dipstick (nitrites or leukocyte esterase)
  - Main exclusion criteria:
    - Pregnancy, lactation
    - Concomitant or recent (≤7 days) antibiotic therapy
    - Complicated and/or upper urinary tract infection
    - Recent (≤4 weeks) urinary tract infection
    - Immunosuppression
    - Known resistance to study antibiotics

Huttner A, Kowalczyk A, Turjeman A, et al. *JAMA.* 2018;319(17):1781–1789. doi:10.1001/jama.2018.3627

Nitrofurantoin vs fosfomycin for urinary tract infection in women: a randomized clinical trial

Geneva, Tel Aviv, Lodz

- Primary outcome: **clinical response** in the 28 days following therapy
  - Success: complete resolution of all symptoms
  - Failure: need for additional or change in antibiotics due to UTI/ discontinuation due to lack of efficacy
  - Indeterminate: persistence of symptoms without objective evidence of infection
- Secondary outcomes:
  - Microbiologic response 14 and 28 days after therapy
  - Incidence of adverse events throughout the study period

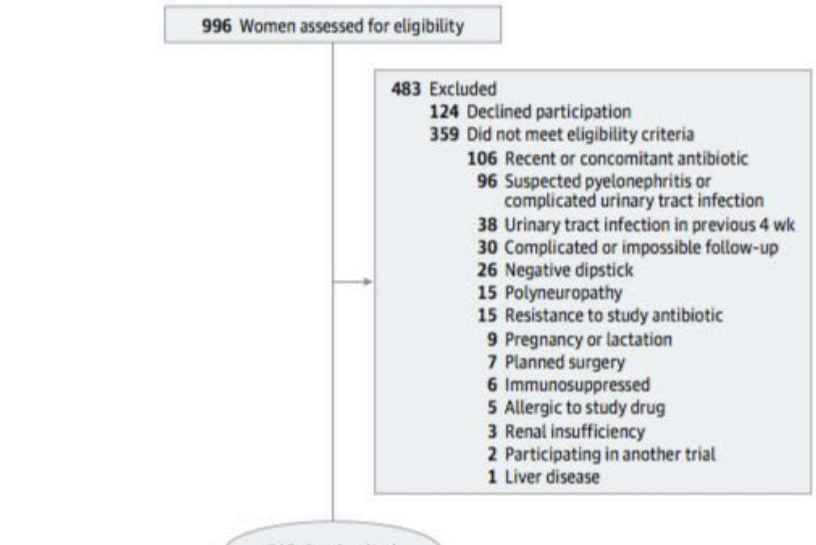
Huttner A, Kowalczyk A, Turjeman A, et al. *JAMA.* 2018;319(17):1781–1789. doi:10.1001/jama.2018.3627

996 screened

513 randomized (ITT)

(5.6% missing data for primary outcome)

Figure. Study Flowchart of the Nitrofurantoin and Fosfomycin Groups



Huttner A, Kowalczyk A, Turjeman A, et al. *JAMA*. 2018;319(17):1781–1789. doi:10.1001/jama.2018.3627

Baseline demographics by treatment group and site

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)

Huttner A, Kowalczyk A, Turjeman A, et al. *JAMA.* 2018;319(17):1781–1789. doi:10.1001/jama.2018.3627

Baseline urine cultures by treatment group

→

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)

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Clinical and microbiologic 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)		

CLINICAL SUCCESS
70% vs 58%

MICROBIOLOGIC SUCCESS
74% vs 63%

Huttner A, Kowalczyk A, Turjeman A, et al. *JAMA.* 2018;319(17):1781–1789. doi:10.1001/jama.2018.3627

Clinical response in patients with *Escherichia coli* infections

Table S6. 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)	28.1 (15.3-40.0)	<.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 (69)	25.0 (13.1-35.9)	<.001
Clinical failure (%)	14 (13)	45 (39)		
Indeterminate, no improvement (%)	3 (3)	2 (2)		

*Chi square test, one degree of freedom.

CLINICAL SUCCESS
78% vs 50%

Huttner A, Kowalczyk A, Turjeman A, et al. *JAMA.* 2018;319(17):1781–1789. doi:10.1001/jama.2018.3627

Microbiologic response in patients with *Escherichia coli* infections

Table S7. 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)	14.7 (1.6-26.9)	.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)	14.6 (3.2-25.3)	.01
Bacteriologic failure (%)	15 (15)	33 (30)		

*Chi square test, one degree of freedom.

MICROBIOLOGIC SUCCESS
72% vs 58%

Huttner A, Kowalczyk A, Turjeman A, et al. *JAMA.* 2018;319(17):1781–1789. doi:10.1001/jama.2018.3627

Adverse events

- Few adverse events in either group
  - No related serious adverse events
- Primarily gastrointestinal
- Mild to moderate in severity
- Pyelonephritis was rare (1 vs 5 cases, p=.22)

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 (.04)	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)

Huttner A, Kowalczyk A, Turjeman A, et al. *JAMA.* 2018;319(17):1781–1789. doi:10.1001/jama.2018.3627

Limitations

- Open-label design
  - Fosfomycin dummies prohibitively expensive
  - Microbiologic response confirms clinical response
- Laboratory analyses not centralized

Huttner A, Kowalczyk A, Turjeman A, et al. *JAMA.* 2018;319(17):1781–1789. doi:10.1001/jama.2018.3627

Conclusions (I)

- Single-dose fosfomycin appears to be inferior to nitrofurantoin for lower UTI
  - Clinical success 70% (nitrofurantoin) versus 58% (fosfomycin) study-wide
    - 78% versus 50% in patients with *E. coli* infections
  - Additional AIDA data show that the problem is likely pharmacokinetic: one dose is not enough

Huttner A, Kowalczyk A, Turjeman A, et al. *JAMA.* 2018;319(17):1781–1789. doi:10.1001/jama.2018.3627

Conclusions (II)

- Both drugs performed more poorly than in previous studies BUT
  - Earlier studies allowed success to be defined by
    - Symptomatic improvement and/or
    - Reduction (but not eradication) of bacteriuria

- Adverse events of both antibiotics are very similar
  - Mild to moderate
  - Primarily gastrointestinal

- Guidelines will need to be rethought & reworked

Huttner A, Kowalczyk A, Turjeman A, et al. *JAMA.* 2018;319(17):1781–1789. doi:10.1001/jama.2018.3627

THANK YOU

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- Prof. Johan Mouton
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- Serenella Ferro Rojas (CRC)
- Jocelyne Chabert (CRC)
- Angèle Gayet-Ageron

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AIDA

CRC: Centre de recherche clinique, University Hospitals of Geneva